ORGANIC LETTERS

2005
Vol. 7, No. 21
4753−4756

Pyrazolo[1,5-a]pyridines as p38 Kinase Inhibitors

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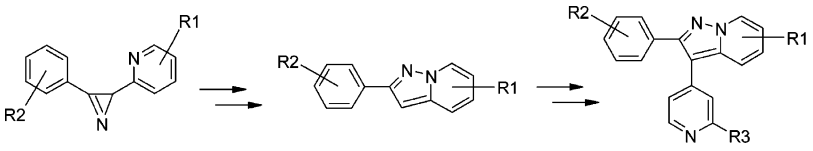
Received August 15, 2005

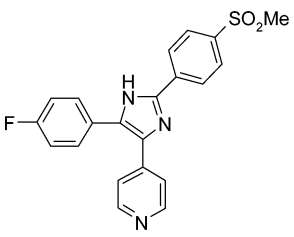
ABSTRACT



1

A convergent synthesis of substituted pyrazolo[1,5-a]pyridines has been achieved either via a regioselective [3 + 2] cycloaddition of *N*-aminopyridines with alkynes or by thermal cyclization of disubstituted azirines. Subsequent palladium-catalyzed introduction of pyridines or de novo synthesis of pyrimidines affords inhibitors of p38 kinase.

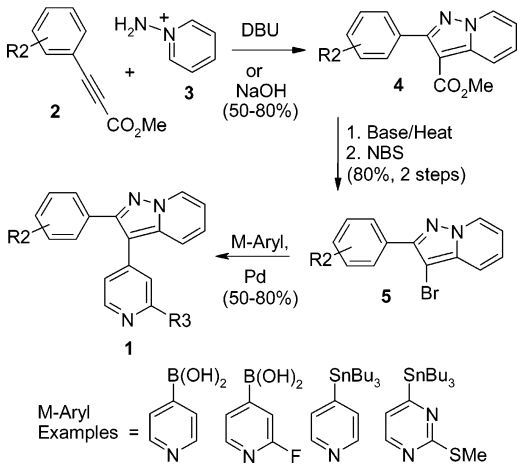
The serine/threonine kinase p38, a member of the MAP kinase superfamily, is activated by a variety of environmental stresses and inflammatory cytokines. A number of inhibitors of p38 kinase are known, and many have demonstrated significant anti-inflammatory activity in standard animal models of rheumatoid arthritis.[1] As a result, the search for potent, selective p38 inhibitors to be used for the clinical management of rheumatoid arthritis remains an active area of research.



SB-203580

Our search for novel p38 inhibitors has been aided by the availability of high-resolution X-ray crystal structure data showing that a prototype inhibitor, SB-203580, binds to p38 via a hydrogen bond between the pyridine nitrogen and a hinge-region amide, and through the interaction of the fluorophenyl ring deep within the hydrophobic back-pocket.[2] 1,2-Diaryl heterocycles, such as SB-203580, a 4,5-diaryl imidazole, have been a common motif and highly emulated in the p38 arena. Using this information, we became interested in the design of novel p38 inhibitors based on the pyrazolo[1,5-a]pyridine template. Our efforts led to the preparation and investigation of a series of heterocyclic kinase inhibitors of general structure **1** (see Scheme 4).

Scheme 1. Initial Cyclization Steps



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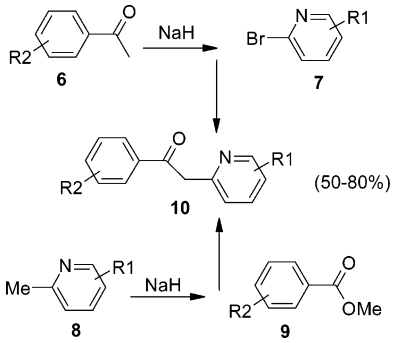
(1) (a) Adams, J. L.; Badger, A. M.; Kumar, S.; Lee, J. C. *Prog. Med. Chem.* **2001**, *38*, 1. (b) Dumas, J.; Sibley, R.; Riedl, B.; Monahan, M. K.; Lee, W.; Lowinger, T. B.; Redman, A. M.; Johnson, J. S.; Kingery-Wood, J.; Scott, W. J.; Smith, R. A.; Bobko, M.; Schoenleber, R.; Ranges, G. E.; Housley, T. J.; Bhargava, A.; Wilhelm, S. M.; Shrikhande, A. *Bioorg. Med. Chem. Lett.* **2000**, *10* (18), 2047. (c) Pargellis, C.; Tong, L.; Churchill, L.; Cirillo, P. F.; Gilmore, T.; Graham, A. G.; Grob, P. M.; Hickey, E. R.; Moss, N.; Pav, S.; Regan, J. *Nat. Struct. Biol.* **2002**, *9*, 268.

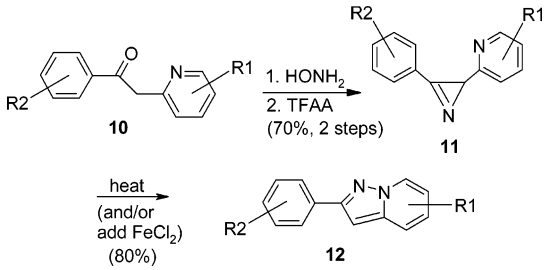
10.1021/ol0519745 CCC: $30.25
Published on Web 09/23/2005

Scheme 2. Synthetic Steps to Intermediate **10**



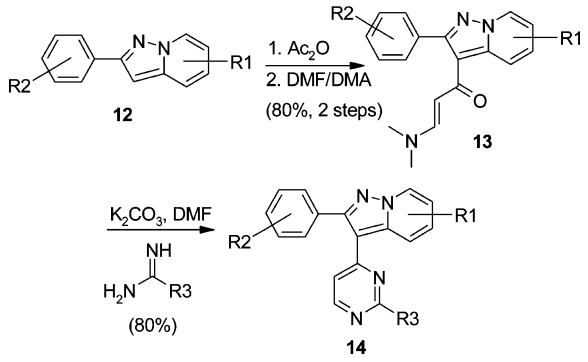
Synthetic approaches to the pyrazolo[1,5-a]pyridine nucleus are under-represented in the literature.[3] The most commonly employed method for synthesis involves a [3 + 2] cycloaddition of *N*-aminopyridines (**3**) with alkynoic esters (Scheme 1). The use of functionalized arylalkynoic esters (**2**) would allow ready access to a variety of 2-arylpyrazolo[1,5-a]pyridines. Chemistry was developed to investigate the SAR of the pyrazolo[1,5-a]pyridine core. Several iterations of chemistry were followed so the routes would allow for a large range of analogues to be made.

Scheme 3. Pyrazolopyridines via Azirine Intermediate



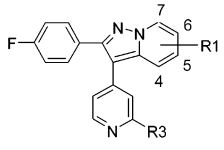
A variety of groups on the aryl ring (R2), including *ortho*, *meta*, or *para* alkyl, halo, or alkoxy substituents were prepared via this method. We have found that the cyclization can be mediated by a variety of bases (DBU, NaOH, K_2CO_3, etc.) and can be run in organic solvents (CH_2Cl_2, DMF, DMSO, etc.) or biphasic mixtures (CH_2Cl_2/H_2O). The pyrazolo[1,5-a]pyridines (**4**) were then decarboxylated efficiently in strong base followed by electrophilic halogenation with NBS. These compounds (**5**) were suitable partners for transition-metal-mediated cross-coupling reactions with heteroaryl stannanes or boronic acids/esters to provide compounds (such as **1**) in good yields (Scheme 1).

Scheme 4. Final Elaboration of Pyrazolo[1,5-a]pyridines

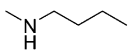
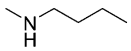


Compounds (**1**) were evaluated for their p38 enzyme inhibition. Those compounds with appropriate substitutions could be elaborated further via displacement of the 2′-fluoropyridine or the 2′-thiomethylpyrimidine. The 2′-fluoro group could be displaced directly by amine nucleophiles (neat in amine, sealed tube). The 2′-thiomethyl group required activation via mCPBA or oxone oxidation to the sulfone/sulfoxide followed by displacement with amines (reflux in amine). A summary of some of the compounds synthesized in this way is shown in Table 1 with their corresponding p38 enzyme inhibitory profile.

Table 1. Basic Enzyme SAR−Pyridines[a]



1

entry	R1	R3	p38 IC_{50}
1a	H	NMe_2	1.0
1b	H		0.16
1c	H	NHPh	0.16
1d	4-F		0.16
1e	7-OMe	H	0.10
1f	6-CF_3	NH_2	0.10
1g	6-$CONH_2$		0.08
1h	7-OMe		0.06
1i	6-CN		0.05

[a] The p38 IC_{50} values (μM) are mean values with minimum two tests and standard deviation of the mean typically less than 0.03.

(2) (a) Wilson, K. P.; Fitzgibbon, M. J.; Caron, P. R.; Griffith, J. P.; Chen, W.; McCaffrey, P. G.; Chambers, S. P.; Su, M. S.-S. *J. Biol. Chem.* **1996**, *271*, 27696. (b) Wang, Z.; Harkins, P. C.; Ulevitch, R. J.; Han, J.; Cobb, M. H.; Goldsmith, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94* (6), 2327. (c) Tong, L.; Pav, S.; White, D. M.; Rogers, S.; Crane, K. M.; Cywin, C. L.; Brown, M. L.; Pargellis, C. A. *Nat. Struct. Biol.* **1997**, *4*, 311.

(3) (a) Awano, K.; Suzue, S.; Segawa, M. *Chem. Pharm. Bull.* **1986**, *34*, 2828. (b) Miki, Y.; Yagi, S.; Hachiken, H.; Ikeda, M. *Heterocycles* **1994**, *38*, 1881. (c) Koeckritz, P.; Riemer, B.; Michler, A.; Hassoun, A.; Liebscher, J. *J. Heterocycl. Chem.* **1994**, *31*, 1157. (d) Bondo, H. J.; Weis, J.; Suzdak, P. D.; Eskesen, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 695.

All of the compounds shown in Table 1 contain a *p*-fluoro substituent on the 2-phenyl ring (R2) since larger groups at the *para* position resulted in poor p38 inhibition. In addition, *p*-fluoro was the preferred substituent for metabolic stability. Modification on the pyrazolo[1,5-a]pyridine core (R1) was well tolerated, and compounds were prepared with substituents at C(4)−C(7). Amine substituents on the pyridine (R1) were key to the potency of the molecules and improved physiochemical properties. Tertiary amine substitutions (**1a**) resulted in lower p38 enzyme inhibition. Within the pyridine series, the most promising combination of substitutions on the pyrazolo[1,5-a]pyridine core was an alkylamine (R3), *para*-fluorophenyl (R2), and an electron-withdrawing substituent at C(6) or an electron-donating group at the 7-position (R1) (Table 1, **1e**−**i**).

This general strategy (depicted in Scheme 1) was limiting in a number of ways. First, aminated pyridines have scarce substitutional availability from commercial sources. Several substituted pyridines were aminated (HOSA or MSH)[4] with variable results. Additionally, the requirement to convert the ester to a cross-coupling partner, usually a halogen, was efficient, but cost two extra steps. The availability of metalated heteroaryl species for the cross-coupling reaction was also a limitation, and the preparation of these cross-coupling partners often required a number of undesired additional steps.

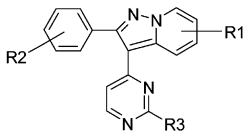
Having confirmed the overall value of the template in the context of potent p38 inhibition, we developed a complimentary route that would allow for ease of synthesis and improved substituent flexibility.

The improved route constructs the pyrazolo[1,5-a]pyridine core template with starting materials that are much more flexible than the initial route. Substituted acetophenones (**6**) are deprotonated (NaH) then alkylated via an appropriately substituted halo pyridine (**7**) (Scheme 2). Alternatively, substituted methylpyridines (**8**) can be deprotonated and combined with methylbenzoates (**9**) to yield the identical product (**10**), which is a key intermediate. R1 and R2 can be easily diversified with these two complimentary routes.

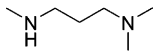
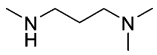
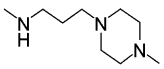
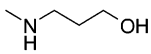
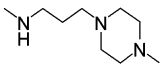
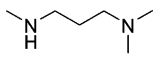
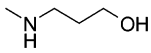
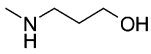
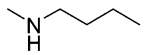
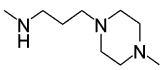
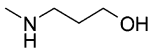
Ketones (**10**) are efficiently converted to pyrazolo[1,5-a]-pyridines via azirine intermediates (**11**, Scheme 3). The ketone is first converted to the oxime with hydroxylamine followed by treatment with trifluoroacetic anhydride, giving spontaneous rearrangement to the azirine. The azirines (**11**) are converted to pyrazolo[1,5-a]pyridines via heating (170 °C, neat or 75 °C with catalytic $FeCl_2$ in DME).[5] Accessing pyrazolo[1,5-a]pyridines (**12**) via azirine intermediates still requires three synthetic steps; however, these starting materials are derived from commercial sources with no limitations for substitutions at R1 and R2.

Our initial routes to pyrazolo[1,5-a]pyridines (Scheme 1) employed the use of a 3-halogenated species to cross-couple with a metalated heteroaryl partner, but as noted previously, that limited our chemistry to cross-coupling partners that were often several steps and required syntheses that had their own difficulties. We turned our attention to a de novo pyrimidine synthesis that would take advantage of the nucleophilic nature of the 3-position of the pyrazolo[1,5-a]-

Table 2. Basic Enzyme SAR−Pyrimidines[a]



14

entry	R1	R2	R3	p38 IC_{50}
14a	6-CF_3	*p*-CF_3		1.25
14b	6-CF_3	*di-Cl*		1.25
14c	H	*p*-F	H	0.63
14d	6-CF_3	*p*-F		0.63
14e	7-Me	*p*-F	H	0.50
14f	6-CF_3	*p*-CF_3		0.40
14g	6-CF_3	*m*-CF_3		0.20
14h	6-CF_3	*p*-F	NH_2	0.20
14i	7-SMe	*p*-F	H	0.16
14j	6-CF_3	*p*-F		0.13
14k	H	*p*-F	NH_2	0.10
14l	6-CF_3	*m*-Cl		0.10
14m	6-$CONMe_2$	*m*-CF_3		0.06
14n	6-$CONMe_2$	*p*-F		0.06
14o	6-CF_3	*p*-F		0.06
14p	6-Cl	*p*-F		0.04
14q	7-OCH_2CH_2F	*p*-F		0.04
14r	6-$CONH_2$	*p*-F		0.04
14s	6-CF_3	*p*-F		0.04
14t	6-CN	*p*-F		0.03
14u	6-$CONH_2$	*p*-F		0.02
14v	6-$CONH_2$	*p*-F		0.01

[a] The p38 IC_{50} values (μM) are mean values with minimum two tests and standard deviation of the mean typically less than 0.03.

(4) HOSA = Hydroxylamine *O*-Sulfonic Acid; MSH = Mesityl *O*-Hydroxylamine.

(5) Fitzgerald, R. N.; Jung, D. K.; Eaddy, J. F. *PCT Int. Appl.* **2001**, WO0183479A2.

pyridines (similar to indole).[6] This chemistry would allow for future incorporation of diversity on the pyrimidine ring—important for the two-point hydrogen bonding (of the 2-aminopyrimidine) within the ATP binding pocket. Toward this goal, pyrazolo[1,5-a]pyridines (**12**) were treated with acetic anhydride and a drop of acid to yield acylated species which were converted to dimethyl enamines (**13**) by heating in neat DMF/dimethylacetal (Scheme 4). These enamine species are excellent partners for cyclization with substituted guanidines in the principal pyrimidine synthesis to give final compounds (**14**) in good yields.

Many guanidines are commercially available or can easily be prepared via condensation of amines with cyanamide in the presence of nitric acid.[7] By the methods described in Schemes 1−4, compounds were provided, where R1, R2, and R3 were varied widely, and the resulting compounds were tested for their p38 kinase inhibition activity. A brief SAR is shown in Table 2.

In general, the pyrimidine series was more potent for p38 enzyme inhibition than the pyridine series. *p*-Fluoro was again the preferred substituent on the C(2) phenyl ring (R2), though *m*-Cl and *m*-CF_3 were also tolerated (Table 2, **14m**, **14n**). An amine substituent on the pyrimidine (R3) was also preferred (Table 2, compare **14c** and **14k**). As observed with the pyridine series, electron-withdrawing groups at C(6) and electron-donating groups at C(7) (R1) are strongly preferred for p38 enzyme inhibition (Table 2, **14q**-**14v**).

In summary, a convergent synthesis of pyridine-substituted pyrazolo[1,5-a]pyridines was achieved via [3 + 2] cycloaddition reactions of *N*-aminopyridines with alkynes followed by an organometallic cross-coupling reaction to form compounds that are inhibitors of p38 kinase. Alternatively, pyrimidine-substituted pyrazolo[1,5-a]pyridines were prepared via thermal cyclization of disubstituted azirines followed by de novo pyrimidine synthesis to afford inhibitors of p38 kinase. Some brief SAR of these molecules has been described.

Supporting Information Available: Complete experimental details for selected compounds from Table 1 (**1a**, **1b**, **1c**, **1i**) and Table 2 (**14c**, **14d**, **14h**, **14j**, **14k**, **14o**, **14s**, **14t**, **14u**, **14v**) as well as all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0519745

(6) Ryang, H.-S.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1972**, 77.

(7) (a) Palat, K.; Celadnik, M.; Danek, J.; Varkonda, S. *Collect. Czech. Chem. Commun.* **1992**, *57*, 1127. (b) Kreutzberger, A.; Tantawy, A. *Arch. Pharm.* **1979**, *312*, 426.