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Synthesis and SAR studies of indole-based MK2 inhibitors

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This Paper is dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

Abstract—Chemistry has been developed to specifically functionalize two structurally similar classes of indole-based MK2 inhibitors at positions prompted by a combination of X-ray crystallographic and computer assisted drug design. A gain in molecular potency was obtained by introducing aminomethyl groups to the lactam rings of 6-arylcarbamoyl-tetrahydro-β-carbolinone and 6-arylcarbamoyl-dihydropyrazino[1,2-*a*]indolone MK2 inhibitors. In addition, improvements in molecular potency were achieved by expansion of the lactam from a 6- to 7-membered ring leading to 7-arylcarbamoyl-tetrahydro-[1,4]diazepino[1,2-*a*]indolones.

Tumor necrosis factor alpha (TNFα) has been implicated in many inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis. To date, several anti-TNFα biologics including Enbrel®, Remicade®, and Humira® have been approved for use as anti-inflammatory therapies.[1] Mitogen-activated protein kinase-activated protein kinase 2 (MK2) is a Ser/Thr kinase that plays a critical role in the signal transduction pathway regulating the production of TNFα.[2] It has been reported[2a] that MK2 knockout mice challenged with lipopolysaccharide produce significantly less TNFα than the wild-type control mice. In addition, these MK2 knockout mice are resistant to disease in arthritis models. Moreover, the MK2 knockout mice were reported to be fertile and healthy.[2a] These reports suggest the inhibition of MK2 may provide a safe and effective treatment of TNFα mediated diseases.[3]

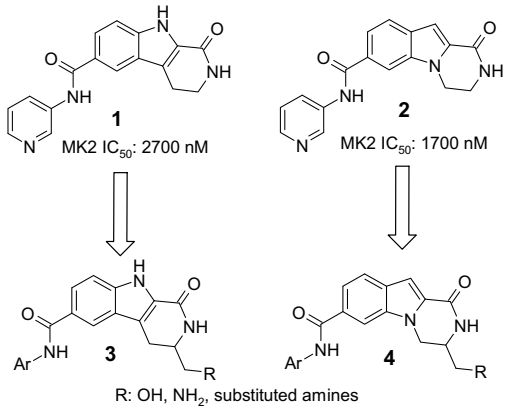

Figure 1. SAR targets.

Recently we identified two series of structurally similar indole-based MK2 inhibitors as exemplified by compounds **1** and **2** (Fig. 1).[4] An X-ray structure of a close analogue of **1** revealed a number of polar residues (e.g., Asn191 and Asp207) in close proximity to the lactam ring, suggesting that it may be possible to engage these polar residues and further improve the potency of our MK2 inhibitors. Molecular modeling indicated that a polar group (e.g., CH_2OH, CH_2NH_2) substituted at 3-position of the lactam ring as shown by general structures **3** and **4** may be able to pick up new interactions with these polar residues (Fig. 2). In addition, the amine group could be used as a functional handle (substituted amines) to further explore SAR in this region. Herein we report the synthesis and the SAR results of compounds shown by general structures **3** and **4**[5] and lactam ring-expanded analogues (vide infra).

Keywords: MAPKAP-k2; MK2; β-Carbolinone; Pyrazino[1,2-*a*]indolone; Diazepino[1,2-*a*]indolone.
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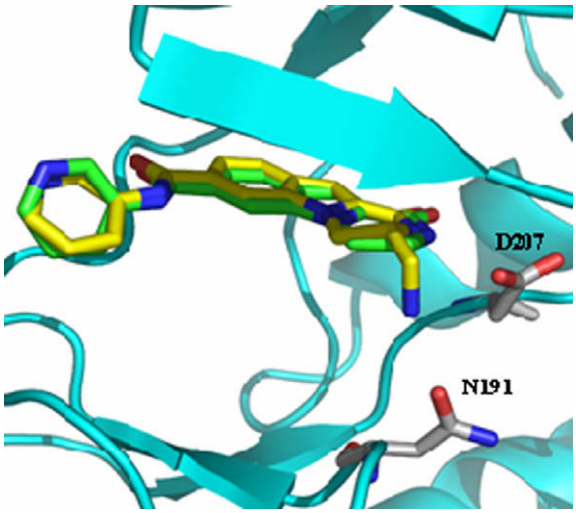
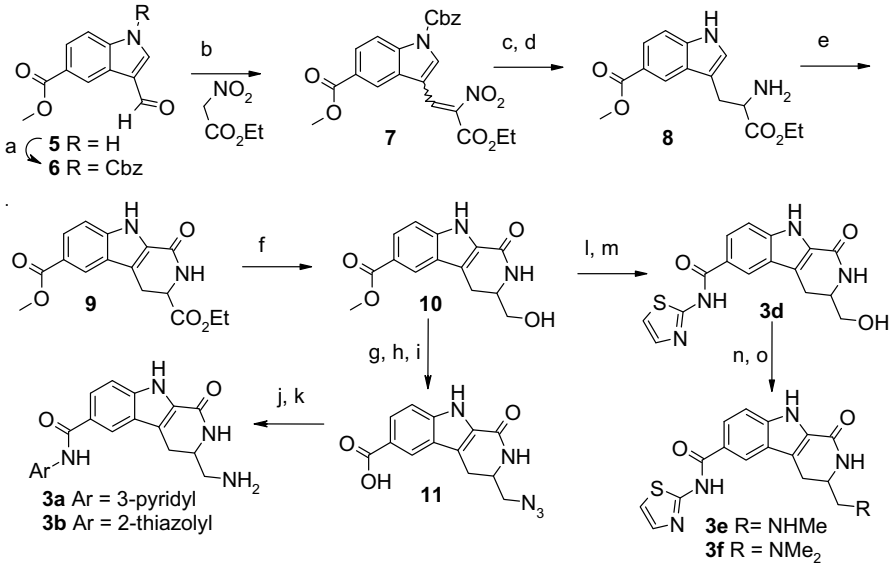


Figure 2. Model of overlap of **2** (in green) with **4a** (in yellow).

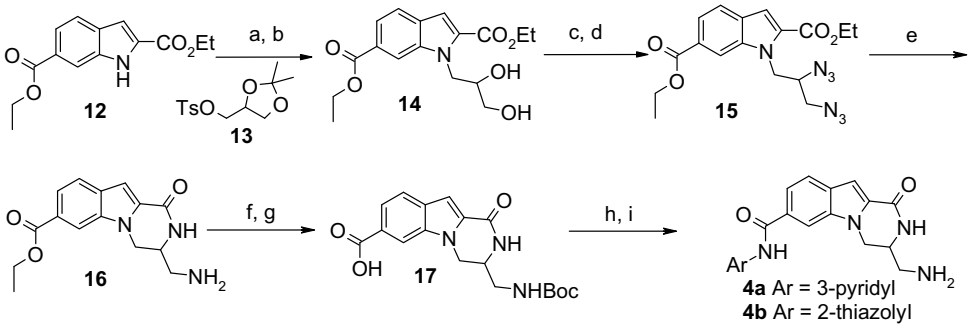
The synthesis of compounds exemplified by structure **3** (tetrahydro-β-carbolinones)[6] is summarized in Scheme 1. Methyl 2-formylindole-5-carboxylate **5** was first protected as benzyl carbamate **6**. Knoevenagel condensation of **6** with ethyl nitroacetate provided a 1:1 mixture of *E*- and *Z*-olefins **7**.[7,8] Conversion to the amino ester **8** was accomplished by $NaBH_4$ reduction of the double bond and hydrogenation of the nitro with simultaneous removal of the Cbz group. Treatment of amine **8** with triphosgene generated the corresponding isocyanate, which was converted to lactam **9** in situ when treated with 30% HBr in acetic acid.[9] The aliphatic ester of **9** was selectively reduced by $LiBH_4$ to give alcohol **10**, which served as a key intermediate. Mesylation of the alcohol and azide displacement followed by ester hydrolysis provided **11**. This allowed us to functionalize the left part of the inhibitors first. Hydrogenation of the azide group provided amines **3a** and **3b**. Alternatively, substituted amines derivatives (e.g., **3e** and **3f**) could be prepared from **10** by first ester hydrolysis and amide coupling, and then mesylate formation and displacement with aliphatic amines.

The syntheses of compounds exemplified by structure **4** (dihydropyrazino[1,2-*a*]indolones)[10] proceeded through two different routes (Schemes 2 and 3). Alkylation of indole diester **12** with tosylate **13** provided diol **14** after ketal group removal. Diol **14** was bis-mesylated and displaced by azide to give diazide **15**, which, when reduced[11] by Me_3P, cyclized in situ to form lactam **16**. Compound **16** was converted to primary amines **4a** and **4b** by Boc-protection followed by ester hydrolysis, amide coupling and Boc-deprotection. The synthesis also allowed us to examine the effect of chirality through preparing both enantiomers[12] of **4a** and **4b** using enantiomerically pure tosylate **13**.

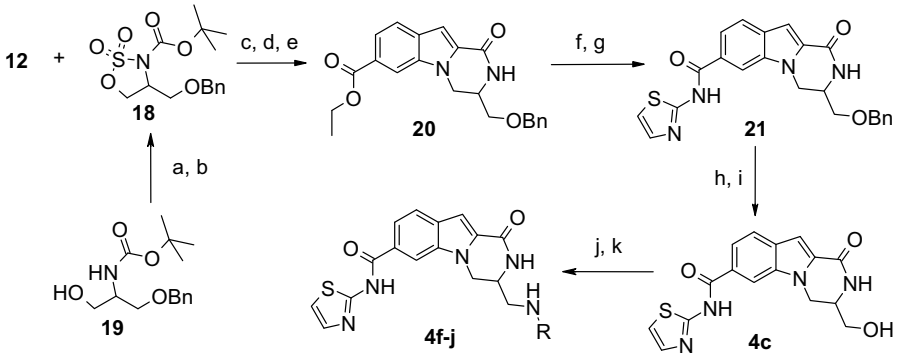
As shown in Scheme 3, substituted amines **4f–j** were synthesized from **12** through alkylation with **18** which was prepared from racemic Boc-*O*-benzyl-serinol **19** through cyclization with $SOCl_2$ and oxidation with $NaIO_4$ and catalytic amount of $RuCl_3$.[13,14] Alkylation[13] of **12** with **18** followed by Boc-deprotection and lactamization afforded **20** in excellent yield. Ester hydrolysis and amide coupling gave amide **21**. Debenzylation of **21** with 30% HBr in HOAc gave the acetate of the corresponding alcohol, which was hydrolyzed to alcohol **4c**. Substituted amines **4f–j** were prepared from **4c** by mesylation and displacement with a variety of amines.



Scheme 1. Reagents and conditions: (a) NaH, CbzCl, DMF, 0–23 °C, 14 h, 84%; (b) nitroacetate, $TiCl_4$, NMMO, THF, 0 °C, 6 h, 85%; (c) $NaBH_4$, MeOH, 1 h; (d) H_2, 10% Pd–C, HOAc–EtOH, 15 h, 75% over 2 steps; (e) triphosgene (0.4 equiv), Et_3N, toluene–CH_2Cl_2 (1:2), 0 °C, 1 h, then 30% HBr in HOAc, 23 °C, 2 h, 80%; (f) $LiBH_4$, THF, 23 °C, 6 h, 91%; (g) MsCl, Et_3N, THF–DMA (2:1), 0–23 °C; (h) NaN_3, DMSO, 80 °C, 12 h; (i) NaOH, THF–MeOH, 70 °C, 3 h, 58% over 3 steps; (j) $ArNH_2$, HATU, HOAt, *i*-Pr_2NEt, DMF, 50 °C, 2 day, 85%; (k) H_2, 10% Pd–C, DMA–MeOH, 2 h, 65%; (l) NaOH, THF–MeOH, 70 °C, 2 h, 96%; (m) 2-aminothiazole, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 14 h, 58%; (n) MsCl, Et_3N, THF–DMA (2:1), 0–23 °C, 2 h, 85%; (o) $MeNH_2$ or Me_2NH, DMSO, 100 °C, 75%.



Scheme 2. Reagents and conditions: (a) **13**, K_2CO_3, DMF, 100 °C, 36 h, 90%; (b) 3 N HCl (2 equiv), THF, 50 °C, 1 h, 81%; (c) MsCl, Et_3N, THF–DME, 0 °C, 1 h, 98%; (d) NaN_3, DMSO, 90 °C, 14 h; (e) Me_3P, THF–H_2O (5:1), 45% over the 3 steps; (f) Boc_2O, Et_3N, 14 h, 100%; (g) NaOH, THF–MeOH, 70 °C, 2 h, 98%; (h) 2-aminothiazole, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 14 h, 62%; (i) TFA, CH_2Cl_2, 16 h, 92%.



Scheme 3. Reagents and conditions: (a) $SOCl_2$, pyridine, CH_2Cl_2, 0–23 °C, 14 h, 98%; (b) $RuCl_3$ (0.1 mol %), $NaIO_4$, EtOAc–H_2O, 0–23 °C, 3 h, 92%; (c) NaH, **18**, DMF, 0–23 °C, 14 h; (d) TFA, CH_2Cl_2, 14 h; (e) K_2CO_3, EtOH, 80 °C, 2 h, 99% over 3 steps; (f) NaOH, THF–MeOH, 70 °C, 2 h, 95%; (g) 2-aminothiazole, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 14 h, 94%; (h) 30% HBr in HOAc, 23 °C, 1.5 h; (i) K_2CO_3, MeOH–DMA, 23 °C, 1 h, 88% over 2 steps; (j) MsCl, Et_3N, THF–DMA (2:1), 0–23 °C, 5 h, 64%; (k) RNH_2, DMSO, 100 °C, 25–44%.

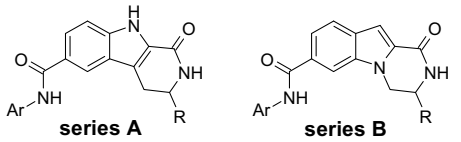
In general, the aminomethyl group consistently improves the MK2 potency for both series [**3a** vs **1**, and (*R*)-**4a** vs **2**], with a more substantial effect observed in the tetrahydro-β-carbolinone series (**3**). Our modeling predicted that the (*R*)-enantiomers would be more likely to engage either Asn191 or Asp207 than the (*S*)-enantiomers (Fig. 2). The SAR results are consistent with that prediction [(*R*)-**4a** vs (*S*)-**4a**, (*R*)-**4b** vs (*S*)-**4b**]. The hydroxylmethyl group also improves the potency compared to the unsubstituted lactams, but not to the same extent as the amine in the tetrahydro-β-carbolinone series (**3a** vs **3c**, and **3b** vs **3d**). However, in the other series, the alcohol shows similar potency to the amine [(*R*)-**4b** vs **4c**], indicating subtle differences in the SAR between the two series (vide infra). Methyl group[15] itself does not improve the potency (**4d** vs **2**, and **4e** vs **22**) conforming that a polar group (NH_2, OH) is responsible for the potency gains. Mono-methylation of the amino group is tolerated (**3e** and **4f**) while disubstitution or substituents larger than a methyl are detrimental to potency (**3f**, **4g**–**j**). In addition, acylation of the amino group results in a loss of the potency (**4k**) (Table 1).

We next examined the effect of increasing the size of the lactam by one carbon hypothesizing that this may affect the position of the amine group and perhaps provide an improved binding interaction with either Asp207 or Asn191. Due to synthetic feasibility, the effect of lactam ring size was examined in the dihydropyrazino[1,2-*a*]indolone core. This effect was firstly explored on the unsubstituted lactams. The 7-membered lactams **23a** and **23b** (tetrahydro-[1,4]diazepino[1,2-*a*]indolones)[17] were synthesized from **12** by alkylation with acrylonitrile, reduction with $CoCl_2/NaBH_4$,[18] lactamization, ester hydrolysis, and amide coupling (Scheme 4). Unexpectedly, the 7-membered lactam improved potency over the 6-membered lactam by 4-fold (Table 2, **23a** vs **2**, and **23b** vs **22**).

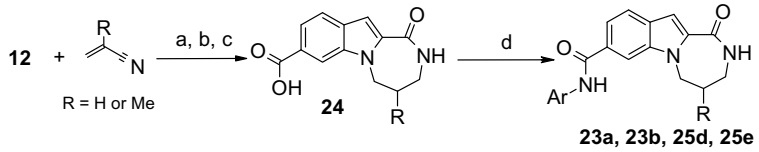
Combining this result with the addition of the aminomethyl group further improved potency by 5- to 10-fold for this series (Table 2, **25a** vs **23a**, and **25b** vs **23b**). The alcohol analogue **25c** showed similar potency to the corresponding amine **25b**, which is consistent with the SAR of 6-membered lactams of this series (vide sufra). As before, we found that a methyl group does not have much effect on the potency (**23a** vs **25d**, and **23b** vs **25e**). Substitutions on the amine decrease the potency significantly (**25f**–**h**). The acetamide **25i** is much less potent as well.

The syntheses of these compounds are summarized in Scheme 5. The primary amines **25a**,**b** were synthesized by the same method described for compound **4a**,**b**, using

Table 1. MK2 inhibition activity results for 6-membered lactams

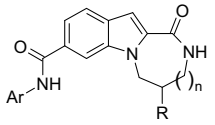


Entry	Compound	Series	Ar	R	MK2 inhibition, IC_{50} (nM)[16]
1	**1**	A	3-Pyridyl	H	2600
2	**3a**	A	3-Pyridyl	CH_2NH_2	260
3	**3c**	A	3-Pyridyl	CH_2OH	1200
4	**3b**	A	2-Thiazolyl	CH_2NH_2	140
5	**3d**	A	2-Thiazolyl	CH_2OH	1000
6	**3e**	A	2-Thiazolyl	CH_2NHMe	210
7	**3f**	A	2-Thiazolyl	CH_2NMe_2	>10,000
8	**2**	B	3-Pyridyl	H	1700
10	(*R*)-**4a**	B	3-Pyridyl	*R*-CH_2NH_2	320
11	(*S*)-**4a**	B	3-Pyridyl	*S*-CH_2NH_2	2300
12	**4d**	B	3-Pyridyl	CH_3	1200
13	**22**	B	2-Thiazolyl	H	1100
14	(*R*)-**4b**	B	2-Thiazolyl	*R*-CH_2NH_2	160
15	(*S*)-**4b**	B	2-Thiazolyl	*S*-CH_2NH_2	1400
16	**4c**	B	2-Thiazolyl	CH_2OH	550
17	**4e**	B	2-Thiazolyl	CH_3	4000
18	**4f**	B	2-Thiazolyl	CH_2NHMe	580
19	**4g**	B	2-Thiazolyl	CH_2NHEt	3000
20	**4h**	B	2-Thiazolyl	CH_2NHPr	4000
21	**4i**	B	2-Thiazolyl	CH_2NH*i*-Pr	>10,000
22	**4j**	B	2-Thiazolyl	CH_2NMe_2	>10,000
23	**4k**	B	2-Thiazolyl	CH_2NHAc	6900

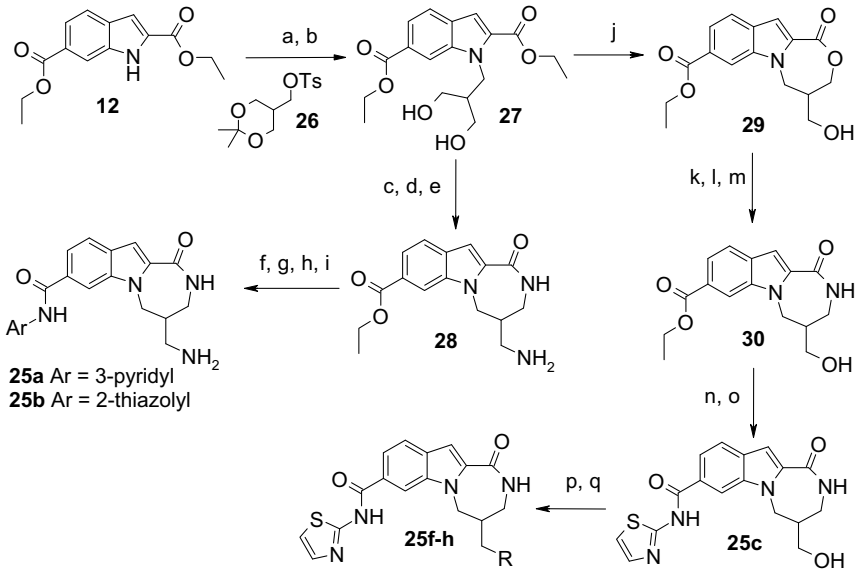


Scheme 4. Reagents and conditions: (a) $BnMe_3NOH$ (40% in MeOH), dioxane, 23 °C, 18 h; (b) $CoCl_2$, $NaBH_4$, THF–MeOH, 0 → 23 °C, 2 h, then 70 °C, 14 h; (c) NaOH, THF–MeOH, 70 °C, 2 h, 54–70% over 3 steps; (d) $ArNH_2$, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 14 h, 23–70%.

Table 2. MK2 inhibition activity results for 7-membered lactams



Entry	Compound	Ar	*n*	R	MK2 inhibition, IC_{50}[16] (nM)
1	**2**	3-Pyridyl	0	H	1700
2	**23a**	3-Pyridyl	1	H	270
3	**22**	2-Thiazolyl	0	H	1100
4	**23b**	2-Thiazolyl	1	H	190
5	**25a**	3-Pyridyl	1	CH_2NH_2	29
6	**25d**	3-Pyridyl	1	CH_3	320
7	**25b**	2-Thiazolyl	1	CH_2NH_2	35
8	**25c**	2-Thiazolyl	1	CH_2OH	52
9	**25e**	2-Thiazolyl	1	CH_3	530
10	**25f**	2-Thiazolyl	1	CH_2NHMe	690
11	**25g**	2-Thiazolyl	1	CH_2NHEt	560
12	**25h**	2-Thiazolyl	1	CH_2NMe_2	310
13	**25i**	2-Thiazolyl	1	CH_2NHAc	1200



Scheme 5. Reagents and conditions: (a) **26**, K_2CO_3, DMF, 100 °C, 20 h; (b) 3 N HCl (2 equiv), THF–H_2O, 1 h, 75% over 2 steps; (c) MsCl, Et_3N, CH_2Cl_2, 23 °C, 2 h; (d) NaN_3, DMSO, 90 °C, 16 h; (e) Me_3P, THF–H_2O, 23 °C, 4 h, then added toluene, 100 °C, 14 h, 72% over 3 steps; (f) Boc_2O, Et_3N, 3 h, 100%; (g) NaOH, THF–MeOH, 70 °C, 2 h, 95%; (h) $ArNH_2$, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 14 h, 67–91%; (i) TFA, CH_2Cl_2, 14 h, 88–96%; (j) TsOH, toluene, reflux, 32%; (k) MsCl, Et_3N, CH_2Cl_2, 23 °C, 2 h, 98%; (l) NaN_3, DMSO, 90 °C, 14 h, 94%; (m) Me_3P, THF–H_2O, 23 °C, 4 h, then, 100 °C, 14 h, 79%; (n) NaOH, THF–MeOH, 70 °C, 2 h, 75%; (o) 2-aminothiazole, EDC, HOBt, *i*-Pr_2NEt, DMAP, DMF, 50 °C, 15 h, 36%; (p) MsCl, Et_3N, THF–DMA (2:1), 0–23 °C, 5 h; (q) RNH_2, DMSO, 100 °C, 34–44% over 2 steps.

alkylating reagent **26**.[19] For the synthesis of methylamine **25d**, the two symmetric hydroxyl groups of **27** were differentiated by lactonization and the remaining hydroxyl group was then converted to the azide by mesylation and azide displacement. Reduction of the azide and in situ lactamization (lactone-lactam exchange) upon heating yielded **30**. Ester hydrolysis and amide coupling gave **25c**, which was converted to **25f–h** by mesylation and amine displacement.

In summary, we developed chemistry to access polar substitutions on the lactam portion of two series of indole-based MK2 inhibitors. In doing so, we have been able to improve the potency of both series through either introduction of an aminomethyl group or lactam expansion to a 7-membered ring. Furthermore, combining both of these features provides potent MK2 inhibitors suitable for further evaluation.[20]

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12. The e.e.s are >95% as determined on OD-H column under chromatographic conditions: 25% (EtOH:MeOH:DEA, 1:1:0.1)/hexanes, 1 ml/min, 310 nm.
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16. MK2 IC_{50} values were determined by the same method described in Ref. 4a.
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20. Some of the compounds (e.g., **25a**, **b**, **c**) were tested for cellular efficacy in an assay measuring the inhibition of LPS-induced TNFα production from THP-1 cell. All of them show $EC_{50} > 10\ \mu M$. As discussed in our previous paper,[4b] this is probably due to the poor membrane permeability of these compounds as indicated by low permeability (e.g., $0.1 \times 10^{-6}\ cm\ s^{-1}$ for **25a** and $0.6 \times 10^{-6}\ cm\ s^{-1}$ for **25b**) in the parallel artificial membrane permeability assay (PAMPA).