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Brief Article

Unexpected Reaction of 2-Alkylsulfanylimidazoles to Imidazol-2-ones: Pyridinylimidazol-2-ones as Novel Potent p38α Mitogen-Activated Protein Kinase Inhibitors

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While optimizing the synthesis of 2-alkylsulfanyl-5-(2-aminopyridin-4-yl)imidazoles, we identified an unexpected reaction to pyridinylimidazol-2-ones. 2-Alkylsulfanylimidazoles, bearing a 2-hydroxyethyl or a 2,3-dihydroxypropyl moiety at the imidazole C2-S position, were converted by heating into imidazol-2-ones. These imidazol-2-ones were tested for their ability to inhibit p38α MAP kinase and LPS-stimulated TNF-α release in HWB. Introduction of an amino moiety at the pyridine C2 position led to compounds showing potent enzyme inhibitory activity with double-digit nanomolar IC_{50} values (**5a**: IC_{50} = 23 nM).

Introduction

Imidazole derivatives display a wide range of biological activities as exemplified by the amino acid histidine. Many tri- and tetrasubstituted pyridinylimidazoles, derived from the early lead SKF86002,[1] have been investigated as potent adenosine triphosphate (ATP[a]) competitive inhibitors of p38α MAP kinase, e.g., the prototype inhibitor SB203580[2] or the recently reported 2-alkylsulfanyl-4-(4-fluorophenyl)-5-(2-aminopyridin-4-yl)-substituted imidazoles **1** (Figure 1).[3−5] The p38α mitogen-activated protein (MAP) kinase, a serine/threonine kinase, is a key component of the cascade leading to proinflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-1β.[6] Inhibition of p38α MAP kinase is therefore a promising therapeutic strategy for the treatment of cytokine driven disorders.

The synthesis of the trisubstituted imidazole derivatives **1** bearing a polar moiety at the imidazole C2-S position (R^2) was published recently.[5] Imidazoles **1** were prepared starting from *N*-boc protected 2-amino-4-methylpyridine or 2-bromo-4-methylpyridine in six or seven steps. The limitation of this synthetic strategy is the introduction of the amino moiety (R^1) in the first step of the synthesis, which requires the addition and removal of a protecting group.

To overcome this drawback, we developed another synthetic strategy to **1** in which variable moieties R^1 and R^2 were introduced in the last two steps of the synthesis (Scheme 1). The key compound for this route was 4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**2**), which was prepared in four steps starting from 2-fluoro-4-methylpyridine.[7] The alkylsulfanyl moiety (R^2) was introduced by nucleophilic substitution of thione **2** and the appropriate alkyl halide. In the last step, the fluorine atom of **3** was displaced by a primary amine **4** to obtain the imidazole derivative **1**.

The reaction to (1*R*,4*R*)-4-{4-[4-(4-fluorophenyl)-2-(2-hydroxyethylthio)-1*H*-imidazol-5-yl]pyridin-2-ylamino}cyclohexanol (**1a**) using this synthetic strategy was published recently (Scheme 2).[4] Thione **2** was treated under basic conditions with 2-bromoethanol to obtain 2-[4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1*H*-imidazol-2-ylthio]ethanol (**3a**). Finally, the fluorine atom of **3a** was displaced under microwave conditions using an excess (8 equiv) of *trans*-4-aminocyclohexanol (**4a**) to yield imidazole derivative **1a**.

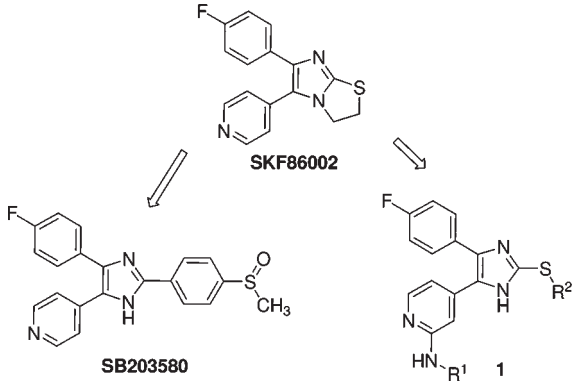

Figure 1. Vicinal 4-fluorophenyl/pyridin-4-yl-substituted imidazoles under investigation for p38α MAP kinase inhibition derived from the early lead SKF86002.

To extend this strategy to the synthesis of different substituted imidazole derivatives **1**, we observed an unexpected reaction, the conversion of 2-alkylsulfanylimidazoles bearing a 2-hydroxyethyl or a 2,3-dihydroxypropyl moiety at the imidazole C2-S position (Figure 1, R^2) to imidazol-2-ones.

Results and Discussion

Chemistry. Compound **3b** was prepared from thione **2** and 3-bromopropane-1,2-diol under basic conditions (Scheme 3). The reaction of imidazole derivative **3b** and primary amine **4a** under the same conditions as for reaction of **3a** and **4a** depicted in Scheme 2 (135 °C, 250 W) yielded two products. In addition to the formation of the desired product (imidazole derivative **1b**), **5a** was identified (Scheme 3). Compound **5a** bears the amino function at the pyridine C2 position, but the sulfur moiety at the imidazole C2 position was exchanged by an oxygen atom. This reaction was monitored via HPLC (Table 1). After 2 h, the starting material **3b** was consumed. The imidazol-2-one derivative **5a** accumulates with increasing

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[a] Abbreviations: ATP, adenosine triphosphate; MAP, mitogen-activated protein; LPS, lipopolysaccharide; SEM, standard error of the mean; TNF-α, tumor necrosis factor α; HWB, human whole blood.

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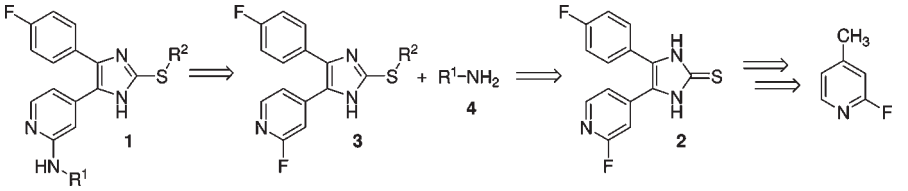
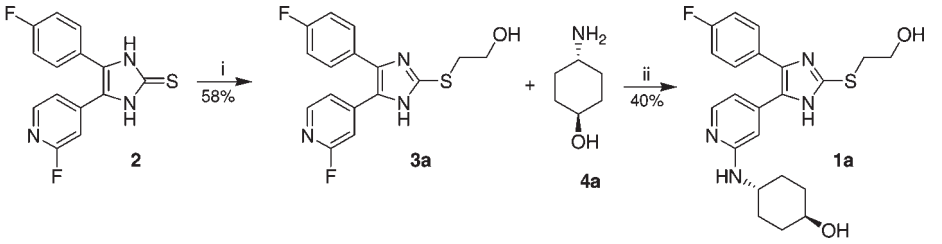
Scheme 1. Retrosynthetic View of an Alternative Synthetic Strategy to Imidazole Derivative **1**

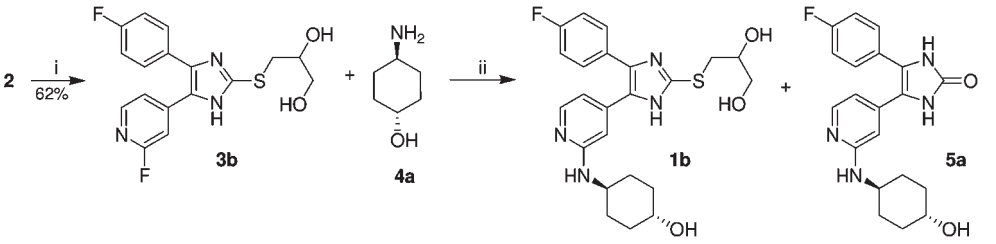


Scheme 2. Nucleophilic Aromatic Substitution of **3a** and **4a**[a]



[a] Reagents and conditions: (i) 2-bromoethanol, sodium ethoxide, methanol, 4 h, room temp; (ii) 135 °C, 250 W, microwave irradiation.

Scheme 3. Nucleophilic Aromatic Substitution of **3b** and **4a**[a]



[a] Reagents and conditions: (i) 3-bromopropane-1,2-diol, sodium ethoxide, methanol, 16 h, room temp; (ii) 135 °C, 250 W, microwave irradiation.

Table 1. Reaction of **3b** and **4a**: Quantitation of Reactants and Products by HPLC[a] (Microwave Conditions, 250 W, 135 °C)

time, h	**3b**, %	**1b**, %	**5a**, %
0	100	0	0
1	21	59	17
2	0	18	75
4	0	1	91

[a] For HPLC conditions, see General in the Experimental Section.

reaction time, with the intermediate 2-alkylsulfanylimdazole compound **1b** being converted into the imidazol-2-one compound **5a**.

In a variation of this reaction, **3a**, bearing a hydroxyethyl moiety at the imidazole C2-S position, was reacted with 3-methylbut-2-ylamine (**4b**) (Scheme 4). This reaction was monitored via HPLC (Table 2). Formation of the imidazol-2-one compound **5b** occurred at a slower rate compared to the reaction to the imidazol-2-one compound **5a** monitored in Table 1.

The progress of the reaction was temperature dependent (Table 2). Decreasing the reaction temperature to 110 °C provided only 3% of the desired imidazole **1c**, and none of the imidazol-2-one **5b** was formed. Increasing the reaction temperature to 160 °C resulted in a faster conversion of **1c** and **5b**. HPLC studies indicated that the first reaction to occur was the nucleophilic aromatic substitution to afford the 2-alkylsulfanylimidazole **1c**, which reached a maximum by 4 h. After that point, the conversion of **1c** to the imidazol-2-one **5b** was the predominant reaction. By 6 h, 36% of **1c** and 28% of **5b** had been formed. After 10 h, the 2-alkylsulfanylimidazole **1c** was converted completely into the imidazol-2-one compound **5b** (Table 2).

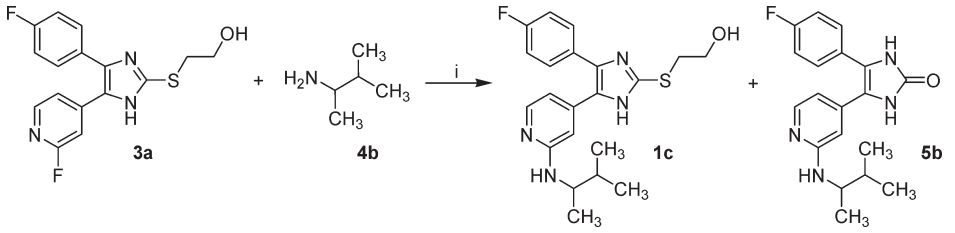
The formation of the imidazol-2-one compound was not observed by the reaction of imidazoles bearing an *S*-methyl, *S*-ethyl, or *S*-benzyl moiety at the imidazole C2 position (Scheme 5),[7,8] but rather, the formation of the imidazol-2-one depends on the presence of hydroxy function(s) of the *S*-alkyl moiety. A possible mechanism for the conversion of 2-alkylsulfanylimidazoles bearing a 2-hydroxyethyl or a 2,3-dihydroxypropyl moiety at the imidazole C2-S position into imidazol-2-ones is presented in Scheme 6 (exemplified by reaction of **3a** and primary amine **4**). After the nucleophilic aromatic displacement of the fluorine atom at the pyridine moiety of **3a** has taken place, the hydroxyethyl moiety at the imidazole C2-S position of the alkylsulfanylimidazole **1** could react intramolecularly to the 1,3-oxathiolane **9**. Compound **9** will finally be directly converted (maybe by hydrolysis) into the thermodynamically more stable imidazol-2-one **5**.

This unexpected reaction was used to synthesize additional imidazol-2-ones **5c**−**e** (Scheme 7). Imidazol-2-one **5c** was prepared by heating **3b** and 1-phenylethylamine (**4c**) under reflux conditions. Imidazol-2-ones **5d** and **5e** were synthesized by heating **3a** and amine **4d** or **4e** in a sealed glass tube at 160 °C for 10 h.

To evaluate the influence of the pyridine-C2-amino moiety on biological activity, we attempted to prepare **5f**, which lacked a substituent at this position (Scheme 8). 2-Bromo-2-(4-fluorophenyl)-1-(pyridin-4-yl)ethanone hydrobromide was reacted with urea in a microwave reactor. X-ray analysis of the product[9] showed that the oxazole **6** was formed and not the desired imidazol-2-one **5f**.

Another synthetic strategy toward imidazol-2-one **5f** starting from 2-(2-bromopyridin-4-yl)-1-(4-fluorophenyl)ethanone

Scheme 4. Nucleophilic Aromatic Substitution of **3a** and **4b**[a]



[a] Conditions: (i) 135 °C, 250 W, microwave irradiation.

Table 2. Reaction of **3a** and **4b**: Quantitation of Reactants and Products by HPLC[a] (Microwave Conditions, 250 W, 135 °C, 110 °C, and 160 °C)

time, h	**3a**, %	**1c**, %	**5b**, %
	135 °C		
0	100	0	0
1	91	6	0.2
3	74	16	2
5	51	25	6
	110 °C		
0	100	0	0
1	99	1	0
2	98	2	0
4	97	3	0
	160 °C		
0	100	0	0
1	79	17	2
2	61	31	2
4	45	37	16
6	29	36	28
10	0	0	89

[a] For HPLC conditions, see general part of the experimental section.

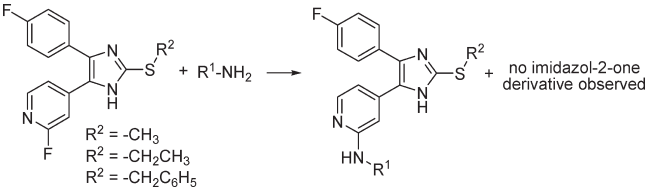
is depicted in Scheme 9. The bromosubstituted derivative **7** smoothly underwent a hydrogenolytic cleavage, yielding pure unsubstituted pyridine **8**. By use of an adaption of the Marckwald synthesis, α-aminoketone **8** was treated with potassium cyanate to yield 4-(4-fluorophenyl)-5-(pyridin-4-yl)-1,3-dihydroimidazol-2-one (**5f**).

Biological Data. The inhibitory potencies of the title compounds were evaluated using an isolated p38α MAP kinase assay, wherein pyridinylimidazole SB203580 was used as a reference.[10] The LPS-stimulated TNF-α release was tested using a human whole blood (HWB) assay (see Supporting Information).

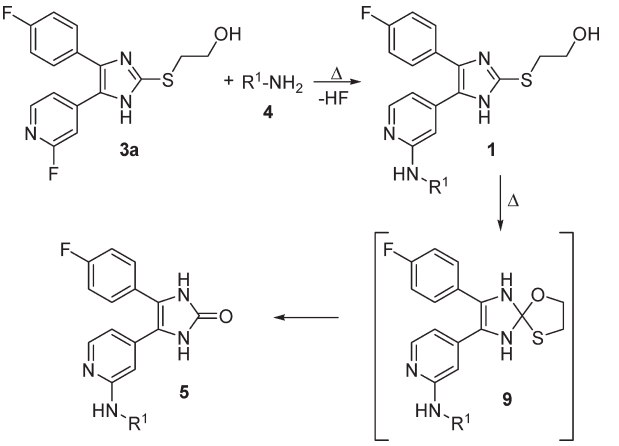
The 4(5)-aryl-5(4)-heteroaryl-substituted imidazolones **5a**,**d**−**f** were potent inhibitors of p38α MAP kinase (Table 3). Introduction of an amino moiety at the pyridine C2 position (**5a**,**d**,**e**) increased the inhibitory activity and led to IC_{50}s in the isolated p38α MAP kinase assay in the low double-digit nanomolar range. Imidazol-2-one **5a**, bearing a 4-hydroxycyclohexylamino moiety at the pyridine C2 position, was 20 times more potent than the pyridine-C2-unsubstituted derivative **5f**. The release of LPS-stimulated TNF-α from HWB was inhibited by the target compounds at concentrations in the low to submicromolar range (Table 3). Compound **5a** exhibited an IC_{50} similar to that of the reference compound SB203580 with respect to the LPS-stimulated TNF-α release, while **5d** showed a clear, ∼4× improvement in inhibitory potency compared to SB203580.

Compound **5d** was docked into the ATP binding site of p38α MAP kinase (Figure 2). The binding mode of the imidazol-2-ones **5** is essentially identical to the binding mode of the imidazole compound SB203580 except for the direct imidazole

Scheme 5. Nucleophilic Aromatic Substitution of Imidazoles Bearing an *S*-Methyl, *S*-Ethyl, or *S*-Benzyl Moiety at the Imidazole C2 Position and Different Amines



Scheme 6. Possible Mechanism for the Conversion of 2-Alkylsulfanylimidazoles Bearing a 2-Hydroxyethyl Moiety at the Imidazole C2-S Position into Imidazol-2-ones **5**



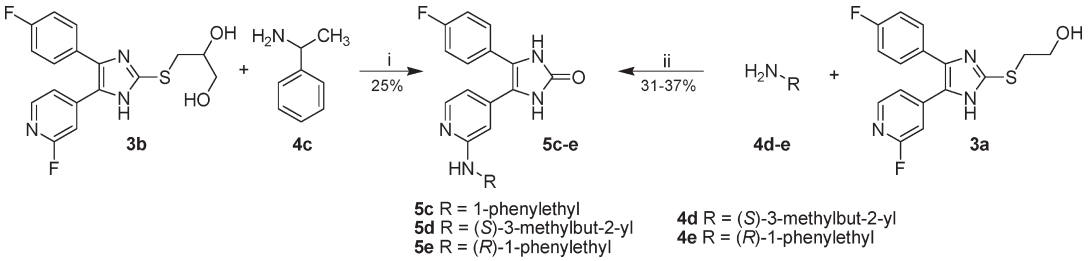
N3−Lys53 hydrogen bond interaction.[11] The 4-fluorophenyl ring binds to the hydrophobic region I (selectivity pocket), which is mediated by the presence of the gatekeeper residue Thr106 in the ATP-binding site of p38α MAP kinase. The nitrogen of the pyridin-4-yl moiety forms a crucial hydrogen bond to the backbone NH of Met109 in the hinge region. In addition to the binding mode of SB203580, the amino function at the pyridine C2 position interacts with the carbonyl function of Met109 via a hydrogen bond and the 3-methylbut-2-yl moiety of **5d** is situated in the hydrophobic region II.

Conclusion

Under elevated temperature, we observed the unexpected transformation of 2-alkylsulfanylimidazoles, bearing a 2-hydroxyethyl or a 2,3-dihydroxypropyl moiety at the imidazole C2-S position, into imidazol-2-ones.

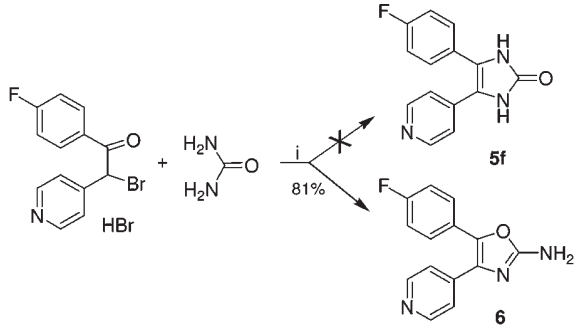
These imidazol-2-ones were identified as novel potent inhibitors of p38α MAP kinase with IC_{50} values down to the low double-digit nanomolar range. Introduction of an amino function at the pyridine C2 position results in an increase of

Scheme 7. Synthesis of 4-(4-Fluorophenyl)-5-(2-aminopyridin-4-yl)imidazol-2-ones **5c**−**e**[a]



[a] Reagents and conditions: (i) reflux temperature, 7 h; (ii) 160 °C, 10 h, sealed tube.

Scheme 8. Ring Closing Reaction of 2-Bromo-2-(4-fluorophenyl)-1-(pyridin-4-yl)ethanone Hydrobromide and Urea[a]



[a] Reagents and conditions: (i) DMF, 135 °C, 250 W, microwave irradiation.

inhibitory activity caused, on the one hand, by an additional hydrogen bond interaction to the hinge region and, on the other hand, by interaction possibilities with the hydrophobic region II.

Experimental Section

General. All commercially available reagents and solvents were used without further purification. The microwave reactions were performed on a CEM Discover system. The optical rotation data were obtained on a Perkin-Elmer polarimeter model 241 (589 nm). NMR data were recorded on a Bruker Spectrospin AC 200 at ambient temperature. Chemical shifts are reported in ppm relative to the solvent resonance. High-resolution spectra (FT-ICR) were obtained on a Bruker APEX II with electron spray ionization. The purity of the final compounds was determined by HPLC on a Hewlett-Packard HP 1090 series II liquid chromatograph using a Betasil C8 column (150 mm × 4.6 mm i.d., dp = 5 μm, Thermo Fisher Scientific, Waltham, MA) at 230 and 254 nm, employing a gradient of 0.01 M KH_2PO_4 (pH 2.3) and methanol as the solvent system with a flow rate of 1.5 mL/min. All final compounds have a purity of >96% (see Supporting Information for details).

4-(4-Fluorophenyl)-5-{2-[(1*R*,4*R*)-4-hydroxycyclohexylamino]-pyridin-4-yl}-1,3-dihydroimidazol-2-one (5a). Compound **3b** (0.18 g, 0.50 mmol) and *trans*-4-aminocyclohexanol (0.46 g, 4.0 mmol) were combined in a reaction vessel. The reaction vessel was heated in a microwave reactor for 4 h at 135 °C (initial power 250 W), after which a stream of compressed air cooled the reaction vessel to room temperature. The reaction mixture was purified by flash chromatography (SiO_2, DCM/EtOH, 8:1 to 1:1) to yield 62 mg (34%) of **5a** as a colorless solid. $C_{20}H_{21}FN_4O_2$ (M_r = 368.40); ^{1}H NMR (DMSO-d_6) δ 1.14−1.21 (m, 4H, cyclohexyl), 1.73−1.89 (m, 4H, cyclohexyl), 3.40−3.55 (m, 3H, 2 × CH cyclohexyl, OH), 6.19−6.29 (m, 3H, C^3/C^5-H Pyr, NH), 7.06−7.15 (m, 2H, C^3/C^5-H 4-F-Phe), 7.35−7.43 (m, 2H, C^2/C^6-H 4-F-Phe), 7.80 (d, J = 5.4 Hz, 1H, C^6-H Pyr), 10.52 (bs, 1H, NH), 10.59 (bs, 1H, NH); ESI-HRMS calcd, $C_{20}H_{22}FN_4O_2$ $[M + H]^+$ 369.1721, obsd 369.1724.

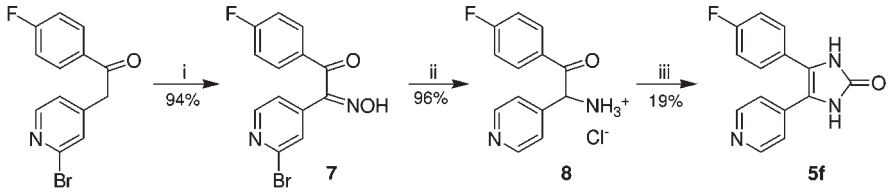
4-(4-Fluorophenyl)-5-[2-(1-phenylethylamino)pyridin-4-yl]-1,3-dihydroimidazol-2-one (5c). Compound **3b** (0.54 g, 1.5 mmol) and 1-phenylethylamine (1.81 g, 15 mmol) were heated for 7 h to reflux temperature. After cooling to room temperature the mixture was treated with an aqueous solution of citric acid (10%), which had been brought to pH 5 with an aqueous solution of NaOH (20%). The emulsion was extracted with ethyl acetate (3×). The combined organic extracts were washed with citric acid (10%, pH 5), an aqueous solution of Na_2CO_3 (10%), and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude brown oily residue was treated with diethyl ether, and a yellow precipitate was formed which was filtered and dried. Yield 0.14 g (25%); $C_{22}H_{19}FN_4O$ (M_r = 374.41); ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 6.9 Hz, 3H, CH_3), 4.79−4.86 (m, 1H, CH), 6.28−6.32 (m, 2H, C^3/C^5-H Pyr), 6.95 (d, J = 7.9 Hz, 1H, NH), 7.13−7.27 (m, 7H, C_6H_5, C^3/C^5-H 4-F-Phe), 7.32−7.40 (m, 2H, C^2/C^6-H 4-F-Phe), 7.78 (d, J = 5.4 Hz, 1H, C^6-H Pyr), 10.50 (bs, 1H, NH), 10.58 (bs, 1H, NH); ESI-HRMS calcd, $C_{22}H_{20}FN_4O$ $[M + H]^+$ 375.1616, obsd 375.1617.

(*S*)-4-(4-Fluorophenyl)-5-[2-(3-methylbutan-2-ylamino)pyridin-4-yl]-1,3-dihydroimidazol-2-one (5d). Compound **3a** (0.25 g, 0.75 mmol) and (*S*)-3-methylbutyl-2-amine (0.52 g, 6.0 mmol) were stirred in a sealed glass tube for 10 h at 160 °C. After the mixture was cooled to room temperature, the solvent was removed and the residue was purified by flash chromatography (SiO_2, DCM/EtOH, 95:5 to 8:2) to afford 79 mg (31%) of a yellow solid. $C_{19}H_{21}FN_4O$ (M_r = 340.39); $[\alpha]_D^{20}$ −21.2° (*c* 0.90, methanol); ^{1}H NMR (DMSO-d_6) δ 0.79−0.84 (m, 6H, 2 × CH_3), 0.96 (d, J = 6.4 Hz, 3H, CH_3), 1.61−1.75 (m, 1H, CH), 3.48−3.63 (m, 1H, CH), 6.20 (d, J = 8.2 Hz, 1H, NH), 6.26 (d, J = 5.5 Hz, 1H, C^5-H Pyr), 6.32 (s, 1H, C^3-H Pyr), 7.15−7.24 (m, 2H, C^3/C^5-H 4-F-Phe), 7.35−7.42 (m, 2H, C^2/C^6-H 4-F-Phe), 7.79 (d, J = 5.4 Hz, 1H, C^6-H Pyr), 10.52 (m, 2H, 2x NH); ESI-HRMS calcd, $C_{19}H_{22}FN_4O$ $[M + H]^+$ 341.1772, obsd 341.1773.

(*R*)-4-(4-Fluorophenyl)-5-[2-(1-phenylethylamino)pyridin-4-yl]-1,3-dihydroimidazol-2-one (5e). Compound **3a** (0.20 g, 0.6 mmol) and (*R*)-1-phenylethylamine (0.58 g, 6.0 mmol) were stirred in a sealed glass tube for 10 h at 160 °C. After the mixture was cooled to room temperature, the solvent was removed and the residue was purified by flash chromatography (SiO_2, DCM/EtOH, 95:5 to 8:2) to afford 82 mg (37%) as a yellow solid. $C_{22}H_{19}FN_4O$ (M_r = 374.41); $[\alpha]_D^{20}$ +36.4° (*c* 0.70, methanol); ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 6.8 Hz, 3H, CH_3), 4.79−4.89 (m, 1H, CH), 6.29−6.32 (m, 2H, C^3/C^5-H Pyr), 6.94 (d, J = 7.2 Hz, 1H, NH), 7.16−7.26 (m, 7H, C_6H_5, C^3/C^5-H 4-F-Phe), 7.32−7.48 (m, 2H, C^2/C^6-H 4-F-Phe), 7.78 (d, J = 5.0 Hz, 1H, C^6-H Pyr), 10.52 (bs, 1H, NH), 10.60 (bs, 1H, NH); ESI-HRMS calcd, $C_{22}H_{20}FN_4O$ $[M + H]^+$ 375.1616, obsd 375.1619.

5-(4-Fluorophenyl)-4-(pyridin-4-yl)oxazol-2-amine (6). 2-Bromo-2-(4-fluorophenyl)-1-(pyridin-4-yl)ethanone hydrobromide (150 mg, 0.40 mmol), urea (24 mg, 0.40 mmol), and DMF (1 mL) were combined in a reaction vessel. The reaction vessel was heated in a CEM microwave reactor for 10 min at 160 °C (initial power 250 W), after which a stream of compressed air cooled the reaction vessel to room temperature. Water and ethyl acetate were added, and the organic layer was separated. This layer was washed with water (3×), dried over Na_2SO_4, and concentrated in vacuo. The yellow

Scheme 9. Synthesis of 4-(4-Fluorophenyl)-5-(pyridin-4-yl)-1,3-dihydroimidazol-2-one (**5f**)[a]



[a] Reagents and conditions: (i) $NaNO_2$, acetic acid, 10 °C to room temp; (ii) Pd/C 10%, iPrOH/HCl, H_2, atmospheric pressure, room temp; (iii) KOCN, DMF, reflux temperature.

Table 3. Evaluation of the Prepared Compounds **5a**,**d**,**e**,**f** for p38α MAP Kinase Inhibitory and LPS-Stimulated TNF-α Release from HWB

	IC_{50}, μM	
compd	p38α[a]	TNF-α[b]
5a	$0.023 \pm 5.9e^{-4}$	2.92 ± 0.40
5d	0.049 ± 0.001	0.381 ± 0.05
5e	0.324 ± 0.017	nd[c]
5f	0.468 ± 0.101	nd[c]
SB203580	0.044 ± 0.004	1.76 ± 0.43

[a] Mean ± SEM of three experiments. [b] Mean ± SEM of two experiments. [c] Not determined.

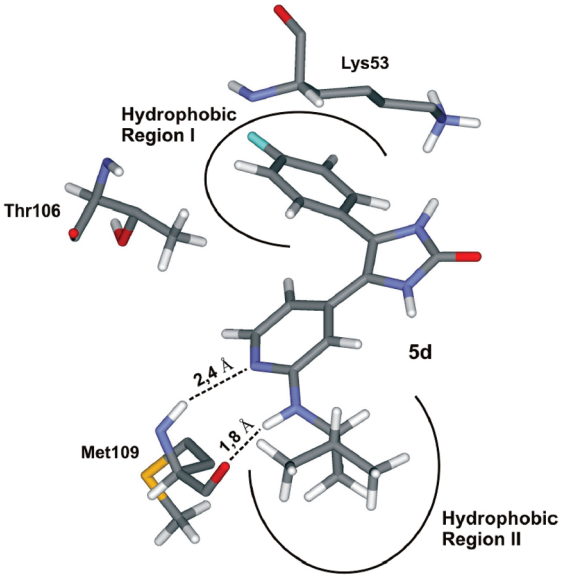


Figure 2. After geometric optimization, inhibitor **5d** was docked in the p38α active center. Possible hydrogen bonding interactions are shown as dashed lines.

residue was suspended twice with DCM/EtOH, 95:5, filtered, and finally dried. Yield 83 mg (81%); $C_{14}H_{10}FN_3O$ (M_r = 255.25); ^{1}H NMR (DMSO-d_6) δ 7.04 (s, 2H, NH_2, exchangeable), 7.24−7.33 (m, 2H, C^3/C^5-H 4-F-Phe), 7.46−7.55 (m, 4H, C^3/C^5-H Pyr, C^2/C^6-H 4-F-Phe), 8.51−8.54 (m, 2H, C^2/C^6-H Pyr); ESI-HRMS calcd, $C_{14}H_{11}FN_3O$ $[M + H]^+$ 256.0881, obsd 256.0879. The crystal structure of **6** has been proven by X-ray analysis: Enraf-Nonius CAD-4, Cu Kα, SIR92, SHELXL97. Further details of the crystal structure analysis are available in ref 9.

4-(4-Fluorophenyl)-5-(pyridin-4-yl)-1,3-dihydroimidazol-2-one (5f). Compound **8** (0.26, 1.0 mmol) was dissolved in absolute DMF (15 mL), and potassium cyanate (0.30 g, 2.0 mmol) was added. The reaction mixture was heated to reflux temperature for 2.5 h. The suspension was cooled to room temperature and diluted with water (60 mL). The mixture was extracted three times with ethyl acetate (80 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resulting yellow liquid (containing a small amount of DMF) was treated with diethyl ether, and a yellow solid was precipitated. The precipitate was filtered and purified by flash chromatography (SiO_2, EtOAc/MeOH, 1:0 to 1:1) to yield 48 mg (19%) as a yellow solid. $C_{14}H_{10}FN_3O$ (M_r = 255.25); ^{1}H NMR (DMSO-d_6) δ 7.18−7.30 (m, 4H, C^3/C^5-H 4-F-Phe, C^3/C^5-H Pyr), 7.40−7.47 (m, 2H, C^2/C^6-H 4-F-Phe), 8.41 (d, J = 4.8 Hz, 2H, C^2/C^6-H Pyr), 10.80 (bs, 2H, 2 × NH); ESI-HRMS, $C_{14}H_{11}FN_3O$ $[M + H]^+$ 256.0881, obsd 256.0878.

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Supporting Information Available: Experimental procedures and analytical data for **3a**,**b**, **5a**,**c**−**f**, and **6**−**8**. Descriptions of the HWB assay and the molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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