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In vivo and in vitro SAR of tetracyclic MAPKAP-K2 (MK2) inhibitors. Part II

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ABSTRACT

Spirocyclopropane- and spiroazetidine-substituted tetracycles **13D–E** and **16A** are described as orally active MK2 inhibitors. The spiroazetidine derivatives are potent MK2 inhibitors with IC_{50} <3 nM and inhibit the release of TNFα (IC_{50}<0.3 μM) from hPBMCs and hsp27 phosphorylation in anisomycin stimulated THP-1 cells. The spirocyclopropane analogues are less potent against MK2 (IC_{50} = 0.05–0.23 μM), less potent in cells (IC_{50} <1.1 μM), but show good oral absorption. Compound **13E** (100 mg/kg po; bid) showed oral activity in rAIA and mCIA, with significant reduction of swelling and histological score.

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Mitogen-activated protein kinases (MAPKs) belong to the Ser/Thr kinase family[1], control cytoskeletal architecture, cell-cycle progression and are implicated in inflammation and cancer.[2] The p38/MAPKAP kinase-2 (MAPKAP-K2; MK2) cascade plays a pivotal role in the production of proinflammatory cytokines, such as TNFα, IL-6 and IFNγ.[3] Moreover, MK2 knock-out mice are resistant to developing disease in arthritis models.[4] Thus, MK2 has emerged as a highly desirable target in the search for efficacious and safe anti-inflammatory drugs. MK2 inhibitors from a variety of structural classes were published, including aminocyanopyridines, tetrahydro-γ-carbolines and pyrrolopyridines, pyrrolo-pyrimidinones, benzothiophenes, 2,4-diamino-pyrimidines[5] and 3-aminopyrazoles.[6] A breakthrough with low-molecular MK2-inhibitors is still awaited.[7]

Our screening efforts for MK2 inhibitors identified the pyrrolo[2,3-*f*]isoquinoline amide **1** (Fig. 1) as a modest MK2 inhibitor with an IC_{50} value of 3.8 μM. **1** demonstrated structural similarities to the recently disclosed MK2 inhibitors **2**[5g] with a pyrrolopyridine scaffold and submicromolar IC_{50}. Combining the structural features of **1** and **2** resulted in the tetracyclic MK2 inhibitor **3**[8] with an IC_{50} of 10 nM. In spite of potent cellular activity, **3** was lacking oral bioavailability. Here we report our efforts towards orally active MK2 inhibitors by modifying the tetracyclic αβγδ-ring system of **4**.

Pyrrole-tetracycles **4a** (Scheme 1) were prepared via the Hantzsch[9] reaction of bromoketone **5** and piperidinedione **6** followed by Suzuki coupling[10] with R^1-substituents **A–F**. Furan-tetracycles **4b** with a furan as γ-ring (Scheme 1) were obtained in a similar fashion, first by reacting **5** and **6** to a 1,4-diketone intermediate which was then cyclised to the furan-ring in the presence of H_2SO_4.

Desired bromoketones **5a–c** (Scheme 2) were prepared in eight steps[11] from cyclopentanone, cyclohexanone and cycloheptanone. Bromoketone **5d** was gained from 2-ethoxycarbonyl cyclohexanone in six steps.[11] Piperidinediones **6** were synthesized starting from β-aminoesters **9a–f** by their reaction with mono-chloromalonate, followed by Dieckmann condensation (MeONa in refluxing

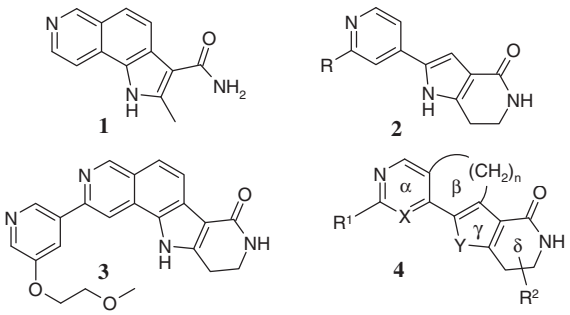

Figure 1. MK2 inhibitors.

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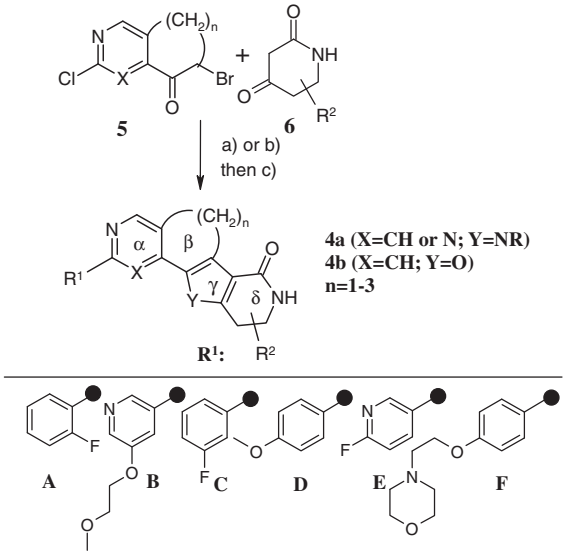
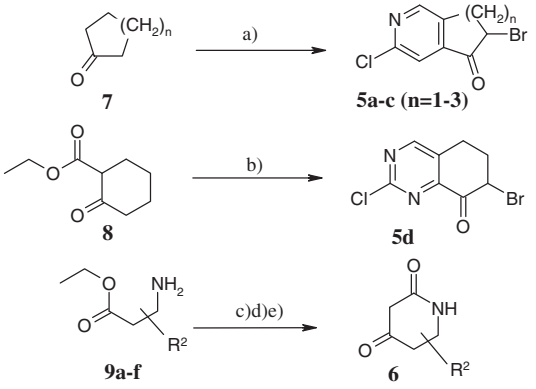
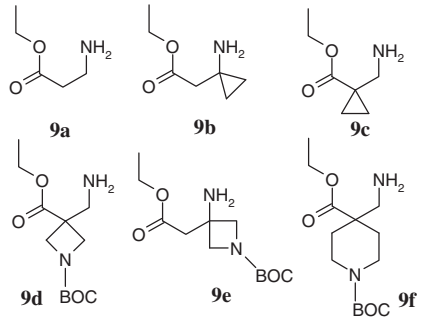


Scheme 1. Reagents and conditions: (a) MeOH, NH_4OAc, rt, 12 h, 25–60% of **4a** (R^1 = Cl; X = CH or N); (b) (i) MeOH, NaOAc, 12 h, rt, then evaporate, (ii) H_2SO_{4concd}, rt, 10 min., 23–55% of **4b** (R^1 = Cl; X = CH); (c) R^1–$B(OH)_2$ or its pinacol ester, $Pd(PPh_3)_2Cl_2$, PPh_3, 2 N Na_2CO_3, 1-propanol, 150 °C, 20 min., microwave, 60–80%.



Scheme 2. Reagents and conditions: (a) eight; (b) six steps as described[11]; (c) ethyl malonyl chloride, NEt_3, CH_2Cl_2, rt, 30 min, 40–60%; (d) MeONa, toluene, reflux 45 min., quant; (e) $MeCN/H_2O$ reflux, 1 h, 85%.

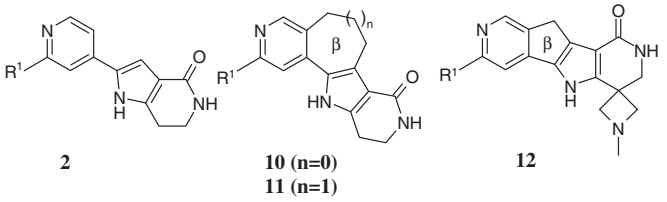


Scheme 3. 3-Amino propionic acid ethyl esters.

toluene) of the obtained amides and decarboxylation in refluxing wet acetonitrile.[11]

β-Aminoesters **9a–c** and **9f** are commercially available, while derivatives **9d–e** are novel and were prepared as described previously[11] (Scheme 3).

Regarding MK2-inhibition and cellular activity, the conformationally restricted tetracycles **10** and **11** (Scheme 4) proved to be



Scheme 4. Conformationally restricted MK2 inhibitors **10–12**.

Table 1
Conformationally restricted MK2 inhibitors **10–12**

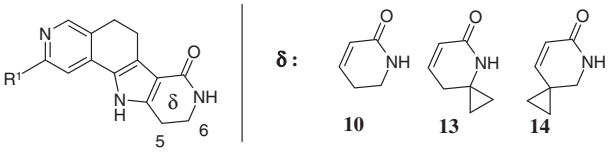
Compd	MK2[a] (M)	TNFα [b] (μM)	*p*-hsp27[c] (μM)	Sol.[d] (μM)
2A	0.560	>10	8.9	337
3	0.010	0.3	1.5	<4
10A	0.037	1.5	2.7	11
10B	0.040	0.4	1.7	8
11B	0.180	1.1	4.3	21
12A	0.230	>10	10.0	69

[a] IC_{50} values are measured as described[6] and are reported as a mean of ⩾2 measurements with a standard deviation of less than ±50%.
[b] Inhibition of LPS stimulated release of TNFα from hPBMC is performed as described.[6]
[c] Inhibition of anisomycin stimulated phosphorylation of hsp27 in THP-1 cells is measured as described.[6]
[d] Thermodynamic solubility measured at pH 6.8.

clearly superior to the non-cyclised pyrrolopyridines **2** (Table 1). Thus, a comparison of **2A**[5g] with **10A** revealed that the former was a weak MK2 inhibitor devoid of cellular activity in contrast to its cyclised analogue **10A**, which was 15-times more potent against MK2 and inhibited LPS-induced release of TNFα from hPBMCs and hsp27 phosphorylation with low micromolar IC_{50}s. Compound **10B** was slightly less potent than its fully aromatic analogue **3**, but with improved solubility (8 μM vs <4 μM). Ring expansion of **10B** to **11B** with a seven-membered β-ring resulted in ~3-fold lower MK2- and cellular potency. Ring contraction of **10B** to a five-membered β-ring yielded **12A** again with lower MK2-affinity (IC_{50} = 0.23 μM) lacking cellular activity.

Keeping the six-membered β-ring unchanged, the influence of three- and four-membered spirocycles attached to the lactam δ-ring was investigated (Scheme 5, Table 2). Spirocyclopropanes **13**, **14** and the unsubstituted analogue **10** showed similar MK2- and cellular inhibition profiles. IC_{50} for MK2 inhibition was in the range of 8 nM (**10C**) to 0.23 μM (**13C**), the IC_{50} for inhibition of TNFα from hPBMCs in the range of 0.1 μM (**10D**) to 1.7 μM (**14D**). Intracellular *p*-hsp27 was inhibited at a slightly higher range from IC_{50} = 0.5 μM (**13C**) to 2.7 μM (**10A**). Solubilities were modest, best values reaching 10–11 μM at pH 6.8 (**10A** and **13A**). Whereas R^1-substituents **A–F** had no major effect on kinase affinity or cellular potency, the *o*-fluorophenyl substituent **A** had a favourable effect on solubility. Solubilising groups **B** and **F** failed to enhance solubilities probably due to the rigid flat tetracyclic core leading to a tight crystal packing.

MK2 inhibition and cellular potency of the spiroazetidines (Scheme 6, Table 3) appeared to depend upon their position on the δ-ring.



Scheme 5. δ-Ring modifications.

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