Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1123–1126

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Phenoxypyrimidine Inhibitors of p38α Kinase: Synthesis and Statistical Evaluation of the p38 Inhibitory Potencies of a Series of 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl) Imidazoles

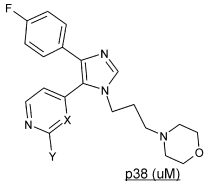
Jeffrey C. Boehm,[a,*] Michael J. Bower,[b] Timothy F. Gallagher,[a] Shouki Kassis,[c] Stephen R. Johnson[d] and Jerry L. Adams[a]

[a]*Department of Medicinal Chemistry, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[b]*Department of Physical and Structural Chemistry, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[c]*Department of Bone and Cartilage Biology, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[d]*Department of Cheminformatics, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*

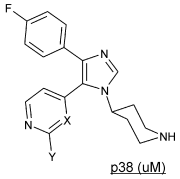
Received 2 January 2001; accepted 20 February 2001

Abstract—As a continuation of our work with 1,4,5 substituted imidazole inhibitors of p38α, we report a series of 1-(4-piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyrimidinyl) imidazoles related to **7**. The compounds have IC_{50}'s for inhibition of p38α ranging from 6.0 to 650 nM. Statistical analysis of the p38α inhibitor potencies shows a correlation of IC_{50}'s with the electron donating strength of low molecular weight substituents.

Previously, we described a series of 4-aryl-5-(pyridin-4-yl) imidazole p38 inhibitors containing substitution at the imidazole N-1, and exemplified by **1**.[1] Later, we found that replacement of the pyridyl group with a variety of substituted pyrimidinyl rings afforded more potent inhibitors (**2**–**4**).[2] Subsequent work seeking to enhance the in vitro and in vivo potency of this series led to the development of analogues such as **5**, and **6**, containing a piperidinyl at the imidazole N-1.[3]

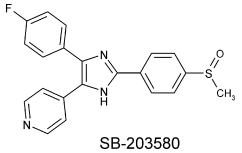


	p38 (uM)
1, X = CH, Y = H	1.3
2, X = N, Y = H	0.22
3, X = N, Y = NH_2	0.48
4, X = N, Y = OCH_3	0.30



	p38 (uM)
5, Y = H, X = CH,	0.060
6, Y = NH_2, X = N,	0.020
7, Y = OPh, X = N,	0.019

Another variation of this general structure is the phenoxypyrimidine **7**, a potent inhibitor of p38α. For comparison, the prototypical p38α inhibitor SB-203580 inhibits the enzyme with an IC_{50} of 48 nM while the corresponding value for **7** was 19 nM. In the present report we describe the effects of substitution on the phenoxy substituent of **7** on p38α inhibition.

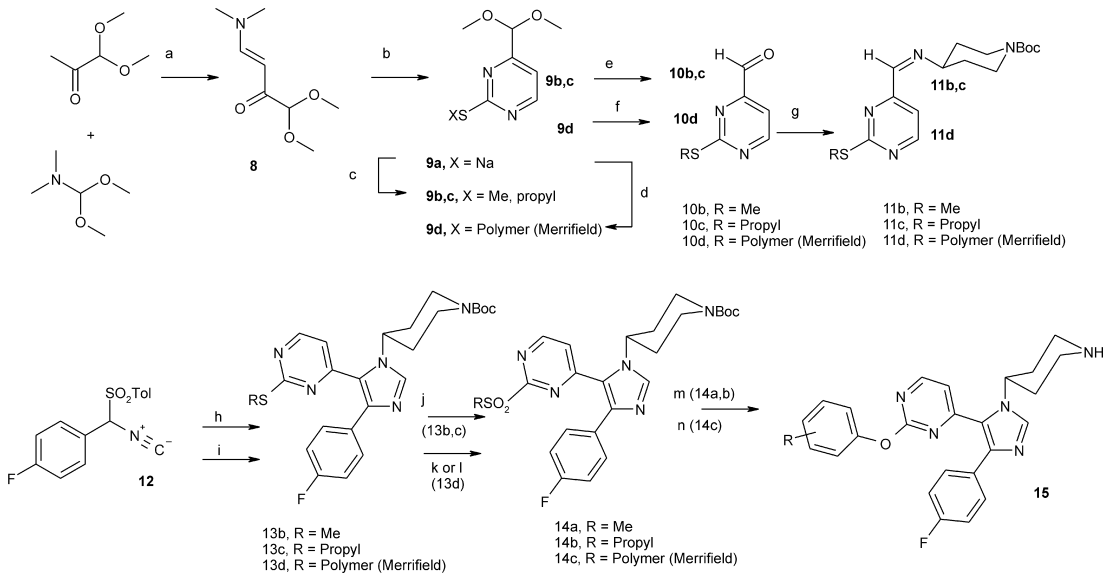


SB-203580

Solution-phase synthesis of 1-(piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-aryloxypyrimidin-4-yl) imidazoles proceeded through either the methyl or propyl sulfides **9b**,**c**[4] by procedures similar to those described previously (Scheme 1).[5] As depicted, slight modification of the solution-phase methodology permitted solid-phase synthesis.[6] About half of the compounds in Table 1 were prepared by the resin-based approach.

*Corresponding author. Tel.: +1-610-270-6595; fax: +1-610-270-4490; e-mail: jeffrey_c_boehm@sbphrd.com

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00163-9



Scheme 1. (a) Neat, 100 °C; (b) thiourea, NaOMe; (c) alkyl halide (methyl iodide, propyl bromide); (d) Merrifield resin; (e) 3 N HCl 23 °C then Na_2CO_3; (f) TFA, Δ; (g) 4-amino-1-Boc-piperidine, CH_2Cl_2; (h) **11b** or **11c**, K_2CO_3, DMF; (i) **11d**, TBD, CH_2Cl_2; (j) oxone, THF, H_2O; (k) tetrabutylammonium oxone, CH_2Cl_2; (l) MCPBA; (m) ArOH, NaH, THF then TFA then OH^-; (n) ArOH, TMS_2N^- Na^+, THF then TFA.

It has been reported that p38α inhibition is improved in a series of 2-(4-fluorophenyl)-3-(pyridin-4-yl) pyrrolopyridines when electron rich substituents were placed on the core heterocycle pyridine.[7] This is likely the result of increased electron density on the 3-pyridyl nitrogen. Co-crystallographic studies of the imidazole p38 inhibitors have previously shown that this pyridyl nitrogen forms a hydrogen bond to the ATP binding region of p38 and is a key interaction required for potent inhibition by the pyridyl imidazole class of p38 inhibitors.[8] With this in mind, it seemed that the potency of the analogues in Table 1 might correlate with the electron density of phenoxy substituents.

As a simple test of this idea, the Hammet σ_{para} for the 4-phenoxy substituted analogues were plotted against log IC_{50}.[9] Consistent with the hypothesis, a correlation was obtained (R = 0.64). If a single high molecular weight analogue (**15ao**) is omitted, the correlation improves (R = 0.78) (Fig. 1).

This improvement is understandable on the basis of a comparison of the MacroModel[10] structural searches for **7** and **15ao**, in which the low energy binding conformations prevalent for **7** differ from those determined for **15ao** (Fig. 2). The latter inhibitor appears to favor conformations in which the phenoxy π-stacks over the 4-fluorophenyl rather than over the piperidine. It is likely that the preferred binding conformation is the low energy conformation for **7** rather than that of **15ao**. If this conformational effect is generally true, then it may be expected that the IC_{50}'s of analogues containing larger, aromatic substituents will not correlate with electronic effects. This prediction is supported by the observation that the feature which correlates most with the log(1/IC_{50}) data for all the compounds in Table 1 is the molecular weight (R = −0.75).

Further analysis was restricted to the low molecular weight compounds in Table 1 (M_r < 460). A pool of 62 structural features was analyzed using a stochastic optimization method. From these, three structural features were selected which afforded a multiple linear regression model which is statistically sound, with R = 0.92 and F = 36.6 with the removal of one outlier.[11] The parameters are the sum of the squared partial atomic charges (SSAC), the autocorrelated topological distance three lone-pair electronegativity, and the solvent-accessible surface area of atoms with a negative partial charge.

The sum of the squared partial atomic charges (SSAC) of the structure is calculated over all the atoms in the compound, $\sum(q_i^2)$. Of the three structural features, SSAC has the least effect on the IC_{50}'s. The autocorrelated[12,13] electronegativity of lone pair electrons feature is calculated as:

$$A_{\mathrm{ENLP}}(3) = \sum_{i,j} P_i P_j$$

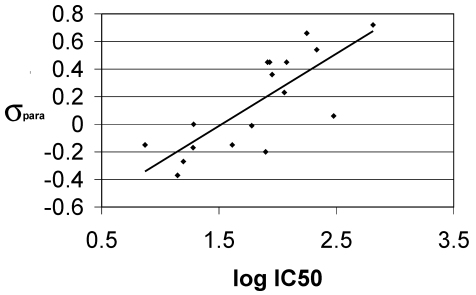
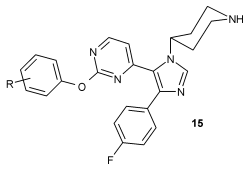


Figure 1. p38 inhibition correlates with the electron donating strength of the low M_r 4-phenoxy substituents.

Table 1. IC_{50} for p38 inhibition by phenoxypyrimidines (**15**)



15

Compound	R	IC_{50} (nM)	M_r	σ_{para}[9]
15a	2,4-Dimethyl	6.0	443	
15b	2-Hydroxy	6.6	431	
15c	4-Ethyl	7.4	443	−0.15
15d	2,5-Dimethyl	10.7	443	
15e	2-Fluoro	13.0	433	
15f	4-Hydroxy	14.0	431	−0.37
15g	2-Methyl	15.0	429	
15h	2,3-Dimethyl	15.2	443	
15i	4-Methoxy	15.7	445	−0.27
15j	3-Methoxy	18.7	445	
15k	4-Methyl	19.0	429	−0.17
7	H	19.2	415	0
15l	3-Hydroxy	20.0	431	
15m	3,4-Dimethyl	21.6	443	
15n	3,4-Methylenedioxy	23.0	459	
15o	2-Methoxy	25.0	445	
15p	2,6-Dimethyl	34.3	443	
15q	4-Isopropyl	41.0	457	−0.15
15r	3,5-Dimethyl	41.0	443	
15s	3-Carboxamidyl	56.0	458	
15t	4-Phenyl	60.0	491	−0.01
15u	3-*N*-Methylcarboxamidyl	75.0	472	
15v	4-*tert*-Butyl	79.0	471	−0.20
15w	4-Carboxy	82.0	459	0.45
15x	4-Carboxyethyl	85.4	487	0.45
15y	4-Carboxamidyl	89.7	458	0.36
15z	3-Fluoro	95.0	433	
15aa	4-Chloro	114	449	0.23
15ab	4-Carboxymethyl	119	473	0.45
15ac	4-Phenoxy	130	507	
15ad	3-Trifluormethyl	132	483	
15ae	2-Acetamido	134	472	
15af	2-Propionamido	151	486	
15ag	3,4-Dichloro	165	484	
15ah	4-Carboxypropyl	174	501	
15ai	4-Cyano	177	440	0.66
15aj	3-*N*-Isopropylcarboxamidyl	189	500	
15ak	3,4-Difluoro	209	451	
15al	4-Trifluoromethyl	215	483	0.54
15am	4-Fluoro	300	433	0.06
15an	3-*N*,*N*-Dimethylcarboxamidyl	312	486	
15ao	4-Benzyloxy	317	521	−0.23
15ap	3-(Piperazin-1-yl)carboxamidyl	406	527	
15aq	3-(Piperazin-1-yl)carboxamidomethyl	453	541	
15ar	3-(Piperidin-1-yl)carboxamidyl	599	526	
15as	4-Methylsulfonyl	650	493	0.72

where P_i is the atom-based lone-pair electronegativity of atom *i*. Atoms *i* and *j* are atom pairs separated by three bonds. This feature encodes how the lone-pair electronegativity is distributed across the molecule. For this data, substitution at the 2 position of the phenoxy has a greater effect on potency than substitution at the 3 or 4 positions. The presence of the partial negative surface area is likely encoding the presence of electron-withdrawing groups that, for this data, have larger exposed surfaces of heteroatoms. The partial negative surface area has the highest correlation, with the $\log(1/IC_{50})$ p38 inhibition data ($R = -0.76$). The solvent-exposed electron withdrawing groups are on the least potent inhibitors.

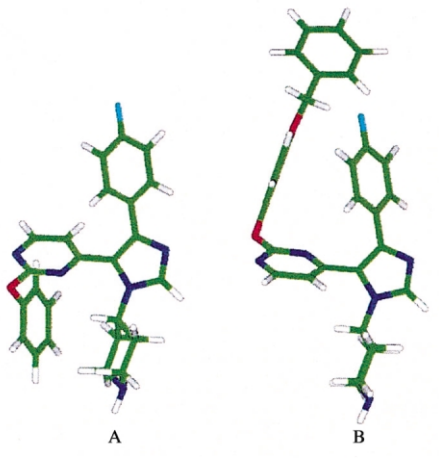


Figure 2. Comparison of low energy (MacroModel) structures for **7** (A) and **15ao** (B).

These features represent a correlative relationship that is not necessarily causal. However, the statistical analysis seems to support the generalization that small electron rich substituents *ortho* to the phenoxy oxygen have the greatest effect on boosting potency. Conversely, large electron deficient substituents *para* to the phenoxy oxygen have a deleterious effect.[14] The results can be partially rationalized as the consequence of changes in the H bond acceptor properties of the pyrimidine N-4.

The best p38α inhibitors in Table 1 have potencies less than 10 nM. This level of activity is an improvement over the p38 inhibitors reported by our group up to this time.[15]

References and Notes

1. Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, D. E.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem.* **1996**, *39*, 3929.
2. Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111.
3. (a) Jackson, R. J.; Bolognese, B.; Hillegass, L.; Kassis, S.; Adams, J.; Griswold, D. E.; Winkler, J. D. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 687. (b) Adams, J. L.; Gallagher, T. F.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Gum, R. J.; Webb, E. F.; Sorenson, M. E.; Smietana, J. M.; Garigapati, R. S.; Hall, R. F.; Aryton, A.; Badger, A.; Griswold, D. E.; Young, P. R.; Lee, J. C. *Book of Abstracts;* XVth International Medicinal Chemistry Symposium; Cambridge, UK, September 1998.
4. Bredereck, H.; Sell, R.; Effenberger, F. *Chem. Ber.* **1964**, *97*, 3407.
5. Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516.
6. Gallagher, T. F.; Boehm, J. C.; Osifo, I. K.; Kassis, J.; Lee, J. C.; Aryton, A.; Griswold, D. E.; Adams, J. L.; Wang, Z.;

Goldsmith, E. J. *Book of Abstracts*, 215th ACS National Meeting, Dallas, 29 March–2 April 1998.
7. Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. *J. Med. Chem.* **1998**, *41*, 4196.
8. (a) 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*, 31116. (b) Wilson, K. P.; McCaffrey, P. G.; Hsiao, K.; Pazhinisamy, S.; Galullo, V.; Bemis, G. W.; Fitzgibbon, M. J.; Caron, P. R.; Murcko, M. A.; Su, M. S. S. *Chem. Biol.* **1997**, *4*, 423. (c) Wang, Z.; Canagarajah, B. J.; Boehm, J. C.; Kassis, S.; Cobb, M. H.; Young, P. R.; Abdel-Meguid, S.; Adams, J. L.; Goldsmith, E. J. *Structure (London)* **1998**, *6*, 117.
9. Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR. Hydrophobic, Electronic, and Steric Constants*; American Chemical Society: Washington, DC, 1995.
10. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
11. The lone outlier in this model is the 2,6-dimethyl substituted analogue (**15p**). This compound is expected to have high potency based on the inhibition of other 2-methyl substituted analogues (**15a**, **15d**, **15g**, and **15h**); the model predicts a value in line with this expectation. In actuality, **15p** is substantially less potent. We hypothesize that the 2,6-substitution partially occludes the 4-pyrimidinyl N thus making H-bond formation less favorable. As it is the only 2,6-substituted example in this data set, this hypothesis is only weakly supported.
12. Moreauo, G.; Broto, P. *Nouv. J. Chim.* **1980**, *4*, 359.
13. Wagener, M.; Sadowski, J.; Gasteiger, J. *J. Am. Chem. Soc.* **1995**, *117*, 7769.
14. Of interest is a comparison of **15e**, 2-fluoro (13 nM), **15z**, 3-fluoro (95 nM), and **15am**, 4-fluoro (300 nM). This unexpected steric effect may illustrate steric differences between electron donating conjugative effects and electron withdrawing inductive effects in aryl fluorides.
15. Gallagher, T. F.; Seibel, G. L.; Kassis, S.; Laydon, J. T.; Blumenthal, M. J.; Lee, J. C.; Lee, D.; Boehm, J. C.; Fier-Thompson, S. M.; Abt, J. W.; Sorenson, M. E.; Smietana, J. M.; Hall, R. F.; Garigapati, G. S.; Bender, P. E.; Erhard, K. F.; Krog, A. J.; Hofmann, G. A.; Sheldrake, P. L.; McDonnell, P. C.; Kumar, S.; Young, P. R.; Adams, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 49.