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A novel Pd-catalyzed cyclization reaction of ureas for the synthesis of dihydroquinazolinone p38 kinase inhibitors

Achim Schlapbach,* Richard Heng and Franco Di Padova

Novartis Institute for Biomedical Research, Arthritis and Bone Metabolism, Lichtstrasse, CH-4002 Basel, Switzerland

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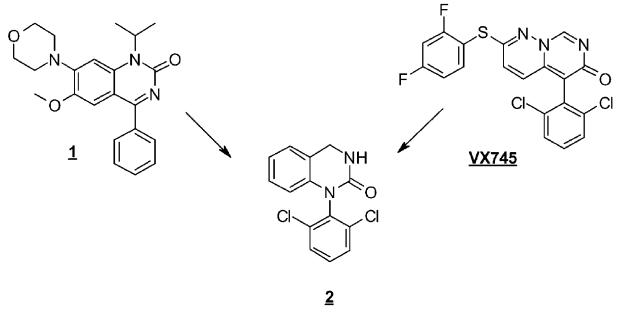
Abstract—A series of potent p38 inhibitors based on the dihydroquinazoline scaffold was synthesized using a novel Pd-catalyzed cyclization reaction of aryl-benzyl ureas. Optimization of this compound class led to compound **20**, which inhibits p38α in vitro with $IC_{50} = 14$ nM and is active in the mouse TNFα-release model.

1. Introduction

In recent years enormous interest has been generated in the evaluation of inhibitors of p38 MAP kinase as anti-inflammatory drugs.[1] It is well established that inhibition of p38 blocks release of IL-1, TNFα, IL-6 and other cytokines from monocytes.[2] As these cytokines are recognized as key players in the development and progression of inflammatory conditions like RA, an orally bioavailable small molecule p38 inhibitor would be highly desirable.

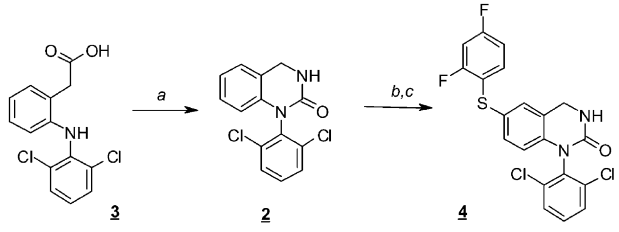
2. Results and discussion

While the prototypic p38 inhibitor SB203580,[3] a pyridyl-imidazole served as lead in our initial drug design efforts,[4] we performed a high throughput screen to identify structurally novel p38 inhibitors. One of the hits identified was the quinazolinone **1**, which inhibited p38 with an IC_{50} of 14 μM. At the same time a vaguely related structure VX475 was published by Vertex.[5] We recognized some similarities of these two novel templates and speculated that they could adopt similar binding modes. Variations of the initial hit structure based on this hypothesis led to the dihydroquinazolinone template, exemplified by the prototype compound **2**. Herein, we now wish to report on the synthesis as well as the SAR of this novel series of p38 inhibitors (Scheme 1).[8]



Scheme 1.

Synthesis of the dihydroquinazolinones started with α-arylamino phenylacetic acids, the most prominent example being diclofenac **3** (Scheme 2). Curtius degradation using DPPA[6] led directly to the formation of the desired core structure **2** via intramolecular ring closure of the intermediate isocyanate. The 6-position could now easily be further functionalized. Bromination of the dihydroquinazolinone **2** followed by Pd-catalyzed coupling with 2,4-difluoro-thiophenol gave diaryl sulfide **4**.



Scheme 2. (a) Diphenylphosphoryl azide, NEt_3, dimethoxyethane, reflux, 2 h, 63%; (b) Br_2, CH_2Cl_2, rt, 12 h, 35%; (c) 2,4-difluoro-thiophenol, $Pd(PPh_3)_4$, NaOtBu, toluene, reflux, 16 h, 10%.

* Corresponding author. Tel.: +41-61-324-4308; fax: +41-61-324-8847; e-mail: achim.schlapbach@pharma.novartis.com

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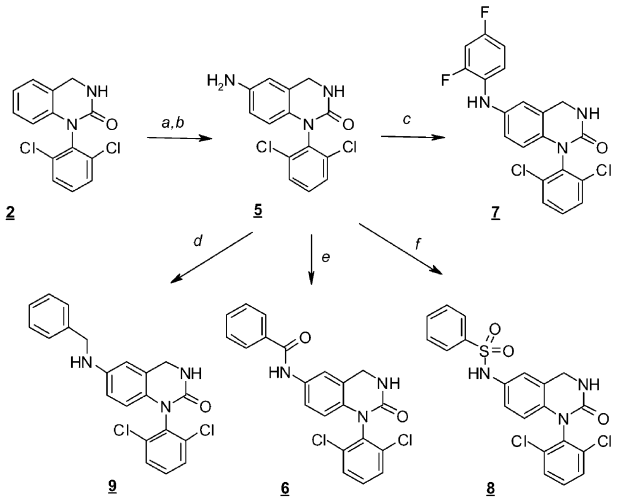
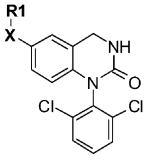
Nitration (Scheme 3), followed by reduction of the nitro group with H_2/Pd gave the 6-amino-dihydroquinazolinone **5**, which served as starting material for arylamines, benzylamines, carboxamides or sulfonamides.



Scheme 3. (a) KNO_3, H_2SO_4, 0 °C–rt, 18 h, 81%; (b) H_2, Pd/C, ethanol, rt, 16 h, 88%; (c) 2,4-difluoro-bromobenzene, Pd_2dba_3, DPEphos, NaOtBu, toluene, reflux 5 h, 10%; (d) benzaldehyde, $NaBH_3CN$, 3% AcOH in DMF, rt, 16 h, 31%; (e) benzoyl chloride, NEt_3, THF, rt, 3 h, 90%; (f) benzenesulfonyl-chloride, cat. DMAP, pyridine, rt, 16 h, 56%.

In Table 1, p38 inhibition data[9] as well as cellular activities, TNFα release from LPS stimulated hPBMCs[10] of these initial 6-substituted derivatives are given.

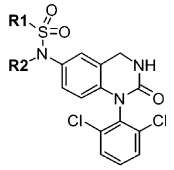
Table 1. SAR of the dihydroquinazolinone-6-substituent



	R1	X	p38α IC_{50} (μM)	TNFα-release IC_{50} (μM)
2	H	—	11.8	n.d.
6	Phenyl	CONH	8.5	10
4	2,4-Difluorophenyl	S	0.47	0.96
7	2,4-Difluorophenyl	N	0.38	0.29
8	Phenyl	SO_2NH	0.053	0.140
9	Phenyl	CH_2–N	0.150	1.20

As expected from our binding hypothesis, an aromatic substituent in the 6-position of the dihydroquinazolinone is crucial for potent inhibition of p38. Furthermore the linking unit has a great influence on potency as well. Thus, the benzamide **6** is only marginally more potent than the unsubstituted core structure. In contrast to our expectations, a 2,4-difluorophenyl thioether **4** as well as the corresponding diarylamine **7** improved potency only modestly and both were still rather weak p38 inhibitors. We were, however, pleased to see that a sulfonamide moiety improved potency significantly. Encouraged by this initial result the sulfonamide series was chosen for further optimization. SAR around the sulfonamide moiety is given in Table 2.

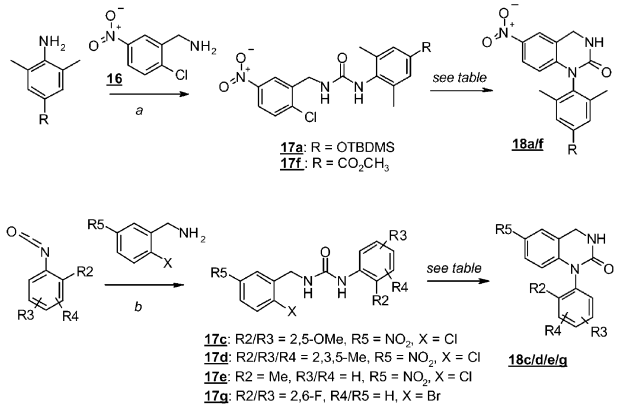
Table 2. SAR of sulfonamide derivatives



	R1	R2	p38α IC_{50} (μM)	TNFα-release IC_{50} (μM)
8	Phenyl	H	0.053	0.140
10	2-Chlorophenyl	H	0.180	0.510
11	2,5-Dichlorophenyl	H	0.100	0.390
12	2-Hydroxy-5-chlorophenyl	H	0.570	n.d.
13	4-Tolyl	H	1.80	> 10
14	3-Chloro-4-fluorophenyl	H	0.034	0.084
15	2,5-Dichlorophenyl	CH_3	0.780	1.20

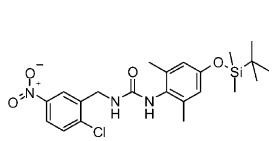
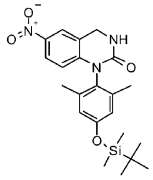
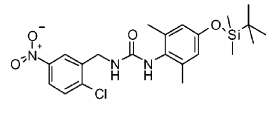
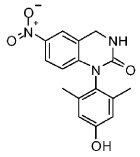
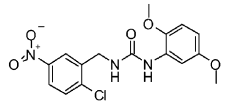
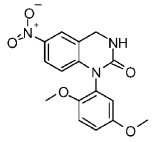
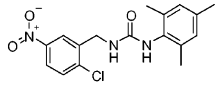
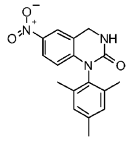
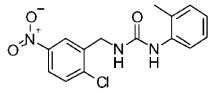
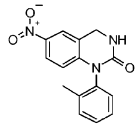
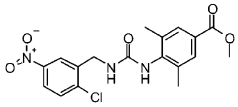
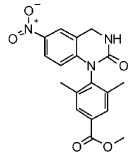
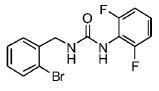
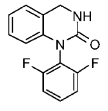
The unsubstituted benzene sulfonamide **8** is already a very potent inhibitor of p38. Substituents in *ortho* position reduce activity; the same is true for substitutions in *para* position. A lipophilic substituent in *meta* position, however, leads to an increase in potency. The optimal substitution pattern is present in the 3-chloro-4-fluorobenzene sulfonamide **14**. Interestingly, alkylation of either the sulfonamide nitrogen, or the dihydroquinazolinone nitrogen (data not shown) reduce activity dramatically.

Next, we turned our attention to the 1-aryl substituent of the dihydroquinazolinone core. It quickly became apparent that for compounds containing aryl residues which did not have two *ortho* substituents, a different synthesis strategy was necessary as in these cases the main product from the Curtius reaction protocol was simply the cyclic amide. Thus we explored the intramolecular cyclization reaction of phenyl-benzyl ureas to give the desired dihydroquinazolinone core structure. (Scheme 4).



Scheme 4. (a) Boc_2O, DMAP, CH_2Cl_2, rt–40 °C, 16 h, 59%; (b) CH_2Cl_2, rt, 16 h, 49–91%.

Table 3. Intramolecular cyclization of phenyl benzyl ureas

	Urea	Product	Yield (%)[a,b]
1			53[c]
2			92[d]
3			60[e]
4			88[e]
5			67[e]
6			89[d]
7			93[e]

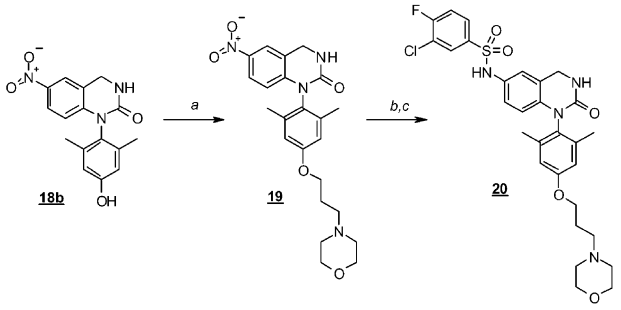
[a] All reactions were performed using 0.04 equiv Pd_2dba_3, 0.12 equiv 2-(dicyclohexyl-phosphino)biphenyl and 1.4 equiv K_3PO_4 at 100 °C for 16 h.
[b] Isolated yield.
[c] Reaction performed in 1,4-dioxane.
[d] Reaction performed in DMF.
[e] Reaction performed in DME.

N-Benzyl-*N*-phenyl ureas were obtained either by direct condensation of the benzylamine with phenyl isocyanates, or by treatment of the 4-substituted 2,6-dimethyl-phenylamine with Boc_2O, DMAP in dichloromethane[7] followed by the addition of 2-chloro-4-nitrobenzylamine **16**.

Even though Pd-catalyzed intramolecular cyclizations are well documented,[11] intramolecular cyclizations of unprotected ureas using Pd have not been reported so far.[12] In order to quickly access diverse dihydroquinazolinones the direct Pd-catalyzed cyclization route was investigated.

Monodentate ligands, for example P(*o*-tolyl)$_3$ or P(2-furyl)$_3$ have been reported for the intramolecular cyclization of secondary amides.[11b] Some of the most efficient ligands for the amination of aryl chlorides are bulky electron rich ones.[13] In our hands, for the cyclization of ureas, 2-(dicyclohexylphosphino)-biphenyl was found to be the ligand of choice. Employing K_3PO_4 as base and Pd_2dba_3 as the palladium source, aryl-benzyl ureas cyclized smoothly to the desired dihydroquinazolinones (Table 3). The reaction works using either activated aryl-chlorides (entries 1–6) or aryl bromides (entry 7). Good to excellent yields were obtained regardless of the substitution pattern of the aryl substituent. Suitable solvents were found to be dimethoxyethane, dioxane or DMF. In the case of the silyl-protected phenol **17a** cyclization and removal of the silyl group to give **18b** could be achieved in one step using DMF instead of dimethoxyethane (entry 2).[14]

Further elaboration of compound **18b** via alkylation of the phenolic hydroxy group, nitro reduction and finally acylation using 3-chloro-4-fluoro-benzene-sulfonyl chloride led to compound **20** (Scheme 5).



Scheme 5. (a) Chloropropyl-morpholine, cat. CsI, DMF, 130 °C, 16 h, 49%; (b) H_2, Pd/C, MeOH, rt, 16 h, 98%; (c) 3-chloro-4-fluoro benzenesulfonylchloride, pyridine, DMAP, CH_2Cl_2, rt, 16 h, 27%.

Compound **20** now has a much more favorable polarity profile, while still being highly potent (14 nM) on p38. **20** was profiled in an acute in vivo model and showed a 42% inhibition of TNFα release after LPS stimulation in mice at a dose of 30 mg/kg, po.[15] The compound is highly selective over a series of other kinases and does not interfere with Cyp450 enzymes.

3. Summary

In summary, we herein described a novel, very efficient Pd-catalyzed cyclization sequence leading to potent and selective p38 inhibitors based on a dihydroquinazolinone scaffold which could be used as a starting point for further optimization.

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9. A phosphorylated form of His-p38α MAP kinase of murine origin (10 ng/well) and immobilized GST-ATF-2 as substrate in the presence of 120 μM cold ATP was used to perform the kinase assay.
10. Human peripheral blood mononuclear cells were incubated with the inhibitor and stimulated with LPS/IFNγ for 3 h. TNFα levels in the supernatants were determined by ELISA.
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12. A related cyclization reaction using dibenzyl ureas was reported recently: Ferraccioli, R.; Carenzi, D. *Synthesis* **2003**, 1383. Stelmach et al.[8b] describe a similar CuI driven cyclization starting from protected ureas. Pd catalyzed reactions of aryl halides with ureas leading to linear derivatives have also been reported: Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.
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14. Representative experimental procedure: 79 mg of Pd_2dba_3, 90 mg of 2-(dicyclohexyl-phosphino) biphenyl, 640 mg of K_3PO_4 are added to 1.0 g of 1-(4-(*t*-butyl-dimethyl-silanoxy)-2,6-dimethyl-phenyl)-3-(2-chloro-5-nitro-benzyl)-urea **17a** in 20 mL DMF. The mixture was stirred for 16 h at 135 °C under Ar atmosphere. After removal of the DMF, the residue is taken up in EtOAc/H_2O and filtered over Hyflo. The organic phase was washed with H_2O and brine. Crystallization from ether yielded 620 mg (92%) of the cyclic urea **18b** as a brown powder. ^{1}H NMR (DMSO-d_6) δ 1.9 (6H, s), 4.55 (2H, s), 6.12 (2H, d), 6.52 (2H, s), 7.54 (1H, s, NH), 7.95 (1H, dd), 8.18 (1H, s), 9.55 (1H, s, OH); MS (ESI–): *m*/*z*: 312 (100%, $(M-H)^-$).
15. 8-Week old female OF1 mice were dosed perorally by gavage with solutions of the compound in DMSO/cornoil. 1 h after dosing LPS (20 mg/kg) was injected iv. After another hour blood was collected and TNFα levels were determined using a mouse-specific ELISA.