Design, Synthesis, and Structure−Activity Relationship of 6-Alkynylpyrimidines as Potent Adenosine Kinase Inhibitors

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Adenosine (ADO) is an extracellular signaling molecule within the central and peripheral nervous system. Its concentration is increased at sites of tissue injury and inflammation. One of the mechanisms by which antinociceptive and antiinflammatory effects of ADO can be enhanced consists of inhibition of adenosine kinase (AK), the primary metabolic enzyme for ADO. Novel nonnucleoside AK inhibitors based on 4-amino-6-alkynylpyrimidines were prepared, and the importance of the length of the linker at the 5-position for high affinity AK inhibition was demonstrated. Compounds with 2- and 3-atom linkers were the most potent AK inhibitors. Optimization of their physicochemical properties led to **31a** and **37a** that effectively reduced pain and inflammation in animal models.

Introduction

Adenosine (ADO) is an endogenously released neuromodulator that functions as an extracellular signaling molecule within the central nervous system (CNS) and peripheral nervous system.[1,2] Under adverse conditions (e.g., pain, inflammation, tissue damage, etc.), the local tissue levels of extracellular ADO are markedly increased.[3] Adenosine kinase (AK) is a key intracellular enzyme regulating intra- and extracellular ADO concentrations. It rapidly phosphorylates ADO, maintaining intracellular ADO concentrations at low levels. Because ADO uptake is driven by its concentration gradient, AK inhibition reduces the cellular uptake of ADO,[4] thus potentiating the local concentration of ADO in the extracellular compartment. Consequently, AK inhibition can enhance the endogeneous protective action of ADO.[2] The identification of compounds that mimic or modulate the antinociceptive and antiinflammatory actions of ADO represents a potential approach to the treatment of pain and inflammation.

Recently, our group reported the synthesis of the novel nonnucleoside AK inhibitor **1**[5] and described its in vitro[6] and in vivo[7] properties. AK inhibitor **1** is a member of the pyridopyrimidine class of compounds on which we have performed several structure−activity relationship (SAR) studies[8,9] resulting in the development of potent AK inhibitors with improved pharmacokinetic and toxicological properties as compared to the prototypic nucleoside AK inhibitors.[10−13] Our efforts to widen the structural diversity of AK inhibitors led to a novel nonnucleoside class of AK inhibitors, 6-ethynylpyrimidines, that were derived from the pyridopyrimidine class by replacing a fused pyridine ring with an acetylenic unit at the 6-position of pyrimidine (Figure 1). The overlay of compounds **1** and **2** showed good

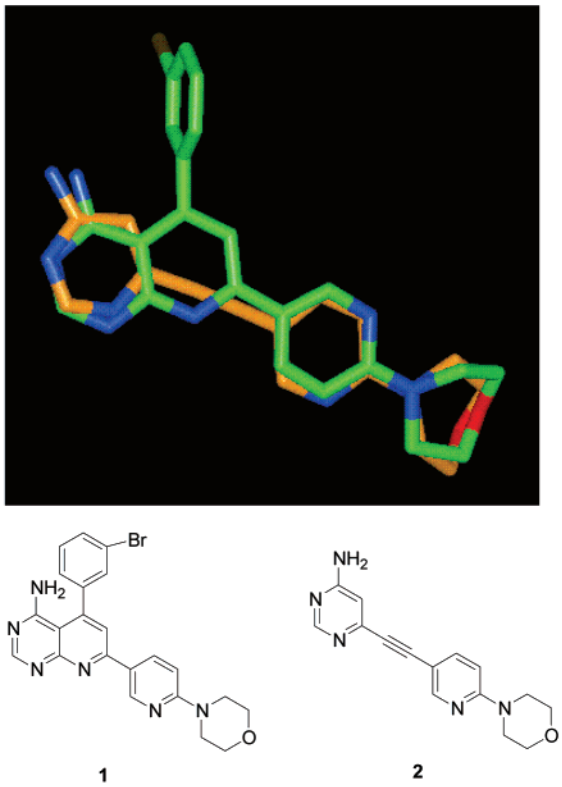

Figure 1. Overlay of pyridopyrimidine **1** (green) and ethynylpyrimidine **2** (brown).

superposition of the major fragments of the pyridopyrimidine core of **1** and the ethynylpyrimidine core of **2**. It also became apparent that the evaluation of substituents at the 5-position could be an important direction for SAR studies since that position appeared to be the key point for filling a putative hydrophobic pocket of the protein that in the case of pyridopyrimidine substrate **1** is occupied by a 3-bromophenyl fragment. The potential usefulness of such an approach to SAR optimization of the 6-ethynylpyrimidines was

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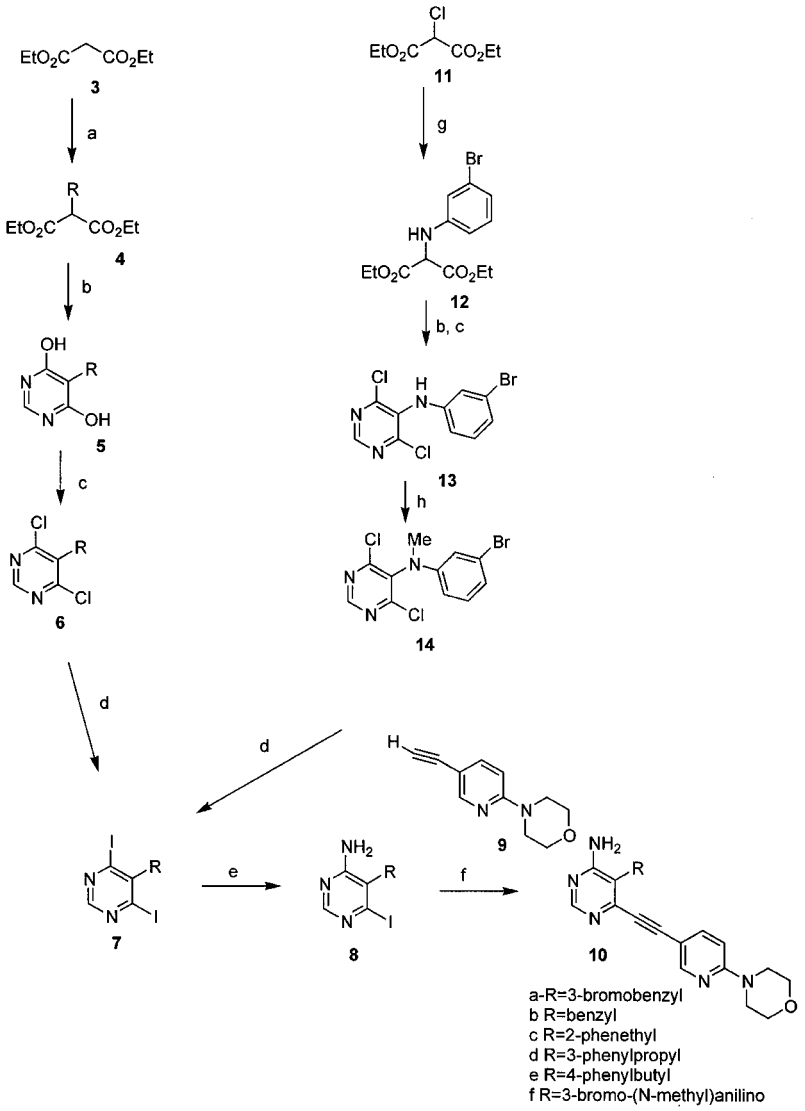
Scheme 1[a]



[a] Reagents: (a) (i) Na, EtOH; (ii) RBr, EtOH, reflux, 16 h. (b) Na, EtOH, formamidine acetate, 0 °C, and then add **4**, room temperature, 16 h. (c) $POCl_3$, reflux, 14 h. (d) NaI, 45% HI, acetone, room temperature, 16 h. (e) NH_3, EtOH, sealed tube, 100 °C, 16 h. (f) Compound **9**, $Pd(PPh_3)_2Cl_2$, CuI, MeCN−Et_3N, room temperature, 1.5 h. (g) 3-Bromoaniline, 40-50 °C, 15 h. (h) NaH, MeI, THF, room temperature, 16 h.

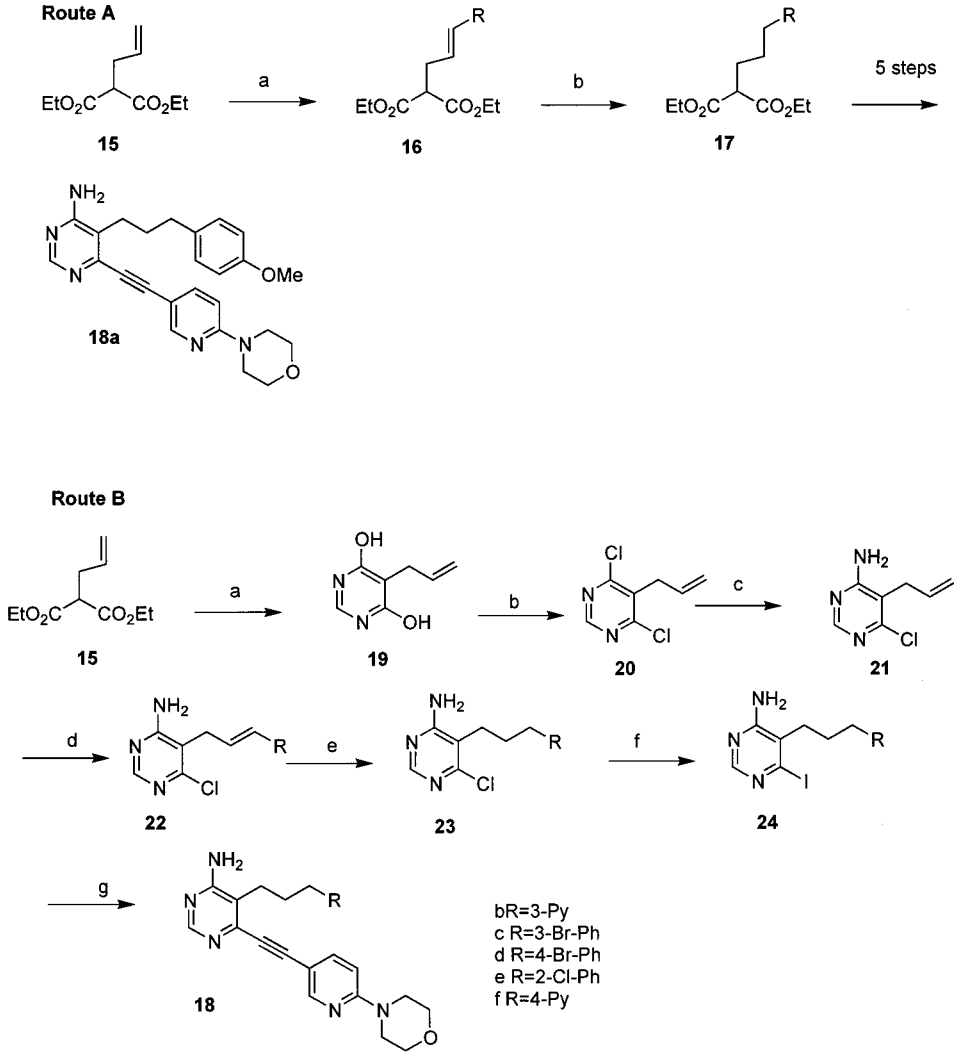
indirectly confirmed by the previous successful utilization of **2** as a core fragment in a nuclear magnetic resonance (NMR)-based lead optimization of AK inhibitors.[14]

Synthesis

The preparation of benzyl-, phenethyl-, phenylpropyl-, and phenylbutyl-substituted compounds **10a**−**e** was carried out in six steps from diethyl malonate **3** as outlined in Scheme 1. Alkylation of **3** followed by cyclization with formamidine gave dihydroxypyrimidine **5**, which was subjected to a three step sequence of chlorination, iodination, and ammonolysis to afford the 4-amino-6-iodo-derivative **8**. The latter underwent Sonogashira coupling with 5-ethynylpyridine **9** (prepared in three steps from 2,5-dibromopyridine by amination with morpholine, coupling with trimethylsilyl acetylene and silyl group deprotection) to provide target molecules **10a**−**e**. The last three steps of this procedure, iodination of **6** followed by ammonolysis and a coupling reaction, can be replaced by a shorter two step sequence of coupling of **6** with **9** followed by ammonolysis. However, the coupling reaction turned out to be an inefficient process; therefore, a longer three step procedure was more practical. For the anilino derivative **10f**, diethyl chloromalonate **11** was chosen as the starting material. It reacted with 3-bromoaniline, and the resulting **12** was subjected to cyclization followed by chlorination to obtain dichloro-pyrimidine **13**. The latter was N-methylated with MeI and further elaborated to **10f**.

Because there are not many commercially available 3-arylpropyl halides, Scheme 1 was not suited for the synthesis of analogues of **10d** with different substituents in phenyl ring or heteroaromatic replacements. We devised two synthetic routes (Scheme 2, routes A and B) for the synthesis of such compounds. Both routes utilized diethyl allylmalonate **15** as a starting material. In route A, **15** was cross-coupled with 3-iodo-anisole to give propenyl derivative **16**, which was hydrogenated to **17**. The latter then was transformed to the target compound **18a** by a five step procedure shown in

Scheme 2[a]



[a] Reagents: Route A: (a) 4-Iodoanisole, *n*-Bu_3N, $Pd(OAc)_2$, MeCN, reflux, 4 h. (b) H_2, 10% Pd/C, EtOAc, 15 h, 1 atm. (c) See Scheme 1, steps b−f. Route B: (a) Na, EtOH, formamidine acetate, 0 °C, and then add **15**, room temperature, 16 h. (b) $POCl_3$, reflux, 14 h. (c) NH_3, EtOH, sealed tube, 100 °C, 16 h. (d) 3-Br-pyridine, *N*,*N*-diisopropylethylamine, $Pd(PPh_3)_4$. tri-o-tolylphosphine, dioxane, reflux, 14 h. (e) H_2, 4 atm, 10% Pd/C, EtOAc−MeOH, 17 h. (f) NaI, 40% HI, 70 °C, 10 min. (g) Compound **9**, $Pd(PPh_3)_2Cl_2$, CuI, MeCN−Et_3N, room temperature, 1.5 h.

Scheme 1. In the shorter route B, we prepared advanced intermediate 4-amino-5-allyl-6-chloropyrimidine **21**, which was elaborated to the desired arylpropyl compounds **18b**−**f** by the sequence of cross-coupling with aryl bromides or iodides, hydrogenation, iodination, and Sonogashira coupling with **9**. Overall yields of target molecules in routes A and B were comparable. However, the syntheses of **18** in route B required only four steps from common intermediate **21**, while a seven step sequence needed to be applied in route A.

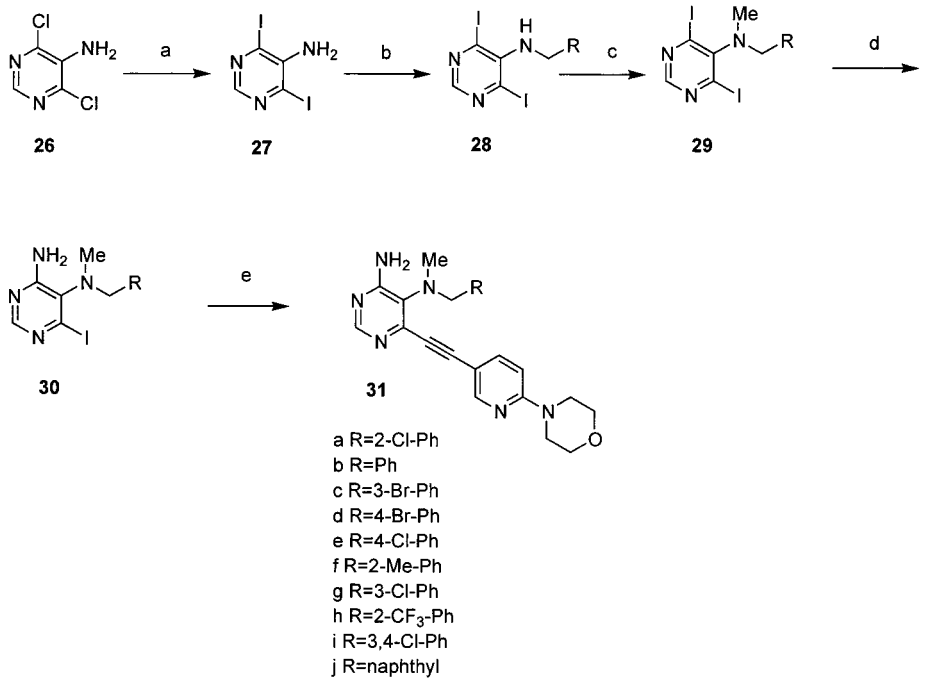
The preparation of 5-N-benzyl compounds **31** (Scheme 3) started from commercially available 5-amino-4,6-dichloropyrimidine **26**. Iodination followed by consecutive N-benzylation and N-methylation gave an intermediate **29** from which target molecules **31a**−**j** were obtained in two steps as illustrated in Scheme 1. It should be noted that the addition of tetrabutylammonium iodide helped to increase the yield of **27** and **28**.

The synthesis of 5-aminomethyl derivatives **37** (Scheme 4) required 5-formyl-4.6-dichloropyrimidine **33**, which was synthesized from corresponding 4,6-dihydroxypyrimidine **32** according to a literature procedure.[15] Ammonolysis of **33** at 50−60 °C for 1 h afforded monoamino compound **34**, which was treated with the appropriate secondary amine under reductive amination conditions[16] to provide **35**. The synthesis of desired **37a**−**c** was achieved by iodination of **35** followed by cross-coupling reactions with pyridyl-acetylene **9** as shown in Scheme 2.

Results and Discussion

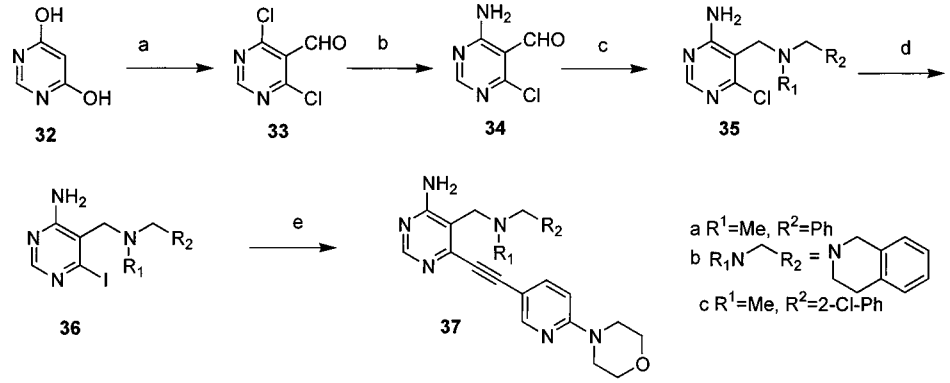
The synthesized 6-ethynylpyrimidines were tested for their ability to inhibit AK enzyme activity and to inhibit ADO phosphorylation in intact cells. The importance of the latter assay stems from the fact that AK is an intracellular target; therefore, the ability of AK inhibitors to cross cell membranes is a physiologically relevant property. The in vitro AK inhibition results are summarized in Table 1 (the protocols used are described in the Experimental section). 5-Unsubstituted pyrimidine **2**, as it was expected, did not display high inhibitory activity because of the absence of a lipophilic fragment at the 5-position to fill a putative hydrophobic pocket of the protein (Figure 1). Introduction of a 3-bromo-

Scheme 3[a]



[a] Reagents: (a) NaI, 40% HI, room temperature, 3 h. (b) 95% NaH, THF, 0 °C, and then benzyl bromide, Bu_4NI, room temperature, 2 h. (c) 95% NaH, THF, 0 °C, and then MeI, Bu_4NI, room temperature, 14 h. (d) NH_3, EtOH, sealed tube, 80 °C, 14 h. (e) Compound **9**, $Pd(PPh_3)_2Cl_2$, CuI, MeCN−Et_3N, room temperature, 1.5 h.

Scheme 4[a]

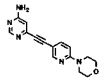
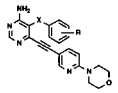
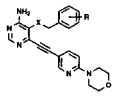
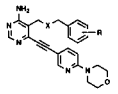
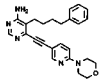


[a] Reagents: (a) $POCl_3$, DMF, 1 h, 0 °C, and then add **32**, stir 0.5 h at room temperature, and then reflux, 3 h. (b) NH_3, toluene, 50-60 °C, 0.5 h, TLC monitoring. (c) *N*-Methylbenzylamine, AcOH, NaB $(OAc)_3H$, CH_2Cl_2, room temperature, 15 h. (d) NaI, 40% HI, 70 °C, 10 min, and then Na_2CO_3 work-up. (e) Compound **9**, $Pd(PPh_3)_2Cl_2$, CuI, MeCN−Et_3N, room temperature, 1.5 h.

benzyl group makes compound **10a** closely resemble the pyridopyrimidine counterpart **1**. Because the activity of **10a** was markedly higher as compared with the unsubstituted **2**, we decided to further investigate the effect of the substituent, especially the length of the chain between the pyrimidine fragment of the core and the aromatic group of the substituent. Thus, compounds with 1−4 carbon atom linkers in the 5-position were prepared to introduce the corresponding benzyl, phenethyl, phenylpropyl, and phenylbutyl groups. 2-Phenethyl and 3-phenylpropyl derivatives **10c**,**d** exhibited high AK potencies having IC_{50} values below 5 nM, which were 5−10-fold better than those observed for benzyl and 4-phenylbutyl analogues **10b**,**e**. Therefore, additional work was directed toward the synthesis of target molecules with 2- and 3-atom linkers in the 5-position of the pyrimidine core. It should be noted that early SAR by NMR studies[14] have also indirectly proven the relevance of such approximation.

The first stage of exploring the SAR of 3-atom-linked compounds consisted of introducing arylpropyl groups where an aryl group was represented by substituted phenyl and pyridyl moieties and the linker was an all carbon chain. The resulting compounds **18a**−**f** exhibited high but very similar inhibitory potencies at cytosolic AK (IC_{50} values of 2.5−4 nM) and more variable activity in the intact cell AK assay. Among the best in this latter category were the unsubstituted phenylpropyl compound **10d** and the pyridylpropyl analogues **18b**,**f**. However, despite high inhibitory activities and, in some instances, good cell-penetrating properties, these compounds did not show potent activity in the formalin test or in the carrageenan-induced thermal hyperalgesia animal models (Table 2). One of the possible reasons

Table 1. In Vitro Activity of AK Inhibitors

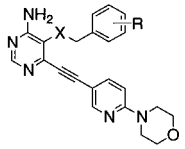
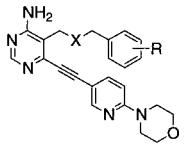
Compounds	AK Inhibition IC_{50} (nM)[a]	Inhibition of ADO Phosphorylation in Intact Cells IC_{50} (nM)[a]
		
2	120±25	>1000
		
10a R=3-Br, X=CH_2	22±8	1000±290
10b R=H, X=CH_2	40±5	700±85
10f R=3-Br, X=NMe	28±6	280±42
		
10c R=H, X=CH_2	4.5±3	220±55
31a R=2-Cl, X=NMe	15±3	100±18
31b R=H, X=NMe	30±4	124±37
31c R=3-Br, X=NMe	5±2	725±26
31d R=4-Br, X=NMe	90±10	515±145
31e R=4-Cl, X=NMe	106±18	360±35
31f R=2-Me, X=NMe	6±1	94±12
31g R=3-Cl, X=NMe	22±4	225±17
31h R=2-CF_3, X=NMe	40±6	276±56
31i R=3,4-Cl, X=NMe	200±228	345±16
31j R=naphthyl, X=NMe	246±42	388±50
		
10d R=H, X=CH_2	2.5±1	70±18
18a R=4-OMe, X=CH_2	3.5±1	198±36
18b R=3-pyridyl, X=CH_2	4±0.5	94±8
18c R=3-Br, X=CH_2	3.5±1.5	580±260
18d R=4-Br, X=CH_2	2±0.5	565±93
18e R=2-Cl, X=CH_2	2.5±1	188±10
18f R=4-pyridyl, X=CH_2	4±1	46±3
37a R=H, X=NMe	2±0.5	118±46
37b XCH_2Ph=tetrahydroisoquinoline	40±14	1000±100
37c R=2-Cl, X=NMe	5±0.5	146±10
		
10e	45±14	>1000

[a] The data represent mean ± SEM from at least three determinations.

for such in vitro−in vivo discrepancy could have been a poor water solubility of the synthesized compounds. To test this assumption, we have synthesized **37a**−**c** where one of the carbon units in the linker was replaced with the nitrogen atom. As a result, compound **37a** showed markedly increased in vivo activity with an ED_{50} value of 5−7 μM/kg in the thermal hyperalgesia assay, a model of inflammatory pain. Interestingly, this compound was not active in the formalin model of persistent pain, thus showing selectivity for inflammatory pain.

Encouraged by the fact that in vivo activity was achievable in these series of compounds, we began to explore the SAR of phenethyl-substituted molecules, another class of compounds that we originally selected based on their AK in vitro activity. However, instead of focusing on an all carbon linker, we replaced one carbon atom with nitrogen to prepare **31a**−**j** that were anilino analogues of phenethyl derivative **10c**. The substituent position in the phenyl ring of the N-benzyl moiety had a clear effect on the in vitro potency of these compounds. Unsubstituted or ortho- and meta-substituted compounds showed increased AK inhibitory potencies as compared with the para-substituted compounds. On the other hand, compounds with the ortho substitution, for

Table 2. Activity (ip) of Selected AK Inhibitors in Animal Pain Models

Compounds	Rat Formalin Nociception ED_{50} (μMol/kg)[a]	Rat Thermal Hyperalgesia ED_{50} (μMol/kg)[a]
		
10b R=H, X=CH_2	30±5	nt[b]
31a R=2-Cl, X=NMe	10±2	3±2
31b R=H, X=NMe	10±2	10±2
31f R=2-Me, X=NMe	na[c]	na
31g R=3-Cl, X=NMe	na	na
		
10d R=H, X=CH_2	8±2	>30
18a R=4-OMe, X=CH_2	20±5	>30
18b R=3-pyridyl, X=CH_2	na	nt
18f R=4-pyridyl, X=CH_2	na	46±3
37a R=H, X=NMe	na	5±2
37c R=2-Cl, X=NMe	30	>30

[a] The data represent mean ± SEM; n = 6−8 per dose group. [b] nt = not tested. [c] na = not active up to 100 μM/kg.

example, **31a**,**f** and the unsubstituted **31b**, appeared to be better inhibitors of cytosolic AK activity. From several compounds in these series that were tested in in vivo models, **31a** produced significant reduction of flinching in the formalin test with an ED_{50} value of 10−12 μM/kg and blocked carrageenan-induced thermal hyperalgesia with an ED_{50} value of 3−5 μM/kg. It should be noted, however, that pharmacokinetic profiles of in vivo active **31a** and inactive **31f** were very similar ($t_{1/2}$ = 0.5 vs 0.6 h; V_β = 3.7 vs 3.4 L/kg; CL_p = 5.4 vs 4.5 L/hr·kg; F = 4 vs 5%). These data suggest that the differential in vivo activity of **31a**, as compared to **31f**, may be due to the relative ability of **31a** to penetrate into the CNS. Previous data with nucleoside-like AK inhibitors indicated that the majority of the analgesic effects in the inflammatory hyperalgesia model are spinally mediated.[17]

Conclusion

We have identified a novel nonnucleoside class of potent AK inhibitors that contain a 4-amino-6-[6-(4-morpholynyl)-3-pyridinylethynyl]pyrimidine core. The substituent at the 5-position plays one of the most important roles for AK potency as it is responsible for the hydrophobic interactions with the protein. It was shown that the length of the linker between the lipophilic fragment of the 5-substituent and the pyrimidine core affects the AK inhibitory potency. Compounds with 2- and 3-atom linkers provided the highest AK inhibition. The critical step toward active compounds in vivo was the introduction of a nitrogen unit in the linkers of both types of series. Thus, compound **37a** with a 3-atom linker in the 5-position of the pyrimidine core exhibited good efficacy (ED_{50} = 5−7 μM/kg) in an animal model of inflammatory pain. Additionally, compound **31a** with a 2-atom linker was very effective in both the inflammatory (ED_{50} = 3−5 μM/kg) and the persistent chemical pain (ED_{50} = 10−12 μM/kg) models.

Experimental Section

^{1}H NMR spectra were obtained at 300 and 400 MHz using tetramethylsilane as internal standard. The mass spectra (electron spray ionization (ESI) and dissolvable chemical ionization (DCI)) and high-resolution mass spectra were recorded on a Finnigin-4000 instrument. Elemental combustion analyses were within +0.4% of theoretical values and obtained from Robertson Microlit Laboratories. Chromatographic separations were performed on silica gel 60 (230−400 mesh).

4-Amino-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (2). This compound was synthesized from 4,6-dichloropyrimidine in three steps by the procedure described below for the synthesis of **10a** from **6a** (yield 61%). ^{1}H NMR (DMSO-d_6): δ 8.38 (d, J = 2.0 Hz, 1H), 8.32 (s, 1H), 7.72 (dd, J = 2.0 and 7.5 Hz, 1H), 7.00 (broad s, 2H), 6.87 (d, J = 7.5 Hz, 1H), 6.53 (s, 1H), 3.70 (m, 4H), 3.58 (m, 4H). MS (DCI/NH_3): m/e 282 $(M + H)^+$. Anal. Calcd. ($C_{15}H_{15}N_5O\cdot 0.1H_2O$): C, H, N.

General Procedure for the Preparation of Compounds 10a−e: Diethyl (3-Bromobenzyl)malonate (4a). A solution of sodium (0.88 g, 38 mmol) in ethanol (50 mL) was treated with diethyl malonate **3** (6.40 g, 40 mmol) dropwise over 15 min. A solution of 3-bromobenzyl bromide (10.0 g, 40 mmol) in ethanol (40 mL) was added dropwise over 1 h, and the heterogeneous solution was refluxed for 16 h. The solvent was removed in vacuo, and the residue was diluted in EtOAc, washed with aqueous NH_4Cl and water, and concentrated. The residue was chromatographed (EtOAc−hexane, 5:95) to provide 11.0 g (88%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 2H), 7.15 (m, 2H), 4.19 (q, J = 7.5 Hz, 4H), 3.60 (t, J = 9.0 Hz, 1H), 3.19 (d, J = 9.0 Hz, 2H), 1.21 (t, J = 7.5 Hz, 6H). MS (DCI/NH_3): m/z 329 $(M + H)^+$.

4,6-Dihydroxy-5-(3-bromobenzyl)pyrimidine (5a). A solution of sodium ethoxide in ethanol (prepared from 3.87 g, 168.4 mmol of sodium, and 100 mL of ethanol) was treated at 0 °C with formamidine acetate (5.5 g, 53 mmol), the resulting mixture was stirred for 20 min, and then, the solution of diethyl (3-bromobenzyl)malonate **4a** (15.84 g, 48.1 mmol) in ethanol (10 mL) was added. The mixture was stirred at ambient temperature for 16 h, the solvent was removed at reduced pressure, water was added, and the pH was adjusted to 6−7 with 3 N HCl. The heterogeneous mixture was stirred for 15 min, and the pale yellow precipitate was filtered. The solid was suspended in EtOAc, refluxed for 30 min, filtered, and dried to give 7.41 g (55%) of the title compound. ^{1}H NMR (DMSO-d_6): δ 7.98 (s, 1H), 7.33 (m, 2H), 7.20 (m, 2H), 3.58 (s, 2H). MS (DCI/NH_3): m/e 281 $(M + H)^+$.

4,6-Dichloro-5-(3-bromobenzyl)pyrimidine (6a). A solution of 4,6-dihydroxy-5-(3-bromobenzyl)pyrimidine **5a** (2.8 g, 10 mmol) in $POCl_3$ (20 mL) was refluxed for 16 h. After the excess of $POCl_3$ was removed at reduced pressure, the residue was dissolved in CH_2Cl_2, washed twice with water, and dried over $MgSO_4$. The solvent was removed, and the residue was precipitated from ethanol to give 2.46 g (77%) of the product. ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 7.38 (m, 2H), 7.15 (m, 2H), 4.24 (s, 2H). MS (DCI/NH_3): m/e 318 $(M + H)^+$.

4,6-Diiodo-5-(3-bromobenzyl)pyrimidine (7a). A solution 4,6-dichloro-5-(3-bromobenzyl)pyrimidine **6a** (4.93 g, 15.5 mmol) in acetone (75 mL) was treated with NaI (11.6 g, 77 mmol) and HI (45% solution, 15 mL) at ambient temperature for 16 h. The resulting mixture was poured into a beaker with ice water, filtered, and air-dried to give 6.17 g (80%) of the desired product. ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H), 7.40−7.08 (m, 4H), 4.40 (s, 2H). MS (DCI/NH_3): m/e 501 $(M + H)^+$.

4-Amino-6-iodo-5-(3-bromobenzyl)pyrimidine (8a). A solution of diiodo derivative **7a** (1.0 g, 2 mmol) in ethanol (3 mL) was treated with ammonia, and the solution was heated in the sealed tube at 100 °C for 16 h. After the mixture was cooled to ambient temperature and concentrated, the residue was precipitated from ethanol to give 0.52 g (48%) of the desired product. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (s, 1H), 7.23 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 4.82 (broad s, 2H), 4.03 (s, 2H). MS (DCI/NH_3): m/e 390 $(M + H)^+$.

2-Morpholinyl-5-ethynylpyridine (9). A solution of 2,5-dibromopyridine (2.10 g, 8.86 mmol) in morpholine (4 mL) was heated to 90 °C for 15 h. The mixture was concentrated, and the residue was chromatographed (EtOAc−hexane, 1:1) to provide 5-bromo-2-morpholinylpyridine (1.93 g, 89%). MS (DCI/NH_3): m/e 243/245 $(M + H)^+$. To a slurry of this compond in piperidine (5 mL) was added trimethylsilyl acetylene (4.03 g, 41.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.20 g, 0.29 mmol), and copper(I) iodide (0.15 g, 0.79 mmol), and the mixture was heated in the sealed tube at 90 °C for 3 days. The reaction mixture was concentrated, and the residue was chromatographed (EtOAc−hexane, 1:3) to give 2-(4-morpholinyl)-5-pyridinylethynyltrimethylsilane (1.43 g, 69%). MS (DCI/NH_3): m/e 261 $(M + H)^+$. Desilylation of this product was carried out in methanol with 1 M aqueous K_2CO_3. After 2 h, the solvent was removed in vacuo, the residue was partitioned between water and dichloromethane, and the organic phase was dried (Na_2SO_4) and concentrated to obtain the desired product **9** (1.42 g, 95%) that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 8.32 (d, J = 1.5 Hz, 1H), 7.58 (dd, J = 11 and 1.5 Hz, 1H), 6.55 (d, J = 11 Hz, 1H), 3.80 (m, 4H), 3.57 (m, 4H), 3.07 (s, 1H). MS (DCI/NH_3): m/e 189 $(M + H)^+$.

4-Amino-5-(3-bromobenzyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10a). A solution of 4-amino-6-iodo-5-(3-bromobenzyl)pyrimidine **8a** (0.38 g, 0.97 mmol) in MeCN (8 mL) and triethylamine (6 mL) at ambient temperature was treated with 2-morpholinyl-5-ethynylpyridine **9** (0.2 g, 1.07 mmol), $Pd(PPh_3)_2Cl_2$ (0.034 g, 0.046 mmol), and copper(I) iodide (0.009 g, 0.06 mmol) for 1.5 h, filtered, and crystallized from ethanol to give 0.34 g (80%) of the desired product **10a**; mp 229−231 °C. ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 1H), 8.38 (d, J = 2 Hz, 1H), 7.60 (dd, J = 7.5 and 2 Hz, 1H), 7.15−7.43 (m, 4H), 6.60 (d, J = 7.5 Hz, 1H), 4.82 (s, 2H), 4.17 (s, 2H), 3.80 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H). MS (DCI/NH_3): m/e 450 $(M + H)^+$. Anal. Calcd. ($C_{22}H_{20}BrN_5O\cdot 0.25H_2O$): C, H, N.

4-Amino-5-benzyl-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10b). Compound **10b** was synthesized using benzyl bromide, and the process was described for the synthesis of **10a** (yield 77%). ^{1}H NMR (DMSO-d_6): δ 8.28 (d, J = 2.0 Hz, 1H), 8.22 (s, 1H), 7.63 (dd, J = 7.5 and 2.0 Hz, 1H), 7.32−7.12 (m, 5H), 6.95 (broad s, 2H), 6.87 (d, J = 7.5 Hz, 1H), 4.09 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H). MS (DCI/NH_3): m/e 372 $(M + H)^+$. Anal. Calcd. ($C_{22}H_{21}N_5O\cdot 0.4H_2O$): C, H, N.

4-Amino-5-(2-phenethyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10c). Compound **10c** was synthesized using (2-bromoethyl)benzene and the process described for the synthesis of **10a** (yield 83%). ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 7.5 and 2 Hz, 1H), 7.18−7.37 (m, 5H), 6.62 (d, J = 7.5 Hz, 1H), 4.80 (s, 2H), 4.17 (s, 2H), 3.82(t, J = 4.5 Hz, 4H), 3.60 (t, J = 4.5 Hz, 4H), 3.00 (t, J = 3.0 Hz, 4H). MS (DCI/NH_3): m/e 386 $(M + H)^+$. Anal. Calcd. ($C_{23}H_{23}N_5O$): C, H, N.

4-Amino-5-(3-phenylpropyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10d). Compound **10d** was synthesized using 1-bromo-3-phenylpropane and the process described for the synthesis of **10a** (yield 76%). ^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 7.5 and 2.0 Hz, 1H), 7.32−7.18 (m, 5H), 6.60 (d, J = 7.5 Hz, 1H), 4.78 (s, 2H), 3.82 (t, J = 4.5 Hz, 4H), 3.60 (t, J = 4.5 Hz, 4H), 2.75 (m, 4H), 1.95 (m, 2H). MS (DCI/NH_3): m/e 400 $(M + H)^+$. Anal. Calcd. ($C_{24}H_{25}N_5O$): C, H, N.

4-Amino-5-(4-phenylbutyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10e). Compound **10e** was synthesized using 1-bromo-3-phenylbutane[18] and the process described for the synthesis of **10a** (yield 75%). ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 7.5 and 2.0 Hz, 1H), 7.31−7.16 (m, 5H), 6.59 (d, J = 7.5 Hz, 1H), 4.90 (s, 2H), 3.82 (t, J = 4.5 Hz, 4H), 3.60 (t, J = 4.5 Hz, 4H), 2.78−2.55 (m, 4H), 1.94−1.60 (m, 4H). MS (DCI/NH_3): m/e 414 $(M + H)^+$. Anal. Calcd. ($C_{25}H_{27}N_5O$): C, H, N.

Diethyl 2-(3-Bromoanilino)malonate (12). A solution of 3-bromoaniline (150 g, 872 mmol) was treated with diethyl

chloromalonate **11** (69.5 g, 291 mmol) for 15 h at 40−50 °C. Diethyl ether was added, and 3-bromoaniline hydrobromide was filtered off. The filtrate was washed twice with water, 1 N HCl, and water. The organic phase was dried (Na_2SO_4), decolorized with charcoal, concentrated, and crystallized from hexane to obtain the desired product **12** (73.9 g, 77%); mp 83−84 °C. ^{1}H NMR ($CDCl_3$): δ 7.03 (t, J = 8.0 Hz, 1H), 6.90 (m, 1H), 6.81 (t, J = 2.5 Hz, 1H), 6.58 (m, 1H), 4.90 (broad s, 1H), 4.68 (s, 1H), 4.26 (q, J = 7.5 Hz, 4H), 1.30 (t, J = 7.5 Hz, 6H). MS (DCI/NH_3): *m/e* 330 (M + H)$^+$.

4,6-Dihydroxy-5-(3-bromoanilino)pyrimidine. This compound was prepared using the procedure described for the synthesis of **5a** (yield 63%). ^{1}H NMR (DMSO-d_6): δ 7.91 (s, 1H), 7.00−6.90 (m, 2H), 6.65 (m, 1H), 6.59 (d, J = 4.0 Hz, 1H), 6.50 (m, 1H). MS (DCI/NH_3): *m/e* 282 (M + H)$^+$.

4,6-Dichloro-5-(3-bromoanilino)pyrimidine (13). A solution of dihydroxy intermediate (2.2 g, 7.8 mmol), $POCl_3$ (8 mL), and dimethylformamide (DMF, 3 mL) was refluxed for 15 h. The resulting viscous mixture was poured into a beaker with ice, the pH was adjusted between 6 and 7 with concentrated NH_4OH, extracted twice with Et_2O, dried (Na_2SO_4), and concentrated, and the residue was chromatographed (EtOAc−hexane, 1:9) to obtain the desired compound **13** (0.94 g, 38%). ^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 7.13 (m, 2H), 6.92 (m, 1H), 6.65 (m, 1H), 5.93 (broad s, 1H). MS (DCI/NH_3): *m/e* 318 (M + H)$^+$.

4,6-Dichloro-5-[(3-bromophenyl)methylamino]pyrimidine (14). A solution of **13** (1.1 g, 3.5 mmol) in tetrahydrofuran (THF, 10 mL) was treated with NaH (0.095 g, 4.15 mmol) at ambient temperature. The mixture was stirred for 10 min and then treated with MeI (5.0 g, 35 mmol). After 15 h, the mixture was diluted with EtOAc, washed with aqueous NH_4Cl and water. The organic phase was concentrated to give the desired product **14** (1.05 g, 90%). ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 7.15−6.95 (m, 2H), 6.70 (t, J = 1.5 Hz, 1H), 6.37 (m, 1H), 3.21 (s, 3H). MS (DCI/NH_3): *m/e* 332 (M + H)$^+$.

4-Amino-5-[(3-bromophenyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (10f). Compound **10f** was prepared from **14** following the procedures described for the synthesis of **10a** (yield 78%). ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 7.98 (d, J = 2 Hz, 1H), 7.36 (dd, J = 7.5 and 2 Hz, 1H), 7.18−7.00 (m, 3H), 6.88−6.78 (m, 3H), 6.69 (m, 1H), 6.53 (d, J = 2 Hz, 1H), 3.65 (t, J = 4.5 Hz, 4H), 3.55 (t, J = 4.5 Hz, 4H), 3.12 (s, 3H). MS (DCI/NH_3): *m/e* 465 (M + H)$^+$. Anal. Calcd. ($C_{22}H_{22}BrN_6O\cdot 0.5H_2O$): C, H, N.

Diethyl 2-[3-(4-Methoxyphenyl)prop-2-enyl]malonate (16). To a solution of diethyl allylmalonate **15** (2.0 g, 10 mmol) in MeCN (10 mL) were added 4-iodoanisole (2.33 g, 10 mmol), *n*-tributylamine (2.4 mL), and palladium acetate (0.04 g). After it was refluxed for 4 h, the resulting mixture was cooled, concentrated, diluted with Et_2O, and washed with 1 N HCl, water, and brine. The organic phase was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (EtOAc−hexane, 2:3) to give the desired product **16** (1.76 g, 58%). ^{1}H NMR ($CDCl_3$): δ 7.35−7.22 (m, 2H), 6.90−6.80 (m, 2H), 6.42 (d, J = 15.0 Hz, 1H), 6.02 (m, 1H), 4.26−4.12 (m, 4H), 3.70 (s, 3H), 3.47 (t, J = 6.0 Hz, 1H), 2.79 (m, 2H), 1.25 (t, J = 7.5 Hz, 6H). MS (DCI/NH_3): *m/e* 307 (M + H)$^+$.

Diethyl 2-[3-(4-Methoxyphenyl)propyl]malonate (17). A mixture of **16** (1.63 g, 5.3 mmol) and 10% Pd/C (0.17 g) in EtOAc (25 mL) was hydrogenated at 1 atm for 15 h. The resulting mixture was filtered through Celite and concentrated to give the desired product **17** (1.47 g, 92%). ^{1}H NMR ($CDCl_3$): δ 7.09 (m, 2H), 6.82 (m, 2H), 4.18 (q, J = 7.5 Hz, 4H), 3.79 (s, 3H), 3.33 (t, J = 9.0 Hz, 1H), 2.57 (t, J = 9.0 Hz, 2H), 1.91 (m, 2H), 1.60 (m, 2H), 1.25 (t, J = 7.5 Hz, 6H). MS (DCI/NH_3): *m/e* 309 (M + H)$^+$.

4-Amino-5-[3-(4-methoxyphenyl)propyl]-6-[-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18a). Compound **18a** was prepared from **17** using a synthetic sequence described for the synthesis of **10a** (yield 54%). ^{1}H NMR (DMSO-d_6): δ 8.19 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 7.49 (dd, J = 7.5 and 2.0 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 6.93−6.75 (m, 5H), 3.73−3.67 (m, 7H), 3.57 (t, J = 4.5 Hz, 4H), 2.73−2.60 (m, 4H), 1.71 (m, 2H). MS (DCI/NH_3): *m/e* 430 (M + H)$^+$. Anal. Calcd. ($C_{25}H_{27}N_5O_2$): C, H, N.

4-Amino-5-allyl-6-chloropyrimidine (21). Compound **21** was prepared by ammonolysis of 5-allyl-4,6-dichloropyrimidine[19] **20** as described for the synthesis of **8a** (yield 88%). ^{1}H NMR ($CDCl_3$): δ 8.27 (s, 1H), 5.71 (m, 1H), 5.22−5.08 (m, 4H), 3.40 (m, 2H). MS (DCI/NH_3): *m/e* 170 (M + H)$^+$.

4-Amino-5-(3-pyridin-3-ylprop-2-enyl)-6-chloropyrimidine (22b). A solution of 4-amino-5-allyl-6-chloropyrimidine **21** (5.0 g, 29.6 mmol) in dioxane (50 mL) was treated with diisopropylethylamine (5 mL), 3-bromopyridine (4.9 g, 31.0 mmol), tri-o-tolylphosphine (0.31 g), and $Pd(PPh_3)_4$ (0.8 g), and the mixture was refluxed for 14 h. After it was cooled to ambient temperature, the mixture was concentrated, and the residue was diluted in EtOAc and washed with water. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (CH_2Cl_2−MeOH, 95:5) to obtain the desired product **22b** (1.25 g, 17%). ^{1}H NMR (DMSO-d_6): δ 8.55(d, J = 2.5 Hz, 1H), 8.40 (d, J = 4.0 Hz, 1H), 8.11 (s, 1H), 7.81 (m, 1H), 7.31 (dd, J = 4.0 and 7.5 Hz, 1H), 7.16 (broad sd, 2H), 6.50−6.32 (m, 2H), 3.50 (d, J = 5.0 Hz, 2H). MS (DCI/NH_3): *m/e* 247 (M + H)$^+$.

4-Amino-5-(3-pyridin-3-ylpropyl)-6-chloropyrimidine (23b). A mixture of **22b** (0.7 g, 2.84 mmol), Pt/C (5%, 0.35 g) in EtOAc (25 mL), and MeOH (25 mL) was hydrogenated at 4 atm for 17 h. The resulting mixture was filtered through Celite and concentrated to obtain the desired product **23b** (0.42 g, 60%). ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1H), 8.40 (d, J = 4.5 Hz, 1H), 8.05 (s, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.30 (m, 1H), 7.20 (broad s, 2H), 2.69 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 1.72 (m, 2H). MS (DCI/NH_3): *m/e* 249 (M + H)$^+$.

4-Amino-5-(3-pyridin-3-ylpropyl)-6-iodopyrimidine (24b). A solution of **23b** (0.19 g, 0.76 mmol) in 40% HI (4 mL) was treated with NaI (0.57 g, 3.8 mmol) and stirred for 10 min at 70 °C. The precipitate was filtered, taken up in aqueous $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), and concentrated to give the desired product **24b** (0.17 g, 67%). ^{1}H NMR (DMSO-d_6): δ 8.43 (d, 2.0 Hz, 1H), 8.39 (dd, J = 2.0 and 4.5 Hz, 1H), 8.04 (s, 1H), 7.64 (m, 1H), 7.30 (m, 1H), 7.18 (broad s, 2H), 2.70 (t, J = 8.0 Hz, 2H), 2.58 (t, J = 8.0 Hz, 2H), 1.72 (m, 2H). MS (DCI/NH_3): *m/e* 341 (M + H)$^+$.

4-Amino-5-[3-(3-pyridinyl)propyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18b). Compound **18b** was prepared from **24b** and 2-morpholinyl-5-ethynylpyridine **9** according to the procedure described for the synthesis of **10a** (yield 29%). ^{1}H NMR (DMSO-d_6): δ 8.45−8.35 (m, 2H), 8.21 (d, J = 2.0 Hz, 1H), 8.18 (s, 1H), 7.61 (m, 1H), 7.51 (dd, J = 7.5 and 2.0 Hz, 1H), 7.25 (dd, J = 8 and 4.5 Hz, 1H), 6.90 (broad s, 2H), 6.88 (d, J = 7.5 Hz, 1H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.78−2.67 (m, 4H), 1.89−1.72 (m, 2H). MS (DCI/NH_3): *m/e* 401 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{24}N_6O\cdot 1.22H_2O$): C, H, N.

4-Amino-5-[3-(3-bromophenyl)propyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18c). Compound **18c** was prepared from the 1-bromo-3-iodobenzene and using the synthetic sequence described for the synthesis of **18b** (yield 42%). ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1H), 8.32 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 7.5 and 2.0 Hz, 1H), 7.39−7.29 (m, 2H), 7.15−7.08 (m, 2H), 6.60 (d, J = 7.5 Hz, 1H), 4.88 (s, 2H), 3.81 (t, J = 4.5 Hz, 4H), 3.61 (t, J = 4.5 Hz, 4H), 2.79−2.66 (m, 4H), 2.01−1.87 (m, 2H). MS (APCI): *m/e* 478/480 (M + H)$^+$. Anal. Calcd. ($C_{24}H_{24}BrN_5O$): C, H, N.

4-Amino-5-[3-(4-bromophenyl)propyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18d). Compound **18d** was prepared from the 1-bromo-4-iodobenzene and using the synthetic sequence described for the synthesis of **18b** (yield 40%). ^{1}H NMR (DMSO-d_6): δ 8.40 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 7.5 and 2.0 Hz, 1H), 7.41−7.35 (m, 2H), 7.11−7.04 (m, 2H), 6.61 (d, J = 7.5 Hz, 1H), 4.81 (s, 2H), 3.81 (t, J = 4.5 Hz, 4H), 3.60 (t, J = 4.5 Hz, 4H), 2.77−2.66 (m, 4H), 2.01−1.89 (m, 2H). MS (DCI/NH_3): *m/e* 478/480 (M + H)$^+$. Anal. Calcd. ($C_{24}H_{24}BrN_5O$): C, H, N.

4-Amino-5-[3-(2-chlorophenyl)propyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18e). Compound **18e**

was prepared from the 1-chloro-2-iodobenzene and using the synthetic sequence described for the synthesis of **18b** (yield 56%). ^{1}H NMR (DMSO-d_6): δ 8.24 (d, J = 2.0 Hz, 1H), 8.18 (s, 1H), 7.53 (dd, J = 8.0 and 2.0 Hz, 1H), 7.36 (m, 2H), 7.24 (m, 2H), 6.95 (s, 2H), 6.88 (d, J = 9.0 Hz, 1H), 3.70 (m, 4H), 3.56 (m, 4H), 2.83 (m, 2H), 2.74 (m, 2H), 1.77 (m, 2H). MS (ESI): m/e 434 (M + H)$^+$. Anal. Calcd. ($C_{24}H_{24}ClN_5O\cdot0.2H_2O$): C, H, N.

4-Amino-5-[3-(4-pyridinyl)propyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (18f). Compound **18f** was prepared from the 4-bromopyridine and using the synthetic sequence described for the synthesis of **18b** (yield 46%). ^{1}H NMR (DMSO-d_6): δ 8.40 (broad s, 2H), 8.26 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 7.53 (dd, J = 7.5 and 2.0 Hz, 1H), 7.22 (d, J = 4.5 Hz, 2H), 6.95 (broad s, 2H), 6.89 (d, J = 7.5 Hz, 1H), 3.70 (t, J = 4.5 Hz, 4H), 3.55 (t, J = 4.5 Hz, 4H), 2.79−2.65 (m, 4H), 1.87−1.71 (m, 2H). MS (DCI/NH_3): m/e 401 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{24}N_6O\cdot2.0H_2O$): C, H, N.

4,6-Diiodo-5-aminopyrimidine (27). A mixture of 5-amino-4,6-dichloropyrimidine **26** (4.0 g, 24.2 mmol), sodium iodide (18.0 g, 120 mmol), and 40% HI (60 mL) was stirred for 3 h at ambient temperature. After it was filtered, the precipitate was washed with aqueous $NaHCO_3$ and dried to give the desired product (8.0 g, 94%). MS (DCI/NH_3): m/e 348 (M + H)$^+$.

4,6-Diiodo-5-(2-chlorobenzylamino)pyrimidine (28a). A solution of **27** (3.5 g, 10 mmol) in THF (100 mL) was treated with 95% NaH (0.29 g, 12 mmol) at 0 °C, then the mixture was warmed to ambient temperature, and 2-chlorobenzyl bromide (1.6 mL, 12 mmol) and tetrabutylammonium iodide (4.4 g, 12 mmol) were added. The mixture was stirred for 2 h, concentrated, and chromatographed (EtOAc−hexane, 1:4) to give the desired product **28a** (3.5 g, 74%). ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H), 7.49−7.20 (m, 4H), 4.52 (m, 2H), 4.12 (t, J = 7.5 Hz, 1H). MS (DCI/NH_3): m/e 472 (M + H)$^+$.

4,6-Diiodo-5-[*N*-methyl-*N*-(2-chlorobenzylamino)]pyrimidine (29a). A solution of **28a** (4.0 g, 8.5 mmol) in THF (80 mL) was treated with 95% NaH (0.25 g, 10.2 mmol) at 0 °C, then the mixture was warmed to ambient temperature, and methyl iodide (0.8 mL, 12.8 mmol) and tetrabutylammonium iodide (3.1 g, 8.5 mmol) were added. The mixture was stirred for 14 h, concentrated, and chromatographed (EtOAc−hexane, 5:95) to give desired product **29a** (2.8 g, 68%). ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.56 (m, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 4.47 (s, 2H), 2.91 (s, 3H). MS (DCI/NH_3): m/e 486 (M + H)$^+$.

4-Amino-5-[(2-chlorobenzyl)methylamino]-6-iodopyrimidine (30a). A solution of diiodo derivative **29a** (0.49 g, 1.0 mmol) in ethanol (3 mL) was treated with ammonia, and the solution was heated in the sealed tube at 80 °C for 14 h. After the mixture was cooled to ambient temperature and concentrated, the residue was precipitated from ethanol to give **30a** (0.2 g, 51%). ^{1}H NMR (DMSO-d_6): δ 7.80 (s, 1H), 7.56 (m, 1H), 7.42 (m, 1H), 7.30 (m, 2H), 6.92 broad s, 2H), 4.43−4.15 (m, 2H), 2.75 (s, 3H). MS (DCI/NH_3): m/e 375 (M + H)$^+$.

4-Amino-5-[(2-chlorobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31a). Compound **31a** was prepared from **30a** and 2-morpholinyl-5-ethynylpyridine **9** as described for the synthesis of **10a** (60%). ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J = 2.0 Hz, 1H), 8.10 (s, 1H), 7.70 (dd, J = 7.5 and 2.0 Hz, 1H), 7.56 (m, 1H), 7.38 (m, 1H), 7.30−7.21 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 4.43 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.77 (s, 3H). MS (DCI/NH_3): m/e 435 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{23}ClN_6O\cdot0.6H_2O$): C, H, N.

4-Amino-5-(benzylmethylamino)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31b). Compound **31b** was prepared from the benzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 72%). ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J = 1.5 Hz, 1H), 8.03 (s, 1H), 7.73 (dd, J = 7.5 and 2.0 Hz, 1H), 7.40−7.18 (m, 5H), 6.95 (d, J = 7.5 Hz, 1H), 6.87 (broad s, 2H), 4.30 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.75 (s, 3H). MS (DCI/NH_3): m/e 401 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{24}N_6O\cdot0.4H_2O$): C, H, N.

4-Amino-5-[(3-bromobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31c). Compound **31c** was prepared from the 3-bromobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 28%). ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 1.5 Hz, 1H), 8.05 (s, 1H), 7.72 (dd, J = 7.5 and 2.0 Hz, 1H), 7.60 (s, 1H), 7.41−7.30 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 6.95 (broad s, 2H), 6.91 (d, J = 7.5 Hz, 1H), 4.30 (s, 2H), 3.72 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.75 (s, 3H). MS (DCI/NH_3): m/e 479/481 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{23}BrN_6O\cdot0.3H_2O$): C, H, N.

4-Amino-5-[(4-bromobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31d). Compound **31d** was prepared from the 4-bromobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 70%). ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 1.5 Hz, 1H), 8.08 (s, 1H), 7.73 (dd, J = 7.5 and 2.0 Hz, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.31 (d, J = 7.0 Hz, 2H), 7.05−6.90 (m, 3H), 4.28 (s, 2H), 3.71 (t, J = 4.5 Hz, 4H), 3.59 (t, J = 4.5 Hz, 4H), 2.72 (s, 3H). MS (DCI/NH_3): m/e 479/481 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{23}BrN_6O\cdot2.2H_2O\cdot0.2EtOH$): C, H, N.

4-Amino-5-[(4-chlorobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31e). Compound **31e** was prepared from the 4-chlorobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 51%). ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J = 1.5 Hz, 1H), 8.05 (s, 1H), 7.73 (dd, J = 7.5 and 2.0 Hz, 1H), 7.40−7.29 (m, 4H), 6.91 (broad s, 2H), 6.91 (d, J = 7.5 Hz, 1H), 4.29 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.73 (s, 3H). MS (DCI/NH_3): m/e 435 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{23}ClN_6O\cdot0.1H_2O$): C, H, N.

4-Amino-5-[(2-methylbenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31f). Compound **31f** was prepared from the 2-methylbenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 40%). ^{1}H NMR ($CDCl_3$): δ 8.37 (d, J = 1.5 Hz, 1H), 8.08 (s, 1H), 7.71 (dd, J = 7.5 and 2.0 Hz, 1H), 7.34 (m, 1H), 7.15−7.07 (m, 3H), 6.92 (d, J = 7.5 Hz, 1H), 6.78 (broad s, 2H), 4.31 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.57 (t, J = 4.5 Hz, 4H), 2.71 (s, 3H), 2.27 (s, 3H). MS (DCI/NH_3): m/e 415 (M + H)$^+$. Anal. Calcd. ($C_{24}H_{26}N_6O\cdot0.2H_2O$): C, H, N.

4-Amino-5-[(3-chlorobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31g). Compound **31g** was prepared from the 3-chlorobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 67%). ^{1}H NMR ($CDCl_3$): δ 8.35 (d, J = 1.5 Hz, 1H), 8.12 (s, 1H), 7.70 (overlapped d, 1H), 7.70 (dd, J = 7.5 and 2.0 Hz, 1H), 7.46 (d, J = 7.0 Hz, 2H), 7.32 (dd, J = 8.5 and 2.0 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 4.50 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.59 (t, J = 4.5 Hz, 4H), 2.79 (s, 3H). MS (DCI/NH_3): m/e 435 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{23}ClN_6O\cdot0.7H_2O$): C, H, N.

4-Amino-5-[methyl(2-trifluoromethylbenzyl)amino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31h). Compound **31h** was prepared from the 2-trifluorobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 68%). ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J = 1.5 Hz, 1H), 8.14 (s, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.75−7.63 (m, 3H), 7.48 (t, J = 6.0 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 4.53 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.59 (t, J = 4.5 Hz, 4H), 2.70 (s, 3H). MS (DCI/NH_3): m/e 469 (M + H)$^+$. Anal. Calcd. ($C_{24}H_{23}F_3N_6O\cdot0.25H_2O$): C, H, N.

4-Amino-5-[(3,4-dichlorobenzyl)methylamino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31i). Compound **31i** was prepared from the 3,4-dichlorobenzyl bromide and using the synthetic sequence described for the synthesis of **31a** (yield 56%). ^{1}H NMR ($CDCl_3$): δ 8.49 (d, J = 2.0 Hz, 1H), 8.08 (s, 1H), 7.72 (dd, J = 7.5 and 2.0 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 7.53 (d, J = 6.0 Hz, 1H), 7.30 (dd, J = 6.0 and 1.0 Hz, 1H), 7.00 (broad s, 2H), 6.92 (d, J = 7.5 Hz, 1H), 4.29 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.73 (s, 3H). MS (DCI/NH_3): m/e 469 (M + H)$^+$. Anal. Calcd. ($C_{23}H_{22}Cl_2N_6O\cdot0.25H_2O$): C, H, N.

4-Amino-5-[methyl(2-naphthylmethyl)amino]-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (31j). Compound **31j** was prepared from the 2-(bromomethyl)naphthalene and using the synthetic sequence described for the synthesis of **31a** (yield 47%). ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.86−7.78 (m, 4H), 7.71 (dd, J = 7.5 and 2.0

Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.50−7.41 (m, 2H), 6.94 (broad s, 2H), 6.90 (d, J = 7.5 Hz, 1H), 4.49 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 4.5 Hz, 4H), 2.80 (s, 3H). MS (DCI/NH_3): m/e 451 $(M + H)^+$. Anal. Calcd. ($C_{27}H_{26}N_6O \cdot 0.2H_2O$): C, H, N.

4,6-Dichloro-5-formylpyrimidine (33). A mixture of DMF (64 mL) and $POCl_3$ (200 mL) at 0 °C was stirred for 1 h, treated with 4,6-dihydroxypyrimidine **32** (50.0 g, 446 mmol), and stirred for 0.5 h at ambient temperature, and the heterogeneous mixture was refluxed for 3 h. The volatiles were removed at reduced pressure, and the residue was poured into ice water and extracted six times with diethyl ether. The organic phase was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, concentrated, and crystallized (EtOAc−petroleum ether) to give the desired product **33** (43.5 g, 55%); mp 67−69 °C (literature[15] 69−70 °C). ^{1}H NMR ($CDCl_3$): δ 10.45 (s, 1H), 8.90 (s, 1H). MS (DCI/NH_3): m/e 177 $(M + H)^+$.

4-Amino-6-chloro-5-formylpyrimidine (34). Ammonia was bubbled through a solution of **33** (5.0 g, 28.4 mmol) in toluene (250 mL) for 3−4 min, and the solution was heated to 60 °C. After 0.5 h, more ammonia gas was bubbled and stirring was continued for 0.5 h at 50−60 °C. The reaction was monitored by thin-layer chromatography (TLC) to avoid formation of 4,6-diamino-5-formylpyrimidine. The mixture was cooled to ambient temperature and concentrated, and the residue was chromatographed (EtOAc−hexane, 3:7) to give the desired compound **34** (3.0 g, 67%). ^{1}H NMR (DMSO-d_6): δ 10.25 (s, 1H), 8.72 (broad s, 1H), 8.58 (broad s, 1H), 8.40 (s, 1H). MS (DCI/NH_3): m/e 158 $(M + H)^+$.

4-Amino-5-benzylmethylaminomethyl-6-chloropyrimidine (35a). A solution of **34** (0.5 g, 3.18 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was treated with *N*-methylbenzylamine (0.4 mL, 3.18 mmol), acetic acid (0.2 mL, 3.18 mmol), and sodium triacetoxyborohydride (1.0 g, 4.77 mmol). After 15 h, the mixture was concentrated and the residue was chromatographed (EtOAc−hexane, 35:65) to give the desired product **35a** (0.38 g, 46%). ^{1}H NMR (DMSO-d_6): δ 8.12 (s, 1H), 7.30 (m, 7H), 3.60 (s, 2H), 3.50 (s, 2H), 2.06 (s, 3H). MS (DCI/NH_3): m/e 263 $(M + H)^+$.

4-Amino-5-benzylmethylaminomethyl-6-iodopyrimidine (36a). A solution of **35a** (0.2 g, 0.76 mmol) in 40% HI (4 mL) was treated with NaI (0.57 g, 3.8 mmol) and stirred for 10 min at 70 °C. The precipitate was filtered, taken up in aqueous $NaHCO_3$, and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to give the desired product **36a** (0.18 g, 67%). ^{1}H NMR (DMSO-d_6): δ 7.92 (s, 1H), 7.30 (m, 7H), 3.60 (s, 2H), 3.52 (s, 2H), 2.08 (s, 3H). MS (DCI/NH_3): m/e 355 $(M + H)^+$.

4-Amino-5-(benzylmethylaminomethyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (37a). Compound **37a** was prepared by using **36a** and 2-morpholinyl-5-ethynylpyridine **9** as described for the synthesis of **10a** (yield 62%). ^{1}H NMR (DMSO-d_6): δ 8.35 (d, J = 2.0 Hz, 1H), 8.28 (s, 1H), 7.68 (dd, J = 7.5 and 2.0 Hz, 1H), 7.33−7.20 (m, 5H), 7.10 (broad s, 2H), 6.90 (d, J = 7.5 Hz, 1H), 3.72 (m, 6H), 3.58 (m, 6H), 2.05 (s, 3H). MS (DCI/NH_3): m/e 415 $(M + H)^+$. Anal. Calcd. ($C_{24}H_{26}N_6O \cdot 0.2H_2O$): C, H, N.

4-Amino-5-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (37b). Compound **37b** was synthesized according to a scheme described for the synthesis of **37a** (yield 46%). ^{1}H NMR (DMSO-d_6): δ 8.32 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 7.67 (dd, J = 7.5 and 2.0 Hz, 1H), 7.13−7.03 (m, 4H), 6.87 (d, J = 7.5 Hz, 1H), 3.83 (s, 2H), 3.70−3.51 (m, 10H), 2.88−2.70 (m, 4H). MS (DCI/NH_3): m/e 427 $(M + H)^+$. Anal. Calcd. ($C_{25}H_{26}N_6O$): C, H, N.

4-Amino-5-[(2-chlorobenzyl)methylaminomethyl)-6-[6-(4-morpholinyl)-3-pyridinylethynyl]pyrimidine (37c). Compound **37c** was synthesized according to a scheme described for the synthesis of **37a** (yield 61%). ^{1}H NMR (DMSO-d_6): δ 8.40 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H), 7.73 (dd, J = 7.5 and 2.0 Hz, 1H), 7.52 (m, 2H), 7.35 (m, 2H), 7.08 (broad s, 2H), 6.90 (d, J = 7.5 Hz, 1H), 3.78 (s, 2H), 3.75−3.64 (m, 6H), 3.59 (t, J = 4.5 Hz, 4H), 2.09 (s, 3H). MS (DCI/NH_3): m/e 449 $(M + H)^+$. Anal. Calcd. ($C_{24}H_{25}ClN_6O \cdot 0.4H_2O$): C, H, N.

AK Inhibition Assay. Routine AK inhibition assays were carried out at 23 °C in a volume of 100 μL. The reaction mixture contained 64 mM Tris-HCl (pH 7.5), 0.2 mM $MgCl_2$, 1mM ATP, 0.2 μM [U-^{14}C]ADO or [2-^{3}H]ADO, and appropriate volumes of rat brain cytosol as a source of AK.[7] The reaction was incubated for 15 min and terminated by aliquoting 40 μL of the reaction mixture into DE-81 anion exchange filter disks. The filter disks were air-dried, washed for 15 min in 2 mM ammonium formate, rinsed with water, methanol, and acetone, and dried under an atmosphere of nitrogen. Bound radioactivity was determined by standard scintillation spectrometry.

Intact Cell ADO Phosphorylation Assay. Routine ADO phosphorylation assays in intact cells were conducted by using IMR-32 human neuroblastoma cells (American Type Culture Collection, Gaithersburg, MD). Appropriate concentrations of test compounds (10^{-11} to 10^{-4} M) were added to each well, and the cells were incubated for 10 min. The reaction was initiated by the addition of 50 μL of 2 μM [U-^{14}C]ADO. After a 20 min incubation, the assay buffer was rapidly aspirated, and the cells were quickly frozen by the addition of liquid nitrogen. The plates were allowed to thaw at room temperature for 20 min, and a 50 μL aliquot of the supernatant was placed onto DE-81 filter disks. The filter disks were then processed as described above for the AK enzyme assay.

In Vivo Evaluation of AK Inhibitors. Nociceptive paw flinching in rats (Formalin test) was assessed 30 min following an intraplantar injection of 5% formalin (50 μL) into the right hindpaw. The antihyperalgesic effects of AK inhibitors were assessed in the carrageenan-induced thermal hyperalgesia pain model.[20] Compounds were administered intraperitoneally 30 min before injection of 100 μL of 1% solution of λ-carrageenan. The hyperalgesia to thermal stimulation was determined 2 h after carrageenan injection.

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