Pyrido[2,3-*d*]pyrimidin-7-ones as Specific Inhibitors of Cyclin-Dependent Kinase 4

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Inhibition of the cell cycle kinase, cyclin-dependent kinase-4 (Cdk4), is expected to provide an effective method for the treatment of proliferative diseases such as cancer. The pyrido[2,3-*d*]-pyrimidin-7-one template has been identified previously as a privileged structure for the inhibition of ATP-dependent kinases, and good potency against Cdks has been reported for representative examples. Obtaining selectivity for individual Cdk enzymes, particularly Cdk4, has been challenging. Here, we report that the introduction of a methyl substituent at the *C*-5 position of the pyrido[2,3-*d*]pyrimidin-7-one template is sufficient to confer excellent selectivity for Cdk4 vs other Cdks and representative tyrosine kinases. Further optimization led to the identification of highly potent and selective inhibitors of Cdk4 that exhibit potent antiproliferative activity against human tumor cells in vitro. The most selective Cdk4 inhibitors were evaluated for antitumor activity against MDA-MB-435 human breast carcinoma xenografts in mice.

Introduction

A defining characteristic of cancer is cellular proliferation that continues without regard for the regulatory mechanisms that exist in normal cells.[1,2] In healthy tissue, cell division occurs in the context of a highly regulated series of events known as the cell cycle, which is composed of four phases.[3] DNA replication occurs in S phase and cell division occurs in M phase. S phase is preceded by the gap phase, G_1, during which cells are preparing for DNA synthesis. A second gap phase, G_2, separates the S and M phases, allowing an opportunity for cells to perform surveillance of the newly prepared DNA and to prepare for cell division. Transitions through each of these phases are controlled by serine-threonine kinases called cyclin dependent kinases (Cdks), and their partner cyclins that act as regulatory subunits.[4] The activity of the holoenzymes is controlled by extracellular and intracellular signals that dictate the level of cyclins in the cell.

The Cdk/cyclin pairs that appear to be most essential for the regulation of progression through the cell cycle are Cdk1/cyclin B (Cdk1/B), Cdk2/A, Cdk2/E, and Cdk4/D or its orthologue Cdk6/D. Passage through S-phase is controlled by Cdk2/A, while Cdk1/B regulates passage through G_2 and entry into M-phase. Cdk4/D and Cdk2/E restrict the passage through G_1 and the commitment to DNA synthesis via phosphorylation of the retinoblastoma protein (pRb), a transcriptional regulator. Hyperphosphorylated pRb dissociates from the transcription factor E2F making this protein available to direct the expression of proteins essential for DNA synthesis. The INK4 (e.g. p15, p16, p18, p19) and CIP/KIP (e.g. p21, p27, p57) proteins are endogenous inhibitors of Cdk/cyclin complexes that provide a mechanism for the regulation of Cdk activity.[5]

Considerable evidence implicates misregulation of the Cdk4/p16/Rb pathway in diseases of uncontrolled cell growth.[6] For example, up-regulation of this pathway is associated with more than 90% of all human tumors. Overexpression of cyclin D_1, mutation of Cdk4, mutation or deletion of pRb, or deletion of p16 have all been observed. Consequently, it has been postulated that specific inhibitors of Cdk4 may restore normal cell activity and could be used for the treatment for cancer and other diseases of uncontrolled cell growth.[7]

Since the first characterization of cyclin-dependent kinases as key modulators of the cell cycle, these enzymes have been targeted for small molecule intervention in a variety of proliferative diseases.[8−15] By far the largest effort has focused on the discovery of novel agents for the treatment of cancer, but other diseases that might potentially be treatable with Cdk inhibitors include restenosis, malaria, and some neurodegenerative diseases. The first Cdk inhibitors identified were relatively nonspecific agents such as butyrolactone, flavopiridol and UCN-01 (Figure 1).[6,13] Several of these compounds were advanced to clinical trials before their mechanisms of action were thoroughly understood. Consequently, a great deal of information regarding the effect of putative Cdk inhibitors in patients may be misleading due to a lack of specificity of the compounds employed. A second generation of Cdk inhibitors was drawn largely from the class of purines,[16−27] following the initial discovery of olomoucine,[25] roscovitine[26] and subsequently, purvalanols,[22] as potent and moderately selective Cdk1/2 inhibitors. *R*-Roscovitine, known as CYC-202, is currently in phase-II human clinical trials and is reported to be relatively nontoxic.[28] The purine template has provided a rich source of Cdk inhibitors,

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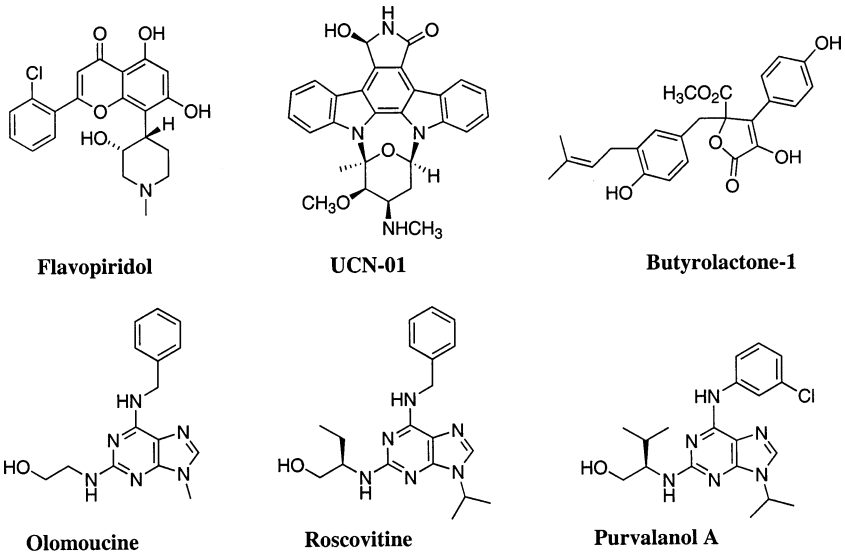


Figure 1. First and second generation Cdk inhibitors.

but the majority of these compounds are more potent against Cdk1 and Cdk2 than Cdk4. A third generation of Cdk inhibitors is now appearing in the literature that encompasses a broad array of structural classes.[29−78] Among this generation of inhibitors are compounds that display quite remarkable levels of selectivity for specific Cdks. It is still the case that more Cdk1/2 inhibitors have been reported than Cdk4 inhibitors, but modest selectivity for Cdk4 has been achieved with a variety of structurally dissimilar inhibitors. For example, Honma and co-workers[58,59] used a Cdk4 homology model to design a urea derivative that is 190-fold selective for Cdk4 versus Cdk2/Cyclin A in vitro. Cdk4 selectivity also has been reported for pyrimidine derivatives,[60−62] and carbazoles.[63−68] Preliminary reports have started to appear of highly selective Cdk4 inhibitors based on the diaminothiazole template.[76]

The discovery of pyrido[2,3-*d*]pyrimidin-7-ones as inhibitors of Cdks,[77−79] followed by optimization of the substituents at *C*-2 and *N*-8, identified compound **1** as a potent but poorly selective inhibitor of Cdk4/D versus Cdk2/A, Cdk2/E and Cdk1/B. While related compounds did achieve improved levels of selectivity, changes to the *C*-2 and *N*-8 substituents alone failed to contribute significantly to selectivity for one enzyme over another in any general way. Consequently, a more extensive investigation of the structure−activity relationships for pyrido[2,3-*d*]pyrimidin-7-one inhibition of Cdk4 was initiated, and the interesting results associated with modifications at the *C*-5 and *C*-6 positions of this template are detailed here. Remarkable levels of selectivity for Cdk4 vs other kinases have been achieved by appropriate substitution at these two positions.

Results and Discussion

The initial impetus for focusing on the *C*-5 position derived from a comparison of pyrido[2,3-*d*]pyrimidin-7-one and purine Cdk inhibitors bound to the ATP binding site of Cdk2. In the absence of structural data for Cdk4, crystal structure data obtained using Cdk2 has been used widely to guide Cdk inhibitor design. From previous crystal structures obtained by this group of pyrido[2,3-*d*]pyrimidin-7-ones bound to Cdk2, it had been postulated that space might be limited around the inhibitor *C*-5 and *C*-6 positions because of their proximity to Phe-80 (Cdk2 numbering). This residue is conserved in Cdk4 (Phe-93), but without a crystal structure its precise location in Cdk4 is not known.

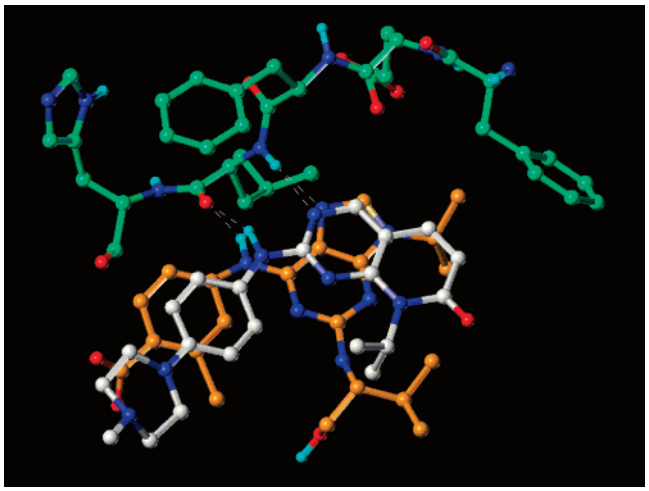
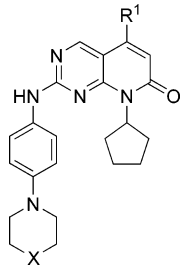


Figure 2. Binding mode of purvalanol B and compound **66** from ref 77.

Purine-based Cdk ligands adopt a variety of binding modes in the Cdk2 ATP site, as exemplified by olomoucine, NU2058 and ATP itself, each of which display a different binding orientation.[80] The purvalanols are potent purine-based Cdk2 inhibitors, which adopt a binding conformation similar to olomoucine.[22] A comparison of purvalanol B with pyrido[2,3-*d*]pyrimidin-7-one Cdk inhibitors bound in the ATP binding site of Cdk2 revealed that the isopropyl group at *N*-9 of purvalanol B occupies the same region of the space in the ATP binding pocket as the *C*-5 hydrogen of the pyrido[2,3-*d*]pyrimidin-7-ones, suggesting that additional potency might be realized by substitution at the *C*-5 position of pyrido[2,3-*d*]pyrimidin-7-ones (Figure 2).

To explore this hypothesis, a selection of previously described pyrido[2,3-*d*]pyrimidin-7-one Cdk inhibitors were modified to include a methyl substituent at the

Table 1. Effect of the C5 Methyl Group on Enzyme Selectivity[a]



compd	R^1	X	Cdk4/D IC_{50} (μM)	Cdk1/B IC_{50} (μM)	Cdk2/A IC_{50} (μM)	Cdk2/E IC_{50} (μM)
1	H	N-Me	0.007	NA	0.014	0.039
2	H	O	0.010	0.275	0.028	0.085
3	H	CH_2	0.010	0.570	0.660	0.246
4	H	$CH(CH_2)_3OH$	0.034	>5	NA	4.550
5	H	NH	0.006	NA	0.024	0.080
6	Me	N-Me	0.018	>5	>5	>5
7	Me	O	0.116	1.120	>5	>5
8	Me	CH_2	0.180	NA	>5	NA
9	Me	$CH(CH_2)_3OH$	0.114	>5	>5	>5
10	Me	NH	0.014	>5	>5	>5

[a] NA means data not available.

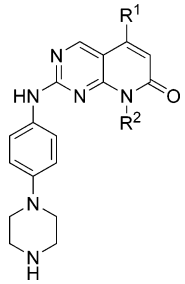
C-5 position. These compounds were assessed for their ability to inhibit a set of four cyclin-dependent kinases including Cdk1/B, Cdk2/A, Cdk2/E, and Cdk4/D (Table 1). Contrary to the hypothesis, the *C*-5-methyl analogues proved to be less active against all four kinases than their *C*-5-hydrogen counterparts. Unexpectedly, however, the *C*-5-methyl analogues all exhibited exquisite selectivity for Cdk4/D versus the other Cdks. This effect appears to be quite general and independent of the nature of the *C*-2 and *N*-8 substituents.

The observation that *C*-5 methyl substituted pyrido-[2,3-*d*]pyrimidin-7-ones do not inhibit Cdk1 and Cdk2 is consistent with the postulate that there is a space limitation imposed at the back of the ATP binding site by the side chain of Phe-80 (Cdk2 numbering). However, it is not clear why a similar substituent protruding into this region of space is tolerated when it is presented on a purine template. Intriguingly, in the absence of detailed information on the three-dimensional structure of Cdk4, these selective inhibitors reinforce the notion that the structure of Cdk4 differs in significant ways from the structures of other cell cycle-associated Cdks.

To further explore what groups might be tolerated by Cdk4/D at the *C*-5 position of the pyrido[2,3-*d*]pyimidin-7-one template, a small set of closely related substituents were explored (Table 2). First, the size of the substituent was increased from methyl to ethyl as in compound **11**. This change diminished the potency for Cdk4/D nearly 50-fold, indicating that the binding pocket in the enzyme is quite small and that further increases in substituent size would be futile. Satisfyingly, however, the selectivity for Cdk4/D appeared to be retained. A similar result was observed when the *C*-5-methyl group was replaced with trifluoromethyl as in compound **12**. In this case, either the size of the trifluoromethyl group was too great, or the negative charge associated with the fluorines being forced adjacent to the π-electron cloud of Phe-93 was detrimental to potency.

With compound **10** showing the best profile thus far with respect to potency and selectivity for Cdk4/D,

Table 2. Varying the C5 and N8 Substituents



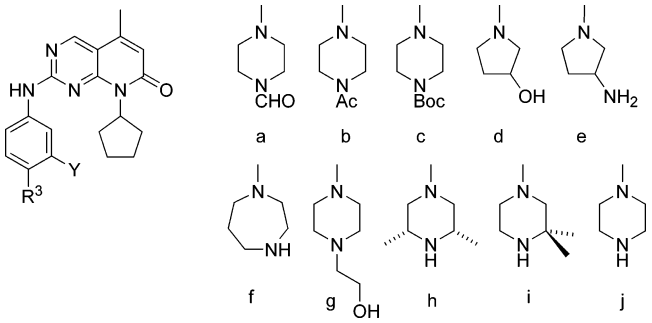
compd	R^1	R^2	Cdk4/D IC_{50} (μM)	Cdk1/B IC_{50} (μM)	Cdk2/A IC_{50} (μM)	Cdk2/E IC_{50} (μM)
11	Et	c-pentyl	0.655	>5	>5	>5
12	CF_3	c-pentyl	2.650	>5	>5	>5
13	Me	isopropyl	0.265	>5	>5	>5
14	Me	isopentyl	1.075	>5	>5	>5

attention was turned to substituents at the *N*-8 position, which are proposed to occupy the ATP ribose-binding pocket, upon binding to Cdk4. Changes in this position did not further enhance potency, but also did not appear to diminish the selectivity for Cdk4. Compound **13** with the *iso*-propyl group at *N*-8 was 20-fold less potent versus Cdk4/D than the cyclopentyl derivative, compound **10**, while opening the *cyclo*-pentyl ring to an *iso*-pentyl group as in compound **14**, led to a more substantial loss in activity. In our previous study, substitutions at *N*-8 as large as norbornyl were tolerated by the enzyme and inhibitory potency appeared to increase with increasing size of the alkyl. In contrast, for *C*-5-methyl pyrido[2,3-*d*]pyrimidin-7-ones, the data indicate that substitution at the *C*-5 position places a limitation on the size of substituent that can be accommodated in the ribose-binding pocket.

With the *C*-5 and *N*-8 positions fixed as methyl and *cyclo*-pentyl, respectively, the heterocycle connected to the phenylamine at the *C*-2 position of the pyrido[2,3-*d*]pyrimidin-7-one was varied in an attempt to further improve the potency for Cdk4. Previous work from this lab has demonstrated the potential for achieving significant changes in potency against Cdk4/D purely as a function of varying the nature of the *C*-2 side chain. In addition, Schultz and co-workers have described a specific hydrogen bonding interaction between a chlorophenyl group in purvalanol and residue Asp-86 in Cdk2 that contributes to inhibitor binding.[22] Honma and co-workers similarly attributed improvements in potency displayed by urea-based inhibitors to specific interactions between the ATP-competitive ligand and residues Thr-102 and Asp-99 in the mouth of the ATP binding site.[58,59]

Acylation of the piperazine nitrogen led to a substantial drop in potency for Cdk4/D as seen for the formyl, acetyl, and *tert*-butyl carbamoyl derivatives **15**, **16**, and **17** (Table 3). The racemic 3-hydroxy-pyrrolidine derivative, **18**, also displayed a sizable drop in potency (Cdk4/D IC_{50} = 0.26 μM); in contrast, the racemic 3-aminopyrrolidine, **19**, inhibited Cdk4/D with IC_{50} = 0.064 μM, only 4−5-fold less potent than piperazine **10**. These data suggest the presence of a productive binding interaction between an ionizable amine and a residue in the protein, located in the mouth of the ATP binding pocket, tentatively identified as Asp-99. In general, analogues closely resembling compound **10** retained

Table 3. Reoptimizing the C2 Substituent[a]



compd	R^3	Y	Cdk4/D IC_{50} (μM)	Cdk1/B IC_{50} (μM)	Cdk2/A IC_{50} (μM)	Cdk2/E IC_{50} (μM)
15	a	H	0.161	>5	>5	>5
16	b	H	0.103	>5	>5	>5
17	c	H	0.425	NA	>5	>5
18	d	H	0.260	>5	>5	>5
19	e	H	0.064	>5	>5	>5
20	f	H	0.052	>5	>5	>5
21	g	H	0.035	>5	>5	>5
22	h	H	0.240	>5	>5	>5
23	i	H	0.065	>5	>5	>5
24	j	Cl	0.028	>5	>5	>5

[a] NA means data not available.

most of the potency and selectivity of compound **10**, as seen for example with homopiperazine **20**, *N*-(2-hydroxyethyl)-piperazine **21**, and *gem*-3,3-dimethylpiperazine **23**. One exception was the *cis*-3,5-dimethylpiperazine derivative, **22**, which displayed a drop in activity of greater than 1 order of magnitude, suggesting that the piperazine ring binds quite snugly to the protein leaving only limited room for substitution, in contrast to some models that suggest that this terminal extension of the *C*-2 side chain projects out into solvent. An attempt to exploit the hydrogen bond that is proposed to assist purvalanol binding to Cdk2 by adding a chlorine to the side chain phenyl ring led to a 2-fold drop in potency suggesting the absence of any special stabilizing force in this case.

Attention was focused next on the *C*-6 position. As for the *C*-5 position, models of pyrido[2,3-*d*]pyrimidin-7-ones bound to Cdk2 suggested that there may be a limitation on the size of substituent tolerated at *C*-6 due to its proximity to Phe-80. The results obtained with *C*-5 substituted pyrido[2,3-*d*]pyrimidin-7-ones suggested that this hypothesis should be examined closely for inhibitors of Cdk4. Initial forays in this direction were discouraging. For example, the *C*-5, *C*-6 dimethyl derivative (**25**) was 10-fold less potent than compound **10** although selectivity for Cdk4/D was maintained (Table 4). However, the *C*-5 methyl, *C*-6 ethyl derivative **26** retained good potency for Cdk4/D, but was only 61-fold selective for Cdk4/D vs Cdk2/A. When alkyl groups were replaced by halogens at *C*-6, a similar trend was observed. As the size of the halogen was increased the potency for Cdk4/D increased, but the compounds became less selective for Cdk4/D versus other Cdks. For example, fluoro analogue **27** is less potent, but more selective than chloro analogue **28**, and iodo analogue **30** is the most potent and least selective member of the series (Table 4). These unexpected trends indicated a subtle balance between the two desirable properties of potency and selectivity and suggested that the optimal inhibitor may not be the most potent.

In an attempt to simulate the electron-withdrawing character of a halogen while maintaining a relatively small volume, ketones and carboxyl derivatives were investigated. This approach identified methyl ketone **31** as the most potent compound of this study, but this inhibitor lacked the level of selectivity versus Cdk2/A now known to be achievable. Interestingly, ketone **31** is selective for Cdk4/D vs Cdk1/B and Cdk2/E and against a wide selection of additional serine/threonine and tyrosine kinases (Table 5), while retaining substantial potency against Cdk2/A. Carboxylic acid **32** regained the desired selectivity for Cdk4/D, but was 2-fold less potent than compound **10** and 16-fold less potent than compound **31**. In contrast, both potency and selectivity was achieved with the methyl ester **33** (IC_{50} = 0.004 μM) and the ethyl ester **34** (IC_{50} = 0.006 μM). The ethyl ester represents one of the most selective Cdk4/D inhibitors reported to date. This set of compounds (Table 4) was further evaluated for the ability to inhibit tumor cell proliferation in vitro as measured by the incorporation of [^{14}C]-thymidine into two cell lines, HCT116 human colon carcinoma and MDA-MB-435 human breast carcinoma. Potent inhibition of cell proliferation was observed (IC_{50} = 0.032−1.35 μM for active compounds), and pleasingly the most potent Cdk4 inhibitors were among the most potent inhibitors in cells, with the exception of carboxylic acid **32**, which was inactive in cells. In general, the HCT116 and MDA-MB-435 cell lines exhibited comparable sensitivity (within a factor of 2, except for compound **34**) to the Cdk inhibitors tested, however, HCT116 cells appeared to be less readily inhibited by the most selective Cdk4 inhibitors (Table 4 and data not shown).

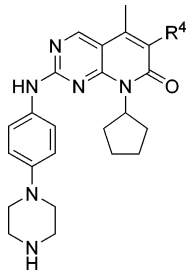
Compounds, **31**, **33**, and **34** were tested for antitumor activity in vivo, using the MDA-MB-435 human tumor xenograft model in nude mice. The two esters were strikingly inactive, possibly due to metabolism of the esters to give **32**, which is inactive in cells. Although, in vitro experiments employing either mouse plasma, or chemical hydrolysis at room temperature, indicated only very slow conversion to the acid under these conditions, related to steric encumbrance imposed by the adjacent methyl group. In contrast, ketone **31** caused significant reductions in the growth rate of MDA-MB-435 tumors, giving a tumor growth delay compared to untreated controls (T − C) of 9.4 days for a 14 day, once daily dosing regimen of 75 mg/kg.

Despite success in treating tumors with compound **31**, the question remained whether a truly selective Cdk4 inhibitor, with no activity against other Cdks, could inhibit tumor growth in vivo. Since the failure to achieve efficacy with compounds **33** and **34** could be explained by potential metabolic instability, it seemed likely that the optimal experiment to address this question had yet to be performed. A metabolically more stable, highly selective Cdk4 inhibitor was required to provide a sufficiently reliable and definitive tool for in vivo studies. The pursuit of such a tool was ultimately rewarded as described in the accompanying manuscript.[87]

Chemistry

The compounds described in this manuscript were obtained via small modifications and additions to the chemistry described previously.[77] The general synthetic

Table 4. Investigations of the C6 Substituent[a]



compd	R^4	Cdk4/D IC_{50} (μM)	Cdk1B IC_{50} (μM)	Cdk2/A IC_{50} (μM)	Cdk2/E IC_{50} (μM)	HCT116 IC_{50} (μM)	MDAMB435 IC_{50} (μM)
25	Me	0.165	>5	NA	>5	NA	NA
26	Et	0.025	4.119	1.538	1.650	0.75	0.425
27	F	0.030	>5	>5	>5	1.35	NA
28	Cl	0.016	>5	1.625	1.500	0.329	NA
29	Br	0.005	2.615	0.439	0.950	0.220	NA
30	I	0.005	1.865	0.443	0.365	0.104	NA
31	COMe	0.002	NA	0.230	NA	NA	0.032
32	CO_2H	0.032	>5	>5	>5	>3	>3
33	CO_2Me	0.004	>5	2.819	>5	0.340	0.190
34	CO_2Et	0.006	>5	>5	>5	0.830	0.170

[a] NA means data not available.

Table 5. Inhibitory Activity of Compound **31** against a Panel of Protein Kinases

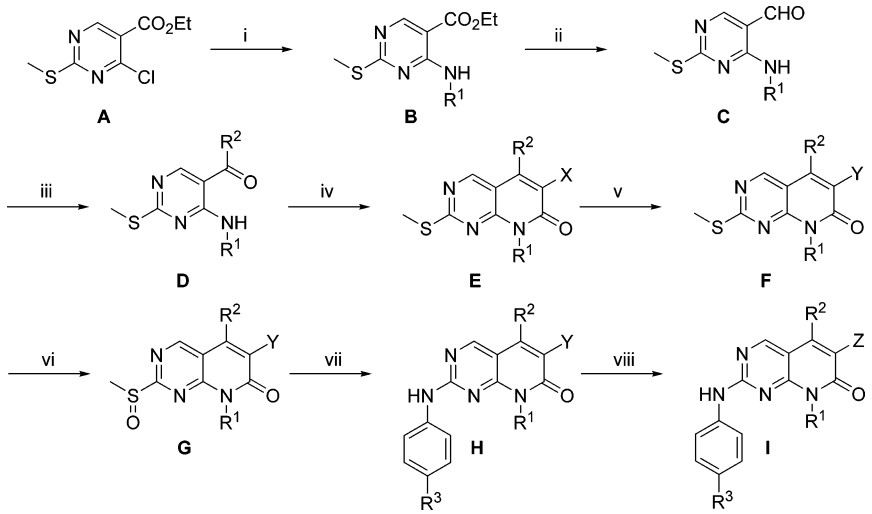
protein kinase	IC_{50} (μM)[a]
fibroblast growth factor receptor (FGFr)	1.86
platelet growth factor receptor (PDGFr)	2.46
C-terminal src kinase (CSK)	>10
glycogen synthase kinase-3β (GSK3β)	>10
c-Jun N-terminal kinase (JNK)	>10
mitogen-activated protein kinase (MAPK2/erk2)	>10
MAPK-activated protein kinase-2 (MAPKAP−K2)	>10
MAPK kinase (MKK1)	>10
mitogen and stress-activated protein kinase-1 (MSK1)	>10
P70 ribosomal protein S6 kinase (p70S6K1)	>10
3-phosphoinositide-dependent protein kinase-1 (PDK-1)	>10
phosphorylase kinase (PHK)	>10
protein kinase A (PKA)	>10
protein kinase B (PKB)	>10
protein kinase C (PKC)	>10
P38-regulated/activated kinase (PRAK)	>10
stress-activated protein kinase-2a (SAPK2a)	>10
stress-activated protein kinase-2b (SAPK2b)	>10
stress-activated protein kinase-3 (SAPK3)	>10
stress-activated protein kinase-4 (SAPK4)	>10

[a] Concentration of compound **31** necessary to inhibit activity by 50%. Values represent the mean of at least two separate determinations.

approach is summarized in Scheme 1. Starting from commercially available 4-chloro-2-methylthio-5-pyrimidinecarboxylic acid ethyl ester (**A**), pyrimidines **B** were obtained by displacement of the chlorine with amines including ammonia, isopentylamine and cyclopentylamine. The ester functional group then was converted to an aldehyde via a two-step reduction−oxidation sequence employing lithium aluminum hydride followed by manganese(IV) oxide to give aldehydes **C**. Introduction of alkyl substituents at what will become the *C*-5 position of the pyrido[2,3-*d*]pyrimidin-7-ones was achieved most commonly using Grignard chemistry. Aldehydes **C** were treated with methylmagnesium bromide or ethylmagnesium bromide to yield secondary alcohols, which then were oxidized to ketones **D** using either *N*-methylmorpholine *N*-oxide (NMO) and catalytic tetra-*n*-propylammonium perruthenate (TPAP),[81] or manganese(IV) oxide. The trifluoromethyl group was installed using Ruppert's reagent ($TMS-CF_3$)[82,83] followed by oxidation with the Dess−Martin periodinane (DMP).[84] Ketones **D** were converted to pyrido[2,3-*d*]-pyrimidin-7-ones **E** using Horner−Wadsworth−Emmons chemistry. Thus, each ketone was treated with triethyl phosphonoacetate (or a substituted version thereof) and sodium hydride in THF with warming until condensation and elimination were complete. This approach permitted the introduction of hydrogen, alkyl groups or fluorine at the *C*-6 position of the pyrido[2,3-*d*]pyrimidin-7-one. Compounds substituted at *C*-6 with bromine were obtained by treatment of compounds **E** with *N*-bromosuccinimide. A similar reaction to install iodine with *N*-iodosuccinimide was not successful, but iodo-derivatives were available by treatment of pyrido-[2,3-*d*]pyrimidin-7-ones **E** with iodine and bis(trifluoroacetoxy)iodobenzene. Treatment of a representative compound **E** with *N*-chlorosuccinimide resulted in *C*-6 chlorination but also caused oxidation and chlorination of the methyl sulfide as shown in Scheme 2. This sulfoxide was used in subsequent displacement reactions to introduce the *C*-2 aniline in an identical manner to sulfoxides **G** in Scheme 1. For compounds **E** in which R^1 = hydrogen, *N*-8 alkyl substituents were introduced at this stage by treatment with sodium hydride and an alkyl halide such as 2-iodopropane.

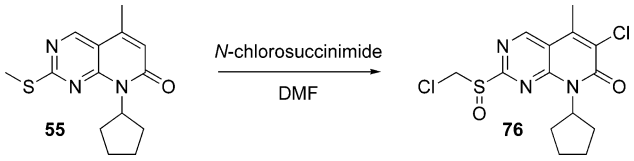
The methyl sulfides **F** (including when step v is omitted and Y = X) were oxidized to methyl sulfoxides **G** using 2-benzenesulfonyl-3-phenyl-oxaziradine[85,86] in preparation for installation of the *C*-2 aniline. Side chain anilines were prepared in two steps as shown in Scheme 3. Aromatic nucleophilic substitution of fluorine in 1-nitro-4-fluorobenzene by amines was readily achieved in acetonitrile under reflux. The resulting nitrobenzenes were reduced to anilines using Raney nickel and generally used without further purification. Sulfoxide displacement reactions were typically performed in DMSO with heating to 80−100 °C. In many cases the product **H** precipitated from the reaction mixture upon cooling. When this was not the case, an aqueous workup and extraction into ethyl acetate or methylene chloride was sufficient to isolate the crude product, which was further

Scheme 1. General Scheme for the Synthesis of Pyrido[2,3-*d*]pyrimidine CDK Inhibitors[a]

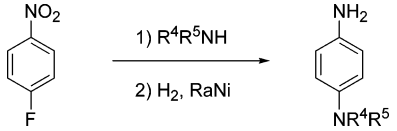


[a] (i) R^1-NH_2, Et_3N, THF. (ii) *a*. $LiAlH_4$, THF. *b*. MnO_2, CH_2Cl_2, or TPAP, NMO, CH_2Cl_2. (iii) *a*. R^2MgBr, THF or Rupperts reagent, THF. *b*. MnO_2, CH_2Cl_2 or DMP. (iv) $(EtO)_2P(O)CHXCO_2Et$, NaH, THF. (v) For Y = Br: NBS, DMF; For Y = I: I_2, $(CF_3CO_2)_2$I-Ph, DMF; this step is skipped when Y = X. (vi) Davis oxaziridine, CH_2Cl_2. (vii) R^3-Ph-NH_2, DMSO. (viii) Z-Met, palladium catalysis.

Scheme 2. Chlorination of a Representative Compound **E** (X = H) Using NCS



Scheme 3. Preparation of the Side Chain Anilines. Amines R^4R^5NH Include *N*-Boc-piperazine, 3-(*N*-Boc-amino)-pyrrolidine, Piperidine, Morpholine



purified by silica gel chromatography. Compounds **2**−**4**, **6**−**9**, **15**−**18**, and **21** required no deprotection after the aniline side chains were installed and were tested in their free base form. In contrast, compounds **H** and **I** containing Boc-piperazines, Boc-homopiperazine, or Boc-aminopyrrolidines were deprotected using a solution containing either hydrochloric acid or trifluoroacetic acid (TFA) to give final compounds **5**, **10**−**14**, **19**, **20**, **22**−**24**, and **25**−**34**, which were tested as their HCl or TFA salts. Compound **15** was obtained by refluxing compound **10** in ethyl formate with a catalytic amount of formic acid.

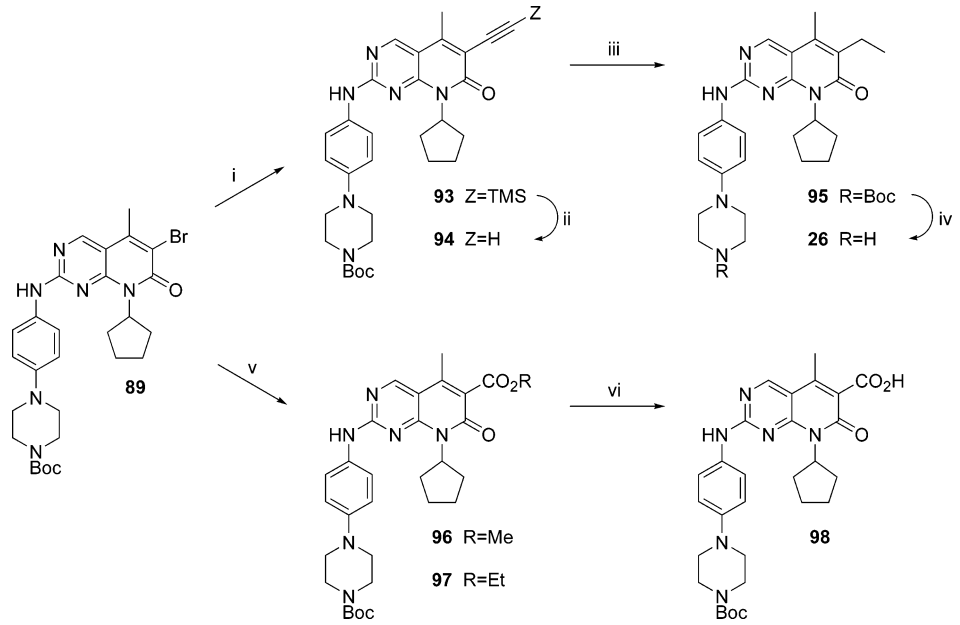
Methods for further elaboration of the *C*-6 position in compounds **H** are represented generically in Scheme **1** and further detailed in Scheme 4. Starting from *C*-6 bromo-pyrido[2,3-*d*]pyrimidin-7-ones, a variety of organometallic coupling reactions may be employed for replacement of the halogen with other groups. For example, compound **89** was combined with TMS-acetylene under Suzuki conditions (CuI, $Pd(PPh_3)_4$, and butylamine), to give alkyne **93**. The ethynyl group was deprotected to give intermediate **94**, then hydrogenated to give the *C*-6 ethyl derivative **95**. Compound **95** was deprotected with acid to provide compound **26**. The *C*-6 esters were readily obtained by treating bromide **89** with $Pd(OAc)_2$ under pressurized CO_2 in the presence of methanol or ethanol to give the methyl and ethyl esters **96** and **97**, respectively. The ethyl ester was hydrolyzed under forcing conditions to give acid **98**. Compounds **96**−**98** were deprotected with hydrochloric acid yield final products **33**, **34**, and **32**. Similar palladium-mediated cross-coupling reactions also could be performed at an earlier stage in the synthetic route, notably starting from intermediates **F** (Y = Br). Thus, compound **63** (Scheme 5) was treated with (1-ethoxyvinyl)tributyltin under Stille conditions to give the ketone **65** after aqueous workup (Scheme 5). This compound then was oxidized at sulfur and coupled to the *N*-Boc-piperazinyl-phenylamine side chain to give intermediate **91**. Cleavage of the Boc group generated the *C*-5 methyl, *C*-6 methyl ketone analogue **31**.

Experimental Section

General Methods. NaH refers to 60 wt % NaH in mineral oil. All solvents and reagents were used as obtained. Anhydrous solvents were obtained commercially and used without further drying. Melting points were determined with a Thomas-Hoover capillary melting point apparatus or a MEL-TEMP melting point apparatus and are uncorrected. ^1H NMR spectra were recorded using a Varian Unity 400-MHz spectrometer. Chemical shifts are in parts per million (δ) referenced to Me_4-Si (0.00 ppm) or $CHCl_3$ (7.24 ppm). The amount of solvent or water present in the molecular formula was determined by ^1H NMR and microanalysis. Chemical ionization mass spectra (CI) were recorded on a VG Trio 2 mass spectrometer instrument using a reagent gas of 1% NH_3 in CH_4. Atmospheric pressure chemical ionization mass spectra (APCIMS) were recorded using a VG Trio 2000 mass spectrometer in a matrix of MeOH/MeCN/DMSO. Combustion analyses (CHN) were determined by Robertson Microlit Laboratories, Inc., Madison, NJ.

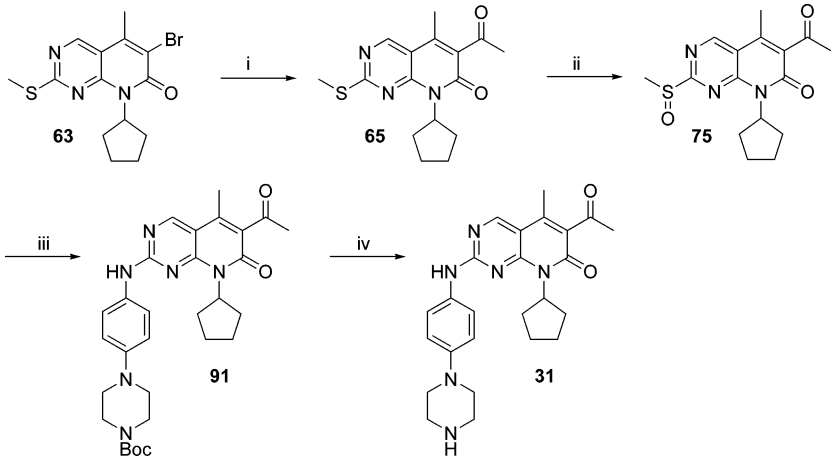
4-Cyclopentylamino-2-methylsulfanyl-pyrimidine-5-carboxylic Acid Ethyl Ester (36): 4-Chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (50.0 g, 215 mmol) was dissolved in THF (1.2 L) to which triethylamine (65.2 g, 645 mmol) was added and stirred for 14 h. The precipitated salts were filtered and the solvent evaporated in vacuo. The resultant oil was dissolved in EtOAc (600 mL) and washed with sodium bicarbonate (2 × 200 mL), then dried over $MgSO_4$. The salts were filtered, and the solvent was evaporated in vacuo to give **36** as an orange oil (45.7 g, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.24 (br s, 1H), 4.43−4.47 (m, 1H),

Scheme 4. Elaborated at C6 by Pd-Mediated Cross-Coupling Reactions[a]



[a] (i) TMS-acetylene, $Pd(PPh_3)_4$, $^nBuNH_2$, CuI. (ii) KOH. (iii) H_2, Pd/C. (iv) HCl. (v) CO, $Pd(OAc)_2$, ROH, 500 psi, 125 °C. (vi) *a*. NaOH (aq), heat.

Scheme 5. Introduction of the C6 Acetyl Group[a]



[a] (i) (1-Ethoxyvinyl)tributyltin, $Pd(PPh_3)_4$, HCl. (ii) Davis oxaziridine, CH_2Cl_2. (iii) 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester, DMSO. (iv) HCl.

4.23−4.28 (q, J = 7.4 Hz, 2H), 2.50 (s, 3H), 1.99−2.07 (m, 2H), 1.45−1.74 (m, 6H), 1.32 (t, J = 7.1 Hz, 3H).

4-Amino-2-methylsulfanyl-pyrimidine-5-carboxylic Acid Ethyl Ester (37): Starting from 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (50 g, 215 mmol), 41.6 g (91%) of **37** was obtained according to the method described for the synthesis of **36**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.98 (s, 1H), 7.60 (s, 1H), 4.18−4.24 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.22−1.25 (t, J = 7.1 Hz, 3H).

4-(1-Ethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carboxylic Acid Ethyl Ester (38): Starting from 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (39.3 g, 169 mmol), 35.6 g (81%) of **38** was obtained according to the method described for the synthesis of **36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (br s, 1H), 4.22−4.26 (m, 2H), 4.08−4.13 (m, 2H), 2.42 (s, 3H), 1.43−1.65 (m, 4H), 1.22−1.30 (m, 2H), 0.80−0.85 (m, 6H); *m/z* 284.0 (M + 1).

(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-methanol (39): Under a nitrogen atmosphere, LAH (9.22 g, 243 mmol) was suspended in THF (500 mL) and cooled with an ice bath. Compound **36** (45.72 g, 162 mmol) was dissolved in THF (160 mL) and added dropwise to the cooled LAH solution while keeping the reaction temperature below 12 °C. After stirring for 6 h at room temperature, the reaction was quenched by the addition of water (18 mL), then 15% NaOH (18 mL) and then water again (30 mL). The white solid that precipitated was filtered and the mother liquor evaporated in vacuo. The resultant solid was triturated with heptane (150 mL) and filtered to give **39** as a pale yellow solid (33.4 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 5.86−5.91 (m, 1H), 4.42 (s, 2H), 4.34−4.37 (m, 1H), 2.45 (s, 3H), 1.99−2.07 (m, 2H), 1.39−1.70 (m, 6H).

(4-Amino-2-methylsulfanyl-pyrimidin-5-yl)-methanol (40): Starting from **37** (40 g, 188 mmol), 31.6 g (98%) of **40** was obtained according to the method described for the synthesis of **39**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 6.66 (br s, 2H), 5.04 (br s, 1H), 4.23 (s, 2H), 2.45 (s, 3H); *m/z* 172.1 (M + 1).

[4-(1-Ethyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-methanol (41): Starting from **38** (38.6 g, 136 mmol), 30.0 g (92%) of **41** was obtained according to the method described for the synthesis of **39**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 6.22−6.27 (m, 1H), 5.12−5.15 (m, 1H), 4.29 (s, 2H), 3.29

(s, 1H), 2.35 (s, 3H), 1.26−1.51 (m, 4H), 0.79−0.82 (m, 6H); *m/z* 284.0 (M + 1).

4-Cyclopentylamino-2-methylsulfanyl-pyrimidine-5-carbaldehyde (42): Compound **39** (30.0 g, 125 mmol) was dissolved in $CHCl_3$ (1.2 L) to which MnO_2 (62 g, 713 mmol) was added and stirred for 16 h. An additional portion of MnO_2 (16.6 g, 191 mmol) was added and stirred for 4 h. The solids were removed by filtration through a Celite pad and washed with $CHCl_3$ (4 × 200 mL). The $CHCl_3$ was evaporated in vacuo to give **42** as a pale yellow solid (29 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.56 (br s, 1H), 8.23 (s, 1H), 4.45−4.49 (m, 1H), 2.51 (s, 3H), 2.01−2.07 (m, 2H), 1.47−1.76 (m, 6H).

4-Amino-2-methylsulfanyl-pyrimidine-5-carbaldehyde (43): Starting from **40** (31.6 g, 185 mmol), 23.6 g (74%) of **43** was obtained according to the method described for the synthesis of **42**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.51 (s, 1H), 8.24 (br s, 1H), 7.97 (br s, 1H), 2.43 (s, 3H); *m/z* 170.1 (M + 1).

4-(1-Ethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde (44): Starting from **41** (28.2 g, 117 mmol), 18.5 g (66%) of **44** was obtained according to the method described for the synthesis of **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.49(s, 1H), 8.40−8.42 (d, J = 8.6 Hz, 1H), 4.08−4.13 (m, 1H), 2.45 (s, 3H), 1.44−1.64 (m, 4H), 0.80−0.84 (m, 6H); *m/z* 240.1 (M + 1).

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethanol (45): Compound **42** (1.1 g 4.64 mmol) was dissolved in THF (30 mL) under nitrogen then cooled with an ice bath, to which MeMgBr was slowly added (4.4 mL, 13.2 mmol, Aldrich 3 M in ether) and stirred for 1 h. The reaction mixture was quenched with a small amount of saturated aqueous NH_4Cl then partitioned between water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine then dried over $MgSO_4$, and after filtration, the solvent was removed in vacuo to give **45** as an oil (1.09 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.28−6.30 (d, J = 6.2 Hz, 1H), 4.69−4.74 (m, 1H), 4.38−4.43 (m, 1H), 2.49 (s, 3H), 2.04−2.06 (m, 2H), 1.60−1.76 (m, 4H), 1.42−1.59 (m, 5H); *m/z* 254.1 (M + 1).

1-(4-Amino-2-methylsulfanyl-pyrimidin-5-yl)-ethanol (46): Starting from **43** (5.00 g, 29.5 mmol), 4.80 g (88%) of **46** was obtained according to the method described for the synthesis of **45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.66 (br s, 1H), 5.22−5.24 (d, J = 4.4 Hz, 1H), 4.62−4.64 (m, 1H), 2.34 (s, 3H), 1.22−1.25 (d, J = 6.4, 3H); *m/z* 185.9 (M + 1).

1-[4-(1-Ethyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-ethanol (47): Starting from **44** (7.79 g, 32.5 mmol), 6.30 g (76%) of **47** was obtained according to the method described for the synthesis of **45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.22−6.23 (d, J = 6.4 Hz, 1H), 4.74−4.79 (m, 1H), 4.08−4.14 (m, 1H), 2.48 (s, 3H), 1.44−1.68 (m, 7H), 0.87−0.93 (m, 6H); *m/z* 256.1 (M + 1).

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-ol (48): Aldehyde **42** (4.07 g 17.1 mmol) was dissolved in THF (120 mL) under nitrogen then cooled with an ice bath, to which EtMgBr was slowly added (13.4 mL, 40.3 mmol, Aldrich 3 M in ether) and stirred for 15 min. The reaction was quenched with a small amount of saturated aqueous NH_4Cl then partitioned between water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine then dried over $MgSO_4$, and after filtration, the solvent was removed in vacuo to give **48** as an oil (4.50 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.66 (d, J = 7.0 Hz, 1H), 5.49−5.51 (d, J = 4.1 Hz, 1H), 4.42−4.46 (m, 1H), 4.28−4.33 (m, 1H), 2.40 (s, 3H), 1.89−1.95 (m, 2H), 1.39−1.69 (m, 8H), 0.77−0.83 (t, J = 7.3 Hz, 3H); *m/z* 268.0 (M + 1).

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-2,2,2-trifluoro-ethanol (49): To an oven dried flask and stir bar were added **42** (1.5 g, 6.32 mmol), THF (30 mL) and cesium fluoride (5 mg). (Trifluoromethyl)trimethylsilane (75 mL, 37.9 mmol) was then added via syringe to the reaction and stirred at room temperature for 48 h. The reaction was quenched with 0.5 N HCl (10 mL) and partitioned between EtOAc and water. The layers were separated, the organic layer washed with brine then dried over $MgSO_4$. The salts were filtered and the solvent evaporated in vacuo to give a crude oil that was purified by silica gel chromatography eluting with EtOAc and hexanes to give **49** as a light oil (160 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.63−6.64 (d, J = 6.3, 1H), 4.78−4.84 (m, 1H), 4.37−4.43 (m, 1H), 2.48 (s, 3H), 1.98−2.02 (m, 2H), 1.46−1.70 (m, 6H); *m/z* 308.0 (M + 1).

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethanone (50): Compound **45** (1.09 g, 4.3 mmol) was dissolved in CH_2Cl_2 (15 mL) to which powdered molecular sieves (4 Å), *N*-methyl morpholine oxide (NMO, 1.07 g, 8.6 mmol) and tetrapropylammonium perruthenate (TPAP, 0.227 g, 0.645 mmol) were added successively. The reaction was stirred at ambient temperature for 2 h. The reaction mixture was then purified using silica gel chromatography (1:1, EtOAc: Hex) to yield **50** as a light yellow solid (0.74 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H) 8.53 (s, 1H), 4.47−4.53 (m, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.02−2.08 (m, 2H), 1.51−1.78 (m, 6H); *m/z* 252.2 (M + 1).

1-(4-Amino-2-methylsulfanyl-pyrimidin-5-yl)-ethanone (51): Starting from **46** (4.75 g, 25.6 mmol), 1.95 g (42%) of **51** was obtained according to the method described for the synthesis of **50**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.39 (br s, 1H), 8.04 (br s, 1H), 2.43 (s, 3H); *m/z* 184.1 (M + 1).

1-[4-(1-Ethyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-ethanone (52): Compound **45** (6.10 g, 23.9 mmol) was dissolved in toluene (150 mL), MnO_2 (5.19 g, 59.17 mmol) added and the reaction mixture heated to reflux for 4 h. The solid was filtered from the reaction and the solvent evaporated in vacuo to give **52** as a clear oil (5.85 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04−9.06 (d, J = 8.3 Hz, 1H), 8.69 (s, 1H), 4.07−4.12 (m, 1H), 2.45 (s, 3H), 1.41−1.63 (m, 6H), 0.80−0.83 (m, 6H); *m/z* 254.0 (M + 1).

1-(4-Cyclopentylamino-2-methyl-pyrimidin-5-yl)-propan-1-one (53): Starting from **46** (4.57 g, 17.1 mmol), 3.79 g (84%) of **53** was obtained according to the method described for the synthesis of **52**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d, J = 6.8, 1H), 8.72 (s, 1H), 4.35 (m, 1H), 2.93 (q, J = 7.1, 2H), 2.45 (s, 3H), 1.93−2.01 (m, 2H), 1.40−1.67 (m, 6H), 0.99 (t, J = 7.1 Hz, 3H); *m/z* 266.2 (M + 1).

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-2,2,2-trifluoro-ethanone (54): Compound **49** (0.160 g, 0.52 mmol) was dissolved in CH_2Cl_2 (5 mL) and Dess−Martin periodinane (0.255 g, 0.60 mmol). After 30 min the reaction was diluted with CH_2Cl_2 (5 mL) and 1 N NaOH (2 mL) and stirred an additional 5 min. The layers were separated and the organic layer washed with brine and dried over $MgSO_4$, the salts were filtered, and the solvent was evaporated in vacuo to give **54** as an oil (0.160 g, 25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.61 (s, 1H), 4.52−4.58 (m, 1H), 2.54 (s, 3H), 2.03−2.12 (m, 2H), 1.51−1.79 (m, 6H); *m/z* 306.0 (M + 1).

8-Cyclopentyl-5-methyl-2-methylsulfanyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (55): Under nitrogen, a cooled flask containing THF (50 mL) was charged with NaH (1.23 g, 30.7 mmol, 60% dispersion in mineral oil) to which was added triethyl phosphonoacetate (6.09 mL, 30.7 mmol). The cooling bath was removed, and a solution of **50** (3.0 g, 11.9 mmol) in THF (70 mL) was slowly added to the preformed anion. The reaction was brought to reflux for 60 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine and dried over $MgSO_4$, the salts were filtered, and the filtrate was concentrated in vacuo to give **55** as a waxy solid (2.67 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 6.41 (s, 1H), 5.75−5.80 (m, 1H), 2.54 (s, 3H), 2.37 (s, 3H), 2.13−2.19 (m, 2H), 1.91−1.95 (m, 2H), 1.71−1.79 (m, 2H), 1.57−1.60 (m, 2H); *m/z* 276.1 (M + 1).

5-Methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (56): Starting from **51** (1.90 g, 10.3 mmol), 2.13 g (35%) of **56** was obtained according to the method described for the synthesis of **55**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 6.00 (s, 1H), 2.41 (s, 3H), 2.22 (s, 3H); *m/z* 208.0 (M + 1).

8-Isopropyl-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (57): Sodium hydride (0.127 g, 5.28 mmol, 60% dispersion in mineral oil) was suspended in DMF (5 mL) to which compound **56** (0.75 g, 3.61 mmol) was added. This mixture was heated to 50 °C for 20 min, at which point iodopropane (0.898 g, 5.28 mmol) was added. Heating was continued for 2 h, and then the reaction mixture was poured into water and extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give an orange solid which was further purified using silica gel chromatography (1:1, hexanes: EtOAc) to give **57** as a light yellow solid (0.210 g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 6.40 (s, 1H), 5.60−5.70 (m, 1H), 2.56 (s, 3H), 2.36 (s, 3H), 1.48−1.49 (d, J = 6.8, 6H); *m/z* 250.1 (M + 1).

8-(1-Ethyl-propyl)-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (58): Starting from **52** (5.85 g, 23.1 mmol), 3.82 g (61%) of **58** was obtained according to the method described for the synthesis of **55**: ^{1}H NMR (400 MHz, DMSO-d_6) − a mixture of rotamers, δ 8.88 (s, 1H), 6.48 (s, 1/2H), 6.41 (s, 1/2H), 5.45−5.55 (m, 1/2H), 5.12−5.18 (m, 1/2H), 2.56 (s, 3H), 2.10 (s, 3H), 2.13−2.38 (m, 2H), 1.76−1.91 (m, 2H), 0.65−0.71 (m, 6H); *m/z* 278.1 (M + 1).

8-Cyclopentyl-5-ethyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (59): Starting from **53** (3.70 g, 13.9 mmol), 2.67 g (66%) of **59** was obtained according to the method described for the synthesis of **55**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 6.37 (s, 1H), 5.75−5.79 (m, 1H), 2.77−2.82 (q, J = 7.1, 2H), 2.55 (s, 3H), 2.05−2.20 (m, 2H), 1.83−1.95 (m, 2H), 1.68−1.78 (m, 2H), 1.50−1.63 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); *m/z* 290.1 (M + 1).

8-Cyclopentyl-2-methylsulfanyl-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (60): Starting from **54** (0.240 g, 0.786 mmol), 0.255 g (99%) of **60** was obtained according to the method described for the synthesis of **55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.02 (s, 1H), 5.79−5.84 (m, 1H), 2.58 (s, 3H), 2.14−2.19 (m, 2H), 1.59−1.95 (m, 6H); *m/z* 330.1 (M + 1).

8-Cyclopentyl-5,6-dimethyl-2-methylsulfanyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (61): Under nitrogen, NaH (0.63 g, 26.3 mmol, 60% dispersion in mineral oil) was suspended in THF (25 mL) and triethyl 2-phosphonopropionate (5.64 mL, 26.3 mmol) was added inducing a small exotherm. To this mixture was added compound **50** (3.0 g, 11.9 mmol) a solid, and the reaction mixture was heated to reflux for 36 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$, the salts were filtered and the filtrate was concentrated in vacuo to give **61** as a dark orange oil (0.425 g, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 5.96−6.00 (m, 1H), 2.59 (s, 3H), 2.38 (s, 3H), 2.27−2.32 (m, 2H), 2.18 (s, 3H), 2.04−2.08 (m, 2H), 1.82−1.85 (m, 2H), 1.64−1.68 (m, 2H); *m/z* 290.0 (M + 1).

8-Cyclopentyl-6-fluoro-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (62): Sodium hydride (771 mg, 19.3 mmol) was suspended in dry THF (20 mL), and the mixture was cooled to 0 °C in an ice bath. Triethyl 2-fluoro-2-phosphonoacetate (3.9 mL, 19.3 mmol) was added dropwise with stirring, and the solution was stirred at room temperature for 30 min. A solution of **50** (2.27 g, 9.05 mmol) in dry THF (40 mL) was added via a cannula, then the reaction mixture was left to stir at room-temperature overnight. The reaction was quenched by the addition of water (0.5 mL), then the THF was evaporated in vacuo. The residue was partitioned between EtOAc and saturated aqueous sodium chloride. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$. After removal of the drying agent and evaporation of the solvent, the crude product was purified using silica gel chromatography (4:1 to 7:3, hexanes:EtOAc) to give **62** as a colorless solid (0.61 g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 5.81−5.85 (m, 1H), 2.55 (s, 3H), 2.46 (s, 3H), 2.17 (br s, 2H), 1.95 (br s, 2H), 1.79 (br s, 2H), 1.60 (br s, 2H); *m/z* 294.1 (M + 1).

6-Bromo-8-cyclopentyl-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (63): Compound **55** (1.0 g, 3.64 mmol) was dissolved in dry DMF (15 mL) and *N*-bromosuccinimide (0.97 g, 5.45 mmol) was added followed by benzoylperoxide (0.13 g, 0.5 mmol). The resulting solution was stirred overnight at room temperature then partitioned between EtOAc and water. The organic layer was washed with water and saturated aqueous NaCl, then dried over $MgSO_4$. Removal of the drying agent and evaporation of the solvent gave **63** (0.86 g, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 6.01−6.06 (m, 1H), 2.61 (s, 6H), 2.24−2.29 (m, 2H), 2.07−2.11 (m, 2H), 1.85−1.88 (m, 2H), 1.64−1.68 (m, 2H); *m/z* 356.1 (M + 1).

8-Cyclopentyl-6-iodo-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (64): Compound **55** (7.03 g, 25.51 mmol) and iodine (7.12 g, 28.06 mmol) were dissolved in CH_2Cl_2 (210 mL). The apparatus was covered with aluminum foil and the solution stirred at room temperature for 30 min. Bis(trifluoroacetoxy)iodobenzene (13.16 g, 30.61 mmol) was added in one portion and the dark purple solution heated to 37 °C for 2 h and then cooled to room temperature for 2 h. 50% Aqueous (w/v) sodium thiosulfate (114 mL) was added to the reaction mixture, and the dark purple mixture became red, then blue, red and finally yellow within 1 min. The two phases were stirred for 30 min and then separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL), and the combined organic phases were washed with 50% aqueous (w/v) sodium thiosulfate (50 mL) and water (4 × 130 mL). The organic phase was dried, filtered and concentrated in vacuo to give a crude product (15.85 g) which was purified using silica gel chromatography (15% heptane/CH_2Cl_2) to give **64** as a white solid (5.94 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 6.00−6.12 (m, 1H), 2.70 (s, 3H), 2.62 (s, 3H), 2.24−2.30 (m, 2H), 2.08−2.15 (m, 2H), 1.81−1.93 (m, 2H), 1.57−1.75 (m, 2H); *m/z* 402 (M + 1).

6-Acetyl-8-cyclopentyl-5-methyl-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (65): Under an argon atmosphere, Compound **63** (1.29 g, 3.64 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (0.5 g, 0.8 mmol) were added to toluene (8 mL). (1-Ethoxyvinyl)tributyltin (3.5 g, 20 mmol) was added over 5 h at 110 °C. The mixture was taken up into EtOAc and extracted with 6 N HCl. The pH of the aqueous phase was adjusted to pH 7 by addition of 50% NaOH solution then extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a solid (1.2 g). This solid was purified using silica gel chromatography on a Biotage 12m column eluted with a gradient of hexanes to 10% ethyl acetate in hexanes. The combined fractions were evaporated to a solid and crystallized from diethyl ether giving **65** (0.6 g, 52%) as a white solid. ^{1}H NMR (400 MHz, CDCl3) δ 8.78 (s, 1H), 5.90 (m, 1H), 2.61 (s, 3H), 2.53 (s, 3H), 2.35 (s, 3H), 2.28−2.37 (m, 2H), 2.03−2.06 (m, 2H), 1.84−1.87 (m, 2H), 1.64−1.69 (m, 2H); *m/z* 318.0 (M + 1).

8-Cyclopentyl-2-methanesulfinyl-5-methyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (66): Comopund **55** (2.57 g, 8.88 mmol) was dissolved in CH_2Cl_2 (50 mL), and 2-benzylsulfonyl-3-phenyl-oxaziradine was added (3.02 g, 11.5). The reaction mixture was stirred for 16 h. The solution was evaporated in vacuo to give an orange oil. EtOAc was added and a white precipitate formed. This precipitate was filtered and washed with hexanes to yield **66** as a white solid (2.12 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 6.60 (s, 1H), 5.86−5.95 (m, 1H), 2.94 (s, 3H), 2.48 (s, 3H), 2.02−2.22 (m, 4H), 1.85−1.90 (m, 2H), 1.66−1.73 (m, 2H); *m/z* 292.1 (M + 1).

8-Isopropyl-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (67): Starting from 57 (0.200 g, 0.800 mmol), 0.125 g (61%) of 67 was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz,

DMSO-d_6) δ 9.18 (s, 1H), 6.23 (s, 1H), 5.60−5.68 (m, 1H), 2.89 (s, 3H), 2.45(s, 3H), 1.50−1.52 (d, J = 7.0, 6H); *m/z* 266.0 (M + 1).

8-(1-Ethyl-propyl)-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (68): Starting from **58** (1.00 g, 3.60 mmol), 0.80 g (75%) of 68 was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, DMSO-d_6)—a mixture of rotamers, δ 9.20 (s, 1H), 6.68 (s, 1/2H), 6.61 (s, 1/2H), 5.48−5.55 (m, 1/2H), 5.08−5.15 (m, 1/2H), 2.86 (s, 3H), 2.46 (s, 3H), 2.05−2.20 (m, 2H), 1.80−1.95 (m, 2H), 0.64−0.67 (m, 6H); *m/z* 294.0 (M + 1).

8-Cyclopentyl-5-ethyl-2-methanesulfinyl-8*H*-pyrido-[2,3-*d*]pyrimidin-7-one (69): Starting from **59** (2.57 g, 8.88 mmol), 2.12 g (78%) of **69** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 6.60 (s, 1H), 5.76−5.85 (m, 1H), 2.87−2.91 (m, 5H), 2.15−2.20 (m, 2H), 1.98−2.10 (m, 2H), 1.77−1.82 (m, 2H), 1.52−1.60 (m, 2H), 1.19−1.23 (t, J = 7.3 Hz, 3H); *m/z* 306.1 (M + 1).

8-Cyclopentyl-2-methanesulfinyl-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (70): Starting from **60** (0.250 g, 0.785 mmol), 0.185 g (68%) of **70** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.31 (s, 1H), 5.80−5.88 (m, 1H), 2.92 (s, 3H), 2.17−2.21 (m, 2H), 2.07−2.10 (m, 2H), 1.83−1.85 (m, 2H), 1.60−1.63 (m, 2H); *m/z* 330.1 (M + 1).

8-Cyclopentyl-2-methanesulfinyl-5,6-dimethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (71): Starting from **61** (0.420 g, 1.45 mmol), 0.267 g (60%) of **71** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 5.85−5.93 (m, 1H), 2.87 (s, 3H), 2.45 (s, 3H), 2.13−2.20 (m, 2H), 2.13 (s, 3H), 2.04−2.08 (m, 2H), 1.76−1.85 (m, 2H), 1.57−1.62 (m, 2H); *m/z* 306.1 (M + 1).

8-Cyclopentyl-6-fluoro-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (72): Starting from **62** (6.00 g, 20.5 mmol), 5.10 g (81%) of **72** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 5.94−6.03 (1H, m), 2.95 (s, 3H), 2.46 (s, 3H), 2.21−2.24 (m, 2H), 2.12 (br s, 2H), 1.92−1.95 (m, 2H), 1.66−1.70 (m, 2H); *m/z* 310.0 (M + 1).

6-Bromo-8-cyclopentyl-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (73): Starting from **63** (40.3 g, 114 mmol), 39.8 g (94%) of **73** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 6.04−6.09 (m, 1H), 2.97 (s, 3H), 2.70 (s, 3H), 2.11−2.24 (m, 4H), 1.92−1.96 (m, 2H), 1.67−1.72 (m, 2H); *m/z* 372.1 (M + 1).

8-Cyclopentyl-6-iodo-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (74): Starting from **64** (1.51 g, 3.76 mmol), 1.16 g (74%) of **74** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 6.02−6.14 (m, 1H), 2.98 (s, 3H), 2.80 (s, 3H), 2.06−2.27 (m, 4H), 1.87−2.00 (m, 2H), 1.63−1.72 (m, 2H); *m/z* 418 (M + 1).

6-Acetyl-8-cyclopentyl-2-methanesulfinyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (75): Starting from **65** (0.6 g, 1.89 mmol), 0.51 g (81%) of **75** was obtained according to the method described for the synthesis of **66**: ^{1}H NMR (400 MHz, CDCl3) δ 9.08 (s, 1H), 5.94 (m, 1H), 2.96 (s, 3H), 2.54 (s, 3H), 2.43(s, 3H), 2.21−2.26 (m, 2H), 2.09−2.20 (m, 2H), 1.79−1.92 (m, 2H), 1.64−1.70 (m, 2H); *m/z* 333.1 (M + 1).

6-Chloro-2-chloromethanesulfinyl-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (76). Compound **55** (2.00 g, 7.27 mmol) and *N*-chlorosuccinimide (1.46 g, 10.9 mmol, 1.5 equivalents) were suspended in DMF (30 mL), and benzoyl peroxide (0.35 g, 1.45 mmol) was added, resulting in a color change from white to orange. Additional DMF (20 mL) was added, and the resulting solution was stirred at room temperature under nitrogen. Additional *N*-chlorosuccinimide was added after 1 day (0.65 g) and after 3 days (1.25 g) along with additional benzoyl peroxide (~50 mg after 1 day and 0.29 g after 3 days). After stirring for a total of 5 days, the solvent was evaporated and replaced by 20% ethyl acetate in hexanes. The resulting solid was collected by filtration. Chromatography on silica gel, eluting with 30−50% EtOAc in hexanes, gave **76** (0.58 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 5.98−6.08 (m, 1H), 4.86 (AB q, J = 44, 14 Hz, 2H), 2.04−2.44 (m, 4H), 1.86−2.00 (m, 2H), 1.62−1.76 (m, 2H); *m/z* 362 (M + 1), 360 (M + 1).

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (17): Compound **66** (0.70 g, 2.4 mmol) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.70 g, 2.52 mmol) were dissolved in DMSO (8 mL) and heated to 100 °C for 24 h. The reaction mixture was then cooled to room temperature and partitioned between EtOAc and water, the layers were separated and the organic layer was dried over $MgSO_4$. The inorganic salts were filtered, and the solvent was evaporated in vacuo to yield a crude solid that was further purified using silica gel chromatography (EtOAc and hexanes) and/or trituration with MeCN and water to yield **17** as a yellow solid (0.549 g, 45%): mp 100−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.43−7.45 (d, J = 9.1 Hz, 2H), 7.18 (s, 1H), 6.93−6.95 (d, J = 8.8 Hz, 2H), 6.21 (s, 1H), 5.78−5.83 (m, 1H), 3.57−3.59 (m, 4H), 3.08−3.13 (m, 4H), 2.33 (s, 3H), 2.24−2.31 (m, 2H), 1.78−1.90 (m, 4H), 1.58−1.62 (m, 2H), 1.46 (s, 9H); Exact Mass: Calculated ($C_{28}H_{36}N_6O_3$ + H) 505.2927, found 505.2936 (M + 1); HPLC purity 98.5%.

8-Cyclopentyl-2-(4-morpholin-4-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (2): Starting from 8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.250 g, 1.00 mmol), 0.51 g (32%) of **2** was obtained according to the method described for the synthesis of **17**: mp 239−241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.68 (s, 1H), 7.50−7.54 (d, J = 8.3 Hz, 2H), 6.96−7.00 (d, J = 8.6 Hz, 2H), 6.68 (s, 1H), 5.76−5.81 (m, 1H), 3.26−3.35 (m, 4H), 3.10−3.23 (m, 4H), 2.12−2.21 (m, 2H), 1.75−1.92 (m, 4H), 1.47−1.60 (m, 2H); *m/z* 392.1 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$·0.25H_2O) C, H, N.

8-Cyclopentyl-2-(4-piperidin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (3): Starting from 8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.171 g, 0.617 mmol), 0.157 g (65%) of **3** was obtained according to the method described for the synthesis of **17**: mp 198−199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (br s, 1H), 8.68 (s, 1H), 7.71−7.73 (d, J = 9.2, 1H), 7.47−7.49 (d, J = 9.2, 2H), 6.90−6.92 (d, J = 9.2, 2H), 6.26−6.28 (d, J = 9.2, 1H), 5.78−5.83 (m, 1H), 3.04−3.11 (m, 4H), 2.20−2.29 (m, 2H), 1.48−1.95 (m, 12H); *m/z* 389.9 (M + 1); Anal. ($C_{23}H_{27}N_5O_1$) C, H, N.

8-Cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (6): Starting from **66** (0.200 g, 0.650 mmol), 0.054 g (20%) of **6** was obtained according to the method described for the synthesis of **17**: mp 211−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (br s, 1H), 8.71 (s, 1H), 7.45−7.47 (d, J = 8.8 Hz, 2H), 6.86−6.88 (d, J = 8.8 Hz, 2H), 6.10 (s, 1H), 5.76−5.81 (m, 1H), 3.00−3.08 (m, 4H), 2.40−2.50 (m, 4H), 2.31 (s, 3H), 2.17 (s, 3H), 2.15−2.22 (m, 2H), 1.78−1.90 (m, 2H), 1.65−1.75 (m, 2H), 1.47−1.60 (m, 2H); Exact Mass: Calculated ($C_{24}H_{30}N_6O$ + H) 419.2559, found 419.2569 (M + 1); HPLC purity 96.7%.

8-Cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (7): Starting from **66** (0.200 g, 0.686 mmol), 0.031 g (11%) of **7** was obtained according to the method described for the synthesis of **17**: mp 227−229; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.72 (s, 1H), 7.48−7.51 (d, J = 8.8 Hz, 2H), 6.88−6.90 (d, J = 9.1 Hz, 2H), 6.11 (s, 1H), 5.75−5.80 (m, 1H), 3.69−3.72 (m, 4H), 3.00−3.04 (m, 4H), 2.31 (s, 3H), 2.15−2.24 (m, 2H), 1.80−1.92 (m, 2H), 1.65−1.75 (m, 2H), 1.45−1.58 (m, 2H); *m/z* 406.2 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$) C, H, N.

8-Cyclopentyl-5-methyl-2-(4-piperidin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (8): Starting from **66** (0.161 g, 0.55 mmol), 0.083 g (37%) of **8** was obtained according to the method described for the synthesis of **17**: mp 205−207; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.40−7.51 (m, 2H), 6.90−7.10 (m, 3H), 6.23 (s, 1H), 5.78−5.87 (m, 1H), 3.14−

3.22 (m, 4H), 2.35 (s, 3H), 2.25−2.33 (m, 2H), 1.50−1.98 (m, 12H); *m/z* 404.2 (M + 1); Anal. ($C_{25}H_{29}N_5O_1 \cdot 0.41C_2H_3N_1$) C, H, N.

8-Cyclopentyl-2-{4-[4-(3-hydroxy-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (9): Starting from **66** (0.600 g, 2.06 mmol) and **102** (0.483 g, 2.06 mmol), 0.510 g (54%) of **9** was obtained according to the method described for the synthesis of **17**: mp 180−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.71 (s, 1H), 7.43−7.45 (d, J = 9.3 Hz, 2H), 6.86−8.89 (d, J = 8.5 Hz, 2H), 6.10 (s, 1H), 5.76−5.81 (m, 1H), 4.31−4.35 (m, 1H), 3.55−3.59 (m, 2H), 3.34−3.38 (m, 2H), 2.50−2.56 (m, 2H), 2.31 (s, 3H), 2.15−2.23 (m, 2H), 1.75−1.92 (m, 2H), 1.63−1.85 (m, 4H), 1.13−1.60 (m, 8H); *m/z* 462.2 (M + 1); Anal. ($C_{27}H_{35}N_5O_2$) C, H, N.

4-[4-(8-Cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (77): Starting from 8-cyclopentyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (1.00 g, 3.61 mmol), 1.00 g (56%) of **77** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.40−7.45 (m, 3H), 7.13 (br s, 1H), 6.93−6.95 (m, 2H), 6.36−6.39 (d, J = 9.3 Hz, 1H), 5.78−5.83 (m, 1H), 3.56−3.61 (m, 4H), 3.05−3.12 (m, 4H), 2.16−2.22 (m, 2H), 1.82−1.93 (m, 2H), 1.62−1.68 (m, 2H), 1.48−1.53 (m, 2H), 1.47 (s, 9H); *m/z* 491.1 (M + 1).

4-[4-(8-Cyclopentyl-5-ethyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (78): Starting from **69** (0.200 g, 0.654 mmol), 0.160 g (47%) of **78** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.78 (s, 1H), 7.48−7.50 (d, J = 9.0 Hz, 2H), 6.90−6.92 (d, J = 8.0 Hz, 2H), 6.09 (s, 1H), 5.78−5.83 (m, 1H), 3.41−3.46 (m, 4H), 2.98−3.04 (m, 4H), 2.71−2.76 (q, J = 7.6 Hz, 2H), 2.16−2.22 (m, 2H), 1.82−1.93 (m, 2H), 1.62−1.68 (m, 2H), 1.48−1.53 (m, 2H), 1.38 (s, 9H), 1.11−1.18 (m, 3H); *m/z* 519.3 (M + 1).

4-[4-(8-Cyclopentyl-7-oxo-5-trifluoromethyl-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (79): Starting from **70** (0.065 g, 0.188 mmol), 0.066 g (63%) of **79** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.46−7.49 (d, J = 9.1 Hz, 2H), 6.92−6.94 (d, J = 8.8 Hz, 2H), 6.66 (s, 1H), 5.78−5.83 (m, 1H), 3.41−3.46 (m, 4H), 3.00−3.08 (m, 4H), 2.13−2.18 (m, 2H), 1.74−1.90 (m, 4H), 1.52−1.58 (m, 2H), 1.38 (s, 9H); *m/z* 559.3 (M + 1).

4-[4-(8-Isopropyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (80): Starting from **67** (0.120 g, 0.452 mmol), 0.040 g (19%) of **80** was obtained according to the method described for the synthesis of **17**: *m/z* 479.4 (M + 1).

4-{4-[8-(1-Ethyl-propyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic Acid *tert*-Butyl Ester (81): Starting from **68** (0.425 g, 1.44 mmol), 0.285 g (39%) of **81** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, DMSO-d_6)—a mixture of rotamers δ 9.80 (s, 1/2H), 9.58 (s, 1/2H), 8.72 (s, 1H), 7.46−7.59 (m, 2H), 6.86−6.95 (m, 2H), 6.16 (s, 1/2H), 6.08 (s, 1/2H), 5.38−5.45 (m, 1/2H), 5.04−5.13 (m, 1/2H), 3.40−3.50 (m, 4H), 2.95−3.08 (m, 4H), 2.33 (s, 3H), 2.11−2.16 (m, 2H), 1.78−1.90 (m, 2H), 1.46 (s, 9H), 0.60−0.78 (m, 6H); *m/z* 507.4 (M + 1).

2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (16): Starting from **66** (0.100 g, 0.343 mmol), 0.049 g (32%) of **16** was obtained according to the method described for the synthesis of **17**: mp 261−263 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (br s, 1H), 8.73 (s, 1H), 7.50−7.52 (d, J = 8.5 Hz, 2H), 6.91−6.94 (d, J = 8.9 Hz, 2H), 6.12 (s, 1H), 5.78−5.83 (m, 1H), 3.73−3.80 (m, 4H), 3.00−3.08 (m, 4H), 2.33 (s, 3H), 2.18−2.23 (m, 2H), 2.01 (s, 3H), 1.80−1.88 (m, 2H), 1.65−1.75 (m, 2H), 1.50−1.58 (m, 2H); Exact Mass: Calculated ($C_{25}H_{30}N_6O_2$ + H) 447.2508, found 447.2496 (M + 1); HPLC purity 99.3%.

8-Cyclopentyl-2-[4-(3-hydroxy-pyrrolidin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (18): Starting from **66** (0.600 g, 2.06 mmol), 0.510 g (54%) of **18** was obtained according to the method described for the synthesis of **17**: mp 225−226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.68 (s, 1H), 7.38 (d, J = 7 Hz, 2H), 6.43−6.45 (d, J = 8 Hz, 2H), 6.07 (s, 1H), 5.75 (br s, 1H), 4.90 (s, 1H), 4.35 (s, 1H), 3.20−3.40 (m, 3H), 2.98−3.00 (d, J = 10 Hz, 1H), 2.30 (s, 3H), 2.12−2.24 (m, 2H), 1.90−2.10 (m, 2H), 1.60−1.90 (m, 4H), 1.45−1.60 (m, 2H); Exact Mass: ($C_{23}H_{27}N_5O_2$ + H) 406.2243, found 406.2239 (M + 1); HPLC purity 91%.

{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-pyrrolidin-3-yl}-carbamic Acid *tert*-Butyl Ester (82): Starting from **66** (0.150 g, 0.515 mmol), 0.100 g (38%) of **82** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.33−7.36 (d, J = 9.0 Hz, 2H), 7.13 (br s, 1H), 6.53−6.56 (d, J = 9.1 Hz, 2H), 6.18 (s, 1H), 5.75−5.83 (m, 1H), 4.75−4.80 (br m, 1H), 4.34−4.39 (m, 1H), 3.88 − 3.93 (m, 1H), 3.53−3.56 (m, 2H), 3.41−3.46 (m, 2H), 3.27−3.33 (m, 2H), 3.15−3.20 (m, 2H), 2.31 (s, 3H), 2.21−2.31 (m, 2H), 1.78−1.95 (m, 4H), 1.55−1.60 (m, 2H), 1.43 (s, 9H); *m/z* 505.2 (M + 1).

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-[1,4]diazepane-1-carboxylic Acid *tert*-Butyl Ester (83): Starting from **66** (0.400 g, 1.52 mmol), 0.230 g (29%) of **83** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.29 (br s, 2H), 7.16 (br s, 1H), 6.65 (br s, 2H), 6.16 (br s, 1H), 5.74 (br t, J = 8 Hz, 1H), 3.52 (br s, 6H), 3.26 (br s, 1H), 3.16 (br s, 1H), 2.28 (s, 3H), 2.24 (br s, 2H), 1.93 (br s, 2H), 1.74−1.80 (m, 4H), 1.51 (br s, 2H), 1.39 (s, 4.5H), 1.34 (s, 4.5H); *m/z* 519.3 (M + 1).

8-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenylamino}-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (21): Starting from **66** (0.200 g, 0.690 mmol), 0.050 g (31%) of **21** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.74 (s, 1H), 7.47−7.49 (d, J = 9 Hz, 2H), 6.89 (d, J = Hz, 2H), 6.13 (s, 1H), 5.70−5.84 (m, 1H), 4.44 (s, 1H), 3.50−3.52 (dd, J = 6, 12 Hz, 2H), 3.07 (s, 4H), 2.55 (s, 4H), 2.43 (s, 2H), 2.33 (s, 3H), 2.10−2.28 (m, 2H), 1.60−1.90 (m, 4H), 2.42−2.60 (m, 2H); *m/z* 449.3 (M + 1); Anal. ($C_{25}H_{32}N_6O_2 \cdot 0.26H_2O$) C, H, N.

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-2,6-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (84): Starting from **66** (0.169 g, 0.580 mmol), 0.050 g (16%) of **84** was obtained according to the method described for the synthesis of **17**: *m/z* 533.4 (M + 1).

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-2,2-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (85): Starting from **66** (0.150 g, 0.515 mmol), 0.100 g (36%) of **85** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (br s, 1H), 8.70 (s, 1H), 7.40−7.43 (d, J = 7.8 Hz, 2H), 6.71−6.73 (d, J = 8.5 Hz, 2H), 6.09 (s, 1H), 5.76−5.81 (m, 1H), 3.60−3.65 (m, 2H), 3.20 − 3.28 (m, 4H), 2.30 (s, 3H), 2.13−2.18 (m, 2H), 1.60−1.90 (m, 4H), 1.45−1.53 (m, 2H), 1.38 (s, 9H), 1.31 (s, 6H); *m/z* 533.4 (M + 1).

4-[2-Chloro-4-(8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (86): Starting from **66** (0.150 g, 0.515 mmol), 0.095 g (34%) of **86** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92 (s, 1H), 7.35 (br s, 1H), 7.23 (br s, 1H), 6.96−6.99 (d, J = 8.6 Hz, 2H), 6.24 (s, 1H), 5.79−5.83 (m, 1H), 3.57−3.61 (m, 4H), 2.93−2.99 (m, 4H), 2.35 (s, 3H), 2.24−2.35 (m, 2H), 1.92−1.99 (m, 2H), 1.80−1.86 (m, 2H), 1.60−1.65 (m, 2H), 1.46 (s, 9H); *m/z* 539.2 (M + 1).

4-[4-(8-Cyclopentyl-5,6-dimethyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (87): Starting from **66** (0.060 g, 0.196 mmol), 0.030 g (29%) of **87** was obtained according to the method described for the synthesis of **17**: *m/z* 519.3 (M + 1).

4-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (88). Starting from **72** (0.300 g, 0.971 mmol), 0.230 g (45%) of **88** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.44−7.46 (d, J = 8 Hz, 2H), 7.10 (br s, 1H), 6.98 (br s, 2H), 5.84−5.88 (m, 1H), 3.60 (br s, 4H), 3.11 (br s, 4H), 2.34 (s, 3H), 2.27−2.31 (m, 2H), 1.96 (br s, 2H), 1.83 (br s, 2H), 1.60−1.62 (m, 2H), 1.47 (s, 9H); *m/z* 523.2 (M + 1).

4-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (89): Starting from **73** (0.300 g, 0.809 mmol), 0.410 g (81%) of **89** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.55 (br s, 1H), 7.44−7.46 (d, J = 8.9 Hz, 2H), 6.91−6.94 (d, J = 8.6 Hz, 2H), 5.90−5.96 (m, 1H,), 3.55−3.58 (m, 4H), 3.06−3.13 (m, 4H), 2.53 (s, 3H), 2.20−2.25 (m, 2H), 1.90−1.98 (m, 2H), 1.78−1.84 (m, 2H), 1.55−1.60 (m, 2H),1.44 (s, 9H); *m/z* 585.0 (M + 1).

4-[4-(8-Cyclopentyl-6-iodo-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (90): Starting from **74** (0.32 g, 0.766 mmol), 0.40 g (83%) of **90** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.46−7.48 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 6.94−6.96 (d, J = 8.9 Hz, 2H), 5.96−5.98 (p, J = 8.8 Hz, 1H,), 3.58−3.61 (m, 4H), 3.10−3.13 (m, 4H), 2.66 (s, 3H), 2.20−2.32 (m, 2H), 1.94−2.08 (m, 2H), 1.76−1.90 (m, 2H), 1.58−1.68 (m, 2H), 1.49 (s, 9H); *m/z* 631 (M + 1).

4-[4-(6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (91): Starting from **75** (0.493 g, 1.48 mmol), 0.294 g (36%) of **91** was obtained according to the method described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.7 (s, 1H), 7.43−7.46 (br m, 2H), 7.39−7.42 (br m, 1H), 7.03−7.07 (br m, 2H), 5.80−5.85 (m, 1H), 3.63−3.66 (m, 4H), 3.12−3.17 (m, 4H), 2.52 (s, 3H), 2.34 (s, 3H), 2.25−2.30 (m, 2H), 1.88−1.95 (m, 2H), 1.79−1.83 (m, 2H), 1.57−1.64 (m, 2H), 1.47 (s, 9H); *m/z* 547.1 (M + 1).

4-[4-(6-Chloro-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (92). Compound **76** (0.2 g, 0.56 mmol) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.309 g, 1.1 mmol) were combined in dry DMSO (3 mL) and heated to 80 °C over 1 h. After cooling to room temperature, EtOAc was added and the pale green precipitate was removed by filtration. The filtrate was washed twice with water, then once with saturated aqueous NaCl solution and dried over $MgSO_4$. Following removal of the drying agent and evaporation of the solvent, the crude product was purified by column chromatography on silica gel eluting with 30−50% ethyl acetate in hexanes to give **92** as a yellow solid (110 mg, 36%); *m/z* 541.2 (M + 1), 539.2 (M + 1).

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-6-trimethylsilanyl-ethynyl-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (93): Compound **89** (1.4 g, 1.78 mmol) was dissolved in THF (20 mL) to which were successively added CuI (0.032 g, 0.17 mmol), *n*-butylamine (1.24 g, 17 mmol) and $Pd(PPh_3)_4$ (0.098 g, 0.17 mmol). The reaction was sparged with N_2 for 10 min after which TMS-acetylene was added and the reaction mixture refluxed for 2 h. More TMS-acetylene was added and again refluxed for 2 h. The solvent was removed in vacuo and the crude dissolved in EtOAc and washed with water (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL) and saturated aqueous NaCl. The organic layer was then dried over $MgSO_4$, the salts were filtered and the solvent was evaporated in vacuo to give a crude material. This was further purified by silica gel chromatography eluting with EtOAc and hexanes to give **93** as a yellow foam (0.160 g, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.19−7.21 (d, J = 8.8 Hz, 2H), 7.08 (br s, 1H), 6.66−6.68 (d, J = 8.8 Hz, 2H), 5.58−5.61 (m, 1H,), 3.31−3.35 (m, 4H), 2.83−2.87 (m, 4H), 2.29 (s, 3H), 2.00−2.10 (m, 2H), 1.70−1.78 (m, 2H), 1.48−1.56 (m, 2H), 1.26−1.34 (m, 2H), 1.21 (s, 9H), 0.00 (s, 9H); *m/z* 601.1 (M + 1).

4-[4-(8-Cyclopentyl-6-ethyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic Acid *tert*-Butyl Ester (95): Compound **93** (0.150 g, 0.25 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (0.076 g, 0.55 mmol) and stirred at room temprature for 16 h. The solvent was evaporated and the crude material dissolved in EtOAc, washed with water and saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo to give 4-[4-(8-cyclopentyl-6-ethynyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**94**) as a yellow solid (0.130 g, 99%). *m/z* 529.1 (M + 1). Compound **94** (0.05 g, 0.095 mmol) was dissolved in EtOH (20 mL) to which 5% Pd/C (0.050 g) was added. This mixture was treated to 44 PSI under an H_2 atmosphere for 3 days. The catalyst was filtered and the solvent evaporated to give **95** (0.050 g, 38%) as a green-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.46−7.48 (d, J = 8.8 Hz, 2H), 6.95−6.97 (d, J = 8.8 Hz, 2H), 5.80−5.89 (m, 1H), 3.58−3.62 (m, 4H), 3.10−3.14 (m, 4H), 2.60−2.67 (m, 2H), 2.35 (s, 3H), 2.24−2.30 (m, 2H), 1.82−1.92 (m, 2H), 1.75−1.82 (m, 2H), 1.58−1.63 (m, 2H), 1.03−1.10 (m, 3H); *m/z* 533.3 (M + 1).

2-[4-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (96): Compound **89** (2.0 g, 3.4 mmol) was dissolved in EtOH (75 mL) to which Hunig's base (1.5 mL, 8 mmol), $Pd(OAc)_2$ and DPPP (0.424 g, 1.03 mmol) were added then subjected to 500 psi of CO at 100 °C for 30 h. The reaction mixture was diluted with EtOAc and washed with H_2O, sat. $NaHCO_3$ and saturated aqueous NaCl. Then dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow solid which was recrystallized to give **96** (1.23 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.42−7.46 (d, J = 8.8 Hz, 2H), 7.26 (br s, 1H), 6.93−6.95 (d, J = 7.3 Hz, 2H), 5.78−5.85 (m, 1H), 4.35−4.41 (q, J = 7.1 Hz, 2H), 3.58−3.62 (m, 4H), 3.10−3.14 (m, 4H), 2.34 (s, 3H), 2.24−2.30 (m, 2H), 1.82−1.92 (m, 2H), 1.75−1.82 (m, 2H), 1.58−1.63 (m, 2H), 1.34−1.37 (t, J = 7.3 Hz, 3H); *m/z* 577.1 (M + 1).

2-[4-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Methyl Ester (97): Starting from **75** (0.300 g, 0.510 mmol), 0.100 g (35%) of **97** was obtained according to the method described for the synthesis of 96: *m/z* 563.2 (M + 1).

2-[4-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (98). Compound **96** (0.97 g, 1.7 mmol) and 1.0 N NaOH (5.1 mL) were added to EtOH (5 mL) and THF (5 mL) and refluxed for 16 h. The solvent was removed in vacuo, the solid washed with ether, then acidified with 1 N HCl (5.1 mL) and extracted with EtOAc. This solution was dried over $MgSO_4$, filtered and concentrated in vacuo to give a solid that was recrystallized from EtOAc and hexanes to provide **98** (0.41 g, 44%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.00 (br s, 1H), 9.03 (s, 1H), 7.46−7.50 (m, 2H), 7.00−7.04 (m, 2H), 5.91−5.99 (m, 1H), 4.58−4.63 (m, 2H), 3.58−3.62 (m, 4H), 3.10−3.14 (m, 4H), 2.99 (s, 3H), 2.24−2.30 (m, 2H), 1.82−2.03 (m, 4H), 1.58−1.63 (m, 2H), 1.47 (s, 9H); *m/z* 549.2 (M + 1).

8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (10): Method A: Compound **17** was dissolved in dioxane (4 mL) and 6 N HCl (4 mL) and stirred for 1.5 h. The solvent was evaporated in vacuo to give **10** as a yellow solid (0.075 g, 58%): ^{1}H NMR (400 MHz,

DMSO-d_6) δ 9.87 (s, 1H), 9.36 (s, 2H), 8.80 (s, 1H), 7.53−7.55 (d, J = 8.8 Hz, 2H), 6.99−7.02 (d, J = 9.0 Hz, 2H), 6.14 (s, 1H), 5.75−5.80 (m, 1H), 3.26−3.35 (m, 4H), 3.10−3.23 (m, 4H), 2.32 (s, 3H), 2.15−2.24 (m, 2H), 1.78−1.92 (m, 2H), 1.65−1.75 (m, 2H), 1.47−1.60 (m, 2H); *m/z* 405.1 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$·2.75HCl) C, H, N.

Method B: Compound **17** (0.280 g, 0.555 mmol) was dissolved in of dichloromethane (10 mL) to which trifluoroacetic acid (5 mL) was added and stirred at room temperature for 15 h. The solvent was evaporated, and the solid isolated from diethyl ether to give **10** as a fluffy gray solid (0.343 g, 85%): Anal. ($C_{23}H_{28}N_6O_1$·2.8$C_2H_1O_2F_3$·0.35H_2O) C, H, N.

8-Cyclopentyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (5): Starting from **77** (7.95 g, 16.2 mmol), 4.44 g (57%) of **5** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (br s, 1H), 9.34 (br s, 2H), 8.69 (s, 1H), 7.70−7.72 (d, J = 9.3 Hz, 2H), 7.53−7.55 (d, J = 8.8 Hz, 2H), 6.99−7.02 (d, J = 5.9 Hz, 2H), 6.25−6.27 (d, J = 9.3 Hz, 2H), 5.75−5.80 (m, 1H), 3.30−3.38 (m, 4H), 3.14−3.23 (m, 4H), 2.15−2.22 (m, 2H), 1.72−1.92 (m, 4H), 1.47−1.60 (m, 2H); *m/z* 391.1 (M + 1); Anal. ($C_{22}H_{26}N_6O_1$·2.0HCl·1.1H_2O) C, H, N.

8-Cyclopentyl-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (11): Starting from **78** (0.160 g, 0.308 mmol), 0.128 g (75%) of **11** was obtained according to Method B described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.79 (s, 1H), 8.73 (s, 2H), 7.52−7.54 (d, J = 8.8 Hz, 2H), 6.92−6.96 (d, J = 9.0 Hz, 2H), 6.10 (s, 1H), 5.76−5.83 (m, 1H), 3.20−3.30 (m, 8H), 2.72−2.77 (q, J = 7.6 Hz, 2H), 2.19−2.21 (m, 2H), 1.82−1.91 (m, 2H), 1.62−1.72 (m, 2H), 1.45−1.58 (m, 2H), 1.15−1.19 (t, J = 7.5 Hz, 3H); *m/z* 419.3 (M + 1); Anal. ($C_{24}H_{30}N_6O_1$·1.21$C_2H_1F_3O_2$) C, H, N.

8-Cyclopentyl-2-(4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (12): Starting from **79** (0.066 g, 0.118 mmol), 0.040 g (65%) of **12** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 2H), 8.68 (s, 1H), 7.50−7.54 (d, J = 8.3 Hz, 2H), 6.96−7.00 (d, J = 8.6 Hz, 2H), 6.68 (s, 1H), 5.76−5.81 (m, 1H), 3.26−3.35 (m, 4H), 3.10−3.23 (m, 4H), 2.12−2.21 (m, 2H), 1.75−1.92 (m, 4H), 1.47−1.60 (m, 2H); *m/z* 459.2 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$·1.44HCl·0.11EtOAc) C, H, N.

8-Isopropyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (13): Starting from **80** (0.040 g, 0.083 mmol), 0.038 g (86%) of **13** was obtained according to Method B described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.72 (s, 2H), 7.56−7.58 (d, J = 8.3 Hz, 2H), 6.94−6.96 (d, J = 8.3 Hz, 2H), 6.11 (s, 1H), 5.63−5.70 (m, 1H), 3.18−3.29 (m, 8H), 2.31 (s, 3H), 1.44−1.49 (d, J = 6.4 Hz, 6H); *m/z* 379.2 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$·1.33$C_2H_1F_3O_2$) C, H, N.

8-(1-Ethyl-propyl)-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (14): Starting from **81** (0.260 g, 0.51 mmol), 0.217 g (80%) of **14** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6)—a mixture of rotamers δ 9.89 (s, 1/2H), 9.67 (s, 1/2H), 9.03 (s, 1H), 8.72−8.74 (m, 1H), 7.52−7.62 (m, 2H), 6.95−6.99 (m, 2H), 6.18 (s, 1/2H), 6.08 (s, 1/2H), 5.38−5.42 (m, 1/2H), 5.04−5.13 (m, 1/2H), 3.26−3.35 (m, 4H), 3.19−3.24 (m, 4H), 2.34 (s, 3H), 2.09−2.13 (m, 2H), 1.77−1.87 (m, 2H), 0.63−0.69 (m, 6H); *m/z* 407.2 (M + 1); Anal. ($C_{23}H_{30}N_6O_1$·2.88HCl·0.24$C_4H_8O_1$) C, H, N.

2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (19): Starting from **82** (0.100 g, 0.200 mmol), 0.062 g (54%) of **19** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (br s, 1H), 8.70 (s, 1H), 8.03 (br s, 3H), 7.44−7.48 (d, J = 8.7 Hz, 2H), 6.53−6.56 (d, J = 9.0 Hz, 2H), 6.09 (s, 1H), 5.70−5.83 (m, 1H), 3.88−3.93 (m, 1H), 3.40−3.48 (m, 2H), 3.20−3.26 (m, 2H), 2.31 (s, 3H), 1.95−2.02 (m, 2H), 1.80−1.90 (m, 2H), 1.64−1.78 (m, 2H), 1.48−1.60 (m, 2H); *m/z* 405.2 (M + 1); Anal. ($C_{24}H_{30}N_6O_1$·1.4$C_2H_1O_2F_3$·1.2H_2O) C, H, N.

8-Cyclopentyl-2-(4-[1,4]diazepan-1-yl-phenylamino)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (20): Starting from **83** (0.230 g, 0.444 mmol), 0.090 g (36%) of **20** was obtained according to Method A described for the synthesis of **10**: mp 172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (br s, 1H), 9.13 (br s, 2H), 8.73 (s, 1H), 7.47 (d, J = 8 Hz, 2H), 6.82 (d, J = 8 Hz, 2H), 5.66−5.83 (m, 1H), 3.71 (br s, 2H), 3.50 (br t, J = 5 Hz, 2H), 3.22 (br s, 2H), 3.08 (br s, 2H), 2.33 (s, 3H), 2.02−2.28 (m, 4H), 1.60−1.93 (m, 4H), 1.43−1.60 (m, 2H); *m/z* 419.3 (M + 1); Anal. ($C_{24}H_{30}N_6O_1$·2.22HCl) C, H, N.

8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (22): Starting from **84** (0.050 g, 0.094 mmol), 0.036 g (65%) of **22** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (br s, 1H), 9.40 (br s, 2H), 8.74 (s, 1H), 7.52−7.54 (d, J = 8.7 Hz, 2H), 6.97−6.99 (d, J = 8.2 Hz, 2H), 6.13 (s, 1H), 5.76−5.81 (m, 1H), 3.75−3.81 (m, 2H), 3.25−3.40 (m, 2H), 2.58−2.66 (m, 2H), 2.33 (s, 3H), 2.15−2.21 (m, 2H), 1.80−1.92 (m, 2H), 1.64−1.76 (m, 2H), 1.48−1.57 (m, 2H), 1.26−1.29 (d, J = 6.3 Hz, 6H); *m/z* 433.3 (M + 1); Anal. ($C_{25}H_{32}N_6O_1$·2.25HCl·0.1$C_4H_8O_2$·0.75$C_4H_{10}O_3$) C, H, N.

8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (23): Starting from **85** (0.100 g, 0.188 mmol), 0.065 g (65%) of **23** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (br s, 1H), 9.23 (br s, 2H), 8.74 (s, 1H), 7.52−7.54 (d, J = 9.0 Hz, 2H), 6.94−6.96 (d, J = 8.9 Hz, 2H), 6.14 (s, 1H), 5.76−5.81 (m, 1H), 3.20−3.31 (m, 4H), 3.10 (s, 2H), 2.33 (s, 3H), 2.15−2.21 (m, 2H), 1.80−1.92 (m, 2H), 1.65−1.80 (m, 2H), 1.47−1.60 (m, 2H), 1.38 (s, 6H); *m/z* 433.3 (M + 1); Anal. ($C_{25}H_{32}N_6O_1$·2.0HCl·0.1$C_4H_8O_2$·0.25$C_4H_{10}O_3$) C, H, N.

2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (24): Starting from **86** (0.095 g, 0.176 mmol), 0.059 g (58%) of **24** was obtained according to Method B described for the synthesis of **10**: mp 234−237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (br s, 1H), 8.80 (s, 1H), 8.74 (br s, 1H), 8.07 (s, 1H), 7.44−7.46 (d, J = 9.3 Hz, 1H), 7.15−7.18 (d, J = 8.8 Hz, 1H), 6.18 (s, 1H), 5.78−5.85 (m, 1H), 3.18−3.22 (m, 4H), 3.05−3.12 (m, 4H), 2.34 (s, 3H), 2.18−2.21 (m, 2H), 1.85−1.92 (m, 2H), 1.65−1.75 (m, 2H), 1.48−1.56 (m, 2H); *m/z* 439.2 (M + 1); Anal. ($C_{23}H_{27}Cl_1N_6O_1$·1.25$C_2H_1O_2F_3$) C, H, N.

8-Cyclopentyl-5,6-dimethyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (25): Starting from **87** (0.030 g, 0.058 mmol), 0.012 g, (50%) of **25** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (br s, 1H), 8.89 (br s, 2H), 8.79 (s, 1H), 7.53−7.55 (d, J = 9.0 Hz, 2H), 6.93−6.96 (d, J = 9.1 Hz, 2H), 5.80−5.86 (m, 1H), 3.20−3.26 (m, 8H), 2.32 (s, 3H), 2.01 (s, 3H), 2.15−2.20 (m, 2H), 1.82−1.92 (m, 2H), 1.65−1.75 (m, 2H), 1.47−1.57 (m, 2H); *m/z* 419.2 (M + 1); Anal. ($C_{23}H_{28}N_6O_1$·2.75HCl) C, H, N.

8-Cyclopentyl-6-ethyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (26): Starting from **95** (0.030 g, 0.058 mmol), 0.012 g, (50%) of **26** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (br s, 1H), 9.25 (br s, 2H), 8.78 (s, 1H), 7.53−7.55 (d, J = 9.1 Hz, 2H), 6.96−6.99 (d, J = 9.0 Hz, 2H), 5.80−5.86 (m, 1H), 3.30−3.37 (m, 4H), 3.12−3.20 (m, 4H), 2.56−2.59 (m, 2H), 2.34 (s, 3H), 2.15−2.20 (m, 2H), 1.82−1.92 (m, 2H), 1.65−1.75 (m, 2H), 1.47−1.57 (m, 2H), 0.94−0.99 (m, 3H); *m/z* 433.2 (M + 1); Anal. ($C_{25}H_{32}N_6O_1$·3.0HCl·0.15CH_2Cl_2·0.90EtOH) C, H, N.

8-Cyclopentyl-6-fluoro-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (27): Starting from **88** (0.230 g, 0.441 mmol), 0.210 g, (73%) of **27** was obtained according to Method B described for the synthesis of **10**: mp 254−255 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.77 (br s, 2H), 7.52 (d, J = 9 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 5.83 (br s, 1H), 3.22 (br s, 8H), 2.31 (s, 3H), 2.14−2.21

(m, 2H), 1.86 (br s, 2H), 1.73−1.75 (m, 2H), 1.54−1.56 (m, 2H); *m/z* 423.2 (M + 1); Anal. ($C_{23}H_{27}N_6O_1F_1 \cdot 1.93C_2H_1O_2F_3$) C, H, N.

6-Chloro-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (28): Starting from **92** (0.110 g, 0.205 mmol), 0.057 g, (52%) of **28** was obtained according to Method A described for the synthesis of **10**: mp 188 °C (decomposed); *m/z* 441.2 (M + 1), 439.2 (M + 1); Anal. ($C_{23}H_{27}N_6O_1Cl_1 \cdot 2.00HCl \cdot 1.24\ H_2O$) C, H, N.

6-Bromo-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (29): Starting from **89** (0.400 g, 0.690 mmol), 0.400 g, (83%) of **29** was obtained according to Method B described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (br s, 1H), 8.89 (s, 1H), 8.71 (br s, 2H), 7.54 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 5.88 (br s, 1H), 3.23 (br d, J = 11 Hz, 4H), 2.53 (s, 3H), 2.14−2.2 (m, 2H), 1.8−1.96 (m, 2H), 1.65−1.8 (m, 2H), 1.48−1.60 (m, 2H). *m/z* 485.1 (M + 1); Anal. ($C_{23}H_{27}N_6O_1Br_1 \cdot 1.92C_2H_1O_2F_3$) C, H, N.

8-Cyclopentyl-6-iodo-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (30): Starting from **90** (0.140 g, 0.222 mmol), 0.110 g, (79%) of **30** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.15 (s, 2H), 8.89 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 6.97 (d, J = 8 Hz, 2H), 5.89 (br s, 1H), 3.29 (s, 4H), 3.19 (s, 4H), 2.59 (s, 3H), 2.11 (s, 2H), 1.87 (s, 2H), 1.71 (s, 2H), 1.55 (s, 2H). *m/z* 531.2 (M + 1); Anal. ($C_{23}H_{27}N_6O_1I_1 \cdot 2.00\ HCl \cdot 1.44H_2O$) C, H, N.

6-Acetyl-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (31): Starting from **91** (0.274 g, 0.47 mmol), 0.200 g, (80%) of **31** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.2 (br s, 2H), 8.9 (s, 1H), 7.53−7.55 (d, 2H), 6.97−6.94 (d, 2H), 5.5−5.9 (br m, 4H), 3.29−3.30 (m, 4H), 3.19−3.22 (m, 4H), 2.38 (s, 3H), 2.26 (s, 3H), 2.15−2.22 (m, 2H), 1.79−1.83 (m, 2H), 1.72−1.84 (m, 2H), 1.53−1.56 (m, 2H); *m/z* 447.2 (M + 1). ($C_{25}H_{30}N_6O_2 \cdot$ 2.5 HCl, $0.5H_2O$) C, H, N.

8-Cyclopentyl-5-methyl-7-oxo-2-(4-piperazin-1-yl-phenylamino)-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (32): Starting from **98** (0.200 g, 0.370 mmol), 0.170 g, (77%) of **32** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (br s, 1H), 9.19 (br s, 2H), 8.88 (s, 1H), 7.53−7.55 (d, J = 8.8 Hz, 2H), 6.99−7.04 (d, J = 9.5 Hz, 2H), 5.78−5.83 (m, 1H), 3.32−3.40 (m, 4H), 3.12−3.20 (m, 4H), 2.38 (s, 3H), 2.15−2.20 (m, 2H), 1.75−1.96 (m, 4H), 1.47−1.57 (m, 2H); *m/z* 459.2 (M + 1); Anal. ($C_{25}H_{32}N_6O_1 \cdot 2.0HCl \cdot 0.47CH_2Cl_2 \cdot 0.11C_4H_8O_1 \cdot 1.35H_2O$) C, H, N.

8-Cyclopentyl-5-methyl-7-oxo-2-(4-piperazin-1-yl-phenylamino)-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Methyl Ester (33): Starting from **97** (0.274 g, 0.47 mmol), 0.200 g, (80%) of **33** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.04 (br s, 2H), 8.85 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 5.78 (br s, 1H), 3.76 (s, 3H), 3.28 (d, J = 5 Hz, 4H), 3.18 (br s, 4H), 2.30 (s, 3H), 2.08−2.20 (m, 2H), 1.66−1.90 (m, 4H), 1.46−1.60 (m, 2H); *m/z* 463.2 (M + 1).

8-Cyclopentyl-5-methyl-7-oxo-2-(4-piperazin-1-yl-phenylamino)-7,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (34): Starting from **96** (0.320 g, 0.555 mmol), 0.270 g, (77%) of **34** was obtained according to Method A described for the synthesis of **10**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (br s, 1H), 9.37 (br s, 2H), 8.86 (s, 1H), 7.53−7.55 (d, J = 8.9 Hz, 2H), 7.01−7.04 (d, J = 9.0 Hz, 2H), 5.78−5.83 (m, 1H), 3.32−3.40 (m, 4H), 3.12−3.20 (m, 4H), 2.31 (s, 3H), 2.15−2.20 (m, 2H), 1.65−1.90 (m, 4H), 1.47−1.57 (m, 2H), 1.23−1.28 (t, J = 7.1 Hz, 3H); *m/z* 477.2 (M + 1); Anal. ($C_{25}H_{32}N_6O_1 \cdot 2.0HCl \cdot 1.08CH_2Cl_2$) C, H, N.

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido-[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carbaldehyde (15): Compound **10** (0.150 g, 0.297 mmol) suspended in ethyl formate (5 mL) was treated with a drop of formic acid and heated to 45 °C for 16 h. The reaction mixture was partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. The layers were separated, and then the organic layer was dried over $MgSO_4$. The salts were filtered and the solvents evaporated in vacuo to give a solid that was triturated with EtOAc and hexanes to yield **15** as a yellow solid (0.05 g, 39%). mp 244−247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.31 (s, 1H), 7.76−7.79 (d, J = 8.8 Hz, 2H), 7.19−7.22 (d, J = 8.8 Hz, 2H), 6.39 (s, 1H), 6.00−6.08 (m, 1H), 6.00 (s, 1H), 3.73−3.80 (m, 4H), 3.26−3.34 (m, 4H), 2.59 (s, 3H), 2.43−2.49 (m, 2H), 2.02−2.16 (m, 2H), 1.89−1.96 (m, 2H), 1.76−1.82 (m, 2H); *m/z* 433.2 (M + 1); Anal. ($C_{24}H_{28}N_6O_2 \cdot 0.28$EtOAc) C, H, N.

General Procedure for Side Chain Preparation: 1-Fluoro-4-nitro-benzene (6.11 g, 43.3 mmol) was dissolved in acetonitrile (100 mL) to which *N*,*N*-diisopropylethylamine (8.1 mL, 46.22 mmol) and piperazine-1-carboxylic acid *tert*-butyl ester (8.61 g, 46.22 mmol) were added and heated to reflux for 14 h. After cooling the reaction mixture to room temperature, a precipitate formed and was filtered to give a yellow solid. The solid was dissolved in THF (120 mL), and RaNi (5 g) was added and placed under a H_2 atmosphere at 50 psi for 5 h. The catalyst was removed by filtration through Celite and the solvent evaporated in vacuo to give 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester as a light tan powder (6.94 g, 59%).

4-(4-Amino-phenyl)-piperazine-1-carboxylic Acid *tert*-Butyl Ester (99): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78−6.80 (d, J = 8.5 Hz, 2H), 6.62−6.64 (d, J = 8.6 Hz, 2H), 3.54−3.58 (m, 4H), 3.53 (br s, 2H), 2.95−2.99 (m, 4H), 1.45 (s, 9H); *m/z* 278.1 (M + 1).

4-(4-Methyl-piperazin-1-yl)-phenylamine (100): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77−6.79 (d, J = 8.8 Hz, 2H), 6.61−6.63 (d, J = 8.8 Hz, 2H), 3.39 (br s, 2H), 3.01−3.06 (m, 4H), 2.53−2.55 (m, 4H), 2.31 (s, 3H); *m/z* 192.1 (M + 1).

4-Piperidin-1-yl-phenylamine (101): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.61−6.64 (d, J = 8.9 Hz, 2H), 6.42−6.44 (d, J = 8.8 Hz, 2H), 4.50 (s, 2H), 2.77−2.84 (m, 4H), 1.53−1.58 (m, 4H), 1.3−1.39 (m, 2H); *m/z* 177.0 (M + 1).

3-[1-(4-Amino-phenyl)-piperidin-4-yl]-propan-1-ol (102): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.63 (d, J = 9 Hz, H), 6.42 (d, J = 9 Hz, 2H), 4.49 (s, 2H), 4.33 (t, J = 5 Hz, 1H), 3.25−3.36 (m, 4H), 2.38 (t, J = 11 Hz, 2H), 1.66 (br d, J = 9 Hz, 2H), 1.40−1.43 (m, 2H), 1.15−1.31 (m, 4H); *m/z* 235.1 (M + 1).

1-[4-(4-Amino-phenyl)-piperazin-1-yl]-ethanone (103): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.6−6.9 (m, 4H), 3.3−3.9 (br s, 2H), 3.7−3.8 (m, 2H), 3.55−3.65 (m, 2H), 2.95−3.05 (m, 4H), 2.1 (s, 3H).

1-(4-Amino-phenyl)-pyrrolidin-3-ol (104): *m/z* 179.2 (M + 1).

[1-(4-Amino-phenyl)-pyrrolidin-3-yl]-carbamic Acid *tert*-Butyl Ester (105): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07−7.10 (d, J = 6.6 Hz, 1H), 6.42−6.45 (d, J = 8.6 Hz, 2H), 6.25−6.29 (d, J = 8.6 Hz, 2H), 4.24 (s, 1H), 4.01−4.04 (m, 1H), 3.25−3.28 (m, 1H), 3.12−3.16 (m, 1H), 3.01−3.05 (m, 1H), 2.82−2.85 (m, 1H), 2.05−2.08 (m, 1H), 1.74−1.76 (m, 1H), 1.35 (s, 9H); *m/z* 278.2 (M + 1).

4-(4-Amino-phenyl)-[1,4]diazepane-1-carboxylic Acid *tert*-Butyl Ester (106): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.57 (s, 2H), 3.4−3.6 (m, 6H), 3.29 (t, J = 6 Hz, 1H), 3.18 (t, J = 6 Hz, 1H), 1,90−1.96 (m, 2H), 1.42 (s, 5H), 1.37 (s, 4H); *m/z* 292.1 (M + 1).

2-[4-(4-Amino-phenyl)-piperazin-1-yl]-ethanol (107): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (d, J = 8 Hz, 2H), 6.48 (d, J = 7 Hz, 2H), 5.27 (s, 1H), 4.69 (s, 2H), 3.84 (s, 2H), 3.43−3.55 (m, 4H), 3.1−3.3 (m, 4H); *m/z* 236.1 (M + 1).

4-(4-Amino-phenyl)-2,6-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (108): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.63−6.66 (d, J = 8.5 Hz, 2H), 6.44−6.46 (d, J = 8.6 Hz, 2H), 4.60 (br s, 2H), 3.96−4.04 (m, 2H), 3.03−3.09 (m, 2H), 2.55−2.60 (m, 2H), 1.38 (s, 9H), 1.22−1.25 (d, J = 6.5 Hz, 6H); *m/z* 306.2 (M + 1).

4-(4-Amino-phenyl)-2,2-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (109): ^{1}H NMR (400 MHz, $CDCl_3$)

δ 6.55−6.57 (d, J = 8.3 Hz, 2H), 6.44−6.46 (d, J = 8.8 Hz, 2H), 4.47 (br s, 2H), 3.44−3.48 (m, 2H), 2.95−2.99 (m, 2H), 2.82 (s, 2H), 1.37 (s, 9H), 1.31 (s, 6H); *m/z* 306.2 (M + 1).

4-(4-Amino-2-chloro-phenyl)-piperazine-1-carboxylic Acid *tert*-Butyl Ester (110): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82−6.85 (d, J = 8.5 Hz, 1H), 6.58 (s, 1H), 6.40−6.44 (d, J = 8.5 Hz, 1H), 5.04 (s, 2H), 3.38−3.42 (m, 4H), 2.68−2.72 (m, 4H), 1.37 (s, 9H); *m/z* 312.0 (M + 1).

Cdk Assays (Cdk4/cyclin D1, Cdk2/cyclin E, Cdk2 cyclin A, and Cdc2/cyclin B). All Cdks were human recombinant proteins expressed in insect cells through baculovirus infection. Enzyme assays for IC_{50} determinations and kinetic evaluation were performed in 96-well filter plates (Millipore MADVN6550). The total volume was 0.1 mL containing a final concentration of 20 mM Tris (tris[hydroxmethyl]aminomethane), pH 7.4, 50 mM NaCl, 1 mM dithiothreitol, 10 mM $MgCl_2$, 25 μM ATP (for Cdk4) or 12 μM ATP (for Cdk2/E, Cdk2/A, and Cdc2/B) containing 0.25 μCi of [^{32}P]ATP, 20 ng of enzyme, 1 μg of GST-retinoblastoma and appropriate dilutions of inhibitor. All components except the ATP were added to the wells, and the plate was placed on a plate mixer for 2 min. The reaction was started by adding [^{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). 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 ^{32}P incorporation was determined with a beta plate counter (Wallac Inc., Gaithersburg, MD).

Tyrosine Kinase Assays. PDGF, FGF and SRC were obtained and assayed as previously described.[78]

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Supporting Information Available: Purity data for target compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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