Orally-Effective, Long-Acting Sorbitol Dehydrogenase Inhibitors: Synthesis, Structure−Activity Relationships, and in Vivo Evaluations of Novel Heterocycle-Substituted Piperazino-Pyrimidines

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Received September 19, 2001

Optimization of a previously disclosed sorbitol dehydrogenase inhibitor (SDI, **II**) for potency and duration of action was achieved by replacing the metabolically labile *N*,*N*-dimethylsulfamoyl group with a variety of heterocycles. Specifically, this effort led to a series of novel, in vitro potent SDIs with longer serum half-lives and acceptable in vivo activity in acutely diabetic rats (e.g., **62**, **67**, and **69**). However, the desired in vivo potency in chronically diabetic rats, $ED_{90} \leq 5$ mg/kg/day, was achieved only through further modification of the piperazine linker. Several members of this family, including **86**, showed better than the targeted potency with ED_{90} values of 1−2 mg/kg/day. Compound **86** was further profiled and found to be a selective inhibitor of sorbitol dehydrogenase, with excellent pharmacodynamic/pharmacokinetic properties, demonstrating normalization of sciatic nerve fructose in a chronically diabetic rat model for ∼17 h, when administered orally at a single dose of 2 mg/kg/day.

Introduction

Diabetes mellitus is a disease characterized by abnormal glucose metabolism. Diabetic patients are at risk for developing long-term complications including neuropathy, nephropathy, retinopathy, and cardiovascular disease.[1] The clinical consequences of these complications include lower limb amputation, end-stage renal failure, and loss of vision. The Diabetes Complications and Control Study[2] and the United Kingdom Prospective Diabetes Study[3] demonstrated that strict and sustained control of glucose excursions through interventions including intensive insulin therapy ($HbA_{1c} \leq$ 7%) reduces the risk of developing these complications in type 1 and type 2 diabetics. However, relatively few diabetics have adopted this strict, physician-monitored regimen, and this type of round-the-clock control is not practical for patients at large. At present, there is no specific therapy available for diabetic complications. A metabolic approach to control excess glucose flux in diabetic tissues through the first step of the polyol pathway (Figure 1) by aldose reductase inhibitors[4] has shown promising results, particularly for diabetic neuropathy, in both preclinical models and early clinical trials.[5] An alternate, recent hypothesis proposes that the redox changes caused by increased oxidation of sorbitol to fructose in the second step of the pathway,

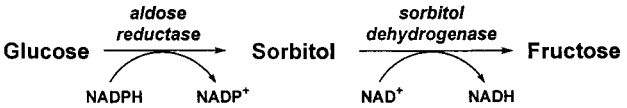

Figure 1. Polyol pathway.

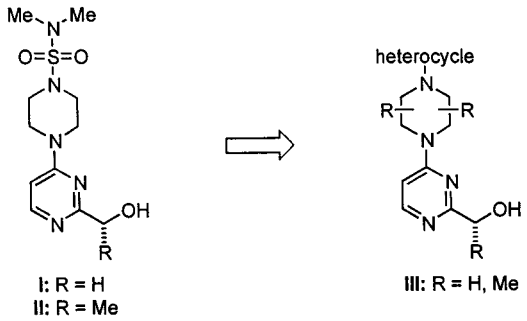

Figure 2. Prototype SDIs **I** and **II** and their heterocyclic analogue **III**.

accompanied by a net imbalance of the reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NAD^+) ratio, could be the underlying cause of the vascular complications of diabetes.[6]

In chronically diabetic rats, a prototype sorbitol dehydrogenase inhibitor (SDI), CP-166 572 [7] (**I**, Figure 2) has been shown to prevent albumin leakage and fructose accumulation in sciatic nerve as well as other diabetic tissues, but seemingly contrary results have been reported with regard to neural function,[8,9] as has already been iterated.[10] Because of the possibility that these conflicting accounts may be a consequence of differing experimental protocols used in the animal models, as well as the pharmacokinetic/pharmacodynamic issues with **I**, a weak and short-lived SDI,[11] initial efforts focused on potency improvements, which led to the enantiomeric SDI **II**.[10] Although **II** is sub-

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10.1021/jm010440g CCC: $22.00 © 2002 American Chemical Society
Published on Web 12/20/2001

stantially more potent than **I** in vitro, it still retains the metabolically labile *N*,*N*-dimethylsulfamoyl moiety. Therefore, a program to identify potent, orally active SDIs with longer serum half-lives was initiated, with the objective of providing better tools to probe the biological consequences of blocking the second step of the polyol pathway. The immediate medicinal chemistry strategy became the replacement of the sulfamoyl moiety with a more metabolically stable heterocyclic group.

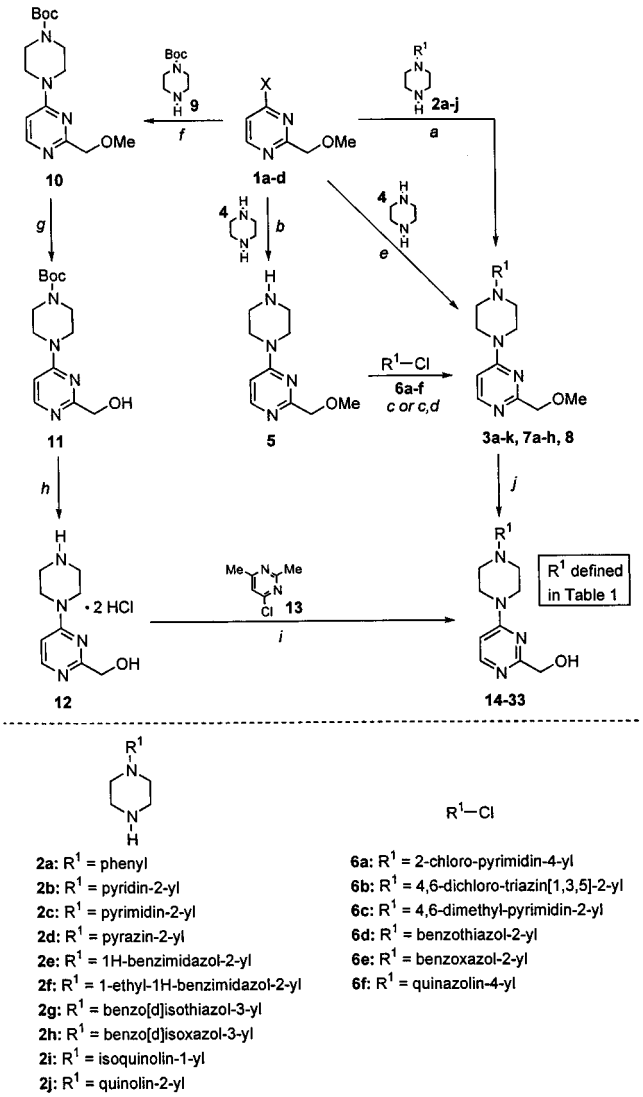
Chemistry

Starting with the activated pyrimidines **1a**−**d** (X = Cl,[12] OMs,[13] OSO_2[2,4,6-triisopropyl]Ph, and OTf, respectively), the target compounds **14**−**33** were for the most part prepared using two methods, differing primarily in order of addition (Scheme 1). The first approach proceeds with the reaction of **1a**−**c** with substituted piperazines **2a**−**j**[14] to provide compounds **3a**−**k**. Removal of the methyl ether protecting group under standard conditions afforded the target compounds. Alternatively, mesylate **1b** may be first reacted with piperazine (**4**) to provide piperazino-pyrimidine **5**. Subsequent reaction with heterocyclic chlorides **6a**−**f**[14] afforded compounds **7a**−**h** that are deprotected as before to give the target compounds.[15] When the highly reactive trifluoromethylsulfonylpyrimidine **1d** was reacted with piperazine (**4**), the *N*,*N*′-bis-substituted intermediate **8** (R^1 = 2-methoxymethyl-pyrimidin-4-yl) was obtained, which upon deprotection gave compound **22**. Finally, one compound in this series was synthesized via the reaction of chloropyrimidine **1a** with Boc-piperazine (**9**) followed by deprotection of the methyl ether (Me_2BBr) and Boc group (HCl) to provide the amino alcohol bis(HCl) salt **12**. Subsequent reaction with 4-chloro-2,6-dimethyl-pyrimidine (**13**) gave the desired target compound. This latter method provides a late-stage common intermediate (e.g., **12**) from which analogues can be produced in one step.

Synthesis of analogues bearing the *R*-(+)-hydroxyethyl side chain at the pyrimidine 2-position, compounds **50**−**62** and **65**−**71**, follows similarly (Scheme 2). For example, reaction of the activated pyrimidines **34a**−**c** (R = Ac and X = Cl or OMs, R = butyryl and X = Cl, respectively)[13] with R^1-substituted piperazines **2g**−**j** and **35a**−**j**[14] provides compounds **36a**−**o**, which are hydrolyzed under basic conditions to provide the target compounds.[16] Alternatively, the reaction of mesylate **34b** with piperazine (**4**) provides piperazino-pyrimidine **37a**, which upon reaction with activated heterocyclic chlorides **6c**,**e**, **13**, and **38** gives the penultimate precursors **39a**−**d**. Deprotection of the acetate protecting group as before provides the target compounds. Reaction of two equivalents of chlorobutyrate **34c** with piperazine (**4**) cleanly gave the *N*,*N*′-bis-substituted intermediate **40** (R^1 = (*R*)-2-(1-butyrloxyethyl)-pyrimidin-4-yl), which was bis-deprotected under the standard conditions to provide the target compound. Again, one target compound in this series was synthesized via the reaction of piperazino-pyrimidine **37b** (obtained by the hydrolysis of acetate ester **37a**) with quinoxaline chloride **41**, exemplifying a method that would allow a one-step synthesis of analogues from a common intermediate.

For those analogues with R^1 = 4,6-disubstituted-pyrimidin-2-yl, the requisite substituted piperazines

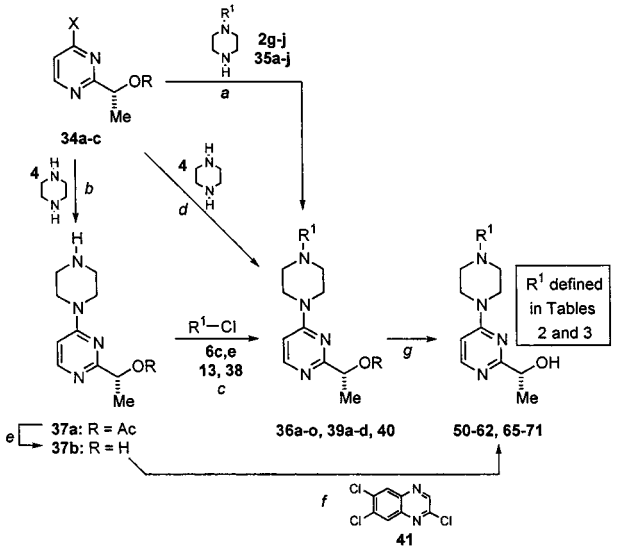
Scheme 1[a]



[a] Reagents and conditions: (a) Et_3N or *i*-Pr_2NEt, THF or DME or *i*-PrOH, reflux [general procedure A]. (b) THF, reflux. (c) Et_3N or *i*-Pr_2NEt, CH_2Cl_2 or THF or *i*-PrOH or *n*-BuOH, −78 °C → reflux [general procedure B]. (d) H_2 (50 psi), 10% Pd/C, NaOAc, EtOH [general procedure C]. (e) (From **1d**), CH_2Cl_2, room temperature. (f) (From **1a**), Et_3N, THF, reflux. (g) Me_2BBr, Et_3N, CH_2Cl_2, 0 °C → room temperature. (h) 4 N HCl, dioxane, room temperature. (i) *i*-Pr_2NEt, *n*-BuOH, reflux. (j) BBr_3, CH_2Cl_2, 0 °C → room temperature or Me_2BBr, Et_3N, CH_2Cl_2, 0 °C → room temperature [general procedure D].

35a−**d** were synthesized following the route shown in Scheme 3. The reaction of 1-benzylpiperazine (**42**) with *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (**43**) in the presence of $HgCl_2$ provided bis(Boc)-protected guanidine **44** that was deprotected with trifluoroacetic acid (TFA) to give the guanidinium trifluoroacetate salt **45**.[20] The reaction of **45** with diketones **46a**−**d**[14] in a refluxing solution of *i*-PrONa/*i*-PrOH gave the desired 4,6-disubstituted-pyrimidino-piperazines.[18] Removal of the benzyl group under transfer hydrogenolysis conditions provided compounds **35a**−**d**. As this methodology proved useful in preparing analogues of this type, a more convergent route was also realized by replacing the benzyl group with the (*R*)-2-(1-acetoxy)-pyrimidin-4-yl group such that the final target compounds **63** and **64** were directly obtained after the reaction with the diketone **46e** or

Scheme 2[a]



35a: R^1 = 4,6-bis-trifluoromethyl-pyrimidin-2-yl
35b: R^1 = 4,6-diethyl-pyrimidin-2-yl
35c: R^1 = 4,6-diisopropyl-pyrimidin-2-yl
35d: R^1 = 4-hydroxymethyl-6-methyl-pyrimidin-2-yl
35e: R^1 = oxazolo[4,5-b]pyridin-2-yl
35f: R^1 = oxazolo[4,5-c]pyridin-2-yl
35g: R^1 = oxazolo[5,4-c]pyridin-2-yl
35h: R^1 = oxazolo[5,4-b]pyridin-2-yl
35i: R^1 = quinoxalin-2-yl
35j: R^1 = 3-methyl-quinoxalin-2-yl
38: R^1 = 4-methyl-pyrimidin-2-yl

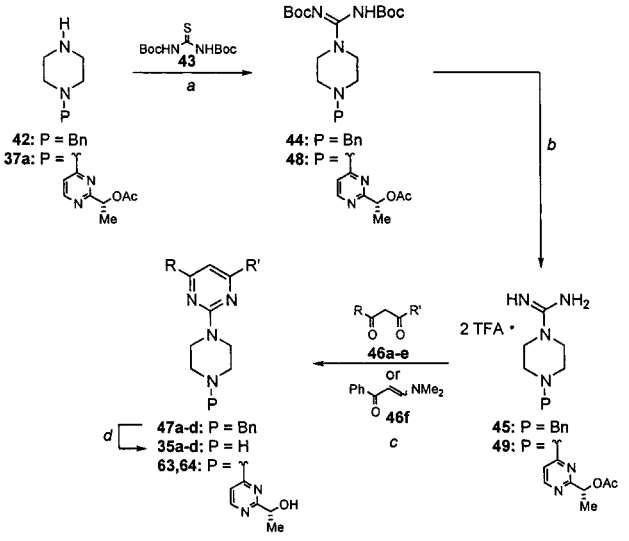
[a] Reagents and conditions: (a) Et_3N, THF or *i*-PrOH, room temperature → reflux [general procedure E]. (b) (From **34b**), THF, reflux. (c) Et_3N or *i*-Pr_2NEt, *i*-PrOH or *n*-BuOH, room temperature → reflux [general procedure F]. (d) (From **34c**), Et_3N, *i*-PrOH, reflux. (e) LiOH·H_2O, 3:1:1 THF/MeOH/H_2O, room temperature. (f) Et_3N, *i*-PrOH, reflux. (g) LiOH·H_2O, THF/MeOH/H_2O, 0 °C → room temperature or K_2CO_3, MeOH, room temperature [general procedure G].

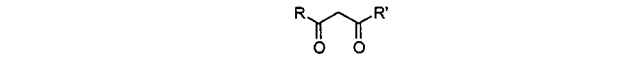
dicarbonyl equivalent **46f** (see **37a** → **48** → **49** → **63** and **64**).

The synthesis of analogues containing mono- or dimethyl-substituted piperazine linkers is based essentially on the chemistry shown for the unsubstituted piperazine linker derivatives above (Scheme 4). However, the reaction sequence and conditions are dictated by the availability and reactivity of the differentially protected piperazines **72a**−**c** ($R^2 = R^6 = \beta$-Me,[19] $R^2 = \alpha$-Me,[20] and $R^2 = \beta$-Me,[20] respectively).[21] Furthermore, the substituted piperazines may be linked to the chiral pyrimidine with the methyl group(s) proximal to or distal to said chiral pyrimidine. As a consequence of these considerations, three major routes were used in the preparation of analogues **85**−**97**.

For those compounds with the piperazine methyl group(s) proximal (positions R^2 and R^6) to the chiral pyrimidine, the protected piperazines **72a**−**c** were condensed with the chloropyrimidine **34c** in the first step to give compounds **73a**−**c**, with more forcing conditions required in the case of *cis*-dimethylpiperazine **72a** (neat, 155 °C) as compared with the monomethyl piperazines **72b**,**c** (*n*-butanol, reflux). In the former case, scale-dependent epimerization was observed resulting

Scheme 3[a]





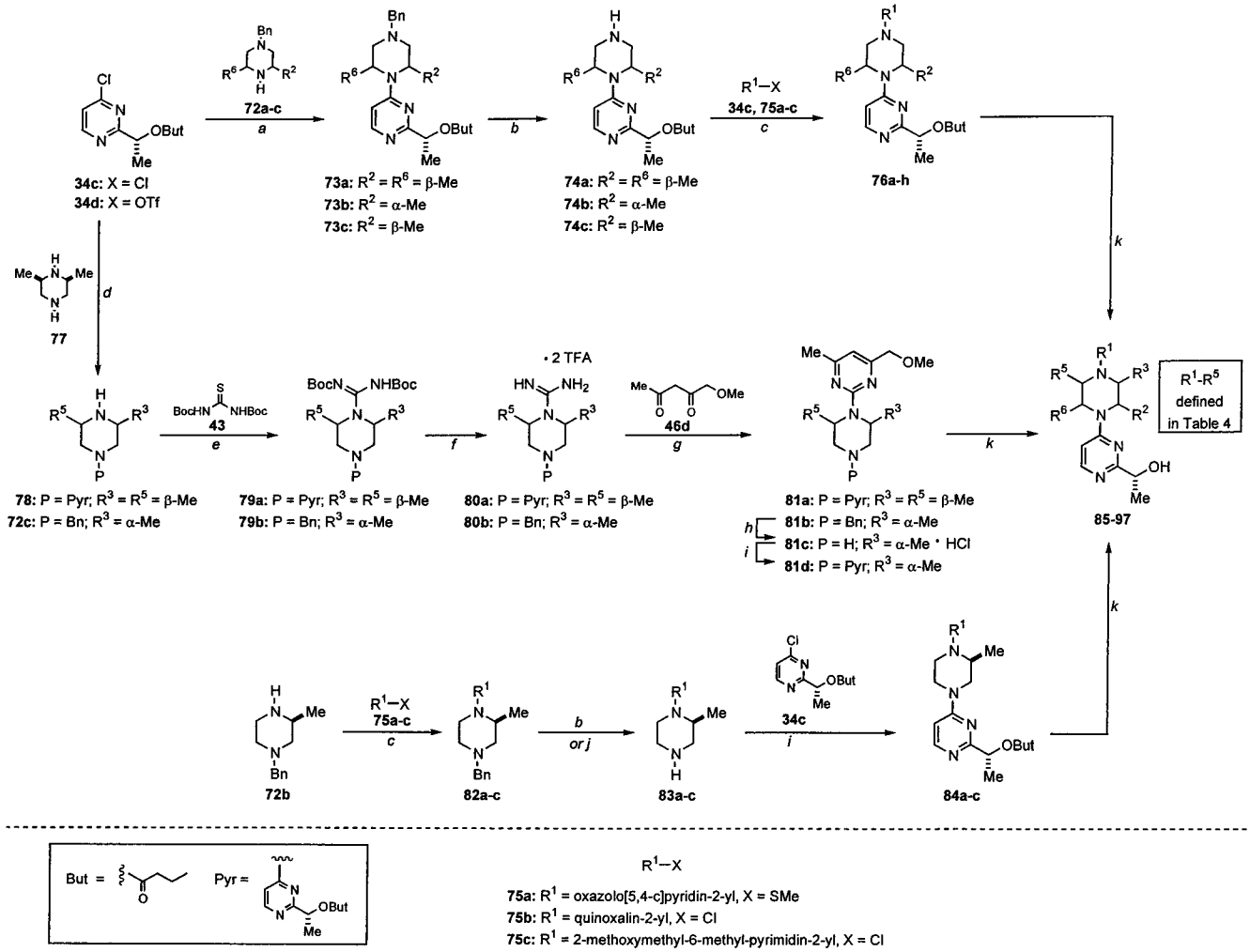
46a: R = R' = CF_3
46b: R = R' = Et
46c: R = R' = *i*-Pr
46d: R = CH_2OMe, R' = Me
46e: R = Ph, R' = Me

[a] Reagents and conditions: (a) Et_3N, $HgCl_2$, DMF, 0 °C → room temperature [general procedure H]. (b) TFA/CH_2Cl_2, room temperature [general procedure I]. (c) *i*-PrONa/*i*-PrOH, reflux [general procedure J]. (d) 10% Pd/C, HCO_2NH_4, MeOH, reflux [general procedure K].

in ∼80−90% ee for a <10 g scale in a continuum to complete racemization for a >100 g scale. Thus, on a large scale, the synthesis of **73a** was more conveniently performed using the more reactive triflate[13] **34d** with *cis*-dimethylpiperazine **72a** at 80 °C, routinely providing compound **73a** in 80−90% ee. Separation of the enantiomers by chiral high-performance liquid chromatography (HPLC) was easily accomplished to provide the desired (*R*)-enantiomer in >98% ee.[22] Removal of the benzyl protecting group was accomplished under transfer hydrogenolysis conditions following in situ formation of the HCl salt of **73a**−**c** to give the free amines **74a**−**c**. Reaction of **74a**−**c** with activated heterocycles **34c** and **75a**−**c** under standard conditions provided the butyrate-protected penultimate precursors **76a**−**h**. Removal of the ester protecting group was accomplished in general with LiOH, although in some instances K_2CO_3 or HCl was used. In the event that deprotection of a heterocyclic head piece containing a methyl ether was necessary, treatment with BBr_3 effected both methyl ether and concomitant butyrate cleavage to give the target compounds.

For those analogues where the methyl group(s) is/are distal to the chiral pyrimidine, several related routes were used depending on the methyl substitution pattern. First, 2,6-*cis*-dimethylpiperazine (**77**) was condensed with chloropyrimidine **34c**, selectively on the less-hindered nitrogen, providing compound **78**. Derivatization of pyrimidino-piperazine **78** and benzyl-piperazine **72c** with the 4-methoxymethyl-6-methyl-pyrimidin-2-yl group follows that procedure previously described in Scheme 3, i.e., construction of the heterocycle via reaction with bis(Boc)-thiourea **43** followed by Boc

Scheme 4[a,b]



[a] Reagents and conditions. [b] Compounds containing the descriptors R^2, R^3, R^5, and R^6 are hydrogen unless otherwise specified. (a) (From **34c** and **72a**), 155 °C, neat; (from **34d** and **72a**), Et_3N, CH_3CN, reflux; (from **34d** and **72b**,**c**), *i*-Pr_2NEt, *n*-BuOH, reflux. (b) HCl, MeOH then 10% Pd/C, HCO_2NH_4, MeOH, reflux [general procedure L]. (c) Et_3N or *i*-Pr_2NEt, *i*-PrOH or *n*-BuOH, reflux or 130 °C, neat [general procedure M]. (d) THF, reflux. (e) Et_3N, $HgCl_2$, DMF, 0 °C → room temperature [general procedure H]. (f) TFA/CH_2Cl_2, room temperature [general procedure I]. (g) *i*-PrONa/*i*-PrOH, reflux [general procedure J]. (h) HCl, MeOH then 10% Pd/C, HCO_2NH_4, MeOH, reflux. (i) **34c**, Et_3N, *i*-PrOH, reflux [general procedure N]. (j) ACE–Cl, NaI, acetone, room temperature then MeOH, reflux. (k) LiOH, THF/MeOH/H_2O, room temperature or K_2CO_3, MeOH, room temperature or HCl, MeOH, room temperature or BBr_3, CH_2Cl_2, 0 °C → room temperature [general procedure O].

deprotection and condensation with diketone **46d** to give **81a**,**b**. The benzyl-substituted analogue **81b** was deprotected under transfer hydrogenolysis conditions and the chiral pyrimidine was appended to give compound **81d**. The thusly synthesized precursors **81a**,**d** were each simultaneously demethylated and de-esterified with BBr_3 to give the target compounds.

Finally, monomethyl benzyl piperazine **72b** was reacted with activated heterocycles **75a–c**, debenzylated under standard transfer hydrogenolysis conditions or using the ACE–Cl/NaI method of Buchwald,[23] and condensed with chloropyrimidine **34c** as before to provide penultimate precursors **84a–c**, which were deprotected to give the target compounds.

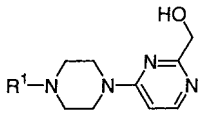
Biology

Primary in vitro data were initially generated using commercially available sheep liver sorbitol dehydrogenase (*s*-SDH) and then changed over to recombinant human sorbitol dehydrogenase (*h*-SDH) as it became available.[24,25] Compounds of interest were progressed to the first-line in vivo screen measuring the prevention of sciatic nerve fructose accumulation (acute model) in streptozocin (STZ)-induced diabetic rats. Test compounds were dosed 4, 7, and 24 h post STZ treatment, and for select compounds, ED_{50} values were generated (represented as mg/kg/day, total dose) to determine which compounds were sufficiently robust enough for further characterization. Those compounds with acute in vivo $ED_{50} \leq 1$ mg/kg/day were then advanced to the secondary in vivo screen where compounds were tested for their ability to normalize (ED_{90}) elevated sciatic nerve fructose in a reversal protocol (chronic model) rather than a prevention protocol. In this more relevant model, rats were made diabetic (STZ) for 1 week, and on day 8, compound dosing was initiated and continued once a day for 5 days.

Structure–Activity Relationships

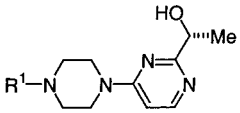
Initial substitution of the *N*,*N*-dimethylsulfamoyl moiety of **I** with phenyl or simple heterocycles such as pyridine, pyrimidine, pyrazine, and triazine (e.g., **14**–

Table 1. Structure–Activity Relationships for Compounds **14**–**33**: Heterocyclic Analogues of CP-166 572 (**I**)



compd no.	R^1	mp (°C)	*s*-SDH IC_{50} (μM) ± se (*n*)	*h*-SDH IC_{50} (μM) ± se (*n* = 3)
14	phenyl	131–133	9.4 (1)	
15	pyridin-2-yl	139–141	3.0 (1)	
16	pyrimidin-2-yl	164–166	1.1 ± 0.2 (2)	
17	pyrimidin-4-yl	185–186.5	2.3 (1)	
18	pyrazin-2-yl		1.3 (1)	
19	[1,3,5]triazin-2-yl	195–196.5	2.6 (1)	
20	4,6-dimethyl-pyrimidin-2-yl	175–176	0.35 ± 0.05 (2)	0.093 ± 0.025
21	2,6-dimethyl-pyrimidin-4-yl	171.5–173.5	0.48 (1)	0.14 ± 0.04
22	2-hydroxymethyl-pyrimidin-4-yl	237–239	1.1 (1)	0.26 ± 0.13
23	4,6-dichloro-[1,3,5]triazin-2-yl	250–255	0.49 (1)	
24	1H-benzimidazol-2-yl	235–237	6.5 (1)	
25	1-ethyl-1H-benzimidazol-2-yl	124–126	4.8 (1)	
26	benzothiazol-2-yl	192–193	3.2 (1)	
27	benzoxazol-2-yl	200–201.5	0.74 ± 0.04 (2)	0.19 ± 0.04
28	benzo[*d*]isothiazol-3-yl *S*,*S*-dioxide	278–281	3.2 (1)	
29	benzo[*d*]isothiazol-3-yl	134–136	0.33 ± 0 (2)	0.064 ± 0.004
30	benzo[*d*]isoxazol-3-yl	139–141.5	0.41 ± 0.07 (2)	0.12 ± 0.02
31	isoquinolin-1-yl	144–145	0.43 (1)	0.15 ± 0.03
32	quinolin-2-yl	172–174	0.59 (1)	0.087 ± 0.009
33	quinazolin-4-yl	207.5–209	0.89 (1)	
CP-166 572 (**I**)				0.24 ± 0.01

Table 2. Structure–Activity Relationships for Compounds **50**–**57**: Effect of the (*R*)-Hydroxyethyl Group at the Pyrimidine 2-Position



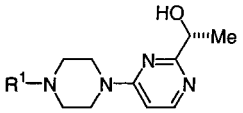
compd no.	R^1	mp (°C)	*h*-SDH IC_{50} (μM) ± se (*n* = 3)	acute in vivo ED_{50} (mg/kg/day)
50	4,6-dimethyl-pyrimidin-2-yl	132–133	0.023 ± 0.003	1.3
51	2,6-dimethy-pyrimidin-4-yl	125.5–127	0.031 ± 0.003	5
52	(*R*)-2-hydroxyethyl-pyrimidin-4-yl	158–160	0.040 ± 0.001	1.0
53	benzoxazol-2-yl	139–141	0.035 ± 0.004	12
54	benzo[*d*]isothiazol-3-yl		0.012 ± 0.003	
55	benzo[*d*]isoxazol-3-yl	129–131	0.037 ± 0.015	
56	isoquinolin-1-yl		0.034 ± 0.002	
57	quinolin-2-yl		0.044 ± 0.005	

19) provided modestly active compounds, with IC_{50} values vs *s*-SDH in the low micromolar range (Table 1). The addition of hydrophobic substituents such as methyl and chloro to the pyrimidine and triazine core heterocycles, respectively, increased activity by ~3–5× (e.g., **20**, **21**, and **23**). Because hydrophobic groups appeared to be beneficial for binding to the enzyme, a series of fused heterocycles was also surveyed. In general, the less polar heterocycles such as benzoxazole **27**, benzo[*d*]isothiazole **29**, benzo[*d*]isoxazole **30**, isoquinoline **31**, quinoline **32**, and quinazoline **33** were favored over the more polar benzimidazoles **24** and **25** and benzo[*d*]isothiazole *S*,*S*-dioxide **29**. The intrinsic potency of these fused bicyclic heterocycles was comparable to the substituted monocyclic heterocycles.

On the basis of concurrent structure–activity relationships (SAR) investigations that showed the importance of the enantiomeric 2-hydroxyethylpyrimidine core,[10] select compounds from the heterocycle series were synthesized, which incorporated that side chain (Table 2). In vitro testing against *h*-SDH for these derivatives and their related hydroxymethyl congeners[26] showed that in vitro activity generally increased ~3–7-fold after the incorporation of the (*R*)-hydroxyethyl side chain. Preliminary in vivo analysis of compounds **50**–**53** showed reasonable activity in the acute model with ED_{50} values ranging from 1 to 12 mg/kg/day.

With the above results in hand, further optimization of the heterocycle was pursued (Table 3). Exploration of the 4,6-dimethylpyrimidine in **50** showed that this substitution pattern was optimal vs having just one methyl substituent (**58**) or increasing the size of the alkyl groups to CF_3, ethyl, or isopropyl (**59**–**61**). Incorporation of an aromatic substituent (**63** and **64**) was also less well-tolerated. Pharmacokinetic analysis of **50** (data not shown) revealed the metabolite **62**, where one of the methyl substituents in **50** was oxidized to a hydroxymethyl group. The in vitro IC_{50} and in vivo acute ED_{50} of **62** were very similar to that of **50**. SAR around the benzoxazole derivative **53** revealed that the oxazolopyridines **65**–**68** were reasonable replacement analogues, with the latter two having equivalent in vitro potency with the parent benzoxazole. More interesting, however, was an ~20× increase in the in vivo acute assay for the oxazolopyridines **67** and **68** vs the benzoxazole **53**. Quinoxaline-substituted derivatives **69**–**71**

Table 3. Structure–Activity Relationships for Compounds **58**–**71**: Refinement of the Heterocyclic Head-Piece



compd no.	R^1	mp (°C)	*h*-SDH IC_{50} (μM) ± se (n = 3)	acute in vivo ED_{50} (mg/kg/day)	chronic in vivo ED_{90} (mg/kg/day)
58	4-methyl-pyrimidin-2-yl	116–117.5	0.11 ± 0.04		
59	4,6-bis-trifluoromethyl-pyrimidin-2-yl	156.5–158	0.19 ± 0.06		
60	4,6-diethyl-pyrimidin-2-yl	104–105	0.080 ± 0.010		
61	4,6-diisopropyl-pyrimidin-2-yl	82–83.5	0.072 ±0.013		
62	4-hydroxymethyl-6-methylpyrimidin-2-yl	139–140	0.020 ± 0.003	0.5	
63	4-methyl-6-phenyl-pyrimidin-2-yl		0.22 ± 0.10		
64	4-phenyl-pyrimidin-2-yl		0.067 ± 0.010		
65	oxazolo[4,5-b]pyridin-2-yl	190–191.5	0.17 ± 0.03		
66	oxazolo[4,5-c]pyridin-2-yl	178–180	0.080 ± 0.017		
67	oxazolo[5,4-c]pyridin-2-yl	181–183	0.024 ± 0.002	0.5	10
68	oxazolo[5,4-b]pyridin-2-yl	153–156	0.032 ± 0.005	0.5	
69	quinoxalin-2-yl	106–108	0.036 ± 0.012	1.0	>20
70	3-methyl-quinoxalin-2-yl	145–147	0.008 ± 0.001		
71	6,7-dichloro-quinoxalin-2-yl	143–145	0.12 ± 0.04		

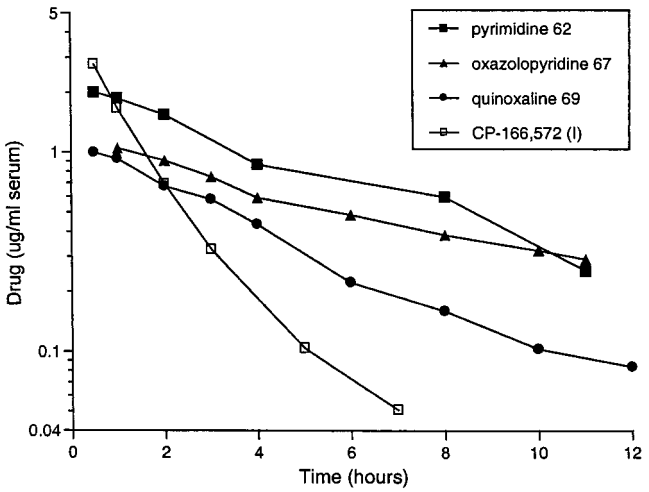


Figure 3. Rat pharmacokinetic profile of compounds **62**, **67**, **69**, and **I** dosed orally at 5 mg/kg. Cp-166 572 (**I**) was dose-normalized from a 20 mg/kg, po, PK study.

exemplify some of the fused bicyclic heterocycles that were explored, with quinoxaline **69** showing good in vivo activity.

Rat pharmacokinetic analysis of pyrimidine **62**, oxazolopyridine **67**, and quinoxaline **69** revealed good systemic exposure and extended $t_{1/2}$ (6, 6, and 3 h, respectively) relative to the lead SDI **I** (0.5 h) (Figure 3). These increases in half-life of the heterocycle derivatives, along with improved in vitro activity, have resulted in an approximate 20-fold increase in acute in vivo activity relative to **I**. On the basis of this result, two compounds, **67** and **69**, were advanced to the more clinically relevant and challenging chronic in vivo screen. However, their ED_{90} values for normalization of sciatic nerve fructose were disappointingly high at 10 mg/kg/day and >20 mg/kg/day, respectively.

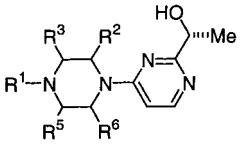
In order to improve the in vivo potency of these compounds, attention was focused on modulating the lipophilicity of the compounds. Because our initial target is the peripheral nerve, which is wrapped by a fatty myelin sheath, additional lipophilic methyl substituents were appended to the piperazine nucleus to address tissue penetration. That is, mono- and dimethyl piperazine congeners were synthesized in almost all different combinations while retaining the four heterocycle groups that were previously shown to give good in vitro potency: 4-hydroxymethyl-6-methylpyrimidin-2-yl, (*R*)-2-hydroxyethyl-pyrimidin-4-yl, 4-oxazolo[5,4-c]pyridin-2-yl, and quinoxalin-2-yl (Table 4). In general, the enzyme potencies did not vary greatly from linker to linker in any given heterocyclic series (e.g., see **85**, **89**, **90**, **92**, **94**, and **97**). However, in most cases, a decrease in potency was observed in comparison to the parent piperazine linker, except perhaps for the (*R*)-2-hydroxyethyl-pyrimidin-4-yl series.

Nonetheless, because the hypothesis was that the increased lipophilicity was proposed to improve in vivo activity, these compounds were all screened in the acute in vivo assay at 1 mg/kg/day. For the most part, these inhibitors performed better in this assay relative to their parent piperazine congeners (data not shown). Those that showed complete normalization of sciatic nerve fructose were progressed to the chronic in vivo assay. Results from the latter assay are shown in Table 4. Interestingly, three of the four most potent compounds were from the 4-hydroxymethyl-6-methylpyrimidin-2-yl series (**85**, **89**, and **94**), and the fourth was from the (*R*)-2-hydroxyethyl-pyrimidin-4-yl series (**86**).

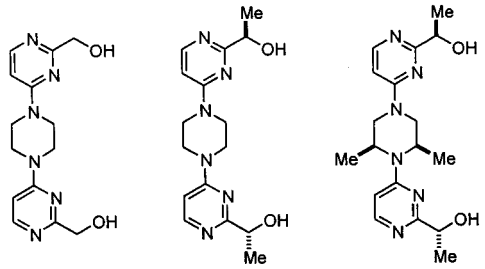
The progression in SAR of the latter series is shown in the compound progression **22** → **52** → **86** (Figure 4). Starting with the symmetrical *N*,*N*′-bis-substituted analogue **22**, the intrinsic potency was increased by ~6–7× by replacing the (*R*)-hydroxyethyl groups with the hydroxymethyl groups, providing compound **52**. The next big SAR advance occurred in the replacement of the 2,6-dimethylpiperazine for the piperazine-linking moiety, producing compound **86**, which exhibited superior in vivo properties relative to its predecessor. Overall, addition of these four properly placed methyl groups provided a >20× increase in intrinsic activity and at least a 15× increase in in vivo activity. On the basis of both in vitro IC_{50} value and in vivo performance in the chronic model, compound **86** was selected for further preclinical profiling.

Compound **86** selectively inhibits SDH and is inactive against a number of other dehydrogenases including

Table 4. Structure–Activity Relationships for Compounds **85**–**97**: Effect of the Piperazine Linker



compd no.	R^1	R^2	R^3	R^5	R^6	mp (°C)	*h*-SDH IC_{50} (μM) ± se (n = 3)	chronic in vivo ED_{90} (mg/kg/day)
85	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	β-Me	H	H	β-Me	139–141	0.10 ± 0.01	1
86	(*R*)-2-hydroxyethyl-pyrimidin-4-yl	β-Me	H	H	β-Me	163–164.5	0.010 ± 0.001	2
87	oxazolo[5,4-c]pyridin-2-yl	β-Me	H	H	β-Me	175–178	0.27 ± 0.04	
88	quinoxalin-2-yl	β-Me	H	H	β-Me		0.18 ± 0.06	1
89	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	H	β-Me	β-Me	H	149–151	0.13 ± 0.02	
90	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	α-Me	H	H	H		0.20 ± 0.03	
91	(*R*)-2-hydroxyethyl-pyrimidin-4-yl	α-Me	H	H	H	158–160	0.059 ± 0.025	
92	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	β-Me	H	H	H		0.17 ± 0.02	52% (1)
93	(*R*)-2-hydroxyethyl-pyrimidin-4-yl	β-Me	H	H	H	155–157	0.012 ±0.002	
94	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	H	β-Me	H	H		0.080 ± 0.016	2
95	oxazolo[5,4-c]pyridin-2-yl	H	β-Me	H	H		0.023 ± 0.006	
96	quinoxalin-2-yl	H	β-Me	H	H		0.099 ± 0.024	
97	4-hydroxymethyl-6-methyl-pyrimidin-2-yl	H	α-Me	H	H		0.14 ± 0.027	



	22	**52**	**86**
h-SDH IC_{50} (μM)	0.26	0.040	0.010
acute ED_{90} (mpk/d)	ND	5	0.3

Figure 4. SAR progression for compounds **22**, **52**, and **86**.

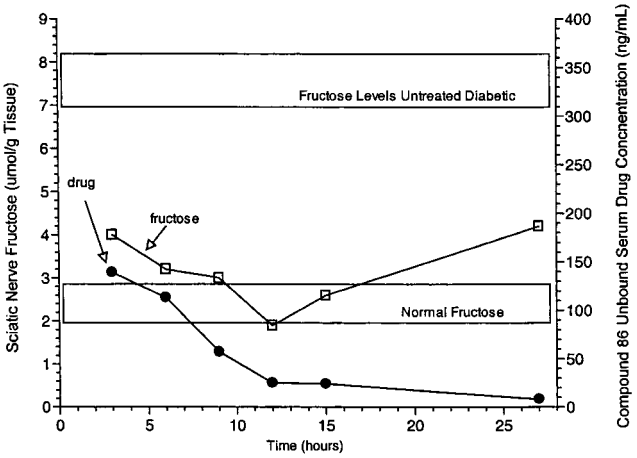


Figure 5. Pharmacokinetic/pharmacodynamic relationship for compound **86** (2 mg/kg/day).

lactate dehydrogenase, alcohol dehydrogenase, fructose dehydrogenase, and glucose-6-phosphate dehydrogenase. Pharmacokinetic/pharmacodynamic studies of compound **86** in 5 day STZ diabetic rats demonstrated a good correlation between sciatic nerve fructose normalization and unbound serum drug concentrations (Figure 5). Compound **86** at a single dose of 2 mg/kg/day normalized sciatic nerve fructose for ~17 h, with some persistent effects even at the last time point (27 h).

Conclusions

In conclusion, novel SDIs with heterocyclic groups replacing the *N*,*N*-dimethylsulfamoyl moiety in **I**/**II** were identified, which were orally effective, highly potent, and long-acting in a key diabetic tissue. The following are the SAR highlights leading to the discovery of **86**, the overall most promising SDI. Replacement of the sulfamide group in CP-166 572 (**I**) with various heterocycles provided modestly active (low micromolar) compounds, demonstrating the initial potential of this series. Incorporation of the (*R*)-hydroxyethyl moiety at the pyrimidine 2-position provided a significant boost in in vitro potency and provided compounds with a good exposure and longer half-life. Although the potency and pharmacokinetics of these new analogues appeared sufficient to provide in vivo activity, there seemed to be another factor that prevented these compounds from achieving maximal activity. On the basis of the hypothesis that penetration into the nerve tissue was a contributing factor, modulation of the overall physical properties of the compounds was accomplished by installing methyl groups on the piperazine linker, which dramatically improved in vivo potency, culminating in identification of **86**. Further testing of **86** showed it to be a selective SDI with excellent pharmacokinetic and pharmacodynamic properties. Additional aspects of the metabolism of **86** in vitro and in different animal species will be reported in due course.

Experimental Section

Chemistry. General Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker AM-250, a Bruker AM-300, a Varian XL-300, or a Varian Unity 400. Chemical shifts are reported in parts per million (δ) relative to residual chloroform (7.26 ppm), dimethyl sulfoxide (2.49 ppm), or methanol (3.30 ppm) as an internal reference with coupling constants (*J*) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; c, complex; br, broad.

Low-resolution mass spectra (MS) were obtained under thermospray (TS) conditions on a Fisons Trio 1000 mass spectrometer, under chemical ionization (CI) conditions on a

Hewlett-Packard 5989A particle beam mass spectrometer, under fast atom bombardment conditions (FAB) conditions on a Kratos Concept 1S mass spectrometer, or under atmospheric pressure chemical ionization (APCI) on a Fisons Platform II spectrometer. Low-resolution gas chromatography (GC) mass spectra were obtained on a Hewlett-Packard 5890 Series II mass chromatograph. High-resolution mass spectra (HRMS) were obtained under FAB conditions on a VG analytical ZAB high field mass spectrometer by M-Scan Inc., West Chester, PA 19830, or under electron impact (EI) conditions on a Kratos Concept 1S mass spectrometer.

Optical rotations were obtained on a Perkin-Elmer 241 MC polarimeter using a standard path length of 1 dcm. Liquid column chromatography was performed using forced flow (flash chromatography) of the indicated solvent on either Baker Silica Gel (40 μm) or EM Sciences Silica Gel 60 in glass columns. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY 11377.

The terms "concentrated" and "evaporated" refer to the removal of solvent using a rotary evaporator at water aspirator pressure or at similar pressures generated by a Büchi B-171 Vacobox or a Büchi B-177 Vacobox with a bath temperature equal to or less than 50 °C. Unless otherwise noted, reagents were obtained from commercial sources and were used without further purification.

2-Methoxymethylpyrimidin-4-yl 2,4,6-Triisopropylbenzenesulfonate (1c). To a solution of 2-methoxymethyl-3H-pyrimidin-4-one[12] (1.50 g, 10.7 mmol), DMAP (0.06 g, 0.15 mmol), and Et_3N (5.94 mL, 42.8 mmol) in CH_2Cl_2 (45 mL) at room temperature was added 2,4,6-triisopropylbenzenesulfonyl chloride (3.90 g, 12.8 mmol). This mixture was allowed to stir at room temperature for 30 min, concentrated, and purified by flash column chromatography ($CHCl_3 \rightarrow$ 1% MeOH/$CHCl_3$) to give 3.96 g (91%) of compound **1c** as a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.72 (d, J = 5.6 Hz, 1 H), 7.20 (s, 2 H), 6.98 (d, J = 5.5 Hz, 1 H), 4.74 (s, 2 H), 4.17 (pentet, J = 6.7 Hz, 2 H), 3.40 (s, 3 H), 2.92 (pentet, J = 6.9 Hz, 1 H), 1.24 (d, J = 6.7 Hz, 18 H).

General Procedure A. Preparation of Compounds 3a−k by Reaction of Activated Pyrimidines 1a−c with Substituted Piperazines 2a−j. A representative experimental procedure for **3a** is given below.

2-Methoxymethyl-4-(4-phenyl-piperazin-1-yl)pyrimidine (3a: R^1 = Phenyl). To a solution of mesylate **1b**[13] (0.72 g, 3.32 mmol) in DME (17 mL) was added Et_3N (1.38 mL, 9.96 mmol) followed by 1-phenyl-piperazine (**2a**, 0.76 mL, 4.98 mmol). This mixture was allowed to stir at reflux for 3 h, cooled to room temperature, and concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give 0.64 g (68%) of compound **3a** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, J = 6.2 Hz, 1 H), 7.32−7.26 (c, 2 H), 6.97−6.88 (c, 3 H), 6.43 (d, J = 6.2 Hz, 1 H), 4.49 (s, 2 H), 3.84−3.81 (c, 4 H), 3.52 (s, 3 H), 3.28−3.24 (c, 4 H); MS (CI/NH_3) 285 (MH^+).

2-Methoxymethyl-4-piperazin-1-yl-pyrimidine (5). To a solution of mesylate **1b** (43.6 g, 0.20 mol) in THF (400 mL) was added piperazine (**4**, 34.4 g, 0.4 mol). This mixture was heated to reflux for 0.5 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated to give 36.6 g (85%) of piperazino-pyrimidine **5** as a light tan solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 6.2 Hz, 1 H), 6.38 (d, J = 6.2 Hz, 1 H), 4.46 (s, 2 H), 3.73−3.66 (c, 4H), 3.45 (s, 3 H), 3.03−2.93 (c, 4H), 2.45 (br s, 1 H); MS (TS) 219 (MH^+).

General Procedure B. Preparation of Compounds 7a−f by Reaction of 2-Methoxymethyl-4-piperazin-1-yl-pyrimidine (5) with Heterocylic Chlorides 6a−f. A representative experimental procedure for **7e** is given below.

2-Methoxymethyl-4-(4-benzoxazol-2-yl-piperazin-1-yl)-pyrimidine (7e: R^1 = Benzoxazol-2-yl). To a solution of piperazino-pyrimidine **5** (0.41 g, 1.98 mmol) in *i*-PrOH (9 mL) was added Et_3N (0.55 mL, 3.96 mmol) followed by 2-chlorobenzoxazole (**6e**, 0.37 mL, 2.85 mmol). This mixture was allowed to stir at room temperature for 0.5 h and concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (2×). The combined organic extracts were washed with water (1×) and brine (1×), dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography ($CHCl_3 \rightarrow$ 5% MeOH, $CHCl_3$) to give 0.46 g (71%) of compound **7e** as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, J = 6.2 Hz, 1 H), 7.37 (d, J = 7.7 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 1 H), 7.18 (td, J = 7.7, 1.1 Hz, 1 H), 7.04 (td, J = 7.7, 1.2 Hz, 1 H), 6.45 (d, J = 6.2 Hz, 1 H), 4.49 (s, 2 H), 3.91−3.79 (c, 8 H), 3.52 (s, 3 H); MS (CI/NH_3) 326 (MH^+).

General Procedure C. Preparation of Compounds 7 g,h by Hydrogenation of Heteroaromatic Chloride Intermediates 7a,b. A representative experimental procedure for **7g** is given below.

2-Methoxymethyl-4-(4-pyrimidin-4-yl-piperazin-1-yl)-pyrimidine (7 g: R^1 = Pyrimidin-4-yl). A mixture of chloropyrimidine **7a** (50 mg, 0.16 mmol), 10% Pd/C (12.5 mg, 25 wt %), and NaOAc (25 mg, 0.31 mmol) in EtOH (50 mL) was hydrogenated at 50 psi for 23 h on a Parr apparatus and then filtered through Celite. The filtrate was evaporated, and the residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to give 38 mg (84%) of compound **7g** as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1 H), 8.24 (d, J = 6.2 Hz, 1 H), 8.21 (d, J = 6.3 Hz, 1 H), 6.48 (d, J = 6.2 Hz, 1 H), 6.38 (d, J = 6.2 Hz, 1 H), 4.45 (s, 2 H), 3.83−3.71 (c, 8 H), 3.48 (s, 3 H); MS (CI/NH_3) 287 (MH^+).

2-Methoxymethyl-4-[4-(2-methoxymethyl-pyrimidin-4-yl)piperazin-1-yl]pyrimidine (8: R^1 = 2-Methoxymethyl-pyrimidin-4-yl). To a solution of 2-methoxymethyl-3H-pyrimidin-4-one[12] (10.0 g, 71.4 mmol), DMAP (0.87 g, 7.14 mmol), and Et_3N (10.9 mL, 78.6 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added Tf_2O (13.2 mL, 78.6 mmol) dropwise. This mixture was allowed to stir at −78 °C for 1 h to give 2-methoxymethyl-pyrimidin-4-yl trifluoromethanesulfonate (**1d**), which was used directly in the next reaction without workup or isolation.

Piperazine (**4**, 6.14 g, 71.4 mmol) was added to the above, and the mixture was slowly warmed to room temperature and allowed to stir overnight, quenched with saturated aqueous $NaHCO_3$, and extracted with dichloromethane (3×). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (10% MeOH/EtOAc) followed by recrystallization (EtOAc) to give compound **8** (3.60 g, 30% based on triflate **1d**) as a white solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.28 (d, J = 6.2 Hz, 2 H), 6.42 (d, J = 6.2 Hz, 2 H), 4.51 (s, 4 H), 3.84−3.76 (c, 8 H), 3.53 (s, 6 H); MS (GC) 330 (M^+).

4-(2-Methoxymethyl-pyrimidin-4-yl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (10). A mixture of chloride **1a** (4.54 g, 28.6 mmol), Boc-piperazine (**9**, 7.68 g, 40.1 mmol), and Et_3N (8.0 mL, 57.2 mmol) in THF (100 mL) was heated to reflux for 3 h, cooled to room temperature, and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (1 → 3% MeOH/$CHCl_3$) to give 8.7 g (99%) of compound **10** as a reddish oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, J = 6.2 Hz, 1 H), 6.37 (d, J = 6.2 Hz, 1 H), 4.56 (s, 2 H), 3.69−3.62 (c, 4 H), 3.54−3.46 (c, 4 H), 3.50 (s, 3 H), 1.46 (s, 9 H); MS (CI/NH_3) 309 (MH^+).

4-(2-Hydroxymethyl-pyrimidin-4-yl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (11). To a solution of methoxymethyl compound **10** (0.74 g, 2.39 mmol) in CH_2Cl_2 (8 mL) at 0 °C with stirring under N_2 was added Et_3N (66 μL, 0.48 mmol) followed by Me_2BBr (1.0 M in DCE, 3.11 mL, 3.11 mL). The ice bath was removed, and this mixture was allowed to stir at room temperature for 1.5 h and then quenched by the careful addition of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with 10% *i*-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (2.5 → 5% MeOH/$CHCl_3$) to give 0.54 g (76%) of the hydroxymethyl compound **11** as a pale yellow

solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.22 (d, J = 6.2 Hz, 1 H), 6.38 (d, J = 6.2 Hz, 1 H), 4.59 (s, 2 H), 3.73−3.62 (c, 4 H), 3.57−3.48 (c, 4 H), 1.49 (s, 9 H).

[4-(4-Piperazin-1-yl)pyrimidin-2-yl]methanol Dihydrochloride Salt (12). A heterogeneous mixture of Boc compound **11** (0.53 g. 1.82 mmol) and 4 N HCl/dioxane (13.7 mL, 54.6 mmol) was allowed to stir at room temperature for 3 h and concentrated to give 0.48 g (99%) of the dihydrochloride salt **12** as a white solid. ^{1}H NMR (CD_3OD, 250 MHz) δ 8.25 (d, J = 6.2 Hz, 1 H), 7.19 (d, J = 6.2 Hz, 1 H), 4.71 (s, 2 H), 4.39−4.27 (c, 2 H), 4.17−4.01 (c, 2 H), 3.51−3.33 (c, 4 H).

{4-[4-(2,6-Dimethyl-pyrimidin-4-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (21). A mixture of the dihydrochloride **12** (0.20 g, 0.74 mmol), 4-chloro-2,6-dimethyl-pyrimidine[27] (**13**, 0.13 g, 0.74 mmol), and i-Pr_2NEt (2.54 mL, 14.7 mmol) in n-BuOH was heated at reflux for 14 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated, diluted with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$ (4×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give 0.085 g (39%) of compound **21** as a white solid. mp 171.5−173.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 6.2 Hz, 1 H), 6.39 (d, J = 6.2 Hz, 1 H), 6.19 (s, 1 H), 4.60 (s, 2 H), 3.87−3.75 (c, 8 H), 2.49 (s, 3 H), 2.34 (s, 3 H); MS (CI/NH_3) 301 (MH^+). Anal. ($C_{15}H_{20}N_6O\cdot0.25H_2O$) C, H, N.

General Procedure D. Preparation of Compounds 14−20 and 22−33 by Deprotection of the Methyl Ether Penultimate Intermediates 3a−k, 7b−h, and 8. BBr_3 Method. [4-(4-Phenyl-piperazin-1-yl)pyrimidin-2-yl]methanol (14: R^1 = Phenyl). To a solution of methyl ether **7a** (0.64 g, 2.25 mmol) in CH_2Cl_2 (22.5 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 6.74 mL, 6.74 mmol). This mixture was allowed to stir with warming to room temperature for 3 h, quenched by the slow addition of saturated aqueous $NaHCO_3$, and stirred vigorously for 1 h. The layers were separated, and the aqueous phase was extracted with 10% i-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (2% MeOH/$CHCl_3$) to give 0.54 g (89%) of compound **14** as a white solid. mp 131−133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J = 6.2 Hz, 1 H), 7.32−7.25 (c, 2 H), 6.97−6.89 (c, 3 H), 6.43 (d, J = 6.2 Hz, 1 H), 4.61 (s, 2 H), 3.84−3.81 (c, 4 H), 3.28−3.25 (c, 4 H); MS (CI/NH_3) 271 (MH^+). Anal. ($C_{15}H_{18}N_4O\cdot0.5H_2O$) C, H, N.

Me_2BBr Method. {4-[4-(1H-Benzimidazol-2-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (24: R^1 = 1H-Benzimidazol-2-yl). To a solution of methyl ether **3e** (0.25 g, 0.77 mmol) in DCE (2.9 mL) at 0 °C was added Et_3N (21.5 μL, 0.15 mmol) followed by a solution of Me_2BBr (1.0 M in DCE, 1.0 mL, 1.0 mmol). The ice bath was removed, and this mixture was allowed to stir at room temperature for 2.5 h, quenched slowly with saturated aqueous $NaHCO_3$, and extracted with 10% i-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography ($CHCl_3$ → 10% MeOH/$CHCl_3$) to give compound **24** (75%) as a light yellow solid. mp 235−237 °C (dec); ^{1}H NMR (CD_3OD, 250 MHz) δ 8.15 (d, J = 6.3 Hz, 1 H), 7.24−7.27 (c, 2 H), 6.99−7.03 (c, 2 H), 6.74 (d, J = 6.3 Hz, 1 H), 4.53 (s, 2 H), 3.90−3.94 (c, 4 H), 3.61−3.65 (c, 4 H); MS (CI/NH_3) 311 (MH^+). Anal. ($C_{16}H_{18}N_6O\cdot0.25H_2O$) C, H, N.

[4-(4-Pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (15: R^1 = Pyridin-2-yl). Prepared from methyl ether **7b** (BBr_3 method) and purified by flash column chromatography (2 → 5% MeOH/$CHCl_3$) to give compound **15** (82%) as a white solid. mp 139−141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20−8.17 (c, 2 H), 7.50 (m, 1 H), 6.67−6.63 (c, 2 H), 6.40 (d, J = 6.2 Hz, 1 H), 4.59 (s, 2 H), 3.81−3.74 (c, 4 H), 3.67−3.64 (c, 4 H); MS (CI/NH_3) 272 (MH^+). Anal. ($C_{14}H_{17}N_5O\cdot0.25H_2O$) C, H, N.

[4-(4-Pyrimidin-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (16: R^1 = Pyrimidin-2-yl). Prepared from methyl ether **7c** (BBr_3 method) and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give compound **16** (76%) as a white solid. mp 164−166 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 4.8 Hz, 2 H), 8.19 (d, J = 6.2 Hz, 1 H), 6.54 (t, J = 4.8 Hz, 1 H), 6.41 (d, J = 6.2 Hz, 1 H), 4.60 (s, 2 H), 3.94−3.91 (c, 4 H), 3.76−3.73 (c, 4 H); MS (CI/NH_3) 273 (MH^+). Anal. ($C_{13}H_{16}N_6O\cdot0.25H_2O$) C, H, N.

[4-(4-Pyrimidin-4-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (17: R^1 = Pyrimdin-4-yl). Prepared from methyl ether **7g** (BBr_3 method) and purified by flash column chromatography (5 → 10% MeOH/CH_2Cl_2) to give compound **17** (quant) as a colorless solid. mp 185−186.5 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.49 (s, 1 H), 8.16 (app d, J = 6.3 Hz, 2 H), 6.81 (d, J = 6.4 Hz, 1 H), 6.69 (d, J = 6.3 Hz, 1 H), 4.53 (s, 2 H), 4.01−3.76 (c, 8 H). HRMS (EI) exact mass calcd for $C_{13}H_{16}N_6O$ 272.1383 (M^+), found 272.1375.

[4-(4-Pyrazin-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (18: R^1 = Pyrazin-2-yl). Prepared from methyl ether **3d** (BBr_3 method) and purified by flash column chromatography (1 → 3% MeOH/CH_2Cl_2) to give compound **18** (95%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, J = 6.2 Hz, 1 H), 8.18 (s, 1 H), 8.11 (d, J = 1.7 Hz, 1 H), 7.92 (d, J = 1.7 Hz, 1 H), 6.43 (d, J = 6.2 Hz, 1 H), 4.52 (s, 2 H), 3.89−3.78 (c, 4 H), 3.78−3.68 (c, 4 H). HRMS (FAB) exact mass calcd for $C_{13}H_{17}N_6O$ 273.1464 (MH^+), found 273.1467.

[4-(4-[1,3,5]Triazin-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (19: R^1 = [1,3,5]-Triazin-2-yl). Prepared from methyl ether **7h** (BBr_3 method) and purified by flash column chromatography (1 → 2.5% MeOH/CH_2Cl_2) to give compound **19** (54%) as a colorless solid. mp 195−196.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 2 H), 8.23 (d, J = 6.2 Hz, 1 H), 6.42 (d, J = 6.2 Hz, 1 H), 4.60 (s, 2 H), 4.02−3.92 (c, 4 H), 3.81−3.70 (c, 4 H). HRMS (EI) exact mass calcd for $C_{12}H_{15}N_7O$ 273.1336 (M^+), found 273.1323.

{4-[4-(4,6-Dimethyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (20: R^1 = 4,6-Dimethyl-pyrimidin-2-yl). Prepared from methyl ether **7c** (BBr_3 method) and purified by flash column chromatography (1 → 10% MeOH/$CHCl_3$ and then 1% NH_4OH in 10% MeOH/$CHCl_3$) to give compound **20** (90%) as a yellow solid. mp 175−176 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, J = 6.1 Hz, 1 H), 6.41 (d, J = 6.2 Hz, 1 H), 6.31 (s, 1 H), 4.60 (s, 2 H), 3.97−3.90 (c, 4 H), 3.79−3.70 (c, 4 H), 2.29 (s, 6 H); MS (APCI) 301 (MH^+). Anal. ($C_{15}H_{20}N_6O\cdot0.25H_2O$) C, H, N.

{4-[4-(2-Hydroxymethyl-pyrimidin-4-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (22: R^1 = 2-Hydroxymethyl-pyrimidin-4-yl). Prepared from methyl ether **8** (BBr_3 method) and tritrated with EtOAc to give compound **22** (65%) as a white solid. mp 237−239 °C (dec); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.14 (d, J = 6.2 Hz, 2 H), 6.67 (d, J = 6.4 Hz, 2 H), 4.52 (s, 4 H), 3.30−3.24 (c, 8 H); MS (APCI) 304 (MH^+). Anal. ($C_{14}H_{18}N_6O_2\cdot0.67H_2O$) C, H; N: calcd, 26.73; found, 26.30.

{4-[4-(4,6-Dichloro[1,3,5]triazin-2-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (23: R^1 = 4,6-Dichloro[1,3,5]triazin-2-yl). Prepared from methyl ether **7b** (BBr_3 method) and purified by flash column chromatography (1 → 2% MeOH/CH_2Cl_2) to give compound **23** (66%) as a white solid. mp 250−255 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J = 6.2 Hz, 1 H), 6.44 (d, J = 6.2 Hz, 1 H), 4.62 (s, 2 H), 4.07−3.92 (c, 4 H), 3.84−3.72 (c, 4 H). HRMS (EI) exact mass calcd for $C_{12}H_{13}Cl_2N_7O$ 341.0558 (M^+), found 341.0517.

[4-(1-Ethyl-1H-benzimidazol-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (25: R^1 = 1-Ethyl-1H-benzimidazol-2-yl). Prepared from methyl ether **3f** (BBr_3 method) and purified by flash column chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$) to give compound **25** (43%) as a white solid. mp 124−126 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, J = 6.2 Hz, 1 H), 7.61 (m, 1 H), 7.26 (m, 1 H), 7.22−7.16 (c, 2 H), 6.46 (d, J = 6.2 Hz, 1 H), 4.61 (s, 2 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.88−3.84 (c, 4 H), 3.52−3.37 (c, 4 H), 1.47 (t, J = 7.2 Hz, 1 H); MS (CI/NH_3) 339 (MH^+). Anal. ($C_{18}H_{22}N_6O\cdot0.25H_2O$) C, H, N.

[4-(Benzothiazol-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (26: R^1 = Benzothiazol-2-yl). Prepared from methyl ether **7d** (BBr_3 method) and purified by flash column chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$) to give compound

26 (62%) as a white solid. mp 192−193 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.62 (d, *J* = 8.3 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.11 (td, *J* = 7.7, 1.1 Hz, 1 H), 6.45 (d, *J* = 6.2 Hz, 1 H), 4.61 (s, 2 H), 3.87−3.83 (c, 4 H), 3.77−3.73 (c, 4 H); MS (CI/NH_3) 328 (MH^+). Anal. ($C_{16}H_{17}N_5OS$) C, H, N.

[4-(4-Benzoxazol-2-yl-piperazin-1-yl)pyrimidin-2-yl]-methanol (27: R^1 = Benzoxazol-2-yl). Prepared from methyl ether **7e** (BBr_3 method) and purified by flash column chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$) to give compound **27** (76%) as a white solid. mp 200−201.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.38 (d, *J* = 7.7 Hz, 1 H), 7.27 (d, *J* = 7.5 Hz, 1 H), 7.19 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.05 (td, *J* = 7.7, 1.2 Hz, 1 H), 6.45 (d, *J* = 6.2 Hz, 1 H), 4.62 (s, 2 H), 3.85−3.79 (c, 8 H); MS (CI/NH_3) 312 (MH^+). Anal. ($C_{16}H_{17}N_5O_2$·0.25H_2O) C, H, N.

{4-[4-(1,1-Dioxo-1H-benzo[*d*]isothiazol-3-yl)piperazin-1-yl]pyrimidin-2-yl}methanol (28: R^1 = 1H-Benzo[*d*]-isothiazol-3-yl *S*,*S*-Dioxide). Prepared from methyl ether **3k** (Me_2BBr method) and purified by flash column chromatography ($CHCl_3$ → 4% MeOH/$CHCl_3$) to give compound **28** (61%) as a pale yellow solid. mp 278−281 °C (dec); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.24 (d, *J* = 5.4 Hz, 2 H), 8.04 (d, *J* = 6.4 Hz, 1 H), 7.90−7.80 (c, 2 H), 6.66 (d, *J* = 6.0 Hz, 1 H), 4.89 (t, *J* = 5.8 Hz, 1 H), 4.39 (d, *J* = 5.8 Hz, 1 H), 4.15−3.85 (c, 8 H); MS (CI/NH_3) 360 (MH^+). Anal. ($C_{16}H_{17}N_5O_3S$·0.25H_2O) C, H, N.

[4-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (29: R^1 = Benzo[*d*]isothiazol-3-yl). Prepared from methyl ether **3g** (Me_2BBr method) and purified by flash column chromatography ($CHCl_3$ → 3% MeOH/$CHCl_3$) to give compound **29** (90%) as a pale yellow solid. mp 134−136 °C (dec); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.52 (td, *J* = 7.5, 0.9 Hz, 1 H), 7.41 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.48 (d, *J* = 6.2 Hz, 1 H), 4.63 (s, 2 H), 3.93−3.89 (c, 4 H), 3.67−3.63 (c, 4 H); MS (CI/NH_3) 328 (MH^+). Anal. ($C_{16}H_{17}N_5OS$·0.5H_2O) C, H, N.

[4-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (30: R^1 = Benzo[*d*]isoxazol-3-yl). Prepared from methyl ether **3h** (BBr_3 method) and purified by flash column chromatography ($CHCl_3$ → 1% MeOH/$CHCl_3$) to give compound **29** (63%) as a light yellow solid. mp 139−141.5 °C (dec); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.53−7.46 (c, 2 H), 7.25 (m, 1 H), 6.47 (d, *J* = 6.2 Hz, 1 H), 4.63 (s, 2 H), 3.93−3.88 (c, 4 H), 3.71−3.66 (c, 4 H); MS (APCI) 312 (MH^+). Anal. ($C_{16}H_{17}N_5O_2$·0.5H_2O) C, H, N.

[4-(4-Isoquinolin-1-yl-piperazin-1-yl)pyrimidin-2-yl]-methanol (31: R^1 = Isoquinolin-1-yl). Prepared from methyl ether **3i** (Me_2BBr method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **31** (70%) as a yellow solid. mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 8.18−8.13 (c, 2 H), 7.80 (d, *J* = 8.3 Hz, 1 H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.56 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.33 (d, *J* = 5.8 Hz, 1 H), 6.49 (d, *J* = 6.2 Hz, 1 H), 4.63 (s, 2 H), 3.96−3.92 (c, 4 H), 3.54−3.50 (c, 4 H); MS (APCI) 322 (MH^+). Anal. ($C_{18}H_{19}N_5O$·0.75H_2O) C, H, N.

[4-(4-Quinolin-2-yl-piperazin-1-yl)pyrimidin-2-yl]methanol (32: R^1 = Quinolin-2-yl). Prepared from methyl ether **3j** (Me_2BBr method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **32** (73%) as a yellow solid. mp 172−174 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J* = 6.2 Hz, 1 H), 7.95 (d, *J* = 9.1 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 1 H), 6.43 (d, *J* = 6.2 Hz, 1 H), 4.62 (s, 2 H), 3.88−3.85 (c, 8 H); MS (APCI) 322 (MH^+). Anal. ($C_{18}H_{19}N_5O$·0.75H_2O) C, H, N.

[4-(4-Quinazolin-4-yl-piperazin-1-yl)pyrimidin-2-yl]-methanol (33: R^1 = Quinazolin-4-yl). Prepared from methyl ether **7f** (Me_2BBr method) and purified by flash column chromatography (1 → 2% MeOH/$CHCl_3$) to give compound **33** (63%) as an off-white solid. mp 207.5−209 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1 H), 8.26 (d, *J* = 6.2 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 6.47 (d, *J* = 6.2 Hz, 1 H), 4.63 (s, 2 H), 3.94−3.90 (c, 8 H); MS (APCI) 323 (MH^+). Anal. ($C_{17}H_{18}N_6O$·H_2O) C, N; H: calcd, 5.92; found, 5.25.

General Procedure K. Preparation of Compounds 35a−d Via Deprotection of *N*-Benzyl Derivatives 47a−d. A representative experimental procedure for **35a** is given below.

1-(4,6-Bis-trifluoromethyl-pyimidin-2-yl)piperazine (35a: R = R′ = Trifluoromethyl). To a solution of *N*-benzyl compound **47a** (0.73 g, 1.80 mmol theory) in MeOH (10 mL) was added HCO_2NH_4 (1.18 g, 18.7 mmol) and 10% Pd/C (145 mg, 20 wt %). This mixture was allowed to stir at reflux for 18 h, cooled to room temperature, filtered through Celite, and concentrated. The residue was purified by flash column chromatography ($CHCl_3$ → 10% MeOH/$CHCl_3$) to give 0.38 g (75% from **45**) of piperazine **35a** as a yellow solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.01 (s, 1 H), 4.03−3.82 (c, 4 H), 3.10−2.88 (c, 4 H); MS (CI/NH_3) 301 (MH^+).

General Procedure E. Preparation of Compounds 36a−h,j−o by Reaction of Activated Pyrimidines 34a−c with Substituted Piperazines 2 g−j and 35a−j. A representative experimental procedure for **36j** is given below.

(*R*)-1-[4-(4-Oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]ethyl Butyrate (36j: R = Butyryl, R^1 = Oxazolo[4,5-b]pyridin-2-yl). To a solution of chlorobutyrate **34c** (0.15 g, 0.73 mmol)[13] in *i*-PrOH (7 mL) was added Et_3N (0.23 mL, 2.0 mmol) followed by 1-(oxazolo[4,5-b]pyridin-2-yl)-piperazine[28] (**35e**, 0.15 g, 0.73 mmol). This mixture was heated at reflux for 15 h, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1.5% MeOH/$CHCl_3$) to give 0.26 g (100%) of compound **36j** as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.33−8.24 (c, 2 H), 7.48 (dd, *J* = 7.8, 1.4 Hz, 1 H), 6.96 (dd, *J* = 7.9, 5.2 Hz, 1 H), 6.44 (d, *J* = 6.2 Hz, 1 H), 5.70 (q, *J* = 6.8 Hz, 1 H), 3.99−3.73 (c, 8 H), 2.41 (t, *J* = 7.5 Hz, 2 H), 1.81−1.66 (c, 2 H), 1.60 (d, *J* = 6.7 Hz, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H); MS (TS) 397 (MH^+).

(*R*)-1-(4-Piperazin-1-yl-pyrimidin-2-yl)ethyl Acetate (37a). A mixture of mesyl acetate **34b** (24.1 g, 92 mmol) and piperazine (**4**, 16.0 g, 184 mmol) in THF (200 mL) was allowed to stir at reflux for 2 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by flash column chromatography (10% MeOH/CH_2Cl_2) to give 24.4 g (88%) of compound **37a** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, *J* = 6.2 Hz, 1 H), 6.34 (d, *J* = 6.2 Hz, 1 H), 5.66 (q, *J* = 6.8 Hz, 1 H), 3.68−3.57 (c, 4 H), 2.98−2.89 (c, 4 H), 2.15 (s, 3 H), 1.58 (d, *J* = 6.8 Hz, 3 H); MS (CI/NH_3) 251 (MH^+).

(*R*)-1-(4-Piperazin-1-yl-pyrimidin-2-yl)ethanol (37b). To a solution of acetate **37a** (1.13 g, 4.51 mmol) in a 3:1:1 mixture of THF/MeOH/H_2O (45 mL) was added LiOH·H_2O (0.57 g, 13.5 mmol). This mixture was allowed to stir at room temperature for 45 min and concentrated. The aqueous residue was extracted with 10% *i*-PrOH/$CHCl_3$ (3×), and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.86 g (92%) of compound **37b** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, *J* = 6.2 Hz, 1 H), 6.34 (d, *J* = 6.2 Hz, 1 H), 4.69 (q, *J* = 6.8 Hz, 1 H), 3.72−3.61 (c, 4 H), 3.03−2.92 (c, 4 H), 1.51 (d, *J* = 6.8 Hz, 3 H); MS (CI/NH_3) 209 (MH^+).

General Procedure F. Preparation of Compounds 39a−d by Reaction of (*R*)-1-(4-Piperazin-1-yl-pyrimidin-2-yl)ethyl Acetate (37a) with Heterocyclic Chlorides 6c,e, 13, and 38. A representative experimental procedure for **39a** is given below.

(*R*)-1-{4-[4-(4,6-Dimethyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethyl acetate (39a: R = Acetyl, R^1 = 4,6-Dimethyl-pyrimidin-2-yl). To a solution of piperazino-pyrimidine **37a** (0.56 g, 2.26 mmol) in *n*-BuOH (7.5 mL) was added *i*-Pr_2NEt (0.79 mL, 4.52 mmol) followed by 2-chloro-4,6-dimethylpyrimidine[29] (**6c**, 0.15 g, 0.73 mmol). This mixture was heated at reflux for 12 h, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous

$NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (EtOAc) to give 0.52 g (65%) of compound **39a** as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, J = 6.2 Hz, 1 H), 6.38 (d, J = 6.2 Hz, 1 H), 6.31 (s, 1 H), 5.67 (q, J = 6.8 Hz, 1 H), 3.96−3.86 (c, 4 H), 3.75−3.67 (c, 4 H), 2.29 (s, 6 H), 2.15 (s, 3 H), 1.58 (d, J = 6.8 Hz, 3 H); MS (CI/NH_3) 357 (MH^+).

1*R*-(4-{4-[2-(1*R*-Butyrloxy-ethyl)pyrimidin-4-yl]piperazin-1-yl}pyrimidin-2-yl)ethyl Butyrate (40: R = Butyryl, R^1 = (*R*)-2-(1-Butyrloxy-ethyl)pyrimidin-4-yl). A mixture of chlorobutyrate **34c** (0.53 g, 2.32 mmol), piperazine (**4**, 0.10 g, 1.16 mmol), and Et_3N (0.48 mL, 3.48 mmol) in *i*-PrOH (11 mL) was heated at reflux for 18 h, cooled to room temperature, and concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (3% MeOH/$CHCl_3$) to give 0.49 g (90%) of compound **40** as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, J = 6.0 Hz, 2 H), 6.36 (d, J = 6.2 Hz, 2 H), 5.67 (q, J = 6.8 Hz, 2 H), 3.84−3.66 (c, 8 H), 2.39 (t, J = 7.5 Hz, 4 H), 1.73−1.62 (c, 4 H), 1.57 (d, J = 6.8 Hz, 6 H), 0.95 (t, J = 7.5 Hz, 6 H); MS (APCI) 471 (MH^+).

General Procedure H. Preparation of Bis(Boc)-guanidines 44 and 48 Using *N,N′*-Bis(*tert*-butoxycarbonyl)-thiourea (43). 4-Benzyl-piperazine-1-*N,N′*-bis(*tert*-butoxycarbonyl)carboxamidine (44). To a solution of 1-benzylpiperazine (**42**, 1.14 mL, 6.58 mmol) and *N,N′*-bis(*tert*-butoxycarbonyl)thiourea[30] (**43**, 2.00 g, 7.24 mmol) in DMF (13 mL) at 0 °C was added Et_3N (1.83 mL, 13.2 mmol) and $HgCl_2$ (1.97 g, 7.24 mmol). This mixture was allowed to warm to room temperature slowly, stirred overnight, diluted with Et_2O, and washed with H_2O (3×) and brine (1×). The organic phase was dried (Na_2SO_4), filtered, and evaporated to give 2.87 g (crude, >100%) of compound **44** as a yellow sticky foam, which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.36−7.20 (c, 5 H), 3.71−3.55 (c, 4 H), 3.53 (s, 2 H), 2.57−2.44 (c, 4 H), 1.52 (s, 9 H), 1.48 (s, 9 H); MS (CI/NH_3) 419 (MH^+).

(*R*)-4-[2-(1-Acetoxy-ethyl)pyrimidin-4-yl]piperazine-1-*N,N′*-bis(*tert*-butoxycarbonyl)carboxamidine (48). Prepared from piperazino-pyrimidine **37a**, to give compound **48** (100%) as a yellow foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, J = 6.2 Hz, 1 H), 6.36 (d, J = 6.2 Hz, 1 H), 5.67 (q, J = 6.8 Hz, 1 H), 3.80−3.63 (c, 8 H), 2.15 (s, 3 H), 1.57 (d, J = 6.8 Hz, 3 H), 1.51 (s, 9 H), 1.49 (s, 9 H); MS (TS) 493 (MH^+).

General Procedure I. Preparation of Guanidine Bis(trifluoroacetate) Salts 45 and 49 by TFA Deprotection of Bis(Boc)-guanidines 44 and 48. 4-Benzyl-piperazine-1-carboxamidine bis(trifluoroacetate) Salt (45). To a solution of bis(Boc)-guanidine **44** (2.87 g, 6.58 mmol theory) in CH_2Cl_2 (52.5 mL) was added TFA (17.5 mL, 25% v/v). This mixture was allowed to stir at room temperature for 3 h, concentrated, and chased with EtOH (1×) and Et_2O (1×) to give 2.70 g (94% from **42**) of guanidine bis(trifluoroacetate) salt **45** as a white solid. ^{1}H NMR (CD_3OD, 250 MHz) δ 7.56−7.38 (c, 5 H), 4.37 (s, 2 H), 3.87−3.69 (c, 4 H), 3.44−3.32 (c, 4 H); MS (CI/NH_3) 219 (MH^+).

(*R*)-4-[2-(1-Acetoxy-ethyl)pyrimidin-4-yl]piperazine-1-carboxamidine Bis(trifluoroacetate) Salt (49). Prepared from bis(Boc)-guanidine **48**, to give compound **49** (76%) as a white solid. ^{1}H NMR (CD_3OD, 250 MHz) δ 8.23 (d, J = 6.2 Hz, 1 H), 7.04 (d, J = 6.2 Hz, 1 H), 5.68 (q, J = 6.8 Hz, 1 H), 4.14−4.03 (c, 4 H), 3.78−3.69 (c, 4 H), 2.16 (s, 3 H), 1.63 (d, J = 6.8 Hz, 3 H); MS (TS) 293 (MH^+).

General Procedure J. Preparation of Compounds 47a−d, 63, and 64 by Condensation of Guanidine Bis(trifluoroacetate) Salts 45 and 49 with Dicarbonyls/Dicarbonyl Equivalents 46a−f. Representative experimental procedures for **47a**, **63**, and **64** are given below.

2-(4-Benzyl-piperazin-1-yl)-4,6-bis-trifluoromethyl-pyrimidine (47a: R = R′ = Trifluoromethyl). To a solution of *i*-PrONa/*i*-PrOH [freshly prepared by refluxing sodium metal (195 mg, 8.50 mmol, washed with hexanes) in freshly distilled *i*-PrOH (8.5 mL) for 15 min] was added guanidine bis(trifluroracetate) salt **45** (0.71 g, 1.70 mmol) followed by an additional aliquot of freshly distilled *i*-PrOH (8.5 mL). After the solution was refluxed for 1 h, hexafluoro-2,4-pentanedione (**46a**, 2.4 mL, 17.0 mmol) was added and the resulting mixture was allowed to stir at reflux for 19 h, cooled to room temperature, and concentrated. The residue was suspended in saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give 0.73 g (>100%) of pyrimidinyl-piperazine **47a** as a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.39−7.26 (c, 5 H), 6.98 (s, 1 H), 3.99−3.88 (c, 4 H), 3.57 (s, 2 H), 2.57−2.48 (c, 4 H); MS (CI/NH_3) 391 (MH^+).

(*R*)-1-{4-[4-(4-Methyl-6-phenyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (63: R = Methyl, R′ = Phenyl). Prepared from pyrimidino-piperazine **49** and 1-benzoylacetone (**46e**) and purified by flash column chromatography ($CHCl_3$ → 10% MeOH/$CHCl_3$) to give compound **63** (94%) as a yellow sticky material. $[\alpha]_D$ +13.5 (c 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.24 (d, J = 6.2 Hz, 1 H), 8.20−8.10 (c, 2 H), 7.52−7.43 (c, 3 H), 6.95 (s, 1 H), 6.44 (d, J = 6.2 Hz, 1 H), 4.74 (q, J = 6.6 Hz, 1 H), 4.37 (br s, 1 H), 4.12−4.03 (c, 4 H), 3.85−3.76 (c, 4 H), 2.45 (s, 3 H), 1.54 (d, J = 6.6 Hz, 3 H); MS (TS) 377 (MH^+). Anal. ($C_{21}H_{24}N_6O$) C, H, N.

(*R*)-1-{4-[4-(4-Phenyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (64: R = Hydrogen, R′ = Phenyl). Prepared from pyrimidino-piperazine **49** and 3-(dimethylamino)-1-phenyl-propenone[31] (**46f**) and purified by flash column chromatography ($CHCl_3$ → 10% MeOH/$CHCl_3$) to give compound **64** (93%) as a reddish oil. $[\alpha]_D$ +12.9 (c 1.8, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.42 (d, J = 5.2 Hz, 1 H), 8.25 (d, J = 6.2 Hz, 1 H), 8.11−8.02 (c, 2 H), 7.53−7.44 (c, 3 H), 7.03 (d, J = 5.2 Hz, 1 H), 6.45 (d, J = 6.2 Hz, 1 H), 4.74 (q, J = 6.8 Hz, 1 H), 4.35 (br s, 1 H), 4.11−4.04 (c, 4 H), 3.89−3.76 (c, 4 H), 1.54 (d, J = 6.6 Hz, 3 H); MS (TS) 363 (MH^+). Anal. ($C_{20}H_{22}N_6O\cdot0.25H_2O$) C, H, N.

General Procedure G. Preparation of Compounds 50−62 and 65−70 by Hydrolysis of the Ester Protecting Group in Penultimate Intermediates 36a−g,i−o, 39a−d, and 40. LiOH Method. (*R*)-1-[4-(4-Oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (65: R^1 = Oxazolo[4,5-b]pyridin-2-yl). To a solution of butyrate **36j** (0.26 g, 0.66 mmol) in a 3:1:1 mixture of THF/MeOH/H_2O (12 mL) at 0 °C was added LiOH·H_2O (36 mg, 0.85 mmol). This mixture was slowly warmed to room temperature, stirred for 2 h, and evaporated. The residue was diluted with H_2O and extracted with $CHCl_3$ (4×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (2% MeOH/$CHCl_3$) to give 0.15 g (69%) of compound **65** as a white solid. mp 190−191.5 °C; $[\alpha]_D$ +14.5 (c 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27−8.24 (c, 2 H), 7.47 (dd, J = 8.0, 1.4 Hz, 1 H), 6.95 (dd, J = 7.8, 5.1 Hz, 1 H), 6.46 (d, J = 6.2 Hz, 1 H), 4.72 (q, J = 6.6 Hz, 1 H), 4.25 (br s, 1 H), 3.87−3.85 (c, 8 H), 1.51 (d, J = 6.6 Hz, 3 H); MS (CI/NH_3) 327 (MH^+). Anal. ($C_{16}H_{18}N_6O_2$) C, H, N.

K_2CO_3 Method. (*R*)-1-[4-(4-Oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (67: R^1 = Oxazolo-[5,4-c]pyridin-2-yl). To a solution of butyrate **36l** (3.27 g, 8.24 mmol) in MeOH (82 mL) was added K_2CO_3 (2.28 g, 16.5 mmol). This mixture was stirred at room temperature for 4 h, quenched with saturated aqueous NH_4Cl (0.88 g, 16.5 mmol), and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (5×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give 2.42 g (90%) of compound **67** as a white solid. mp 181−183 °C; $[\alpha]_D$ +15.3 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, J = 0.5 Hz, 1 H), 8.35 (d, J = 5.3 Hz, 1 H), 8.25 (d, J = 6.2 Hz, 1 H), 7.27 (dd, J = 5.3, 0.7 Hz, 1 H), 6.44 (d, J = 6.2 Hz, 1 H), 4.71 (q, J = 6.6 Hz, 1 H), 4.25 (br s, 1 H), 3.86−3.83 (c, 8 H), 1.50 (d, J = 6.6 Hz, 3 H); MS (CI/NH_3) 327 (MH^+). Anal. ($C_{16}H_{18}N_6O_2$) C, H, N.

(*R*)-1-{4-[4-(4,6-Dimethyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (50: R^1 = 4,6-Dimethyl-pyrimidin-2-yl). Prepared from acetate **39a** (LiOH method) and purified by flash column chromatography ($CHCl_3$ → 1% MeOH/$CHCl_3$) to give compound **50** (100%) as a slightly yellow solid. mp 132−133 °C; $[\alpha]_D$ +16.6 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, *J* = 6.2 Hz, 1 H), 6.40 (d, *J* = 6.2 Hz, 1 H), 6.31 (s, 1 H), 4.73 (q, *J* = 6.6 Hz, 1 H), 4.36 (br s, 1 H), 3.99−3.91 (c, 4 H), 3.81−3.72 (c, 4 H), 2.29 (s, 6 H), 1.50 (d, *J* = 6.6 Hz, 3 H); MS (CI/NH_3) 315 (MH^+). Anal. ($C_{16}H_{22}N_6O$) C, H, N.

(*R*)-1-{4-[4-(2,6-Dimethyl-pyrimidin-4-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (51: R^1 = 2,6-Dimethyl-pyrimidin-4-yl). Prepared from acetate **39b** (LiOH method) and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give compound **51** (78%) as a white solid. mp 125.5−127 °C; $[\alpha]_D$ +17.3 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 6.41 (d, *J* = 6.2 Hz, 1 H), 6.21 (s, 1 H), 4.74 (m, 1 H), 4.30 (d, *J* = 4.4 Hz, 1 H), 3.85−3.80 (c, 8 H), 2.52 (s, 3 H), 2.36 (s, 3 H), 1.53 (d, *J* = 6.8 Hz, 3 H); MS (APCI) 315 (MH^+). Anal. ($C_{16}H_{22}N_6O{\cdot}0.25H_2O$) C, H, N.

1*R*-(4-{4-[2-(1*R*-Hydroxyethyl)pyrimidin-4-yl]piperazin-1-yl}pyrimidin-2-yl)ethanol (52: R^1 = (*R*)-2-(1-Hydroxyethyl)pyrimidin-4-yl). Prepared from dibutyrate **40** (LiOH method, 3:1 MeOH/H_2O) and purified by tritration (EtOAc) to give compound **52** (76%) as a white solid. mp 158−160 °C; $[\alpha]_D$ +32.4 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, *J* = 6.0 Hz, 2 H), 6.40 (d, *J* = 6.2 Hz, 2 H), 4.71 (m, 2 H), 4.27 (m, 2 H), 3.90−3.70 (c, 8 H), 1.51 (d, *J* = 6.8 Hz, 6 H); MS (APCI) 331 (MH^+). Anal. ($C_{16}H_{22}N_6O_2$) C, H, N.

(*R*)-1-[4-(4-Benzoxazol-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (53: R^1 = Benzoxazol-2-yl). Prepared from acetate **39c** (LiOH method) and purified by flash column chromatography (3% MeOH/$CHCl_3$) to give compound **53** (77%) as a white solid. mp 139−141 °C; $[\alpha]_D$ +14.4 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.26 (d, *J* = 6.2 Hz, 1 H), 7.38 (dd, *J* = 7.8, 0.7 Hz, 1 H), 7.30 (dd, *J* = 7.8, 0.5 Hz, 1 H), 7.19 (td, 7.6, 1.2 Hz, 1 H), 7.06 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.46 (d, *J* = 6.2 Hz, 1 H), 4.74 (q, *J* = 6.6 Hz, 1 H), 4.29 (br s, 1 H), 3.90−3.74 (c, 8 H), 1.53 (d, *J* = 6.6 Hz, 3 H); MS (CI/NH_3) 326 (MH^+). Anal. ($C_{17}H_{19}N_5O_2{\cdot}0.5H_2O$) C, H, N.

(*R*)-1-[4-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (54: R^1 = Benzo[*d*]isothiazol-3-yl). Prepared from acetate **36a** (LiOH method) and purified by flash column chromatography (4% MeOH/$CHCl_3$) to give compound **54** (80%) as a white foam. $[\alpha]_D$ +16.2 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.94 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.85 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.51 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1 H), 6.47 (d, *J* = 6.2 Hz, 1 H), 4.75 (q, *J* = 6.6 Hz, 1 H), 3.94−3.89 (c, 4 H), 3.67−3.63 (c, 4 H), 1.54 (d, *J* = 6.6 Hz, 3 H); MS (APCI) 342 (MH^+). Anal. ($C_{17}H_{19}N_5OS$) C, H, N.

(*R*)-1-[4-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (55: R^1 = Benzo[*d*]isoxazol-3-yl). Prepared from acetate **36b** (LiOH method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **55** (70%) as a white solid. mp 129−131 °C; $[\alpha]_D$ +23.0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.53−7.46 (c, 2 H), 7.25 (m, 1 H), 6.47 (d, *J* = 6.2 Hz, 1 H), 4.75 (q, *J* = 6.6 Hz, 1 H), 4.30 (br s, 1 H), 3.93−3.88 (c, 4 H), 3.67−3.63 (c, 4 H), 1.54 (d, *J* = 6.7 Hz, 3 H); MS (APCI) 326 (MH^+). Anal. ($C_{17}H_{19}N_5O_2{\cdot}0.25H_2O$) C, H, N.

(*R*)-1-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (56: R^1 = Isoquinolin-1-yl). Prepared from acetate **36c** (LiOH method) and purified by flash column chromatography (3% MeOH/$CHCl_3$) to give compound **56** (54%) as a colorless gum. $[\alpha]_D$ +16.7 (*c* 1.4, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, *J* = 6.2 Hz, 1 H), 8.18−8.13 (c, 2 H), 7.80 (d, *J* = 7.7 Hz, 1 H), 7.65 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.56 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.32 (d, *J* = 5.7 Hz, 1 H), 6.48 (d, *J* = 6.2 Hz, 1 H), 4.75 (q, *J* = 6.6 Hz, 1 H), 4.48 (br s, 1 H), 3.96−3.92 (c, 4 H), 3.54−3.52 (c, 4 H), 1.54 (d, *J* = 6.6 Hz, 3 H); MS (APCI) 336 (MH^+). Anal. ($C_{19}H_{21}N_5O{\cdot}0.5H_2O$) C, H, N.

(*R*)-1-[4-(4-Quinolin-2-yl-piperazin-1-yl)pyrimidin-2-yl]-ethanol (57: R^1 = Quinolin-2-yl). Prepared from acetate **36d** (LiOH method) and purified by flash column chromatography (0.5% MeOH/$CHCl_3$) to give compound **57** (54%) as a white foam. $[\alpha]_D$ +17.4 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, *J* = 6.1 Hz, 1 H), 7.94 (d, *J* = 9.1 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.56 (t, *J* = 6.1 Hz, 1 H), 7.25 (t, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 1 H), 6.42 (d, *J* = 6.1 Hz, 1 H), 4.73 (q, *J* = 6.6 Hz, 1 H), 3.88−3.85 (c, 8 H), 1.53 (d, *J* = 6.6 Hz, 3 H); MS (APCI) 336 (MH^+). Anal. ($C_{19}H_{21}N_5O{\cdot}1.25H_2O$) C, H, N.

(*R*)-1-{4-[4-(4-Methyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (58: R^1 = 4-Methyl-pyrimidin-2-yl). Prepared from a 1:1 mixture of acetate **39d** and desired compound **58** (LiOH method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **58** (25% for 2 steps from **37a**) as a white solid. mp 116−117.5 °C; $[\alpha]_D$ +14.9 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20 (d, *J* = 6.3 Hz, 1 H), 8.18 (d, *J* = 5.0 Hz, 1 H), 6.45−6.35 (c, 2 H), 4.71 (q, *J* = 6.6 Hz, 1 H), 4.68 (br s, 1 H), 3.98−3.87 (c, 4 H), 3.80−3.67 (c, 4 H), 2.34 (s, 3 H), 1.51 (d, *J* = 6.6 Hz, 3 H); MS (APCI) 301 (MH^+). Anal. ($C_{15}H_{20}N_6O$) C, H, N.

(*R*)-1-{4-[4-(4,6-Bis-trifluoromethyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (59: R^1 = 4,6-Bis-trifluoromethyl-pyrimidin-2-yl). Prepared from acetate **36e** (LiOH method) and purified by flash column chromatography ($CHCl_3$ → 1% MeOH/$CHCl_3$) to give compound **59** (96%) as a pale yellow solid. mp 156.5−158 °C; $[\alpha]_D$ +12.2 (*c* 1.4, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, *J* = 6.2 Hz, 1 H), 7.03 (s, 1 H), 6.42 (d, *J* = 6.2 Hz, 1 H), 4.69 (q, *J* = 6.6 Hz, 1 H), 4.11−3.93 (c, 4 H), 3.89−3.70 (c, 4 H), 1.49 (d, *J* = 6.7 Hz, 3 H); MS (APCI) 423 (MH^+). Anal. ($C_{16}H_{16}F_6N_6O$) C, H, N.

(*R*)-1-{4-[4-(4,6-Diethyl-pyrimidin-2-yl)piperazin-1-yl]-pyrimidin-2-yl}ethanol (60: R^1 = 4,6-Diethyl-pyrimidin-2-yl). Prepared from acetate **36f** (LiOH method) and purified by flash column chromatography ($CHCl_3$ → 2.5% MeOH/$CHCl_3$) to give compound **60** (75%) as a yellow solid. mp 104−105 °C; $[\alpha]_D$ +17.0 (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, *J* = 6.2 Hz, 1 H), 6.39 (d, *J* = 6.2 Hz, 1 H), 6.30 (s, 1 H), 4.39 (m, 1 H), 4.38 (br s, 1 H), 4.01−3.91 (c, 4 H), 3.82−3.68 (c, 4 H), 2.56 (q, *J* = 7.6 Hz, 4 H), 1.49 (d, *J* = 6.6 Hz, 3 H), 1.22 (t, *J* = 7.7 Hz, 6 H); MS (CI/NH_3) 343 (MH^+). Anal. ($C_{18}H_{26}N_6O{\cdot}0.25H_2O$) C, H, N.

(*R*)-1-{4-[4-(4,6-Diisopropyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (61: R^1 = 4,6-Diisopropyl-pyrimidin-2-yl). Prepared from acetate **36g** (LiOH method) and purified by flash column chromatography (5% MeOH/$CHCl_3$) to give compound **61** (85%) as a slightly yellow solid. mp 82−83.5 °C; $[\alpha]_D$ +14.5 (*c* 1.7, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J* = 6.2 Hz, 1 H), 6.42 (d, *J* = 6.2 Hz, 1 H), 6.33 (s, 1 H), 4.75 (m, 1 H), 4.38 (m, 1 H), 4.03−3.94 (c, 4 H), 3.81−3.72 (c, 4 H), 2.80 (septet, *J* = 6.9 Hz, 2 H), 1.53 (d, *J* = 6.6 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 12 H). MS (CI/NH_3): 371 (MH^+); MS (CI/NH_3) 371 (MH^+). Anal. ($C_{20}H_{30}N_6O$) C, H, N.

(*R*)-1-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (62: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl). Prepared from acetate **36i** (LiOH method) and purified by tritration (*i*-PrOH) to give compound **62** (83%) as a white solid. mp 139−140 °C; $[\alpha]_D$ +21.6 (*c* 2.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, *J* = 6.1 Hz, 1 H), 6.41 (d, *J* = 6.2 Hz, 1 H), 6.37 (s, 1 H), 4.71 (m, 1 H), 4.54 (s, 2 H), 4.32 (d, *J* = 4.7 Hz, 1 H), 4.02−3.93 (c, 4 H), 3.78−3.68 (c, 4 H), 3.65 (br s, 1 H), 2.34 (s, 3 H), 1.51 (d, *J* = 6.6 Hz, 3 H); MS (TS) 331 (MH^+). Anal. ($C_{16}H_{22}N_6O_2$) C, H, N.

(*R*)-1-[4-(4-Oxazolo[4,5-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]ethanol (66: R^1 = Oxazolo[4,5-c]pyridin-2-yl). Prepared from butyrate **36k** (LiOH method) and purified by flash column chromatography (2 → 5% MeOH/$CHCl_3$) to give compound **66** (37%) as a white solid. mp 178−180 °C; $[\alpha]_D$ +17.1 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.69 (s, 1 H), 8.34 (d, *J* = 5.3 Hz, 1 H), 8.27 (d, *J* = 6.1 Hz, 1 H), 7.27 (d, *J* = 5.3 Hz, 1 H), 6.46 (d, *J* = 6.1 Hz, 1 H), 4.74 (q, *J* = 6.6 Hz,

1 H), 3.87−3.83 (c, 8 H), 1.52 (d, J = 6.6 Hz, 3 H); MS (TS) 327 (MH^+). Anal. ($C_{16}H_{18}N_6O_2$·0.25H_2O) C, H, N.

(*R*)-1-[4-(4-Oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]ethanol (68: R^1 = Oxazolo[5,4-b]pyridin-2-yl). Prepared from butyrate **36m** (LiOH method) and purified by flash column chromatography (2% MeOH/$CHCl_3$) to give compound **68** (80%) as a white solid. mp 153−156 °C; $[\alpha]_D$ +16.1 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, J = 6.2 Hz, 1 H), 7.95 (dd, J = 5.1, 1.5 Hz, 1 H), 7.58 (dd, J = 7.7, 1.5 Hz, 1 H), 7.15 (dd, J = 7.7, 5.1 Hz, 1 H), 6.45 (d, J = 6.2 Hz, 1 H), 4.72 (q, J = 6.6 Hz, 1 H), 4.25 (br s, 1 H), 3.85−3.82 (c, 8 H), 1.51 (d, J = 6.6 Hz, 3 H); MS (CI/NH_3) 327 (MH^+). Anal. ($C_{16}H_{18}N_6O_2$) C, H, N.

(*R*)-1-[4-(Quinoxalin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (69: R^1 = Quinoxalin-2-yl). Prepared from acetate **36n** (LiOH method) and purified by flash column chromatography (2×; 2% MeOH/$CHCl_3$) followed by tritration (hexanes) to give compound **69** (90%) as a pale yellow solid. mp 106−108 °C; $[\alpha]_D$ +16.6 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.62 (s, 1 H), 8.26 (d, J = 6.1 Hz, 1 H), 7.92 (dd, J = 8.2, 1.0 Hz, 1 H), 7.72 (dd, J = 8.3, 1.1 Hz, 1 H), 7.61 (td, J = 8.4, 1.4 Hz, 1 H), 7.44 (td, J = 8.1, 1.5 Hz, 1 H), 6.45 (d, J = 6.2 Hz, 1 H), 4.75 (m, 1 H), 4.32 (br s, 1 H), 3.95−3.85 (c, 8 H), 1.54 (d, J = 6.8 Hz, 3 H); MS (CI/NH_3) 337 (MH^+). Anal. ($C_{18}H_{20}N_6O$) C, H, N.

(*R*)-1-{4-[4-(3-Methyl-quinoxalin-2-yl)piperazin-1-yl]-pyrimidin-2-yl}ethanol (70: R^1 = 3-Methyl-quinoxalin-2-yl). Prepared from acetate **36o** (LiOH method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **70** (88%) as a yellow solid. mp 145−147 °C; $[\alpha]_D$ +13.7 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, J = 6.1 Hz, 1 H), 7.92 (d, J = 7.7 Hz, 1 H), 7.83 (d, J = 7.7 Hz, 1 H), 7.63−7.52 (c, 2 H), 6.47 (d, J = 6.1 Hz, 1 H), 4.74 (q, J = 6.6 Hz, 1 H), 3.95−3.85 (c, 4 H), 3.55−3.45 (c, 4 H), 2.76 (s, 3 H), 1.54 (d, J = 6.6 Hz, 3 H); MS (APCI) 351 (MH^+). Anal. ($C_{19}H_{22}N_6O$·0.5H_2O) C, N; H: calcd, 6.45; found, 6.04.

(*R*)-1-{4-[4-(6,7-Dichloro-quinoxalin-2-yl)piperazin-1-yl]pyrimidin-2-yl}ethanol (71: R^1 = 6,7-Dichloro-quinoxalin-2-yl). To a solution of amino-alcohol **37b** (60 mg, 0.29 mmol) in *i*-PrOH (6 mL) was added Et_3N (0.12 mL, 0.86 mmol) followed by 2,6,7-trichloroquinoxaline[32] (81 mg, 0.35 mmol). This mixture was heated to reflux for 4 h, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (2×) followed by 10% *i*-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (2% MeOH/$CHCl_3$) followed by tritration (hexanes) to give compound **71** (52%) as a yellow solid. mp 143−145 °C; $[\alpha]_D$ +13.4 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1 H), 8.25 (d, J = 6.1 Hz, 1 H), 7.96 (s, 1 H), 7.78 (s, 1 H), 6.42 (d, J = 6.1 Hz, 1 H), 4.72 (q, J = 6.6 Hz, 1 H), 4.28 (br s, 1 H), 3.95−3.85 (c, 8 H), 1.51 (d, J = 6.6 Hz, 3 H); MS (TS) 405, 407 (MH^+). Anal. ($C_{18}H_{18}Cl_2N_6O$·0.25H_2O) C, H, N.

1*R*-[4-(4-Benzyl-2*R*,6*S*-dimethyl-piperazin-1-yl)pyrimidin-2-yl]ethyl Butyrate (73a). From Chloropyrimidine 34c. A mixture of chloropyrimidine **34c** (1.00 g, 4.38 mmol) and *cis*-1-benzyl-3,5-dimethyl-piperazine[19] (**72a**, 3.57 g, 17.5 mmol) was heated at 150−155 °C for 24 h, cooled to room temperature, and purified by flash column chromatography (1:4 → 1:1 EtOAc/hexanes) to give 1.00 g (58%) of compound **73a** as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 6.2 Hz, 1 H), 7.39−7.24 (c, 5 H), 6.25 (d, J = 6.2 Hz, 1 H), 5.66 (q, J = 6.6 Hz, 1 H), 4.45 (m, 1 H), 4.24 (m, 1 H), 3.52 (s, 2 H), 2.73 (d, J = 11.2 Hz, 2 H), 2.37 (t, J = 7.4 Hz, 2 H), 2.22 (d, J = 10.5 Hz, 2 H), 1.70−1.60 (c, 2 H), 1.55 (d, J = 6.8 Hz, 3 H), 1.30 (d, J = 6.6 Hz, 3 H), 1.27 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); MS (APCI) 397 (MH^+); HPLC (Chiralpak AD, 90:10 hexane/*i*-PrOH +0.1% DEA, 1 mL/min) 6.00 min (89.6 area %), 8.87 min (10.4 area %).

From Triflate 34d. To a solution of (*R*)-1-(4-hydroxy-pyrimidin-2-yl)ethyl butyrate[13] (52 g, 0.25 mol) and Et_3N (36.2 mL, 0.26 mol) in CH_2Cl_2 (700 mL) at 0 °C with stirring under N_2 was added a solution of Tf_2O (44 mL, 0.260 mol) in CH_2Cl_2 (130 mL) dropwise via an addition funnel over 50 min, keeping the internal temperature below 10 °C. After 15 min, the ice bath was removed and the reaction mixture was quenched with water. The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×) and H_2O (1×), dried (Na_2SO_4), filtered, and evaporated to give 85 g (crude, >100%) of triflate **34d** as a dark oil, which was used immediately in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, J = 5.4 Hz, 1 H), 7.03 (d, J = 5.6 Hz, 1 H), 5.82 (q, J = 6.8 Hz, 1 H), 2.41−2.32 (c, 2 H), 1.72−1.60 (c, 2 H), 1.62 (d, J = 6.8 Hz, 3 H), 0.95 (t, J = 7.5 Hz, 3 H); MS (APCI) 343 (MH^+).

A mixture of triflate **34d** (0.25 mol, theory) and *cis*-1-benzyl-3,5-dimethyl-piperazine[19] (**72a**, 101 g, 0.50 mol) in CH_3CN (310 mL) was heated at reflux for 15 h, concentrated, and purified by flash column chromatography (15% EtOAc/hexanes) to give 52 g (53%) of compound **73a** as an orange oil. ^{1}H NMR and MS data as above. HPLC (Chiralpak AD, 90:10 hexane/*i*-PrOH +0.1% DEA, 1 mL/min) 6.17 min (93.5 area %), 9.31 min (6.5 area %).

Compound **73a** (131 g, 79% ee) was purified by chiral HPLC under the following conditions (column: 15 cm id × 25 cm Prochrom column packed with Chiracel AD; mobile phase: 90:10 *n*-heptane/*i*-PrOH; flow rate: ∼1 L/min; loading: 4.2 g/cycle) to provide the (*R*)-enantiomer (109 g, >98% ee) as a yellow oil.

1*R*-[4-(4-Benzyl-2*S*-methyl-piperazin-1-yl)pyrimidin-2-yl]ethyl Butyrate (73b). A mixture of chloropyrimidine **34c** (1.83 g, 8.0 mmol), (*S*)-1-benzyl-3-methyl-piperazine[20] (**72b**, 1.52 g, 8.0 mmol), and *i*-Pr_2NEt (2.78 mL, 16.0 mmol) in *n*-BuOH (20 mL) was allowed to stir at reflux for 22 h, cooled to room temperature, and concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1:4 → 2:1 EtOAc/hexanes) to give 2.12 g (69%) of compound **73b** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 6.2 Hz, 1 H), 7.34−7.23 (c, 5 H), 6.28 (d, J = 6.2 Hz, 1 H), 5.66 (q, J = 6.6 Hz, 1 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.57 (d, J = 13.3 Hz, 1 H), 3.43 (d, J = 13.3 Hz, 1 H), 3.13 (td, J = 12.8, 3.5 Hz, 1 H), 2.89 (d, J = 11.2 Hz, 1 H), 2.71 (d, J = 11.2 Hz, 1 H), 2.36 (t, J = 7.4 Hz, 2 H), 2.19 (dd, J = 11.2, 3.8 Hz, 1 H), 2.09 (td, J = 12.1, 3.6 Hz, 1 H), 1.71−1.61 (c, 2 H), 1.55 (d, J = 6.6 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); MS (APCI) 383 (MH^+).

1*R*-[4-(4-Benzyl-2*R*-methyl-piperazin-1-yl)pyrimidin-2-yl]ethyl Butyrate (73c). Prepared from (*R*)-1-benzyl-3-methyl-piperazine,[20] following the procedure for **73b**, and was purified by flash column chromatography (1:4 → 2:1 EtOAc/hexanes) to give compound **73c** (65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, J = 6.2 Hz, 1 H), 7.34−7.23 (c, 5 H), 6.26 (d, J = 6.2 Hz, 1 H), 5.65 (q, J = 6.6 Hz, 1 H), 4.46 (m, 1 H), 4.10 (m, 1 H), 3.56 (d, J = 13.3 Hz, 1 H), 3.42 (d, J = 13.3 Hz, 1 H), 3.15 (m, 1 H), 2.88 (d, J = 11.2 Hz, 1 H), 2.70 (d, J = 11.2 Hz, 1 H), 2.36 (t, J = 7.4 Hz, 2 H), 2.19 (m, 1 H), 2.08 (m, 1 H), 1.70−1.60 (c, 2 H), 1.54 (d, J = 6.8 Hz, 3 H), 1.23 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H); MS (APCI) 383 (MH^+).

General Procedure L. Preparation of Compounds 74a−c by Debenzylation of Compounds 73a−c. A representative experimental procedure for **74a** is given below.

1*R*-[4-(2*R*,6*S*-Dimethyl-piperazin-1-yl)pyrimidin-2-yl]-ethyl Butyrate (74a). To a solution of benzyl compound **73a** (4.85 g, 12.2 mmol) in MeOH (20 mL) was added HCl (5 M in MeOH, 2.6 mL, 12.9 mmol). After 5 min, HCO_2NH_4 (7.70 g, 122 mmol) was added followed by a slurry of 10% Pd/C (0.73 g, 15 wt %) in MeOH (41 mL). This mixture was stirred at reflux for 1 h and an additional portion of 10% Pd/C (0.1 g) was added. After 30 min, this mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated, diluted with saturated aqueous $NaHCO_3$, and extracted with 10% *i*-PrOH/$CHCl_3$ (2×). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give 3.54 g (95%) of compound **74a** as a yellow oil, which was

sufficiently pure to carry on to the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 6.2 Hz, 1 H), 6.25 (d, J = 6.2 Hz, 1 H), 5.66 (q, J = 6.6 Hz, 1 H), 4.39 (m, 1 H), 4.22 (m, 1 H), 2.95−2.88 (c, 4 H), 2.36 (t, J = 7.5 Hz, 2 H), 1.71−1.62 (c, 2 H), 1.55 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 7.1 Hz, 3 H), 1.23 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H); MS (APCI) 307 (MH^+).

General Procedure M. Preparation of Compounds 76a−h by Reaction of Piperazino-pyrimidines 74a−c with Activated Heterocycles 34c and 75a−c. Representative experimental procedures for **76b**,**c** are given below.

Refluxing *i*-PrOH/*n*-BuOH Method. 1*R*-(4-{4-[2-(1*R*-Butyryloxy-ethyl)pyrimidin-4-yl]-2*R*,6*S*-dimethyl-piperazin-1-yl}pyrimidin-2-yl)ethyl Butyrate (76b: R^1 = (*R*)-2-(1-Butyryloxy-ethyl)pyrimidin-4-yl, R^2 = R^6 = *β*-Me). A mixture of piperazino-pyrimdine **74a** (0.30 g, 0.98 mmol), chloropyrimidine **34c** (0.22 g, 0.98 mmol), and Et_3N (0.27 mL, 1.96 mmol) in *i*-PrOH (5 mL) was allowed to stir at reflux for 18 h, cooled to room temperature, concentrated, and purified by flash column chromatography (1 → 3% MeOH/$CHCl_3$) to give 0.47 g (96%) of compound **76b** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 6.0 Hz, 2 H), 6.41 (d, J = 6.2 Hz, 1 H), 6.31 (d, J = 6.2 Hz, 1 H), 5.69 (q, J = 6.8 Hz, 2 H), 4.72−4.24 (c, 4 H), 3.24−3.21 (c, 2 H), 2.38 (t, J = 7.5 Hz, 4 H), 1.72−1.62 (c, 4 H), 1.56 (d, J = 6.8 Hz, 6 H), 1.28−1.13 (c, 6 H), 0.95 (t, J = 7.5 Hz, 6 H); MS (APCI) 499 (MH^+).

Neat Method. 1*R*-[4-(2*R*,6*S*-Dimethyl-4-oxazolo[5,4-c]-pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethyl Butyrate (76c: R^1 = Oxazolo[5,4-c]pyridin-2-yl, R^2 = R^6 = *β*-Me). A mixture of piperazino-pyrimidine **74a** (0.10 g, 0.33 mmol) and 2-methylthio-oxazolo[5,4-c]pyridine[28] (**75a**, 0.11 g, 0.66 mmol) was heated at 120 °C for 7 h. The residue was purified by flash column chromatography (1% MeOH/$CHCl_3$) to give 125 mg (89%) of compound **76c** as a colorless foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1 H), 8.38 (d, J = 5.0 Hz, 1 H), 8.26 (d, J = 6.2 Hz, 1 H), 7.29 (d, J = 5.0 Hz, 1 H), 6.36 (d, J = 6.2 Hz, 1 H), 5.70 (q, J = 6.7 Hz, 1 H), 4.73 (m, 1 H), 4.29 (m, 1 H), 4.29 (d, J = 12.9 Hz, 2 H), 3.45 (d, J = 12.5 Hz, 2 H), 2.39 (t, J = 7.5 Hz, 2 H), 1.72−1.64 (c, 2 H), 1.58 (d, J = 6.8 Hz, 3 H), 1.33 (d, J = 7.1 Hz, 3 H), 1.31 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H); MS (APCI) 425 (MH^+).

1*R*-[4-(3*R*,5*S*-Dimethyl-piperazin-1-yl)pyrimidin-2-yl]-ethyl Butyrate (78). A mixture of chloropyrimidine **34c** (5.0 g, 21.9 mmol) and *cis*-2,6-dimethyl-piperazine (**77**, 5.0 g, 43.9 mmol) in THF (150 mL) was heated at reflux for 0.5 h, cooled to room temperature, and concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with 10% *i*-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give 7.2 g (crude, >100%) of compound **78** as a yellow oil, which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 6.2 Hz, 2 H), 6.31 (d, J = 6.2 Hz, 1 H), 5.65 (q, J = 6.8 Hz, 1 H), 4.32−4.15 (c, 2 H), 2.88−2.80 (c, 2 H), 2.44−2.35 (c, 4 H), 1.72−1.59 (c, 2 H), 1.56 (d, J = 6.6 Hz, 3 H), 1.11 (d, J = 6.6 Hz, 6 H), 0.94 (t, J = 7.3 Hz, 3 H); MS (APCI) 307 (MH^+).

4-[2-(1*R*-Butyryloxy-ethyl)-pyrimidin-4-yl]-2*R*,6*S*-dimethyl-piperazine-1-*N*,*N*′-bis(*tert*-butoxycarbonyl)carboxamidine (79a). Prepared from piperazino-pyrimidine **78** (general procedure H) and purified by flash column chromatography (0.5 → 2% MeOH/$CHCl_3$) to give compound **79a** (33%) as a colorless foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.62 (br s, 1 H), 8.19 (d, J = 6.2 Hz, 2 H), 6.38 (d, J = 6.2 Hz, 1 H), 5.66 (q, J = 6.8 Hz, 1 H), 4.48−4.12 (c, 4 H), 3.33−3.20 (c, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 1.71−1.62 (c, 2 H), 1.56 (d, J = 6.8 Hz, 3 H), 1.48 (s, 18 H), 1.28 (d, J = 6.6 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 0.95 (t, J = 7.5 Hz, 3 H); MS (APCI) 549 (MH^+).

(*R*)-4-Benzyl-2-methyl-piperazine-1-*N*,*N*′-bis(*tert*-butoxycarbonyl)carboxamidine (79b). Prepared from benzyl-piperazine **72c** (general procedure H) and purified by flash column chromatography (1:9 → 1:4 EtOAc/hexanes) to give compound **79b** (80%) as a light yellow sticky material. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.22 (c, 5 H), 3.78−3.33 (c, 5 H), 2.76 (d, J = 10.8 Hz, 1 H), 2.61 (d, J = 11.2 Hz, 1 H), 2.30 (dd, J = 11.2, 3.7 Hz, 1 H), 2.13 (m, 1 H), 1.48 (s, 9 H), 1.44 (s, 9 H), 1.34 (d, J = 6.7 Hz, 3 H); MS (APCI) 433 (MH^+).

4-[2-(1*R*-Butyryloxy-ethyl)pyrimidin-4-yl]-2*R*,6*S*-piperazine-1-carboxamidine Bis(trifluoroacetate) Salt (80a). Prepared from bis(Boc)-guanidine **79a** (general procedure I) to give compound **80a** (crude, >100%) as a yellow oil that was used directly in the next reaction. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.26 (d, J = 6.2 Hz, 1 H), 7.24 (d, J = 6.2 Hz, 1 H), 5.70 (q, J = 6.8 Hz, 1 H), 4.31−4.19 (c, 2 H), 3.67−3.55 (c, 2 H), 3.45−3.36 (c, 2 H), 2.45 (t, J = 7.4 Hz, 2 H), 1.73−1.61 (c, 5 H), 1.35−1.27 (c, 6 H), 0.97 (t, J = 7.3 Hz, 3 H); MS (CI/NH_3) 349 (MH^+).

(*R*)-4-Benzyl-2-methyl-piperazine-1-carboxamidine Bis(trifluoroacetate) Salt (80b). Prepared from bis(Boc)-guanidine **79b** (general procedure I) to give compound **80b** (crude, >100%) as a white solid that was used directly in the next reaction. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.53−7.43 (c, 5 H), 4.39−4.30 (c, 3 H), 3.92 (m, 1 H), 3.59 (m, 1 H), 3.52 (m, 1 H), 3.40 (m, 1 H), 3.30 (m, 1 H), 3.13 (m, 1 H), 1.39 (d, J = 6.0 Hz, 3 H); MS (CI/NH_3) 233 (MH^+).

1*R*-{4-[4-(4-Methoxymethyl-6-methyl-pyrimidin-2-yl)-3*R*,5*S*-dimethyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (81a). Prepared from guanidine bis(trifluoroacetate) salt **80a** and 1-methoxy-2,4-pentanedione[33] (**46d**) (general procedure J) and purified by flash column chromatography (1 → 2% MeOH/$CHCl_3$) to give compound **81a** (77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, J = 6.2 Hz, 1 H), 6.54 (s, 1 H), 6.42 (d, J = 6.2 Hz, 1 H), 5.15 (br s, 1 H), 4.98−4.93 (c, 2 H), 4.69 (m, 1 H), 4.37−4.27 (c, 4 H), 3.39 (s, 3 H), 3.28−3.22 (c, 2 H), 2.32 (s, 3 H), 1.50 (d, J = 6.6 Hz, 3 H), 1.19 (d, J = 6.7 Hz, 6 H); MS (APCI) 373 (MH^+).

(*R*)-2-(4-Benzyl-2-methyl-piperazin-1-yl)-4-methoxy-methyl-6-methyl-pyrimidine (81b). Prepared from guanidine bis(trifluoroacetate) salt **80b** and 1-methoxy-2,4-pentanedione[33] (**46d**) (general procedure J) and purified by flash column chromatography (1:9 EtOAc/hexanes) to give compound **81b** (70%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.20 (c, 5 H), 6.50 (s, 1 H), 4.92 (m, 1 H), 4.51 (m, 1 H), 4.35 (s, 2 H), 3.61 (d, J = 13.3 Hz, 1 H), 3.52−3.38 (c, 4 H), 3.20 (td, J = 12.6, 3.4 Hz, 1 H), 2.88 (d, J = 10.2 Hz, 1 H), 2.70 (d, J = 11.2 Hz, 1 H), 2.33 (s, 3 H), 2.21 (dd, J = 11.0, 3.5 Hz, 1 H), 2.09 (td, J = 11.7, 3.6 Hz, 1 H), 1.25 (d, J = 6.6 Hz, 3 H); MS (APCI) 327 (MH^+).

(*R*)-4-Methoxymethyl-6-methyl-2-(2-methyl-piperazin-1-yl)pyrimidine Hydrochloride (81c). To a solution of benzyl compound **81b** (0.39 g, 1.18 mmol) in MeOH (4 mL) was added HCl (5.85 M in MeOH, 0.21 mL, 1.25 mmol) followed by HCO_2NH_4 (0.74 g, 11.8 mmol) and 10% Pd/C (39 mg, 10 wt %). This mixture was stirred at reflux for 1 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated and dried under high vacuum to give compound **81c** (100%) as a sticky foam. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.64 (s, 1 H), 5.19 (m, 1 H), 4.79 (d, J = 12.2 Hz, 1 H), 4.31 (s, 2 H), 3.42 (s, 3 H), 3.34−3.15 (c, 4 H), 2.99 (td, J = 12.5, 3.9 Hz, 1 H), 2.33 (s, 3 H), 1.28 (d, J = 7.3 Hz, 3 H); MS (APCI) 237 (MH^+).

General Procedure N. Reaction of Substituted Piperazine 81c with Chloropyrimidine 34c. 1*R*-{4-[4-(4-Methoxymethyl-6-methyl-pyrimidin-2-yl)-3*R*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethyl Butyrate (81d). A mixture of piperazine hydrochloride salt **81c** (0.32 g, 1.17 mmol), chloropyrimidine **34c** (0.27 g, 1.17 mmol), and Et_3N (0.49 mL, 3.52 mmol) in *i*-PrOH (4 mL) was allowed to stir at reflux for 4 h, cooled to room temperature, concentrated, and purified by flash column chromatography (1:1 EtOAc/hexanes → EtOAc) to give 0.46 g (91%) of compound **81d** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 6.2 Hz, 1 H), 6.54 (s, 1 H), 6.35 (d, J = 6.0 Hz, 1 H), 5.68 (q, J = 6.8 Hz, 1 H), 4.98 (m, 1 H), 4.56 (m, 1 H), 4.33 (s, 2 H), 4.23−4.11 (c, 2 H), 3.45 (s, 3 H), 3.40−3.28 (c, 2 H), 3.12 (m, 1 H), 2.39 (t, J = 7.4 Hz, 2 H), 2.34 (s, 3 H), 1.72−1.63 (c, 2 H), 1.57 (d, J = 6.8 Hz, 3 H), 1.15 (d, J = 6.5 Hz, 3 H), 0.95 (t, J = 7.5 Hz, 3 H); MS (APCI) 429 (MH^+).

(*S*)-2-(4-Benzyl-2-methyl-piperazin-1-yl)-4-methoxymethyl-6-methyl-pyrimidine (82a: R^1 = 4-Methoxymethyl-6-methyl-pyrimidin-2-yl). Prepared from benzyl piperazine **72b** and 2-chloro-4-methoxymethyl-6-methyl-pyrimidine[34] (**75c**) (general procedure M, refluxing *n*-BuOH method) and purified by flash column chromatography (1:9 EtOAc/hexanes) to give compound **82a** (31%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.21 (c, 5 H), 6.46 (s, 1 H), 4.86 (m, 1 H), 4.46 (d, J = 13.5 Hz, 1 H), 4.29 (s, 2 H), 3.56 (d, J = 13.3 Hz, 1 H), 3.46−3.38 (c, 4 H), 3.17 (td, J = 12.6, 3.3 Hz, 1 H), 2.85 (d, J = 10.4 Hz, 1 H), 2.67 (d, J = 11.2 Hz, 1 H), 2.29 (s, 3 H), 2.17 (dd, J = 11.0, 3.8 Hz, 1 H), 2.07 (td, J = 11.8, 3.5 Hz, 1 H), 1.23 (d, J = 6.6 Hz, 3 H); MS (APCI) 327 (MH^+).

(*S*)-4-Methoxymethyl-6-methyl-2-(2-methyl-piperazin-1-yl)pyrimidine (83a: R^1 = 4-Methoxymethyl-6-methyl-pyrimidin-2-yl). Prepared from benzyl compound **82a** (general procedure L) to give compound **83a** (100%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (s, 1 H), 4.88 (m, 1 H), 4.49 (m, 1 H), 4.33 (s, 2 H), 3.47 (s, 3 H), 3.12−3.02 (c, 2 H), 2.99 (dd, J = 11.1, 3.6 Hz, 1 H), 2.88 (d, J = 11.0 Hz, 1 H), 2.76 (td, J = 11.0, 3.7 Hz, 1 H), 2.33 (s, 3 H), 1.21 (d, J = 6.6 Hz, 3 H); MS (APCI) 237 (MH^+).

1*R*-{4-[4-(4-Methoxymethyl-6-methyl-pyrimidin-2-yl)-3*S*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethyl Butyrate (84a: R^1 = 4-Methoxymethyl-6-methyl-pyrimidin-2-yl). Prepared from piperazine **83a** (general procedure N) and purified by flash column chromatography (1:1 EtOAc/hexanes → EtOAc) to give compound **84a** (87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, J = 6.0 Hz, 1 H), 6.53 (s, 1 H), 6.33 (d, J = 6.3 Hz, 1 H), 5.66 (q, J = 6.8 Hz, 1 H), 4.97 (m, 1 H), 4.55 (dt, J = 13.5, 3.3 Hz, 1 H), 4.32 (s, 2 H), 4.21 (m, 1 H), 3.47−3.44 (c, 4 H), 3.37−3.27 (c, 2 H), 3.09 (m, 1 H), 2.38 (t, J = 7.4 Hz, 2 H), 2.33 (s, 3 H), 1.72−1.63 (c, 2 H), 1.56 (d, J = 6.6 Hz, 3 H), 1.12 (d, J = 6.4 Hz, 3 H), 0.95 (t, J = 7.5 Hz, 3 H); MS (APCI) 429 (MH^+).

General Procedure O. Preparation of Compounds 85−97 by Methyl Ether and/or Butyrate Ester Deprotection of Penultimate Precursors 76a−h, 81a,d, and 84a−c. LiOH Method. 1*R*-(4-{4-[2-(1*R*-Hydroxyethyl)pyrimidin-4-yl]-2*R*,6*S*-dimethyl-piperazin-1-yl}pyrimidin-2-yl)ethanol (86: R^1 = (*R*)-2-(1-Hydroxyethyl)pyrimidin-4-yl, R^2 = R^6 = β-Me). To a solution of dibutyrate **76b** (0.47 g, 0.94 mmol) in a 3:1 mixture of MeOH/H_2O (4 mL) was added LiOH·H_2O (0.20 g, 4.71 mmol). This mixture was stirred at room temperature for 1 h and concentrated. The aqueous residue was extracted with 10% *i*-PrOH/$CHCl_3$ (3×), and the combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (3% MeOH/$CHCl_3$) to give 0.26 g (76%) of compound **86** as a white solid. mp 163−164.5 °C; $[\alpha]_D$ +42.3 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, J = 6.0 Hz, 1 H), 8.21 (d, J = 6.2 Hz, 1 H), 6.45 (d, J = 6.2 Hz, 1 H), 6.35 (d, J = 6.2 Hz, 1 H), 4.74−4.28 (c, 8 H), 3.32−3.27 (c, 2 H), 1.50 (d, J = 6.6 Hz, 6 H), 1.24 (d, J = 6.9 Hz, 6 H); MS (APCI) 359 (MH^+). Anal. ($C_{18}H_{26}N_6O_2$) C, H, N.

HCl Method. 1*R*-[4-(2*R*,6*S*-Dimethyl-4-oxazolo[5,4-c]-pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (87: R^1 = Oxazolo[5,4-c]pyridin-2-yl, R^2 = R^6 = β-Me). To a solution of butyrate **76c** (0.12 g, 0.28 mmol) in MeOH (2.8 mL) was added concentrated HCl (0.24 mL, 2.8 mmol). This mixture was stirred for 64 h, quenched to pH 7 by the addition of 6 N aqueous NaOH followed by 1 N aqueous NaOH, and concentrated. The aqueous residue was extracted with 10% *i*-PrOH/$CHCl_3$ (3×), and the combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1 → 3% MeOH/$CHCl_3$) to give 45 mg (45%) of compound **87** as a white solid. mp 175−178 (dec); $[\alpha]_D$ +8.1 (*c* 1.3, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.53 (d, J = 0.6 Hz, 1 H), 8.28 (d, J = 5.4 Hz, 1 H), 8.20 (d, J = 6.2 Hz, 1 H), 7.34 (dd, J = 5.3, 0.7 Hz, 1 H), 6.68 (d, J = 6.4 Hz, 1 H), 4.90−4.72 (c, 2 H), 4.69 (q, J = 6.6 Hz, 1 H), 4.32 (d, J = 13.3 Hz, 2 H), 3.56 (dd, J = 13.3, 4.4 Hz, 2 H), 1.47 (d, J = 6.6 Hz, 3 H), 1.33 (d, J = 6.9 Hz, 6 H); MS (APCI) 355 (MH^+). HRMS (FAB) exact mass calcd for $C_{18}H_{23}N_6O_2$ 355.1882 (MH^+), found 355.1851.

BBr_3 Method. 1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2*S*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (90: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^2 = α-Me). To a solution of methyl ether butyrate **76e** (0.77 g, 1.80 mmol) in CH_2Cl_2 (9 mL) at 0 °C with stirring under N_2 was added BBr_3 (1.0 M in CH_2Cl_2, 9.0 mL, 9.0 mmol) slowly dropwise. This mixture was allowed to stir with slow warming to room temperature for 18 h, quenched by careful addition of saturated aqueous $NaHCO_3$, and extracted with 10% *i*-PrOH/$CHCl_3$ (3×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1 → 5% MeOH/$CHCl_3$) to give 0.34 g (55%) of compound **90** as a yellow sticky material. $[\alpha]_D$ +66.5 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 6.0 Hz, 1 H), 6.36 (d, J = 6.2 Hz, 1 H), 6.32 (s, 1 H), 4.69 (q, J = 6.6 Hz, 1 H), 4.60−4.53 (c, 3 H), 4.52 (s, 2 H), 4.38−4.18 (c, 2 H), 3.63 (m, 1 H), 3.40−3.29 (c, 2 H), 3.24 (m, 1 H), 2.32 (s, 3 H), 1.49 (d, J = 6.6 Hz, 3 H), 1.20 (d, J = 6.6 Hz, 3 H); MS (APCI) 345 (MH^+). Anal. ($C_{17}H_{24}N_6O_2$·0.25H_2O) C, H, N.

K_2CO_3 Method. 1*R*-[4-(3*S*-Methyl-4-oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (95, R^1 = Oxazolo[5,4-c]pyridin-2-yl, R^3 = β-Me). A mixture of butyrate **84b** (0.20 g, 0.49 mmol) and K_2CO_3 (0.20 g, 1.47 mmol) in MeOH (5 mL) was stirred at room temperature for 4 h, diluted with saturated aqueous $NaHCO_3$, and extracted with 10% *i*-PrOH/$CHCl_3$ (4×). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated, and purified by flash column chromatography (1.5 → 5% MeOH/$CHCl_3$) to give 0.12 g (72%) of compound **95** (65%) as a white foam. $[\alpha]_D$ +61.6 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1 H), 8.37 (d, J = 5.4 Hz, 1 H), 8.25 (d, J = 6.2 Hz, 1 H), 7.29 (d, J = 5.2 Hz, 1 H), 6.43 (d, J = 6.0 Hz, 1 H), 4.72 (m, 1 H), 4.65 (m, 1 H), 4.45 (m, 1 H), 4.29 (m, 1 H), 4.26−4.20 (c, 2 H), 3.58 (td, J = 13.2, 3.3 Hz, 1 H), 3.48 (dd, J = 13.4, 3.9 Hz, 1 H), 3.26 (td, J = 12.6, 3.7 Hz, 1 H), 1.51 (d, J = 6.6 Hz, 3 H), 1.34 (d, J = 6.7 Hz, 3 H); MS (APCI) 341 (MH^+). Anal. ($C_{17}H_{20}N_6O_2$·0.75H_2O) C, H; N: calcd, 23.75; found, 23.22.

1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2*R*,6*S*-dimethyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (85: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^2 = R^6 = β-Me). Prepared from methyl ether butyrate **76a** (LiOH method, 3:1:1 MeOH/THF/H_2O, followed by BBr_3 method) and purified by flash column chromatography (1 → 3% MeOH/$CHCl_3$) to give compound **85** (69% for two steps) as a white solid. mp 139−141 °C; $[\alpha]_D$ +14.8 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J = 6.2 Hz, 1 H), 6.37 (d, J = 6.3 Hz, 1 H), 6.33 (s, 1 H), 4.80 (d, J = 13.2 Hz, 2 H), 4.72 (q, J = 6.5 Hz, 1 H), 4.68−4.47 (c, 2 H), 4.54 (s, 2 H), 4.39 (br s, 1 H), 3.64 (br s, 1 H), 3.21 (dd, J = 13.1, 4.5 Hz, 2 H), 2.34 (s, 3 H), 1.52 (d, J = 6.6 Hz, 3 H), 1.26 (d, J = 6.6 Hz, 6 H); MS (APCI) 359 (MH^+). Anal. ($C_{18}H_{26}N_6O_2$) C, H, N.

1*R*-[4-(2*R*,6*S*-Dimethyl-4-quinoxalin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (88: R^1 = Quinoxalin-2-yl, R^2 = R^6 = β-Me). Prepared from butyrate **76d** (LiOH method, 2:1:1 MeOH/THF/H_2O) and purified by flash column chromatography (1% MeOH/$CHCl_3$) to give compound **88** (82%) as a yellow foam. $[\alpha]_D$ +11.1 (*c* 1.4, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.77 (s, 1 H), 8.17 (d, J = 6.4 Hz, 1 H), 7.82 (dd, J = 8.3, 1.1 Hz, 1 H), 7.66 (dd, J = 8.5, 1.4 Hz, 1 H), 7.59 (m, 1 H), 7.40 (m, 1 H), 6.65 (d, J = 6.4 Hz, 1 H), 4.84−4.62 (c, 5 H), 3.41−3.30 (c, 2 H), 1.47 (d, J = 6.6 Hz, 3 H), 1.31 (d, J = 6.8 Hz, 6 H); MS (APCI) 365 (MH^+). Anal. ($C_{20}H_{24}N_6O$·0.5H_2O) C, H, N.

1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3*R*,5*S*-dimethyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (89: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^3 = R^5 = β-Me). Prepared from methyl ether **81a** (BBr_3 method) and purified by flash column chromatography (1% MeOH/$CHCl_3$) followed by recrystallization (MeOH/EtOAc) to give compound **89** (46%) as a white solid. mp 149−151 °C; $[\alpha]_D$ +18.9 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J

= 6.2 Hz, 1 H), 6.44 (d, J = 6.2 Hz, 1 H), 6.32 (s, 1 H), 5.02−4.97 (c, 2 H), 4.71 (m, 1 H), 4.53 (s, 2 H), 4.48−4.24 (c, 3 H), 3.73 (br s, 1 H), 3.31−3.24 (c, 2 H), 2.33 (s, 3 H), 1.51 (d, J = 6.7 Hz, 3 H), 1.23 (d, J = 6.9 Hz, 3 H); MS (APCI) 359 (MH^+). Anal. ($C_{18}H_{26}N_6O_2$) C, H, N.

1*R*-(4-{4-[2-(1*R*-Hydroxyethyl)pyrimidin-4-yl]-2*S*-methyl-piperazin-1-yl}pyrimidin-2-yl)ethanol (91: R^1 = (*R*)-2-(1-Hydroxyethyl)pyrimidin-4-yl, R^2 = α-Me). Prepared from dibutyrate **76f** (LiOH method, 4:1 MeOH/H_2O) and purified by flash column chromatography (5 → 10% MeOH/$CHCl_3$) to give compound **91** (78%) as a white solid. mp 158−160 °C; $[\alpha]_D$ +82.5 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 6.2 Hz, 2 H), 6.39 (d, J = 6.0 Hz, 1 H), 6.38 (d, J = 6.2 Hz, 1 H), 4.71 (q, J = 6.6 Hz, 2 H), 4.55 (br s, 1 H), 4.32−4.16 (c, 5 H), 3.60 (dd, J = 13.5, 3.7 Hz, 1 H), 3.48 (m, 1 H), 3.35 (m, 1 H), 1.52 (d, J = 6.6 Hz, 6 H), 1.24 (d, J = 6.4 Hz, 3 H); MS (APCI) 345 (MH^+). Anal. ($C_{17}H_{24}N_6O_2$) C, H, N.

1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2*R*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (92: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^2 = β-Me). Prepared from methyl ether butyrate **76g** (LiOH method, 3:1 MeOH/H_2O, followed by BBr_3 method) and purified by flash column chromatography (1 → 2% MeOH/$CHCl_3$) to give compound **92** (84% for two steps) as a white foam. $[\alpha]_D$ −35.0 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 6.2 Hz, 1 H), 6.37 (d, J = 6.2 Hz, 1 H), 6.33 (s, 1 H), 4.72 (m, 1 H), 4.67−4.54 (c, 3 H), 4.54 (s, 2 H), 4.34 (m, 1 H), 4.20 (m, 1 H), 3.58 (br s, 1 H), 3.42−3.32 (c, 2 H), 3.26 (m, 1 H), 2.34 (s, 3 H), 1.51 (d, J = 6.5 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H); MS (APCI) 345 (MH^+). Anal. ($C_{17}H_{24}N_6O_2$·0.25H_2O) C, H, N.

1*R*-(4-{4-[2-(1*R*-Hydroxyethyl)pyrimidin-4-yl]-2*R*-methyl-piperazin-1-yl}pyrimidin-2-yl)ethanol (93: R^1 = (*R*)-2-(1-Hydroxyethyl)pyrimidin-4-yl, R^2 = β-Me). Prepared from dibutyrate **76h** (LiOH method, 4:1 MeOH/H_2O) and purified by flash column chromatography (5 → 10% MeOH/$CHCl_3$) to give compound **93** (77%) as a white solid. mp 155−157 °C; $[\alpha]_D$ −30.4 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 6.0 Hz, 2 H), 6.39 (d, J = 6.0 Hz, 1 H), 6.38 (d, J = 6.0 Hz, 1 H), 4.74−4.71 (c, 2 H), 4.58 (br s, 1 H), 4.32−4.16 (c, 5 H), 3.59 (m, 1 H), 3.50 (m, 1 H), 3.38 (m, 1 H), 1.52 (d, J = 6.6 Hz, 6 H), 1.25 (d, J = 6.5 Hz, 3 H); MS (APCI) 345 (MH^+). Anal. ($C_{17}H_{24}N_6O_2$·0.33H_2O) C, H, N.

1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3*S*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (94: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^3 = β-Me). Prepared from methyl ether butyrate **84a** (BBr_3 method) and purified by flash column chromatography (2% MeOH/$CHCl_3$) to give compound **94** (31%) as a yellow oil. $[\alpha]_D$ +68.1 (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, J = 6.2 Hz, 1 H), 6.36 (d, J = 6.2 Hz, 1 H), 6.33 (s, 1 H), 4.99 (m, 1 H), 4.97 (m, 1 H), 4.69 (m, 1 H), 4.58 (m, 1 H), 4.52 (s, 2 H), 4.40−4.11 (c, 3 H), 3.60 (br s, 1 H), 3.45−3.34 (c, 2 H), 3.19 (m, 1 H), 2.32 (s, 3 H), 1.49 (d, J = 6.6 Hz, 3 H), 1.16 (d, J = 6.7 Hz, 3 H); MS (APCI) 345 (MH^+). HRMS (FAB) exact mass calcd for $C_{17}H_{25}N_6O_2$ 345.2039 (MH^+), found 345.2037.

1*R*-[4-(3*S*-Methyl-4-quinoxalin-2-yl-piperazin-1-yl)pyrimidin-2-yl]ethanol (96: R^1 = Quinoxalin-2-yl, R^3 = β-Me). Prepared from butyrate **84c** (LiOH method, 4:1 MeOH/H_2O) and purified by flash column chromatography (2% MeOH/$CHCl_3$) to give compound **96** (78%) as a yellow foam. $[\alpha]_D$ +57.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1 H), 8.23 (d, J = 6.2 Hz, 1 H), 7.89 (d, J = 8.3 Hz, 1 H), 7.69 (d, J = 8.5 Hz, 1 H), 7.59 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 6.42 (d, J = 6.2 Hz, 1 H), 4.78 (m, 1 H), 4.73 (m, 1 H), 4.43 (m, 1 H), 4.38−4.23 (c, 2 H), 3.64−3.52 (c, 2 H), 3.38 (m, 1 H), 1.52 (d, J = 6.6 Hz, 3 H), 1.30 (d, J = 6.6 Hz, 3 H); MS (APCI) 351 (MH^+). HRMS (FAB) exact mass calcd for $C_{19}H_{23}N_6O$ 351.1902 (MH^+), found 351.1933.

1*R*-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3*R*-methyl-piperazin-1-yl]pyrimidin-2-yl}ethanol (97: R^1 = 4-Hydroxymethyl-6-methyl-pyrimidin-2-yl, R^3 = α-Me). Prepared from methyl ether butyrate **81d** (BBr_3 method) and purified by flash column chromatography (1 → 5% MeOH/$CHCl_3$) to give compound **97** (48%) as a colorless oil. $[\alpha]_D$ −40.6 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 6.2 Hz, 1 H), 6.39 (d, J = 6.2 Hz, 1 H), 6.34 (s, 1 H), 5.03 (m, 1 H), 4.74 (q, J = 6.8 Hz, 1 H), 4.62 (dt, J = 12.3, 3.2 Hz, 1 H), 4.56 (s, 2 H), 4.42−4.13 (c, 3 H), 3.68 (br s, 1 H), 3.50−3.37 (c, 2 H), 3.20 (m, 1 H), 2.33 (s, 3 H), 1.53 (d, J = 6.8 Hz, 3 H), 1.19 (d, J = 6.7 Hz, 3 H); MS (APCI) 345 (MH^+). HRMS (FAB) exact mass calcd for $C_{17}H_{25}N_6O_2$ 345.2039 (MH^+), found 345.2031.

Biology. SDH Inhibition Activity. Recombinant *h*- or *s*-SDH was purchased from Pan Vera Corp. (Madison, WI) or Boehringer (Germany), respectively. Experimental compounds were dissolved at 5 mM in 20% (v/v) aqueous DMSO, and 25 μL aliquots were added to 0.2 mL of potassium phosphate buffer (pH 7.0) containing NAD^+, iodonitrotetrazolium violet (INT), and *h*- or *s*-SDH. Following a 15 minute incubation at 25 °C, the reaction was initiated by the addition of 20 mM sorbitol (25 μL). Final concentrations in the assay were 90 mM potassium phosphate, 1 mM NAD^+, 1 mM INT, 2 mM sorbitol, and 2 nM *h*-SDH or 8 nM *s*-SDH. Enzyme activity was assayed with a SLT340 ATTC plate reader (model 16-925, SLT Lab-Instruments, Austria), which measured the increase in the rate of INT reduction at 495 nm at 25 °C over 10 min. IC_{50}s were calculated using a log-linear regression analysis.

Normalization of Nerve Fructose in Diabetic Rats: Acute Prevention Model. Male CD Sprague−Dawley rats (175−225 g) were made diabetic by injection of STZ (17 mg/mL in 0.01 M citrate buffer, pH 4.5, 85 mg/kg body wt) into the tail vein of conscious rats. STZ was administered at approximately 9:00 a.m. on day 1. The animals were maintained with free access to food and water. Test compound was administered by oral gavage (volume of 5 mL/kg) at 4, 7, and 24 h after STZ administration. Four hours after the final dose (28 h after STZ administration), animals were sacrificed by cervical dislocation. The left sciatic nerve was excised, weighed, and placed in 1 mL of ice-cold 6% perchloric acid and frozen for fructose analysis at a later date.

Weighed sciatic nerves in 6% (w/v) perchloric acid (1 mL) were thawed and homogenized with a polytron (Kinematica, Switzerland). After the mixture was centrifuged, the decanted supernatant was neutralized by the addition of 3.0 M potassium carbonate (100 μL) and recentrifuged. The fructose contents of the supernatants were determined enzymatically.[35] Briefly, fructose was oxidized to 5-keto-fructose by fructose dehydrogenase (FDH) with concomitant reduction of resazurin to the highly fluorescent resorufin. Final assay concentrations were 0.2 M citric acid, pH 4.5, containing 13.2 μM resazurin, 1.7 units/mL of FDH, and 0.068% (v/v) Triton X-100. Reaction mixtures were incubated for 60 min at room temperature in a closed drawer. The sample fluorescence was determined at excitation = 560 nm, emission = 580 nm, and slits of 5 mm each (Perkin-Elmer model LS50B fluorescence spectrophotometer). After the appropriate blanks from each sample were subtracted, nanomole of fructose in each sample was then determined by comparison with a linear regression of the fructose standards.

Normalization of Nerve Fructose in Diabetic Rats: Chronic Reversal Model. Male CD Sprague−Dawley rats (175−225 g) were made diabetic by the injection of STZ (17 mg/mL in 0.01 M citrate buffer, pH 4.5, 85 mg/kg body wt) into the tail vein of conscious rats. STZ was administered at approximately 9:00 a.m. on day 1. The animals were maintained with free access to food and water. On day 8, at 9:00 a.m., test compound was administered by oral gavage (volume of 5 mL/kg). Dosing continued once daily at 9:00 a.m. for 5 days. Four hours after the final dose (day 12), animals were sacrificed by cervical dislocation. The left sciatic nerve was excised, weighed, and placed in ice-cold 6% (w/v) perchloric acid (1 mL) and frozen for fructose analysis at a later date, using the methods described above.

Pharmacokinetic Evaluation. Rat Studies. Male CD Sprague−Dawley rats[36] were fasted overnight and then dosed by oral gavage at 5 mg/kg/day (compounds **62**, **67**, **69**, and **86**) or 20 mg/kg/day (compound **I**). The compounds were formulated in pH-adjusted deionized water (pH ∼4−5). Water was provided ad libitum. Blood samples (800 μL) were collected

via venous orbital bleed at designated time points, and serum was stored at −20 °C until assay.

Analytical Methods. Serum samples (300 μL) were analyzed at selected time points and combined with an internal standard. This mixture was diluted with distilled H_2O (1 mL), extracted with EtOAc (5 mL), evaporated to dryness, and reconstituted in the mobile phase (150 μL). These extracts (120 μL) were analyzed by reverse phase HPLC using a Kromasil C4 column (250 × 4.6 mm) and elution with a 1:1 MeOH/H_2O mobile phase containing 10 mL Pic-B7[37]/liter solution. The flow rate was set at 1.0 mL/min, and UV detection at 237 nM was used. The standard curves for tested analogues were linear from 50 to 5000 ng/mL.

Phamacokinetic/Pharmacodynamic Evaluation of Compound 86. Male CD Sprague−Dawley rats (150−175 g) were made diabetic by injection of STZ (17 mg/mL in 0.01 M citrate buffer, pH 4.5, 85 mg/kg body wt). The animals were maintained with free access to food and water. On the fifth day following STZ administration, rats were dosed with compound **86** via oral gavage at 6 a.m. At selected time points thereafter, animals (n = 5/group) were sacrificed by decapitation. Blood was collected for assay of serum drug levels (see above, pharmacokinetic evaluation analytical methods). A sciatic nerve was excised, stripped of adhering fat, blotted, and weighed before being placed in 6% (w/v) perchloric acid (1.0 mL) for subsequent fructose assay.[35]

Supporting Information Available: Complete experimental procedures for the preparation of compounds **3b**−**k**; **7a**−**d**,**f**,**h**; **35b**−**d**; **36a**−**i**,**k**−**o**; **39b**−**d**; **47b**−**d**; **74b**,**c**; **76a**,**d**−**h**; **82b**,**c**; **83b**,**c**; **84b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. We thank F. Michael Mangano and Michael S. Dina for the preparation of **22** and **52**, respectively.

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(14) These compounds are commercially available or known in the literature. See Experimental Section for details.

(15) In certain cases, oxidation of the sulfur-containing heterocycle in R^1 (**3g**: R^1 = benzo[*d*]isothiazol-3-yl → **3k**: R^1 = benzo[*d*]-isothiazol-3-yl *S*,*S*-dioxide) or hydrogenation of heteroaromatic chlorines in R^1 (**7a**: R^1 = 2-chloropyrimidin-4-yl → **7g**: R^1 = pyrimidin-4-yl, **7b**: R^1 = 4,6-dichlorotriazin-2-yl → **7h**: R^1 = triazin-2-yl) was necessary to ultimately provide the desired target compounds. See Experimental Section for details.

(16) In one case, deprotection of a methyl ether protecting group was necessary prior to hydrolysis of the ester protecting group to provide the desired compound (**36h**: R^1 = 4-methoxymethyl-6-methylpyrimidin-2-yl → **36i**: R^1 = 4-hydroymethyl-6-methyl-pyrimidin-2-yl). See Experimental Section for details.

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(21) Compounds containing the descriptors R^2, R^3, $R,^5$ and R^6 in Scheme 4 are hydrogen unless otherwise specified.

(22) Further studies pertaining to this reaction will be published forthwith (see Murry, J.; et al. *Org. Prep. Proceed. Int*). We thank Jerry Murry for initial examination of the triflate reaction, Christina Lydon for developing the chiral HPLC conditions, and Sam Guhan and Mike Hintz for performing the preparative separation of **73a**.

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(37) Pic-B7 (0.005 M 1-heptanesulfonic acid) is supplied by Waters.

JM010440G