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Benzimidazolone p38 inhibitors

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Abstract—The synthesis and in vitro p38α activity of a novel series of benzimidazolone inhibitors is described. The p38α SAR is consistent with a mode of binding wherein the benzimidazolone carbonyl serves as the H-bond acceptor to Met109 of p38α in a manner analogous to the pyridine nitrogen of prototypical pyridylimidazole p38 inhibitors. Potent p38α activity comparable to that of several previously reported p38 inhibitors is observed for this novel chemotype.

The proinflammatory cytokines Interleukin-1 (IL-1) and Tumor Necrosis Factor-α (TNF-α) are thought to have critical roles in the pathogenesis of Rheumatoid Arthritis (RA).[1] The proven clinical effectiveness of the anti-cytokine biological agents etanercept, infliximab, anakinra, and more recently adalimumab in patients with RA reinforces the central role of these cytokines.[2] In spite of their success, these large protein-based agents have limitations including cost of therapy and ease of administration. Small molecule cytokine inhibitors such as TACE inhibitors,[3] IL-1 processing and release inhibitors,[4] and Interleukin-1β Converting Enzyme (ICE) inhibitors such as pralnacasan[5] all have the potential to provide similar benefits in an orally administered agent.

Inhibitors of the mitogen activated protein (MAP) kinase p38α[6] through their downstream blockage of the production of TNF-α, IL-1β, IL-6, cyclooxygenase-2 (COX-2), and arachadonic acid mobilization[7] also have tremendous therapeutic potential. The archetypal small molecule p38 inhibitors are the pyridylimidazoles[8] and these structures formed the basis for much of the early research.[9–11] More recently a number of non-pyridyl based p38 inhibitors have been described such as the diaryl ureas,[12,13] the triaza-naphthalenones,[14] dihydro-pyridopyrimidone,[15] and the dihyroquinazolinones.[16,17]

Early work in our labs focused on the development of tools to understand the in vivo biology of p38,[18] the in vitro biology of prototype inhibitors,[19] and to identify structurally novel antagonists. Herein we report a novel series of benzimidazolone p38 inhibitors identified during the course of this work.

The synthesis of the benzimidazolone nucleus begins with the assembly of intermediates **2**–**6** from diamino-benzoic acid as shown in Scheme 1. These compounds proved to be versatile starting points for the assembly of a variety of substituted heterocycles, including imid-azoles, pyrazoles, oxazoles, triazoles, tetrazoles, pyrroles and pyridines (Schemes 2–5).

With the completion of the benzimidazolone core the synthesis of various imidazole analogues was conducted as detailed in Scheme 2.

Minimally substituted benzimidazolones inhibitors such as **12f** and **12g** bear close resemblance to their pyridylimidazole counterpart **15** in terms of both structure and intrinsic potency[21] (cf. **12f** and **12g** with **15** Fig. 1).

Based on crude overlap of the molecules, a reasonable hypothesis is that the imidazolone carbonyl serves as the hydrogen bond acceptor to Met109NH of p38α in analogy with the pyridyl nitrogen of a prototypical pyridylimidazole. However, due to the increased size of the benzimidazolone ring relative to pyridine the crossover

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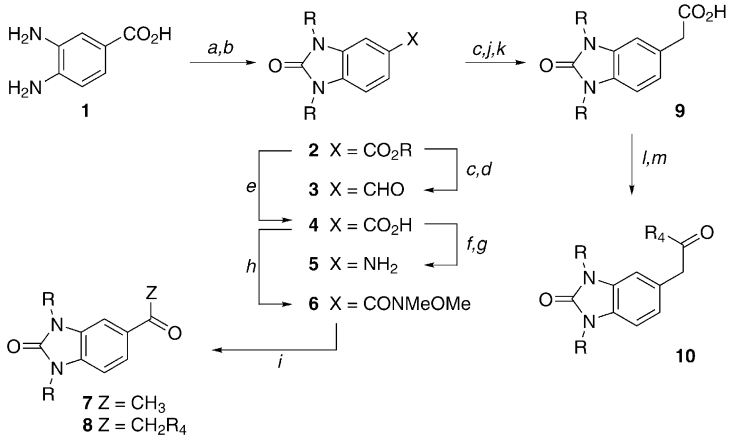
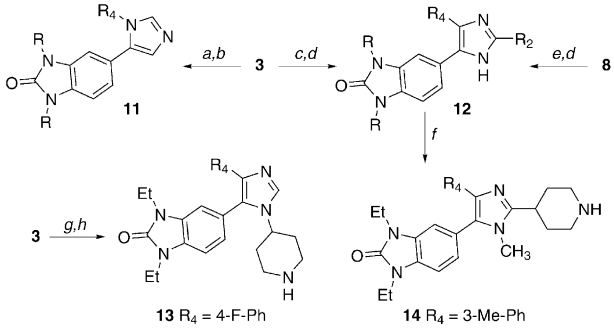
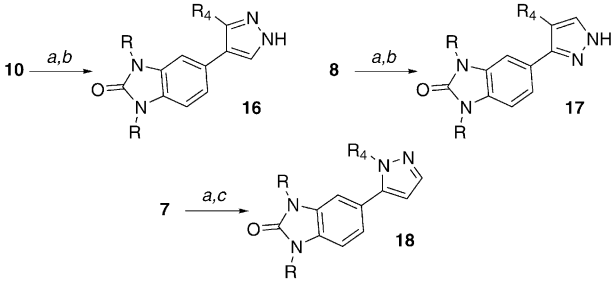


Scheme 1. Synthesis of benzimidazolone nuclei. (a) $COCl_2$, AcOH; (b) 3.3 equiv NaH, 3.3 equiv R–I, DMF, 50%; (c) $LiBH_4$, MeOH/THF, reflux, 18 h, 79%; (d) TEMPO, NCS, Bu_4NCl, CH_2Cl_2/pH 8.6 buffer, 5.5 h, 42%; (e) LiOH·H_2O, THF/H_2O, 50 °C, 2 h, 100%; (f) DPPA, Et_3N, *t*-BuOH, dioxane, reflux, 16 h, 37%; (g) 6N HCl, EtOH, 22 °C, 24 h, 78%; (h) oxalyl chloride, Et_3N, CH_2Cl_2/cat DMF, 1.5 h, then CH_3NHOCH_3·HCl, 0–22 °C, 18 h, 100%; (i) CH_3MgCl, THF, 0 °C, 98% (**7**) or $ArCH_2MgX$, dioxane, 23–55 °C, (**8**); (j) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, then NaCN, DMSO, 90 °C, 1 h, 91%; (k) 2 M LiOH, reflux, 18 h, 83%; (l) CDI, $CHCl_3$, 1 h, 23 °C, then MeNHOMe/HCl, 18 h, 23 °C, 76%; (m) R_4-MgX, THF, −78–23 °C.

connection or hinge region may be distorted in a manner similar to what is observed for the Vertex and Merck crystal structures[14,16] rather than what is observed in soaked[23] or co-crystallized[24] X-ray structures of p38α and pyridyl imidazole analogues. Although we have not yet obtained structural support for this hypothesis follow-up work on the benzimidazolones was designed to establish if the SAR was consistent with that of pyridylimidazoles and to compare the benzimidazolones to other known p38 inhibitors.

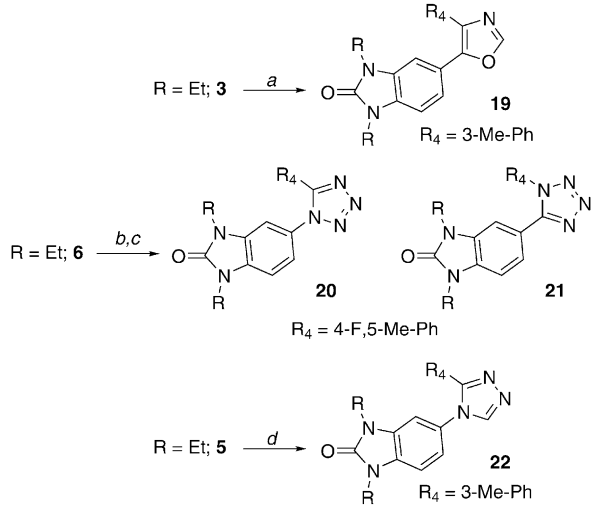


Scheme 2. Synthesis of imidazole benzimidazolones. (a) *m*-Toluidine, $MgSO_4$, CH_2Cl_2, 90%; (b) Tos-MIC, NaH, DME, then K_2CO_3, MeOH, 21%; (c) R_4-CHO, KCN, EtOH/H_2O 7–21%; (d) R_2-CHO, $Cu(OAc)_2$, NH_4OAc, AcOH, 41–85%; (e) Br_2, AcOH, then NaOMe, MeOH/H_2O, 75%; (f) CH_3I, NaH, THF, then H_2, 10% Pd/C, EtOH, 6%; (g) 4-amino-1-benzylpiperidine, piperazine, α-(*p*-toluensulfonyl)-4-fluorobenzylisonitrile, THF, 20 h, 20%;[20] (h) 40 psi H_2, Pd/C, concd HCl, MeOH, 22 °C, 4 h, 10%.

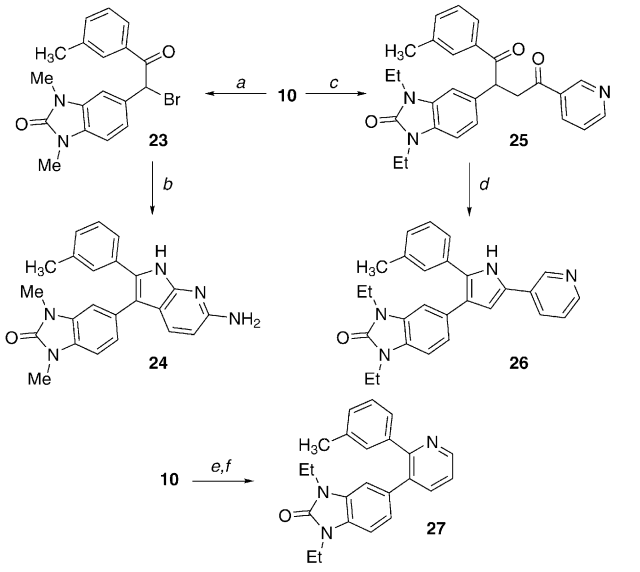


Scheme 3. Synthesis of pyrazole benzimidazolones. (a) DMF-dimethylacetal, 90 °C; (b) hydrazine hydrate, EtOH, 23 °C, 18 h, 65–93%; (c) R_4-$NHNH_2$-HCl, EtOH, 23 °C, 18 h, 71%.

Much of the early SAR work focused on the aryl group that presumably binds the lipophilic pocket of p38α. For convenience much of this work is presented in the context of a benzimidazolone-imidazole with a thiophene at C2 since the potency is unchanged relative to hydrogen (cf. **12b** with **12h**). By comparison the C4 aryl group is more sensitive to change and has a large influence on the overall potency. As shown in Table 1 small halogens (F, Cl) show no particular positional preference on the phenyl ring, while small alkyls are optimal at the meta position (see **12d**, **12e**, and **12r**). Alkyl groups larger than ethyl are not well tolerated. These findings for the



Scheme 4. Synthesis of oxazole, tetrazoles, and triazole benzimidazolones. (a) α-(*p*-toluensulfonyl)-3-methylbenzyl-isonitrile, K_2CO_3, THF, 4 h 22 °C, reflux, 18 h, 39%;[20] (b) 4-F-5-Me-phenylmagnesium bromide, THF, 22 °C, 3 h, 77%; (c) $TiCl_4$, NaN_3, CH_3CN, reflux, 4 h, 58%, 1:4 ratio **20** to **21**;[25] (d) P_2O_5, *m*-toluic acid 2-formylhydrazide, 190 °C, 5 h, 21%.



Scheme 5. Synthesis of pyrrole,[26] pyrrolopyridine,[27] and pyridine[28] benzimidazolones. (a) LiHMDS, Br_2, THF, 98%; (b) 2,6-diaminopyridine, H_2SO_4, DME, 44%; (c) 2-Bromo-1-pyridin-3-yl-ethanone, 2 equiv NaH, DMA, 88%; (d) NH_4OAc, AcOH, 6%; (e) $(CH_3)_2NCHCClCHN(CH_3)_2^+PF_6^-$, KO*t*-Bu, then AcOH, TFA, THF, then NH_4OH reflux, 23%; (f) H_2, 10% Pd/C, EtOH, 30%.

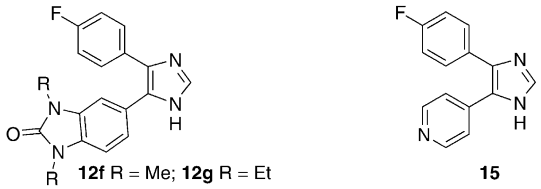


Figure 1. Comparison of benzimidazolone and pyridylimidazole p38 inhibitors. 12f p38α $IC_{50} = 0.14$ μM; 12g p38α $IC_{50} = 0.10$ μM; 15 p38α $IC_{50} = 0.10$ μM, 0.21 μM[22].

Table 1. Benzimidazolone imidazole SAR: C4 Aryl and C2

Sch 2 Compd	R_4	R_2	R	p38α IC_{50} (μM)
12a	H	H	Et	>1.0
12b	Ph	H	Me	0.29
12c	Ph	H	Et	0.14
12d	3-Me-Ph	H	Me	0.10
12e	3-Me-Ph	H	Et	0.05
12f	4-F-Ph	H	Me	0.14
12g	4-F-Ph	H	Et	0.10
12h	Ph	2-Thiophene	Me	0.26
12i	2-F-Ph	2-Thiophene	Me	0.37
12j	3-F-Ph	2-Thiophene	Me	0.39
12k	4-F-Ph	2-Thiophene	Me	0.27
12l	2-Cl-Ph	2-Thiophene	Me	0.54
12m	3-Cl-Ph	2-Thiophene	Me	0.38
12n	4-Cl-Ph	2-Thiophene	Me	0.68
12o	3-CF_3O-Ph	2-Thiophene	Me	15.8
12p	3-CF_3-Ph	2-Thiophene	Me	1.5
12q	2-Me-Ph	2-Thiophene	Me	6.2
12r	3-Me-Ph	2-Thiophene	Me	0.14
12s	4-Me-Ph	2-Thiophene	Me	1.8
12t	3-Et-Ph	2-Thiophene	Me	0.5
12u	4-Et-Ph	2-Thiophene	Me	8.0
12v	3-*i*-Pr-Ph	2-Thiophene	Me	>32
12w	3-Me-Ph	3-Pyridyl	Me	0.20
12x	3-Me-Ph	3-Pyridyl	Et	0.07
12y	3-Me-Ph	4-Piperidyl	Et	0.07
12z	4-F-Ph	4-Methanesulfinyl-Ph	Me	4.0

C4 aryl group are consistent with the published[22] SAR for pyridylimidazoles.

Other comparisons focused on the nature of the core 5-membered heterocycle. The synthesis of many of these analogues is shown in Schemes 3–5.

Changing the core heterocycle from imidazole to oxazole had a detrimental effect on the potency (cf. **12d** in Table 1 with **19** in Table 2). The regioisomeric pyrazoles **16** and **17** tested the published suggestion[26] regarding the need for a nitrogen atom to interact with the ε-ammonium group of the catalytic Lys53 in the p38α active site. In the case of these benzimidazolone pyrazoles the presence of this nitrogen in **16** and absence in **17** is dramatic and supports the importance of the proposed interaction with Lys53Nε. However, not all compounds with this nitrogen are well tolerated. The pyrrole **26** is substantially less active than the corresponding imidazole **12x**, perhaps because of the obligatory presence of a hydrogen atom, which can be avoided by imidazoles and pyrazoles by tautomerization. In principle the triazole **22**, the tetrazoles **20** and **21**, the isomeric pyrazole **18**, and the pyridyl **27** all have a suitable nitrogen to interact with Lys53Nε, but none of these compounds are active. With the exception of the pyridyl analogue **27** these analogues share in common a nitrogen atom at the connection of the core 5-membered ring and the aryl or benzimidazolone group. One possible explanation for the loss in potency for these compounds is that this seemingly minor change at the linkage with the benzimidazolone or aryl group causes a change to the propeller like twist of the two groups off of the central 5-membered ring. However, electronic factors cannot be ruled out. Of the core heterocycles explored the compounds with the best potency are confined to certain imidazole and pyrazole patterns, with **16e** having an intrinsic potency comparable to L-790070, one of the most potent reported pyridylimidazole inhibitors.

In a separate comparison we incorporated structural motifs similar to those found in published compounds (Fig. 2). As shown in Table 3 none of these changes yielded the improvements in potency observed for the compounds after which they were modeled. In fact,

Table 2. Core ring SAR

Sch 2–5 Compd	R_4	R_2	R	p38α IC_{50} (μM)
26	Scheme 5			>1.0
16a	4-F,5-Me-Ph	—	Et	0.03
16b	3-CF_3-Ph	—	Et	0.06
16c	Ph	—	Me	0.2
17a	Ph	—	Me	2.50
16d	Ph	—	Et	0.20
17b	Ph	—	Et	0.68
16e	3-Me-Ph	—	Et	0.009
17c	3-Me-Ph	—	Et	0.73
22	3-Me-Ph	—	Me	12.5
19	3-Me-Ph	—	Et	0.80
20	4-F,5-Me-Ph	—	Et	>1.0
21	4-F,5-Me-Ph	—	Et	>1.0
11	3-Me-Ph	—	Me	14.4
18	3-Me-Ph	—	Et	0.69
27	3-Me-Ph	—	Et	>1.0

Table 3. Comparison to published inhibitors

Compd	p38α IC_{50} (μM)
SB-203580[8]	0.038
RWJ-68354[27]	0.052
SB-242235[29]	0.040
L-790070[30]	0.002
12z Table 1	4.0
24	0.26
13	0.090
14	1.25

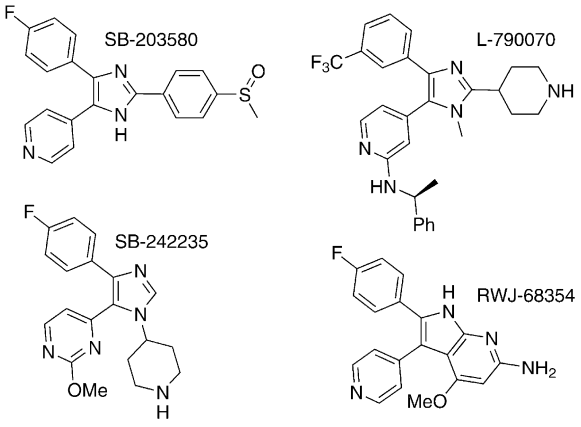


Figure 2. Comparison of benzimidazolones with published compounds.

these changes had no potency advantage over some of the simplest benzimidazolone analogues such as **12e** and **16e**. A potential unifying explanation for these results, especially where groups are projected off of the C2 position of the 5-membered ring core (e.g., **12z**, **24**, and **14**) is that the active site cannot accommodate the span of groups such as a sulfinylphenyl or piperidine given the already greater length of the benzimidazolone nucleus relative to pyridine.

In summary we have introduced a novel series of benzimidazolone p38 inhibitors whose SAR suggests a mode of binding to p38 analogous to traditional pyridylimidazole inhibitors. Nevertheless, there are differences likely due to the greater size of the benzimidazolone nucleus relative to pyridyl-based inhibitors, and there are potentially more specific orientation requirements for the imidazolone carbonyl lone pairs to serve as H-bond acceptors. Although certain benzimidazolone analogues are as potent as selected pyridylimidazoles further optimization specifically around the imidazolone moiety is needed to fully explore the potential of this series. This work will be reported in subsequent publications.

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