ACS Medicinal Chemistry Letters

Letter

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Discovery of a Potent Dihydrooxadiazole Series of Non-ATP-Competitive MK2 (MAPKAPK2) Inhibitors

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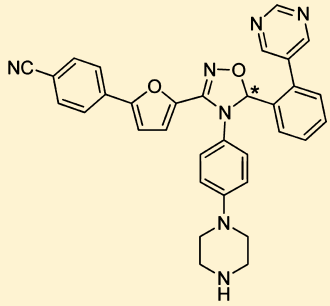
Supporting Information

ABSTRACT: Inhibition of MK2 has been shown to offer advantages over that of p38 MAPK in the development of cures for inflammatory diseases such as arthritis. P38 MAPK knockout in mice was lethal, whereas MK2-null mice demonstrated strong inhibition of disease progression in collagen-induced arthritis and appeared normal and viable. However, it is challenging to develop ATP-competitive MK2 inhibitors due to high ATP binding affinity to the kinase. Non-ATP-competitive MK2 inhibitors interact and bind to the kinase in a mode independent of ATP concentration, which could provide better selectivity and cellular potency. Therefore, it is desirable to identify non-ATP-competitive MK2 inhibitors. Through structure optimization of lead compound **1**, a novel series of dihydrooxadiazoles was discovered. Additional structure−activity relationship (SAR) study of this series led to the identification of compound **38** as a non-ATP-competitive MK2 inhibitor with potent enzymatic activity and good cellular potency. The SAR, synthesis, and biological data of dihydrooxadiazole series are discussed.

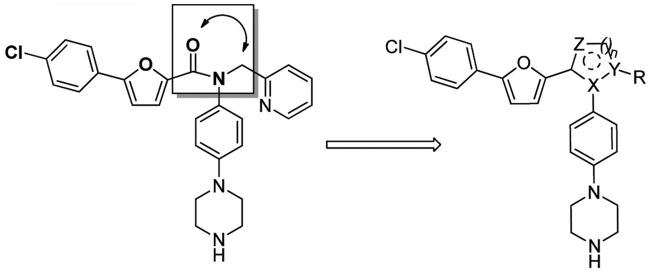


KEYWORDS: *mitogen-activated protein kinase-activated protein kinase 2, non-ATP-competitive inhibitors*

Activation of the p38/mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2 or MK2) pathway has been associated with promoting inflammatory diseases, such as rheumatoid arthritis, due to overproduction of pro-inflammatory cytokines including tumor necrosis factor α (TNFα) and interleukin 6 (IL6).[1−3] The role that p38 MAPK kinase plays in proinflammatory cytokine production has been well documented, and it is known to regulate many downstream cellular processes. However, inhibition of p38 MAPK has been shown to cause unwanted side effects. Therefore, despite numerous efforts to identify p38 MAPK inhibitors, no clinical compounds have progressed beyond phase II trials due to related toxicity and limited efficacy.[4−6] MK2 is the downstream substrate kinase activated by p38 in response to inflammatory stimuli (e.g., lipopolysaccharides, LPS) and environmental stress.[7−9] MK2 knockout mice show no LPS-induced TNFα release and appear normal and viable, whereas knockout of p38 in mice is lethal.[9,10] Furthermore, MK2-null mice demonstrated strong inhibition of disease progression in collagen-induced arthritis.[10]

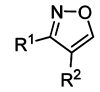
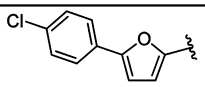
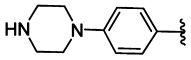
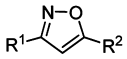
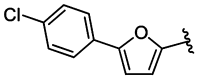
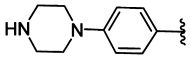
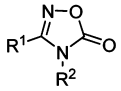
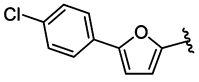
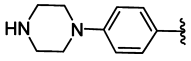
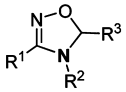
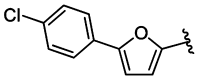
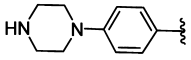
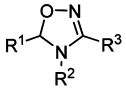
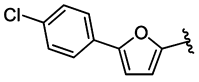
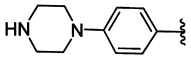
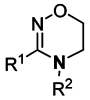
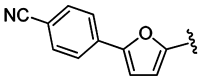
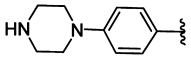
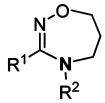
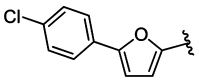
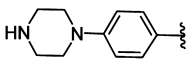
Several small molecule MK2 inhibitors from different research laboratories have been reported.[11−25] Adenosine-5′-triphosphate (ATP)-competitive MK2 inhibitors have demonstrated efficacy in cellular and animal assays, such as Pfizer's compound PF-3644022.[14] However, it is challenging to develop ATP-competitive MK2 inhibitors due to high ATP binding affinity to the kinase (ATP K_m = 2 μM), resulting in difficulty in obtaining sufficient selectivity and cellular potency. Non-ATP-competitive MK2 inhibitors interact and bind to the kinase in a mode independent of ATP concentration, which can offer an advantage over the issues associated with ATP-competitive inhibitors.[26] In a program to identify non-ATP-competitive MK2 inhibitors in our laboratory, compound **1** (Scheme 1), a furan-2-carboxamide-based scaffold, was discovered through high-throughput screening and initial lead optimization.[27] It showed good enzymatic and cellular activity as a non-ATP-competitive inhibitor. Inspired by this amide motif, we decided

Scheme 1. Design of Novel Heterocyclic Non-ATP-Competitive Inhibitors



Received: October 11, 2011
Accepted: December 16, 2011
Published: December 23, 2011

Table 1. In Vitro Potency of Compounds 2−8 in Enzyme and Cell Assay

Compound	Heterocyclic core	R^1	R^2	R^3	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)
2					3400	n.d.[c]
3					>10000	n.d[c]
4					6200	n.d.[c]
5					50	6700±370[d]
6					3700	n.d.[c]
7					110	n.d.[c]
8					1400	n.d.[c]

[a]Data represent an average of multiple determinations ($n \geq 2$). [b]Assays were conducted in the presence of 100 μM ATP. [c]n.d., not determined. [d]An average of multiple determinations ± standard deviations ($n \geq 2$).

to modify the core linkage of **1** by forming a heterocyclic ring to fix the conformation of the rotameric amide bond. We hypothesized that this modification could potentially improve potency by offering a rigidified conformation with limited bond rotation, although structure modeling needs to be performed to provide future guidance. On the basis of this hypothesis, we designed and synthesized a series of compounds with different heterocyclic core structures (Table 1). The SAR data showed that the ring size and geometry affect the potency significantly. Compound **2** with a 3,4-substituted isoxazole core was 30-fold less active than **1**. The isomeric isoxazole analogue **3** with different substitution geometry was inactive in the assay. The related oxadiazolone **4** also displayed reduced activity. However, analogue **5** that contained a dihydrooxadiazole core demonstrated potency 2-fold better than compound **1**. Relocation of the stereocenter in **5** led to analogue **6**, which offered much weaker activity than **5**. A six-membered dihydrooxadiazine compound **7** possessed similar potency to compound **1**. In contrast, analogue **8**, which had a seven-membered tetrahydrooxadiazepine core, lost 10-fold activity as compared with **1**. From this initial amide replacement and structure−activity relationship (SAR) study, the novel dihydrooxadiazole core structure was taken as a lead for further optimization.

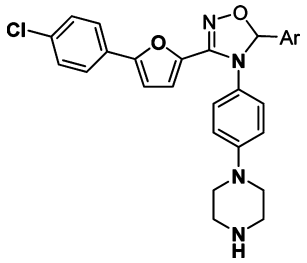
We then turned our attention to modifying the right-hand side of the dihydrooxadiazole. A series of compounds with different aromatic groups were prepared to explore the potential in this region (Table 2). Pyridyl (**9**−**12**) and pyrimidyl (**13**−**14**) groups were well tolerated and maintained good potency in enzymatic assay. Compounds with fluoro-substituted phenyl rings (**15**−**17**) were slightly less active than **5**. Imidazoyl derivative (**18**) also showed good activity. It was noted that the 5-(2-phenyl)pyrimidyl group of **19** and the 4-(2-pyrimidyl)phenyl group of **20** were detrimental to the potency, whereas 4-(5-pyrimidyl)phenyl analogue **21** retained similar activity to that of pyrimidyl compound **14**. Relocation of the pyrimidyl substitution on the phenyl ring from *para*- (**21**) to *meta*- (**22**) caused a loss of 4-fold in potency. However, *ortho*-(5-pyrimidyl)phenyl analogue **23** was twice as active as **21**. Additional SAR showed that similar *ortho*-(3-pyridyl)phenyl and *ortho*-biphenyl analogues **24** and **25** were inferior to compound **23**.

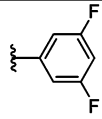
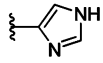
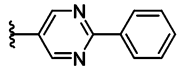
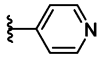
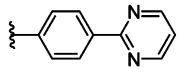
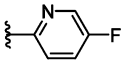
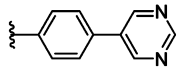
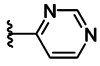
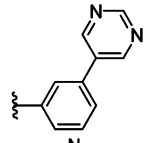
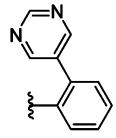
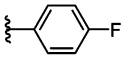
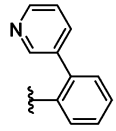
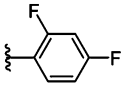
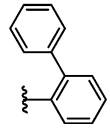
Further optimization of the left-hand side aromatic group showed very tight SARs (Table 3). Changing the position of chloro substitution on the phenyl ring from *para* to *meta* was not tolerated (**23** vs **26**). However, 4-fluorophenyl analogue **27** retained similar activity to **23**. Compounds with dihalogen-substituted phenyl (**28**, **29**), pyridyl (**30**), or 4-methoxyphenyl (**31**) groups showed much weaker activity. 4-(*N*-Methylformyl)phenyl substitution of **32** was not tolerated. However, a breakthrough was achieved when a 4-cyanophenyl group was introduced in compound **33**. This analogue showed excellent activity [MK2/immobilized metal ion affinity-based fluorescence polarization (IMAP) IC_{50} = 8 nM]. On the other hand, the 3-cyanophenyl group of **34** was detrimental to the activity.

Having explored SAR in the right- and left-hand sides, we continued the optimization efforts at the bottom part of the

dx.doi.org/10.1021/ml200238g | ACS Med. Chem. Lett. 2012, 3, 100−105

Table 2. In Vitro Potency of Compounds 9−25 in Enzyme and Cell Assay



Compound	Ar	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)	Compound	Ar	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)
5		50	6700±370[d]	**17**		190	n.d.[c]
9		30	3000±300[d]	**18**		70	2400±800[d]
10		50	n.d.[c]	**19**		1200±160[d]	n.d.[c]
11		30	2700±1100[d]	**20**		330±50[d]	n.d.[c]
12		60	3700±2000[d]	**21**		100±40[d]	820±140[d]
13		60	n.d.[c]	**22**		380±30[d]	n.d.[c]
14		70	n.d.[c]	**23**		40	730±120[d]
15		160	n.d.[c]	**24**		180	n.d.[c]
16		100	n.d.[c]	**25**		480	n.d.[c]

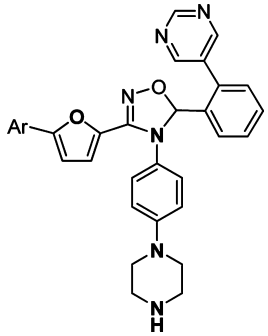
[a]Data represent an average of multiple determinations ($n \geq 2$). [b]Assays were conducted in the presence of 100 μM ATP. [c]n.d., not determined. [d]An average of multiple determinations ± standard deviations ($n \geq 2$).

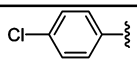
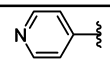
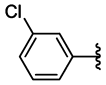
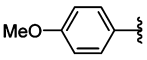
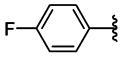
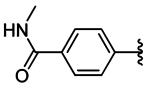
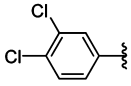
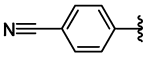
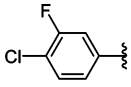
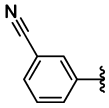
structure (Table 4). It was clear that 4-(piperazin-1-yl)phenyl group was the optimal substitution. Replacement of either one of nitrogen atom in the piperazine ring caused the loss of activity (**35**−**36** vs **11**). Compound **37** with 4-(piperazin-1-yl)benzyl substitution was inactive, suggesting that the length of the substitution at this position was critical for the potency.

Compound **33** was resolved by chiral separation to provide two enantiomers **38** and **39**.[28] Enantiomer **38** retained excellent enzymatic activity and good cellular potency [MK2/IMAP IC_{50} = 6 ± 1 nM, phospho heat-shock protein 27 (pHSP27) EC_{50} = 170 ± 20 nM], whereas isomer **39** was much less active (MK2/IMAP IC_{50} = 340 nM). From the data presented above, it can be seen that this series of compounds demonstrated poor correlations between enzymatic and cellular potency in general. Solubility and plasma protein binding could be two of the most common factors affecting shifts in cell data as compared to isolated enzyme potencies, although we did not perform routine evaluation of plasma protein binding and solubility for these compounds (compound **38** solubility = 20 μM in 10 mM sodium phosphate buffer/2% DMSO solution, pH = 7.4; plasma protein binding = 96.5% human, 96.9% rat). The binding of compound **38** to MK2 was determined in house to be non-ATP

dx.doi.org/10.1021/ml200238g | ACS Med. Chem. Lett. 2012, 3, 100−105

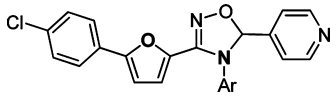
Table 3. In Vitro Potency of Compounds 26−34 in Enzyme and Cell Assay

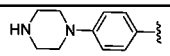
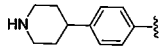
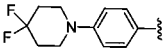
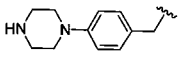


Compound	Ar	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)	Compound	Ar	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)
23		40	730±120[d]	**30**		790	n.d.[c]
26		1300±10[d]	n.d.[c]	**31**		310	n.d.[c]
27		50±20[d]	760±20[d]	**32**		>10000	n.d.[c]
28		970±200[d]	n.d.[c]	**33**		8±1[d]	1200±680[d]
29		220±10[d]	n.d.[c]	**34**		5300±2000[d]	n.d.[c]

[a]Data represent an average of multiple determinations ($n \geq 2$). [b]Assays were conducted in the presence of 100 μM ATP. [c]n.d., not determined. [d]An average of multiple determinations ± standard deviations ($n \geq 2$).

Table 4. In Vitro Potency of Compounds 35−37 in Enzyme and Cell Assay



Compound	Ar	MK2/IMAP IC_{50}(nM)[a,b]	pHSP27 EC_{50}(nM)
11		30	2700±1100[d]
35		190	n.d.[c]
36		>10000	n.d.[c]
37		>10000	n.d.[c]

[a]Data represent an average of multiple determinations ($n \geq 2$). [b]Assays were conducted in the presence of 100 μM ATP. [c]n.d., not determined. [d]An average of multiple determinations ± standard deviations ($n \geq 2$).

competitive (Figure 1). As is illustrated in the figure, as the ATP concentration increases above the K_m for ATP (MK2's K_m for ATP ~ 2 μM), the IC_{50} value of the inhibitor **38** does not change, indicating that the molecule is not affected by the binding of ATP or may not occupy the same binding pocket. Compound **38** showed a poor pharmacokinetic (PK) profile in rat (rat po 10 mg/kg AUC_{0-6h} = 0 nM·h). We hypothesized that this could be due to low/zero bioavailability and/or high in vivo clearance and other undetermined reasons, although we do not have these data in hand to support at the moment (compound **38** rat hepatocyte clearance = 35 μL/min/M cell, Caco 2 permeability absorption = moderate). With these preliminary data in hand, additional structure optimization is needed to improve the PK profile of this series.

The synthesis of compounds **2**−**8** is summarized in the Supporting Information. Analogues **9**−**39** were prepared by a similar method to that described for **5**.

In summary, we have explored several series of heterocyclic scaffolds as MK2 inhibitors. Among these series, the dihydrooxadiazoles were identified as a promising new lead series that led to discovery of compound **38** as a potent non-ATP-competitive inhibitor. Additional structure optimization is needed to further improve the PK profile of this series. The results will be the subject of a future publication.

dx.doi.org/10.1021/ml200238g | ACS Med. Chem. Lett. 2012, 3, 100−105

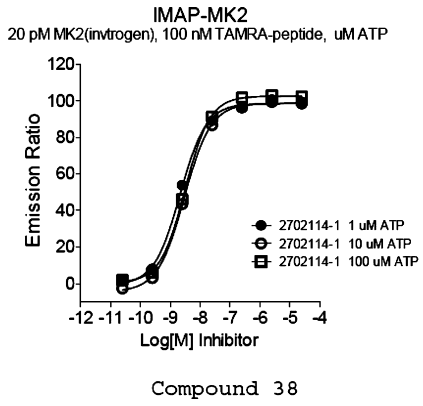


Figure 1. Characterization of non-ATP-competitiveness for compound **38**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for assay protocols and synthesis and characterization of compounds **2**−**37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Drs. Chad Bennett and Jared Cumming for proofreading and comments on the preparation of manuscript.

■ ABBREVIATIONS

MAPKAPK2 or MK2, mitogen-activated protein kinase-activated protein kinase 2; TNFα, tumor necrosis factor α; IL6, interleukin 6; ATP, adenosine-5′-triphosphate; LPS, lipopolysaccharides; IMAP, immobilized metal ion affinity-based fluorescence polarization; pHSP27, phospho heat-shock protein 27; PK, pharmacokinetic

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