# Discovery of a Potent and Selective Inhibitor of Cyclin-Dependent Kinase 4/6

Peter L. Toogood,*,† Patricia J. Harvey,‡ Joseph T. Repine,† Derek J. Sheehan,† Scott N. VanderWel,† Hairong Zhou,† Paul R. Keller,‡ Dennis J. McNamara,† Debra Sherry,† Tong Zhu,§ Joanne Brodfuehrer,§ Chung Choi,† Mark R. Barvian,† and David W. Fry‡

*Medicinal Chemistry, Cancer Pharmacology, and Pharmacokinetics, Dynamics and Metabolism, Pfizer Global Research and Development, Michigan Laboratories, 2800 Plymouth Road, Ann Arbor, Michigan 48105*

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A pharmacological approach to inhibition of cyclin-dependent kinases 4 and 6 (Cdk4/6) using highly selective small molecule inhibitors has the potential to provide novel cancer therapies for clinical use. Achieving high levels of selectivity for Cdk4/6, versus other ATP-dependent kinases, presents a significant challenge. The pyrido[2,3-*d*]pyrimidin-7-one template provides an effective platform for the inhibition of a broad cross-section of kinases, including Cdks. It is now demonstrated that the modification of pyrido[2,3-*d*]pyrimidin-7-ones to include a 2-aminopyridine side chain at the *C*2-position provides inhibitors with exquisite selectivity for Cdk4/6 in vitro. This selectivity profile is recapitulated in cells where the most selective inhibitors create a $G_1$ block at concentrations up to 100-fold the $IC_{50}$ for cell proliferation. On the basis of its selectivity profile and pharmacokinetic profile, compound **43** (PD 0332991) was identified as a drug candidate for the treatment of cancer.

## Introduction

Inhibition of cyclin-dependent kinases (Cdks) associated with cell cycle regulation is anticipated to provide an effective approach to the control of tumor growth in the clinic.[1] To this end, we[2] and others[3−8] have been studying inhibitors of Cdks 1, 2, and 4 in vitro, with the goal of identifying Cdk-selective small molecule inhibitors with physical properties amenable to achieving high exposure in vivo. Such agents may then be used to test the hypothesis, first in animal models and then in patients, that pharmacological inhibition of one or more Cdks will inhibit tumor growth. Although much biochemical evidence supports targeting Cdk4/D as the most important Cdk for regulating cell proliferation,[1f,9] many chemical series and programs have actually tended to favor inhibition of Cdk1 and 2 over inhibition of Cdk4/D.[3−7] Consequently, the more advanced Cdk inhibitors in terms of preclinical and clinical evaluation, such as CYC-202 (**1**)[10] and BMS-387032 (**2**),[11] may be better characterized as inhibitors of Cdk2 rather than inhibitors of Cdk4/D. Flavopiridol (**3**),[12] a Cdk inhibitor that has been studied clinically for several years and is currently being evaluated in combination therapy, probably exerts its activity through inhibition of Cdk9 and inhibition of cyclin D1 expression.[13] While these compounds are all effective at inhibiting the growth of human tumor xenografts in mice, none has yet shown efficacy for the treatment of cancer in human patients.[14] Moreover, as more has been learned about the roles of various Cdks in regulating cell-cycle transitions, evidence has been presented that Cdk2 activity is not essential for cells to undergo mitosis,[15] and may be substituted by another kinase, possibly Cdk4/D or Cdk6.

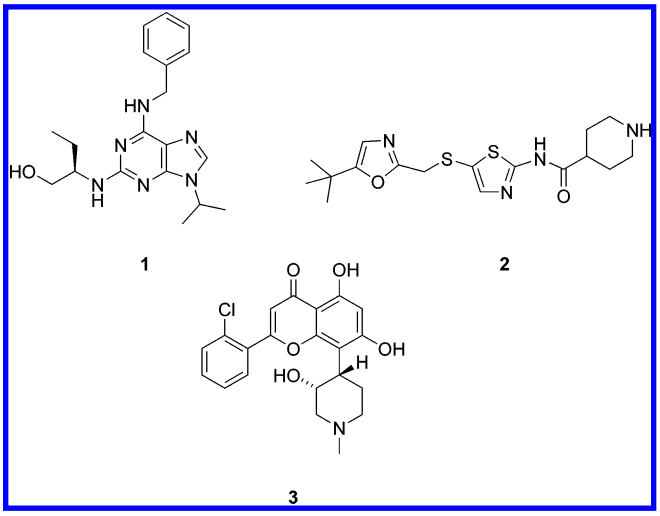


**Figure 1.** Cdk inhibitors CYC-202 (**1**), BMS 387032 (**3**) and flavopiridol (**3**).

In addition, Cdk2 inhibition by siRNA fails to halt the proliferation of osteosarcomas and Rb-negative cervical cancers, suggesting that Cdk2 may not be a good target for inhibition by small molecules intended to treat cancer.[16] These recent results have shifted attention back toward Cdk4/D as the primary cell cycle Cdk target for cancer drug discovery.

Selective inhibitors of Cdk4/D have been described in the literature[8] and it is noteworthy that higher selectivity can be achieved for inhibition of Cdk4/D versus other Cdks than for inhibition of Cdk2 versus Cdk1. This latter pair appears to present a higher level of structural similarity in three dimensions than Cdk4/D and Cdk2, making the design of truly selective Cdk2 inhibitors especially challenging. Some Cdk2 inhibitors also inhibit extraneous kinases such as Cdk5 and Gsk3, further complicating their biochemical profile. Among the Cdk4/D inhibitors that have been described, CINK4 (**4**),[8g] is

* Corresponding author. Tel: 734 622 1335. Fax: 734 622 5165. E-mail: Peter.toogood2@pfizer.com.
† Medicinal Chemistry.
‡ Cancer Pharmacology.
§ Pharmacokinetics, Dynamics and Metabolism.

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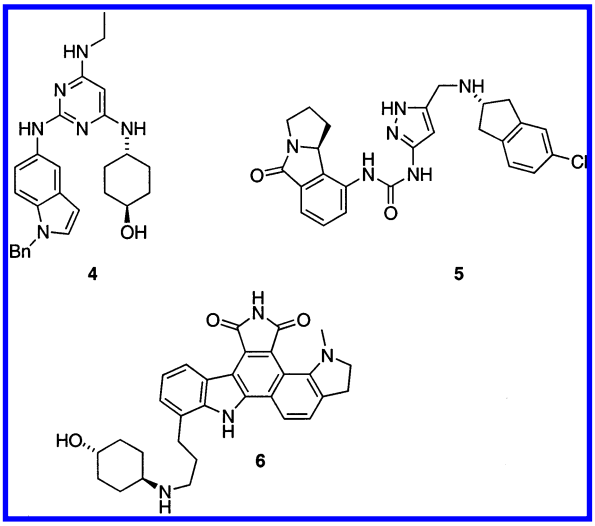
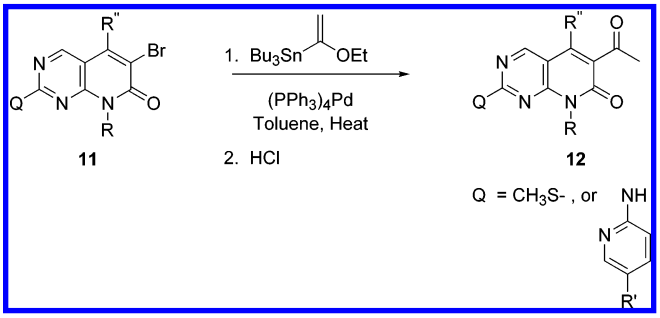



**Figure 2.** Selective Cdk4 inhibitors.

somewhat selective for Cdk4/D and inhibits the growth of HCT116 tumors in mice. However, the relatively weak potency of this compound ($IC_{50}$ = 1.5 $\mu$M) raises questions regarding its mechanism of action in vivo. Urea derivatives from Banyu (e.g. **5**),[8j,k] also are somewhat selective for Cdk4/D in vitro, but only limited cell-based activity data and no in vivo data have been disclosed for these compounds. Scientists from Lilly have reported two series of related carbazoles (e.g. **6**)[8c–f,n] that display selectivity for Cdk4/D, and selected examples are active versus HCT116 tumors in vivo. However, many of these compounds retain significant potency against Cdk2/cyclin E.

Our goal is to identify potent (nanomolar) inhibitors of Cdk4/D that possess sufficient selectivity against other kinases to test the hypothesis that pharmacological inhibition of Cdk4/D will provide a mild and effective treatment for the inhibition of tumor growth. Here, we describe structural modifications to a series of pyrido-[2,3-*d*]pyrimidin-7-ones that have led to the discovery of some of the most potent and selective Cdk4/D inhibitors yet reported.[17] Specifically, modification of the *C*2-side chain to a 2-aminopyridine confers exquisite selectivity for Cdk4/D versus all other kinases tested. Moreover, distinct biochemical differences have been identified between selective Cdk4/D inhibitors and mixed inhibitors that inhibit both Cdk4/D and Cdk2. These observations provide confidence that the compounds described here also act selectively upon Cdk4/D in the more challenging context of the intracellular environment.

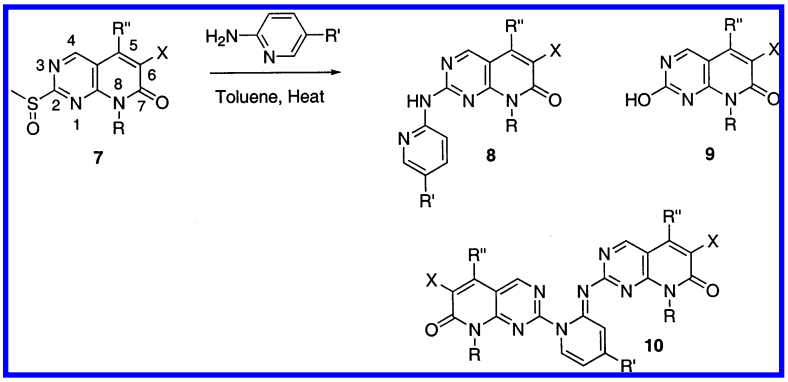
**Scheme 2**



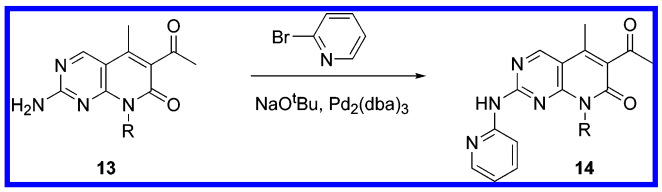

## Chemistry

The compounds described in this report were prepared following the general approach that has been disclosed previously.[2] Introduction of the aminopyridyl side chains by displacement of a sulfoxide at the *C*2 position of the pyrido[2,3-*d*]pyrimidin-7-one core was achieved in moderate to low yields by heating the starting sulfoxides in toluene to 110 °C overnight (Scheme 1). In most cases the product precipitated from the reaction mixture upon cooling, considerably facilitating the isolation of pure material. The reaction mixtures also contained several side products, including significant quantities of the corresponding 2-hydroxy pyrido[2,3-*d*]pyrimidin-7-ones (**9**) and a 2:1 adduct tentatively identified as structure **10** (Scheme 1). Attempts to exclude water from the reaction mixtures failed to eliminate the formation of hydroxy-pyrimidinones suggesting that a non-hydrolytic pathway to these compounds exists, possibly involving rearrangement of the starting sulfoxide. The 2:1 adduct could be minimized but never entirely eliminated by increasing the ratio of aminopyridine to sulfoxide in the reaction mixture. Changes in reaction temperature and solvent failed to substantially improve the yield of desired product. *tert*-Butyl carbamate protected side chains such as piperazines and aminopyrrolidines were deprotected by acidolysis in ethereal hydrochloric acid and isolated as their hydrochloride salts. Compounds containing a *C*6-acetyl group (**12**) were accessed from the corresponding *C*6 bromides (**11**) via Stille coupling with (ethoxyvinyl)tributylstannane, followed by hydrolysis, either before or after installation of the *C*2-side chain (Scheme 2). In some cases, it was possible to install the *C*2 side chain late in the synthesis via a palladium-mediated arylation reaction of pyrimidine

**Scheme 1**



**Scheme 3**




amines **13** to provide products **14** as shown in Scheme 3. This latter approach was explored as an alternative to sulfoxide displacement but was not as general and provided no improvement in overall yields. All target compounds were characterized by $^1$H NMR and mass spectroscopy. Purity was assessed by combustion analysis or by reversed phase HPLC and high-resolution mass spectroscopy.

## Results and Discussion

The first pyrido[2,3-*d*]pyrimidin-7-one prepared containing a 2-aminopyridine substituent at *C*2 was compound **15a**. A comparison of **15a** with its aniline counterpart **15b** identified a remarkable difference in selectivity profile between the two analogues, with the pyridyl analogue (**15a**) substantially favoring inhibition of Cdk4/D over inhibition of Cdk2/A (Figure 3). Contemporaneously, the nonspecific Cdk inhibitor, compound **16** (Figure 3), was identified as a potent inhibitor of Cdk4/D ($IC_{50}$ = 0.002 $\mu$M), Cdk2A ($IC_{50}$ = 0.043 $\mu$M) and the fibroblast growth factor receptor (FGFr: $IC_{50}$ = 0.080 $\mu$M). Bromide **16** was shown to inhibit the growth of human tumor xenografts in mice (not shown), demonstrating an ability to reach its molecular target(s) in vivo. Consequently, this compound was selected as a starting point for addressing whether replacing aniline side chains with aminopyridine-containing side chains would provide a general method for achieving selective inhibition of Cdk4/D, with compounds possessing the potential to inhibit this target in vivo.

To our great satisfaction, the next compound prepared, compound **17** (Figure 4), was found to exhibit excellent selectivity for Cdk4/D versus other Cdks and the receptor tyrosine kinases FGFr and PDGFr (platelet-derived growth factor receptor). Moreover, compound **17** imposed a $G_1$ block on asynchronously growing Rb-positive MDA-MB453 cells that was maintained at concentrations of inhibitor up to 10 $\mu$M. This remarkable observation led to a more thorough exploration of pyrido[2,3-*d*]pyrimidin-7-ones containing 2-aminopyridine side chains at the *C*2 position and the resulting SAR trends are detailed below.

A brief examination of the *N*8 substituent was performed to determine whether changing the nature of the *C*2 side chain would alter the previously observed preference for a cycloalkyl group at *N*8. A limited survey of *N*8 substituents (Table 1) indicated that a cyclopentyl group at *N*8 provided the best combination of potency and selectivity for Cdk4/D. Consequently, all remaining analogues were prepared holding this group constant.

Attention was turned next to the *C*6 substituent. Although the bromine atom in compound **17** conferred good potency for Cdk4/D inhibition, the size and lipophilicity of this atom suggested that a more optimal substituent might exist for this position. Specifically, an improvement in overall physical properties was anticipated with substituents that could lower the total molecular weight and introduce some polarity at the *C*6 position, while retaining potency for Cdk4/D. Therefore, the substituents examined were generally small and polar in nature as shown in Table 2. Historical data for

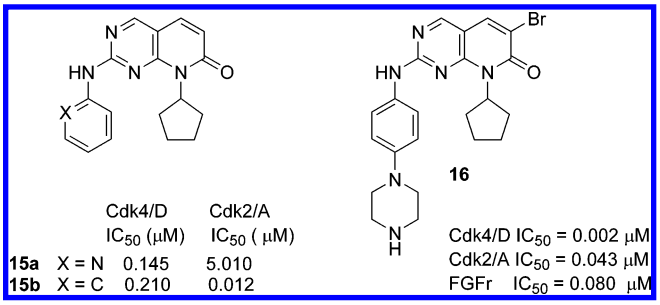



**Figure 3.** Initial leads in the discovery of compound **43**.

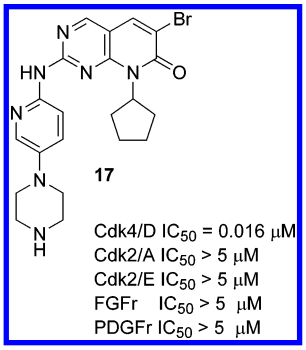
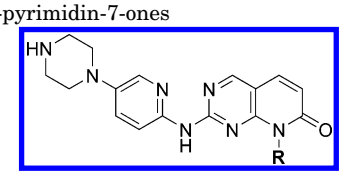


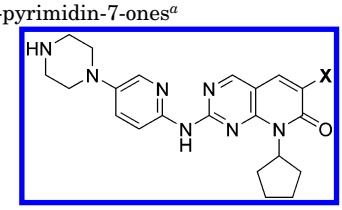

**Figure 4.** A potent and selective Cdk4 inhibitor.

**Table 1.** SAR at the *N*8-Position of Pyrido-[2,3-*d*]-pyrimidin-7-ones



| compd | R | Cdk4/D $IC_{50}$ ($\mu$M) | Cdk2A $IC_{50}$ ($\mu$M) |
|---|---|---|---|
| **18** | isopropyl | >5 | >5 |
| **19** | cyclopropyl | 0.92 | >5 |
| **20** | cyclopentyl | 0.015 | 2.5 |
| **21** | cyclohexyl | 0.013 | 0.835 |

**Table 2.** SAR at the *C*6-Position of Pyrido-[2,3-*d*]-pyrimidin-7-ones[a]



| compd | X | Cdk4/D $IC_{50}$ ($\mu$M) | Cdk2A $IC_{50}$ ($\mu$M) | MDA-MB435 $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|
| **17** | Br | 0.016 | 6.05 | 0.09 |
| **22** | F | 0.051 | >5 | 1.10 |
| **23** | $NH_2$ | 0.019 | >5 | 0.19 |
| **24** | Me | 0.027 | 4.05 | 0.29 |
| **25** | Et | 0.022 | >5 | 1.08 |
| **26** | $CH_2OH$ | 0.013 | >5 | 0.56 |
| **27** | $CH_2OMe$ | 0.013 | 3.8 | 0.33 |
| **28** | $CH_2OEt$ | 0.018 | >5 | 1.00 |
| **29** | $CH_2O(CH_2)_2OMe$ | 0.031 | >5 | 2.15 |
| **30** | $(CH_2)_2OEt$ | 0.124 | >5 | NA |
| **31** | $O(CH_2)_2OEt$ | 0.037 | >5 | NA |
| **32** | $OCH_2{}^iPr$ | 1.760 | >5 | NA |
| **33** | Ac | 0.123 | >5 | 2.77 |
| **34** | $CO_2Et$ | 0.595 | >5 | NA |

[a] NA means data not available.

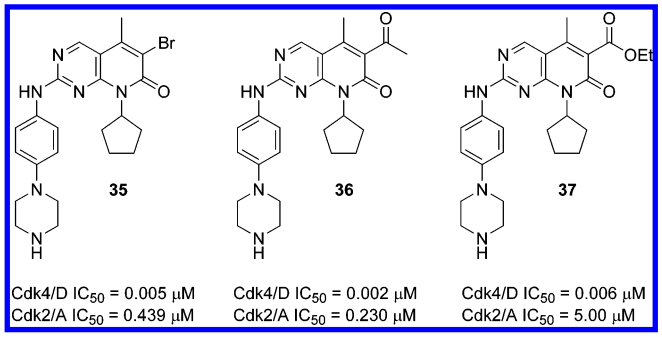
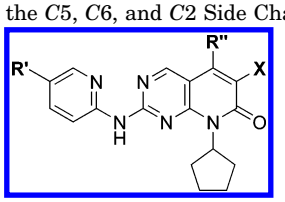



**Figure 5.** Selective Cdk4 inhibitors containing aniline side chains.

**Table 3.** Varying the *C*5, *C*6, and *C*2 Side Chain Substituents



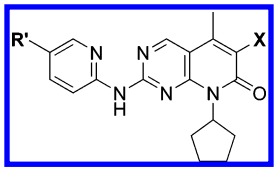
| compd | R″ | R′ | X | Cdk4/D $IC_{50}$ ($\mu$M) | Cdk2A $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|
| **38** | Me | piperazine | H | 0.580 | >5 |
| **39** | H | H | Br | 0.95 | >5 |
| **40** | Me | H | Br | >5 | >5 |
| **17** | H | piperazine | Br | 0.016 | 6.05 |
| **41** | Me | piperazine | Br | 0.16 | >5 |
| **42** | Me | H | Ac | 0.440 | >5 |
| **33** | H | piperazine | Ac | 0.123 | >5 |
| **43** | Me | piperazine | Ac | 0.011 | >5 |
| **34** | H | piperazine | $CO_2Et$ | 0.595 | >5 |
| **44** | Me | piperazine | $CO_2Et$ | 0.049 | >5 |

pyrido[2,3-*d*]pyrimidin-7-one inhibitors of Cdks indicated that selectivity for Cdk4/D was most difficult to achieve versus Cdk2/A. Thus, inhibition of Cdk4/D and Cdk2/A was measured routinely for these compounds to provide a first-pass indication of inhibitor selectivity. In all cases in Table 2, significant selectivity for Cdk4/D was retained. In general, a range of substituents appeared to be tolerated at the *C*6 position, including small polar groups such as $NH_2$ (**23**), nonpolar substituents such as ethyl (**25**), and extended chains such as methoxyethoxymethyl (**29**). Four compounds displayed potency for Cdk4/D comparable to compound **17**, namely compounds **23**, **26**, **27**, and **28**. Strikingly, the branched *sec*-butoxy substituent in compound **32** was not well tolerated and resulted in a drop in potency against Cdk4/D of 2 orders of magnitude, indicating a possible size limitation in this region of the binding site. These observations are consistent with expectations based on a structural model in which the *C*6 substituent projects into the back of the ATP binding pocket.[2a]

Selected examples from Table 2 were evaluated in cell-based assays for inhibition of [$^{14}$C]-thymidine incorporation into MDA-MB435 human breast carcinoma cells. Cdk4/D inhibitors cause cells to accumulate in $G_1$ and since DNA synthesis occurs in S-phase, inhibition of DNA synthesis, and consequently thymidine incorporation, provides a useful surrogate for inhibition of cell proliferation. Of the compounds examined, only compound **23** was considered sufficiently potent in cell-based assays for further studies. Unfortunately, this compound displayed very low solubility (less than 3 $\mu$g/mL) and was not pursued further. Nonetheless, encouraged that the effect of the pyridyl side chain on selectivity was general, SAR studies were continued in search of compounds more suitable for in vivo studies.

As described in the accompanying manuscript,[18] another structural modification in the pyrido[2,3-*d*]-pyrimidin-7-one series that led to improved selectivity for Cdk4/D was the introduction of a methyl substituent at the *C*5 position. To determine whether the *C*5-methyl and the *C*2-pyridyl groups could work together to provide even greater selectivity for Cdk4/D, compounds were prepared containing both of these structural features. Since compounds **35**, **36**, and **37** (Figure 5) had already been identified as potent and quite selective inhibitors of Cdk4/D,[18] these structures were chosen as

**Table 4.** Optimizing the *C*2 Side Chain[a]



| compd | X | R′ | Cdk4/D $IC_{50}$ ($\mu$M) | Cdk2A $IC_{50}$ ($\mu$M) | MDA-MB435 $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|
| **41** | Br | piperazine | 0.16 | >5 | NA |
| **45** | Br | $(CH_3OCH_2CH_2)_2N$- | 1.1 | >5 | NA |
| **46** | Br | 3,5-dimethylpiperazine | 0.063 | >5 | 0.570 |
| **47** | Br | *N*-methylpiperazine | 0.136 | >5 | NA |
| **48** | Br | homopiperazine | >5 | >5 | NA |
| **49** | Br | piperidine | >5 | >5 | NA |
| **50** | Br | 4-hydroxypiperidine | 0.074 | >5 | 1.400 |
| **51** | Br | morpholine | 1.95 | >5 | NA |
| **43** | Ac | piperazine | 0.011 | >5 | 0.160 |
| **52** | Ac | $(CH_3OCH_2CH_2)_2N$ | 0.051 | 2.05 | NA |
| **53** | Ac | 3,3-dimethylpiperazine | 0.021 | >5 | 0.420 |
| **54** | Ac | 3,5-dimethylpiperazine | 0.037 | >5 | 0.570 |
| **55** | Ac | *N*-methylpiperazine | 0.005 | >5 | 0.325 |
| **56** | Ac | 3-aminopyrrolidine | 0.014 | >5 | 0.340 |
| **57** | Ac | homopiperazine | 0.012 | >5 | 0.070 |
| **58** | Ac | piperidine | 0.005 | >5 | 1.930 |
| **59** | Ac | 4-hydroxypiperidine | 0.019 | >5 | 0.200 |
| **60** | Ac | morpholine | 0.004 | >5 | 0.220 |
| **61** | Ac | 3,5-dimethylmorpholine | 0.030 | >5 | 2.040 |

[a] NA means data not available.

starting points for the study of *C*5-methyl/*C*2-pyridyl additivity. In each case, changing the aniline to a 2-aminopyridine in the *C*2 side chain rendered the compounds less potent for Cdk4/D, (compare **35** to **41**, **36** to **43**, and **37** to **44**: Figure 5 and Table 3). Where it could be determined, an increase in selectivity for Cdk4/D versus Cdk2/A was observed (compare **36** to **43**). The effect of the *C*5 methyl group depended very much on the exact nature of the *C*6 substituent. Addition of a *C*5 methyl group to compounds that contained a 2-aminopyridine in the *C*2 side chain led to an increase in potency when there was an acetyl or ethyl ester substituent at *C*6 (compare **33** to **43** and **34** to **44**), but a drop in potency when there was a bromine atom at *C*6 (compare **17** to **41**). This disparity suggests that the *C*6 acetyl or ester carbonyl group is forming an additional interaction with the protein when it is oriented by the adjacent methyl group out of the plane defined by the pyrido[2,3-*d*]pyrimidin-7-one rings.

The data in Table 3 identified compound **43** as a remarkably potent and selective Cdk4/D inhibitor, exhibiting a near optimal biochemical profile. However, to this point there had been no investigation of the heterocyclic group attached to the pyridine ring to determine whether the piperazine substituent was optimal with regard to potency and physical properties. Thus, a series of piperazine replacements was investigated using both the *C*5-methyl/*C*6-acetyl pyrido[2,3-*d*]pyrimidin-7-one, and the *C*5-methyl/*C*6-bromo pyrido-[2,3-*d*]pyrimidin-7-one cores. These compounds are listed in Table 4. It is noteworthy that the *C*6 bromides are less potent than the *C*6-acetyl derivatives in every case, although the 3,5-dimethylpiperazine derivative **46** displays an $IC_{50}$ = 0.063 $\mu$M for Cdk4/D, which is only 2-fold less potent than acetyl analogue **54**. Several of the *C*6-acetyl derivatives displayed potencies for Cdk4/D, and selectivities against Cdk2/A comparable to compound **43**. In cell based assays, four compounds displayed $IC_{50}$ values of ~0.200 $\mu$M or less. Of these four, compounds **43** and **57** are both more potent and more soluble (data not shown) than compounds **59** and **60**, identifying them as excellent biochemical tools for studying the effects of selective Cdk4/D inhibition in cells.

Selective Cdk4 inhibitors are expected to block cell cycling by imposing a $G_1$ block in an Rb-dependent manner. Five compounds, including compound **43**, were compared by flow cytometry for their effect on cell cycling in MDA-MB453 human breast carcinoma cells (Figure 6, Table 5). The five compounds were chosen to span a range of selectivity for Cdk4/D vs Cdk2A as well as to represent a variety of different structural features. Thus, compound **16** is a nonselective Cdk inhibitor containing an aniline side chain; compounds **36** and **37** contain aniline side chains and are moderately to highly selective for Cdk4/D in enzyme assays. Compounds **17** and **43** contain pyridyl side chains and are both highly selective for Cdk4/D. Compound **16** imposed a $G_1$ block on cells at 0.1 $\mu$M, at which concentration it may functionally inhibit Cdk4/D more than Cdk2. At higher concentrations, however, substantial populations of cells in $G_2$ were observed. Compound **36** is approximately 100-fold selective for Cdk4/D versus Cdk2A, but this compound only produced a clean $G_1$ block in cells at concentrations less than 3 $\mu$M. Compound **37** appears to be highly selective for Cdk4/D versus other Cdks based on comparative enzyme inhibition data obtained in vitro. It also lacks antiproliferative activity against the Rb-negative cell line, MDA MB468, however, in MDA-MB453 cells, concentrations of this compound greater than or equal to 3 $\mu$M, similarly produced a significant population of cells in $G_2$. In contrast, compounds **17** and **43**, produced sustained $G_1$ blocks at 3 $\mu$M and even up to 10 $\mu$M (not shown). Thus, flow cytometry provides a method of distinguishing the most highly selective inhibitors of Cdk4/D. Even apparently selective Cdk4/D inhibitors such as **36** and **37** arrest some cells in $G_2$ at concentrations >1 $\mu$M. This profile

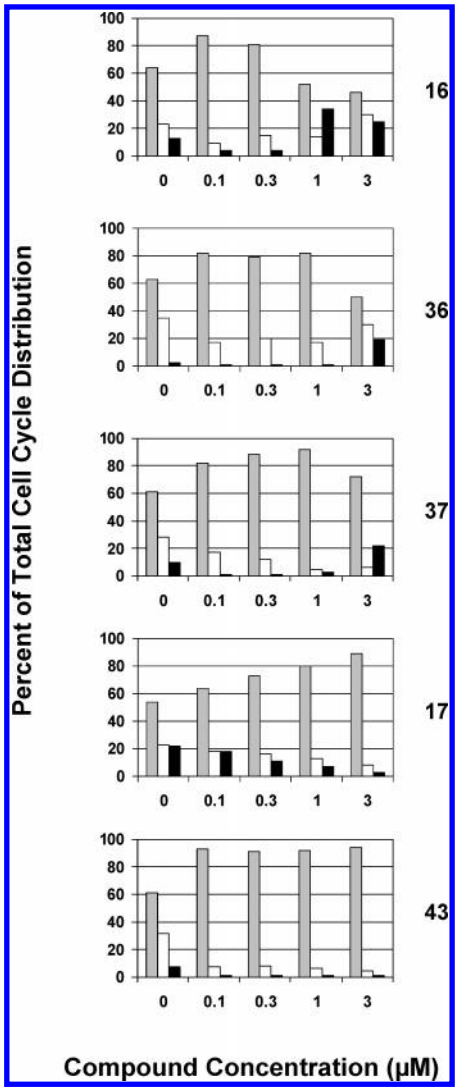



**Figure 6.** Cell cycle flow cytometry histograms for a selection of Cdk inhibitors exhibiting various levels of selectivity for Cdk4. Data were recorded using MDA-MB453 cells as described in Experimental Methods. Gray bars: cells in $G_1$ phase; unfilled bars: cells in S phase; filled bars: cells in $G_2$ phase.

**Table 5.**

| compd | Cdk4/D $IC_{50}$ ($\mu$M) | Cdk2/A $IC_{50}$ ($\mu$M) | MDA-MB435 $IC_{50}$ ($\mu$M) | MDA-MB468 $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|
| **16** | 0.002 | 0.043 | 0.020 | 0.600 |
| **36** | 0.002 | 0.230 | 0.030 | 1.1 |
| **37** | 0.006 | >5 | 0.170 | >3 |
| **17** | 0.016 | >5 | 0.090 | >3 |
| **43** | 0.011 | >5 | 0.160 | >3 |

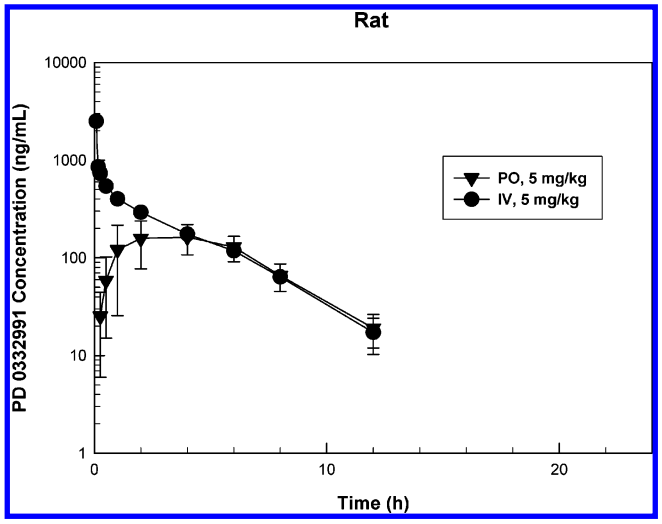



**Figure 7.** Pharmacokinetic profile of compound **43** in rat following intravenous or oral dosing.

is not well understood, but is likely related to the inhibition of kinases other than Cdk4/D in cells by the less selective inhibitors. A sustained $G_1$ block at concentrations $\geq 3$ $\mu$M appears to be a hallmark of more highly selective Cdk4/D inhibitors. This observation provides encouragement that compounds such as **17** and **43** display *functional selectivity* for Cdk4/D in cells and suggests a method for screening for Cdk4/D selectivity that is supplementary to performing extensive in vitro enzyme assays. To be considered selective for Cdk4/D, inhibitor molecules must exhibit selectivity in enzyme assays, selectively inhibit proliferation of Rb-positive and not Rb-negative cell lines, and produce a robust $G_1$ block at concentrations of inhibitor close to 100-fold the $IC_{50}$ for inhibition of cell proliferation.

On the basis of the data in Table 4, compounds **43**, **57**, **59**, and **60** appeared comparable in terms of their potency and selectivity for Cdk4/D, and activity in cells; however, upon further evaluation, compound **43** stood out as a superior candidate. In particular, compound **43** is equipotent versus Cdk4 and Cdk6,[17] displays good pharmacokinetic properties in rats (Figure 7, Table 6; CL = 37.5 ± 1.7 mL/min/kg, 56% oral bioavailability), and excellent pharmaceutical properties (not shown).

In summary, the introduction of a 2-aminopyridyl substituent at the *C*2-position of pyrido[2,3-*d*]pyrimidin-7-ones substantially biases the selectivity of these compounds toward selective inhibition of Cdk4/D versus other serine/threonine and tyrosine kinases. This effect appears to be general and to apply across a wide range of kinases. The reason the pyridyl group at *C*2 confers such excellent selectivity for Cdk4/D on these compounds is not understood at the present time and will likely have to await the solution of a crystal structure for a Cdk4/D/inhibitor complex. Compound **43** specifically displays a high level of selectivity for Cdk4/D versus over 36 other kinases.[17] This selectivity is further reflected in cell-based assays in the form of a $G_1$ cell cycle block in Rb-positive cells that is maintained at high concentrations of the inhibitor. This latter property is unique to the most highly selective Cdk4/D inhibitors and among the pyrido[2,3-*d*]pyrimidin-7-ones is only observed with compounds possessing a 2-aminopyridyl substituent in the *C*2 position. Among these highly selective inhibitors, compound **43** displays a superior overall profile including the combined attributes of potency, selectivity, and pharmaceutical properties. A more extensive biochemical and biological characterization of compound **43** will be published separately.[17] Compound **43** is currently under exploratory development for the treatment of cancer.

## Experimental Section

**8-Cyclopentyl-2-(pyridin-2-ylamino)-8*H*-pyrido[2,3-d]-pyrimidin-7-one (15a).** 8-Cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (200 mg, 0.7 mmol) and 2-aminopyridine (130 mg, 1.4 mmol) were combined in a 10 mL round-bottomed flask. The flask was purged with nitrogen (10 min) and then heated in a 160 °C oil bath (30 min). After cooling, the orange residue was triturated with water to afford an orange solid, which was further purified by reversed-phase HPLC to provide **15a** (15 mg, 7%) as a yellow solid. mp: >250 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) 8.83 (s, 1H), 8.33 (d, $J$ = 4 Hz, 1H), 7.91 (m, 2H), 7.83 (d, $J$ = 9 Hz, 1H), 7.13 (m, 2H), 6.41 (d, $J$ = 9 Hz, 1H), 5.81 (m, 1H), 2.20 (m, 2H), 1.90 (m, 2H), 1.75 (m, 2H), 1.56 (m, 2H).

**6-Bromo-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (17).** Under a dry argon atmosphere were combined 6-bromo-8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.78 g, 2.19 mmol) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (63, 0.67 g, 2.4 mmol) without solvent. The flask was evacuated and heated to 120 °C for 1 h. The mixture was purified by chromatography on silica gel, eluting with chloroform, to give a yellow foam, 0.288 g. Recrystalization from acetonitrile gave 4-[6-(6-bromo-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**62** (0.266 g, 21%). MS (APCI) *m/z* 570.0 (M + 1). Compound **62** (0.26 g, 0.46 mmol) was dissolved in 1:1 chloroform/methanol (15 mL), to which was added diethyl ether (25 mL). The solution was purged with anhydrous hydrogen chloride gas and stoppered for 18 h. The resulting white solid was collected by filtration, washed with diethyl ether and dried in vacuo at 60 °C to give **17** as a pale yellow solid (0.254 g). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.32 (s, 2 H), 8.86 (s, 1 H), 8.47 (s, 1 H), 8.02 (s, 1 H), 7.82 (m, 1 H), 7.79 (d, $J$ = 9.28 Hz, 1 H), 5.88 (m, 1 H), 3.40 (s, 4 H), 3.22 (s, 4 H), 2.16 (m, 2 H), 1.93 (m, 2 H), 1.77 (m, 2 H), 1.58 (m, 2 H); MS (APCI) *m/z* = 470.0 (M + 1). Anal. ($C_{21}H_{24}BrN_2O\cdot1.25H_2O\cdot2.2HCl$) C, H, N, Cl, $H_2O$.

**4-[6-(8-Isopropyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (64).** A mixture of 2-chloro-8-isopropyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (338 mg, 1.5 mmol) and compound **63** (460 mg, 2.0 mmol) in toluene (6 mL) was heated at 110 °C for ~20 h and then cooled to room temperature. The solid was collected by filtration, washed with toluene, and dried. The sample was dissolved in $CH_2Cl_2$ and purified by two preparative TLC plates eluted in 10% MeOH/$CH_2Cl_2$. The band with $R_f$ = 0.23 was extracted to give **64** as a yellow solid (180 mg, 26%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.29(s, 1H), 8.80 (br, 1H), 8.90~8.17 (m, 2H), 7.70 (d, $J$ = 2.5 Hz,1H), 7.2

**Table 6.**

| route | dose (mg/kg) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $t_{1/2}$(h) | AUC(0 − ∞) (ng·h/mL) | AUC(0 − $t$) (ng.h/mL) | CL (mL/min/kg) | $V_d$ (L/kg) | $F$ (%) |
|---|---|---|---|---|---|---|---|---|---|
| iv | 5 | - | - | 2.4 ± 0.3 | 2230 ± 103 | 2160 ± 71 | 37.5 ± 1.7 | 7.0 ± 0.4 | - |
| po | 5 | 178 ± 47 | 3.5 ± 1.9 | 2.1 ± 0.1 | 1200 ± 393 | 1140 ± 384 | - | - | 56.1 |

(d, $J$ = 9.8 Hz, 1 H), 6.88 (d, $J$ = 9.6 Hz,1H), 5.6∼5.5 (m, 1H), 4.06 (m, 1 H), 3.9−3.4 (m, 4H), 3.14 (d, $J$ = 5.2 Hz, 2H), 2.98 (m, 4H), 1.52 (s, 3H), 1.1.50 (s, 3H), 1.38 (s, 9H); MS (APCI) *m/z* 466.2 (M + 1).

**8-Isopropyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride Salt (18).** HCl gas was bubbled through a solution of **64** (180 mg, 0.39 mmol) in $CH_2Cl_2$ (5 mL) at room temperature. The light yellow solid formed was collected by filtration 5 h later. The solid was hygroscopic so it was dissolved in MeOH and a few drops of water were added to the solution. The solvent was then removed under reduced pressure to generate a glass solid. The solid was washed with acetone and dried further to yield **18** (101 mg, 66%). mp 237−240 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.38 (br s, 1 H), 9.28 (s, 1 H), 8.88 (br s, 1 H), 8.14 (d, $J$ = 9.5 Hz, 1 H), 8.07 (d, $J$ = 9.0 Hz, 1 H), 7.73 (s, 1 H), 7.23 (d, $J$ = 9.5 Hz, 1 H), 6.85 (d, $J$ = 9.5 Hz, 1 H), 5.57−5.01 (m, 1 H), 3.23 (br s, 4 H), 3.17 (br s, 4 H), 1.49 (s, 3 H), 1.47(s, 3 H); MS (APCI) *m/z* 366.2 (M + 1). Exact Mass: Calculated ($C_{19}H_{23}N_7O_1$) 366.2039, found 366.2039 (M + 1); HPLC purity 93%.

**8-Cyclopropyl-2-methylsulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (65).** A solution of 8-cyclopropyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.5 g, 2.1 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (0.84 g, 3.2 mmol) in $CH_2Cl_2$ (5 mL) was stirred at room temperature for 20 h. The white solid formed was collected by filtration and washed with hexane, then dried to give **65** (0.388 g, 74%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.15 (s, 1H), 8.0 (d, $J$ = 9.5 Hz, 1H), 6.74 (d, $J$ = 9.5 Hz, 1 H), 2.92 (s, 1H), 1.18−1.14 (m, 2H), 0.83−0.79 (m, 2H).

**4-[6-(8-Cyclopropyl-7-oxo-7,8-dihhydro-pyrido[2,3-*d*]-pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (66).** A mixture of 8-cyclopropyl-2-methylsulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (388 mg, 1.56 mmol) and compound **63** (462 mg, 2.0 mmol) in toluene (5 mL) was heated at 100 °C for 18 h. It was cooled to room temperature, and the solid was collected by filtration and washed with toluene and dried to give **66** (96 mg, 13%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.97 (s, 1H), 8.67 (s, 1H), 8.39 (d, $J$ = 9.3 Hz, 1H), 8.0 (d, $J$ = 2.95 Hz, 1 H), 7.71 (d, $J$ = 9.3 Hz, 1H), 6.28 (d, $J$ = 9.3 Hz, 1H), 3.42 (br, 4H), 3.05 (br, 4H0, 2.80 (m, 1H), 1.37 (s, 9H), 1.20 (d, $J$ = 6.1 Hz, 2H), 0.76 (br, 2H).

**8-Cyclopropyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride Salt (19).** HCl gas was bubbled through a solution of **66** (96 mg, 0.21 mmol) in $CH_2Cl_2$ (5 mL) for a few min until a solid started to form. The mixture was stirred at room temperature for 18 h and then the solid was collected by filtration and washed with $CH_2Cl_2$ then dried in vacuo to give **19** (83 mg, 85%). mp >300 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.07 (br s, 2H), 8.80 (s, 1H), 8.08 (br s, 1H), 8.07 (d, $J$ = 2 Hz, 1H), 7.86 (br s, 1H), 7.88 (d, $J$ = 9 Hz, 1H), 6.40 (d, $J$ = 9 Hz, 1H), 3.37 (br s, 4H), 3.21 (br s, 4H), 2.92−2.90 (m, 1H), 1.23 (d, $J$ = 6 Hz, 2H), 0.81−0.77 (m, 2H). Anal. ($C_{19}H_{21}N_7O$·2.1HCl·1.5$H_2O$): C, H, N.

**4-[6-(8-Cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (67).** A mixture of 8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidine-7-one (416 mg, 1.5 mmol) and compound **63** (460 mg, 2.0 mmol) in toluene (6 mL) was heated at 110 °C for ∼20 h then cooled to room temperature. The solid formed was collected by filtration, washed with toluene and dried to give **67** (143 mg, 19%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.97 (s, 1H), 8.72 (s, 1H), 8.03 (d, $J$ = 3.0 Hz, 1H), 7.85 (m, 1H), 7.74 (d, $J$ = 9.2 Hz, 1 H), 7.25 (m, 1H), 6.31 (d, $J$ = 9.3 Hz, 1H), 5.80 (m, 1 H), 3.4 (m, 4H), 3.28 (m, 4H), 2.47 (m, 2H), 1.9 (m, 2H), 1.87 (br, 2H), 1.6−1.8 (br, 2H), 1.6−1.5 (m, 2H), 1.39 (s, 9H); MS (APCI) *m/z* 492.2 (M + 1).

**8-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (20).** A solution of **67** (143 mg, 0.29 mMol) in $CH_2Cl_2$/MeOH (6 mL/1.5 mL) was treated with HCl gas at room temperature for ∼3 min. The solution was stirred at room temperature for ∼6 h then filtered to collect the solid. This solid was washed with $CH_2Cl_2$ and dried in vacuo to provide compound **20** (98 mg, 66%). mp 213−215 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.11 (br s, 2H), 8.86 (s, 1H), 8.01 (s, 1H), 7.86 (d, $J$ = 9.5 Hz, 1H), 7.85 (br s, 1H), 7.77 (d, $J$ = 9 Hz, 1H), 6.44 (d, $J$ = 9 Hz, 1H), 5.83−5.77 (m, 1H), 3.87 (br s, 4H), 3,23 (br s, 4H), 2.21 (br s, 2H), 1.92 (br s, 2H), 1.75 (br s, 2H), 1.58 (br s, 2H); MS (APCI) *m/z* 392.1 (M + 1). Anal. ($C_{21}H_{25}N_7O$·2.0HCl·2.5$H_2O$): C, H, N.

**4-[6-(8-Cyclohexyl-7-oxo-7,8-dihhydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *Tert*-Butyl ester (68).** A mixture of 8-cyclohexyl-2-methanesufinyl-8*H*-pyrido[2,3-*d*]pyrimidine-7-one (430 mg, 1.47 mmol) and **63** (556 mg, 2.43 mmol) in toluene (5 mL) was heated at 100 °C for 18 h. It was cooled to room temperature and the solid formed was collected and washed with toluene then dried to give **68** (105 mg, 14%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.02 (s, 1H), 8.70 (s, 1H), 8.04 (d, $J$ = 3.0 Hz, 1H), 7.72 (d, $J$ = 9.2 Hz, 1H), 7.44 (dd, $J$ = 9.2, 3.1 Hz, 1 H), 6.28 (m, 1H), 3.60 (m, 4H), 3.08 (m, 4H), 1.6−1.8 (m, 10H), 1.39 (s, 9H);. MS (APCI) *m/z* 506.1 (M + 1).

**8-Cyclohexyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (21).** HCl gas was bubbled through a solution of **68** (105 mg, 0.21 mmol) in $CH_2Cl_2$ (3 mL) at room temperature until a solid was formed. The mixture was stirred at room temperature for 6 h, and the solid formed was collected by filtration. The solid was hygroscopic. It was recrystalized from MeOH with addition of a few drops of water to yield **21** (40 mg, 35%). mp 228−230 °C; $^1$H NMR $\delta$ (400 MHz, DMSO-$d_6$) 9.34 (br s, 2 H), 8.85 (s, 1 H), 8.03 (s, 2 H), 7.86−7.84 (m, 3 H), 6.42 (d, $J$ = 8 Hz, 1 H), 5.25 (br s, 1 H), 3.40 (s, 4 H), 3.39 (s, 4 H), 1.79−1.19 (m, 10 H); MS (APCI) *m/z* 506.1 (M + 1). Anal. ($C_{22}H_{27}N_7O$·2.0HCl·3.5$H_2O$): C, H, N, Cl.

**8-Cyclopentyl-6-fluoro-2-methanesulfinyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (69).** 8-Cyclopentyl-6-fluoro-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (10.5 g, 37.9 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (11.8 g, 45.4 mmol) were combined in dichloromethane (120 mL) and stirred at room temperature for 18 h. The mixture was evaporated to an oil, crystallized from ethyl acetate/diethyl ether, filtered and dried in vacuo to provide **69** as a white solid (8.88 g, 80%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.94 (s, 1H), 7.25 (d, 1H), 6.06−5.99 (m, 1H), 2.98 (s, 3H), 2.28−2.21 (m, 2H), 2.18−2.12 (m, 2H), 2.02−1.94 (m, 2H), 1.74−1.67 (m, 2H).

**4-[6-(8-Cyclopentyl-6-fluoro-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (70).** Compounds **69** (2.0 g, 6.77 mmol) and **63** (6.0 g, 21 mmol) were added to toluene (8 mL) and heated to 98 °C for 18 h. The mixture was filtered and washed with toluene and the solid suspended in diethyl ether. The mixture was filtered and the solid was dissolved in chloroform, washed with 1 N citric acid, brine and dried over anhydrous magnesium sulfate. The crude product was triturated with diethyl ether and dried in vacuo to provide **70** as a solid (0.88 g, 25%). MS (APCI) *m/z* 510.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58 (s, 1 H) 8.20 (d, $J$ = 9.04 Hz, 1 H) 8.01 (d, $J$ = 2.69 Hz, 1 H) 7.36 (dd, $J$ = 9.28 Hz, 1 H) 7.23 (s, 1 H) 5.91 (m, 1 H) 3.60 (m, 4 H) 3.11 (m, 4 H) 2.34 (m, 2 H) 2.09 (m, 2 H) 1.90 (m, 2 H) 1.69 (m, 2 H) 1.47 (s, 9 H).

**8-Cyclopentyl-6-fluoro-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (22).** Compound **70** (0.195 g, 0.38 mmol) was dissolved in 1:1 chloroform/methanol (8 mL), purged with anhydrous hydrogen chloride gas and stirred for 2.5 h at room temperature. To the mixture was added diethyl ether (15 mL) giving a precipitate that was filtered, washed with ether and dried in vacuo to provide **22** as a yellow solid (0.177 g, 88%). MS (APCI) *m/z* 410.3 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.54 (s, 2 H) 8.91 (s, 1 H) 8.01 (s, 1 H) 7.92 (d, $J$ = 9.04 Hz, 1 H) 7.77 (d, $J$ = 9.77 Hz, 1 H) 5.85 (m, 1 H) 3.43 (m, 4 H) 3.21 (s, 4 H) 2.20 (m, 2 H) 1.96 (m, 2 H) 1.80 (m, 2 H) 1.58 (m, 2 H). Anal. ($C_{21}H_{24}N_7O$·1.0$H_2O$·2.0HCl): C, H, N.

**(8-Cyclopentyl-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-6-yl)-carbamic Acid *tert*-Butyl Ester (71).** To anhydrous *tert*-butyl alcohol (30 mL) were added 8-cyclopentyl-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-d]-pyrimidine-6-carboxylic acid, **72** (2.48 g, 8.02 mmol), triethylamine (0.974 g, 9.63 mmol) and over 5 min, diphenylphosphoryl azide (2.65 g, 9.63 mmol) with stirring. This mixture was heated at 75 °C for 18 h. The mixture was filtered, and the solid was washed with ethyl acetate. The washings were concentrated to an oil enriched in the desired product. The oil was triturated with hexane/diethyl ether and the washings were filtered through silica gel and Celite. The filtrate was concentrated in vacuo yielding **71** as a crystalline solid (1.37 g, 45%). MS (APCI) *m/z* 377.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58 (s, 1 H) 8.12 (s, 1 H) 7.77 (s, 1 H) 5.99 (m, 1 H) 2.57 (s, 3 H) 2.26 (m, 2 H) 2.04 (m, 2 H) 1.87 (m, 2 H) 1.68 (m, 2 H) 1.47 (s, 9 H).

**6-Amino-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (23).** Compound **71** (1.3 g, 3.45 mmol) was added to 1:1 dichloromethane:methanol (12 mL) followed by 2-benzenesulfonyl-3-phenyl-oxaziridine (1.08 g, 4.14 mmol). The mixture was stirred at 25 °C for 3.5 h, evaporated to an oil and eluted through silica gel with chloroform. Fractions containing the product were evaporated to yield (8-cyclopentyl-2-methanesulfinyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-6-yl)-carbamic acid *tert*-butyl ester (**73**) as a solid (1.2 g, 89%). MS (APCI) *m/z* 393.1 (M + 1). Compound **73** (1.2 g, 3.06 mmol) and **63** (2.36 g, 8.48 mmol) were combined in toluene (4 mL) and heated to 105 °C for 12 h. The resulting paste was diluted with toluene, filtered, washed with toluene and partitioned between diethyl ether and 1 N citric acid. The mixture was filtered, and the solid was washed with water and diethyl ether. The solid then was dissolved in chloroform, dried over anhydrous magnesium sulfate, and filtered, and the filtrate diluted with diethyl ether, giving a solid precipitate. This solid was collected by filtration and dried in vacuo to give 4-[6-(6-*tert*-butoxycarbonylamino-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**74**) as a solid (0.311 g, 17%). MS (APCI) 607.2 (M + 1). Compound **74** (0.31 g, 0.511 mmol) was added to 1:1 chloroform:methanol (20 mL), and the mixture was purged with anhydrous hydrogen chloride gas then stirred at room temperature for 18 h. The resulting solid was collected by filtration, washed with diethyl ether, and dried in vacuo to **23** as a yellow solid (0.202 g, 100%). MS (APCI) *m/z* 407.4 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.25 (s, 2 H) 8.72 (s, 1 H) 8.05 (d, 1 H) 7.91 (s, 1 H) 7.58 (d, 1 H) 6.75 (s, 1 H) 5.94 (m, 1 H) 3.37 (m, 4 H) 3.23 (m, 4 H) 2.20 (m, 2 H) 2.00 (m, 2 H) 1.85 (s, 2 H) 1.61 (m, 2 H). Anal. ($C_{21}H_{26}N_8O\cdot1.25H_2O\cdot2HCl$): C, H, N.

**8-Cyclopentyl-6-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (75).** 2-(Diethoxy-phosphoryl)-propionic acid ethyl ester (15.24 g, 64 mmol) was dissolved in tetrahydrofuran (100 mL) to which *n*-butyllithium (47.7 mL, 119 mmol, 2.5 M in hexanes) was slowly added at −70 °C. 4-Cyclopentylamino-2-methylsulfanyl-pyrimidine-5-carbaldehyde (**76**) (15 g, 63 mmol) was dissolved in tetrahydrofuran (70 mL) then added to the reaction mixture allowing the reaction to warm to −40 °C. After 3 h the reaction was warmed to room temperature, poured into cold 1 N citric acid and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil which was purified by silica gel chromatography. The resulting oil was dissolved to 1,8-diazabicyclo[5.4.0]undec-7-ene (75 mL) and heated to 150 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (350 mL), washed with 5% HCl and brine, dried over $MgSO_4$, then filtered and concentrated in vacuo. The remaining residue was diluted with diethyl ether and the precipitated solid was filtered off to give **75** as a white solid (6.33 g, 31%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (s, 1H), 7.39 (d, $J$ = 1.2 Hz, 1H), 5.96, (m, 1H), 2.59 (s, 3H), 2.30 (m, 2H), 2.19 (d, $J$ = 1.2 Hz, 3H), 2.07 (m, 2H), 1.86 (m, 2H), 1.67 (m, 2H).

**8-Cyclopentyl-2-methanesulfinyl-6-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (77).** Compound **75** (2.56 g, 9.30 mmol) was dissolved in dichloromethane (17 mL) and methanol (17 mL) to which 2-benzenesulfonyl-3-phenyl-oxaziridine was added and the reaction mixture was stirred for 16 h. The solvent was removed and diethyl ether added. The precipitated solid was collected by filtration to give **77** as a white solid (2.30 g, 85%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.85 (s, 1H), 7.54 (s, 1H), 5.99, (m, 1H), 2.95 (s, 3H), 2.27 (d, $J$ = 1.2 Hz, 3H), 2.24 (m, 2H), 2.13 (m, 2H), 1.94 (m, 2H), 1.70 (m, 2H).

**8-Cyclopentyl-6-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (24).** Compound **77** (1.0 g, 3.43 mmol) was added to **63** (1.91 g, 6.86 mmol) in toluene (5 mL). The mixture was heated to 100 °C over 18 h then treated with diethyl ether to produce a precipitate. This precipitate was collected by filtration then dried in vacuo to provide 4-[6-(8-cyclopentyl-6-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**78**) as a yellow solid (0.411 g). MS (APCI) *m/z* 506.2 (M + 1). Compound **78** (0.411 g, 0.813 mmol) was dissolved in a 1:1 mixture of methanol:chloroform, purged with anhydrous hydrogen chloride gas and stirred for 2 h at room temperature. A solid was precipitated by addition of diethyl ether. The suspension was filtered and the residue dried in vacuo yielding **24** as a yellow solid (0.393 g). (APCI) *m/z* 406.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.34 (s, 2 H) 8.75 (s, 1 H) 8.02 (d, $J$ = 2.93 Hz, 1 H) 7.82 (d, 1 H) 7.75 (s, 1 H) 7.71 (d, $J$ = 1.22 Hz, 1 H) 5.84 (m, 1 H) 3.39 (s, 4 H) 3.21 (s, 4 H) 2.20 (m, 2 H) 2.04 (m, 3 H) 1.93 (m, 2 H) 1.74 (m, 2 H) 1.58 (m, 2 H). Anal. ($C_{22}H_{27}N_7O\cdot2.85H_2O\cdot2.2HCl$): C, H, N, Cl.

**8-Cyclopentyl-6-ethyl-2-methanesulfonyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (79)**. To a cooled (0 °C, ice bath) solution of 8-cyclopentyl-6-ethyl-2-methylsulfanyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one, **80** (5.0 g, 17.28 mmol), in dichloromethane (25 mL) under nitrogen was added *m*-chloroperbenzoic acid (MCPBA) (7.4 g, 30.0 mmol). The cold bath was removed, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into aq. $NaHCO_3$ (saturated solution, 100 mL) and extracted three times with dichloromethane (300 mL total). The organic layers were combined and dried over magnesium sulfate. Removal of the drying agents and evaporation of the solvent gave a dark orange oil which was chromatographed on silica gel eluting with an ethyl acetate/dichloromethane gradient to give **79** as a white powder. Recrystalization from dichloromethane/hexanes gave pure **79** as white needles (3.56 g, 11.1 mmol). mp 174−176 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (s, 1H), 7.50 (s, 1H), 5.98−5.89 (m, 1H), 3.36 (s, 3H), 2.68 (q, $J$ = 7.3 Hz, 2H), 2.30−2.22 (m, 2H), 2.16−2.11 (m, 1H), 1.97−1.89 (m, 1H), 1.72−1.68 (m, 1H), 1.26 (t, $J$ = 7.3 Hz, 3H); MS (APCI) 322 (M + 1, 100).

**8-Cyclopentyl-6-ethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (25).** Compounds **79** (0.80 g, 2.62 mmol) and **63** (1.82 g, 6.55 mmol) in toluene (10 mL) were heated to 105 °C over 10 h. The resulting suspension was filtered and the solid washed with toluene and dried in vacuo yielding 4-[6-(8-cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**81**) as a solid (0.204 g). MS (APCI) *m/z* 520.1 (M + 1). Compound **81** (0.204 g, 0.39 mmol) was dissolved in 1:1 chloroform: methanol (16 mL) and purged with anhydrous hydrogen chloride gas. After stirring for 3.5 h, addition of diethyl ether (8 mL) gave a solid precipitate. The solid was filtered, washed with diethyl ether and dried in vacuo yielding 25 (0.180 g) as a yellow solid. MS (APCI) *m/z* 420.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.61 (s, 1 H) 8.90 (s, 1 H) 8.09 (d, $J$ = 11.72 Hz, 1 H) 7.99 (d, $J$ = 2.93 Hz, 1 H) 7.79 (s, 1 H) 7.73 (d, $J$ = 9.53 Hz, 1 H) 5.86 (m, 1 H) 3.43 (m, 4 H) 3.21 (m, 4 H) 2.19 (m, 2 H) 1.99 (m, 2 H) 1.77 (m, 2 H) 1.58 (d, $J$ = 4.88 Hz, 2 H) 1.14 (t, $J$ = 7.45 Hz, 3H). Anal. ($C_{34}H_{29}N_7O\cdot1.2H_2O\cdot2.1HCl$): C, H, N, Cl.

**6-Bromomethyl-8-cyclopentyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (82).** Compound **77** (3.5 g, 12.7 mmol) and *N*-bromosuccinimide (2.6 g, 14.6 mmol) in carbon tetrachloride (100 mL) were irradiated with ultraviolet light allowing the temperature to reach 45 °C over 3 h. The mixture was filtered, washed with dilute sodium sulfite solution, then brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel eluting with 1:1 ethyl acetate:hexane to provide **82** as a crystalline solid (1.46 g, 32%), mp 103−105 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 1 H), 7.72 (s, 1 H), 5.94 (m, 1 H), 4.45 (s, 2 H), 2.60 (s, 3 H), 2.32 (m, 2 H), 2.06 (m, 2 H), 1.87 (m, 2 H), 1.67 (m, 2 H).

**Acetic Acid 8-Cyclopentyl-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-6-ylmethyl Ester (83).** Compound **82** (1.33 g, 3.75 mmol) and silver acetate (1.03 g, 6.2 mmol) were added to glacial acetic acid (10 mL) and heated to 110 °C for 5 h. The solvents then were evaporated at reduced pressure, and the resulting residue was suspended in ethyl acetate and filtered. The solid obtained was recrystallized from ethyl acetate to provide **83** as a solid (0.89 g, 71%). MS (APCI) *m/z* 334.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1 H), 7.57 (s, 1 H), 5.93 (m, 1 H), 5.09 (s, 2 H), 2.61 (s, 3 H), 2.32 (m, 2 H), 2.15 (s, 3 H), 2.06 (m, 2 H), 1.88 (m, 2 H), 1.68 (m, 2 H).

**Acetic Acid 8-Cyclopentyl-2-methanesulfinyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-6-ylmethyl Ester (84).** Compound **83** (0.85 g, 2.55 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (0.8 g, 3.06 mmol) were mixed in dichloromethane (20 mL) and stirred at room temperature for 5 h. To this mixture was added diethyl ether giving a solid precipitate, which was filtered and dried in vacuo to provide **84** as a solid (0.81 g, 91%). MS (APCI) *m/z* 350.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.94 (s, 1 H), 7.69 (s, 1 H), 5.96 (m, 1 H), 5.14 (s, 2 H), 2.96 (s, 3 H), 2.22 (m, 2 H), 2.18 (s, 3 H), 2.11 (m, 2 H), 1.93 (m, 2 H), 1.69 (m, 2 H).

**4-[6-(6-Acetoxymethyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (85).** Compounds **84** (0.80 g, 2.29 mmol) and **63** (1.17 g, 4.20 mmol) were added to toluene (8 mL) and heated to 96 °C for 6 h. The reaction mixture was allowed to cool then filtered and the residue washed with toluene. The resulting solid was dried in vacuo then recrystallized from chloroform/diethyl ether to provide **85** as a solid (0.213 g, 17%). MS (APCI) *m/z* 564.3 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1 H), 8.29 (d, $J$ = 9.04 Hz, 1 H), 7.96 (s, 1 H), 7.56 (s, 1 H), 7.41 (d, $J$ = 9.28 Hz, 1 H), 5.89 (m, 1 H), 5.08 (s, 2 H), 3.60 (m, 4 H), 3.11 (m, 4 H), 2.34 (m, 2 H), 2.14 (s, 3 H), 2.09 (m, 2 H), 1.88 (m, 2 H), 1.69 (m, 2 H), 1.47 (s, 9 H).

**8-Cyclopentyl-6-hydroxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (26).** Compound **85** (0.21 g,0.36 mmol) was dissolved in 1:1 chloroform:methanol (8 mL), and the solution was purged with anhydrous hydrogen chloride gas then allowed to stir for 3 h at room temperature. This mixture was added to diethyl ether (50 mL) to give a solid, which was collected by filtration, washed with diethyl ether, then dried in vacuo to provide **26** as a solid (0.17 g, 93%). MS (APCI) *m/z* 422.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.26 (s, 2 H), 8.96 (s, 1 H), 7.99 (d, $J$ = 2.93 Hz, 1 H), 7.93 (d, $J$ = 8.30 Hz, 1 H), 7.88 (s, 1 H), 7.75 (d, $J$ = 9.52 Hz, 1 H), 5.85 (m, 1 H), 4.36 (d, $J$ = 1.47 Hz, 2 H), 3.39 (m, 4 H), 3.23 (m, 4 H), 2.20 (m, 2 H), 1.95 (m, 2 H), 1.76 (m, 2 H), 1.58 (m, 2 H). Anal. ($C_{22}H_{27}N_7O_2 \cdot 1.0H_2O \cdot 2.0HCl$): C, H, N, Cl.

**8-Cyclopentyl-6-methoxymethyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (86).** 3-Methoxy-propionic acid methyl ester (9.95 g, 84.2 mmol) was dissolved in tetrahydrofuran (40 mL) to which LiHMDS (89 mL, 88.9 mmol, 1.0 M in THF) was slowly added. Aldehyde **76** (10.0 g, 42.2 mmol) was then added neat and the reaction mixture brought to reflux for 7 days. The reaction mixture was diluted with ethyl acetate and water, the layers were separated, the organic layer was dried over $MgSO_4$ and the solvent was evaporated to give a crude oil. The crude product was dissolved in ethyl acetate and diluted with hexanes to give a precipitate which was collected by filtration to give **86** as an off-white solid (3.11 g, 24%). MS (APCI) *m/z* 306.0 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.46 (s, 1H), 7.49 (t, $J$ = 1.7 Hz, 1H), 5.81 (m, 1H), 4.28 (d, $J$ = 1.7 Hz, 1H), 3.37 (s, 3H), 2.47 (s, 3H), 2.18 (m, 2H), 1.93 (m, 2H), 1.73 (m, 2H), 1.55 (m, 2H).

**8-Cyclopentyl-2-methanesulfinyl-6-methoxymethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (87).** Compound **86** (4.44 g, 14.54 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (4.94 g, 18.90 mmol) were dissolved in dichloromethane (100 mL) and stirred at ambient temperature for 12 h. The solvent volume was reduced to approximately 50 mL and was then purified by silica gel chromatography to give **87** as an off-white solid (2.51 g, 54%). MS (APCI) *m/z* 322.0 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.93 (s, 1H), 7.78 (t, $J$ = 1.7 Hz, 1H), 5.99 (m, 1H), 4.46 (d, $J$ = 1.7 Hz, 1H), 3.53 (s, 3H), 2.96 (s, 3H), 2.23 (m, 2H), 2.12 (m, 2H), 1.93 (m, 2H), 1.69 (m, 2H).

**4-[6-(8-Cyclopentyl-6-methoxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (88).** Compounds **87** (2.5 g, 7.78 mmol) and **63** (2.99 g, 10.73 mmol) were heated to reflux in toluene (25 mL) for 16 h. The reaction mixture was cooled to room temperature and purified by silica gel chromatography to give **88** as a yellow solid (1.24 g, 31%). MS (APCI) *m/z* 536.4 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 1H), 8.26 (d, $J$ = 9.3 Hz, 1H), 7.97 (d, $J$ = 2.7 Hz, 1H), 7.6 (t, $J$ = 1.5 Hz, 1H), 7.38 (dd, $J$ = 2.7, 9.0 Hz, 1H), 5.89 (m, 1H), 4.55 (d, $J$ = 1.2 Hz, 1H), 3.66 (q, $J$ = 7.1 Hz, 2H), 3.60 (m, 4H), 3.11 (m, 4H), 2.34 (m, 2H), 2.07 (m, 2H), 1.88 (m, 2H), 1.69 (m, 2H), 1.48 (s, 9H), 1.30 (t, $J$ = 6.8 Hz, 3H).

**8-Cyclopentyl-6-methoxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (27).** Compound **88** (0.110 g, 0.205 mmol) was dissolved in dichloromethane (2 mL). 2 N HCl in diethyl ether (2 mL) was added, and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated to give **27** as a yellow hydrochloride salt (0.096 g, 92%). mp >300 °C. MS (APCI) *m/z* 436.4 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.15 (s, 2H), 8.92 (s, 1H), 7.95 (s, 1H), 7.92 (m, 1H), 7.85 (s, 1H), 7.70 (d, $J$ = 9.0 Hz, 1H), 5.81 (m, 1H), 4.26 (s, 2H), 3.36 (m, 7H), 3.20 (s, 4H), 2.17 (m, 2H), 1.91 (m, 2H), 1.73 (m, 2H), 1.55 (m, 2H). Exact Mass: Calculated ($C_{23}H_{29}N_7O_{21}$) 436.2461, found 436.2467 (M + 1); HPLC purity 95%.

**8-Cyclopentyl-6-ethoxymethyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (89).** 3-Ethoxy-propionic acid ethyl ester (12.31 g, 84.2 mmol) was dissolved in tetrahydrofuran (40 mL) to which LiHMDS (89 mL, 88.9 mmol, 1.0 M in THF) was slowly added. Aldehyde **76** (10.0 g, 42.2 mmol) was then added neat, and the reaction mixture was stirred at ambient temperature for 17 h then brought to reflux for 7 h. The reaction mixture was diluted with ethyl acetate and water, the layers were separated, organic layer was dried over $MgSO_4$ and the solvent was evaporated to give a crude oil. The crude product was dissolved in ethyl acetate and diluted with hexanes to give a precipitate, which was collected by filtration to give **89** as an off-white solid (4.70 g, 35%). MS (APCI) *m/z* 320.1 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.47 (s, 1H), 7.52 (t, $J$ = 1.5 Hz, 1H), 5.82 (m, 1H), 4.32 (d, $J$ = 1.7 Hz, 1H), 3.53 (q, $J$ = 7.1 Hz, 2H), 2.47 (s, 3H), 2.17 (m, 2H), 1.93 (m, 2H), 1.73 (m, 2H), 1.54 (m, 2H), 1.15 (t, $J$ = 7.1 Hz, 3H).

**8-Cyclopentyl-6-ethoxymethyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (90).** Compound **89** (4.60 g, 14.40 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (4.89 g, 18.72 mmol) were dissolved in dichloromethane (30 mL) and stirred at ambient temperature for 12 h. The crude product was then purified by silica gel chromatography to give **90** as a white waxy solid (2.67 g, 55%). MS (APCI) *m/z* 336.1 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.94 (s, 1H), 7.81 (t, $J$ = 1.7 Hz, 1H), 5.98 (m, 1H), 4.50 (d, $J$ = 1.7 Hz, 1H), 3.68 (q, $J$ = 7.1 Hz, 2H), 2.96 (s, 3H), 2.22 (m, 2H), 2.12 (m, 2H), 1.94 (m, 2H), 1.69 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H).

**4-[6-(8-Cyclopentyl-6-ethoxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (91).** Compounds

**90** (1.0 g, 2.86 mmol) and **63** (1.10 g, 3.95 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature and purified by silica gel chromatography to give **91** as a yellow solid (0.140 g, 15%). MS (APCI) *m/z* 550.4 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 1H), 8.26 (d, $J$ = 9.3 Hz, 1H), 7.97 (d, $J$ = 2.7 Hz, 1H), 7.6 (t, $J$ = 1.5 Hz, 1H), 7.38 (dd, $J$ = 2.7, 9.0 Hz, 1H), 5.89 (m, 1H), 4.55 (d, $J$ = 1.2 Hz, 1H), 3.66 (q, $J$ = 7.1 Hz, 2H), 3.60 (m, 4H), 3.11 (m, 4H), 2.34 (m, 2H), 2.07 (m, 2H), 1.88 (m, 2H), 1.69 (m, 2H), 1.48 (s, 9H), 1.30 (t, $J$ = 6.8 Hz, 3H).

**8-Cyclopentyl-6-ethoxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (28).** Compound **91** (0.140 g, 0.242 mmol) was dissolved in dichloromethane (2 mL). 2 N HCl in diethyl ether (2 mL) was added, and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated to give **28** as a yellow solid (0.116 g, 86%). Foams >190 °C. MS (APCI) *m/z* 450.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.12 (s, 2H), 8.34 (s, 1H), 8.01 (d, $J$ = 2.7 Hz, 1H), 7.86 (s, 1H), 7.83 (s, 1H), 7.76 (d, $J$ = 9.5 Hz, 1H), 5.84 (m, 1H), 4.32 (d, $J$ = 1.2 Hz, 1H), 3.57 (q, $J$ = 6.8 Hz, 2H), 3.38 (m, 4H), 3.23 (m, 4H), 2.26 (m, 2H), 1.89 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H), 1.19 (t, $J$ = 6.8 Hz, 3H). Exact Mass: Calculated ($C_{23}H_{29}N_7O_2$) 450.2617, found 450.2633 (M + 1); HPLC purity 96%.

**8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (92).** Compound **82** (1.33 g, 3.75 mmol) was dissolved in 2-methoxyethanol (10 mL) to which potassium carbonate (0.778 g, 5.63 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was then filtered and the salts washed with ethyl acetate. The combined organics were evaporated to give **92** as a waxy solid (1.00 g, 76%). MS (APCI) *m/z* 350.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1H), 7.71 (t, $J$ = 1.6 Hz, 1H), 5.95 (m, 1H), 4.52 (d, $J$ = 1.6 Hz, 1H), 3.76 (m, 2H), 3.63 (m, 2H), 3.41 (s, 3H), 2.60 (s, 3H), 2.32 (m, 2H), 2.06 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H).

**8-Cyclopentyl-2-methanesulfinyl-6-(2-methoxy-ethoxymethyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (93).** Compound **92** (1.46 g, 4.18 mmol) and 2-benzenesulfonyl-3-phenyl-oxaziridine (1.31 g, 5.01 mmol) were dissolved in dichloromethane (10 mL) and stirred at ambient temperature for 12 h. The reaction mixture was then purified by silica gel chromatography to give **93** as a white waxy solid (0.60 g, 39%). MS (APCI) *m/z* 366.0 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.94 (s, 1H), 7.88 (t, $J$ = 1.7 Hz, 1H), 5.95 (m, 1H), 4.52 (d, $J$ = 1.7 Hz, 1H), 3.80 (m, 2H), 3.65 (m, 2H), 3.43 (s, 3H), 2.98 (s, 3H), 2.25 (m, 2H), 2.13 (m, 2H), 1.94 (m, 2H), 1.70 (m, 2H).

**4-{6-[8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic Acid *tert*-Butyl Ester (94).** Compounds **93** (1.0 g, 2.86 mmol) and **63** (1.10 g, 3.95 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature and purified by silica gel chromatography to give **94** as a yellow solid (0.140 g, 15%). MS (APCI) *m/z* 580.5 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1H), 8.34 (m, 1H), 7.95 (s, 1H), 7.69 (t, $J$ = 1.4 Hz, 1H), 7.42 (m, 1H), 5.91 (m, 1H), 4.53 (d, $J$ = 1.2 Hz, 1H), 3.78 (m, 1H), 3.63 (m, 6H), 3.43 (s, 3H), 3.11 (m, 4H), 2.35 (m, 2H), 2.08 (m, 2H), 1.88 (m, 2H), 1.69 (m, 2H), 1.48 (s, 9H).

**8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one hydrochloride (29).** Compound **94** (0.140 g, 0.242 mmol) was dissolved in dichloromethane (2 mL). 2 N HCl in diethyl ether (2 mL) was added, and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated to give **29** as a yellow solid (0.116 g, 86%). Foams >190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.22 (s, 2H), 8.93 (s, 1H), 8.01 (d, $J$ = 2.69 Hz, 1H), 7.83 (s, 2H), 7.78 (d, $J$ = 9.04 Hz, 1H), 5.80−5.87 (m, 1H), 4.36 (d, $J$ = 1.22 Hz, 2H), 3.65 (dd, $J$ = 5.62, 3.66 Hz, 2H), 3.46−3.52 (m, 2H), 3.35−3.42 (m, 4H), 3.24 (d, $J$ = 10.01 Hz, 7H), 2.16−2.24 (m, 2H), 1.90−1.98 (m, 2H), 1.72 − 1.79 (m, 2H), 1.53−1.59 (m, 2H). MS (APCI) *m/z* 480.2 (M + 1). Anal. ($C_{25}H_{33}N_7O_2$·2.16HCl): C, H, N.

**8-Cyclopentyl-6-(2-ethoxy-ethyl)-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (95).** To a cooled (−78 °C) solution of 4-ethoxy-butyric acid ethyl ester (9.85 g, 61.47 mmol) in THF (25 mL) was added lithium bis(trimethylsilyl)-amide (77.0 mL, 76.85 mmol, 1 M solution in THF). The reaction mixture was stirred for 10 min to form the anion. Aldehyde **76** (7.29 g, 30.7 mmol) was then added and the reaction allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with 10% aqueous HCl (100 mL). The aqueous layer was extracted with ethyl acetate (150 mL total), and the organic layers were combined and concentrated to give a yellow oil. Chromatographic purification on silica gel (chloroform/ethyl acetate gradient) gave **95** (3.22 g, 9.65 mmol, 31%). MS (APCI) *m/z* 334 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.54 (s, 1H), 7.47−7.46 (m, 1H), 5.99−5.90 (m, 1H), 3.69 (t, $J$ = 6.25 Hz, 2H), 3.49 (q, $J$ = 7.03 Hz, 2H), 2.84 (t, $J$ = 6.25 Hz, 2H), 2.59 (s, 3H), 2.34−2.29 (m, 2H), 2.08−2.02 (m, 2H), 1.88−1.83 (m, 2H), 1.69−1.65 (m, 3H), 1.17 (t, $J$ = 7.04 Hz, 3H).

**4-{6-[8-Cyclopentyl-6-(2-ethoxy-ethyl)-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic Acid *tert*-Butyl Ester (96).** Compounds **95** (1.0 g, 2.86 mmol) and **63** (1.10 g, 3.95 mmol) were heated to reflux in toluene (10 mL) for 16 h. The mixture was cooled to room temperature and purified by silica gel chromatography to give **96** as an orange solid (0.328 g, 20%). MS (APCI) *m/z* 564.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.54 (s, 1H), 8.26 (d, $J$ = 9.0 Hz, 1H), 7.98 (d, $J$ = 2.9 Hz, 1H), 7.45 (s, 1H), 7.38 (dd, $J$ = 2.9, 9.3 Hz, 1H), 5.90 (m, 1H), 3.70 (t, $J$ = 6.3, 1H), 3.61 (m, 4H), 3.51 (q, $J$ = 7.1, 1H), 3.11 (m, 4H), 2.84 (t, $J$ = 5.9, 1H), 2.33 (m, 2H), 2.08 (m, 2H), 1.87 (m, 2H), 1.69 (m, 2H), 1.48 (s, 9H), 1.19 (t, $J$ = 7.1, 1H).

**8-Cyclopentyl-6-(2-ethoxy-ethyl)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (30).** Compound **96** (0.325 g, 0.577 mmol) was dissolved in dichloromethane (4 mL). 2 N HCl in diethyl ether (4 mL) was added and the mixture was stirred at room temperature for 18 h. The solvent was evaporated to give **30** as a yellow solid (0.292 g, 98%). MS (APCI) *m/z* 464.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.36 (s, 2H), 8.86 (s, 1H), 7.97 (d, $J$ = 2.68 Hz, 2H), 7.78 (s, 1H), 7.71 (d, $J$ = 10.01 Hz, 1H), 5.80−5.87 (m, 1H), 3.54 (t, $J$ = 6.59 Hz, 2H), 3.36−3.46 (m, 6H), 3.20 (s, 4H), 2.67 (t, $J$ = 6.47 Hz, 2H), 2.10−2.23 (m, 2H), 1.90−1.98 (m, 2H), 1.71−1.79 (m, 2H), 1.52−1.59 (m, 2H), 1.05 (t, $J$ = 6.95 Hz, 3H). Anal. ($C_{25}H_{33}N_7O_2$·2.6HCl·0.35$H_2O$): C, H, N.

**8-Cyclopentyl-6-(2-ethoxy-ethoxy)-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (97).** To a suspension of sodium hydride (45 mg, 1.1 mmol, 60% oil dispersion) in THF (10 mL), under nitrogen, was added 2-ethoxyethanol (113 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 30 min. To this mixture, 8-cyclopentyl-6-fluoro-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**98**, 280 mg, 1.0 mmol) was added. The reaction mixture was then heated to reflux and stirred overnight. The cooled solution was quenched with water (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was subsequently washed twice with aq. $NH_4Cl$ (20 mL each) and brine (20 mL). The organic layer was dried over magnesium sulfate. Removal of the drying agents and evaporation of the solvent gave a yellow oil, which was chromatographed on silica gel eluted with an ethyl acetate/hexane gradient to **97** as a colorless oil (289 mg, 0.83 mmol, 83%). MS (APCI) *m/z* 350 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (s, 1H), 6.77 (s, 1H), 6.04−5.95 (m, 1H), 4.16 (t, $J$ = 4.0 Hz, 2H), 3.86 (t, $J$ = 4.0 Hz, 2H), 3.58 (q, $J$ = 8.0 Hz, 2H), 2.59 (s, 3H), 2.34−2.25 (m, 2H), 2.13−2.03 (m, 2H), 1.91−1.82 (m, 2H), 1.71−1.60 (m, 2H), 1.20 (t, $J$ = 8.0 Hz, 3H).

**8-Cyclopentyl-6-(2-ethoxy-ethoxy)-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (99).** To a solution of 97 (289 mg, 0.83 mmol) in chloroform (5 mL) was added 2-benzenesulfonyl-3-phenyl-oxaziridine (281 mg, 1.07 mmol). The reaction mixture was stirred at room-temperature overnight, under nitrogen. The solvents were removed, and the crude product was chromatographed on silica gel, eluting with a 5%

methanol−ethyl acetate/hexane gradient to give **99** as a colorless oil (210 mg, 67%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (s, 1H), 6.89 (s, 1H), 6.06−5.98 (m, 1H), 4.23 (t, $J$ = 4.0 Hz, 2H), 3.89 (t, $J$ = 4.0 Hz, 2H), 3.60 (q, $J$ = 6.9 Hz, 2H), 2.95 (s, 3H), 2.28−2.19 (m, 2H), 2.15−2.10 (m, 2H), 1.97−1.88 (m, 2H), 1.71−1.64 (m, 2H), 1.21 (t, $J$ = 6.9 Hz, 3H).

**4-{6-[8-Cyclopentyl-6-(2-ethoxy-ethoxy)-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic Acid *tert*-Butyl Ester (100).** Compounds **99** (1.2 mL of a 0.46 M solution in toluene, 0.552 mmol) and **63** (0.307 g, 1.1 mmol) were combined in toluene under nitrogen and heated to 110 °C. After 4 h the toluene was replaced by xylenes (1 mL) and heating was continued under reflux overnight. After cooling to room temperature, the crude reaction mixture was dissolved in $CH_2Cl_2$ and washed with saturated aqueous ammonium chloride solution then with brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Chromotagraphy on silica gel eluting with 5% $CH_3OH$ in $CH_2Cl_2$ followed by a second chromatography step eluting with ethyl acetate provided **100** (70 mg, 22%) as a yellow solid. MS (APCI) *m/z* 580.2 (M + 1). $^1$H NMR (400 MHz, DMSO- $d_6$) $\delta$ 8.50 (s, 1H), 8.26 (d, $J$ = 9 Hz, 1H), 7.94 (d, $J$ = 3 Hz, 1H), 7.39 (dd, $J$ = 3, 9 Hz, 1H), 6.78 (s, 1H), 5.89−5.98 (m, 1H), 4.15 (t, $J$ = 5 Hz, 2H), 3.86 (t, $J$ = 5 Hz, 2H), 3.56−3.62 (m, 6H), 3.09 (br t, $J$ = 5 Hz, 4H), 2.29−2.33 (m, 2H), 2.07−2.10 (m, 2H), 1.84−1.92 (m, 2H), 1.63−1.69 (m, 2H), 1.47 (s, 9H), 1.22 (t, $J$ = 7 Hz, 3H).

**8-Cyclopentyl-6-(2-ethoxy-ethoxy)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (31).** Compound **100** (70 mg, 0.12 mmol) was dissolved in $CH_2Cl_2$ (2.5 mL), and 2 M HCl in ether (2.5 mL) was added. This mixture was stirred for 2 h at room temperature, and a yellow precipitate formed. The solvents were removed under reduced pressure, and the resulting solid was suspended in ether and collected by filtration then dried overnight in vacuo at 50 °C to give **31** (30 mg, 52%). MS (APCI) *m/z* 480.4 (M + 1). Anal. ($C_{25}H_{33}N_7O_3$·2HCl·3.44$H_2O$): C, H, N. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.29 (s, 2H), 8.80 (s, 1H), 7.96 (s, 2H), 7.71 (d, $J$ = 9 Hz, 1H), 7.31 (s, 1H), 5.93−5.85 (m, 1H), 4.08 (t, $J$ = 4 Hz, 2H), 3.72 (t, $J$ = 4 Hz, 2H), 3.50 (q, $J$ = 7 Hz, 2H), 3.39 (s, 4H), 3.38 (s, 4H), 2.21−2.16 (m, 2H), 1.97 (s, 2H), 1.80−1.78 (m, 2H), 1.61−1.58 (m, 2H), 1.11 (t, $J$ = 7 Hz, 3H).

**8-Cyclopentyl-6-isobutoxy-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one hydrochloride (32).** 60% Sodium hydride in oil (0.182 g, 4.4 mmol) was washed with hexane and added to 2-methyl-1-propanol (10 mL). This mixture effervesced and formed a solution. To this solution was added 4-[6-(8-cyclopentyl-6-fluoro-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester, **102** (0.225 g, 0.44 mmol), and the mixture was heated at 95 °C for 72 h. The solvents were evaporated, and the residue was dissolved in diethyl ether then filtered. The filtrate was evaporated to provide 4-[6-(8-cyclopentyl-6-isobutoxy-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**101**) as a crystalline solid (0.092 g, 37%). MS (APCI) *m/z* 564.3 (M + 1). Compound **101** (0.067 g, 0.119 mmol) was dissolved in chloroform (5 mL), cooled to 0 °C. This solution was purged with anhydrous hydrogen chloride gas and stoppered for 3 h. Diethyl ether was added to the mixture giving a precipitate that was filtered and dried in vacuo to **32** as a solid (0.056 g, 36%). MS (APCI) *m/z* 464.3 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.25 (s, 2 H), 8.80 (s, 1 H), 7.95 (s, 1 H), 7.71 (s, 1 H), 7.29 (s, 1 H), 5.89 (m, 1 H), 3.73 (s, 4 H), 3.38 (m, 4 H), 3.23 (d, 2 H), 2.19 (s, 2 H), 1.97 (m, 2 H), 1.78 (m, 2 H), 1.58 (m, 2 H), 0.98 (d, $J$ = 5.86 Hz, 6 H). Anal. ($C_{25}H_{33}N_7O_2$·1.0$H_2O$·2.0HCl): C, H, N, Cl.

**4-[6-(6-Acetyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (103).** Tributyl(1-ethoxyvinyl)tin (0.39 mL, 1.15 mmol) was added to a mixture of 4-[6-(6-bromo-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (**104**) (440 mg, 0.77 mmol) and tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.077 mmol) in toluene (5 mL). The reaction mixture was heated at 110 °C for 1 h then cooled to room temperature. The solid so formed was collected by filtration and washed with toluene, then dried to give **103**. MS (APCI) *m/z* 534.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.07 (s, 1H), 8.46 (s, 1H), 7.97 (s, 1H), 7.90 (br s, 1H), 7.72 (d, $J$ = 9 Hz, 1H), 5.83 (m, 1H), 3.47 (br s, 4H), 3.16 (br s, 4H), 2.55 (s, 3H), 2.20 (br s, 2H), 1.94 (br s, 2H), 1.78 (br s, 2H), 1.58 (br s, 2H), 1.39 (s, 9H).

**6-Acetyl-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one hydrochloride (33).** Anhydrous HCl gas was bubbled through a solution of **103** (398 mg, 0.74 mmol), in MeOH/$CH_2Cl_2$ (10 mL/10 mL) at room temperature for ∼5 min. The reaction mixture was stirred overnight, and then solvent was removed under reduced pressure. The remaining solid was triturated with hot ethyl acetate and dried to provide **33** (329 mg, 76%). mp >300 °C. MS (APCI) *m/z* 434.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.99 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.83 (d, $J$ = 9 Hz, 1H), 7.65 (br s, 1H), 5.84−5.79 (m, 1H), 3.37 (br s, 4H), 2.54 (s, 3H), 2.24 (br s, 2H), 1.89 (br s, 2H), 1.76 (br s, 2H), 1.58 (br s, 2H). Anal. ($C_{23}H_{27}N_7O_2$·4.25HCl): C, H, N.

**2-[5-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]-pyrimidine-6-carboxylic Acid Ethyl Ester (105).** 8-Cyclopentyl-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester, **106** (1.2 g, 3.6 mmol), was dissolved in $CH_2Cl_2$ (20 mL) and treated with 2-benzenesulfonyl-3-phenyl-oxaziridine (1.13 g, 4.32 mmol) at room temperature and stirred for 1 day. Following concentration under reduced pressure, the crude reaction mixture was chromatographed on silica gel eluting with ethyl acetate to give 8-cyclopentyl-2-methanesulfinyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (**107**) as a white solid (0.85 g, 68%). MS (APCI) *m/z* 350.0 (M + 1). Compounds **107** (0.936 g, 2.68 mmol) and **63** (3.0 g, 10.8 mmol) were added to toluene (5 mL) and heated to 100 °C for 1 h. Diethyl ether (10 mL) was added causing a solid to precipitate. This solid was collected by filtration, washed with diethyl ether, and dried in vacuo yielding **105** as a yellow solid (0.42 g, 28%). MS (APCI) *m/z* 564.3 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.67 (s, 1 H), 8.22 (s, 1 H), 8.16 (d, $J$ = 9.04 Hz, 1 H), 8.05 (d, $J$ = 2.44 Hz, 1 H), 7.30 (dd, $J$ = 9.28, 2.93 Hz, 1 H), 5.85 (m, 1 H), 4.34 (q, $J$ = 7.08 Hz, 2 H), 3.57 (m, 4 H), 3.09 (m, 4 H), 2.33 (m, 2 H), 2.05 (m, 2 H), 1.82 (m, 2 H), 1.62 (m, 2 H), 1.44 (s, 9 H), 1.34 (t, $J$ = 7.08 Hz, 3 H).

**8-Cyclopentyl-7-oxo-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester Hydrochloride (34).** Compound **105** (0.40 g, 0.709 mmol) was dissolved in a mixture of chloroform (15 mL) and ethanol (15 mL) and the solution was purged with anhydrous hydrogen chloride gas. After 2 h, the addition of ethyl acetate precipitated a solid that was filtered, washed with diethyl ether and dried in vacuo to yield **34** (0.4 g) as a yellow solid. MS (APCI) *m/z* 464.4 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.46 (s, 2 H), 9.00 (s, 1 H), 8.47 (s, 1 H), 8.03 (d, $J$ = 2.4 Hz, 1 H), 7.89 (s, 1 H), 7.79 (s, 1 H), 5.79 (m, 1 H), 4.23 (q, $J$ = 7.0 Hz, 4 H), 3.41 (m, 4 H), 2.17 (m, 2 H), 1.91 (m, 2 H), 1.74 (m, 2 H), 1.55 (d, $J$ = 4.6 Hz, 2 H), 1.25 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{24}H_{29}N_7O_3$·0.75$H_2O$·2.0HCl): C, H, N.

**4-[6-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (108).** 8-Cyclopentyl-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**109**) (0.40 g, 1.37 mmol) and **63** (0.497 g, 1.78 mmol) were heated to reflux in toluene (4 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL) to give **108** as a dark brown-gray solid (0.100 g, 16%). MS (APCI) *m/z* 506.2, (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.92 (s, 1H), 8.78 (s, 1H), 8.02 (d, $J$ = 2.9 Hz, 1H), 7.87 (d, $J$ = 9.3 Hz, 1H), 7.50 (dd, $J$ = 2.9, 9.0 Hz, 1H), 6.18 (s, 1H), 5.77 (m, 1H), 3.44 (m, 4H), 3.07 (m, 4H),

2.39 (s, 3H), 2.20 (m, 2H), 1.85 (m, 2H), 1.71 (m, 2H), 1.55 (m, 2H), 1.39 (s, 9H).

**8-Cyclopentyl-5-methyl-2-(5-piperazin-4-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one hydrochloride (38).** Compound **108** (0.093 g, 0.184 mmol) was dissolved in dichloromethane (3 mL) to which 2 N HCl in diethyl ether (2 mL) was added, and the resulting mixture was stirred for 2 days. Additional 2 N HCl was added and stirring was continued for 16 h. The solvent was removed to **38** as a yellow solid (0.080 g, 91%). Decomposes >212 °C. MS (APCI) *m/z* 406.1, (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.27 (s, 2H), 8.85 (s, 1H), 8.02 (d, $J$ = 2.9 Hz, 1H), 7.91 (d, $J$ = 9.3 Hz, 1H), 7.78 (d, $J$ = 9.3 Hz, 1H), 6.33 (s, 1H), 5.86−5.74 (m, 1H), 3.44−3.35 (m, 4H), 3.26−3.19 (m, 4H), 2.39 (s, 3H), 2.23−2.15 (m, 2H), 1.94−1.86 (m, 2H), 1.74 (m, 2H), 1.59−1.51 (m, 2H). Exact Mass: Calculated ($C_{22}H_{27}N_7O_1$) 406.2355, found 450.2671 (M + 1); HPLC purity 97%.

**6-Bromo-8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (110).** Prepared from 6-bromo-8-cyclopentyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**111**) following the procedure described for **69**. MS (APCI) *m/z* 358 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.14 (s, 1H), 8.63 (s, 1H), 5.91−5.86 (m, 1H), 2.89 (s, 3H), 2.15 (br s, 2H), 2.04 (br s, 2H), 1.87−1.79 (m, 2H), 1.61−1.58 (m, 2H).

**6-Bromo-8-cyclopentyl-2-(pyridin-2-ylamino)-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (39).** Compound **110** and 2-aminopyridine were reacted according to the procedure described for compound **108** to **39** in 37% yield. mp: 273∼275 °C. MS (APCI) *m/z* 385.9 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.33 (s, 1H), 8.80 (s, 1H), 8.38 (s, 1H), 8.31 (dd, $J$ = 5 Hz, 1 Hz, 1H), 8.04 (d, $J$ = 8.5 Hz, 1H), 7.81−7.77 (m, 1H), 7.07−7.04 (m, 1H), 5.90−5.71 (m, 1H), 2.27 (br s, 2H), 1.91 (br s, 2H), 1.79 (br s, 2H), 1.58 (br s, 2H). Anal. ($C_{17}H_{16}BrN_5O\cdot0.1H_2O$): C, H, N.

**6-Bromo-8-cyclopentyl-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (112).** Compound **112** was prepared from 6-bromo-8-cyclopentyl-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**113**) following the procedure described for compound **69**. MS (APCI) *m/z* 372.9 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.01 (s, 1H), 6.06−5.97 (m, 1H), 2.93 (s, 3H), 2.67 (s, 3H), 2.21−2.11 (m, 2H), 2.10−2.04 (m, 2H), 1.94−1.87 (m, 2H), 1.67−1.62 (m, 2H).

**6-Bromo-8-cyclopentyl-5-methyl-2-(pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (40).** A mixture of **112** (370 mg, 1 mmol) and 2-aminopyridine (140 mg, 1.5 mmol) in toluene (5 mL) was heated at 110 °C for 18 h then cooled to room temperature. The solid formed was collected by filtration and washed with toluene, then acetone, and dried in vacuo to give **40** as a beige solid (22 mg, 30%). mp 267−268 °C. MS (APCI) *m/z* 402.0 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.29 (s, 1 H), 8.98 (s, 1 H), 8.29 (br s, 1 H), 8.04 (t, $J$ = 7 Hz, 1 H), 7.02 (t, $J$ = 7 Hz, 1 H), 5.92−5.87 (m, 1 H), 2.55 (s, 3 H), 2.16 (br s, 2 H), 1.90 (br s, 2 H), 1.75 (br s, 2 H), 1.56 (br s, 2 H). Anal. ($C_{18}H_{18}BrN_5O\cdot0.33H_2O$): C, H, N.

**4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (114).** A suspension of **112** (10.00 g, 0.027 mol) and **63** (10.37 g, 0.0373 mol) in toluene (100 mL) was heated under nitrogen in an oil bath for 7 h. Thin-layer chromatography ($SiO_2$, 10% MeOH/DCM) indicated that both starting materials remained. The suspension was heated under reflux for a further 18 h. The resulting suspension was cooled to room temperature and filtered to give **114** (5.93 g, 38%). mp >250 °C. MS (APCI) *m/z* 584.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H), 8.36 (br s, 1H), 7.48 (t, $J$ = 8 Hz, 1H), 5.99−5.92 (m, 1H), 3.61 (t, $J$ = 5 Hz, 4H), 3.12 (t, $J$ = 5 Hz, 4H), 2.61 (s, 3H), 2.29 (br s, 2H), 2.12 (br s, 2H), 1.88 (br s, 2H), 1.68 (br s, 2H), 1.48 (s, 9H).

**6-Bromo-8-cyclopentyl-5-methyl-2-(5-piperizin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (41).** Compound **114** (0.04 g, 0.07 mmol) was suspended in $CH_2Cl_2$ (10 mL) and MeOH was added in order to produce a solution (up to ∼6 mL). 2 M HCl in ether (10 mL) was added with stirring. The reaction mixture was stirred at room temperature for a total of 3 days, then the solvents were removed by evaporation at reduced pressure. The remaining solid was suspended in ether and filtered to give **41** as a yellow solid (0.04 g, 100%), which was dried in vacuo at 50 °C. mp > 235 °C. MS (APCI) *m/z* 486.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.17 (s, 2H), 8.98 (s, 1H), 8.04 (s, 1H), 7.84−7.79 (m, 2H), 5.92−5.87 (m, 1H), 3.39 (br s, 4H), 3.29 (br s, 4H), 2.58 (s, 3H), 2.15 (br s, 2H), 1.91 (br s, 2H), 1.76 (br s, 2H), 1.57 (br s, 2H). Anal. ($C_{23}H_{26}N_7OBr\cdot2.64H_2O\cdot2.0HCl$): Calc′d: C, 43.68; H, 5.55; N, 16.21, Cl (ionic), 11.72. Found: C, 44.08; H, 5.32; N, 15.23, Cl (ionic), 11.65.

**6-Acetyl-8-cyclopentyl-5-methyl-2-(pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (42).** 6-Acetyl-2-amino-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**115**, 195 mg, 0.681 mmol) and sodium *tert*-butoxide (92 mg, 0.953 mmol) were suspended in $N_2$-purged toluene (5 mL). To this suspension were added 2-bromo pyridine (78 $\mu$L), tris(dibenzylideneacetone)-dipalladium(0) (25 mg, 0.027 mmol) and BINAP (34 mg, 0.054 mmol). The reaction vial was purged with argon, and the reaction was heated at 70 °C overnight. The reaction mixture was diluted with ether and methanol, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was chromatographed on silica gel eluting with a gradient of 40% to 100% ethyl acetate in hexanes. Compound **42** as a solid (40 mg, 16%). mp >210 °C. MS (APCI) *m/z* 364.1 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (s, 1H), 8.35−8.32 (m, 2H), 8.21 (bs, 1H), 7.75−7.71 (m, 1H), 7.03−7.01 (m, 1H), 5.89−5.85 (m, 1H), 2.54 (s, 3H), 2.37 (s, 3H), 2.03−2.08 (m, 2H), 1.92−1.87 (m, 2H), 1.73−1.67 (m, 2H).

**6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (43).** A suspension of **114** (5.93 g, 0.010 mol), tetrakis(triphenylphosphine)palladium(0) (1.40 g, 0.00121 mol) and tributyl(1-ethoxyvinyl)tin (5.32 mL, 0.0157 mol) in toluene (30 mL) was heated under reflux for 3.5 h. The mixture was cooled and filtered to give a solid. Purification of the solid by silica gel chromatography using a gradient of 5−66% ethyl acetate/hexane over 15 min gave 4-{6-[8-cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid *tert*-butyl ester, **116**, as a yellow foam (4.50 g, 78%). MS (APCI) *m/z* 576.3 (M + 1). This foam was dissolved in dichloromethane (100 mL) and cooled using an ice−water bath. Hydrogen chloride gas was bubbled into the solution, and the resulting suspension was stoppered and stirred at room-temperature overnight, then diluted with diethyl ether (200 mL). The resulting solid was collected by filtration, washed with diethyl ether and dried to give **43** as a yellow solid (4.01 g, 92%). mp 200 °C. MS (APCI) *m/z* 448.3 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.12 (br s, 1H), 8.97 (s, 1H), 8.05 (d, $J$ = 1 Hz, 1H), 7.83 (d, $J$ = 9 Hz, 1H), 7.76−7.74 (m, 1H), 5.83−5.79 (m, 1H), 3,37 (br s, 4H), 3.22 (br s, 4H), 2.40 (s, 3H), 2.30 (s, 3H), 2.21 (br s, 2H), 1.88 (br s, 2H), 1.77 (br s, 2H), 1.56 (br s, 2H). Anal. ($C_{24}H_{29}N_7O_2\cdot2.4H_2O\cdot1.85HCl$): C, H, N, Cl. HPLC purity = 99% (C18 reverse phase, 10−95% gradient of 0.1%TFA/$CH_3$-CN in 0.1%TFA/$H_2O$). Exact Mass: Calculated ($C_{25}H_{31}N_7O_3$) 478.2556, found 478.2570 (M + 1).

**2-[5-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (117).** A mixture of **113** (442 mg, 1.25 mmol), $Pd(OAc)_2$ (312 mg, 1.4 mmol), bis(diphenylphosphinic)propane (400 mg, 0.97 mmol) and *N*,*N*-diisopropylethylamine (1.1 g, 8.87 mmol) in EtOH (20 mL) was stirred under ∼600 psi of CO and heated to 100 °C for 16 h. The solution thus obtained was filtered, and the filtrate was concentrated under reduced pressure to yield an orange oil, which was purified by chromatography (20% ethyl acetate/hexane) to give 8-cyclopentyl-5-methyl-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester, **118**, as an oil (138 mg, 36%). MS (APCI) *m/z* 348.2 (M + 1). Compound **118** (138 mg, 0.40 mmol) was dissolved in $CH_2Cl_2$ (6 mL), and 2-benzenesulfonyl-3-phenyl-oxaziridine (155 mg, 0.6 mmol) was added. The reaction mixture was stirred at room temperature for 18 h, then the solvent was

removed under reduced pressure and the remaining residue was purified by prepative TLC (50% ethyl acetate/hexane). The more polar, product-containing fraction was extracted into $CH_2Cl_2$ and the solvent evaporated to provide 8-cyclopentyl-2-methanesulfinyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester, **119**, as a white solid (110 mg, 76%). MS (APCI) *m/z* 364.2 (M + 1). A solution of **119** (110 mg, 0.30 mmol) and **63** (310 mg, 1.1 mmol) in toluene was heated at 100 °C for 10 h and then cooled to room temperature. Diethyl ether was added to the reaction mixture and the product precipitated. This precipitate was collected by filtration and dried to provide **117** (50 mg, 29%). MS (APCI) *m/z* 578.4 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.10 (s, 1H), 8.89 (s, 1H), 8.04 (d, $J$ = 1 Hz, 1H), 7.84 (d, $J$ = 2 Hz, 1H), 7.48−7.44 (m, 1H), 5.78 (m, 1H), 4.26 (q, $J$ = 7 Hz, 2H), 3.45 (br s, 4H), 3.10 (br s, 4H), 2.32 (s, 3H), 2.29 (br s, 2H), 1.85 (br s, 2H), 1.73 (br s, 2H), 1.55 (br s, 2H), 1.25 (t, $J$ = 7 Hz, 3H).

**8-Cyclopentyl-5-methyl-7-oxo-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester Hydrochloride (44).** Anhydrous HCl gas was bubbled through a solution of **117** (50 mg, 0.086 mmol) in $CH_2Cl_2$/EtOH at room temperature, and the reaction was stirred for 24 h. Diethyl ether was added to the reaction mixture, and a solid precipitated which was isolated and dried to **44** as a yellow solid (12 mg, 29%). mp 216−218 °C. MS (APCI) *m/z* 478.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.91 (s, 1H), 8.83 (br s, 1H), 8.07 (s, 1H), 7.85 (d, $J$ = 9 Hz, 1H), 7.59 (br s, 1H), 5.81−5.76 (m, 1H), 4.26 (q, $J$ = 8 Hz, 2H), ~3.39 (br s, 4H − buried under HDO peak), 3.23 (br s, 4H), 2.34 (s, 3H), 1.85 (br s, 2H), 2.85 (br s, 2H), 2.75 (br s, 2H), 1.25 (t, $J$ = 8 Hz, 3H); HPLC purity 95%.

**2-{5-[Bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino}-6-bromo-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (45).** Compound **112** (0.4 g, 1.08 mmol) and $N^5$,$N^5$-Bis-(2-methoxy-ethyl)-pyridine-2,5-diamine (0.5 g, 2.2 mmol) were combined in toluene (3.5 mL) and heated to 110 °C. After 5 h the reaction mixture was allowed to cool, and the crude product was directly chromatographed on silica gel eluting with a gradient of 25% to 100% ethyl acetate in hexanes to provide **45** (0.49 g, 85%) as an orange gum. mp 94−95 °C. MS (APCI) *m/z* 530.1 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (s, 1H), 8.18 (s, 1H), 7.64 (dd, $J$ = 9, 2 Hz, 1H), 7.05 (br s, 1H), 6.62 (d, $J$ = 9 Hz, 1H), 5.88 (br s, 1H), 3.73 (t, $J$ = 6 Hz, 4H), 3.58 (t, $J$ = 6 Hz, 4H), 3.34 (s, 6H), 2.55 (s, 3H), 2.25−2.22 (m, 2H), 1.93 (br s, 2H), 1.79 (br s, 2H), 1.58 (br s, 2H). Anal. ($C_{24}H_{32}N_6O_3Br_1$·0.13$H_2O$): C, H, N.

**4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-2,6-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (120).** Compounds **112** (1.0 g, 2.70 mmol) and **63** (1.14 g, 3.73 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL) to give **120** as a dark brown-gray solid (0.620 g, 38%). MS (APCI) *m/z* 614.4, 612.4 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H), 8.23 (d, $J$ = 8.8 Hz, 1H), 7.99 (d, $J$ = 2.7 Hz, 1H), 7.36 (dd, $J$ = 2.7, 8.8 Hz, 1H), 5.99 (m, 1H), 4.28 (m, 2H), 3.30 (m, 2H), 2.93 (dd, $J$ = 4.4, 11.7 Hz 2H), 2.61 (s, 3H), 2.30 (m, 2H), 2.11 (m, 2H), 1.89 (m, 2H), 1.68 (m, 2H), 1.49 (s, 9H), 1.38 (d, $J$ = 6.8 Hz, 6H).

**6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (46).** Compound **120** (0.051 g, 0.083 mmol) was dissolved in dichloromethane (3 mL) to which 2 N HCl (2 mL) was added, and the mixture was stirred at room temperature for 2 h. This mixture was concentrated and allowed to sit for 10 days, and it was then dissolved in 2 N HCl (2 mL) and stirred at room temperature for 5 h. The solvent was removed to give **46** as a yellow solid (0.039 g, 71%). decomposes >225 °C. MS (APCI) *m/z* 514.0, 512.0 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.51 (m, 1H), 9.02 (m, 1H), 8.98 (s, 1H), 8.07 (s, 1H), 7.83 (s, 2H), 5.90 (m, 1H), 3.85 (d, $J$ = 11.2 Hz, 2H), 3.35 (m, 2H), 2.76 (dd, $J$ = 12.0, 12.0 Hz 2H), 2.58 (s, 3H), 2.14 (m, 2H), 1.92 (m, 2H), 1.77 (m, 2H), 1.58 (m, 2H), 1.28 (d, $J$ = 6.4 Hz, 6H). Exact Mass: Calculated ($C_{24}H_{30}$-$BrN_7O$) 512.1773, found 512.1792 (M + 1); HPLC purity 95%.

**6-Bromo-8-cyclopentyl-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (47).** Compound **112** (1.0 g, 2.7 mmol) and 5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamine (1.48 g, 7.7 mmol) were combined in toluene (3.0 mL) under nitrogen. The reaction mixture was heated to reflux and stirred for 4 h. The reaction mixture was cooled to room temperature and filtered. The solids were washed with additional toluene (25 mL total) and dried in vacuo to produce **47** as a yellow powder (338 mg, 29%). mp 278−280 °C (dec); MS (APCI) *m/z* 500, 498 (M + 1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.71−10.64 (m, 2H), 9.01 (s, 1H), 8.10−8.09 (m, 1H), 7.89 (d, $J$ = 0.10 Hz, 1H), 7.52−7.30 (m, 1H), 5.97−5.89 (m, 1H), 3.87−3.84 (m, 2H), 3.53−3.50 (m, 2H), 3.22−3.09 (m, 4H), 2.83−2.82 (m, 3H), 2.60 (s, 3H), 2.21−2.15 (m, 2H), 1.94 (br, 2H), 1.81−1.78 (m, 2H), 1.62−1.60 (M, 2H); Anal. ($C_{23}H_{28}BrN_7O_1$·3.00$H_2O$·1.65HCl·0.60$C_2H_5OH$): C, H, N.

**4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-azepane-1-carboxylic Acid *tert*-Butyl Ester (121).** A solution of 4-(6-amino-pyridin-3-yl)-azepane-1-carboxylic acid *tert*-butyl ester (614 mg, 2.10 mmol) in toluene (10 mL) was refluxed in a Dean−Stark apparatus for 3 h. The heat was removed, and when the reflux subsided, compound **112** (700 mg, 1.89 mmol) was added. This mixture was refluxed for 12 h under $N_2$. Succinic anhydride (500 mg) was added and the reflux continued for 3 h. The reaction mixture was cooled and dissolved in ethyl acetate (100 mL), and the organic layer was washed with water (100 mL total). The organic layer was dried over magnesium sulfate, and the solvents were evaporated. The crude product was subjected to chromatography on silica gel and eluted with a chloroform/2-propanol gradient to give **121** as a yellow powder (414 mg, 39%). MS (APCI) *m/z* 600 (M + 1). $^1$H NMR (400 MHz, MeOH-$d_6$) $\delta$ 9.08 (m, 1 H), 8.00 (m, 1 H), 7.74 (m, 1 H), 7.49 (m, 1 H), 6.08 (m, 1 H), 3.68 (m, 6 H), 3.40 (m, 2 H), 2.69 (s, 3 H), 2.24 (m, 2 H), 2.09 (m, 2 H), 1.90 (m, 4 H), 1.69 (m, 2 H), 1.33 (m, 9 H).

**6-Bromo-8-cyclopentyl-2-(5-[1,4]diazepan-1-yl-pyridin-2-ylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (48).** Hydrogen chloride gas was bubbled through a solution of **121** (80 mg, 0.13 mmol) in chloroform (5 mL) for 30 min. The solvents were evaporated, and the residue was triturated with ethanol (5 mL). Compound **48** was obtained as a yellow powder (44 mg, 68%). MS (APCI) *m/z* 501, 499 (M + 1); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.84 (s, 2H), 8.13 (s, 1H), 7.66−7.64 (m, 1H), 7.42−7.39 (m, 1H), 5.86−5.82 (m, 1H), 4.36 (s, 1H), 3.81 (s, 2H), 3.60 (s, 2H), 3.16 (s, 2H), 2.09 (s, 4H), 1.99 (s, 2H), 1.79 (br, 2H), 1.60 (s, 2H), 1.05 (s, 2H); Anal. ($C_{23}H_{28}Br_1N_7O_1$·0.15HCl·2.55$C_2H_5OH$·0.45$CHCl_3$): C, H, N.

**6-Bromo-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-6′-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (49).** Compound **112** (1.0 g, 2.70 mmol) and 3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-6′-ylamine (0.668 g, 3.73 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL) to give **49** as a brown solid (0.358 g, 27%). mp 293−295 °C. MS (APCI) *m/z* 485.0, 483.0 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H), 8.27 (s, 1H), 8.17 (d, $J$ = 9.0 Hz, 1H), 8.01 (s, 1H), 7.38 (d, $J$ = 6.8 Hz, 1H), 5.98 (m, 1H), 3.1 (m, 4H), 2.60 (s, 3H), 2.30 (m, 2H), 2.11 (m, 2H), 1.88 (m, 2H), 1.57−1.75 (m, 8H). Anal. ($C_{23}H_{27}$-$BrN_6O_1$): C, H, N.

**6-Bromo-8-cyclopentyl-2-(4-hydroxy-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-6′-ylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (50).** Compound **112** (2.50 g, 6.76 mmol) and 6′-amino-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4-ol (1.96 g, 10.13 mmol) were combined in toluene (10 mL) under nitrogen. The reaction mixture was heated to reflux and stirred for 4 h. The reaction mixture was cooled to RT and filtered. The solids were washed with additional toluene (75 mL total)

and dried in vacuo to produce **50** as a yellow powder (566 mg, 17%). MS (APCI) *m/z* 501, 499 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.06 (s, 1H), 8.96 (s, 1H), 8.04 (s, 1H), 7.83 (d, $J$ = 9.3 Hz, 1H), 7.46 (d, $J$ = 7.3 Hz, 1H), 5.93−5.89 (m, 1H), 4.71 (s,1H), 3.65−3.60 (m, 1H), 3.53−3.51 (m, 2H), 2.88−2.83 (m, 2H), 2.57 (s, 3H), 2.18 (br, 2H), 1.90−1.81 (m, 5H), 1.59−1.48 (m, 3H). Anal. ($C_{23}H_{27}Br_1N_6O_2$, 0.45 $H_2O$): C, H, N.

**6-Bromo-8-cyclopentyl-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (51).** Compound **112** (1.0 g, 2.70 mmol) and 5-morpholin-4-yl-pyridin-2-ylamine (0.668 g, 3.73 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL). The solid obtained was refluxed in ethyl acetate (15 mL), cooled and filtered to give **51** as a dark brown-gray solid (0.350 g, 27%). mp >300 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (s, 1H), 8.17 (d, $J$ = 9.0 Hz, 1H), 8.02 (d, $J$ = 2.7 Hz, 1H), 7.97 (s, 1H), 7.32 (dd, $J$ = 2.9, 9.0 Hz, 1H), 5.99 (m, 1H), 3.89 (m, 4H), 3.16 (m, 4H), 2.61 (s, 3H), 2.30 (m, 2H), 2.10 (m, 2H), 1.88 (m, 2H), 1.68 (m, 2H). *m/z* 487.0, 485.0 (M + 1). Anal. ($C_{22}H_{25}BrN_6O_2 \cdot 1.37H_2O$): C, H, N.

**6-Acetyl-2-{5-[bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino}-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (52).** Compound **45** (0.4 g, 0.75 mmol), tributyl-(1-ethoxy-vinyl)-stannane (0.42 g, 1.175 mmol) and palladium tetrakistriphenylphosphine (0.1 g, 0.09 mmol) were combined in $N_2$-purged toluene (4 mL) and heated to 110 °C. After 2 h the reaction mixture was allowed to cool, and solid 40% KF on alumina (0.2 g) was added. This mixture was diluted with toluene (15 mL) and mixed by swirling for 2 min. After filtering and removal of the solvents, the crude product was chromatographed on silica gel eluting with 50−65% ethyl acetate in hexanes to give an orange gum (0.298 g). This gum was dissolved in $CH_2Cl_2$ and washed with 10% KF in $H_2O$, then brine and dried ($MgSO_4$). Following removal of the drying agent and evaporation of the solvent, the remaining material was dissolved in ethyl acetate (10 mL) and treated with 1 M HCl (aqueous). The resulting mixture was stirred vigorously for 1 h at room temperature. Sufficient $CH_2Cl_2$ was added to dissolve the precipitate that had formed, and the organic solution was washed with saturated aqueous sodium bicarbonate solution. The aqueous layer was back extracted twice with $CH_2Cl_2$, and the combined organic layers were dried ($MgSO_4$). Removal of the drying agent and evaporation of the solvent gave a foamy solid, which was dissolved in ethyl acetate (20 mL) and filtered then diluted with an equal volume of hexanes and stored at 4 °C. The yellow crystals that formed were collected by filtration and dried in vacuo to give **62** (120 mg, 32%). mp 138−138 °C. MS (APCI) *m/z* 495.3 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.75 (s, 1H), 8.85 (s, 1H), 8.17 (s, 1H), 7.60 (br s, 1H), 6.65 (d, $J$ = 9 Hz, 1H), 5.9 (m, 1H), 3.62 (t, $J$ = 6 Hz, 4H), 3.46 (t, $J$ = 6 Hz, 4H), 3.22 (s, 6H), 2.38 (s, 3H), 2.25 (s, 3H), 2.17 (br s, 2H), 1.67 (br s, 2H), 1.45 (br s, 2H). Anal. ($C_{26}H_{34}N_6O_4$): C, H, N.

**4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-2,2-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (122).** Compound **112** (1.0 g, 2.70 mmol) and 4-(6-amino-pyridin-3-yl)-2,2-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (1.14 g, 3.73 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL) to give **122** as a dark brown-gray solid (0.525 g, 32%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.96 (s, 1H), 8.91 (s, 1H), 7.89 (d, $J$ = 2.7 Hz, 1H), 7.74 (d, $J$ = 8.8 Hz, 1H), 7.26 (dd, $J$ = 3.2, 9.3 Hz, 1H), 6.18 (s, 1H), 5.86 (m, 1H), 3.67 (m, 2H), 3.37 (m, 4H), 2.54 (s, 3H), 2.15 (m, 2H), 1.84 (m, 2H), 1.71 (m, 2H), 1.53 (m, 2H), 1.39 (s, 9H), 1.33 (s, 6H).

**4-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-2,2-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (123).** Compound **122** (0.412 g, 0.673 mmol), tetrakis(triphenylphosphine)palladium (0.093 g, 0.081 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (0.379 g, 1.05 mmol) were dissolved in toluene (3 mL) and slowly brought to reflux for 1 h. The solvent was evaporated and the solid was redissolved in dichloromethane (8 mL) and purified by silica gel chromatography to give **123** as a yellow solid (0.405 g, 99%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.73 (s, 1H), 8.15 (d, $J$ = 9.0 Hz, 1H), 8.00 (s, 1H), 7.85 (d, $J$ = 2.9 Hz, 1H), 7.18 (m, 1H), 5.90 (m, 1H), 4.52 (d, $J$ = 2.4 Hz, 1H), 4.18 (d, $J$ = 2.4 Hz, 1H), 3.93 (q, $J$ = 7.1 Hz, 2H), 3.80 (m, 2H), 3.38 (m, 2H), 3.26 (s, 2H), 2.41 (s, 3H), 2.35 (m, 2H), 2.06 (m, 2H), 1.85 (m, 2H), 1.64 (m, 2H), 1.49 (s, 9H), 1.45 (s, 6H), 1.36 (t, $J$ = 7.1 Hz, 3H).

**6-Acetyl-8-cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (53).** Compound **123** (0.400 g, 0.663 mmol) was dissolved in ethyl acetate (10 mL) and 6 N HCl (10 mL) and stirred at room temperature for 2 h. The solvent was evaporated to give a yellow solid, which was dried in a vacuum oven for 5 h at 50 °C. The solid was triturated with EtOH (20 mL) and filtered to yield **53** as a yellow solid (0.120 g, 38%). MS (APCI) *m/z* 476.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.15 (s, 2H), 8.93 (s, 1H), 8.04 (d, $J$ = 3.2 Hz, 1H), 7.82 (d, $J$ = 9.1 Hz, 1H), 7.64 (m, 1H), 5.78 (m, 1H), 3.31 (m, 2H), 3.24 (m, 2H), 3.18 (s, 2H), 2.38 (s, 3H), 2.28 (s, 3H), 2.18 (m, 2H), 1.85 (m, 2H), 1.73 (m, 2H), 1.54 (m, 2H), 1.35 (s, 6H). Anal. Calc′d for $C_{26}H_{33}N_7O_2 \cdot 2.89HCl \cdot 3.0H_2O$: C, 49.18; H, 6.65; N, 15.44. Found; C, 49.55; H, 6.80; N, 14.76.

**4-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-2,6-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (124).** Compound **120** (0.450 g, 0.735 mmol), tetrakis(triphenylphosphine)palladium (0.102 g, 0.088 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (0.414 g, 1.15 mmol) were dissolved in toluene (4 mL) and slowly brought to reflux for 2 h. The solvent was evaporated and the solid redissolved in dichloromethane (8 mL). This solution was purified by silica gel chromatography to give **124** as a yellow solid (0.275 g, 62%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.73 (s, 1H), 8.20 (d, $J$ = 9.0 Hz, 1H), 8.06 (s, 1H), 8.00 (d, $J$ = 2.7 Hz, 1H), 7.32 (dd, $J$ = 2.7, 9.0 Hz, 1H), 5.89 (m, 1H), 4.51 (d, $J$ = 2.4 Hz, 1H), 4.26 (m, 2H), 4.17 (d, $J$ = 2.4 Hz, 1H), 3.93 (q, $J$ = 6.8 Hz, 2H), 3.28 (d, $J$ = 11.7, 2H), 2.90 (dd, $J$ = 4.2, 11.7 Hz, 1H), 2.41 (s, 3H), 2.35 (m, 2H), 2.06 (m, 2H), 1.85 (m, 2H), 1.65 (m, 2H), 1.48 (s, 9H), 1.45 (s, 6H), 1.36 (m, 9H).

**6-Acetyl-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one Hydrochloride (54).** Compound **124** (0.250 g, 0.414 mmol) was dissolved in dichloromethane (3 mL) to which 2 N HCl in diethyl ether (3 mL) was added, and the mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the solid was dried in a vacuum oven for 24 h at 50 °C to give **54** as a yellow solid (0.120 g, 38%). MS (APCI) *m/z* 476.1 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.51 (m, 2H), 9.0 (m, 1H), 8.97 (s, 1H), 8.08 (d, $J$ = 2.7 Hz, 1H), 7.84 (d, $J$ = 9.3 Hz, 1H), 7.78 (m, 1H), 5.80 (m, 1H), 3.35 (d, $J$ = 11.5 Hz, 2H), 3.35 (m, 2H), 2.75 (dd, $J$ = 12.2, 2H), 2.40 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.57 (m, 2H), 1.29 (d, $J$ = 6.6 Hz, 6H). Anal. Calc′d for $C_{26}H_{33}N_7O_2 \cdot 2.70HCl \cdot 0.10H_2O$: C, 54.23, H, 6.28, N, 17.03. Found: C, 54.60; H, 6.68; N, 16.57.

**8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8*H*-pyrido[2,3-*d*]-pyrimidin-7-one (125).** A 6-dram vial was charged with **47** (266 mg, 0.53 mmol) and tetrakis(triphenylphosphine) palladium(0) (61 mg, 0.053 mmol) and the atmosphere replaced with argon. Toluene (5 mL) was added followed by tributyl-(1-ethoxy-vinyl)-stannane (289 mg, 0.80 mmol). The vial was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with chloroform (25 mL) and adsorbed onto silica gel. Chromatographic purification on silica gel (chloroform/2-propanol + 1%TEA gradient) gave **125** (237 mg, 91%), which was used without further purification. MS (APCI) *m/z* 490 (M + 1).

**6-Acetyl-8-cyclopentyl-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (55).** To a solution of **125** (237 mg, 0.48 mmol) in chloroform (5 mL) was added hydrogen chloride (2 M ethereal solution, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvents were evaporated, and the residue was dissolved in ethanol. The ethanol was evaporated to give **55** (239 mg, 0.52 mmol). MS (APCI) *m/z* 462 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.83 (m, 2H), 9.00 (s, 1H), 8.1 (m, 1H), 7.88−7.82 (m, 2H), 5.89−5.80 (m, 1H), 3.88−3.85 (m, 2H), 3.54−3.51 (m, 2H), 3.23−3.11 (m, 4H), 2.83−2.82 (m, 3H), 2.43 (s, 3H), 2.34 (s, 3H), 2.23−2.11 (m, 2H), 1.93 (br, 2H), 1.81−1.77 (m, 2H), 1.60−1.59 (m, 2H); Anal. ($C_{25}H_{31}N_7O_2$·2.70HCl·1.05$C_2H_5OH$): C, H, N.

**(1-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-pyrrolidin-3-yl)-carbamic Acid *tert*-Butyl Ester (126).** A 6-dram vial was charged with {1-[6-(6-bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-pyridin-3-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (prepared by the method described for compound **122**) (379 mg, 0.65 mmol) and tetrakis(triphenylphosphine) palladium-(0) (75 mg, 0.065 mmol) and the atmosphere replaced with argon. Toluene (5 mL) was added followed by tributyl-(1-ethoxy-vinyl)-stannane (352 mg, 0.97 mmol). The vial was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with chloroform (25 mL) and adsorbed onto silica gel. Chromatographic purification on silica gel (chloroform/2-propanol + 1% TEA gradient) gave **126** as a yellow solid (394 mg, 100%) that was used without further purification. MS (APCI) *m/z* 576 (M + 1).

**6-Acetyl-2-[5-(3-amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (56).** To a solution **126** (394 mg, 0.68 mmol) in chloroform (5 mL) was added hydrogen chloride (2 M ethereal solution, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvents were evaporated, and the residue was dissolved in ethanol. The ethanol was evaporated to give **56** (239 mg, 76%). MS (APCI) *m/z* 487 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.98 (s, 1H), 8.34 (br, 2H), 7.78−7.73 (m, 2H), 7.51 (br, 1H), 5.89−5.80 (m, 1H), 3.98 (br, 2H), 3.62−3.51 (m, 4H), 2.40−3.23 (m, 2H), 2.44 (s, 3H), 3.34 (s, 3H), 2.25−2.20 (m, 2H), 2.16−2.13 (m, 1H), 1.93 (br, 2H), 1.80−1.78 (m, 2H), 1.61−1.58 (m, 2H); Anal. ($C_{24}H_{29}N_7O_2$·2.10HCl·2.85$H_2O$·0.45$C_2H_5OH$): C, H, N, Cl.

**4-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-[1,4]diazepane-1-carboxylic Acid *tert*-Butyl Ester (127).** A 6-dram vial was charged with **121** (123 mg, 0.25 mmol) and tetrakis(triphenylphosphine) palladium(0) (29 mg, 0.025 mmol) and the atmosphere replaced with argon. Toluene (5 mL) was added followed by tributyl-(1-ethoxy-vinyl)-stannane (137 mg, 0.37 mmol). The vial was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with chloroform (25 mL) and adsorbed onto silica gel. Chromatographic purification on silica gel (chloroform/ethyl acetate gradient) gave **127** as a yellow solid (116 mg, 80%), which was used without further purification. MS (APCI) *m/z* 590 (M + 1).

**6-Acetyl-8-cyclopentyl-2-(5-[1,4]diazepan-1-yl-pyridin-2-ylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one hydrochloride (57).** To a solution **127** (116 mg, 0.20 mmol) in chloroform (5 mL) was added hydrogen chloride (2 M ethereal solution, 5.0 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvents were evaporated, and the residue was dissolved in ethanol. The ethanol was evaporated to give **57** (47 mg, 50%). MS (APCI) *m/z* 462 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.19 (br, 2H), 8.99 (s, 1H), 7.91 (s, 1H), 7.78−7.75 (m, 2H), 5.88−5.80 (m, 1H), 3.80−3.77 (m, 3H), 3.25 (br, 3H), 3.16 (br, 2H), 2.44 (s, 3H), 2.34 (s, 3H), 2.49−2.18 (m, 2H), 2.12−2.10 (m, 2H), 1.93 (br, 2H), 1.81−1.78 (m, 2H), 1.61−1.58 (m, 2H); Anal. ($C_{25}H_{31}N_7O_2$·2.80HCl·0.45$C_3H_8O_2$): C, H, N.

**8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (128).** Compound **51** (0.310 g, 0.641 mmol), tetrakis(triphenylphosphine)palladium (0.089 g, 0.077 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (0.361 g, 1.0 mmol) were dissolved in toluene (3 mL) and slowly brought to reflux for 2 h. The reaction mixture was allowed to cool, then purified by silica gel chromatography to give **128** as a yellow solid (0.180 mg, 59%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.73 (s, 1H), 8.16 (d, $J$ = 9.0 Hz, 1H), 8.05 (s, 1H), 8.01 (d, $J$ = 2.9 Hz, 1H), 7.36 (dd, $J$ = 2.9, 9.3 Hz, 1H), 5.90 (m, 1H), 4.52 (d, $J$ = 2.4 Hz, 1H), 4.18 (d, $J$ = 2.2 Hz, 1H), 3.93 (q, $J$ = 7.1 Hz, 2H), 3.14 (m, 4H), 2.41 (s, 3H), 2.36 (m, 2H), 2.06 (m, 2H), 1.84 (m, 2H), 1.56−1.77 (m, 8H), 1.21 (t, $J$ = 7.1 Hz, 3H).

**6-Acetyl-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (58).** Compound **128** (0.180 g, 0.379 mmol) was dissolved in ethyl acetate (10 mL), and 6 N HCl (10 mL) was added then the mixture was stirred at room temperature for 2 h. The mixture was diluted with dichloromethane and aqueous $NaHCO_3$. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and the solvent evaporated to give **58** as a yellow solid (0.120 g, 71%). mp 251−253 °C. MS (APCI) *m/z* 447.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (s, 1H), 8.20 (d, $J$ = 8.5 Hz, 1H), 7.95 (s, 1H), 7.39 (m, 1H), 5.85 (m, 1H), 3.15 (m, 4H), 2.53 (s, 3H), 2.36 (s, 3H), 2.33 (m, 2H), 2.05 (m, 2H), 1.87 (m, 2H), 1.77−1.56 (m, 8H). MS (APCI) *m/z* 447.2. Anal. ($C_{25}H_{30}N_6O_2$·0.35$H_2O$): C, H, N.

**8-Cyclopentyl-6-(1-ethoxy-vinyl)-2-(4-hydroxy-3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (129).** A 6-dram vial was charged with **50** (316 mg, 0.63 mmol) and tetrakis(triphenylphosphine) palladium(0) (72 mg, 0.063 mmol) and the atmosphere replaced with argon. Toluene (5 mL) was added followed by tributyl-(1-ethoxy-vinyl)-stannane (343 mg, 0.95 mmol). The vial was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with chloroform (25 mL) and adsorbed onto silica gel. Chromatographic purification on silica gel (chloroform/2-propanol + 1% TEA gradient) gave **129** (255 mg, 83%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.92 (s, 1 H), 8.85 (s, 1 H), 8.03 (m, 1 H), 7.82 (t, $J$ = 8.42 Hz, 1 H), 7.44 (dd, $J$ = 9.03, 3.17 Hz, 1 H), 5.81 (m, 1 H), 4.70 (d, $J$ = 4.15 Hz, 1 H), 4.44 (d, $J$ = 1.95 Hz, 1 H), 4.04 (d, $J$ = 1.95 Hz, 1 H), 3.81 (q, $J$ = 6.91 Hz, 2 H), 3.62 (m, 1 H), 3.50 (m, 2 H), 2.84 (m, 2 H), 2.36 (s, 3 H), 2.22 (m, 2 H), 1.78 (m, 6 H), 1.50 (m, 4 H), 1.24 (t, $J$ = 6.95 Hz, 3 H).

**6-Acetyl-8-cyclopentyl-2-(4-hydroxy-3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (59).** To a solution of **129** (255 mg, 0.52 mmol) in chloroform (2 mL) was added hydrogen chloride (2 M ethereal solution, 5.0 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvents were evaporated, and the residue was dissolved in ethanol. The ethanol was evaporated to give **59** (213 mg, 88%). MS (APCI) *m/z* 463 (M + 1). $^1$HNMR (400 MHz, DMSO-$d_6$) $\delta$ 10.90 (br, 1H), 9.07 (s, 1H), 8.19 (s, 1H), 7.91 (br, 2H), 5.91−5.89 (m, 1H), 3.77 (br, 1H), 3.62 (br, 2H), 3.07 (br, 2H), 2.58 (s, 3H), 2.40 (s, 3H), 2.30 (br, 2H), 1.98−1.86 (m, 5H), 1.65 (br, 4H); Anal. ($C_{25}H_{30}N_6O_3$, 1.76 $C_3H_8O_1$, 0.36 $CHCl_3$): C, H, N.

**8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (130).** Compound **51** (0.290 g, 0.597 mmol), tetrakis-(triphenylphosphine)palladium (0.083 g, 0.072 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (0.336 g, 0.932 mmol) were dissolved in toluene (4 mL) and slowly brought to reflux for 3 h. The reaction mixture was purified by silica gel chromatography to give **130** as a yellow solid (0.110 g, 39%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.95 (s, 1H), 8.83 (s, 1H), 8.02 (d, $J$ = 2.9 Hz, 1H), 7.86 (d, $J$ = 9.0 Hz, 1H), 7.44 (dd, $J$ = 3.2, 9.3 Hz, 1H), 5.79 (m, 1H), 4.42 (d, $J$ = 2.0 Hz, 1H), 4.01 (d, $J$ = 2.0 Hz, 1H), 3.79 (q, $J$ = 6.8 Hz, 2H), 3.72 (m, 4H), 3.09 (m, 4H), 2.34 (s, 3H), 2.17 (m, 2H), 1.85 (m, 2H), 1.71 (m, 2H), 1.55 (m, 2H), 1.21 (m, 3H).

**6-Acetyl-8-cyclopentyl-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (60).** Compound **130** (0.490 g, 1.03 mmol) was dissolved in dichloromethane (5 mL). 2 N HCl in diethyl ether (3 mL) was added, and the resulting mixture was stirred at room temperature for 4 h. Then, additional 2 N HCl in diethyl ether (2 mL) was added, and the mixture was stirred for an additional 12 h. The reaction mixture was diluted with dichloromethane and aqueous $NaHCO_3$. The layers were separated, the organic layer was dried over $MgSO_4$ and filtered and the solvent evaporated to give a yellow solid. The solid was recrystallized from a mixture of hexanes, ethyl acetate and dichloromethane to give **60** as a yellow solid (0.280 g, 61%). mp 268−270 °C. MS (APCI) *m/z* 449.2 (M + 1). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.79 (s, 1H), 8.17 (d, $J$ = 9.0 Hz, 1H), 8.02 (d, $J$ = 2.7 Hz, 1H), 7.31 (dd, $J$ = 2.9, 9.0 Hz, 1H), 5.86 (m, 1H), 3.88 (m, 4H), 3.15 (m, 4H), 2.54 (s, 3H), 2.36 (s, 3H), 2.32 (m, 2H), 2.05 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H). Exact Mass: Calculated ($C_{24}H_{28}N_6O_3$) 449.2301, found 449.2313 (M + 1); HPLC purity 95%.

**6-Bromo-8-cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (131).** Compound **112** (1.0 g, 2.70 mmol) and 5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamine (0.668 g, 3.73 mmol) were heated to reflux in toluene (10 mL) for 16 h. The reaction mixture was cooled to room temperature, and the precipitate that formed was collected by filtration and washed on the funnel with toluene (3 × 10 mL) to give **131** as a brown solid (0.358 g, 27%). mp 287−289 °C. MS (APCI) *m/z* 515.1, 513.1 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.80 (s, 1H), 8.21 (d, $J$ = 9.3 Hz, 1H), 7.98 (d, $J$ = 2.9 Hz, 1H), 7.34 (dd, $J$ = 3.2, 9.3 Hz, 1H), 5.98 (m, 1H), 3.84 (m, 2H), 3.40 (dd, $J$ = 2.9, 10.2 Hz, 2H), 2.61 (s, 3H), 2.46 (dd, $J$ = 10.2, 10.2 Hz, 2H), 2.30 (m, 2H), 2.11 (m, 2H), 1.88 (m, 2H), 1.68 (m, 2H), 1.28 (d, $J$ = 6.3 Hz, 6H). Anal. ($C_{24}H_{29}BrN_6O_2$): Calc. C, 56.14, H, 5.69, N, 16.37. Found: C, 55.90; H, 5.62; N, 16.10.

**8-Cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-6-(1-ethoxy-vinyl)-5-methyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (132).** Compound **131** (0.062 g, 0.121 mmol), tetrakis(triphenylphosphine)palladium (0.017 g, 0.015 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (0.068 mg, 0.188 mmol) were dissolved in toluene (2 mL) and slowly brought to reflux for 12 h. Additional tetrakis(triphenylphosphine)-palladium (0.010 g) was added and the reaction brought to reflux for 16 h. The reaction mixture was cooled and purified by silica gel chromatography to give **132** as a yellow solid (0.055 g, 90%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.72 (s, 1H), 8.17 (d, $J$ = 9.0 Hz, 1H), 7.99 (d, $J$ = 2.9 Hz, 1H), 7.83 (s, 1H), 7.29 (dd, $J$ = 2.9, 9.0 Hz, 1H), 5.89 (m, 1H), 4.51 (d, $J$ = 2.5 Hz, 1H), 4.17 (d, $J$ = 2.4 Hz, 1H), 3.93 (q, $J$ = 7.1 Hz, 2H), 3.83 (m, 2H), 3.37 (d, $J$ = 10.3 Hz, 2H), 2.44 (dd, $J$ = 10.5, 10.5, 2H), 2.41 (s, 3H), 2.34 (m, 2H), 2.06 (m, 2H), 1.84 (m, 2H), 1.65 (m, 2H), 1.36 (t, $J$ = 7.1 Hz, 3H), 1.26 (d, $J$ = 6.4 Hz, 6H).

**6-Acetyl-8-cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (61).** Compound **132** (0.055 g, 0.109 mmol) was dissolved in ethyl acetate (3 mL) and 1 N aqueous HCl (2 mL) and stirred at room temperature for 48 h. The reaction mixture was diluted with dichloromethane and aqueous $NaHCO_3$. The layers were separated, the organic layer was dried over $MgSO_4$ and filtered and the solvent was evaporated to give **61** (0.020 g, 38%). MS (APCI) *m/z* 477.2 (M + 1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H), 8.1 (d, $J$ = 9.0 Hz, 1H), 8.00 (d, $J$ = 2.7 Hz, 1H), 7.90 (s, 1H), 7.30 (dd, $J$ = 3.1, 9.3 Hz, 1H), 5.87 (m, 1H), 3.83 (m, 2H), 3.37 (d, $J$ = 10.0 Hz, 2H), 2.54 (s, 3H), 2.46 (dd, $J$ = 11.7, 11.7, 2H), 2.37 (m, 2H), 2.05 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H), 1.27 (d, $J$ = 6.3 Hz, 6H). Anal. ($C_{24}H_{29}BrN_6O_2 \cdot 1.45H_2O \cdot 0.15EtOAc$): C, H, N.

**Cyclin Dependent Kinase Assays and Other Protein Kinases.** Cdk assays for $IC_{50}$ determinations were performed in 96-well filter plates (Millipore, MADVN6550). All Cdk-cyclin complexes were expressed in insect cells through baculovirus infection and purified as described previously.[19] The substrate for the assays was amino acids 792−928 of pRb fused to GST (GST-RbCterm).[20] The total volume for each well was 0.1 mL containing a final concentration of 20 mM Tris-HCl (pH 7.4), 50 mM NaCl, 1 mM dithiothreitol (DTT), 10 mM $MgCl_2$, 25 $\mu$M ATP (for Cdk4-cyclin D1 and D3 and Cdk6-cyclin D2) or 12 $\mu$M ATP (for Cdk2-cyclin E, Cdk2-cyclin A and Cdk1-cyclin B) containing 0.25 $\mu$Ci of [$\gamma$-$^{32}$P]ATP, 20 ng of enzyme, 1 $\mu$g of GST-Rb-Cterm and appropriate dilutions of inhibitor. All components except the [$\gamma$-$^{32}$P]ATP were added to the wells, and the plate was placed on a plate mixer for 2 min. The reaction was then started by adding the [$\gamma$-$^{32}$P]ATP, and the plate was incubated at 25 °C for 15 min. The reaction was terminated by addition of 0.1 mL of 20% trichloroacetic acid (TCA), and the plate was kept at 4 °C for at least 1 h to allow the substrate to precipitate. The wells were then washed five times with 0.2 mL of 10% TCA, and radioactive incorporation was determined with a beta plate counter (Wallac Inc., Gaithersburg, MD). Enzyme assays for other protein kinases were performed as described previously.[21−23] The $IC_{50}$ values were determined from five-point titrations performed in duplicate. The mean of two determinations is provided in the tables. When the duplicates differed by greater 2-fold, a third determination was made.

**Cell Culture.** All cell lines were obtained from ATCC and maintained at 37 °C, 5% $CO_2$ in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum (FBS) (Life Technologies, Inc). To measure thymidine incorporation into DNA, cells were seeded at 2 × $10^4$ per well in a 96-well Cytostar T plate (Amersham Corp.) and incubated overnight to allow cells to attach. Predetermined concentrations of test compound were added to the wells and incubated for 24 h at 37 °C. Then, [$^{14}$C]thymidine (0.1 $\mu$Ci) was added to each well and incorporation of the radiolabel allowed to proceed for 72 h. Incorporated radioactivity was determined with a beta plate counter (Wallac Inc., Gaithersburg, MD). $IC_{50}$ values were determined from five-point titration curves by line fitting using SigmaPlot.

**Flow Cytometry.** Cells were harvested and washed in phosphate buffered saline (PBS) containing 5 mM EDTA. They were then washed in PBS containing 1% FBS (1% FBS/PBS), fixed in 85% ethanol and stored at 4 °C for at least 16 h and up to 5 days. Cells were then washed again in 1% FBS/PBS and incubated at 37 °C for 30 min in 1% FBS/PBS containing 40 mg/mL propidium iodide (PI) (Molecular Probes) and 250 mg/mL RNase A (Roche Diagnostics Ltd.). Data were collected using a Coulter EPICS Elite ESP equipped with a Spectra-physics argon-ion laser and analyzed using ModFit (Verity Software House, Inc.). Results represent a minimum of 15 000 cells assayed for each sample.

**Pharmacokinetics Analysis.** Male Sprague−Dawley rats ($n$ = 3 or 4) were administered a single 5 mg/kg dose as a 5 min iv infusion of the HCl salt or a single 5 mg/kg po dose of the isethionate salt by gavage. The iv dose was administered as a solution in 10% DMA/50% Propylene glycol/40% D5W vehicle, and the po dose was administered as a suspension in 5%:95% PEG200/0.5% methylcellulose vehicle. Serial blood samples were collected from each rat over a 24 h period after dosing. Plasma samples were analyzed for compound **43** concentrations by LC/MS/MS (Column: MetaSil Basic 3.0 cm × 2.0 mm; Mobil phase: 90:10/10:90 (10 mM ammonium formate w/0.1% formic acid: acetonitrile); ionization: electrospray positive ion mode; data acquisition: MassChrom V 1.1/Analyst V 1.2). Pharmacokinetic parameters for compound **43** were determined from the plasma concentration−time data using noncompartmental methods.

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**Supporting Information Available:** Purity data for target compounds. Additional experimental details for the synthesis of aminopyridine side chains. This information is available free of charge via the Internet at http://pubs.acs.org.

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