Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 9–12

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

p38 Kinase Inhibitors for the Treatment of Arthritis and Osteoporosis: Thienyl, Furyl, and Pyrrolyl Ureas

Anikó M. Redman,[a] Jeffrey S. Johnson,[a] Robert Dally,[a] Steve Swartz,[a] Hanno Wild,[a] Holger Paulsen,[a] Yolanda Caringal,[a] David Gunn,[a] Joel Renick,[a] Martin Osterhout,[a] Jill Kingery-Wood,[a] Roger A. Smith,[a] Wendy Lee,[a] Jacques Dumas,[a] Scott M. Wilhelm,[b] Timothy J. Housley,[b] Ajay Bhargava,[b] Gerald E. Ranges,[b] Alka Shrikhande,[b] Deborah Young,[b] Michael Bombara[b] and William J. Scott[a,*]

[a]*Department of Chemistry Research, Bayer Research Center, Pharmaceutical Division, 400 Morgan Lane, West Haven, CT 06516, USA*

[b]*Department of Cancer and Osteoporosis Research, Bayer Research Center, Pharmaceutical Division, 400 Morgan Lane, West Haven, CT 06516, USA*

Received 15 August 2000; accepted 2 October 2000

Abstract—Inhibitors of the MAP kinase p38 are potentially useful for the treatment for osteoporosis, arthritis, and other inflammatory diseases. A series of thienyl, furyl, and pyrrolyl ureas has been identified as potent p38 inhibitors, displaying in vitro activity in the nanomolar range.

Members of the MAP kinase family are implicated in the activation of a wide variety of transcription factors and proteins involved in the control of cytokine production. A pair of novel protein kinase homologues (p38) involved in the regulation of cytokine synthesis have been described.[1] Small molecule inhibitors of p38, such as SB 203580 **1**[2,3] (Fig. 1), can potentially lead to the treatment of osteoporosis and inflammatory disorders.

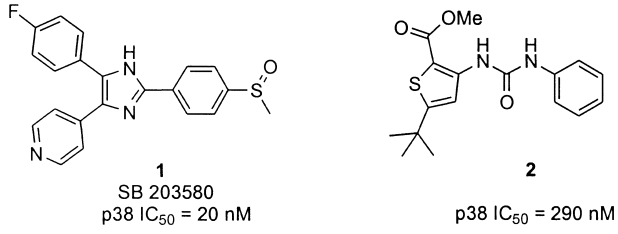
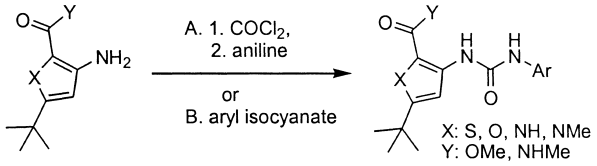


Figure 1. p38 Kinase inhibitors.

Following high throughput screening of the Bayer compound library, the commercially available thienyl urea **2** (Maybridge GK 00687) was identified as a reversible p38 inhibitor (Fig. 1). It was rapidly shown that the corresponding furans and pyrroles were also active. This paper describes our effort to optimize substitutions on both rings of the lead urea.[4]

Chemistry

Ureas were synthesized by the reaction of the heterocyclic amines with phosgene (or a phosgene equivalent), followed by treatment with anilines (Scheme 1). Alternatively, heterocyclic amines were reacted with isocyanates.



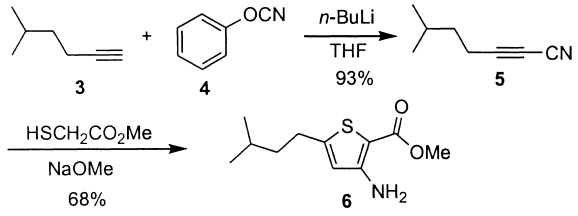
Scheme 1. Synthesis of thienyl, furyl, and pyrrole ureas.

In the case of pyrroles, the ring nitrogen did not need protection during this reaction sequence. Methyl 3-amino-

*Corresponding author. Tel.: +1-203-812-2935; fax: +1-203-812-3655; e-mail: william.scott.b@bayer.com, aniko.redman.b@bayer.com

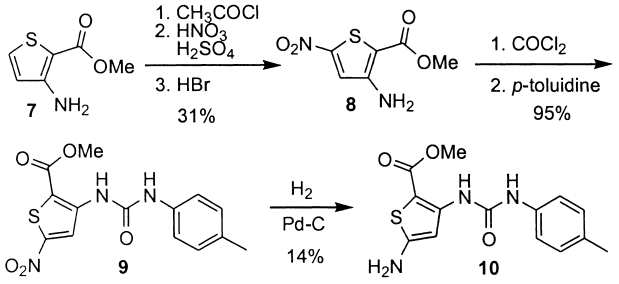
0960-894X/01/$ - see front matter
PII: S0960-894X(00)00574-6

5-*tert*-butyl-2-thiophene carboxylate was obtained by the condensation of methyl thioglycolate with (*Z*)-3-chloro-4,4-dimethyl-2-pentenenitrile[5] according to a published procedure.[6] Other substituted 4-alkylthiophenes could be prepared by the synthesis of cyanoalkynes, such as nitrile **5** and their subsequent treatment with methyl thioglycolate (Scheme 2).[7]



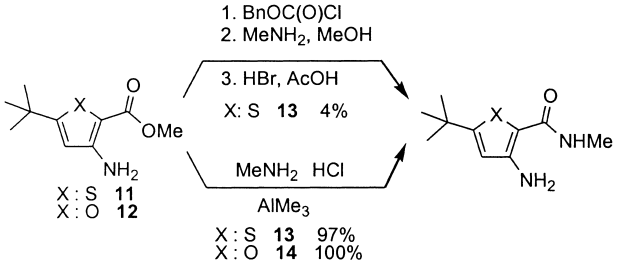
Scheme 2. Synthesis of 4-alkylthiophenes from cyanoalkynes.

4-Nitro- and 4-aminothienyl ureas **9** and **10** were obtained from methyl 3-amino-2-thiophenecarboxylate (**7**) via a protection, nitration, and deprotection protocol. The nitro group was reduced after urea formation (Scheme 3).



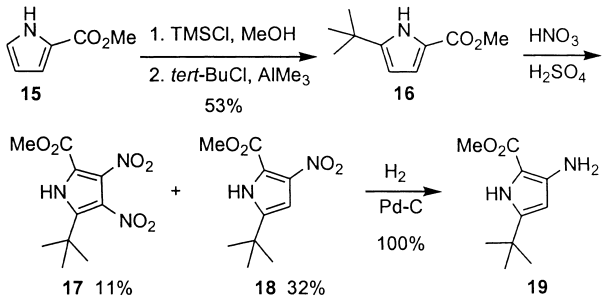
Scheme 3. Synthesis of 4-nitro and 4-aminothienyl ureas.

Variation of the ester moiety was studied by Ti(IV) mediated transesterification,[8] or by BOC-protection of the amine, saponification, ester formation and amine deprotection. Amide analogues, such as thiophene **13**, were obtained from the corresponding esters using a Cbz-protection of the amine, amidation and deprotection protocol, or more simply by Weinreb amidation[9] (Scheme 4).



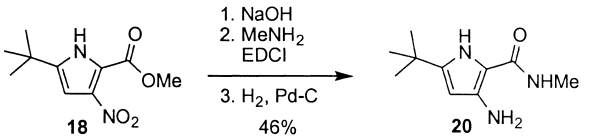
Scheme 4. Amidation of esters.

Furyl amines, such as **12**, were synthesized according to a previously published procedure.[10,11] 3-Aminopyrroles were synthesized by Friedel–Crafts alkylation of methyl pyrrole-3-carboxylate (**15**),[12] followed by electrophilic nitration and reduction of the nitro group (Scheme 5).[13]



Scheme 5. Synthesis of 3-aminopyrroles.

2-Carbamoyl pyrroles were prepared from ester **18** by saponification and EDCI coupling, followed by reduction of the nitro group (Scheme 6). *N*-Alkyl-3-aminopyrrole was generated by treatment of nitropyrrole **18** with an alkylating agent followed by hydrogenation.



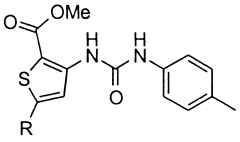
Scheme 6. Synthesis of pyrrole amides.

Results and Discussion

Simple changes in the 5-position of the thiophene ring had a profound effect on potency (Table 1).[14]

Among various alkyl substitutents, *tert*-butyl was optimal (entry **22**). Sterically more demanding groups were not well tolerated (entries **24** and **25**), while smaller alkyl groups also resulted in loss of activity (entry **21**). Surprisingly, urea **10** with an amino group in the 4-position was again a potent inhibitor. Nitrophenyl urea **9** displayed no activity.

Table 1. Thiophene alkyl substituents

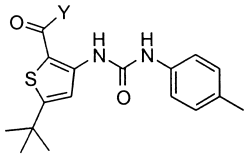


Entry	R	% Inhibition (5 μM)	p38 α2 IC_{50} (nM)
21	*i*Pr	37	
22	$C(CH_3)_3$	94	413
23	2-Methylpropyl	0	
24	3-Methylbutyl	8	
25	1-Hydroxy-1-methylethyl	34	
26	Phenyl	0	
27	2-Phenylethyl	17	
9	NO_2	0	
10	NH_2	90	441

The effect of various ester substitutions is summarized in Table 2. Within the simple alkyl ester series, ana-

logues with bulkier alkyl groups were, in general, weaker inhibitors (entries **28**–**30**).

Table 2. Thiophene ester substituents

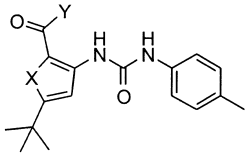


Entry	Y	p38 α2 IC_{50} (nM)
22	OMe	413
28	OEt	3020
29	OPr	482
30	O*i*Pr	741
31	$O(CH_2)_2OH$	57
32	$O(CH_2)_3OH$	56
33	$O(CH_2)_2OCH_3$	464
34	$OCH_2CO_2CH_3$	5310

Esters with free hydroxyl groups, such as ureas **31** and **32**, showed a significant increase in potency. Other polar substituents (entries **33** and **34**) led to a significant decrease in activity.

Replacement of the thiophene ring by furan or pyrrole heterocycles resulted in increased potency, except in the case of *N*-methylcarbamoyl pyrroles (Table 3).

Table 3. Ester versus amide on various heterocycles

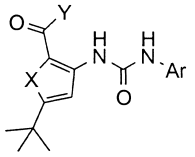


Entry	X	Y	*E. coli* p38 α2 IC_{50} (nM)
22	S	OMe	248
35	S	NHMe	34
36	O	OMe	73
37	O	NHMe	32
38	NH	OMe	33
39	NH	NHMe	67

During further optimization it was found that replacing esters with amides greatly improved the activity of thiophene ureas (Table 3, entry **35** vs **22**). This effect was less significant in the case of furan and pyrrole ureas (entry **37** vs **36** and entry **39** vs **38**). This discrepancy may be due to the thiophene being the most lipophilic of the three heterocycles. The effect of phenyl substitution was first investigated in the thiophene series, followed by a more focused optimization of furan and pyrrole ureas (Table 4).

In the ester series small alkyl groups and halogens were tolerated in the *para* position (Table 3, entry **22**, Table 4, entry **48**). Increasing the size of the *para*-alkyl substituents led to decreased potency (entries **41**, **43**, and **45**). Placing halogens in both the *ortho* and *meta* positions led to the best inhibitors (entries **56**, **58**, **65**, and **71**). Hydrogen bonding amino and hydroxyl substituents, as in ureas **49** and **50**, caused some loss of activity. Acylation of the amine moiety or alkylation of the phenol led to inactive analogues (entries **51** and **52**, respectively), as did the introduction of electron withdrawing groups other than halogen (entries **53**–**55**). The overall trend pointed to halogens and small alkyl groups on the phenyl ring to provide optimal lipophilicity. Among the heterocycles, pyrroles consistently showed higher potency.

Table 4. Substitution of the phenyl moiety



Entry	X	Y	Ar	% Inhibition (0.5 μM)	*E. coli* p38 α2 IC_{50} (nM)
40	S	OMe	Phenyl	68	290
41	S	OMe	4-Ethylphenyl	40	660
42	S	NHMe	4-Ethylphenyl	70	119
43	S	OMe	4-Isopropyl	10	
44	S	NMHe	4-Isopropyl	63	270
45	S	OMe	4-Phenylphenyl	6	
46	S	OMe	4-Fluorophenyl	35	830
47	S	NHMe	4-Fluorophenyl	80	88
48	S	OMe	4-Chlorophenyl	76	220
49	S	OMe	4-Aminophenyl	40	750
50	S	OMe	4-Hydroxyphenyl	44	610
51	S	OMe	4-Acetamidophenyl	23	
52	S	OMe	4-Methoxyphenyl	8	
53	S	OMe	4-Nitrophenyl	16	
54	S	OMe	4-Carboxyphenyl	4	
55	S	OMe	4-Acetylphenyl	21	
56	S	OMe	2,3-Dichlorophenyl	79	180
57	O	OMe	4-Fluorophenyl	67	210
58	O	OMe	2,3-Dichlorophenyl	97	32
59	O	OMe	3,4- Dichlorophenyl		1200
60	NH	OMe	Phenyl		44
61	NH	OMe	4-Fluorophenyl	89	42
62	NH	OMe	2-Chlorophenyl	85	60
63	NH	OMe	3-Chlorophenyl	95	27
64	NH	OMe	4-Chlorophenyl	92	43
65	NH	OMe	2,3-Dichlorophenyl	99	6
66	NH	NHMe	2,3-Dichlorophenyl	95	44
67	NH	OMe	1-Naphthyl		12
68	NH	NHMe	1-Naphthyl	96	28
69	NMe	OMe	Phenyl	32	947
70	NMe	OMe	4- Methylphenyl		400
71	NMe	OMe	4-Fluorophenyl	42	663
72	NMe	OMe	2,3-Dichlorophenyl	50	387
73	NMe	OMe	1-Naphthyl	67	253

A few ureas with significant activity against p38 kinase were selected to measure inhibition of IL-6 production in SW1353 cells treated with both cytokines IL-1 and TNF-α.[15] SB 203580 (**1**) was used as a reference compound. The observed cellular activity of our analogues does not directly correlate with the p38 IC_{50} values. However, data presented in Table 5 suggest that functional activity is driven by the combination of primary target potency and appropriate lipophilicity (clogP < 4.5).

Table 5. Inhibition of IL-6 production in SW1353 cells

Entry	*E. coli* p38 α2 IC_{50} (nM)	Inhibition of IL-6 production IC_{50} (nM)	ClogP (daylight)
1	20	50	3.6
22	248	905	5.6
35	34	1350	4.9
36	73	335	5.0
38	33	1140	4.6
39	67	15	3.4
61	42	464	4.3
65	6	79	4.9
66	44	16	3.8
67	12	309	5.3
68	28	35	4.1

In conclusion, a thienyl urea series has been identified as potent p38 inhibitors.[16] On exploring different substitution effects, a steep structure–activity correlation was established for the C-5 position of the thiophene ring and for the aryl side of the urea. In addition, furans and pyrroles showed analogous trends. Optimization of the lead thienyl urea **2** led to a 50-fold increase in in vitro activity (compound **65**). The best analogues of this new class show potency in a cellular functional assay of cytokine release.

Acknowledgements

We would like to thank Mr. Anthony Paiva for obtaining mass spectra and Dr. Robert Schoenleber for helpful discussions.

References and Notes

1. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Stricker, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Yound, P. R. *Nature* **1994**, *372*, 739. Han, J.; Lee, J.-D.; Bibbs, L.; Ulevitch, R. J. *Science* **1994**, *265*, 808.
2. Gallagher, T. F.; Fier-Thompson, S. M.; Garigipati, R. S.; Sorenson, M. E.; Smietana, J. M.; Lee, D.; Bender, P. E.; Lee, J. C.; Laydon, J. T.; Chabot-Fletcher, M. C.; Breton, J. J.; Adams, J. L. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1171. Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegrass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem*. **1996**, *39*, 3929.
3. Wilson, K.; McCaffrey, P.; Hsiao, K.; Pazhanisamy, S.; Galullo, V.; Bemis, G.; Fitzgibbon, J.; Caron, P.; Murcko, M.; Su, M. *Chem. Biol*. **1997**, *4*, 423.
4. For additional examples of urea-based p38 kinase inhibitors, see: (a) 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*, 2047. (b) Dumas, J.; Hatoum-Mokdad, H.; Sibley, R.; Riedl, B.; Monahan, M. K.; Lowinger, T. B.; Brennan, C. R.; Natero, R.; Turner, T.; Scott, W. J.; Redman, A. M.; Johnson, J. S.; Schoenleber, R.; Wilhelm, S. M.; Housley, T. J.; Ranges, G. E.; Bhargava, A.; Shrikhande, A. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2051.
5. Hackler, R. E.; Burow, K. W.; Kaster, S. V., Jr.; Wickiser, D. I. *J. Heterocycl. Chem*. **1989**, *26*, 1575.
6. Hartmann, H.; Liebscher, J. *Synthesis* **1984**, *3*, 275.
7. A modification of the Klein method was used: Ren, W.; Rao, K. V. B.; Klein, R. S. *J. Heterocycl. Chem*. **1986**, *23*, 1757.
8. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.
9. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *48*, 4171.
10. Gewald, K.; Bellmann, P.; Jänsch, H.-J. *Liebigs Ann. Chem*. **1984**, 1702. Tronchet, J. M. J.; Martin, O. R. *Helv. Chim. Acta* **1976**, *59*, 945. Shiotani, S.; Morita, H.; Ishida, T.; In, Y. *J. Heterocycl. Chem*. **1988**, *25*, 1205.
11. Redman, A. M.; Dumas, J.; Scott, W. J. *Org. Lett*. **2000**, *2*, 2061.
12. For the synthesis of ester **16**, see: Anderson, J. H.; Huang, C. W. *Can. J. Chem*. **1970**, *48*, 1550.
13. For an analogous electrophilic nitration of a furanopyrrole, see: Hendrickson, J. B.; De Vries, J. G. *J. Org. Chem*. **1985**, *50*, 1688.
14. Initial in vitro studies were conducted with bacculovirus-derived p38. Later studies were conducted with *E. coli*-derived enzyme.[4,15]
15. For experimental details on measuring IL-6 production in SW1353 cells, see ref 4.
16. Ranges, G.; Scott, W.; Bombara, M.; Rauner, D.; Redman, A.; Smith, R.; Paulsen, H.; Chen, J.; Gunn, D.; Renick, J. *PCT Int. Appl*. WO 98/52558; *Chem. Abstr*. **1998**, *130*, 32886.