Imidazole Inhibitors of Cytokine Release: Probing Substituents in the 2 Position

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Novel 2,4,5-trisubstituted imidazole derivatives were prepared as potential anticytokine agents. Thirty-seven compounds were tested on their ability to inhibit the release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) from peripheral blood mononuclear cells (PBMC) or human whole blood. SARs (structure activity relationships) for substituents at the 4 and 5 position of the imidazole core were similar to those described for other inhibitors of cytokine release and p38 MAP (mitogen-activated protein) kinase. Starting from benzylsulfanyl imidazole **2b** (IC$_{50}$ p38, 4.0 μM; TNF-α, 1.1 μM; IL-1β, 0.38 μM), the contribution of substituents at the 2 position to enzyme inhibitory and cellular activity of test compounds was investigated. This strategy led to the identification of compound **2q** (IC$_{50}$ p38, 0.63 μM; TNF-α, 0.90 μM; IL-1β, 0.04 μM), which was 6−10 times more potent than the initial lead **2b** with respect to inhibition of p38 and IL-1β release and equipotently inhibited TNF-α release.

Introduction

With the current drug therapy of chronic inflammatory conditions such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) often being limited by severe side effects, there is a continuous medical need for new efficient and safe anti-inflammatory drugs. The antibody Infliximab and the fusion protein Etanercept were successfully launched in 1999 and have shown efficacy in the treatment of RA and IBD ever since by reducing the synovial and circulating blood levels of tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine.[1,2] Therapeutic application of both Infliximab and Etanercept on a large scale is, however, hampered by high costs of therapy[3] and the general disadvantages of protein drugs such as the lack of oral availability and a time-dependent loss of activity. Therefore, attention in inflammation research has focused on the development of small molecular inhibitors of cytokine release.[4,5] An important drug target in this respect is provided by p38 MAP (mitogen-activated protein) kinase, a Ser/Thr kinase involved in the biosynthesis of pro-inflammatory cytokines interleukin-1β (IL-1β) and TNF-α.[6] It has been demonstrated that small molecular inhibitors of p38 significantly reduce the release of both of these cytokines from human monocytes,[6] a highly valuable feature with the synergistic effects of anti-IL-1β and anti-TNF-α therapy becoming increasingly clear.[7] Several potent inhibitors of p38 like SB 203580 (Figure 1, Table 2) compete with ATP at the ATP binding site, which is located in the cleft between the two domains of p38.[8−10] Rigid structure activity relationships (SAR) have been established for these trisubstituted imidazoles.[11,12] A pyridin-4-yl moiety corresponding to the aminopyrimidine fragment of the ATP purin ring system is essential for inhibitory potency in this class of compounds as it

forms a crucial hydrogen bond from the backbone NH of Met 109 to the pyridin N atom.[13] The adjacent 4-fluorophenyl substituent provides inhibitor selectivity for p38 over other kinases, filling a hydrophobic pocket which is left unoccupied by ATP.[13−15] On the other hand, substituents at the 2 position of the core imidazole have mostly served to adjust the physicochemical properties of p38 inhibitors.[16] A number of amino acids in p38 are, however, known as possible sites of interaction if appropriate side chains are attached to the 1 or 2 position of the imidazole nucleus, e.g., the efficacy of an aromatic moiety at the 2 position of SB 203580, has been attributed to its stacking interaction with Tyr 35.[13] In the present study, we investigated whether inhibition of cytokine release in a series of novel pyridinylimidazoles depends on the nature of substituents at the 2 position of the imidazole core. *1H* imidazoles SB 203580 and ML 3163 (**2b**), a known inhibitor of cytokine release, were both derived from the early lead SK&F 86002 (Figure 1).[17−19] Opening the imidazothiazoline system through incision of bonds a and c yielded SB 203580 after insertion of a 4-methanesulfinylphenyl moiety, while dissection of bonds c and d and subsequent insertion of a 4-methanesulfinylphenyl moiety led to **2b**. Superposition of SB 203580 and ATP shows the methanesulfinyl moiety of SB 203580 in close proximity to the phosphates of ATP.[10] For a number of kinases, it has been found that upon binding of ATP, the triphosphate group is coordinated by one or two metal ions which are ligated by amino acids located in the phosphate binding ribbon.[20] The suitability of phenolic structures as metal chelators has been demonstrated.[21] Therefore, we reasoned that the methanesulfinyl part of **2b** interacts with the phosphate binding ribbon of p38 and that analogues of **2b** bearing an additional phenolic functionality at the benzylsulfanyl moiety should subsequently be better suited for interaction with this region of the enzyme. As part of our program to find novel and potent inhibitors of cytokine release, we have

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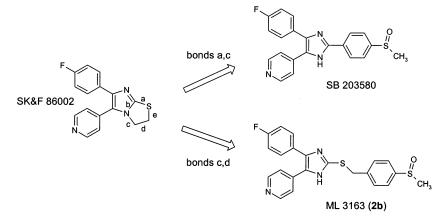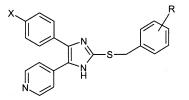† Eberhard-Karls-University Tübingen.
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Figure 1. Dissection of the SK&F 86002 imidazo[2,1-b]thiazoline system. Insertion of a 4-methanesulfinylphenyl moiety gives SB 203580 after incision of bonds a and c and ML 3163 after incision of bonds c and d.

Table 1. Inhibition of Cytokine Release by Benzylsulfanyl Imidazoles[a]

| compd | X | R | IC$_{50}$ ± SEM (μM) PBMC | |
			TNF-α	IL-1β
2a	F−	4-SCH$_3$	4.9 ± 0.1	0.67 ± 0.19
2b (ML 3163)	F−	4-S(O)CH$_3$	1.1 ± 0.4 (4)	0.38 ± 0.13 (4)
2c	F−	4-SO$_2$CH$_3$	2.5 ± 0.4 (4)	0.33 ± 0.10 (4)
2d[b]	F−	4-S(O)CH$_3$	>100	98 ± 23
2e	F−	3-SCH$_3$	12.0 ± 4.4	0.55 ± 0.03
2f	F−	3-S(O)CH$_3$	23.5 ± 6.5	1.0 ± 0.4
2g	F−	2-SCH$_3$	18.3 ± 1.3	6.7 ± 4.4
2h	F−	2-S(O)CH$_3$	15.0 ± 0.5	0.90 ± 0.10
3a	Cl−	4-SCH$_3$	14.0 ± 4.0	2.2 ± 0.4
3b	Cl−	4-S(O)CH$_3$	3.1 ± 1.2	0.32 ± 0.06
3c	Cl−	4-SO$_2$CH$_3$	6.1 ± 4.0	0.32 ± 0.07
4a	Br−	4-SCH$_3$	12.9 ± 4.2	2.4 ± 0.6
4b	Br−	4-S(O)CH$_3$	7.8 ± 0.3	0.82 ± 0.12
4c	Br−	4-SO$_2$CH$_3$	7.3 ± 0.5	0.64 ± 0.45
5a	H−	4-SCH$_3$	17.1 ± 10.0	72.5 ± 32.5
5b	H−	4-S(O)CH$_3$	4.3 ± 1.8	0.84 ± 0.46
5c	H−	4-SO$_2$CH$_3$	8.0 ± 1.0	1.7 ± 0.2
6a	F−	4-HO	6.8 ± 0.2	0.37 ± 0.14
6b	F−	3-HO	5.4 ± 0.6	0.31 (1)
6c	F−	2-HO	24.8 ± 5.3	0.44 ± 0.00

[a] Results are given as the mean of two independent experiments, except where otherwise stated. [b] 3-pyr.

prepared a series of **2b** analogues differing in their respective substituents at the 2 position. Much to our surprise and in contradiction to our initial concept, SAR for these compounds in peripheral blood mononuclear cells (PBMC) revealed the optimum substituent at the 2 position to be a simple methylsulfanyl group. This result contrasts remarkably with published data which claim large substituents at the 1 or 2 position of the imidazole core to be required for cellular activity in this class of compounds.[16,22]
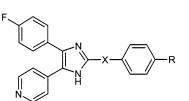
Chemistry

Nucleophilic substitution of appropriate halogenoalkanes with 4-(4-fluorophenyl)-5-pyridin-4-yl-1,3-dihydro-imidazole-2-thione **1a**[17,23] represents the key step in the straightforward synthesis of alkylsulfanyl imi-

dazoles (Scheme 1). Thus compounds **2a**−**c**, **2e**, and **2g**−**q** were obtained from **1a** in good to moderate yields under basic conditions (Scheme 1, pathway a). The analogues **3a**−**c**, **4a**−**c**, and **5a**−**c** were prepared from imidazole thiones **1b**−**d** according to the same synthetic procedures. However, application of this same methodology to benzyl chlorides bearing a phenolic functionality yielded an unseparable mixture of products. The pronounced reactivity of benzyl alcohols toward nucleophilic reagents[24] was exploited in the preparation of compounds **6a**−**d**, **6f**, and **6h** under relatively mild conditions. Acid catalyzed reaction of appropriately substituted benzyl alcohols with **1a** led to compounds **6a**−**d**, **6f**, and **6h** (Scheme 1, pathway b). Sulfides **2e**, **6d**, **6f**, and **6h** were converted into the corresponding sulfoxides **2f**, **6e**, **6g**, and **6i** upon treatment with 1 equiv of 35% H$_2$O$_2$. ^{1}H/^{13}C NMR data for the methylene group indicate that the oxidation state of the sulfur atom proximal to the imidazole nucleus is not altered under these conditions. Benzyl alcohols **10a**−**c** containing a phenolic as well as a methylsulfanyl substituent were prepared from the corresponding benzoic acids **9a**−**c** by LiAlH$_4$ reduction (Scheme 2). The required benzoic acids were obtained by modification of Stewart's methodology[25] for the preparation of methylsulfanyl salicylic acids, which has been previously applied to the synthesis of **9b,c**.[26] We extended this strategy to the synthesis of the regioisomeric 4-hydroxy-3-methylsulfanyl-benzoic acid **9a** starting from 4-methoxybenzoic acid. Initial attempts to introduce the chlorosulfonyl moiety on the corresponding phenolic compound failed. Moreover, chlorosulfonation of 4-methoxybenzoic acid to **7** was achieved only when carried out in CCl$_4$. Subsequent triphenylphosphine reduction[27] of **7** and alkaline methylation of the intermediate thiol was accompagnied by saponification of the benzoic acid ester to yield methylsulfanyl benzoic acid **8**. After cleavage of the protecting group under standard reaction conditions, phenol **9a** was obtained and subsequently converted into benzyl alcohol **10a**. Compounds **12a** and **12b**, which bear an alkyl or alkenyl substituent at the 2 position of the imidazole, were prepared by triethyl phosphite reduction of the corresponding N-hydroxyimidazoles **11a** and **11b** according to literature procedures (Scheme 3).[12]

Biological Results and Discussion

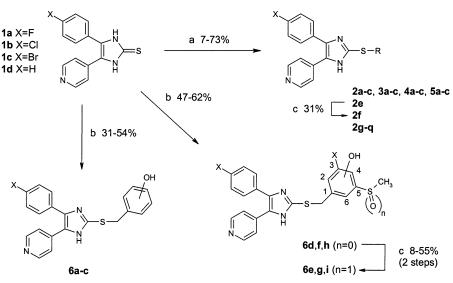In a first series of **2b** analogues, we confirmed that SAR concerning the pyridinyl-, 4-fluorophenyl- and

Table 2. Spacer[a]

compd	X	R	IC$_{50}$ ± SEM (μM) PBMC	
			TNF-α	IL-1β
SB 203580	bond	−S(O)CH$_3$	0.59 ± 0.09 (21)	0.037 ± 0.006 (20)
2i	−S−(CH$_2$)$_2$−	−S(O)CH$_3$	7.3 ± 0.3	0.50 ± 0.09
2j	−S−(CH$_2$)$_3$−	−S(O)CH$_3$	3.6 ± 1.4 (4)	0.18 ± 0.04 (4)
2k	−S−CH$_2$−	−H	3.5 ± 0.5	0.30 ± 0.01
2l	−S−(CH$_2$)$_2$−	−H	23.5 ± 1.5	0.64 ± 0.12
2m	−S−(CH$_2$)$_3$−	−H	16.0 ± 4.0	0.47 ± 0.17
12a	−CH$_2$−CH$_2$−	−H	5.4 ± 0.1	0.14 ± 0.01
12b		−H	6.5 ± 0.7 (4)	0.13 ± 0.07

[a] Results are given as the mean of 2 independent experiments, except where otherwise stated.
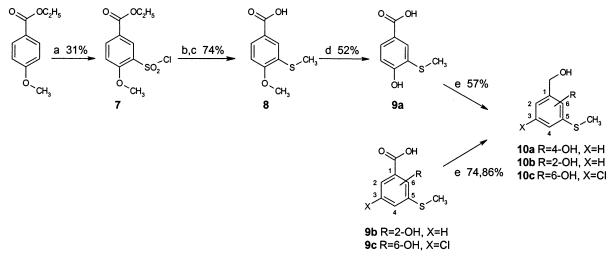
Scheme 1[a]

[a] Reagents: (a) R-hal, Na$_2$CO$_3$, THF/EtOH, reflux; (b) benzyl alcohol derivatives, 10% HCl, acetic acid, rt; (c) 1 aeq 35% H$_2$O$_2$, acetic acid, 10 °C then rt.

methanesulfinyl-moiety correspond to those which have been established for SB 203580 and its analogues.[11,12] The importance of the hydrogen bond between the pyridin-4-yl moiety of **2b** and Met 109 of p38 for inhibition of cytokine release from PBMC is underlined by the poor bioactivity of the pyridin-3-yl analogue **2d** (Table 1). Replacement of the fluoro atom in **2b** with other halogeno atoms in compounds **3b** and **4b** affected neither inhibition of p38 (Table 5) nor inhibition of cytokine release from PBMC significantly (Table 1). However, a simple phenyl group at the 5 position of the core imidazole led to reduced activity for compound **5b** in the enzyme but not in the cellular assay. Within each halogenoaryl series as well as in the aryl series, a remarkable difference in inhibitory potency of the sulfides **2a**, **3a**, **4a** and **5a** compared to the more polar sulfoxides/sulfones **2b,c**, **3b,c**, **4b,c** and **5b,c** was observed in the PBMC (Table 1) and whole blood assay (Table 6, compounds **2a−c**). Placement of the methanesulfinyl functionali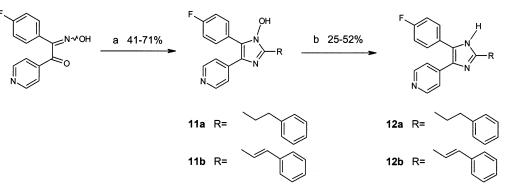ty of **2b** at the 3 or 2 position of the benzyl moiety provided the less potent regioisomers **2f** and **2h**. Moreover, the said difference in bioactivity between sulfides and sulfoxides disappeared in the case of the regioisomeric analogues **2e−h**. All these results concerning substituents at the 2, 4, and 5 position of the imidazole core were in good agreement with data reported for SB 203580 analogues.[11,12] In conclusion we assumed a similar binding mode to p38 for **2b** as for SB 203580. **2b** differs from the more active SB 203580 only in the distance between the imidazole nucleus and the 4-methanesulfinylphenyl moiety (Table 2). Therefore, we investigated how the nature and chain length of the spacer connecting these two parts of the molecule influence biological activity. Elongation of the spacer by one (compound **2i**) or two (compound **2j**) methylene units resulted in enhanced inhibition of p38 compared to the parent compound **2b**. (Table 5). However, this improved inhibitory potency did not show in the cellular assay (Table 2). Likewise, biological activity of compounds lacking the 4-methanesulfinylphenyl moiety
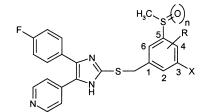
Scheme 2[a]

[a] Reagents: (a) SO$_3$HCl, CCl$_4$, −5 °C then 50 °C; (b) PPh$_3$, toluene, rt; (c) 10% NaOH, SO$_2$(OCH$_3$)$_2$, rt then reflux; (d) acetic acid/HBr 48%, reflux; (e) LiAlH$_4$, THF, rt then 60 °C.

Scheme 3[a]

[a] Reagents: (a) RCHO, ammonium acetate, acetic acid; (b) triethyl phosphite, DMF.

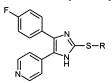**Table 3.** Substitution Patterns at the Benzylsulfanyl Moiety[a]

				IC$_{50}$ ± SEM (μM) PBMC	
compd	n	R	X	TNF-α	IL-1β
6d	0	4-HO	H−	1.1 ± 0.3	0.28 ± 0.14
6e	1	4-HO	H−	5.0 ± 0.3	2.3 ± 0.48
6f	0	2-HO	H−	5.1 ± 2.6	0.74 ± 0.26
6g	1	2-HO	H−	5.8 ± 1.5 (4)	1.0 ± 0.3 (4)
6h	0	6-HO	Cl−	13.3 ± 6.8	0.64 ± 0.22
6i	1	6-HO	Cl−	28.0 ± 1.0	4.4 ± 1.35

[a] Results are given as the mean of two independent experiments, except where otherwise stated.

(compounds **2k**, **2l**, **2m**) depended on the length of the side chain attached to the 2 position. Elongation of the spacer again led to notably decreased inhibition of cytokine release (Table 2). A 7-fold better inhibition of p38 was achieved by replacement of the sulfur in **2k** with a carbon atom in **12a** (Table 5). As with compounds **2i** and **2j**, the increase in potency was also not maintained in the cellular assay (Table 2). No difference was observed whether the spacer contained sp^3 or sp^2 hybrid

Table 4. Replacement of the Benzylsulfanyl Moiety[a]

		IC$_{50}$ ± SEM (μM) PBMC	
compd	R	TNF-α	IL-1β
2n	−CH$_2$—(naphthalenyl)	8.8 ± 2.2	0.82 ± 0.12
2o	−CH$_2$—(cyclohexyl)	33.8 ± 5.3	0.24 ± 0.04
2p	−CH$_2$−C≡N	2.3 ± 0.2	<0.1
2q	−CH$_3$	0.90 ± 0.19 (6)	0.044 ± 0.009 (4)

[a] Results are given as the mean of two independent experiments, except where otherwise stated.

carbon atoms (compounds **12a** and **12b** respectively). Potent inhibition of p38 is not the sole parameter affecting the activity of test compounds in the cellular assay. The different trends found for compounds **2b**, **2i-k**, and **12a** in the enzyme assay and in the PBMC assay may therefore be ascribed to differences in

Table 5. Inhibition of p38 MAP Kinase by Selected Compounds[a]

compd	IC$_{50}$ ± SEM (μM) p38	compd	IC$_{50}$ (μM) p38
SB 203580	0.29 ± 0.03 (7)	3b	1.40
2b (ML 3163)	4.0 ± 1.0 (2)	4b	3.8
2e	2.30	5b	12
2f	2.10	6a	5.7
2i	1.50	6d	3.8
2j	0.75	6e	3.4
2k	35	12a	0.69
2q	0.63 ± 0.08 (2)		

[a] Results are of one experiment, except where otherwise stated.

transport, membrane penetration or intracellular distribution. In general it appears that the presence of the 4-methanesulfinyl moiety (**2b** vs **2k**), the elongation of the spacer (**2i** and **2j** vs **2b**), and the replacement of the sulfur with a carbon atom (**12a** vs **2k**) though favorable for p38 inhibition have a disadvantageous effect on these properties. In a third independent study, we put the concept of an additional polar functionality at the benzylsulfanyl moiety to the test. Results in the PBMC assay for phenols **6a**−**c** showed that, preferably at the 3 and 4 position of the benzyl substituent, replacement of the methanesulfinyl moiety with a hydroxyl group is tolerated (Table 1). We speculated that combination of both polar functionalities should result in enhanced similarity between inhibitor and ATP and may subsequently lead to improved bioactivity. While sulfoxide **6e** indeed reduced the release of TNF-α from PBMC more efficiently than sulfoxide **2f** and phenol **6a**, a reversed result was obtained concerning the release of IL-1β (Table 3). Combination of hydroxyl and sulfide functionalities provided an unambiguous result with compound **6d** exceeding both **2e** and **6a** in potency with respect to inhibition of both cytokines. The same order of efficacy for the sulfide and sulfoxide was displayed by regioisomers **6f**,**g** and **6h**,**i**, albeit on a lower level than that by **6e** and **6f**. However, no such differences in potency between compounds containing either a sulfide or sulfoxide moiety were found in the p38 assay. Within the series of compounds **2e**,**f** and **6d**,**e**, neither the oxidation state of the sulfur nor the presence of an additional phenolic group at the 4 position considerably altered inhibition of p38 kinase activity (Table 5). We attributed these differences between p38 and PBMC results to the possibility that mainly at the 4 position of the benzyl moiety do suitable substituents contribute to enhanced binding properties of p38 inhibitors. A polar functionality is most favorable for this purpose and its benefit is illustrated by the 10-fold better inhibition of TNF-α release from whole blood by 4-OH derivative **6e** compared to 2-OH derivative **6g** (Table 6). Introduction of additional substituents at the 3 or 2 position of the benzyl moiety considerably alters the physicochemical properties of benzylsulfanyl imidazole compounds. In this respect, less polar substituents are better tolerated. The moderate potency of compounds **6h** and **6i** demonstrates that a large additional substituent such as the chloro atom is detrimental for bioactivity. In a final series of compounds, we elucidated the influence of the aromatic ring system as part of the substituent attached to the 2 position on bioactivity. The benzyl moiety of compound **2k** was not replaced neither by an extended aromatic system (compound **2n**) nor by a nonaromatic

ring (compound **2o**) without subsequent loss of activity (Table 4). Biological results comparable to those of **2k** were provided only by compound **2p** with a nonaromatic π-electron system serving as a suitable substitute for the phenyl ring. Following an incremental approach, we formally divided the benzyl moiety of compound **2k** into its C$_1$ and phenyl part. Subsequently we sought to determine the contribution of the phenyl ring to inhibition of cytokine release by preparation of methanesulfanyl imidazole **2q**. Surprisingly, **2q** exceeded parent compound **2k** in potency, being the only compound in this series to inhibit release of TNF-α from PBMC in the nanomolar range and to equal SB 203580 in anti-IL-1β activity (Table 4). Moreover, the improved inhibition of cytokine release from PBMC was also reflected by p38 kinase (Table 5) and whole blood (Table 6) results.

Conclusion

These findings prove that suitably substituted benzylsulfanyl imidazoles are efficient inhibitors of p38 and cytokine release, displaying characteristics comparable to those of model compound SB 203580. In conclusion we suggest for our initial lead **2b** and its analogues a binding mode to p38 similar to that of SB 203580. Substituents at the 2 position of the imidazole nucleus influence the physicochemical as well as the binding properties in this class of compounds. Enzyme data for benzylsulfanyl imidazole **2b**, for phenylalkyl analogues **2i** and **2j**, and for the sulfur-free compound **12a** indicate that the −S−CH$_2$− chain between core imidazole and phenyl moiety of **2b** does not constitute the optimum spacer with respect to inhibition of p38. The inhibitory superiority of imidazole derivatives containing better suited spacer molecules (compounds **2i**, **2j**, **12a**) disappears, however, in the cellular assay, which is probably due to the reduced ability of these compounds to penetrate the cellular membrane. Substituents at the 3 and 4 position of the benzylsulfanyl moiety contribute considerably to inhibition of p38 by compounds **2b**, **2e**−**f**, and **6a** compared to the simple benzylsulfanyl imidazole **2k**, which is about 10 times less active. The benzylsulfanyl group itself therefore seems to be rather unfavorable for inhibition of p38 and to need substituents for additional interactions with the enzyme. Polar substituents at the benzyl moiety enhance inhibition of cytokine release most effectively if attached to the 4 position. In a series of polyfunctionalized benzylsulfanyl imidazoles, combination of a polar and a more lipophilic substituent at the benzyl ring gives better results in the cellular assay than combination of two polar functionalities. On the basis of these results, we suggest that additional substituents at the 2 and 3 position of the benzyl moiety may point outside the ATP cleft, affecting the physicochemical properties of test compounds rather than their interaction with p38, if a polar substituent at the 4 position is already present (Figure 2). The latter may indeed be crucial for enzyme inhibition, interacting with residues on the fringe of the ATP binding site (e.g., in the phosphate binding ribbon or the activation loop). The cellular activity of **6d** may then be attributed to its combination of substituents serving both the purpose of good membrane penetration and tight binding to p38. However, the benefits of completely omitting the aromatic part of the benzyl moiety (compound **2q**) seem to

Table 6. Inhibition of Cytokine Release from Whole Blood by Selected Compounds[a]

	$IC_{50} \pm SEM$ (μM)			$IC_{50} \pm SEM$ (μM)	
compd	TNF-α	IL-1β	compd	TNF-α	IL-1β
SB 203580	0.94 ± 0.14 (12)	0.35 ± 0.09 (12)	2h	47.5 ± 16.5	4.0 ± 2.8
2a	>100	28.5 ± 1.5	2q	4.2 ± 0.7	1.2 ± 0.6
2b (ML 3163)	20.3 ± 4.8	2.78 ± 0.13	6e	9.0 ± 2.1	12.1 (1)
2c	28.8 ± 10.3	2.9 ± 1.7	6g	103 ± 27	13.0 ± 0.0
2f	33.5 ± 6.4 (4)	4.1 ± 3.0 (3)			

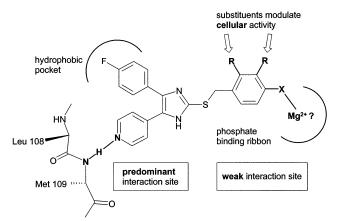[a] Results are given as the mean of two independent experiments, except where otherwise stated.

Figure 2. Weighting of interaction sites in the ATP cleft of p38 MAP kinase. Though an appropriately substituted benzyl moiety at the 2 position of the core imidazole may contribute moderately to biological activity, it is suggested that small substituents at this position allow for deeper penetration into the ATP binding cleft and subsequently much tighter binding of the pyridine and 4-fluorophenyl ring.

contradict this model and to rule out any significant contribution to bioactivity through the benzylsulfanyl moiety. The superior potency of **2q** in all three assays can, however, be reconciled with our initial concept if the importance of the hydrogen bond between the pyridine nitrogen and Met 109 of p38 is taken into account. The absence of any steric hindrance by substituents at the 2 position may allow compound **2q** to penetrate deeper into the ATP cleft of p38 with the pyridin-4-yl ring subsequently binding much tighter to the backbone NH of Met 109 (Figure 2). A strengthened binding at this predominant site of interaction may as a result overcompensate the loss of the comparatively weak interaction between any known substituent at the 2 position and the phosphate binding region or the activation loop of p38. Molecular modeling studies to further substantiate this preliminary concept are currently carried out.

Experimental Section

General. All reagents and solvents were of commercial quality and used without further purification. All reactions were carried out under an inert atmosphere of argon. Melting points were determined on a Buechi Melting Point B-545 apparatus and are thermodynamically corrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Spectrospin AC 200 at 200 MHz. Chemical shifts are reported in parts per million relative to TMS as internal standard. Infrared spectra were recorded using KBr pellets on a Nicolet Impact 410 or by ATR technique on a Perkin-Elmer Spectrum One spectrometer. TLC analyses were performed on fluorescent silica gel 60 plates (Macherey-Nagel Art.-Nr. 805021). Spots were visualized under 254-nm UV illumination. HPLC analyses were carried out on Merck Hitachi (Darmstadt) equipment, using a LiChrospher 100 RP-18 column (5μm) and eluting with MeCN/

NaH$_2$PO$_4$ buffer pH 3.5 (70:30) at a flow rate of 1.00 mL/min at 25 °C (UV detection at 254 nm). HPLC results are presented as retention times (min) and relative purity (%). Microanalyses were carried out on a Perkin-Elmer EA 2400 instrument. The following compounds were prepared according to literature procedures: SB 203580,[12] imidazole-2-thiones **1a−d**,[23] and benzoic acids **9b,c**.[26] Alkylhalides employed in General Procedure A were either commercially available or synthesized as previously reported.[28] 1-(4-Fluorophenyl)-2-pyridin-4-yl-1,2-dione 1-oxime was prepared from 2-(4-fluorophenyl)-1-pyridin-4-yl-ethanone[23] using the standard nitrosation protocol of Gallagher and co-workers.[12]

Preparation of 2-Alkylsulfanyl Imidazoles 2a−e, g−q, 3a−c, 4a−c, 5a−c, General Procedure A. A suspension of an appropriate imidazole-2-thione (1 equiv), Na$_2$CO$_3$ (1.2 equiv) and the appropriate arylalkyl- or alkyl chloride (1 equiv) in ethanol/THF 8"2 was heated to reflux for the given time. After cooling to room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by column chromatography or trituration to give 2-alkylsulfanyl imidazoles **2a−e, g−q, 3a−c, 4a−c, 5a−c**.

4-[5-(4-Fluorophenyl)-2-(4-methylsulfanyl-benzylsulfanyl)-1H-imidazol-4-yl]-pyridine (2a). This compound was prepared from imidazole-2-thione **1a** (1.0 g, 3.7 mmol) and 1-chloromethyl-4-methylsulfanyl-benzene according to general procedure A (4 h). Recrystallization from ethyl acetate yielded 0.11 g (7%) of **2a**: mp 243 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.18−7.55 (m, 10H, 4-Pyr, 4-F-Ph and 4-MeS-Ph), 8.41−8.52 (m, 2H, 4-Pyr), 12.80 (bs, 1H, exchangeable, NH); IR (ATR) 1226 cm^{-1} (C−F); HPLC 3.97 min, 97.4%. Anal. (C$_{22}$H$_{18}$FN$_3$S$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(4-methanesulfinyl-benzylsulfanyl)-1H-imidazol-4-yl]-pyridine (2b). This compound was prepared from imidazole-2-thione **1a** (1.0 g, 3.7 mmol) and 1-chloromethyl-4-methanesulfinyl-benzene according to general procedure A (3 h). Trituration with ethanol yielded 0.62 g (41%) of **2b**: mp 232 °C; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH$_3$), 4.48 (s, 2H, CH$_2$), 7.22−7.53 (m, 6H, 4-Pyr and 4-F-Ph), 7.57−7.65 (m, 4H, 4-MeS(O)-Ph), 8.45−8.48 (m, 2H, 4-Pyr), 12.75 (bs, 1H, exchangeable, NH); IR (ATR) 1226 (C−F), 1039 cm^{-1} (S=O); HPLC 1.92 min, 97.9%. Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(4-methanesulfonyl-benzylsulfanyl)-1H-imidazol-4-yl]-pyridine (2c). This compound was prepared from imidazole-2-thione **1a** (1.0 g, 3.7 mmol) and 1-chloromethyl-4-methanesulfonyl-benzene according to general procedure A (6.5 h). Trituration with hot ethyl acetate yielded 0.59 g (36%) of **2c**: mp 249 °C; ^{1}H NMR (DMSO-d_6) δ 3.19 (s, 3H, CH$_3$), 4.52 (s, 2H, CH$_2$), 7.25−7.51 (m, 6H, 4-Pyr and 4-F-Ph), 7.67 (d, 2H, 8.2 Hz, 4-MeSO$_2$-Ph), 7.89 (d, 2H, 8.3 Hz, 4-MeSO$_2$-Ph), 8.46−8.49 (m, 2H, 4-Pyr), 12.85 (bs, 1H, exchangeable, NH); IR (ATR) 1304 (SO$_2$), 1220 (C−F), 1145 cm^{-1} (SO$_2$); HPLC 2.10 min, 99.7%. Anal. (C$_{22}$H$_{18}$FN$_3$O$_2$S$_2$) C, H, N.

3-[5-(4-Fluorophenyl)-2-(4-methanesulfinyl-benzylsulfanyl)-1H-imidazol-4-yl]-pyridine (2d). This compound was prepared from 4-(4-fluoro-phenyl)-5-pyridin-3-yl-1,3-dihydro-imidazole-2-thione (0.42 g, 1.5 mmol) and 1-chloromethyl-4-methanesulfinyl-benzene according to general procedure A (8 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.05 g (8%) of **2d**: mp 127 °C; ^{1}H NMR (DMSO-d_6) δ 3.19 (s,3H, CH$_3$), 4.46 (s, 2H, CH$_2$), 7.16−7.46 (m, 5H, 3-Pyr and 4-F-Ph), 7.56−7.66 (m, 4H, 4-MeS(O)-Ph),

7.72−7.81 (m, 1H, 3-Pyr), 8.41−8.62 (m, 2H, 3-Pyr), 12.77 (bs, 1H, exchangeable, NH); IR (ATR) 1222 (C−F), 1027 cm^{-1} (S=O). Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(3-methylsulfanyl-benzylsulfa-nyl)-*1H*-imidazol-4-yl]-pyridine (2e). This compound was prepared from imidazole-2-thione **1a** (1.1 g, 4.1 mmol) and 1-chloromethyl-3-methylsulfanyl-benzene according to general procedure A (11 h). Recrystallization from ethanol yielded 1.21 g (73%): mp 218 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 2.40 (s, 3H, CH$_3$), 4.46 (s, 2H, CH$_2$), 7.16−7.43 (m, 6H, 4-F-Ph and 3-MeS-Ph), 7.56−7.63 (m, 2H, 4-F-Ph), 7.90−7.93 (m, 2H, 4-Pyr), 8.66−8.69 (m, 2H, 4-Pyr), NH not detected; ^{13}C NMR (DMSO-*d$_6$*) δ 14.5, 36.0, 116.0, 116.5, 121.4, 124.7, 125.4, 126.2, 129.0, 130.6, 131.1, 131.3, 136.9, 138.2, 138.7, 141.3, 143.3, 148.9, 160.1, 165.1; IR (KBr) 1225 cm^{-1} (C−F); HPLC 4.22 min, 98.3%. Anal. (C$_{22}$H$_{18}$FN$_3$S$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(3-methanesulfinyl-benzylsul-fanyl)-*1H*-imidazol-4-yl]-pyridine (2f). A suspension of **2e** (0.50 g, 1.2 mmol) in glacial acetic acid (7 mL) was treated with 35% aqueous H$_2$O$_2$ (0.13 mL, 1.3 mmol). The mixture was stirred at room temperature for 20.5 h, diluted with H$_2$O (5 mL), adjusted to pH 9 with 25% aqueous ammonia, and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine (3×) and dried over Na$_2$SO$_4$, and the solvent was removed to yield an oily residue, which was crystallized from diethyl ether/ethyl acetate (1:1). The crude product was purified by column chromatography (RP-18, methanol) to give 0.16 mg (31%) of **2f**: mp 171 °C; ^{1}H NMR (CD$_3$OD) δ 2.67 (s, 3H, CH$_3$), 4.37 (s, 2H, CH$_2$), 7.13−7.21 (m, 2H, 4-F-Ph), 7.37−7.58 (m, 8H, 4-Pyr, 4-F-Ph and 3-MeS(O)-Ph), 8.40−8.43 (m, 2H, 4-Pyr); ^{13}C NMR (CD$_3$OD) δ 39.6, 43.7, 116.9, 117.3, 123.0, 123.9, 125.1, 130.9, 131.9, 132.0, 133.2, 141.4, 146.6, 149.8, 150.2, 162.0, 167.0; IR (KBr) 1228 (C−F), 1019 cm^{-1} (S=O); HPLC 2.28 min, 95.8%. Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(2-methylsulfanyl-benzylsulfa-nyl)-*1H*-imidazol-4-yl]-pyridine (2g). This compound was prepared from imidazole-2-thione **1a** (0.28 g, 1.0 mmol) and 1-chloromethyl-2-methylsulfanyl-benzene according to general procedure A (5.5 h). Purification by column chromatography (SiO$_2$, ethyl acetate) yielded 0.24 g (59%) of **2g**: mp 223 °C; ^{1}H NMR (CD$_3$OD) δ 2.51 (s, 3H, CH$_3$), 4.44 (s, 2H, CH$_2$), 7.13−7.48 (m, 10H, 4-Pyr, 4-F-Ph and 2-MeS-Ph), 8.43−8.46 (m, 2H, 4-Pyr); IR (ATR) 1228 cm^{-1} (C−F). Anal. (C$_{22}$H$_{18}$FN$_3$S$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-2-(2-methanesulfinyl-benzylsul-fanyl)-*1H*-imidazol-4-yl]-pyridine (2h). This compound was prepared from imidazole-2-thione **1a** (0.28 g, 1.0 mmol) and 1-chloromethyl-2-methanesulfinyl-benzene according to general procedure A (4 h). Recrystallization from methanol/ethyl acetate yielded 0.23 g (54%) of **2h**: mp 205 °C; ^{1}H NMR (CD$_3$OD) δ 2.87 (s, 3H, CH$_3$), 4.50 (d, 1H, 13.6 Hz, CH$_2$), 4.62 (d, 1H, 13.6 Hz, CH$_2$), 7.24−7.33 (m, 2H, 4-F-Ph), 7.47−7.62 (m, 5H, 4-F-Ph, C^4−/C^5−/C^6−H 2-MeS(O)-Ph), 7.95 (d, 1H, 7.2 Hz, C^3-H 2-MeS(O)-Ph), 7.99−8.03 (m, 2H, 4-Pyr), 8.55−8.58 (m, 2H, 4-Pyr); ^{13}C NMR (CD$_3$OD) δ 35.1, 43.5, 117.5, 117.9, 123.5, 125.0, 126.9, 130.7, 132.0, 132.4, 132.5, 132.8, 133.4, 136.7, 138.9, 142.3, 143.8, 145.3, 152.3, 162.7, 167.6; IR (KBr) 1213 (C−F), 1033 cm^{-1} (S=O); HPLC 2.11 min, 98.7%. Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

4-{5-(4-Fluorophenyl)-2-[2-(4-methanesulfinyl-phenyl)-ethylsulfanyl]-*1H*-imidazol-4-yl}-pyridine (2i). This compound was prepared from imidazole-2-thione **1a** (0.25 g, 0.9 mmol) and 1-(2-chloroethyl)-4-methanesulfinyl-benzene according to general procedure A (50 h) upon treatment with a catalytic amount of NaI. Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.06 g (15%) of **2i**: mp 177 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 2.71 (s, 3H, CH$_3$), 3.06−3.13 (m, 2H, CH$_2$), 3.42−3.49 (m, 2H, CH$_2$), 7.25−7.65 (m, 10H, 4-Pyr, 4-F-Ph and 4-MeS(O)-Ph), 8.40−8.58 (m, 2H, 4-Pyr), 12.80 (bs, 1H, exchangeable, NH); IR (ATR) 1221 (C−F), 1032 cm^{-1} (S=O). Anal. (C$_{23}$H$_{20}$FN$_3$OS$_2$) C, H, N.

4-{5-(4-Fluorophenyl)-2-[3-(4-methanesulfinyl-phenyl)-propylsulfanyl]-*1H*-imidazol-4-yl}-pyridine (2j). This com-pound was prepared from imidazole-2-thione **1a** (0.25 g, 0.9 mmol) and 1-(3-chloropropyl)-4-methanesulfinyl-benzene ac-cording to general procedure A (40 h) upon treatment with a catalytic amount of NaI. Purification by column chroma-tography (SiO$_2$, DCM/ethanol 9:1) yielded 0.11 g (27%) of **2j**: mp 142 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 1.95−2.09 (m, 2H, CH$_2$), 2.71 (s, 3H, CH$_3$), 2.82 (t, 2H, 7.4 Hz, CH$_2$), 3.15 (t, 2H, 7.0 Hz, CH$_2$), 7.25−7.62 (m, 10H, 4-Pyr, 4-F-Ph and 4-MeS(O)-Ph), 8.46−8.49 (m, 2H, 4-Pyr), 12.86 (bs, 1H, exchangeable, NH); IR (ATR) 1222 (C−F), 1043 cm^{-1} (S=O). Anal. (C$_{24}$H$_{22}$FN$_3$OS$_2$) C, H, N.

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-*1H*-imidazol-4-yl]-pyridine (2k). This compound was prepared from imida-zole-2-thione **1a** (0.28 g, 1.0 mmol) and 1-bromomethyl-benzene according to general procedure A (6 h). Trituration with methanol yielded 0.17 g (47%) of **2k**: mp 223 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 4.41 (s, 2H, CH$_2$), 7.23−7.51 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.44−8.47 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchange-able, NH); IR (ATR) 1233 cm^{-1} (C−F). Anal. (C$_{21}$H$_{16}$FN$_3$S) C, H, N.

4-[5-(4-Fluorophenyl)-2-phenethylsulfanyl-*1H*-imida-zol-4-yl]-pyridine (2l). This compound was prepared from imidazole-2-thione **1a** (0.5 g, 1.9 mmol) and (2-chloroethyl)-benzene according to general procedure A (70 h) upon treat-ment with a catalytic amount of NaI. Trituration with ethanol yielded 0.30 g (42%) of **2l**: mp 257 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 2.99 (t, 2H, 7.4 Hz, CH$_2$), 3.40 (t, 2H, 7.5 Hz, CH$_2$), 7.17−7.53 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.44−8.46 (m, 2H, 4-Pyr), NH not detected; IR (ATR) 1223 cm^{-1} (C−F). Anal. (C$_{22}$H$_{18}$FN$_3$S) C, H, N.

4-[5-(4-Fluorophenyl)-2-(3-phenyl-propylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (2m). This compound was prepared from imidazole-2-thione **1a** (0.5 g, 1.9 mmol) and (3-chloro-propyl)-benzene according to general procedure A (70 h) upon treatment with a catalytic amount of NaI. Trituration with ethanol yielded 0.32 g (43%) of **2m**: mp 183 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 1.90−2.04 (m, 2H, CH$_2$), 2.72 (t, 2H, 7.4 Hz, CH$_2$), 3.12 (t, 2H, 7.0 Hz, CH$_2$), 7.18−7.51 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.37−8.44 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchangeable, NH); IR (ATR) 1226 cm^{-1} (C−F). Anal. (C$_{23}$H$_{20}$FN$_3$S) C, H, N.

4-[5-(4-Fluorophenyl)-2-(naphthalen-1-ylmethylsulfa-nyl)-*1H*-imidazol-4-yl]-pyridine (2n). This compound was prepared from imidazole-2-thione **1a** (0.28 g, 1.0 mmol) and 1-chloromethyl-naphthalene according to general procedure A (6.5 h). Purification by column chromatography (SiO$_2$, ethyl acetate) yielded 0.18 g (44%) of **2n**: mp 364 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 4.90 (s, 2H, CH$_2$), 7.25−7.62 (m, 10H, 4-Pyr, 4-F-Ph and Naphthyl), 7.80−7.98 (m, 2H, Naphthyl), 8.20−8.23 (m, 1H, Naphthyl), 8.48−8.52 (m, 2H, 4-Pyr), 12.86 (bs, 1H, exchangeable, NH); IR (ATR) 1225 cm^{-1} (C−F). Anal. (C$_{25}$H$_{18}$FN$_3$S) C, H, N.

4-[2-Cyclohexylmethylsulfanyl-5-(4-fluorophenyl)-*1H*-imidazol-4-yl]-pyridine (2o). This compound was prepared from imidazole-2-thione **1a** (0.25 g, 0.9 mmol) and chloro-methyl-cyclohexane according to general procedure A (47 h) upon treatment with a catalytic amount of NaI. Trituration with ethanol yielded 0.25 g (76%) of **2o**: mp 235 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 0.95−1.23 (m, 5H, c-Hex), 1.51−1.85 (m, 6H, c-Hex), 3.06 (d, 2H, 6.7 Hz, CH$_2$), 7.22−7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.43−8.45 (m, 2H, 4-Pyr), 12.76 (bs, 1H, exchangeable, NH); IR (ATR) 2922, 2852 (c-Hex), 1222 cm^{-1} (C−F). Anal. (C$_{21}$H$_{22}$FN$_3$S) C, H, N.

[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-yl-sulfanyl]-acetonitrile (2p). This compound was prepared from imidazole-2-thione **1a** (1.1 g, 4.0 mmol) and chloroaceto-nitrile according to general procedure A (18 h). Purification by column chromatography (SiO$_2$, ethyl acetate) yielded 0.32 g (26%) of **2p**: mp 219 °C; ^{1}H NMR (DMSO-*d$_6$*) δ 4.32 (s, 2H, CH$_2$), 7.34−7.57 (m, 6H, 4-Pyr and 4-F-Ph), 8.50−8.52 (m, 2H, 4-Pyr), 13.20 (bs, 1H, exchangeable, NH); IR (ATR) 2243 (CN), 1226 cm^{-1} (C−F). Anal. (C$_{16}$H$_{11}$FN$_4$S) C, H, N.

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-*1H*-imidazol-4-yl]-pyridine (2q). This compound was prepared from imida-zole-2-thione **1a** (0.41 g, 0.5 mmol) and iodomethane according

to general procedure A (8 h). Trituration with ethanol yielded 0.11 g (26%) of **2q**: mp 263 °C; ^{1}H NMR (DMSO-d_6) δ 2.61 (s, 3H, CH$_3$), 7.22−7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.42−8.45 (m, 2H, 4-Pyr), NH not detected; IR (ATR) 1226 cm^{-1} (C−F). Anal. (C$_{15}$H$_{12}$FN$_3$S) C, H, N.

4-[5-(4-Chlorophenyl)-2-(4-methylsulfanyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (3a). This compound was prepared from imidazole-2-thione **1b** (0.26 g, 0.9 mmol) and 1-chloromethyl-4-methylsulfanyl-benzene according to general procedure A (6.5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.25 g (66%) of **3a**: mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.18−7.56 (m, 10H, 4-Pyr, 4-Cl-Ph and 4-MeS-Ph), 8.45−8.55 (m, 2H, 4-Pyr), 12.86 (bs, 1H, exchangeable, NH); IR (ATR) 684 cm^{-1} (C−Cl). Anal. (C$_{22}$H$_{18}$ClN$_3$S$_2$) C, H, N.

4-[5-(4-Chlorophenyl)-2-(4-methanesulfinyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (3b). This compound was prepared from imidazole-2-thione **1b** (0.26 g, 0.9 mmol) and 1-chloromethyl-4-methanesulfinyl-benzene according to general procedure A (6.5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.23 g (62%) of **3b**: mp 224 °C; ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 3H, CH$_3$), 4.47 (s, 2H, CH$_2$), 7.31−7.65 (m, 10H, 4-Pyr, 4-Cl-Ph, 4-MeS(O)-Ph), 8.44−8.54 (m, 2H, 4-Pyr), 12.87 (bs, 1H, exchangeable, NH); IR (ATR) 1033 (S=O), 677 cm^{-1} (C−Cl). Anal. (C$_{22}$H$_{18}$ClN$_3$OS$_2$) C, H, N.

4-[5-(4-Chlorophenyl)-2-(4-methanesulfonyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (3c). This compound was prepared from imidazole-2-thione **1b** (0.26 g, 0.9 mmol) and 1-chloromethyl-4-methanesulfonyl-benzene according to general procedure A (6.5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.22 g (54%) of **3c**: mp 232 °C; ^{1}H NMR (DMSO-d_6) δ 3.19 (s, 3H, CH$_3$), 4.52 (s, 2H, CH$_2$), 7.32−7.58 (m, 6H, 4-Pyr and 4-Cl-Ph), 7.67 (d, 2H, 8.2 Hz, 4-MeSO$_2$-Ph), 7.88 (d, 2H, 8.3 Hz, 4-MeSO$_2$-Ph), 8.45−8.55 (m, 2H, 4-Pyr), 12.89 (bs, 1H, exchangeable, NH); IR (ATR) 1300, 1141 (SO$_2$), 681 cm^{-1} (C−Cl). Anal. (C$_{22}$H$_{18}$ClN$_3$O$_2$S$_2$) C, H, N.

4-[5-(4-Bromophenyl)-2-(4-methylsulfanyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (4a). This compound was prepared from imidazole-2-thione **1c** (0.25 g, 0.75 mmol) and 1-chloromethyl-4-methanesulfanyl-benzene according to general procedure A (5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.14 g (40%) of **4a**: ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH$_3$), 4.36 (s, 2H, CH$_2$), 7.16−7.87 (m, 10H, 4-Pyr, 4-Br-Ph and 4-MeS-Ph), 8.45−8.55 (m, 2H, 4-Pyr), 12.90 (bs, 1H, exchangeable, NH). Anal. (C$_{22}$H$_{18}$BrN$_3$S$_2$) C, H, N.

4-[5-(4-Bromophenyl)-2-(4-methanesulfinyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (4b). This compound was prepared from imidazole-2-thione **1c** (0.25 g, 0.75 mmol) and 1-chloromethyl-4-methanesulfinyl-benzene according to general procedure A (10 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.13 g (36%) of **4b**: mp 222 °C; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH$_3$), 4.48 (s, 2H, CH$_2$), 7.40−7.62 (m, 20H, 4-Pyr, 4-Br-Ph and 4-MeS(O)-Ph), 8.49−8.57 (m, 2H, 4-Pyr), 12.90 (bs, 1H, exchangeable, NH); IR (ATR) 1035 cm^{-1} (S=O). Anal. (C$_{22}$H$_{18}$BrN$_3$OS$_2$) C, H, N.

4-[5-(4-Bromophenyl)-2-(4-methanesulfonyl-benzylsulfanyl)-*1H*-imidazol-4-yl]-pyridine (4c). This compound was prepared from imidazole-2-thione **1c** (0.25 g, 0.75 mmol) and 1-chloromethyl-4-methanesulfonyl-benzene according to general procedure A (5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.12 g (32%) of **4c**: mp 226 °C; ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 3H, CH$_3$), 4.50 (s, 2H, CH$_2$), 7.33−7.89 (m, 10H, 4-Pyr, 4-Br-Ph and 4-MeSO$_2$-Ph), 8.45−8.54 (m, 2H, 4-Pyr), 12.91 (bs, 1H, exchangeable, NH); IR (ATR) 1303, 1145 cm^{-1} (SO$_2$). Anal. (C$_{22}$H$_{18}$BrN$_3$O$_2$S$_2$) C, H, N.

4-[2-(4-Methylsulfanyl-benzylsulfanyl)-5-phenyl-*1H*-imidazol-4-yl]-pyridine (5a). This compound was prepared from imidazole-2-thione **1d** (0.38 g, 1.5 mmol) and 1-chloromethyl-4-methanesulfanyl-benzene according to general procedure A (5.75 h). Purification by column chromatography

(SiO$_2$, DCM/ethanol 9:1) yielded 0.26 g (45%) of **5a**: mp 213 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.18−7.58 (m, 11H, 4-Pyr, Ph and 4-MeS-Ph), 8.44−8.47 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchangeable, NH). Anal. (C$_{22}$H$_{19}$N$_3$S$_2$) C, H, N.

4-[2-(4-Methanesulfinyl-benzylsulfanyl)-5-phenyl-*1H*-imidazol-4-yl]-pyridine (5b). This compound was prepared from imidazole-2-thione **1d** (0.38 g, 1.5 mmol) and 1-chloromethyl-4-methanesulfinyl-benzene according to general procedure A (5.5 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.15 g (25%) of **5b**: mp 189 °C; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH$_3$), 4.48 (s, 2H, CH$_2$), 7.32−7.52 (m, 7H, 4-Pyr and Ph), 7.57−7.67 (m, 4H, 4-MeS(O)-Ph), 8.45−8.54 (m, 2H, 4-Pyr), 12.84 (bs, 1H, exchangeable, NH); IR (ATR) 1051 cm^{-1} (S=O). Anal. (C$_{22}$H$_{19}$N$_3$OS$_2$) C, H, N.

4-[2-(4-Methanesulfonyl-benzylsulfanyl)-5-phenyl-*1H*-imidazol-4-yl]-pyridine (5c). This compound was prepared from imidazole-2-thione **1d** (0.38 g, 1.5 mmol) and 1-chloromethyl-4-methanesulfonyl-benzene according to general procedure A (4.25 h). Purification by column chromatography (SiO$_2$, DCM/ethanol 9:1) yielded 0.36 g (57%) of **5c**: mp 247 °C; ^{1}H NMR (DMSO-d_6) δ 3.21 (s, 3H, CH$_3$), 4.54 (s, 2H, CH$_2$), 7.31−7.58 (m, 7H, 4-Pyr and Ph), 7.70 (d, 2H, 8.3 Hz, 4-MeSO$_2$-Ph), 7.91 (d, 2H, 8.3 Hz, 4-MeSO$_2$-Ph), 8.45−8.59 (m, 2H, 4-Pyr), 12.87 (bs, 1H, exchangeable, NH); IR (ATR) 1298, 1145 cm^{-1} (SO$_2$). Anal. (C$_{22}$H$_{19}$N$_3$O$_2$S$_2$) C, H, N.

Preparation of 2-Benzylsulfanyl Imidazoles 6a−i, General Procedure B. 1a (1 equiv) was dissolved in glacial acetic acid (5 mL) by addition of 10% hydrochloric acid (10−15 drops). To the bright yellow solution was added the appropriate benzyl alcohol (1 equiv). After complete consumption of the starting materials (time/temperature), 35% aqueous H$_2$O$_2$ (1 equiv) was added for the preparation of sulfoxides **6e**, **6g**, and **6i**, and the mixture was stirred for another 4 h at room temperature. The reaction was diluted with H$_2$O (5 mL) and adjusted to pH 8 with 25% aqueous ammonia. A precipitate formed which was collected by filtration and washed with H$_2$O. The crude product was purified by column chromatography or trituration to give imidazol-2-yl-sulfanylmethyl-phenols **6a−i**.

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-ylsulfanylmethyl]-phenol (6a). This compound was prepared from imidazole-2-thione **1a** (0.20 g, 0.7 mmol) and 4-hydroxymethyl-phenol according to general procedure B (14 h, rt). Purification by column chromatography (SiO$_2$ 60, DCM/ethanol 9:1) yielded 0.08 g (31%) of **6a**: mp 250 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 4.32 (s, 2H, CH$_2$), 6.69 (d, 2H, 7.5 Hz, 4-HO-Ph), 7.19 (d, 2H, 7.9 Hz, 4-HO-Ph), 7.27−7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.43−8.53 (m, 2H, 4-Pyr), 9.41 (s, 1H, exchangeable, OH), 12.79 (bs, 1H, exchangeable, NH); IR (ATR) 1271 (OH bending), 1232 (C−F), 1004 cm^{-1} (C−O). Anal. (C$_{21}$H$_{16}$FN$_3$OS) C, H, N.

3-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-ylsulfanylmethyl]-phenol (6b). This compound was prepared from imidazole-2-thione **1a** (0.20 g, 0.7 mmol) and 3-hydroxymethyl-phenol according to general procedure B (9 h, reflux). Purification by column chromatography (SiO$_2$ 60, DCM/ethanol 9:1) yielded 0.14 g (54%) of **6b**: mp 230 °C; ^{1}H NMR (DMSO-d_6) δ 4.34 (s, 2H, CH$_2$), 6.65 (dd, 1H, 1.4/8.0 Hz, 3-HO-Ph C^4−H), 6.79−6.82 (m, 2H, 3-HO-Ph C^2−/C^6−H), 7.07−7.15 (m, 1H, 3-HO-Ph C^5−H), 7.27−7.53 (m, 6H, 4-Pyr and 4-F-Ph), 9.45 (s, 1H, exchangeable, OH), 12.83 (bs, 1H, exchangeable, NH); IR (ATR) 1287 (OH bending), 1241 (C−F), 1007 cm^{-1} (C−O). Anal. (C$_{21}$H$_{16}$FN$_3$OS) C, H, N.

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-ylsulfanylmethyl]-phenol (6c). This compound was prepared from imidazole-2-thione **1a** (0.20 g, 0.7 mmol) and 2-hydroxymethyl-phenol according to general procedure B (23 h, rt). Trituration with ethanol yielded 0.09 g (35%) of **6c**: mp 200 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 4.37 (s, 2H, CH$_2$), 6.70−6.85 (m, 2H, 2-HO-Ph), 7.05−7.14 (m, 1H, 2-HO-Ph), 7.23−7.53 (m, 7H, 4-Pyr, 4-F-Ph and 2-HO-Ph), 8.46−8.49 (m, 2H, 4-Pyr), 9.95 (bs, 1H, exchangeable, OH), 12.81 (bs, 1H, exchangeable, NH); IR (ATR) 1266 (OH bending), 1222 (C−F), 1005 (C−O). Anal. (C$_{21}$H$_{16}$FN$_3$OS) C, H, N.

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-yl-sulfanylmethyl]-2-methylsulfanyl-phenol (6d). This compound was prepared from **1a** (0.20 g, 0.7 mmol) and **10a** according to general procedure B (2 h, rt). Trituration with methanol yielded 0.14 g (47%) of **6d**: mp 230 °C (decomp.); ^{1}H NMR (CD$_3$OD) δ 2.21 (s, 3H, CH$_3$), 4.17 (s, 2H, CH$_2$), 6.69 (d, 1H, 8.0 Hz, 4-HO-Ph C^3–H), 6.90–7.01 (m, 2H, 4-HO-Ph C^2–/C^6–H), 7.12–7.21 (m, 2H, 4-F-Ph), 7.32–7.53 (m, 4H, 4-Pyr and 4-F-Ph), 8.39–8.43 (m, 2H, 4-Pyr); IR (KBr) 1227 (C–F), 1019 cm^{-1} (C–O); HPLC 2.41 min, 88.5%. Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-yl-sulfanylmethyl]-2-methanesulfinyl-phenol (6e). This compound was prepared from **1a** (0.20 g, 0.7 mmol), **10a** and 35% aqueous H$_2$O$_2$ according to general procedure B (2.5 h, rt). Trituration with acetone yielded 0.17 g (55%) of **6e**: mp 185 °C (decomp.); ^{1}H NMR (CD$_3$OD) δ 2.70 (s, 3H, CH$_3$), 4.28 (s, 2H, CH$_2$), 6.78 (d, 1H, 8.3 Hz, 4-HO-Ph C^3–H), 7.12–7.21 (m, 2H, 4-F-Ph), 7.28 (dd, 1H, 2.2/8.3 Hz, 4-HO-Ph C^2–H), 7.39–7.46 (m, 5H, 4-Pyr, 4-F-Ph and 4-HO-Ph C^6–H), 8.40 (m, 2H, 4-Pyr); IR (KBr) 1296 (OH bending), 1230 (C–F), 1062 (S=O), 1013 cm^{-1} (C–O); HPLC 1.76 min, 98.7%. Anal. (C$_{22}$H$_{18}$FN$_3$O$_2$S$_2$) C, H, N.

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-yl-sulfanylmethyl]-4-methylsulfanyl-phenol (6f). This compound was prepared from **1a** (0.50 g, 2.9 mmol) and **10b** according to general procedure B (1 h, rt). Trituration with methanol yielded 0.90 g (72%) of **6f**: mp 243 °C; ^{1}H NMR (DMF-d_7) δ 2.36 (s, 3H, CH$_3$), 4.46 (s, 2H, CH$_2$), 6.90 (d, 1H, 8.4 Hz, 2-HO-Ph C^3–H), 7.13 (dd, 1H, 2.3/8.3 Hz, 2-HO-Ph C^4–H), 7.27–7.35 (m, 3H, 4-F-Ph and 2-HO-Ph C^6–H), 7.51–7.53 (m, 2H, 4-Pyr), 7.58–7.65 (m, 2H, 4-F-Ph), 8.52–8.55 (m, 2H, 4-Pyr), 10.30–10.70 (bs, 1H, exchangeable, NH), OH not detected; ^{13}C NMR (DMF-d_7) δ 17.5, 32.5, 116.2, 116.6, 117.5, 120.0, 121.6, 126.5, 127.6, 129.8, 131.2, 131.4, 131.6, 143.5, 150.7, 155.0, 160.7, 162.9, 165.6; IR (KBr) 1275 (OH bending), 1230 (C–F), 1005 cm^{-1} (C–O); HPLC 3.27 min, 91.7%. Anal. (C$_{22}$H$_{18}$FN$_3$OS$_2$) C, H, N.

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-yl-sulfanylmethyl]-4-methanesulfinyl-phenol (6g). This compound was prepared from **1a** (0.27 g, 1.0 mmol), **10b** and 35% aqueous H$_2$O$_2$ according to general procedure B (1 h, rt). Recrystallization from toluene/THF 1:1 yielded 0.10 g (23%) of **6g**: mp 216 °C; ^{1}H NMR (CD$_3$OD) δ 2.60 (s, 3H, CH$_3$), 4.33 (s, 2H, CH$_2$), 6.96 (d, 1H, 8.2 Hz, 2-HO-Ph C^3–H), 7.11–7.21 (m, 2H, 4-F-Ph), 7.41–7.47 (m, 6H, 4-Pyr, 4-F-Ph and 2-HO-Ph C^4–/C^6–H), 8.39–8.42 (m, 2H, 4-Pyr); ^{13}C NMR (CD$_3$OD) δ 34.6, 43.5, 116.8, 117.2, 117.6, 123.0, 126.4, 127.7, 127.8, 128.6, 131.9, 132.0, 134.9, 143.0, 150.3, 160.1, 162.0, 166.9; IR (KBr) 1278 (OH bending), 1232 (C–F), 1031 (S=O), 1003 cm^{-1} (C–O); HPLC 1.79 min, 97.7%. Anal. (C$_{22}$H$_{18}$FN$_3$O$_2$S$_2$) C, H, N.

4-Chloro-2-[5-(4-fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-ylsulfanylmethyl]-6-methylsulfanyl-phenol (6h). This compound was prepared from **1a** (0.80 g, 3.0 mmol) and **10c** according to general procedure B (1.5 h, 75 °C). Trituration with methanol yielded 0.80 g (62%) of **6h**: mp 220 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 6.97 (d, 1H, 2.3 Hz, 3-Cl-Ph C^2–H), 7.17 (d, 1H, 2.3 Hz, 3-Cl-Ph C^4–H), 7.23–7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.48–8.50 (m, 2H, 4-Pyr), 12.74 (bs, 1H, exchangeable, NH), OH not detected; IR (KBr) 1259 (OH bending), 1225 (C–F), 1007 cm^{-1} (C–O); HPLC 5.19 min, 85.0%. Anal. (C$_{22}$H$_{17}$ClFN$_3$OS$_2$) C, H, N.

4-Chloro-2-[5-(4-fluorophenyl)-4-pyridin-4-yl-*1H*-imidazol-2-ylsulfanylmethyl]-6-methanesulfinyl-phenol (6i). This compound was prepared from **1a** (0.27 g, 1.0 mmol), **10c** and 35% aqueous H$_2$O$_2$ according to general procedure B (1.5 h, 75 °C). Purification by column chromatography (SiO$_2$ 60, acetone) yielded 0.04 g (8%) of **6i**: mp 175 °C (decomp.); ^{1}H NMR (CD$_3$OD) δ 2.72 (s, 3H, CH$_3$), 4.39 (s, 2H, CH$_2$), 7.14–7.23 (m, 2H, 4-F-Ph), 7.39 (d, 1H, 2.6 Hz, 3-Cl-Ph C^2–H), 7.42–7.49 (m, 6H, 4-Pyr, 4-F-Ph and 3-Cl-Ph C^4–H), 8.43–8.46 (m, 2H, 4-Pyr); IR (KBr) 1265 (OH bending), 1236 (C–F), 1051

(S=O), 1005 cm^{-1} (C–O); HPLC 2.59 min, 91.9%. Anal. (C$_{22}$H$_{17}$ClFN$_3$O$_2$S$_2$) C, H, N.

3-Chlorosulfonyl-4-methoxy-benzoic acid ethyl ester (7). Chlorosulfonic acid (17.5 mL, 263 mmol) was added dropwise to a solution of 4-methoxy-benzoic acid ethyl ester (15.7 g, 87.2 mmol) in CCl$_4$ while carefully maintaining the temperature below −5 °C. After addition of chlorosulfonic acid was complete the solution was stirred at room temperature for 2 h and finally heated to 50 °C until all of the starting material was consumed. The reaction was cooled to room temperature and poured unto ice/CCl$_4$ (100 mL). After separation of the organic layer the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine (2x), dried over Na$_2$SO$_4$ and the solvent was evaporated. The brown oily residue was crystallized from diethyl ether to yield 7.6 g (31%) of **7** as a white powder: ^{1}H NMR (CDCl$_3$) δ 1.41 (t, 3H, 7.1 Hz, CH$_3$), 4.14 (s, 3H, CH$_3$), 4.42 (q, 2H, 7.1 Hz, CH$_2$), 7.18 (d, 1H, 8.8 Hz, C^5–H), 8.37 (dd, 1H, 2.1/8.8 Hz, C^6–H), 8.63 (d, 1H, 2.1 Hz, C^2–H).

4-Methoxy-3-methylsulfanyl-benzoic acid (8). To a solution of **7** (5.1 g, 18.3 mmol) in toluene (50 mL) was added triphenylphosphine (20.5 g, 78.2 mmol) in small portions. The reaction was stirred at room temperature for 4.5 h. The precipitate was filtered off and the yellllow filtrate was extracted with 10% aqueous NaOH (4x). To the combined alkaline extracts was added sulfuric acid dimethyl ester (2 mL) and the reaction was stirred at room temperature for 2 h. A precipitate formed which was dissolved upon heating to reflux. The aqueous solution was cooled to room temperature and acidified with 20% hydrochloric acid. The precipitate was collected by filtration to yield 2.83 g of **8** (74%) as a white solid: ^{1}H NMR (CD$_3$OD) δ 2.43 (s, 3H, S–CH$_3$), 3.93 (s, 3H, O–CH$_3$), 6.98 (d, 1H, 8.4 Hz, C^5–H), 7.79–7.86 (m, 2H, C^2–/C^6–H).

4-Hydroxy-3-methylsulfanyl-benzoic acid (9a). A suspension of **8** (0.5 g, 2.5 mmol) in glacial acetic acid/hydrobromic acid 48% 1:1 (7 mL) was heated to reflux for 6 h. The reaction was cooled to room temperature, diluted with H$_2$O (20 mL), adjusted to pH 2 with 10% aqueous Na$_2$CO$_3$ and extracted with diethyl ether (4x). The combined organic extracts were dried over Na$_2$SO$_4$ and the solvent was evaporated. The residue was washed with H$_2$O to give 0.24 g (52%) of **9**: ^{1}H NMR (CDCl$_3$) δ 2.38 (s, 3H, CH$_3$), 7.05 (d, 1H, 8.5 Hz, C^5–H), 8.02 (dd, 1H, 2.2/8.5 Hz, C^6–H), 8.29 (d, 1H, 2.2 Hz, C^2–H), OH not detected.

4-Hydroxymethyl-2-methylsulfanyl-phenol (10a). Under cooling (5–10 °C) a solution of **9a** (1.37 g, 7.4 mmol) in THF (15 mL) was slowly added to LiAlH$_4$ (0.6 g, 15 mmol) in THF (25 mL). The reaction was stirred at room temperature for 0.5 h until the evolution of H$_2$ had ceased and stirred at 60 °C for another 17 h. The reaction was quenched by addition of ice, the precipitate dissolved with 10% aqueous H$_2$SO$_4$ and the solution extracted with diethyl ether (3x). The combined organic extracts were extracted with 10% aqueous NaOH (2x) and the combined alkaline extracts neutralized with 10% hydrochloric acid. The precipitate was collected by filtration and the aqueous filtrate extracted with diethyl ether (3x). The combined organic extracts were washed with brine (2x), dried over Na$_2$SO$_4$ and the solvent was evaporated to yield **10** as a white solid, combined yield 0.67 g (57%): ^{1}H NMR (CDCl$_3$) δ 2.34 (s, 3H, CH$_3$), 4.60 (s, 2H, CH$_2$), 6.97 (d, 1H, 8.3 Hz, C^6–H), 7.24 (dd, 2.0/8.4 Hz, C^5–H), 7.50 (d, 1H, 2.0 Hz, C^3–H), OH not detected.

2-Hydroxymethyl-4-methylsulfanyl-phenol (10b). This compound was prepared from 2-hydroxy-5-methylsulfanyl-benzoic acid as described in the synthesis of **10a**, yield 1.18 g (86%): ^{1}H NMR (CDCl$_3$) δ 2.42 (s, 3H, CH$_3$), 4.81 (s, 2H, CH$_2$), 6.82 (d, 1H, 8.4 Hz, C^6–H), 7.01 (d, 1H, 2.1 Hz, C^3–H), 7.17 (dd, 1H, 2.3/8.4 Hz, C^5–H), OH not detected.

4-Chloro-2-hydroxymethyl-6-methylsulfanyl-phenol (10c). This compound was prepared from 5-chloro-2-hydroxy-3-methylsulfanyl-benzoic acid as described in the synthesis of **10a**, yield 1.55 g (74%): ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, CH$_3$), 4.52 (s, 2H, CH$_2$), 5.4 (bs, 1H, exchangeable, OH), 7.03

(d, 1H, 2.6 Hz, C^3–H), 7.11 (d, 1H, 2.4 Hz, C^5–H), 9.02 (bs, 1H, exchangeable, OH).

5-(4-Fluorophenyl)-2-phenethyl-4-pyridin-4-yl-imida-zol-1-ol (11a). To a suspension of 1-(4-fluorophenyl)-2-pyridin-4-yl-ethane-1,2-dione 1-oxime (1.0 g, 4.1 mmol) in glacial acetic acid (15 mL) were added ammonium acetate (0.76 g, 10 mmol) and 3-phenyl-propionaldehyde (0.83 g, 6.2 mmol). The reaction was heated to reflux for 6 h, cooled to room temperature, and diluted with H_2O. The dark brown solution was neutralized with 10% aqueous Na_2CO_3. Upon extraction with DCM, a precipitate formed between aqueous and organic layer which was collected by filtration to give 1.05 g (71%) of **11a** as a gray powder: ^1H NMR (DMSO-d_6) δ 2.55–2.63 (m, 2H, CH_2), 2.82–2.90 (m, 2H, CH_2), 7.08–7.17 (m, 7H, 4-F-Ph and Ph), 7.24–7.30 (m, 4H, 4-Pyr and 4-F-Ph), 8.29–8.32 (m, 2H, 4-Pyr), OH not detected; IR (ATR) 1229 cm^{-1} (C–F).

5-(4-Fluorophenyl)-4-pyridin-4-yl-2-styryl-imidazol-1-ol (11b). This compound was prepared from 1-(4-fluorophenyl)-2-pyridin-4-yl-ethane-1,2-dione 1-oxime (2.2 g, 9.0 mmol), ammonium acetate (1.7 g, 22 mmol), and 3-phenyl-propenal (1.8 g, 13.2 mmol) as described in the synthesis of **11a**, yield 1.3 g (41%): ^1H NMR (DMSO-d_6) δ 7.20 (d, 1H, 16.3 Hz, CH), 7.30–7.72 (m, 12H, 4-Pyr, 4-F-Ph, Ph and CH), 8.43–8.46 (m, 2H, 4-Pyr), 11.95 (bs, 1H, exchangeable, OH); IR (ATR) 1227 cm^{-1} (C–F).

4-[5-(4-Fluorophenyl)-2-phenethyl-1H-imidazol-4-yl]-pyridine (12a). Triethyl phosphite (1.0 mL, 5.7 mmol) was added dropwise to a solution of **11a** (0.95 g, 2.6 mmol) in DMF (20 mL). The reaction was stirred at 100 °C for 20 h. After cooling to room temperature, the mixture was diluted with H_2O (60 mL), and the aqueous solution was extracted with ethyl acetate (3×). The combined organic extracts were washed with brine (3×) and dried over Na_2SO_4, and the solvent was removed to yield a dark orange, semisolid residue, which solidified upon trituration with diethyl ether/ethanol (19:1) to give 0.22 g (25%) of **12a** as a cream-colored powder: mp 225 °C; ^1H NMR (DMSO-d_6) δ 2.96–3.10 (m, 4H, 2x CH_2), 7.23–7.53 (m, 13H, 4-Pyr, 4-F-Ph and Ph), 8.43–8.45 (m, 2H, 4-Pyr), 12.40 (bs, 1H, exchangeable, NH); IR (ATR) 1230 cm^{-1} (C–F). Anal. ($C_{22}H_{18}FN_3$) C, H, N.

4-[5-(4-Fluorophenyl)-2-styryl-1H-imidazol-4-yl]-pyri-dine (12b). This compound was prepared from **11b** (1.2 g, 3.4 mmol) as described in the synthesis of **12a**, yield 0.66 g (52%): mp 270 °C; ^1H NMR (DMSO-d_6) δ 7.10 (d, 1H, 16.5 Hz, CH), 7.29–7.63 (m, 12H, 4-Pyr, 4-F-Ph, Ph and CH), 8.45–8.56 (m, 2H, 4-Pyr), NH not detected; IR (ATR) 1229 (C–F), 963 cm^{-1} (trans db: C–H out of plane). Anal. ($C_{22}H_{16}FN_3$) C, H, N.

Biological Evaluation: PBMC and Whole Blood Assay.[29] Stock solutions of test compounds were prepared by serial dilution in DMSO (PBMC assay) or Cremophor EL/ethanol 70:30 (whole blood assay). Mononuclear cells were isolated from whole blood of healthy human donors by density gradient centrifugation and the resulting suspension adjusted to an approximate cell count of 10^6 mL^{-1} (PBMC assay). Cell samples (PBMC assay) or whole blood samples (whole blood assay) were preincubated for 15 min (37 °C, 5% CO_2) with test compounds (test samples), 1% DMSO (control samples, PBMC assay) or 1% Cremophor EL/ethanol 70:30 (control samples, PBMC assay). DMSO (PBMC assay) or Cremophor EL/ethanol 70:30 (whole blood assay) were present at a concentration of 1% in all samples. Biosynthesis of cytokines was induced in all samples by stimulation with 1μg/mL LPS (from *E. coli*, serotype 026:B6, Sigma Aldrich). All samples were stimulated for 4 h (37 °C, 5% CO_2). The cell reaction was terminated in an ice bath, and the samples were centrifuged. Concentrations of IL-1β and TNF-α in supernatants were determined by ELISA (Beckman Coulter Immunotech). The anticytokine activity of each compound was determined by blotting the percent reduction of cytokine concentration in test samples compared to control samples on semilogarithmic paper over the concentration range of test compounds (10^{-4}–10^{-8} M). Results are given as IC$_{50}$ values (μM). All assays were carried out at least in duplicate.

p38 MAP Kinase Assay.[30] Inhibitor dilutions were made in DMSO. Final DMSO concentrations did not exceed 1%. KB2 buffer was prepared by dissolution of p38 MAP kinase (16 μL) in KB1 buffer (7984 μL) containing 50 mM Tris (pH 7.5), 10 mM MgCl$_2$, 10 mM β-glycerolphosphate, 100 μg/mL BSA, 1mM DTT, 100 μM ATP and 0.1 mM Na$_3$VO$_4$. Samples of KB2 buffer were preincubated for 5 min with test compounds in different concentrations (37 °C). The preincubated samples were transferred to a 96-well Immulon 4HBX plate coated with ATF-2 and incubated for 1 h (37 °C). Control samples were included containing only KB2 buffer. The 96-well plate was thoroughly washed with ultrapure H_2O and incubated with phospho-ATF-2-antibody (Cell Signaling Technology) for 1 h (37 °C). The 96-well plate was thoroughly washed with ultrapure H_2O and incubated with alkaline phosphatase conjugated GAR-antibody (Santa Cruz Biotechnology) for 1 h (37 °C). The 96-well plate was thoroughly washed with ultrapure H_2O, blocking buffer containing Tween 20 (0.05%), BSA (0.25%) and NaN$_3$ (0.02%) in TBS and again with ultrapure H_2O. 4-Nitrophenolphosphate was added to all wells and the optical density was measured at 405 nm. Inhibition of p38 MAP kinase was determined by blotting the percent reduction of phospho-ATF-2 concentration in test samples compared to control samples on semilogarithmic paper over the concentration range of test compounds (10^{-4}–10^{-8} M). Results are given as IC$_{50}$-values (μM).

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