Bioorganic & Medicinal Chemistry Letters 20 (2010) 334–337

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

2,4-Diaminopyrimidine MK2 inhibitors. Part II: Structure-based inhibitor optimization

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ARTICLE INFO

Article history:
Received 18 August 2009
Revised 21 October 2009
Accepted 26 October 2009
Available online 29 October 2009

Keywords:
MAPKAP-K2
MK2
TNFα
Diaminopyrimidine

ABSTRACT

We describe structure-based optimization of a series of novel 2,4-diaminopyrimidine MK2 inhibitors. Co-crystal structures (see accompanying Letter) demonstrated a unique inhibitor binding mode. Resulting inhibitors had IC_{50} values as low as 19 nM and moderate selectivity against a kinase panel. Compounds **15**, **31a**, and **31b** inhibit TNFα production in peripheral human monocytes.

Tumor necrosis factor-α (TNFα) is an important target for biological drugs that are efficacious in rheumatoid arthritis (RA) and related autoimmune diseases.[1] The Ser/Thr kinase MK2 is required for TNFα production in an animal model of arthritis.[2] Although inhibitors of MK2 have been reported, none to our knowledge have progressed to clinical studies.[3–5]

In Part I[6], we described new in vitro tools to characterize MK2 inhibitors and enable structure-based drug design. We presented crystal structures that show an unexpected binding mode for 2,4-diaminopyrimidine inhibitors in the MK2 ATP binding site. The diaminopyrimidine ring was bound proximal to the DFG region, instead of adopting the commonly observed (for analogous inhibitors of other kinases) donor-acceptor mode of binding to the hinge region. This unexpected finding provided an opportunity to improve potency and possibly selectivity by optimizing compounds in several regions (Fig. 1): (1) substituents on the indazole ring to interact with the extended hinge region; (2) substituents on the pyrimidine-2-amine to access residues in the hydrophilic pocket and/or displace an ordered water behind gatekeeper residue

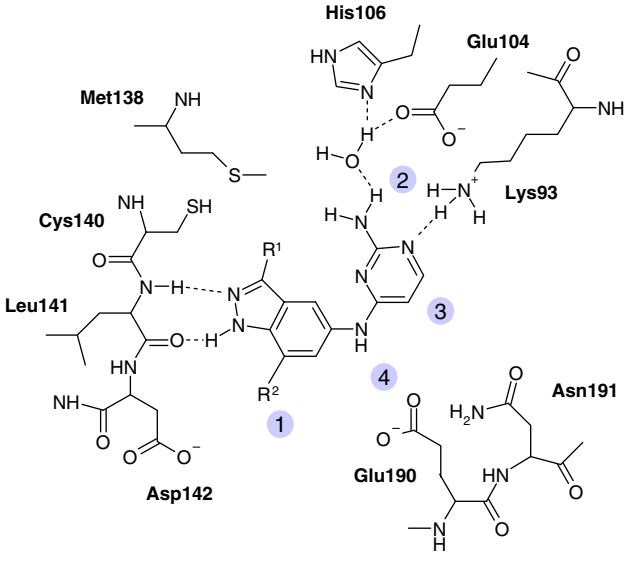

Figure 1. Structure-based optimization of compound **1**, $R^1 = R^2 = H$.

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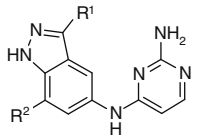
doi:10.1016/j.bmcl.2009.10.103

Table 1
SAR at 3- and 7-positions of the indazole ring



Compound	R^1	R^2	MK2 IC_{50} (μM)
1	H	H	24
4	I	H	14
5a	3-Thiophene	H	5.4
5b	2-Naphthalene	H	0.72
5c	2-Benzothiophene	H	1.6
5d	2-Pyrrole	H	1.3
10	H	I	9.1
11a	H	3-Thiophene	3.4
11b	H	2-Naphthalene	0.31
11c	H	2-Benzothiophene	0.16
11d	H	2-Benzofuran	0.16

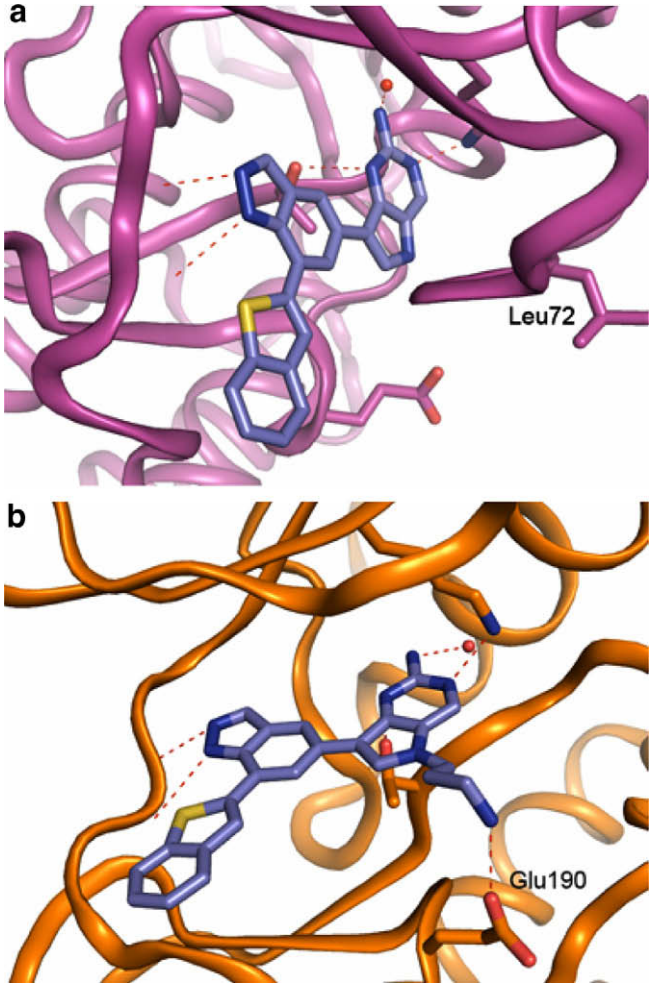
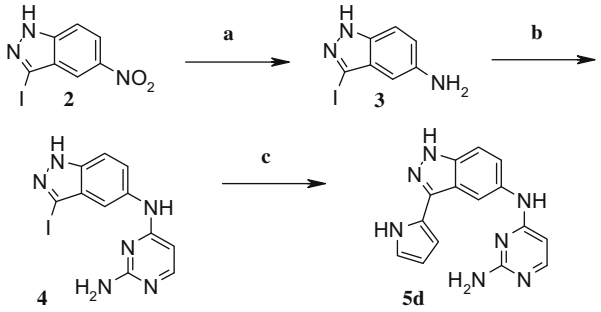
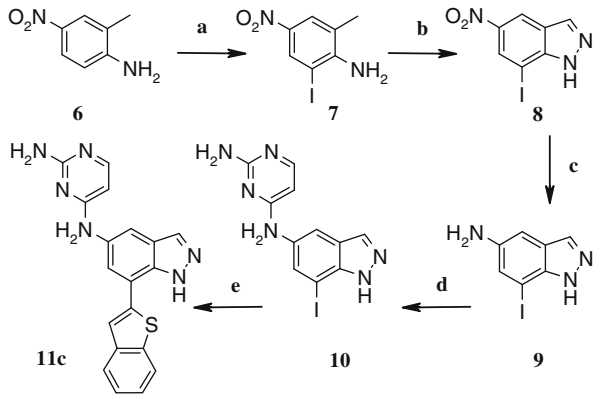


Figure 2. (a) Model of **15** (b) model of **31b** in MK2. Models were manually docked based on optimal hinge and Lys93 interactions.

Met138; (3) replacement of the pyrimidine ring with constrained bicyclic rings to reduce inhibitor conformational flexibility and to interact with the glycine rich loop; and (4) substitutions of the bridging nitrogen, or a similar position in a bicyclic system, to access ribose pocket residues.



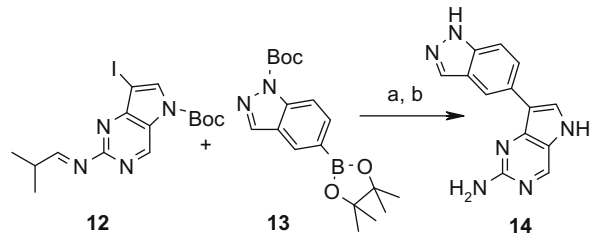
Scheme 1. Reagents and conditions: (a) HI (57% stabilized), 90 °C, 2 h, 82%; (b) 2-amino-4-chloropyrimidine, EtOH, 80 °C, 2 h, 78%; (c) 1-(*tert*-butoxycarbonyl)pyrrole-2-boronic acid, $NaHCO_3$, DMF/H_2O, $Pd(PPh_3)_4$, 150 °C/μW, 15 min, 29%.



Scheme 2. Reagents and conditions: (a) IPy_2BF_4, CF_3SO_3H, DCM, 1 h, rt, 62%; (b) $NaNO_2$, AcOH/H_2O, 4 h, 60%; (c) Fe powder, AcOH, 80 °C, 6 h, 64%; (d) 2-amino-4-chloropyrimidine, EtOH, 80 °C, 2.5 h, 91%; (e) benzo[*b*]thiophene-2-boronic acid, Na_2CO_3, DME/H_2O, $Pd(PPh_3)_4$, 150 °C/μW, 10 min, 43%.

Screening of the Abbott compound collection produced 4-(2-aminopyrimidin-4-ylamino) phenol, with an MK2[7] IC_{50} of 34 μM. Concerns about in vivo liabilities of the phenol moiety led us to test bio-isosteres, resulting in compound **1**, which substitutes a 5-indazolyl group for the phenol (Table 1).

The binding mode (Fig. 1) suggested that 3- or 7-position substituents could make additional interactions with the MK2 extended hinge region (Tactic 1), requiring a 180° flip of the indazole moiety which preserves hinge interactions with Leu141 (Fig. 2a).[6] Representative routes to 3- and 7-substituted indazole analogs are described in Schemes 1 and 2, respectively. 3- or 7-iodo-substitutions had modest effects on inhibitor potency, whereas mono- or bicyclic aromatic groups at these positions gave significant gains (Table 1). 7-Position substitutions were slightly preferred. The 2-benzothiophene moiety, as in compound **11c**, was the optimal indazole 7-substitution and was retained in subse-



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, Cs_2CO_3, DME/H_2O, 60 °C, 24 h; (b) NaOH, EtOH, 100 °C, 2 h, 4% (two steps).