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Adenosine Kinase Inhibitors: Polar 7-Substitutent of Pyridopyrimidine Derivatives Improving Their Locomotor Selectivity

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Abstract—We have discovered that polar 7-substituents of pyridopyrimidine derivatives affect not only whole cell AK inhibitory potency, but also selectivity in causing locomotor side effects in vivo animal models. We have identified compound, **1o**, which has potent whole cell AK inhibitory potency, analgesic activity and minimal reduction of locomotor activity.

Adenosine (ADO) is a key homeostatic inhibitory neuromodulator that contributes to endogenous anti-nociceptive and anti-inflammatory responses following tissue injury. Cellular stress increases the local tissue levels of extracellular ADO.[1] Extracellular ADO acts on specific cell-surface P1 purinergic receptors (A_1, A_{2A}, A_{2B} and A_3) proximal to the site of release to exert its homeostatic effects. Adenosine has an extremely short half-life in extracellular fluids. The endogenous actions of ADO are limited to the tissue and cellular site where it is released. By blocking the intracellular adenosine kinase, which converts ADO to adenosine monophosphate, selective adenosine kinase inhibitors increase the extracellular concentration of endogenously released adenosine,[2] and therefore enhance its antinociceptive and antiinflammatory action.[3–5]

We have pursued pyridopyrimidine derivatives as a novel class of adenosine kinase inhibitors.[6] These derivatives are efficacious in animal pain models. One concern was to reduce the degree of locomotor side effects caused by these new derivatives. Previous studies indicated that AK inhibitors potentially reduce thermal hyperalgesia primarily through interactions with spinal sites, while its ability to depress locomotor activity is predominantly mediated by supraspinal sites.[7] The challenge was to modify our novel type of pyridopyrimidine derivatives to maintain sufficient efficacies in animal pain models, but without significant locomotor side effects.

Compounds with structures shown in Figure 1 are typical pyridopyrimidine adenosine kinase inhibitors. The SAR clearly indicated that R_1 and R_2 groups played a significant role in terms of in vitro/in vivo potencies,[8] and their physicochemical properties. We now report that polarity of these pyridopyrimidine derivatives, caused by incorporating polar R_1 and R_2 moieties, affects not only analgesic efficacy, but also locomotor selectivity.

7-Substituted pyridopyrimidine derivatives, both X = CH and N, can be made via several different approaches. A typical procedure to make these derivatives is shown in Scheme 1. Dinitrile intermediate **3** was generated by condensation of malononitrle with 3-benzaldehyde in a mixture of ethanol and water (1:1) in the presence of catalytic amounts of glycine.[9] The reaction

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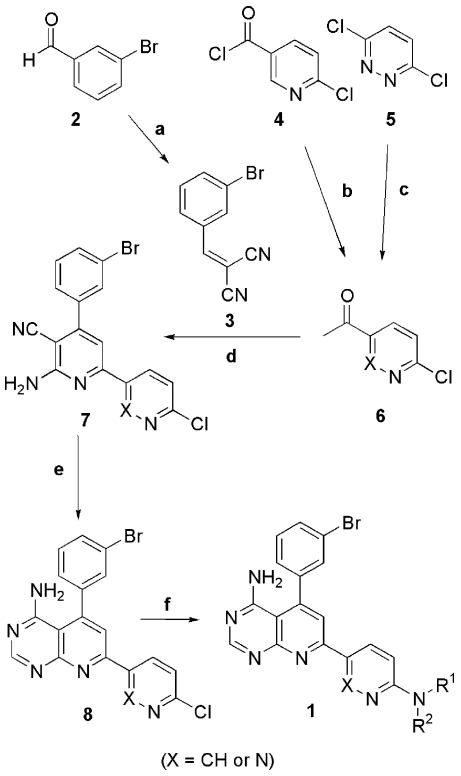


Scheme 1. (a) Malononitrile, glycine (cat); (b) (1) dimethyl malonate, $MgCl_2$, Et_3N; (2) DMSO/H_2O; (c) tributyl(1-ethoxyviny)tin, $Pd_2(dba)_3$, $P(furyl)_3$, DMF, 75–80 °C, 4 h; (d) ammonium acetate, dichloroethane, 80–85 °C; (e) trisformaminomethane, formamide, 110–120 °C; (f) amine, DMSO, 100 °C.

went very quickly, and was completed in a couple of min at room temperature with very good yield. Acetyl intermediates, such as **6**, were prepared via two different routes: when X = CH, 6-chloronicotinyl chloride (**4**) was treated with dimethyl malonate under soft enolisation conditions, $MgCl_2$ and triethylamine, followed by decarboxylation in 9:1 DMSO (methyl sulfoxide)/water to give the desired ketone intermediate **6a** (X = CH).[10] The pyridazine ketone intermediate **6b** (X = N) was obtained, with high chemical yield, by palladium mediated coupling reaction [using tris(di-benzylideneacetone)dipalladium and $P(furyl)_3$] between dichloropyridazine **5** and vinyl stannane in DMF (*N,N*-dimethylformamide), followed by acidic hydrolysis. Condensation of ketone intermediates like **6** with dinitrile intermediate **3** in the presence of ammonium acetate in dichloroethane gave aminocyanopyridine intermediates **7**. These latter intermediates (**7**) were then cyclized to form the pyridopyrimidine ring intermediate **8** with trisformaminomethane in formamide at 110 °C. The final products (**1**) can be obtained by reacting intermediate **8** with the desired amine in DMSO at 100 °C (Scheme 1).

From our earlier SAR studies of these pyridopyrimidine derivatives, R_1/R_2 moieties with less polar groups favored the in vivo efficacies in various pain models.[8] This is an indication that distribution into CNS may be necessary for these analogues to achieve desired in vivo efficacies.[7] We calculated clogP values for all these ana-

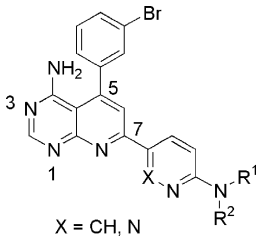
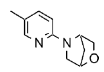
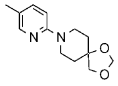
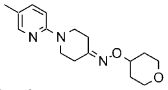
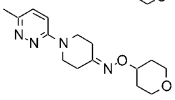
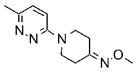
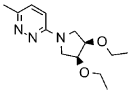
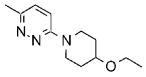
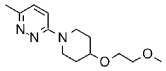
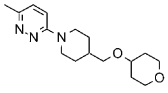
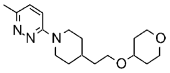
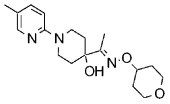
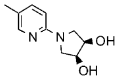
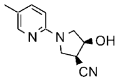
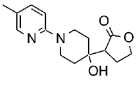


Figure 1. Novel pyridopyrimidine adenosine kinase inhibitors.

logues listed in Table 1. All these analogues, including those polar analogues from **1j** to **1o** are within values from 3 to 5, which is near the optimal range for CNS penetration.[11] While these analogues **1i**–**1o** worked very well in different animal pain models, such as carrageenan-induced thermal hyperalgesia (CARR), reduced locomotor activity was observed (Table 1). Switching X = CH to X = N (**1c** to **1d**, entries 2 and 4) did not make much difference in terms of in vitro/in vivo potencies or locomotor selectivity. We then focused on the variation of R_1 and R_2 moieties to alter the selectivity. Increasing lipophilicity of the R_1/R_2 moiety, from compound **1f** to compound **1j** (entries 6–10), led to a significant decrease of locomotor selectivity. Moreover, compound **1j** is more potent in the locomotor assay [locomotor ED_{50} (po): 9 μmol/kg] than in analgesic assay [CARR ED_{50} (po): 30 μmol/kg], indicating that this compound may distribute into brain more effectively as compared to its closest derivative **1i**, which showed equal potencies for both CARR and locomotor (ED_{50}: 5 μmol/kg, po). The trend of decreased locomotor selectivity with increased lipophilicity of 7-substituents seems to indicate that incorporating more polar R_1/R_2 moieties may help to enhance the desired selectivity. It was also noticed that poor whole cell inhibition of AK did not translate to improved locomotor selectivity, even though this property could also be attributed to poor membrane/CNS permeability. Compound **1b** has a relatively weak whole cell value [whole cell AK IC_{50} = 378.1 (±130.7) nM], yet this compound is still very potent in the locomotor assay (ED_{50} = 6 μmol/kg, po entry 2, Table 1). After introducing some polar moieties on the 7-substitutent, we found the compounds indeed had weaker whole cell AK inhibitory potency (entries 12–14, compounds **1l**, **1m**, and **1n**), with whole cell AK IC_{50} values ranging from 130 to 495 nM. The locomotor selectivity, however, improved significantly. As mentioned above, the clogP values (3–5) of these compounds and in vivo efficacy (CARR) suggest that these new compounds with polar 7-substitutuent penetrate into the CNS. Therefore, the reduced of locomotor side effects of these polar derivatives are not likely to be caused by insufficient CNS penetration. It may be the result of preferential partitioning of these AKIs in the CNS. Efforts were made to adjust the polarity of R_1/R_2 moiety in these derivatives, so that a slightly less polar R_1/R_2 moiety might retain good locomotor selectivity with improved whole cell inhibitory potency. The hydroxybutyrolactone-piperidyl moiety was found to have suitable polarity for reduced locomotor side effects. Compound **1o** (entry 15) has a

Table 1. Analgesic and locomotor activities of 7-substituted pyridopyrimidine adenosine kinase inhibitors

Entry	7-Substitutent		AK IC_{50} (nM)	Cell IC_{50} (nM)	CARR[a] ED_{50} (μmol/kg) (po)	Locomotor ED_{50} (μmol/kg) (po)
1		**1a**	7.5 (±0.3)	19.5 (±0.7)	2	8
2		**1b**	8.3 (±5.1)	378.1 (±130.7)	2	6
3		**1c**	10.0 (±2.0)	71.0 (±23.7)	2	10
4		**1d**	7.1 (±3.4)	52.0 (±13.8)	2	7
5		**1e**	18.8 (±9.7)	74.4 (±2.8)	13	6
6		**1f**	7.2 (±0.5)	40.7 (±26.2)	3	25
7		**1g**	10.4 (±6.0)	51.7 (±14.8)	7	20
8		**1h**	15.1 (±3.4)	81.9 (±11.9)	3	10
9		**1i**	2.8 (±0.1)	17.3 (±4.5)	5	5
10		**1j**	22.8 (±11.1)	89.5 (±31.6)	30	9
11		**1k**	31.7 (±7.3)	43.7 (±14.1)	5	30
12		**1l**	16.2 (±7.8)	153.8 (±53.8)	10	98% @ 30[b] 75% @ 100[b]
13		**1m**	6.5 (±3.4)	130.1 (±17.7)	2	73% @ 30[b]
14		**1n**	7.5 (±2.8)	495.6 (±158.6)	4	91% @ 30[b]
15		**1o**	8.1 (±2.4)	50.2 (±17.5)	4	97% @ 30[b] 87% @ 100[b]

[a]Carrageenan-induced thermal hyperalgesia.
[b]% control @ dose indicated (μmol/kg, po).

potent whole cell IC_{50} value (50.2±17.5 nM) with a minimal decrease of locomotor activity ($ED_{50} \gg 100$ μmol/kg, po).

In conclusion, we have discovered that a polar 7-substituent on these pyridopyrimidine derivatives enhance the locomotor selectivity, while maintaining a high degree of CNS penetration sufficient to allow compounds to be potent analgesics.

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