Aza-Analogue Dibenzepinone Scaffolds as p38 Mitogen-Activated Protein Kinase Inhibitors: Design, Synthesis, and Biological Data of Inhibitors with Improved Physicochemical Properties

Solveigh C. Karcher and Stefan A. Laufer*

Institute of Pharmacy, Department of Pharmaceutical and Medicinal Chemistry, Eberhard-Karls-Universität, Auf der Morgenstelle 8, 72076 Tübingen, Germany

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We recently described a promising novel class of p38 mitogen activated protein (MAP) kinase inhibitors with dibenzepinone-scaffolds. To optimize their physicochemical properties, characterized by calculated log P values and measured lipophilicity (chromatographic hydrophobicity index = CHI), we synthesized aza-analogue dibenzepinones. Here, we present the synthesis and biological data of compounds with the novel aza-dibenzepinone scaffolds. Although these aza-analogues revealed an improved aqueous solubility, introduction of nitrogen was not effective in the p38 MAPK enzyme assay.

Introduction

The p38 mitogen activated protein (MAP[a]) kinase is a key enzyme in inflammatory diseases because it plays a role in the biosynthesis of the pro-inflammatory cytokines TNF-α (tumor necrosis factor-α) and IL-1β (interleukin-1β). Thus, p38 is a promising target for the treatment of chronic inflammatory diseases such as rheumatoid arthritis. The substrate binding site in all protein kinases is highly conserved, which compromises the selectivity for p38 versus other kinases. In fact, a lot of p38 inhibitors in clinical trials are affected by poor selectivity. Moreover, the well-established pyridinyl-imidazole inhibitors of p38 have shown liver toxicity in animal studies. Imidazol ring-containing drugs such as ketoconazole, itraconazole, and clotrimazole are known to be potent cytochrome P450 (CYP) 3A inhibitors.[1,2] Therefore, inhibition of the CYP enzymes may contribute to potential toxicity associated with drug−drug interactions.[3] N-1 substituted pydridinyl-imidazoles lacking the lone pair electrons chelating the ferric heme in CYP enzymes resulted in lower inhibition of CYP450 enzymes,[4] thus indicating that the imidazole ring may contribute to the toxicity. Hence there is still a continuous need for structurally novel inhibitors that overcome the intrinsic problems of the common diaryl-substituted heterocyclic compounds. Previously, we described a novel class of p38 inhibitors with structurally rigid dibenzepinone scaffolds[5] lacking the toxic imidazole ring system (Figure 1). CYP interaction of these dibenzepinones was clearly reduced compared to the pyridinyl-imidazole reference **32** (SB203580), (Figure 1).[6] Although substituted dibenzepinones showed high potency in p38 enzyme assays, they are highly lipophilic and poorly soluble in aqueous media and may therefore suffer from low bioavailability. In the present report, our strategy was to improve the aqueous solubility of the lead compounds by using more hydrophilic scaffolds. We supposed that the desired physicochemical properties could be achieved by the synthesis of aza-analogues of the dibenzepinones (Figure 1). Because the introduction of nitrogen in ring B (see Figure 1) of the benzophenone series[7] reduced potency of the inhibitors, our initial focus was to introduce the nitrogen in ring A (see Figure 1).

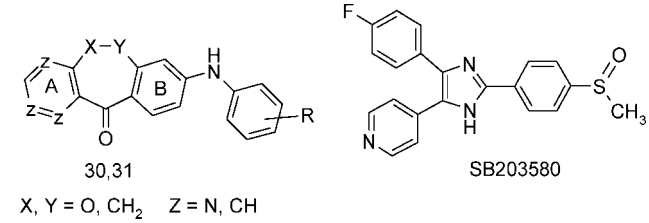
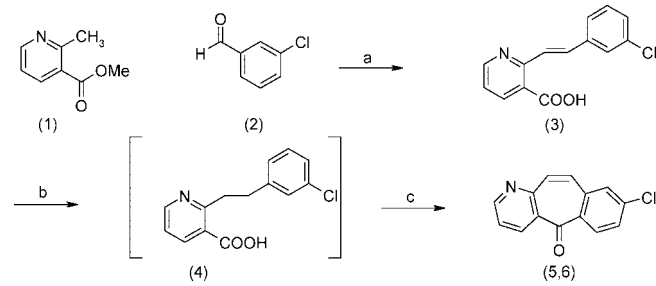


Figure 1. p38 MAP kinase inhibitors with rigid dibenzepinone scaffolds (**30**), novel aza-dibenzepinone scaffolds (**31**) as p38 MAP kinase inhibitors, pyridinyl-imidazole prototype inhibitor SB203580 (**32**).

Scheme 1. Preparation of 8-Chloro-benzo[4,5]cyclohepta-[1,2-*b*]pyridine-5-one (**5**) and 8-Chloro-10,11-dihydro-benzo[4,5]-cyclohepta[1,2-*b*]pyridine-5-one (**6**)[a]



[a] Conditions: (a) NaOMe (sodium methylate), 25%; (b) Pd/$BaSO_4$, 10%, H_2, HCl, 10%, MeOH; (c) PPA.

Chemistry

Synthesis of 8-phenylamino substituted benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ones, 10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ones, benzo[5,6]cyclohepta-[1,2-*c*]pyridin-11-ones, 5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ones, and 11*H*-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-5-ones required new synthetic strategies since only synthesis for unsubstituted aza-dibenzepinones has been described. Therefore, we synthesized a series of 8-chloro-substituted scaffolds that provided the desired target compounds for use in the subsequent Buchwald−Hartwig reaction. The 8-chloro-benzo[4,5]cyclohepta[1,2-*b*]py-

* To whom correspondence should be addressed. Phone: +49-7071-2972459. Fax: +49-7071-295037. E-mail: stefan.laufer@uni-tuebingen.de.

[a] Abbreviations: p38, MAP kinase; p38, mitogen activated protein kinase; CHI, chromatographic hydrophobicity index; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; CYP, cytochrome P450; Pd/C, palladium on carbon; PPA, polyphosphoric acid; MeOH, methanol; RP-HPLC, reversed phase high pressure liquid chromatography; ATF-2, activation transcription factor 2; NaOMe, sodium methylate; LDA, lithium diisopropylamide.

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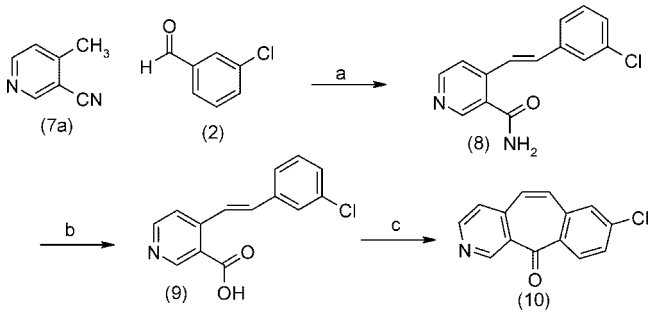
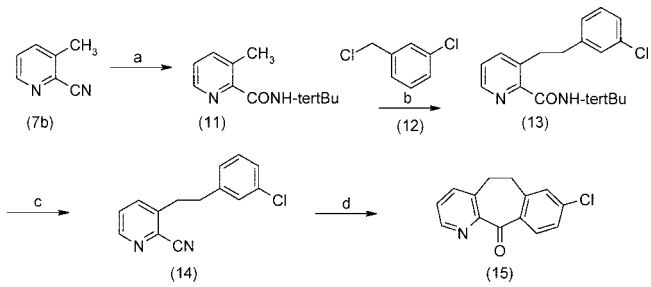
Scheme 2. Preparation of 8-Chloro-benzo[5,6]cyclohepta[1,2-*c*] pyridine-11-one (**10**)[a]



[a] Conditions: (a) NaOMe, 25%; (b) KOH, H_2O, MeOH; (c) PPA.

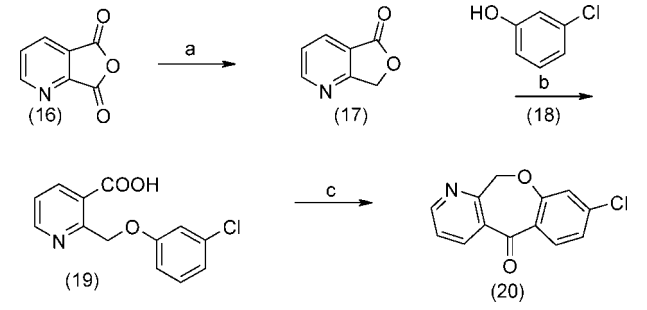
Scheme 3. Preparation of 8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-one (**15**)[a]



[a] Conditions: (a) H_2SO_4, conc, *tert*-BuOH; (b) LDA (lithium diisopropylamide), THF; (c) $POCl_3$ toluene; (d) PPA.

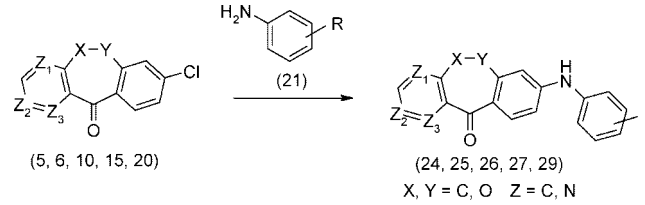
ridin-5-one (**5**) and 8-chloro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (**6**) scaffolds were obtained by a modified synthesis according to Brenner et al.[8] (Scheme 1). Treatment of the 2-methyl nicotinic acid methyl ester with 3-chlorobenzaldehyde under strongly basic conditions generated the *trans*-nicotinic acid analogue (**3**). Reduction of the etheno-linker with H_2 and Pd/C produced the corresponding saturated acid (**4**), which was cyclized by a brief treatment with 200 °C hot polyphosphoric acid (PPA). The 8-chloro-benzo[5,6]cyclohepta-[1,2-*c*]pyridin-11-one (**10**) was synthesized by a modified synthetic pathway according to Villani et al.[9] (Scheme 2). 4-Methylnicotinonitrile was condensed with 3-chlorobenzaldehyde in the presence of sodium methoxide in methanol to give the *trans*-nicotinamide (**8**) in high yield. Saponification of the ester with sodium hydroxide in methanol provided the corresponding acid. Subsequent ring closure with 200 °C hot PPA yielded **10**. Synthesis of the 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**15**) was performed according to Schuhmacher et al.[10] and Piwinski et al.[11] (Scheme 3). As direct alkylation of the 3-methyl-2-cyanopyridine gives low yields, the nitrile must be protected as a *tert*-butylamide formed via Ritter reaction.[12] The dianion of this amide was readily formed with *n*-butyllithium at −70 °C and then alkylated with 3-chlorobenzyl chloride to give the 3-(3-chlorophenethyl)pyridine-2-carbonic *tert*-butylamide (**13**). Compound **13** was converted to the nitrile (**14**) with phosphorus oxychloride. Subsequent ring closure with hot 200 °C PPA yielded ketone **15**. Scheme 4 outlines a synthetic strategy for the assembly of the 8-chloro-11*H*-10-oxa-1-aza-dibenzo[*a*,*d*]cyclohepten-5-one (**20**).[13] Treatment of chinolinic acid anhydride with sodium boron hydride in tetrahydrofurane in the presence of acetic acid resulted in 2-hydroxymethyl-3-pyridinecarbonic acid, which was lactonized by acetic anhydride. Base-catalyzed reaction of the phthalide with 3-chlorophenol afforded the corresponding acid

Scheme 4. Preparation of 8-Chloro-11*H*-10-oxa-1-aza-dibenzo [*a*,*d*]cyclohepten-5-one (**20**)[a]



[a] Conditions: (a) $NaBH_4$, acetic acid, THF; (b) NaOMe, 25%; (c) PPA.

Scheme 5. Nucleophilic Substitution of the Ketones with Respective Residues[a]



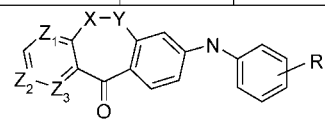
[a] Conditions: $Pd(OAc)_2$, 2-(dicyclohexylphosphino)-2′-, 4′-, 6′-triisopropyl-biphenyl, KO*tert*-Bu, toluene, *tert*-BuOH.

(**19**). Subsequent cyclization of **19** with PPA afforded the corresponding ketone **20**. Buchwald−Hartwig coupling reaction[14] of the ketones with the respective residues yielded the target compounds (Scheme 5). Nitro compounds were reduced to the corresponding amines using tin(II) chloride-dihydrate.

Results and Discussion

Several approaches have been investigated to predict oral bioavailability.[15] A key part of oral bioavailability is absorption that is largely dependent on lipophilicity, hydrogen bonding, and size. To verify the Lipinski "rule of 5", a commonly used model to forecast bioavailability, log P values were calculated and lipophilicity, expressed by the chromatographic hydrophobicity index (CHI (MeOH)) values, was measured by fast-gradient reversed-phase RP-HPLC.[16] As the stationary phase of a RP column is representing the octanol layer and the mobile phase the water layer, an organic modifier with properties similar to water should be used. Among the commonly used organic modifiers, methanol is the most "water-like" solvent in providing both strong hydrogen-bond donor and strong hydrogen-bond acceptor abilities so that the addition of methanol to an aqueous mobile phase will change the ordering of water molecules to a limited extend over a wide range of volume fractions.[17] Therefore, measuring CHI values with MeOH (methanol) as organic layer is a commonly used method.[18,19] The CHI value for a compound approximates to the percentage (by volume) of methanol required to achieve an equal distribution of a compound between the mobile and stationary phases and is calculated from the retention times (t_r) of the test compounds in a fast gradient reversed-phase HPLC (RP-HPLC) method. As control, we chose a structurally unrelated set of compounds and found a good correlation to the calculated log P values. Calculated log P values of the dibenzoheptenone scaffolds ranged from 4.7 ± 0.4 to 6.1 ± 0.5, and those of the dibenzoxepine scaffold from 3.9 ± 0.4 to 5.3 ± 0.4. For the substituted aza-analogue dibenzepinones, calculated log P values ranged from 3.7 ± 0.4 to 5.0 ± 0.5 for the aza-dibenzheptenone

Table 1. Inhibitory Activity of Target Compounds in p38 MAP Kinase Enzyme Assay, Calculated log P Values, Measured CHI(MeOH) Values, and Aqueous Solubility

#	Z_1, Z_2, Z_3	X-Y	R	p38α[a] IC_{50}±SEM (μM) (n=3)	clogP[b]	CHI (MeOH)[c] (%)	aqueous solubility (μg/ml) pH = 1 (HCl/H_2O)
							
22a	CH, CH, CH	$-CH_2-CH_2-$	2-NH_2	0.10±0.02	4.7±0.4	82.6	<10
22b	CH, CH, CH	$-CH_2-CH_2-$	2-NH_2, 4-F	0.13±0.09	5.5±0.5	82.8	n.t.
22c	CH, CH, CH	$-CH_2-CH_2-$	2, 4-F	0.13±0.02	6.1±0.5	88.1	<10
23a	CH, CH, CH	-CH=CH-	2-NH_2	1.06±0.07	4.8±0.4	n.t.	n.t.
23b	CH, CH, CH	-CH=CH-	2, 4-F	2.53±0.56	6.1±0.5	88.7	n.t.
24a	N, CH, CH	-CH=CH-	2-NH_2	1.08±0.23	3.7±0.4	73.4	n.t.
24b	N, CH, CH	-CH=CH-	2, 4-F	0.33±0.05	5.1±0.6	82.9	n.t.
25a	N, CH, CH	$-CH_2-CH_2-$	2-NH_2	0.31±0.09	3.6±0.4	73.9	486
25b	N, CH, CH	$-CH_2-CH_2-$	2-NH_2, 4-F	1.19±0.57	4.5±0.5	72.9	n.t.
25c	N, CH, CH	$-CH_2-CH_2-$	2, 4-F	0.24±0.06	5.0±0.5	81.2	1200
26	CH, N, CH	-CH=CH-	2-NH_2	1.95±0.71	3.7±0.4	71.4	n.t.
27	CH, CH, N	$-CH_2-CH_2-$	2-NH_2	0.44±0.12	3.7±0.4	65.8	n.t.
28a	CH, CH, CH	$-CH_2-O-$	2-NH_2	0.30±0.07	3.9±0.4	75.2	n.t.
28b	CH, CH, CH	$-CH_2-O-$	2-NH_2, 4-F	0.04±0.02	4.8±0.5	n.t.	n.t.
28c	CH, CH, CH	$-CH_2-O-$	2, 4-F	0.24±0.04	5.3±0.6	n.t.	n.t.
29a	N, CH, CH	$-CH_2-O-$	2-NH_2	2.68±0.27	2.9±0.4	67.4	n.t.
29b	N, CH, CH	$-CH_2-O-$	2-NH_2, 4-F	2.73±0.43	3.7±0.5	70.9	n.t.
29c	N, CH, CH	$-CH_2-O-$	2, 4-F	0.18±0.01	4.2±0.6	83.2	n.t.
32[d]	-	-	-	0.05±0.02	-	n.t.	n.t.

[a] p38 MAP kinase activity was assessed based on the rate of phosphorylation of ATF-2 (activation transcription factor 2) in an in vitro assay as described in the given reference. [b] log P calculated using ACD software. [c] CHI (MeOH) = chromatographic hydrophobicity index, measured by fast-gradient RP-HPLC. The CHI value for a compound approximates to the percentage (by volume) of methanol required to achieve an equal distribution of a compound between the mobile and stationary phases. [d] Prototype pyridinyl-imidazole inhibitor (see Figure 1); n.t. = not tested.

scaffold and 2.9 ± 0.4 to 4.2 ± 0.6 for the aza-dibenzoxepinone scaffold (Table 1). CHI (MeOH) values showed good correlation to the calculated octanol/water partition coefficients (Table 1). The aza-dibenzoheptenone series revealed lower lipophilicity, with CHI(MeOH) values ranging from 66% to 81% compared to the corresponding carbon analogues, whose CHI(MeOH) values ranged from 82% to 88%. Comparing aza-dibenzoxepinone **29a** (CHI = 69%) to the corresponding carbon-analogue **28a** (CHI = 75%) reveals that the aza-dibenzoxepinone-series also possess CHI(MeOH) values lower than their carbon analogues. Furthermore, aqueous solubility was tested of four compounds (**22a**, **22c**, **25a**, **25c**, Table 1). While the aza-analogues showed an aqueous solubility of 486 μg/mL (**25c**) to 1200 μg/mL (**25a**), the corresponding carbon analogues **22a** and **22c** were insoluble in water with aqueous solubility below 10 μg/mL. Altogether, the aza-analogues fulfilled the Lipinski "rule

of 5" in contrast to most of the target compounds of the carbon analogue series, suggesting improved bioavailability for aza-dibenzoheptenones. The anti-inflammatory activity of the tested compounds was determined in vitro by measuring the inhibitory effect of p38 MAPK in a cell-free enzyme assay.[20] Our earlier work indicated that the three most potent phenylamino-substituents of the dibenzepinone-series were the 2-aminophenylamino (**22a**, **23a**, **28a**), the 2-amino-4-fluorophenylamino (**22b**, **28b**), and the 2,4-difluorophenylamino (**22c**, **23b**, **28c**) residues, and we introduced these same functionalities into the aza-analogues. On the basis of the inhibition of the p38 enzyme as assessed by the immunosorbent assay (Table 1), the potency of the substituted dibenzepinones (IC_{50} = 40−1020 nM) was equal compared to the reference compound **32** (50 nM). The aza-dihydro-dibenzoheptenones (**25a**, **25b**, **25c**, **27**) were less potent, and the IC_{50} values were elevated by 3- to 8-fold as compared to the corresponding carbon analogues (**22a**, **22b**, **22c**). Variation of the nitrogen position in ring A had no effect on the IC_{50} values of the target compounds. The activity of the aza-dibenzoheptenone series (**24a**, **24b**, **26**) was slightly superior to the dibenzoheptenones (**23a**, **23b**). However, compounds of the unsaturated dibenzoheptenone series (**23a**, **23b**) were generally less potent than those of the dibenzoheptanone series (**22a**−**c**) and dibenzoxepinone series (**28a**−**c**). The IC_{50} values of the aza-analogues of the oxepine series (**29a**−**c**) range from 0.2 μM (2,4-difluorphenylamino derivative) to 2.8 μM (2-amino-4-fluor-phenylamino derivative) in the p38 enzyme assay and are therefore markedly less potent than the corresponding dibenzoxepinones (**28a**−**c**). Taken together, our results indicated that despite improved solubility of the aza-analogues, as based on the log P, CHI(MeOH) values, and measured aqueous solubility, these compounds are less potent inhibitors of p38 MAP kinase. Introduction of nitrogen into the dibenzepinone scaffold had a negative effect on the potency of the aza-analogues class of potential p38 inhibitors that is directly related to their structure. The nitrogen in ring A clearly reduced potency of the compounds in inhibiting p38 MAP kinase, and this effect could be attributed to decreased hydrophobic interaction in the binding pocket dependent upon changes in the electronic properties of ring A. In summary, we have synthesized aza-analogues with improved aqueous solubility. Although aza-analogues dibenzepinones were less potent in inhibiting the p38 in the enzyme assay compared to the pyridinyl-imidazoles, they may be better tolerated at higher doses in vivo.

Experimental Section

8-(2-Amino-phenylamino)-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (24a). A mixture of 0.44 g (1.8 mmol) of **5**, 1.0 g (9.2 mmol) of 1,2-phenylendiamine, 0.05 g of (0.22 mmol) $Pd(OAc)_2$, 0.10 g of (0.21 mmol) 2-(dicyclohexylphosphino)-2′-, 4′-, 6′-triisopropyl-biphenyl, 1.40 g of (12.4 mmol) KO*tert*-Bu, 5 mL of toluene, and 1 mL of *tert*-BuOH was heated at 90 °C under argon. After stirring at this temperature for 6 h, the reaction mixture was poured into water and extracted with 3 × 200 mL ethyl acetate. The residue was purified by flash chromatography (SiO_2, dichloromethane/ethanol, 95 /5). Yield 0.04 g (7%).

Compounds **24b**, **25a**, **25c**, **26**, **27**, **29a**, and **29c** were prepared in a manner similar to **24a**.

8-(2-Amino-4-fluoro-phenylamino)-10,11-dihydro-benzo[4,5]-cyclohepta[1,2-*b*]pyridin-5-one (25b). Compound **6** (44 g, 1.8 mmol), 0.3 g (1.9 mmol) of 2-nitro-4-fluoroaniline, 0.05 g (0.22 mmol) of $Pd(OAc)_2$, 0.10 g (0.21 mmol) of 2-(dicyclohexylphosphino)-2′-, 4′-, 6′-triisopropyl-biphenyl, 0.70 g (6.2 mmol) of KO*tert*-Bu, 5 mL of toluene, and 1 mL of *tert*-BuOH were used as starting materials. The crude product was recrystallized from methanol and was used in the next step without further purification. Then 0.5 g of the nitro compound was dissolved in 4 mL of EtOH, and 2.9 g of $ZnCl_2 \cdot 2H_2O$ was added and stirred for 2 h at 70 °C. After cooling to room temperature, 20 mL of ice−water was added and alkalinized with NaOH (20%). The aqueous phase was extracted with EtOAc, the organic layer was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 60, DCM/MeOH, 95/5). Yield, 0.14 g (23%).

Compound **29b** was prepared in a manner similar to **25b**.

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Supporting Information Available: General synthetic procedures, spectral and analytical data, HPLC purity and HRMS data of test compounds, and lipophilicity measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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