Novel Substituted Pyridinyl Imidazoles as Potent Anticytokine Agents with Low Activity against Hepatic Cytochrome P450 Enzymes

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A series of polysubstituted pyridin-4-yl imidazole inhibitors of p38 MAP (mitogen-activated protein) kinase was prepared as small molecular anticytokine agents and drug candidates for the treatment of chronic inflammatory diseases. The contribution of substituents at the pyridinyl and imidazole moiety to selective inhibition of p38 without concomitant cytochrome P450 interaction was evaluated. Placement of a 1-phenylethyl (**7e**, p38: IC_{50} 0.38 μM) or acetyl substituent at the exocyclic nitrogen of several 2-aminopyridine imidazoles led to the identification of potent p38 inhibitors which exceeded the starting lead ML 3375 (p38: IC_{50} 0.63 μM) in potency. A preliminary modeling study related the enhanced bioactivity of **7e** to a novel interaction between its 1-phenylethylamino side chain and a hydrophobic pocket close to the linker region of p38. The most active p38 inhibitors in this series maintained their efficacy in functional PBMC (peripheral blood mononuclear cells) and whole blood assays. Moreover, cytochrome P450 interaction, which has been linked to the liver toxicity observed for model p38 inhibitors, was very efficiently reduced through introduction of a tetramethylpiperidine substituent at the 1 position of the imidazole nucleus. Combination of both structural features provided **14c** (p38: 0.34 μM, inhibition of CYP1A2 0%, 2C9 2.6%, 2C19 7.6% at 10 μM), which was selected for further development.

Introduction

The stress-induced signal transduction cascade which regulates the biosynthesis and release of the proinflammatory cytokine tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) in various cell types of the mononuclear lineage requires a dual specifity Ser/Thr kinase, termed p38 MAP kinase, as an essential component.[1] TNF-α and IL-1β mediate a multitude of cellular events underlying chronic inflammatory conditions such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).[2,3] In addition to its important role for the secretion of proinflammatory cytokines, p38 is also involved in the activation of matrix metalloproteinases (MMP)[4] and the induction of cyclooxygenase 2 (COX-2) transcription,[5] proteins that are involved in the process of tissue destruction and inflammation. Because of its multiple functions in modulating the inflammatory response, p38 has become a most rewarding molecular target for the development of novel small molecular drugs for the treatment of chronic inflammatory diseases.[6,7] Several inhibitors of p38 MAP kinase have been demonstrated to efficiently reduce cytokine levels in functional assays as well as in animal tests.[8,9] Many of these compounds were derived from the prototypical pyridin-4-yl imidazole SB 203580 (Table 1), and the structural requirements for p38 inhibition have been extensively discussed.[8−12] Crystallographic studies[13−15] facilitated the acquisition of SAR and together with biochemical investigations[16,17] revealed compounds of the pyridinyl imidazole class as competitive inhibitors at the ATP site of p38 (Figure 1).

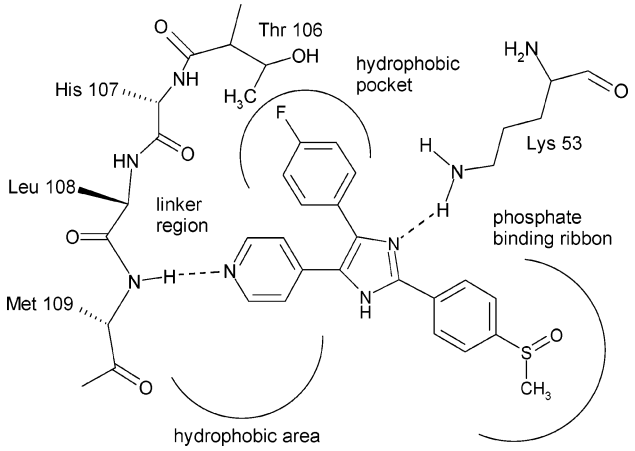

Figure 1. Schematic drawing of important interactions between the prototypical pyridin-4-yl imidazole inhibitor SB 203580 and the ATP binding site of p38 (modified from ref 11). The hydrophobic area below the linker region is not occupied by SB 203580.

The general architecture of the ATP site in protein kinases has recently been reviewed.[18] The linker region between the N- and C-terminal domain, surrounded by two hydrophobic regions, serves as a highly significant anchor for the binding of ATP-site directed kinase inhibitors (Figure 1).[18] A common feature observed in all crystal structures of p38 in complex with respective pyridin-4-yl imidazole derivatives is the formation of a

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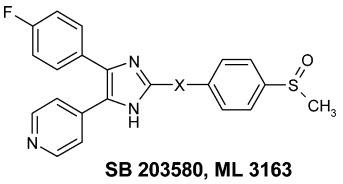
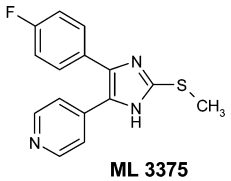
Table 1. Pyridinyl Imidazole Inhibitors of P38 MAP Kinase and Cytokine Release



SB 203580, ML 3163

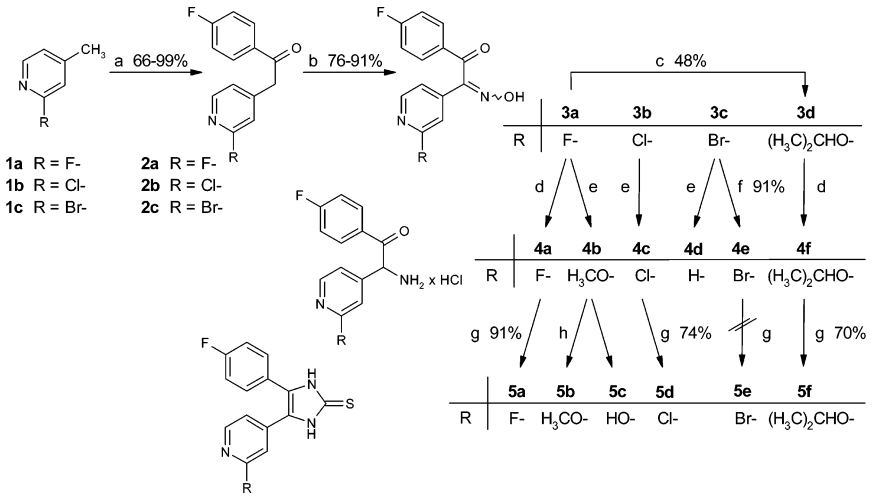


ML 3375

		$IC_{50} \pm$ SEM (μM)	$IC_{50} \pm$ SEM (μM) PBMC	
compd	X	p38[a]	TNF-α[a]	IL-1β[a]
SB 203580	bond	0.29 ± 0.03 (7)	0.59 ± 0.09 (21)	0.037 ± 0.006 (20)
ML 3163	-S−CH_2-	4.0 ± 1.0 (2)	1.1 ± 0.4 (4)	0.38 ± 0.13 (4)
ML 3375	−	0. 63 ± 0.08 (2)	0.90 ± 0.19 (6)	0.044 ± 0.009 (4)

[a] Number in brackets denotes number of experiments.

Scheme 1[a]



[a] Reagents: (a) LDA, 4-fluoro-*N*-methoxy-*N*-methylbenzamide, THF, −85 °C then 0 °C; (b) $NaNO_2$, acetic acid, 10 °C then rt; (c) saturated 2-propanolic hydrogen chloride, reflux; (d) H_2, Pd−C 10%, 1 atm, 2-propanolic hydrogen chloride, rt, all yields: 100%; (e) H_2, Pd−C 10%, 1 atm, methanolic hydrogen chloride, rt, yield: 100%; (f) Zn°, H_2SO_4, ethanol, −10 °C then rt; (g) KSCN, DMF, reflux; (h) KSCN, 10% HCl, reflux, yields: **5b**, 31%; **5c**, 13%.

hydrogen bond between the backbone NH of Met109 in the linker region and the pyridine nitrogen of the inhibitor, thus underlining the crucial importance of this pyridine ring for biological activity (Figure 1).[13−15] While the 4-fluorophenyl ring of SB 203580 binds to a hydrophobic region which in p38 is represented by an unusually spacious pocket, a second hydrophobic area below the linker region is left unoccupied by simple pyridin-4-yl imidazole inhibitors.[13,15]

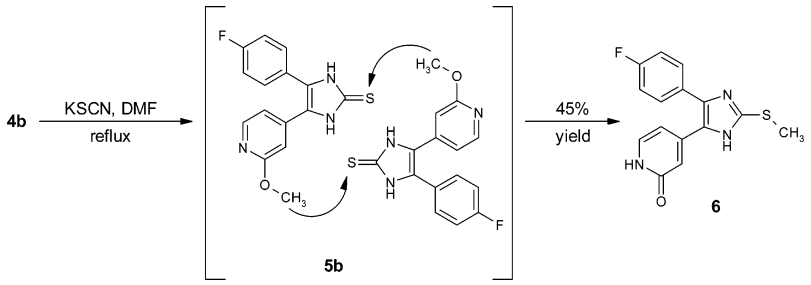
The clinical development of first generation p38 inhibitors has been obstructed by their severe liver toxicity.[19] This has been attributed to interference with hepatic cytochrome P450 enzymes,[19] as both pyridine and imidazole are known ligands for the heme iron of cytochrome P450.[20] It remains unclear to date if one or both of these heterocycles are responsible for the observed liver toxicity of pyridin-4-yl imidazoles, and various strategies have been applied to separate p38 inhibition from cytochrome P450 interaction. The pyridine[9,19] as well as the imidazole[21−24] ring have been replaced with other suitable heterocycles, and sterically demanding substituents have been introduced at the imidazole N1[10] or the 2 position of the pyridine.[9]

Previously we have reported about alkylsulfanyl imidazole derivatives ML 3163 and ML 3375 as potent inhibitors of p38 and cytokine release (Table 1).[25] During the design of these compounds, it was hoped that the reduced basicity of their thioimidazole core as compared to 2-carba analogues such as SB 203580 might lead to reduced cytochrome P450 interaction. However, in the present study we describe that contrary to this initial concept, only against cytochrome P450 1A2 does ML 3163 show decreased inhibition, while various other isoforms of cytochrome P450 are still inhibited by ML 3163 and those alkylsulfanyl imidazole analogues bearing a simple pyridin-4-yl ring. To dissect their desired p38 inhibitory potency from potential liver toxic side effects, we prepared a set of ML 3163 and ML 3375 analogues substituted at the pyridine C2 and imidazole N1 positions. To this end we further extended the scope of our novel synthetic method for the regioselective preparation of N-substituted imidazoles.[26] Suitable combination of substituents at both heterocycles yielded several compounds which displayed a highly promising profile for development as antiinflammatory agents due to their enhanced anticytokine activity and reduced affinity for cytochrome P450.

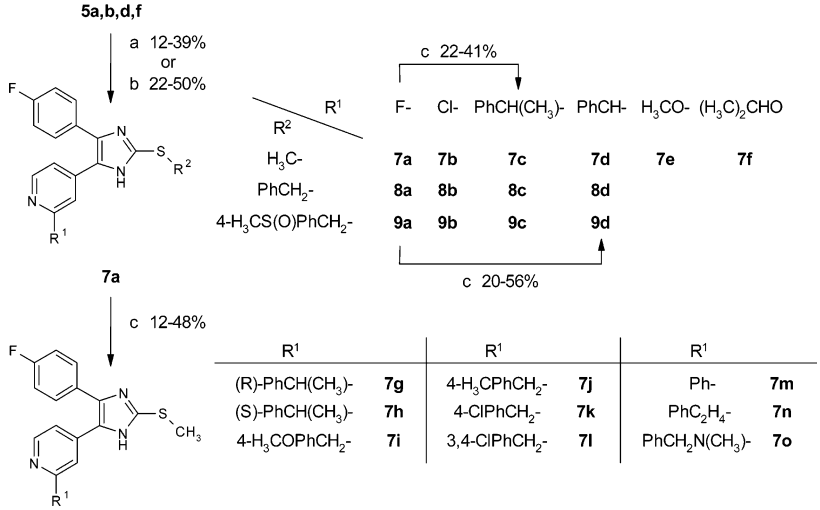
Chemistry

The general synthesis of target compounds **6**−**9** (Schemes 2 and 3) was built around imidazole thiones **5a**−**f** as the key intermediates (Scheme 1). The synthetic pathway devised for **5a**−**f** started from ketones **2a**−**c** and pursued a nitrosation/reduction/cyclization

Scheme 2



Scheme 3[a]



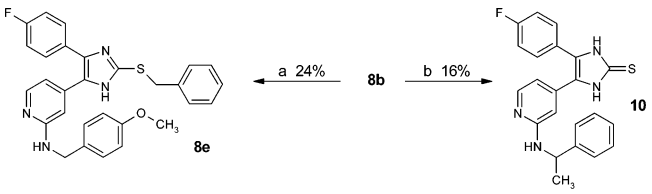
[a] Reagents: (a) R^2-hal, ethanol/THF 8+2, reflux; (b) iodomethane (**7f**) or 1-chloromethyl-4-methanesulfinylbenzene (**9b**), NaH (55−65%), THF, rt; (c) excess R^1-NH_2, neat, 160−180 °C.

strategy. **2a**−**c** were obtained according to the low-temperature protocol described by Liverton for the synthesis of structurally related ketones (Scheme 1).[9] 2-Halogeno-4-methylpyridines **1a**−**c** were deprotonated with LDA and the resulting picolyllithium derivatives reacted with 4-fluoro-*N*-methoxy-*N*-methylbenzamide.[8] Upon treatment with sodium nitrite in acetic acid ketones **2a**−**c** were readily converted into the corresponding α-oximinoketones **3a**−**c**. The TLC and ^{1}H NMR data for the material thus obtained indicated that in each instance only a single oxime regioisomer had been formed. This is in marked contrast to previously reported findings where α-nitrosation of ketones with sodium nitrite in aqueous acetic acid/THF has led to a mixture of oxime regioisomers.[9] Heating of fluoropyridine **3a** in 2-propanolic hydrogen chloride afforded the corresponding isopropanoxy pyridine **3d**.

The conversion of α-oximinoketones **3a**−**d** into the corresponding α-aminoketones was required prior to the ring closure reaction with potassium thiocyanate. Numerous methods for the transformation of oximes into amines have been disclosed,[27,28] the vast majority of which does not avoid concomitant reduction of the oxo functionality. Thus, the treatment of an α-oximinoketone similar to **3a**−**d** with H_2/Pd−C under neutral conditions has been reported to afford the corresponding amino alcohol.[29] However, preliminary studies suggested Pd-catalyzed hydrogenation as a suitable approach toward the selective reduction of the oxime group when carried out under acidic conditions. In alcoholic hydrogen chloride, the oxime functionality in α-oximinoketones **3a**−**d** was reduced to the corresponding amine after 6 h, while simultaneous hydrogenation of the ketone group to the corresponding alcohol was never observed under these conditions. Using this protocol, we prepared α-aminoketones **4a**, **4c**, and **4f**. In the case of **3a**, the successful and selective hydrogenation of the oxime group was accompanied by the premature acid-catalyzed nucleophilic replacement of the fluorine substituent at the pyridine nucleus by the solvent alcohol. In saturated methanolic hydrogen chloride, **3a** was completely converted into alkoxypyridine **4b** during the hydrogenation reaction. Efforts directed at the optimization of this reaction step revealed that use of the sterically less demanding methanol, saturation of the alcohol with hydrogen chloride, and elevated temperatures favored nucleophilic substitution. In 2-propanolic hydrogen chloride, the formation of the corresponding alkoxypyridine **4f** occurred only as a side reaction of negligible proportions. However, treatment of α-oximinoketone **3c** according to this protocol effected the hydrogenolytic cleavage of the bromine−carbon bond and resulted in the formation of the unsubstituted pyridin-4-yl derivative **4d**. We obtained the desired α-aminoketone **4e** by using zinc powder as an alternative reducing agent, but the general applicability of this method was limited by the variable yields obtained and the tedious workup procedure required.[30]

α-Aminoketones **4a**, **4c**, and **4f** were employed in the key cyclization step with potassium thiocyanate in DMF to yield the corresponding imidazole thiones **5a**, **5d**, and **5f**. However, this general method failed in the case of bromopyridine **4e** where only the rapid decomposition of the starting material, but not the formation of

Scheme 4[a]



[a] Reagents: (a) excess 4-methoxybenzylamine, neat, reflux; (b) excess (*RS*)-1-phenylethylamine, neat, reflux.

imidazole-2-thione **5e** was observed. On the other hand, the ring closure reaction of methoxypyridine **4b** with KSCN presumably afforded imidazole-2-thione **5b**, though we were not able to isolate this putative primary reaction product. Instead, the aprotic reaction medium permitted **5b** to undergo an unexpected in-situ intra- or intermolecular transfer reaction of the methyl group which led to the formation of 2-methylsulfanyl imidazole **6** as the sole reaction product (Scheme 2). The structure assigned to **6** is strongly supported by the characteristic singulets for the pyridone (δ = 11.38 ppm) and methylsulfanyl protons (δ = 2.61 ppm) in the ^{1}H NMR spectrum as well as by the presence of the strong NH bending in the IR spectrum (λ^{-1} = 1634 cm^{-1}). We conclude that this rearrangement reaction largely depends on the nature of the solvent, as imidazole-2-thione **5b** could be prepared from **4b** and KSCN in 10% hydrochloric acid. The synthesis of **5b** under aqueous conditions was accompanied by the formation of its hydrolysis product **5c**, while not even traces of **6** were isolated. It should be pointed out that following its formation from **4f** and KSCN in DMF, the sterically more demanding isopropanoxy pyridine **5f** did not rearrange in this fashion.

Methylation or benzylation of the exocyclic sulfur atom in **5a**, **5b**, **5d**, and **5f** according to the procedure previously described[25] furnished the corresponding alkylsulfanyl imidazole derivatives **7a**−**b**, **7e**−**f**, **8a**,**b**, and **9a**,**b** (Scheme 3). Target compounds **7c**−**9c**, **7d**−**9d**, and **7g**−**7o**, bearing a substituted nitrogen functionality at the pyridine ring, were prepared from the corresponding fluoropyridine precursors **7a**−**9a** by nucleophilic replacement with an appropriate amine (Scheme 3).[9] This synthetic procedure allowed for the ready variation of substituents at the pyridine ring as well as for the synthesis of enantiomerically pure benzylethylamines **7g** and **7h**. The racemic analogue **9c**, which contains a second center of chirality at the sulfoxide, was obtained as a mixture of diastereoisomers. In general, the fluoropyridine analogues **7a**−**9a** proved to be better suited for the nucleophilic replacement reaction than the corresponding chloropyridines. Under otherwise identical conditions, the reaction of chloropyridine **8b** with 4-methoxybenzylamine could not be driven to completion even after a prolonged reaction time and afforded **8e** in only 24% yield (Scheme 4). In turn, this prolonged reaction time promoted the base-catalyzed cleavage of the benzylsulfanyl side chain when **8b** was reacted with 1-phenylethylamine. After 22 h imidazole-2-thione **10** was isolated as the only product from this reaction.

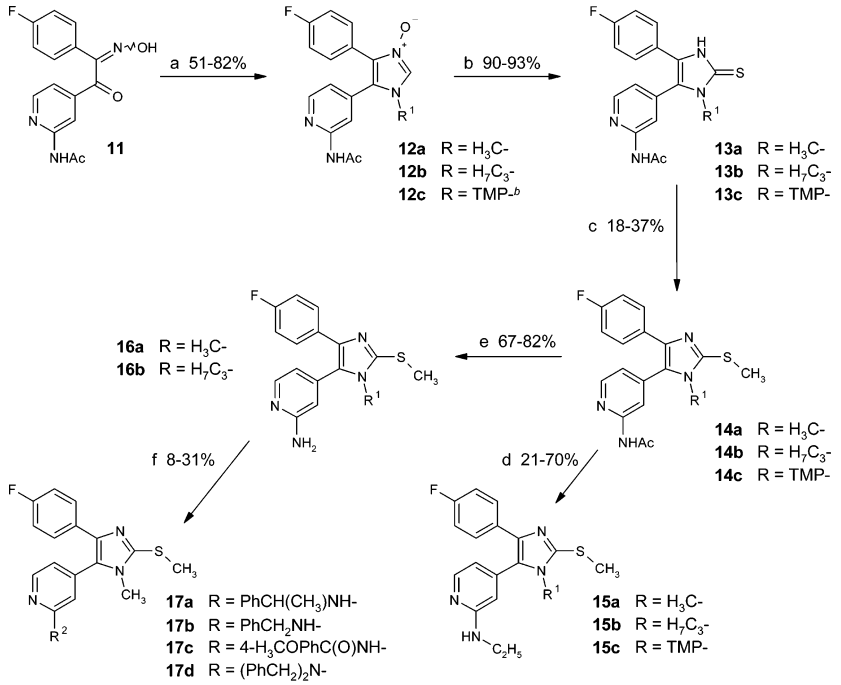
Previously we have developed a general method to regiospecifically prepare *N*1-substituted pyridin-4-yl imidazoles from suitable α-oximinoketones.[26] During the course of this study we extended the scope of this synthetic protocol to the preparation of analogues bearing an acetylamino group at the 2 position of the pyridine ring (Scheme 5). A preliminary account of the reaction sequence starting from α-oximinoketone **11** and leading to *N*-methyl imidazole **17a** via the intermediate imidazole-*N*-oxide **12a**, imidazole-2-thione **13a** and 2-methylsulfanyl imidazole **14a** has appeared.[31] In addition to *N*1-methyl imidazole **14a**, analogues **14b** and **14c** were prepared following the established synthetic procedures. $LiAlH_4$ reduction of the acetylamino group in **14a**−**c** provided the respective ethylamino pyridines **15a**−**c**. Finally, the aminopyridine **16a** resulted from the desacetylation of acetylamino pyridine **14a** and was reacted with appropriate alkyl or acyl halides to yield target compounds **17a**−**d**. The *N*-substituted imidazoles **18a** and **18b** (Scheme 6) were obtained from their *N*-unsubstituted precursors **6** and **7a** by direct alkylation as described previously.[31] Upon treatment with (*RS*)-1-phenylethylamine, fluoropyridine **18b** was converted into phenylethylamino pyridine **18c**.[31]

Biological Results and Discussion

It has been demonstrated in two different series of p38 inhibitors that p38 inhibitory potency correlates with the electron density at the respective heterocyclic ring nitrogen, which forms the crucial hydrogen bond to the enzyme backbone at Met109.[32,33] Starting from parent compound ML 3375,[25] placement of small electron-withdrawing substituents at the 2 position of the pyridin-4-yl moiety resulted in an up to 10-fold decrease in activity for halogenopyridines **7a** and **7b** in the functional assay (Table 2). **7a** also showed diminished activity in the p38 assay. We presume that it is mainly the poor inhibition of p38 which is responsible for poor activity in the cellular assay. In the case of halogenopyridines **7a** and **7b**, the loss of potency can be attributed to the reduced electron density at the pyridine ring nitrogen and the subsequent weakening of the hydrogen bond to the amide NH of Met109. Similarly, the weak activity of the oxygen-containing analogue **6**, which predominantly exists in the pyridone form, can be explained by its completely altered hydrogen bonding properties. The reversed donor/acceptor pattern of pyridone **6** presumably interferes with tight binding at the linker region of the enzyme. Formally replacing the hydroxyl group of **6** with a methoxy group reconstituted the sp^2 hybridization of the pyridine nitrogen and led to slightly enhanced potency (**7e**). However, isopropanoxy pyridine **7f** surpassed the methoxy analogue **7e** in activity by 1 order of magnitude. **7f** inhibited p38 and IL-1β release with similar efficacy as ML 3375 and reduced TNF-α release twice as effectively. This result triggered the search for even better suited substituents at the 2 position of the pyridine ring.

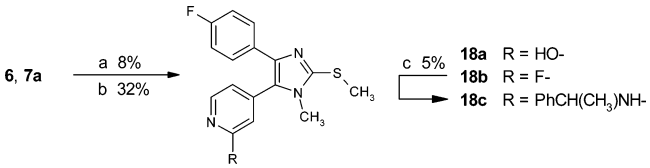
Regarding the benefit gained from the presence of the isopropanoxy residue in **7f**, the superiority of **7f** over **7e** suggests that the branched hydrocarbon side chain rather than the oxygen atom is responsible for the improved inhibitory potency. We hoped to enhance bioactivity further by extending the lipophilic portion of the substituent at the 2 position of the pyridine. Formal replacement of the oxygen in **7f** with a nitrogen and attachment of an aromatic ring at the hydrocarbon

Scheme 5[a]



[a] Reagents: (a) substituted triazinane, ethanol, reflux; (b) 2,2,4,4-tetramethylcyclobutane-1,3-dithione, DCM, ice bath then rt; (c) iodomethane, Na_2CO_3, THF/ethanol 8+2, reflux; (d) $LiAlH_4$, THF, reflux; (e) 10% HCl, reflux; (f) R^2-hal, NaH (55−65%), DMF, reflux; [b]TMP: 2,2,6,6-tetramethylpiperidin-4-yl.

Scheme 6[a]



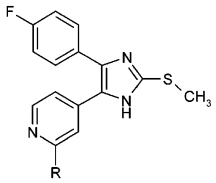
[a] Reagents: (a) iodomethane, methanol, reflux (**18a**); (b) DMF−DMA, toluene, reflux (**18b**); (c) excess (*RS*)-1-phenylethylamine, neat, reflux

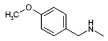
side chain indeed yielded the highly potent 1-phenylethylamino pyridine **7c**, which clearly exceeded lead compound ML 3375 with regard to p38 and TNF-α release inhibition (Table 2). The efficacy of **7c** confirmed the view that the nature of the heteroatom which serves as a linker between the hydrocarbon side chain and the pyridine ring is of minor importance.

On the basis of the molecular modeling of **7g** (i.e., the *R*-enantiomer of **7c**) into the ATP cleft of p38 (Figure 2),[34] the contribution of the hydrocarbon side chain to increased enzyme inhibition can be attributed to its interaction with a hydrophobic area in close proximity to the linker region, which cannot be occupied by simple pyridinyl imidazoles such as SB 203580 and ML 3375. This finding prompted us to explore the structural requirements for interaction with this putative binding site. The stereochemistry in the side chain seems to exert a considerable influence on binding at this position, as the *R*-enantiomer **7g** displayed higher activity against p38 than the *S*-enantiomer **7h**. However, this difference disappeared in the cellular assay. Similar inconsistent correlations between stereochemistry and bioactivity have been described for other imidazole inhibitors of p38.[9] Eradication of the stereocenter (**7d**) led to a notable decrease in activity in all test assays. Next we sought to determine the contribution of substituents at the benzyl moiety to bioactivity by application of the Topliss strategy.[35] These structural modifications were expected to affect the interaction between the aromatic portion of the side chain and the putative hydrophobic binding site. There was, however, no outstanding difference in activity between compounds bearing electron rich (**7i**, **7j**) or electron poor (**7k**, **7l**) substituents. Anilino derivative **7m** and 2-phenylethylamine **7n** were prepared to elucidate the optimum distance between the aryl group and the pyridine nucleus. Compared to **7d**, both extending and shortening this distance led to improved results in the PBMC and enzyme assay. A possible explanation for these results may be provided by the putative binding site stretching both above and below the pyridine ring (Figure 2). The length of the side chain in **7m** and **7n** may be ideal for the respective phenyl ring to interact with either one of both areas. This model also accounts for the similar activities of **7i**−**l** as substituents at the 3 and 4 position of the phenyl ring do not interact with the enzyme but point toward the solvent. The loss of activity for the tertiary amine **7o** illustrates the steric constraints at this position rather than the importance of the exocyclic NH functionality. A hydrogen donor at this position is no prerequisite to activity as is demonstrated by the potency of oxygen analogue **7f**.

Appropriate substituents at the 2 position of the imidazole nucleus have been associated with the improved binding properties[8,15] and enhanced cellular activity[9] of several p38 inhibitors. Most notably it has been reported that imidazole inhibitors of p38 bearing no substituent at both the 1 and 2 position are devoid of cellular and whole blood anticytokine activity.[9] With this in mind we investigated how replacement of the comparatively small methylsulfanyl substituent with a benzylsulfanyl or substituted benzylsulfanyl moiety

Table 2. Methylsulfanylimidazoles



compd	R	IC$_{50}$ (μM) p38[a]	IC$_{50}$ (μM) PBMC TNF-α[b]	IL-1β[b]
ML 3375	-H	0. 63 ± 0.08 (2)	0.90 ± 0.19 (6)	0.044 ± 0.009 (4)
6[c]	-OH	n.d.[d]	3.1 ± 0.3	0.50 ± 0.02
7a	-F	3.8	2.8 ± 1.8	0.30 ± 0.07
7b	-Cl	n.d.	2.2 ± 0.7	0.35 ± 0.05
7c		0.38	0.16 ± 0.03 (4)	0.039 ± 0.009 (3)
7d		0.65	0.63 ± 0.06 (4)	0.108 ± 0.037 (4)
7e	-OCH$_3$	n.d.	1.9 ± 0.6	0.15 ± 0.02
7f	-OCH(CH$_3$)$_2$	0.56	0.40 ± 0.14 (4)	0.047 ± 0.008 (4)
7g	 (R-)	0.34	0.17 ± 0.02 (4)	0.041 ± 0.009 (4)
7h	 (S-)	0.90	0.37 ± 0.12 (3)	0.044 ± 0.013 (3)
7i		0.79	0.64 ± 0.20	0.056 ± 0.035
7j		0.83	0.67 ± 0.07	0.085 ± 0.030
7k		0.95	0.50 ± 0.10	0.15 ± 0.02
7l		0.70	0.72 ± 0.09	0.23 ± 0.17
7m		0.13	0.34 ± 0.12 (4)	0.030 ± 0.005 (4)
7n		0.24	0.35 ± 0.03	0.031 ± 0.001
7o		8.7	4.6 ± 0.3	2.7 ± 0.5

[a] Results are of one experiment except where otherwise stated. [b] Tests were carried out in duplicate except where otherwise stated. [c] **6** predominantly exists in the pyridone form. [d] Not determined.

present in ML 3163 affected biological activity. Imidazole derivatives bearing larger substituents at the 2 position were generally less active than the methylsulfanyl analogues in both the p38 and PBMC assay (Table 3). The unfavorable influence of electron withdrawing substituents at the pyridine was confirmed in the benzylsulfanyl series (**8a**, **8b**, **9a**, **9b**). With respect to inhibition of TNF-α release, this effect was partially overcome by the presence of the polar methylsulfinyl moiety at the 4 position of the benzylsulfanyl substituent (**9a**, **9b**). However, as soon as there were more effective substituents attached to the pyridine the importance of substituents at the 2 position dwindled. Larger groups were better tolerated at the 2 position of the imidazole if at the same time the most effective 1-phenylethylamine (**8c**, **9c**) or a benzylamine substituent (**8d**, **9d**) was placed at the pyridine ring. For these two pairs of compounds the benefits of the methylsulfinyl moiety for inhibition of TNF-α release also

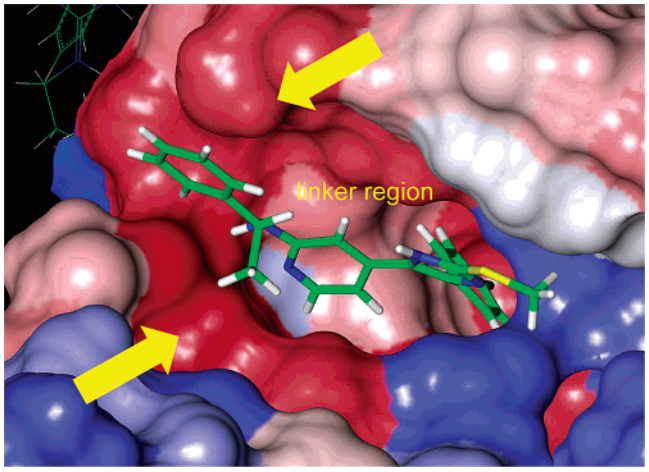
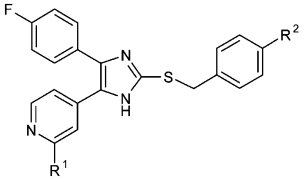
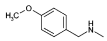


Figure 2. Modeling of **7g** into the ATP cleft of p38 MAP kinase (color code: red = hydrophobic regions, blue = hydrophilic regions). The arrows denote the hydrophobic area in close proximity to the linker region which stretches bot above and below the pyridine ring.

Table 3. Benzylsulfanylimidazoles



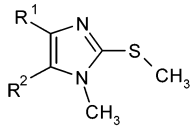
compd	R^1	R^2	IC$_{50}$ (μM) p38[a]	IC$_{50}$ (μM) PBMC TNF-α[b]	IL-1β[b]
8a	-F	-H	4.2	40.5 ± 0.5	2.9 ± 0.5
8b	-Cl	-H	n.d.[c]	60.0 ± 5.0	1.8 ± 0.5
8c		-H	0.38 ± 0.10 (2)	2.7 ± 1.1 (3)	0.045 ± 0.011 (4)
8d		-H	1.42	3.2 ± 0.5	0.20 ± 0.03
8e		-H	n.d.	21.0 ± 9.0	0.18 ± 0.05
9a	-F	-S(O)CH$_3$	9.3	6.9 ± 0.2	2.45 ± 0.05
9b	-Cl	-S(O)CH$_3$	n.d.	12.0 ± 3.0	2.1 ± 0.3
9c		-S(O)CH$_3$	0.27	0.91 ± 0.54 (3)	0.040 ± 0.011 (3)
9d		-S(O)CH$_3$	1.45	2.0 ± 0.7	0.47 ± 0.07

[a] Results are of one experiment except where otherwise stated. [b] Tests were carried out in duplicate except where otherwise stated. [c] Not determined.

disappeared. Modification of the benzylamine substituent at the 4 position was unexpectedly deleterious for bioactivity (**8e**).

In the second part of this study we focused on the interdependency of biological effects exerted by substituents at the imidazole N1 and at the pyridine ring (Tables 4, 5). In full accordance with data for other p38 inhibitors[8] the presence of a substituent at the imidazole ring nitrogen adjacent to the 4-fluorophenyl moiety was detrimental for bioactivity (**18a**, **18c**) (Table 4). This

Table 4. Regioisomers



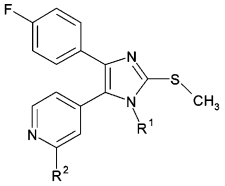
			IC_{50} (μM)	IC_{50} (μM) PBMC	
compd	R^1	R^2	p38[a]	TNF-α[b]	IL-1β[b]
17a	4-F-Ph		0.22	0.11 ± 0.02 (4)	0.015 ± 0.002 (4)
18a[c]		4-F-Ph	n.d.[d]	31.3 ± 5.6	7.2 ± 1.2
18c		4-F-Ph	27	n.d.	n.d.

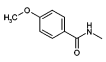
[a] Results are of one experiment except where otherwise stated. [b] Tests were carried out in duplicate except where otherwise stated. [c] **18a** predominantly exists in the pyridone form. [d] Not determined.

observation was ascribed to the repulsive interaction of the respective substituent with the side chain of Lys 53 which otherwise interacts with the lone pair of the imidazole ring nitrogen (Figure 1).[15] In various complexes of p38 with imidazole inhibitors substituents at the imidazole ring nitrogen adjacent to the pyridin-4-yl ring do not cause any unfavorable contact between inhibitor and p38 but are exposed to solvent[13] or interact with the side chain of Asp 168.[14,15] The excellent potency of compound **17a** compared to its regioisomer **18c** strongly supported the validity of this concept in the methylsulfanyl imidazole series presented herein. Previously we have found that small lipophilic substituents (CH_3, C_3H_7) at N1 of the core imidazole are suited best for inhibition of cytokine release in a series of *N*1-substituted pyridin-4-yl imidazoles.[26] *N*-Substituted compounds bearing a simple pyridin-4-yl ring at the 5 position of the imidazole (**19**−**21**) were less active though than the nonsubstituted analogue ML 3375 (Table 5).[26] Formal introduction of a simple amino functionality at the pyridine ring (**16a**, **16b**) did not lead to enhanced potency in this series. However, acetylation (**14a**, **14b**), alkylation (**15a**, **15b**), or benzylation (**17b**) of the exocyclic nitrogen of aminopyridines **16a** and **16b** clearly increased anticytokine activity with **17b** being equipotent to its *N*-unsubstituted analogue **7d**. In the series of *N*-substituted imidazoles this effect was most pronounced when the simple alkyl side chain at the imidazole nitrogen was replaced with the sterically demanding and basic tetramethylpiperidinyl substituent of compounds **14c** and **15c**. Compared to the corresponding pyridine **21**, a more than 50-fold better inhibition of p38 was observed in the case of substituted pyridines **14c** and **15c** although most of this beneficial effect was lost in the PBMC assay. Placement of an aromatic ring at the acetyl group of **14a** resulted in only moderate cellular activity for **17c**. The complete inactivity of dibenzylamine **17d** illustrates the limited space available at the putative binding site.

In the whole blood screen even structurally diverse compounds inhibited the release of both cytokines with similar IC_{50} values in the low micromolar range (Table 6). In general, replacement of the methylsulfanyl benzyl

Table 5. Combination of Substituents at the Imidazole and Pyridine Moiety



			IC_{50} (μM)	IC_{50} (μM) PBMC	
compd	R^1	R^2	p38[a]	TNF-α[b]	IL-1β[b]
14a	$-CH_3$	$-NHC(O)CH_3$	0.5	1.1 ± 0.2 (4)	0.075 ± 0.039
14b	$-C_3H_7$	$-NHC(O)CH_3$	n.d.[c]	0.49 ± 0.20	0.12 ± 0.01
14c		$-NHC(O)CH_3$	0.34	4.5 ± 1.1	0.46 ± 0.02
15a	$-CH_3$	$-NHC_2H_5$	0.7	0.60 ± 0.16 (4)	0.071 ± 0.021 (4)
15b	$-C_3H_7$	$-NHC_2H_5$	n.d.	0.43 ± 0.01	0.15 ± 0.01
15c		$-NHC_2H_5$	0.22	2.9 ± 0.6	0.62 ± 0.15
16a	$-CH_3$	$-NH_2$	2.3	3.2 ± 0.5 (4)	0.27 ± 0.09
16b	$-C_3H_7$	$-NH_2$	n.d.	5.4 ± 1.2	0.50 ± 0.02
17b	$-CH_3$		0.93 ± 0.47 (2)	0.58 ± 0.08 (6)	0.082 ± 0.019
17c	$-CH_3$		n.d.	0.64 ± 0.28	0.44 ± 0.05
17d	$-CH_3$		n.d.	no activity	no activity
19	$-CH_3$	-H	2.2	2.2 ± 0.9	0.45 ± 0.03
20	$-C_3H_7$	-H	2.2	1.3 ± 0.3	0.36 ± 0.03
21		-H	17.0	16.0 ± 1.0	0.85 ± 0.10

[a] Results are of one experiment except where otherwise stated. [b] Tests were carried out in duplicate except where otherwise stated. [c] Not determined.

moiety of ML 3163 with a simple methyl group proved to be favorable for TNF-α inhibition. *N*-Substituted and nonsubstituted imidazole analogues displayed equipotency in the pyridine (**19** vs ML 3375) as well as in the substituted pyridine series (**17a** vs **7c**)**.** However, the acetylamino functionality present in **14a** led to an exceptional loss of activity in whole blood compared to the PBMC results. In the tetramethylpiperidine series (**14c**, **15c**, **21**) conflicting results were obtained, although this substituent was seemingly unfavorable for whole blood activity.

Cytochrome P450 Affinity. Reference compound ML 3163 at a concentration of 10 μM displayed more than 50% inhibition of four isoforms of cytochrome P450 (Table 7). At the same molar concentration ML 3375 exhibited moderate to high affinity for all isoforms included in the assay. It was expected that the reduced electron density of the 2-chloropyridine in **7b** may reduce coordination to the cytochrome heme iron if the pyridine was predominantly responsible for this interaction. However, introduction of electron-withdrawing or large lipophilic substituents at the pyridin-4-yl moiety merely shifted selectivity for reduced cytochrome interaction from CYP1A2 toward CYP2D6 but did not improve the overall affinity profile (**7b**, **7c**, **7f**). The same pattern of P450 inhibition was observed for **17a**, the *N*-methylated analogue of **7c**. Combination of the *N*-methyl imidazole core with an acetylamino pyridine led

Table 6. Whole Blood Results for Selected Compounds[a]

compd	$IC_{50} \pm SEM$ (μM) TNF-α	IL-1β	compd	$IC_{50} \pm SEM$ (μM) TNF-α	IL-1β
SB 203580	0.94 ± 0.14 (12)	0.35 ± 0.09 (12)	**14c**	5.4 ± 3.6	2.15 (1)
ML 3163	20.3 ± 4.8	2.78 ± 0.13	**15a**	5.0 ± 1.3	2.0 ± 0.6
ML 3375	4.2 ± 0.7	1.2 ± 0.6	**15c**	11.0 ±5.5	2.7 ± 1.9
7c	2.7 ± 0.3	0.99 ± 0.46	**17a**	3.0 ± 1.7 (4)	4.1 ± 1.0 (2)
7f	7.2 ± 1.8	2.2 ± 0.8	**19**	5.1 ± 0.4	1.08 ± 0.73
14a	12.5 ± 6.4 (4)	10.8 ± 6.9 (4)	**21**	19.1 ± 8.6 (4)	18.5 ± 13.1 (3)

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

Table 7. Inhibition [%] of Five CYP_{450} Isoforms by Selected Compounds at 10 μM

compd	1A2	2C9	2C19	2D6	3A4
SB 20350[19]	61	75	85	67	61
ML 3163	8.4	72.7	73.6	71.8	87.1
ML 3375	43.5	72.4	79.5	39.8	81.4
7b	92.6	65.0	41.4	18.6	48.8
7c	66.7	79.0	83.5	31.1	79.2
7f	83.2	67.5	62.6	<0	49.6
14a	32.4	27.6	20.3	13.4	16.5
14c	<0	2.6	7.6	14.6	79.0
17a	57.1	83.3	90.9	12.4	85.8
21	9.0	7.9	15.3	19.1	49.6

to promising results with acetylamino pyridine **14a** showing only low to moderate affinity for all tested P450 isoforms. Introduction of the tetramethylpiperidinyl moiety at the imidazole nucleus further minimized the inhibition of P450. Acetylamino pyridine **14c** did practically not interfere with cytochrome P450 isoforms 1A2, 2C9, 2C19, and 2D6, although 3A4 was considerably affected. Similar results for pyridine compound **21** suggest that this beneficial effect primarily has to be attributed to the tetramethylpiperidinyl rather than the acetylamino moiety.

Conclusion

The polysubstituted pyridinyl imidazole inhibitors of p38 presented herein efficiently suppressed the release of TNF-α and IL-1β from PBMC. Different structural features seem to be responsible for efficient inhibition of p38 and cytokine release and unwanted coordination to cytochrome P450. Weakening the crucial hydrogen bond between the ring nitrogen and the amide NH of Met109 led to reduced anticytokine activity (**6**, **7a**, **7b**) but scarcely affected P450 inhibition (**7b**). The presence of an additional aromatic (e.g., **7c**) or aliphatic (**7f**) side chain linked to the pyridine ring via an electron-donating heteroatom enhanced inhibitory potency. While in the present study the issue of the optimum nature of the heteroatom linker has not been systematically addressed, we suggest that with their (aryl-)alkyl part these side chains fit into a hydrophobic region present in all protein kinases.[18] In the case of p38 this hydrophobic region seems to be capable of accommodating large and electronically diverse (**7c**, **7d**, **7g**−**m**) substituents. Introduction of large substituents at the 1 and 2 position of the core imidazole resulted in a general loss of activity. This effect could be overcome by introducing appropriate substituents at the pyridinyl moiety.

These findings corroborate and refine our previously proposed model of a hierarchy of interaction sites:[25] It is predominantly modifications at the pyridine which affect inhibition of p38 and anticytokine activity in this series of compounds. Substituents placed at the 2 position of the imidazole contribute to bioactivity only to a lesser extent. However, this site of interaction becomes more important and can be exploited for enhanced binding if the crucial hydrogen bond between pyridine and Met109 is weakened (**9a**, **9b**). Large substituents at the N1 of the imidazole are unfavorable for inhibition of p38. On the other hand these same substituents at the imidazole N1 (**14c**, **21**) practically eliminated interaction with cytochrome P450 while compounds solely substituted at the pyridine (**7b**, **7c**, **7f**) only displayed moderately decreased affinity for the single P450 isoform 2D6. Therefore we conclude that in this series of pyridinyl imidazoles the substituted pyridine moiety is of critical importance for activity while the imidazole ring is responsible for interference with cytochrome P450. By optimum combination of substituents at both heterocycles we have identified a set of efficient anticytokine agents with considerably reduced P450 interaction. The most promising candidates are currently investigated in animal models of inflammation.

Experimental Section

General. All reagents and solvents were of commercial quality and used without further purification. Melting points were determined on a Buchi Melting Point B-545 apparatus and are thermodynamically corrected. ^1H and ^{13}C NMR spectra were collected 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 by ATR technique on a Perkin-Elmer Spectrum One spectrometer. GC/MS analyses were carried out on a HP 6890 series GC-system equipped with a HP-5MS capillary column (0.25 μm film thickness, 30 m × 0.25-mm i.d.) and a HP 5973 mass selective detector (70 eV). Helium was used as carrier gas, and the following temperature program was employed: initial isothermal period of 1.0 min at 100 °C, then an increase at 15.0 °C/min to 225 °C with an isothermal period of 1.0 min at 290 °C, then an increase at 25.0 °C/min to 270 °C with an isothermal period of 10.0 min at 270 °C. GC data are presented as retention times (min) and MS results as *m*/*z* ratio and intensity (%) relative to the base peak. Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol (TSQ-70). Enantiomeric purity of chiral compounds was determinded by HPLC on a Chiralpak AD column (10 μm, 250 × 4.6 mm) which was eluted isocratically with a *n*-hexane/2-propanol system at a flow rate of 1.0 mL/min (UV detection at 254 or 215 nm). HPLC results are given as retention times (min) and relative purity (%). TLC analyses were performed on fluorescent silica gel 60 plates (Macherey-Nagel Art.-Nr. 805021). Spots were visualized under UV illumination at 254 and 365 nm. Microanalyses were carried out on a Perkin-Elmer EA 2400 instrument. The following compounds were prepared according to literature procedures: SB 203580,[8] **1b**,[36] and **1c**.[37] The syntheses and analytical properties of ML 3163, ML 3375 and compounds **11**, **12a**−**14a**, **16a**, **17a**, **18a**−**c**, and **19**−**21** have been reported elsewhere.[25,26,31]

1-(4-Fluorophenyl)-2-(2-fluoropyridin-4-yl)ethanone (2a). Starting from **1a** (13.9 g, 125 mmol), 28.7 g (99%) of

2a was obtained according to the method described for the synthesis of **2b**: mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 4.32 (s, 2H, CH_2), 6.85−6.86 (m, 1H, C^3-H 2-F-Pyr), 7.08−7.19 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 8.00−8.07 (m, 2H, 4-F-Ph), 8.18 (d, 1H, 5.1 Hz, C^6-H 2-F-Pyr); IR 1684 (C═O), 1235 cm^{-1} (C−F); GC 8.77 min; MS *m*/*z* (%) 233 (6, M$^+$), 123 (100), 95 (94), 75 (56).

2-(2-Chloropyridin-4-yl)-1-(4-fluorophenyl)ethanone (2b). Under an argon atmosphere, *n*-butyllithium (15% in *n*-hexane, 45 mL, 104 mmol) was added to a solution of diisopropylamine (15 mL, 106 mmol) in THF absol (150 mL) at −85 °C. The slightly yellow solution was stirred at −85 °C for 55 min. Upon dropwise addition of a solution of **1b** (8.6 g, 68 mmol) in THF absol (75 mL) at −85 °C, the color of the reaction immediately turned purple. After the addition was complete, the mixture was stirred at −85 °C for 1 h. Within 3 min a solution of 4-fluoro-*N*-methoxy-*N*-methylbenzamide[8] (12.4 g, 68 mmol) in THF absol (75 mL) was added at −85 °C. The purple slurry was stirred at −85 °C for 1 h and warmed to 0 °C during 1 h. The reaction was poured onto a bilayer system of saturated brine (300 mL) and ethyl acetate (300 mL). The aqueous phase was extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were washed with saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The oily residue was dissolved in *tert*-butyl methyl ether, and the ethereal solution was kept at 4 °C overnight, after which period 11.2 g (66%) of **2b** had precipitated as a crystalline solid: mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 2H, CH_2), 7.11−7.26 (m, 4H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 7.99−8.06 (m, 2H, 4-F-Ph), 8.35 (dd, 1H, 0.6/5.1 Hz, C^6-H 2-Cl-Pyr); IR 1685 (C═O), 1232 cm^{-1} (C−F); GC 10.29 min; MS *m*/*z* (%) 249 (3, M$^+$), 123 (100), 95 (44), 75 (11).

2-(2-Bromopyridin-4-yl)-1-(4-fluorophenyl)ethanone (2c). Starting from **1c** (9.6 g, 56 mmol), 15.5 g (94%) of **2c** was obtained according to the method described for the synthesis of **2b**: mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 4.35 (s, 2H, CH_2), 7.17−7.37 (m, 3H, 2-Br-Pyr and4-F-Ph), 7.50 (s, 1H, C^3-H 2-Br-Pyr), 8.07−8.15 (m, 2H, 4-F-Ph), 8.42 (d, 1H, 5.1 Hz, C^6-H 2-Br-Pyr); IR 1685 (C═O), 1228 cm^{-1} (C−F); GC 11.05 min; MS *m*/*z* (%) 293 (2, M$^+$), 123 (100), 95 (43), 75 (12).

1-(2-Fluoropyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione 1-Oxime (3a). Starting from **2a** (10.0 g, 43 mmol), 9.7 g (86%) of **3a** was obtained according to the method described for the synthesis of **3b**: mp 174 °C; ^{1}H NMR (DMSO-d_6) δ 7.19−7.20 (m, 1H, C^3-H 2-F-Pyr), 7.35−7.47 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.91−7.98 (m, 2H, 4-F-Ph), 8.29 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.69 (s, 1H, exchangeable, OH); IR 1669 (C═O), 1263 (C−F), 1235 cm^{-1} (C−F); ^{13}C NMR (DMSO-d_6) δ 105.4 (d, 40.0 Hz, C^3 2-F-Pyr), 116.7 (d, 22.4 Hz, C^2/C^6 4-F-Ph), 118.2 (d, 4.1 Hz, C^5 2-F-Pyr), 130.8 (d, 2.7 Hz, C^4 4-F-Ph), 132.2 (d, 10.1 Hz, C^3/C^5 4-F-Ph), 144.3 (d, 8.5 Hz, C^4 2-F-Pyr), 148.8 (d, 15.6 Hz, C^6 2-F-Pyr), 151.9 (d, 4.1 Hz, oximino), 163.5 (d, 235.8 Hz, C^2 2-F-Pyr), 166.0 (d, 254.9 Hz, C^1 4-F-Ph), 192.1 (carbonyl).

1-(2-Chloropyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione 1-Oxime (3b). A solution of $NaNO_2$ (0.85 g, 12.3 mmol) in H_2O (10 mL) was added dropwise to a solution of **2b** (3.0 g, 12 mmol) in glacial acetic acid at 10 °C. After the addition was complete, the reaction was stirred at room temperature for 30 min. The mixture was diluted with H_2O (60 mL), and the cream-colored slurry was stirred at room temperature for another 3 h. The precipitate was collected by filtration, washed with H_2O, and dried in vacuo over $CaCl_2$ to yield 3.0 g (91%) of **3b**: mp 200 °C; ^{1}H NMR (DMSO-d_6) δ 7.34−7.52 (m, 4H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 7.93−8.00 (m, 2H, 4-F-Ph), 8.47 (d, 1H, 5.2 Hz, C^6-H 2-Cl-Pyr), 12.71 (bs, 1H, exchangeable, OH); IR 1673 (C═O), 1239 cm^{-1} (C−F).

1-(2-Bromopyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione 1-Oxime (3c). Starting from **2c** (5.0 g, 17 mmol), 4.2 g (76%) of **3c** was obtained according to the method described for the synthesis of **3b**: mp 214 °C; ^{1}H NMR (DMSO-d_6) δ 7.40−7.48 (m, 3H, C^3-H 2-Br-Pyr and 4-F-Ph), 7.65 (d, 1H, 0.8 Hz, C^5-H 2-Br-Pyr), 7.93−8.01 (m, 2H, 4-F-Ph), 8.45 (d, 1H, 5.2 Hz, C^6-H 2-Br-Pyr), 12.72 (bs, 1H, exchangeable, OH); IR 1673 (C═O), 1238 cm^{-1} (C−F).

1-(4-Fluorophenyl)-2-(2-isopropoxypyridin-4-yl)ethane-1,2-dione 2-Oxime (3d). A solution of **3a** (200 mg, 0.76 mmol) in saturated 2-propanolic hydrogen chloride was heated to reflux for 2.5 h. The solvent was evaporated, and the slightly yellow residue was triturated with ethanol to yield 0.11 g (48%) of **3d**: mp 227 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 6H, 6.2 Hz, 2 × CH_3), 5.15−5.27 (m, 1H, methine-H), 6.54 (s, 1H, C^3-H 2-Iso-O-Pyr), 7.08 (dd, 1H, 1.2/5.3 Hz, C^5-H 2-Iso-O-Pyr), 7.36−7.49 (m, 2H, 4-F-Ph), 7.88−7.97 (m, 2H, 4-F-Ph), 8.19 (d, 1H, 5.4 Hz, C^6-H 2-Iso-O-Pyr), 12.44 (bs, 1H, exchangeable, OH); IR 1672 (C═O), 1226 cm^{-1} (C−F).

2-Amino-2-(2-fluoropyridin-4-yl)-1-(4-fluorophenyl)-ethanone Hydrochloride (4a). With gentle heating, **3a** (5.0 g, 19 mmol) was dissolved in saturated 2-propanolic hydrogen chloride/2-propanol (1+1, 60 mL). The yellow solution was cooled to room temperature. Pd−C 10% (1.5 g) was added, and the reaction was flushed with hydrogen gas (4×). The slurry was agitated at room temperature under an atmosphere of hydrogen at atmospheric pressure until no starting material was detected by TLC (SiO_2 60, DCM/ethanol 9+1; 6.5 h). The catalyst was filtered off and washed with methanol. The combined filtrates were concentrated in vacuo to yield 5.4 g (100%) of crude **4a** as an amorphous solid which was employed in the subsequent reaction step without further purification: mp 248 °C; ^{1}H NMR (DMSO-d_6) δ 6.58 (bs, 1H, methine-H), 7.33−7.41 (m, 2H, 4-F-Ph), 7.54 (m, 2H, C^3-/C^5-H 2-F-Pyr), 8.14−8.25 (m, 2H, 4-F-Ph), 8.30 (d, 1H, 5.5 Hz, C^6-H 2-F-Pyr), 9.40 (bs, 3H, exchangeable, NH_3^+); ^{13}C NMR (DMSO-d_6) δ 56.7 (methine), 110.4 (d, 39.3 Hz, C^3 2-F-Pyr), 116.8 (d, 22.1 Hz, C^2/C^6 4-F-Ph), 122.2 (d, 4.3 Hz, C^5 2-F-Pyr), 129.9 (d, 2.8 Hz, C^4 4-F-Ph), 132.8 (d, 9.9 Hz, C^3/C^5 4-F-Ph), 147.3 (d, 8.3 Hz, C^4 2-F-Pyr), 149.2 (d, 15.2 Hz, C^6 2-F-Pyr), 163.4 (d, 236.6 Hz, C^2 2-F-Pyr), 166.2 (d, 255.1 Hz, C^1 4-F-Ph), 191.3 (carbonyl); IR 2811 (NH_3^+), 1695 (C═O), 1240 cm^{-1} (C−F).

2-Amino-1-(4-fluorophenyl)-2-(2-methoxypyridin-4-yl)-ethanone Hydrochloride (4b). Upon treatment of **3a** (7.5 g, 29 mmol) under the conditions decribed for the preparation of **4c**, 8.5 g (100%) of **4b** was obtained as the only product: mp 252 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3), 6.44 (bs, 1H, methine-H), 7.13−7.16 (m, 2H, C^3-/C^5-H 2-MeO-Pyr), 7.34−7.46 (m, 2H, 4-F-Ph), 8.16−8.25 (m, 3H, C^6-H 2-MeO-Pyr and 4-F-Ph), 9.29 (bs, 3H, exchangeable, NH_3^+); ^{13}C NMR (DMSO-d_6) δ 53.4 (CH_3), 56.6 (methine), 110.8 (C^3 2-MeO-Pyr), 116.2 (d, 22.1 Hz, C^2/C^6 4-F-Ph), 120.4 (C^5 2-MeO-Pyr), 129.5 (d, 2.9 Hz, C^4 4-F-Ph), 132.3 (d, 9.9 Hz, C^3/C^5 4-F-Ph), 143.9 (C^4 2-MeO-Pyr), 147.3 (C^6 2-MeO-Pyr), 163.8 (C^2 2-MeO-Pyr), 165.7 (d, 254.7 Hz, C^1 4-F-Ph), 191.2 (carbonyl); IR 1693 (C═O), 1235 cm^{-1} (C−F).

2-Amino-2-(2-chloropyridin-4-yl)-1-(4-fluorophenyl)-ethanone Hydrochloride (4c). 3b (1.5 g, 5.4 mmol) was dissolved in methanol (15 mL) and treated, under the conditions as described for the preparation of **4a**, with saturated methanolic hydrogen chloride (20 mL) in place of the mixture of 2-propanol and 2-propanolic hydrogen chloride. Thus 1.6 g (100%) of **4c** was obtained: mp 215°C; ^{1}H NMR (DMSO-d_6) δ 6.53 (bs, 1H, methine-H), 7.35−7.45 (m, 2H, 4-F-Ph), 7.59 (dd, 1H, 1.5/5.2 Hz, C^5-H 2-Cl-Pyr), 7.85 (d, 1H, 0.9 Hz, C^3-H 2-Cl-Pyr), 8.17−8.25 (m, 2H, 4-F-Ph), 8.49 (d, 1H, 4.9 Hz, C^6-H 2-Cl-Pyr), 9.33 (bs, 3H, exchangeable, NH_3^+); ^{13}C NMR (DMSO-d_6) δ 56.6 (methine), 116.8 (d, 22.2 Hz, C^2/C^6 4-F-Ph), 123.3 (C^5 2-Cl-Pyr), 124.7 (C^3 2-Cl-Pyr), 129.9 (d, 2.8 Hz, C^4 4-F-Ph), 132.8 (d, 9.9 Hz, C^3/C^5 4-F-Ph), 145.0 (C^4 2-Cl-Pyr), 151.2 (C^6 2-Cl-Pyr), 151.3 (C^2 2-Cl-Pyr), 166.2 (d, 255.2 Hz, C^1 4-F-Ph), 191.2 (carbonyl); IR 2801 (NH_3^+), 1693 (C═O), 1240 cm^{-1} (C−F).

2-Amino-1-(4-fluorophenyl)-2-pyridin-4-yl-ethanone Hydrochloride (4d). Upon treatment of **3c** (4.0 g, 12.4 mmol) under the conditions decribed for the preparation of **4c**, 3.3 g (100%) of **4d** was obtained as the only product: mp 198 °C; ^{1}H NMR (DMSO-d_6) δ 6.78 (bs, 1H, methine-H), 7.32−7.38 (m, 2H, 4-F-Ph), 8.07−8.13 (m, 2H, 4-Pyr), 8.17−8.27 (m, 2H, 4-F-

Ph), 8.92−8.95 (m, 2H, 4-Pyr), 9.43 (bs, 3H, exchangeable, NH_3^+); IR 2801 (NH_3^+), 1686 (C═O), 1237 cm^{-1} (C−F).

2-Amino-2-(2-bromopyridin-4-yl)-1-(4-fluorophenyl)-ethanone Hydrogensulfate (4e). To a solution of **3c** (1.8 g, 5.6 mmol) in ethanol absol (30 mL) at −10 °C was added concentrated sulfuric acid (1.3 mL). In small portions zinc powder (1.1 g) was added while the temperature was kept at −10 °C. After the addition was complete, the mixture was stirred for 30 min at −10 °C and then warmed to room temperature. The gray-green colored slurry was filtered, and the residue of $ZnSO_4$ was thoroughly washed with ethanol. The combined yellow filtrate was concentrated in vacuo, and the solid residue was dried to give 2.0 g (91%) of **4e**: ^{1}H NMR (DMSO-d_6) δ 6.39 (bs, 1H, methine-H), 7.35−7.44 (m, 2H, 4-F-Ph), 7.56 (dd, 1H, 1.4/5.1 Hz, C^5-H 2-Br-Pyr), 7.91 (s, 1H, C^3-H 2-Br-Pyr), 8.12−8.19 (m, 2H, 4-F-Ph), 8.46 (d, 1H, 5.1 Hz, C^6-H 2-Br-Pyr), 8.94 (bs, 3H, exchangeable NH_3^+).

2-Amino-1-(4-fluorophenyl)-2-(2-isopropoxypyridin-4-yl)ethanone Hydrochloride (4f). Starting from **3d** (2.0 g, 7.6 mmol), 2.5 g (100%) of **4f** was obtained according to the method described for the synthesis of **4a**: mp 271 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (d, 6H, 5.6 Hz, 2 × CH_3), 5.09−5.22 (m, 1H, methine-H $CH(CH_3)_2$), 6.38−6.41 (bs, 1H, methine-H $CH-NH_3^+$), 7.00−7.08 (m, 2H, 2-Iso-O-Pyr), 7.33−7.46 (m, 2H, 4-F-Ph), 8.14−8.23 (m, 3H, 2-Iso-O-Pyr and 4-F-Ph), 9.21 (bs, 3H, exchangeable, NH_3^+); IR 2703 (NH_3^+), 1696 (C═O), 1237 cm^{-1} (C−F).

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (5a). Starting from **4a** (6.1 g, 20 mmol), 5.0 g (91%) of **5a** was obtained according to the method described for the synthesis of **5d**: mp 303 °C; ^{1}H NMR (DMSO-d_6) δ 7.12−7.16 (m, 2H, C^3-/C^5-H 2-F-Pyr), 7.28−7.27 (m, 2H, 4-F-Ph), 7.46−7.55 (m, 2H, 4-F-Ph), 8.13 (d, 1H, 5.1 Hz, C^6-H 2-F-Pyr), 12.85 (bs, 2H, exchangeable, 2 × NH); ^{13}C NMR (DMSO-d_6) δ 106.0 (d, 40.3 Hz, C^3 2-F-Pyr), 116.5 (d, 21.9 Hz, C^2/C^6 4-F-Ph), 118.9 (d, 3.7 Hz, C^5 2-F-Pyr), 121.3, 124.7 (C^4 4-F-Ph), 128.5, 131.5 (d, 8.6 Hz, C^3/C^5 4-F-Ph), 141.5 (d, 9.4 Hz, C^4 2-F-Pyr), 148.4 (d, 16.1 Hz, C^6 2-F-Pyr), 162.9 (d, 247.2 Hz, C^1 4-F-Ph), 162.9 (C^2 imidazole), 163.9 (d, 234.0 Hz, C^2 2-F-Pyr); IR 1497 (C(S)NH), 1223 cm^{-1} (C−F).

4-(4-Fluorophenyl)-5-(2-methoxypyridin-4-yl)-1,3-dihydroimidazole-2-thione (5b). To a solution of **4b** (3.2 g, 10.8 mmol) in 10% hydrochloric acid (50 mL) was added potassium thiocyanate (2 g, 20.6 mmol). The reaction was heated to reflux for 30 min. The mixture was cooled to room temperature and neutralized with 10% aqueous $NaHCO_3$ solution. The precipitate was collected by filtration, washed with H_2O, and dried in vacuo over $CaCl_2$. The crude product was triturated with ethanol. The insoluble residue (**5c**) was filtered off. Upon leaving the filtrate at room temperature 1.0 g (31%) of **5b** precipitated: mp 250 °C; ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H, OCH_3), 6.79−6.82 (m, 2H, C^3-/C^5-H 2-MeO-Pyr), 7.26−7.50 (m, 4H, 4-F-Ph), 8.06 (d, 1H, 5.3 Hz, C^6-H 2-MeO-Pyr), 12.65 (bs, 2H, exchangeable, 2 × NH).

4-[5-(4-Fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]-1*H*-pyridin-2-one (5c). 5c (0.4 g, 13%) was obtained as a side product in the preparation of **5b**: ^{1}H NMR (DMSO-d_6) δ 5.88 (d, 1H, 6.0 Hz, C^5-H pyridone), 6.41 (s, 1H, C^3-H pyridone), 7.26−7.50 (m, 5H, C^6-H pyridone and 4-F-Ph), 11.50 (bs, 1H, exchangeable, pyridone-NH), 12.73 (bs, 2H, exchangeable, 2 × imidazole-NH).

4-(2-Chloropyridin-4-yl)-5-(4-fluorophenyl)-1,3-dihydroimidazole-2-thione (5d). With gentle heating **4c** (2.9 g, ca. 9.6 mmol) was dissolved in DMF absol (75 mL). To the clear orange solution was added potassium thiocyanate (1.9 g, 19.6 mmol). The slurry was heated to reflux for 1.5 h. The reaction was cooled to room temperature and diluted dropwise with H_2O (140 mL). The yellow precipitate was collected by filtration, washed with H_2O, and dried in vacuo over $CaCl_2$ to afford 2.14 g (74%) of **5d**: mp 275 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 7.12−7.52 (m, 6H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 8.27 (d, 1H, 5.2 Hz, C^6-H 2-Cl-Pyr), 12.82 (bs, 2H, exchangeable, 2 × NH); ^{13}C NMR (DMSO-d_6) δ 116.5 (d, 21.8 Hz, C^2/C^6 4-F-Ph), 119.8 (C^5 2-Cl-Pyr), 120.7 (C^3 2-Cl-Pyr), 121.0, 124.6 (d, 3.3 Hz, C^4 4-F-Ph), 128.5, 131.5 (d, 8.7 Hz, C^3/C^5 4-F-Ph), 139.3, 150.5 (C^6 2-Cl-Pyr), 151.2 (C^2 2-Cl-Pyr), 162.9 (d, 247.3 Hz, C^1 4-F-Ph), 162.9 (C^2 imidazole); IR 1515 (C(S)NH), 1219 cm^{-1} (C−F).

4-(4-Fluorophenyl)-5-(2-isopropoxypyridin-4-yl)-1,3-dihydroimidazole-2-thione (5f). Starting from **4f** (2.5 g, 7.6 mmol), 1.8 g (70%) of **5f** was obtained according to the method described for the synthesis of **5d**: mp 217 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 6H, 6.2 Hz, 2 × CH_3), 5.10−5.19 (m, 1H, methine-H), 6.69−6.76 (m, 2H, 2-Iso-O-Pyr), 7.24−7.32 (m, 2H, 4-F-Ph), 7.42−7.49 (m,2H, 4-F-Ph), 8.02 (d, 1H, 5.5 Hz, C^6-H 2-Iso-O-Pyr), 12.68 (bs, 2H, exchangeable, 2 × NH); IR 1518 (C(S)NH), 1226 cm^{-1} (C−F).

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]-*1H*-pyridin-2-one (6). Upon treatment of **4b** (8.8 g, 31 mmol) under the conditions decribed for the preparation of **5d**, 4.2 g (45%) of **6** was obtained as the only product: mp 314 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 2.61 (s, 3H, SCH_3), 6.16 (bs, 1H, C^3-H pyridone), 6.34 (s, 1H, C^5-H pyridone), 7.25−7.33 (m, 3H, C^6-H pyridone and 4-F-Ph), 7.46−7.53 (m, 2H, 4-F-Ph), 11.38 (bs, 1H, exchangeable, pyridone-NH), 12.71 (bs, 1H, exchangeable, imidazole-NH); ^{13}C NMR (DMSO-d_6) δ 14.8 (CH_3), 103.7 (C^5 pyridone), 114.6 (C^3 pyridone), 115.8 (d, 21.9 Hz, C^2/C^6 4-F-Ph), 121.7, 124.5 (d, 3.3 Hz, C^4 4-F-Ph), 127.4, 130.7 (d, 8.3 Hz, C^3/C^5 4-F-Ph), 134.9 (C^6 pyridone), 139.7 (C^4 pyridone), 161.8 (d, 245.3 Hz, C^1 4-F-Ph), 162.1 (C^2 imidazole), 162.4 (C^2 pyridone); IR 1634 (pyridone I), 1557 (pyridone II), 1220 cm^{-1} (C−F); MS *m*/*z* (%) 301 (93, M^+), 300 (100, $M^+ - 1$), 285.1 (13, $M^+ - CH_3$), 268.0 (40, $M^+ - S$), 228.1 (20), 121.1 (16), 95.1 (10). Anal. ($C_{15}H_{12}FN_3OS$) C, H, N.

General Procedure A: Preparation of 2-(Aryl-)Alkylsulfanylimidazoles. Under an inert atmosphere of argon a mixture of the respective imidazole-2-thione and the respective benzyl- or methylhalogenide in ethanol/THF (8+2) was heated to reflux until the imidazole-2-thione had been consumed completely (TLC: SiO_2 60, DCM/ethanol 9+1). The slurry was cooled to room temperature and filtered. The red or orange filtrate was concentrated in vacuo, and the residue was purified by trituration or column chromatography as appropriate.

2-Fluoro-4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridine (7a). According to general procedure A, the title compound was obtained from **5a** (0.95 g, 3.3 mmol) and iodomethane (1.4 g, 9.9 mmol) after 40 h. The crude reaction product was extracted with hot DCM/ethyl acetate (1+1). The color was removed from the organic extract by treatment with Al_2O_3. The basic alumina was filtered off, and the filtrate was concentrated in vacuo. The solid residue was triturated with a small volume of ethanol to yield 0.30 g (30%) of **7a**: mp 224 °C; ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H, CH_3), 7.08 (s, 1H, C^3-H 2-F-Pyr), 7.26−7.35 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.46−7.54 (m, 2H, 4-F-Ph), 8.08 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.85 (bs, 1H, exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 15.3 (CH_3), 105.4 (d, 39.3 Hz, C^3 2-F-Pyr), 116.3 (d, 21.8 Hz, C^2/C^6 4-F-Ph), 118.9 (d, 3.5 Hz, C^5 2-F-Pyr), 119.8, 120.4, 131.2 (d, 8.4 Hz, C^3/C^5 4-F-Ph), 143.6 (C^4 2-F-Pyr), 148.1 (d, 16.1 Hz, 2-F-Pyr), 150.3, 151.1, 162.5 (d, 246.1 Hz, C^1 4-F-Ph), 164.1 (d, 233.3 Hz, C^2 2-F-Pyr); IR 1219 cm^{-1} (C−F); Anal. ($C_{15}H_{11}F_2N_3S$) C, H, N.

2-Chloro-4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridine (7b). According to general procedure A, the title compound was obtained from **5d** (0.5 g, 1.6 mmol) and iodomethane (0.35 g, 2.5 mmol) after 12 h. Purification by column chromatography (basic alumina, DCM/ethyl acetate 1+1) yielded 0.16 g (31%) of **7b**: mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 1H, CH_3), 7.27−7.36 (m, 3H, 2-Cl-Pyr and 4-F-Ph), 7.45−7.55 (m, 3H, 2-Cl-Pyr and 4-F-Ph), 8.24 (d, 1H, 5.1 Hz, C^6-H 2-Cl-Pyr), 12.85 (bs, 1H, exchangeable, NH); IR 1231 cm^{-1} (C−F); Anal. ($C_{15}H_{11}ClFN_3S$) C, H, N.

General Procedure B: Preparation of *N*-Substituted 2-Aminopyridines. Under an inert atmosphere of argon, the respective 5-(2-halogenopyridin-4-yl)imidazole (1 equiv) was suspended in an excess volume of the respective amine (approx 10 equiv). The mixture was stirred at the appropriate tem-

perature until the imidazole starting material had been consumed completely (TLC: SiO_2 60, DCM/ethanol 9+1). The reaction was cooled to room temperature and suspended in an aqueous solution of citric acid (10%), which had been brought to pH 5 with an aqueous solution of NaOH (20%) before. The emulsion was extracted with ethyl acetate (3×). The combined organic extract was 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 oily residue was purified by column chromatography.

(*RS*)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (7c). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and (*RS*)-1-phenylethylamine (0.80 g, 6.6 mmol) after 7 h at 160 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.11 g (41%) of **7c**: mp 117−119 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, 3H, 5.5 Hz, CH_3), 2.58 (s, 3H, SCH_3), 4.82−5.03 (m, 1H, methine-H), 6.39−7.74 (m, 12H, Ph, 2-Amino-Pyr and 4-F-Ph), 12.57 (bs, 1H, exchangeable, NH); ^{13}C NMR (CD_3OD) δ 16.9 (SCH_3), 24.5 (CH_3), 52.6 (methine), 107.1 (C^3 2-Amino-Pyr), 112.1 (C^5 2-Amino-Pyr), 116.7 (d, 22.2 Hz, C^2/C^6 4-F-Ph), 126.9 (C^4 Ph), 127.8 (C^2/C^6 Ph), 128.1, 129.5 (C^3/C^5 Ph), 131.6 (d, 8.3 Hz, C^3/C^5 4-F-Ph), 145.5, 147.4 (C^1 Ph), 149.3, 160.8 (C^2 2-Amino-Pyr), 165.0 (d, 246.3 Hz, C^1 4-F-Ph); IR 1221 cm^{-1} (C−F); MS *m*/*z* (%) 406.2 (16, M + 1$^+$), 403.9 (68, M$^+$), 389.1 (42), 299.1 (12), 285.1 (20), 267.1 (10), 202.2 (15), 178.2 (15), 120.1 (100), 105.3 (48), 79.1 (13), 77.0 (13); HPLC (254 nm) 18.2 min (48.2%), 28.5 min (51.8%); Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

Benzyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (7d). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and benzylamine (0.8 g, 7.5 mmol) after 5 h at 160 °C. The crude product was purified by column chromatography (basic alumina, DCM/ethyl acetate 1+1) to yield 0.11 g (41%) of **7d**: mp 152 °C (decomp.); ^{1}H NMR (CD_3OD) δ 2.59 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 6.56−6.59 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.04−7.44 (m, 9H, Ph and 4-F-Ph), 7.83 (d, 1H, 5.6 Hz, C^6-H 2-Amino-Pyr); IR 3234 (NH), 1225 cm^{-1} (C−F); MS *m*/*z* (%) 390.1 (100, M$^+$), 373.0 (5), 313.0 (10), 285.1 (55), 251.9 (7.5), 212.1 (9.7), 106.0 (87), 91.0 (63); Anal. ($C_{22}H_{19}FN_4S$) C, H, N.

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]-2-methoxypyridine (7e). A methanolic solution of **5b** (1.0 g, 3.3 mmol) and iodomethane (5.6 g, 39 mmol) was heated to reflux for 3 h. The reaction was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue was suspended in ethanol. The insoluble residue was filtered off, and the solvent was removed from the filtrate in vacuo. The residue was suspended in DCM/ethanol (9+1). The insoluble residue was filtered off, and the filtrate was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.27 g (26%) of **7e**: mp 158 °C; ^{1}H NMR (CD_3OD) δ 2.67 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 6.87−6.89 (m, 1H, C^3-H 2-MeO-Pyr), 6.98 (dd, 1H, 1.5/5.5 Hz, C^5-H 2-MeO-Pyr), 7.16−7.24 (m, 2H, 4-F-Ph), 7.46−7.53 (m, 2H, 4-F-Ph), 8.03 (dd, 1H, 0.7/5.5 Hz, C^6-H 2-MeO-Pyr); IR 1222 cm^{-1} (C−F); Anal. ($C_{16}H_{14}FN_3OS$) C, H, N.

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]-2-isopropoxypyridine (7f). To a solution of **5f** (4.0 g, 13.8 mmol) in THF absol (60 mL) was added NaH (55−65%, 1.0 g, approx 23 mmol), and the mixture was stirred at room temperature for 5 min. A solution of iodomethane (2.2 g, 17.3 mmol) in THF absol (5 mL) was added dropwise and with cooling in a water bath. The reaction was stirred at room temperature for 1 h. The clear, brown solution was concentrated in vacuo, and the residue was suspended in H_2O. The aqueous solution was neutralized with 10% hydrochloric acid and extracted with ethyl acetate. The combined organic extract was washed with saturated brine and dried over Na_2SO_4 and the solvent evaporated. The semisolid residue was extracted with hot *tert*-butyl methyl ether (2×). The organic extract was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the solid residue was triturated with *tert*-butyl methyl ether to yield the title compound. A second crop of **7f** was obtained from the ethereal mother liquor by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1), combined yield 2.1 g (50%): mp 141 °C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 6H, 6.1 Hz, 2 × CH_3), 2.63 (s, 3H, SCH_3), 5.08−5.14 (m, 1H, methine-H), 6.76 (s, 1H, C^3-H 2-Iso-O-Pyr), 6.88 (dd, 1H, 1.4/5.4 Hz, C^5-H 2-Iso-O-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.40−7.47 (m, 2H, 4-F-Ph), 7.95 (dd, 1H, 0.7/5.4 Hz, C^6-H 2-Iso-O-Pyr); IR 1222 cm^{-1} (C−F); MS *m*/*z* (%) 343.1 (83, M$^+$), 328 (62), 300 (100), 284.9 (79), 268 (47), 228.1 (22), 205.2 (23), 199.1 (23), 121.2 (24), 43.1 (51); Anal. ($C_{18}H_{18}FN_3OS$) C, H, N.

(*R*)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (7g). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and (*R*)-1-phenylethylamine (0.80 g, 6.6 mmol) after 7 h at 170 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.10 g (36%) of **7g**: mp 117−119 °C; ^{1}H NMR (CD_3OD) δ 1.44 (d, 3H, 6.9 Hz, CH_3), 2.59 (s, 3H, SCH_3), 4.62−4.69 (m, 1H, methine-H), 6.47−6.57 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.05−7.42 (m, 9H, Ph and 4-F-Ph), 7.80 (d, 1H, 5.5 Hz, C^6-H 2-Amino-Pyr); IR 1221 cm^{-1} (C−F); MS *m*/*z* (%) 406.2 (13, M + 1$^+$), 403.9 (70, M$^+$), 389.0 (43), 299.0 (13), 285.1 (16), 267.0 (9), 202.2 (12), 178.2 (12), 120.1 (100), 105.2 (48), 79.1 (12), 77.0 (13); HPLC (254 nm) ee 92.4%; Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

(*S*)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (7h). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and (*S*)-1-phenylethylamine (0.80 g, 6.6 mmol) after 13 h at 170 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.10 g (36%) of **7g**: mp 117−119 °C; ^{1}H NMR (CD_3OD) δ 1.44 (d, 3H, 6.9 Hz, CH_3), 2.59 (s, 3H, SCH_3), 4.62−4.69 (m, 1H, methine-H), 6.47−6.57 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.05−7.42 (m, 9H, Ph and 4-F-Ph), 7.80 (dd, 1H, 0.5/5.5 Hz, C^6-H 2-Amino-Pyr); IR 1221 cm^{-1} (C−F); MS *m*/*z* (%) 406.2 (13, M + 1$^+$), 403.9 (58, M$^+$), 389.0 (33), 299.0 (10), 285.1 (15), 267.0 (8), 202.2 (11), 178.2 (12), 120.1 (100), 105.2 (47), 79.1 (12), 77.0 (13); HPLC (254 nm) ee 96.8%; Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(4-methoxybenzyl)amine (7i). According to general procedure B, the title compound was obtained from **7a** (0.44 g, 1.5 mmol) and 4-methoxybenzylamine (2.0 g, 14.6 mmol) after 7 h at 160 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.30 g (48%) of **7i**: mp 207 °C; ^{1}H NMR (CD_3OD) δ 2.61 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 6.56−6.59 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 6.81−7.30 (m, 6H, 4-MeO-Ph and 4-F-Ph), 7.39−7.46 (m, 2H, 4-F-Ph), 7.84 (d, 1H, 6.0 Hz, C^6-H 2-Amino-Pyr); IR 1217 cm^{-1} (C−F); MS *m*/*z* (%) 420.1 (28, M$^+$), 405.1 (5), 285.1 (8), 210.1 (7), 136.1 (63), 121.1 (100), 71.1 (8); Anal. ($C_{23}H_{21}FN_4OS$) C, H, N.

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(4-methylbenzyl)amine (7j). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and 4-methylbenzylamine (0.85 g, 7.0 mmol) after 6 h at 160 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.05 g (18%) of **7j**: mp 185 °C; ^{1}H NMR (CD_3OD) δ 2.29 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 4.32 (s, 2H, CH_2), 6.57−6.60 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.05−7.50 (m, 8H, 4-Me-Ph and 4-F-Ph), 7.83 (d, 1H, 5.3 Hz, C^6-H 2-Amino-Pyr); IR 1218 cm^{-1} (C−F); MS *m*/*z* (%) 404.2 (54, M$^+$), 389.1 (4), 285.1 (24), 221.1 (22), 120.2 (100), 105.1 (56), 77.1 (12); Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

(4-Chlorobenzyl)-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (7k). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and 4-chlorobenzylamine (1.0 g, 7.0 mmol) after heating to reflux for 5.5 h. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to

yield 0.12 g (40%) of **7k**: mp 195 °C; ^{1}H NMR (CD_3OD) δ 2.60 (s, 3H, SCH_3), 4.38 (s, 2H, CH_2), 6.57−6.60 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.05−7.14 (m, 2H, 4-F-Ph), 7.22−7.30 (m, 4H, 4-Cl-Ph), 7.38−7.45 (m, 2H, 4-F-Ph), 7.83 (d, 1H, 5.7 Hz, C^6-H 2-Amino-Pyr); ^{13}C NMR (CD_3OD) δ 16.9 (CH_3), 45.6 (CH_2), 106.9 (C^3 2-Amino-Pyr), 112.2 (C^5 2-Amino-Pyr), 116.7 (d, 22.0 Hz, C^2/C^6 4-F-Ph), 129.5 (C^3/C^5 4-Cl-Ph), 129.6 (C^4 4-F-Ph), 129.7 (C^2/C^6 4-Cl-Ph), 130.3 (C^6 2-Amino-Pyr), 131.7 (d, 8.3 Hz, C^3/C^5 4-F-Ph), 133.6, 138.9, 140.0, 144.6, 148.4, 160.4 (C^2 2-Amino-Pyr), 163.7 (C^2 imidazole), 164.1 (d, 246.9 Hz, C^1 4-F-Ph); IR 1218 cm^{-1} (C−F); MS *m*/*z* (%) 424.1 (77, M^+), 409.1 (4), 313 (10), 284.8 (100), 251.9 (7), 212.1 (17), 195.0 (12), 178.1 (12), 140.0 (45), 125.0 (44), 89.0 (10); Anal. ($C_{22}H_{18}ClFN_4S$) C, H, N.

(3,4-Dichlorobenzyl)-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (7l). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and 3,4-dichlorobenzylamine (1.2 g, 6.8 mmol) after 7.5 h at 160 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.12 g (38%) of **7l**: mp 212 °C; ^{1}H NMR (CD_3OD) δ 2.60 (s, 3H, SCH_3), 4.39 (s, 2H, CH_2), 6.56−6.62 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.06−7.50 (m, 7H, 3,4-Di-Cl-Ph and 4-F-Ph), 7.84 (d, 1H, 5.5 Hz, C^6-H 2-Amino-Pyr); IR 1225 cm^{-1} (C−F); MS *m*/*z* (%) 460.0 (29, M + 1^+), 458.0 (44, M − 1^+), 343.0 (24), 328.1 (19), 300.0 (35), 285.1 (100), 268.1 (16), 212.1 (21), 174.0 (22), 158.9 (59), 121.1 (17); Anal. ($C_{22}H_{17}Cl_2FN_4S$) C, H, N.

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}phenylamine (7m). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and aniline (0.65 g, 7.0 mmol) after heating to reflux for 6 h. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.03 g (12%) of **7m**: mp 228 °C; ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H, CH_3), 5.95−6.13 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 6.68−7.60 (m, 9H, Ph and 4-F-Ph), 7.97−8.01 (m, 1H, C^6-H 2-Amino-Pyr), 8.99 (bs, 1H, exchangeable, anilino-NH), 12.68 (bs, 1H, exchangeable, imidazole-NH); IR 1225 cm^{-1} (C−F); MS *m*/*z* (%) 377.2 (20, M + 1^+), 375.1 (100, M-1^+), 360.1 (11), 326.9 (7), 302.1 (14), 194.0 (8), 187.8 (24), 171.2 (44), 151.0 (25), 137.1 (10), 95.1 (4), 77.1 (9); Anal. ($C_{21}H_{17}FN_4S$) C, H, N.

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}phenethylamine (7n). According to general procedure B, the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and 2-phenylethylamine (0.85 g, 7.0 mmol) after 5.5 h at 160 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.12 g (38%) of **7n**: mp 99 °C; ^{1}H NMR (CD_3OD) δ 2.61 (s, 3H, SCH_3), 2.81 (t, 2H, 7.7 Hz, NCH_2), 3.41 (t, 2H, 7.7 Hz, CH_2Ph), 6.55−6.57 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.08−7.26 (m, 7H, Ph and 4-F-Ph), 7.42−7.49 (m, 2H, 4-F-Ph), 7.82 (d, 1H, 6.1 Hz, C^6-H 2-Amino-Pyr); IR 1220 cm^{-1} (C−F); Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

Benzyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}methylamine (7o). According to general procedure B the title compound was obtained from **7a** (0.2 g, 0.7 mmol) and *N*-methylbenzylamine (0.85 g, 7.0 mmol) after 7 h at 180 °C. The crude product was purified twice by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.13 g (46%) of **7o**: mp 79 °C; ^{1}H NMR (CD_3OD) δ 2.60 (s, 3H, SCH_3), 2.97 (s, 3H, NCH_3), 4.64 (s, 2H, CH_2), 6.64−6.66 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.02−7.45 (m, 9H, Ph and 4-F-Ph), 7.96 (d, 1H, 5.0 Hz, C^6-H 2-Amino-Pyr); IR 1219 cm^{-1} (C−F); MS *m*/*z* (%) 404.0 (44, M^+), 389.1 (57), 375.1 (11), 313.0 (42), 285.1 (7), 210.1 (44), 202.2 (13), 178.3 (9), 120.1 (35), 106.1 (26), 91.1 (100), 65 (13); Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3*H*-imidazol-4-yl]-2-fluoropyridine (8a). According to general procedure A, the title compound was obtained from **5a** (5.1 g, 17.6 mmol) and benzyl bromide (9.2 g, 54 mmol) after 1.5 h. The crude product was purified by column chromatography (basic alumina, DCM/ethyl acetate 1+1) to yield 0.88 g (12%) of **8a**: mp 174 °C; ^{1}H NMR (DMSO-d_6) δ 4.43 (s, 2H, CH_2), 7.11 (s, 1H, C^3-H 2-F-Pyr), 7.25−7.51 (m, 10H, C^5-H 2-F-Pyr, Ph and 4-F-Ph), 8.10 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.93 (bs, 1H, exchangeable, NH); IR 1228 cm^{-1} (C−F); Anal. ($C_{21}H_{15}F_2N_3S$) C, H, N.

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3*H*-imidazol-4-yl]-2-chloropyridine (8b). According to general procedure A, the title compound was obtained from **5d** (0.3 g, 1.0 mmol) and benzyl chloride (0.12 g, 1.0 mmol) after 6 h. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.12 g (30%) of **8b**: mp 223 °C; ^{1}H NMR (DMSO-d_6) δ 4.43 (s, 2H, CH_2), 7.27−7.47 (m, 11H, 2-Cl-Pyr, Ph and 4-F-Ph), 8.26 (d, 1H, 5.2 Hz, C^6-H 2-Cl-Pyr), 12.94 (bs, 1H, exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 36.6 (CH_2), 116.0 (d, 21.4 Hz, C^2/C^6 4-F-Ph), 119.3 (C^5 2-Cl-Pyr), 119.9 (C^3 2-Cl-Pyr), 126.1, 127.2 (Ph), 128.4 (Ph), 128.8 (Ph), 130.9 (d, 8.1 Hz, C^3/C^5 4-F-Ph), 131.4, 132.7, 137.6 (Ph), 141.2, 147.6 (d, 245.6 Hz, C^1 4-F-Ph), 148.6 (C^2 imidazole), 149.9 (C^6 2-Cl-Pyr), 150.6 (C^2 2-Cl-Pyr); IR 1233 cm^{-1} (C−F); Anal. ($C_{21}H_{15}ClFN_3S$) C, H, N.

(*RS*)-{4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (8c). According to general procedure B the title compound was obtained from **8a** (0.2 g, 0.53 mmol) and (*RS*)-1-phenylethylamine (0.65 g, 5.4 mmol) after 15 h at 150 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.07 g (28%) of **8c**: mp 145 °C; ^{1}H NMR (CD_3OD) δ 1.44 (d, 3H, 6.8 Hz, CH_3), 4.22 (s, 2H, CH_2), 4.61−4.71 (m, 1H, methine-H), 6.44−6.54 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.04−7.35 (m, 9H, Ph and 4-F-Ph), 7.80 (d, 1H, 5.4 Hz, C^6-H 2-Amino-Pyr); IR 1221 cm^{-1} (C−F); HPLC (215 nm) 7.6 min (49.8%), 11.5 min (50.2%); Anal. ($C_{29}H_{25}FN_4S$) C, H, N.

Benzyl-{4-[2-benzylsulfanyl-5-(4-fluorophenyl)-3*H*-imidazol-4-yl]pyridin-2-yl}amine (8d). According to general procedure B, the title compound was obtained from **8a** (0.2 g, 0.53 mmol) and benzylamine (0.60 g, 5.6 mmol) after 6 h at 180 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.14 g (56%) of **8d**: mp 185 °C; ^{1}H NMR (CD_3OD) δ 4.21 (s, 2H, NCH_2), 4.38 (s, 2H, SCH_2), 6.52−6.55 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.03−7.38 (m, 9H, Ph and 4-F-Ph), 7.83 (d, 1H, 5.7 Hz, C^6-H 2-Amino-Pyr); IR 3407 (NH), 1220 cm^{-1} (C−F); Anal. ($C_{28}H_{23}FN_4S$) C, H, N.

{4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3*H*-imidazol-4-yl]pyridin-2-yl}-(4-methoxybenzyl)amine (8e). According to general procedure B, the title compound was obtained from **8b** (0.2 g, 0.5 mmol) and 4-methoxybenzylamine (2.0 g, 14.6 mmol) after heating to reflux for 22 h. The crude product was purified by column chromatography (basic alumina, DCM/ethyl acetate 1+1) to yield 0.06 g (24%) of **8e**: mp 196−200 °C; ^{1}H NMR (DMSO-d_6) δ 4.29 (s, 2H isomers "A" + "B", NCH_2), 4.35 (s, 2H "A" + "B", SCH_2), 6.43−6.47 (m, 1H "A" + 2H "B", C^5-H "A" and C^3-/C^5-H "B" 2-Amino-Pyr), 6.65 (s, 1H "A", C^3-H 2-Amino-Pyr), 6.80−6.84 (m, 2H "A" + "B", 4-MeO-Ph),7.14−7.51 (m, 11H "A" + "B", 4-MeO-Ph, Ph and 4-F-Ph), 7.79 (d, 1H "B", 5.4 Hz, C^6-H 2-Amino-Pyr), 7.91 (d, 1H "A", 5.4 Hz, C^6-H 2-Amino-Pyr), 12.67 (bs, 1H, exchangeable, imidazole-NH), amino-NH not detected; IR 1225 cm^{-1}(C−F); MS *m*/*z* (%) 495.7 (67, M − 1^+), 481.0 (4), 406.2 (9), 360.7 (15), 270.0 (5), 211.0 (7), 136.0 (21), 121.0 (100), 90.7 (20), 77.4 (4), 65.0 (4); Anal. ($C_{29}H_{25}FN_4OS$) C, H, N.

2-Fluoro-4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridine (9a). According to general procedure A, the title compound was obtained from **5a** (4.2 g, 14.5 mmol) and 1-chloromethyl-4-methanesulfinylbenzene[38] (4.1 g, 22 mmol) after 2 h. The crude product was purified twice by column chromatography (1. basic alumina, DCM/ethyl acetate 1+1; 2. SiO_2 60, DCM/ethanol 9+1) to yield 2.5 g (39%) of **9a**: mp 150 °C; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 7.10 (s, 1H, C^3-H 2-F-Pyr), 7.30−7.37 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.47−7.67 (m, 6H, 4-F-Ph and 4-MeS(O)-Ph), 8.11 (d, 1H, 4.8 Hz, C^6-H 2-F-Pyr), 12.95 (bs, 1H, exchangeable, NH); IR 1227 (C−F), 1030 cm^{-1} (S=O); Anal. ($C_{22}H_{17}F_2N_3OS_2$) C, H, N.

2-Chloro-4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridine (9b). To a solution of **5d** (0.31 g, 1.0 mmol) in THF absol (15 mL) was added NaH (55−65%, 0.1 g, appr. 2 mmol), and the mixture was stirred at room temperature for 5 min. 1-Chloromethyl-4-methanesulfinylbenzene[38] (0.19 g, 1.0 mmol) was added, and the reaction was stirred at room temperature for 2 h. The yellow-brown solution was diluted with H_2O and neutralized with 10% citric acid. The organic solvent was removed under reduced pressure, and the aqueous solution was extracted with ethyl acetate (2×). The combined organic extract was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The solid residue was purified by column chromatography (SiO_2 60, DCM/ethanol 9.5+0.5) to yield 0.10 g (22%) of **9b**: mp 179 °C; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.25−8.24 (m, 10H, 2-Cl-Pyr, 4-MeS(O)-Ph and 4-F-Ph), 8.26 (d, 1H, 5.3 Hz, C^6-H 2-Cl-Pyr), 12.94 (bs, 1H, exchangeable, NH); IR 1224 (C−F), 1030 (S=O), 781 cm^{-1} (C−Cl); Anal. ($C_{22}H_{17}ClFN_3OS_2$) C, H, N.

(*RS*)-{4-[5-(4-Fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (9c). According to general procedure B, the title compound was obtained from **9a** (0.3 g, 0.68 mmol) and (*RS*)-1-phenylethylamine (0.85 g, 7.0 mmol) after 10 h at 170 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 9+1) to yield 0.08 g (22%) of **9c**: mp 193 °C; ^{1}H NMR (CD_3OD) δ 1.45 (d, 3H diastereoisomers "A" + "B", 6.8 Hz, CH_3), 2.67 (s, 3H diastereoisomer "A", S(O)-CH_3), 2.69 (s, 3H diastereoisomer "B", S(O)CH_3), 4.28 (s, 2H diastereoisomers "A" + "B", CH_2), 4.62−4.73 (m, 1H diastereoisomers "A" + "B", methine-H), 6.39−6.61 (m, 2H diastereoisomers "A" + "B", C^3-/C^5-H 2-Amino-Pyr), 7.09−7.44 (m, 9H diastereoisomers "A" + "B", Ph and 4-MeS(O)-Ph, 2H diastereoisomer "A" 4-F-Ph and 4H diastereoisomer "B" 4-F-Ph), 7.80 (d, 1H diastereoisomer "B", 5.1 Hz, C^6-H 2-Amino-Pyr), 7.94−8.05 (m, 2H diastereoisomer "A" 4-F-Ph), 8.21 (d, 1H diastereoisomer "A", 5.0 Hz, C^6-H 2-Amino-Pyr); IR 1221 (C−F), 1031 cm^{-1} (S=O); HPLC (215 nm) 34.9 min (25.2%), 40.2 min (24.5%), 62.3 min (24.6%), 64.3 min (25.7%); Anal. ($C_{30}H_{27}FN_4OS_2$) C, H, N.

Benzyl-{4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}amine (9d). According to general procedure B, the title compound was obtained from **9a** (0.3 g, 0.68 mmol) and benzylamine (0.75 g, 7.0 mmol) after 7 h at 170 °C. The crude product was purified by column chromatography (SiO_2 60, DCM/ethanol 19+1) to yield 0.07 g (20%) of **9d**: mp 149 °C; ^{1}H NMR (CD_3OD) δ 2.70 (s, 3H, CH_3), 4.21 (s, 2H, NCH_2), 4.32 (s, 2H, SCH_2), 6.51−6.55 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.03−7.42 (m, 13H, Ph, 4-MeS(O)-Ph and 4-F-Ph), 7.82 (d, 1H, 5.5 Hz, C^6-H 2-Amino-Pyr); IR 1227 (C−F), 1034 cm^{-1} (S=O); Anal. ($C_{29}H_{25}FN_4OS_2$) C, H, N.

4-(4-Fluorophenyl)-5-[2-(1-phenylethylamino)pyridin-4-yl]-1,3-dihydroimidazole-2-thione (10). Upon treatment of **8b** (0.2 g, 0.5 mmol) with (*RS*)-1-phenylethylamine (2.0 g, 16.5 mmol) under the conditions described in the preparation of **8e**, 0.03 g (16%) of **10** was isolated as the only reaction product: mp 204 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (d, 3H, 6.9 Hz, CH_3), 4.86 (m, 1H, methine-H), 6.33−6.37 (m, 2H, C^3-/C^5-H 2-Amino-Pyr), 7.02−7.43 (m, 9H, Ph and 4-F-Ph), 7.83 (d, 1H, 5.3 Hz, C^6-H 2-Amino-Pyr), 12.55 (bs, 1H, exchangeable, NH), amino-NH not detected; IR 1512 (C(S)NH), 1223 cm^{-1} (C−F).

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-propyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (12b).** A solution of **11**[31] (1.2 g, 4.1 mmol) and 1,3,5-tripropyl-[1,3,5]-triazinane (1.0 g, 4.7 mmol) in ethanol absol (20 mL) was heated to reflux for 10 h. The solvent was evaporated in vacuo. The oily residue was triturated with diethyl ether to yield 0.74 g (51%) of **12b**: mp 203 °C; ^{1}H NMR (DMSO-d_6) δ 0.72−0.86 (m, 3H, CH_3), 1.58−1.62 (m, 2H, CH_2), 2.05 (s, 3H, C(O)CH_3), 3.83 (t, 2H, 7.2 Hz, NCH_2), 6.99−7.02 (m, 1H, 2-Amino-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.55 (m, 2H, 4-F-Ph), 8.06 (s, 1H, 2-Amino-Pyr), 8.35−8.37 (m 1H, 2-Amino-Pyr), 8.64 (s, 1H, C^2-H imidazole), 10.73 (s, 1H, exchangeable, NH); IR 1225 cm^{-1} (C−F).

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2,2,6,6-tetramethylpiperidin-4-yl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (12c).** Starting from **11**[31] (1.2 g, 4.1 mmol) and 1,3,5-tris(2,2,6,6-tetramethylpiperidin-4-yl)-[1,3,5]-triazinane (2.4 g, 4.7 mol), 1.5 g (82%) of **12c** was obtained according to the method described for the preparation of **12b**: mp 248 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (s, 6H, 2 × CH_3), 1.02 (s, 6H, 2 × CH_3), 1.44−1.70 (m, 4H, 2 × CH_2), 1.98 (s, 3H, C(O)CH_3), 4.18−4.30 (m, 1H, methine-H), 6.96−7.12 (m, 3H, 4-F-Ph and 2-Amino-Pyr), 7.42−7.49 (m, 2H, 4-F-Ph), 8.06 (s, 1H, 2-Amino-Pyr), 8.30−8.33 (m, 2H, 2-Amino-Pyr), 8.65 (s, 1H, C^2-H imidazole), 10.65 (bs, 1H, exchangeable, NH); IR 1224 cm^{-1} (C−F).

***N*-{4-[5-(4-Fluorophenyl)-3-propyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (13b).** A solution of **12b** (0.7 g, 2.0 mmol) in DCM (12 mL) was cooled in an ice bath. A solution of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (0.35 g, 2.1 mmol) in DCM (6 mL) was added dropwise. After the addition was complete, the mixture was stirred for 30 min in the ice bath, and for another 60 min at room temperature. The solvent was evaporated, and the solid residue was triturated with diethyl ether. Recrystallization from 2-propanol yielded 0.67 g (90%) of **13b**: mp 240 °C; ^{1}H NMR (DMSO-d_6) δ 0.69 (t, 3H, 7.3 Hz, CH_3), 1.43−1.60 (m, 2H, CH_2), 2.07 (s, 3H, C(O)CH_3), 3.84 (t, 2H, 7.1 Hz, NCH_2), 7.07−7.37 (m, 5H, 4-F-Ph and 2-Amino-Pyr), 8.07 (s, 1H, 2-Amino-Pyr), 8.38−8.40 (m, 1H, 2-Amino-Pyr), 10.73 (s, 1H, exchangeable, acetamido NH), imidazole NH not detected; IR 1490 (C(S)NH), 1228 cm^{-1} (C−F).

***N*-{4-[5-(4-Fluorophenyl)-3-(2,2,6,6-tetramethylpiperidin-4-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (13c).** Starting from **12c** (1.4 g, 3.1 mmol) and 2,2,4,4-tetramethyl-cyclobutane-1,3-dithione (0.55 g, 3.2 mmol), 1.35 g (93%) of **13c** was obtained according to the method described for the preparation of **13b**: mp 193 °C; ^{1}H NMR (DMSO-d_6) δ 1.03 (s, 6H, 2 × CH_3), 1.28 (s, 6H, 2 × CH_3), 1.44−1.65 (m, 4H, 2 × CH_2), 2.01 (s, 3H, C(O)CH_3), 6.97−7.31 (m, 5H, 4-F-Ph and 2-Amino-Pyr), 8.00 (s, 1H, 2-Amino-Pyr), 8.25−8.36 (m, 1H, 2-Amino-Pyr), 10.65 (bs, 1H, exchangeable, acetamido NH), methine-H and imidazole NH not detected; IR 1513 (C(S)NH), 1239 cm^{-1} (C−F).

***N*-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-propyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (14b).** Starting from **13b** (0.6 g, 1.6 mmol) and iodomethane (0.4 g, 2.8 mmol), and after addition of a catalytic amount of Na_2CO_3, the title compound was prepared according to general procedure A. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.23 g (37%) of **14b**: mp 164 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, 7.4 Hz, CH_3), 1.57−1.65 (m, 2H, CH_2), 2.24 (s, 3H, C(O)CH_3), 2.73 (s, 3H, SCH_3), 3.85 (t, 2H, 7.7 Hz, NCH_2), 6.88−6.96 (m, 3H, 4-F-Ph and 2-Amino-Pyr), 7.37−7.44 (m, 2H, 4-F-Ph), 8.25−8.28 (m, 2H, 2-Amino-Pyr), NH not detected; IR 1213 cm^{-1} (C−F); Anal. ($C_{20}H_{21}FN_4OS$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-(2,2,6,6-tetramethyl-piperidin-4-yl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (14c).** Starting from **13c** (1.2 g, 2.6 mmol) and iodomethane (0.65 g, 4.6 mmol), and after addition of a catalytic amount of Na_2CO_3, the title compound was prepared according to general procedure A. The crude product was purified by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1) to yield 0.23 g (18%) of **14c**: mp 229 °C; ^{1}H NMR ($CDCl_3$) δ 0.78−0.93 (m, 12H, 4 × CH_3), 1.47−1.52 (m, 2H, equatorial CH_2), 1.81−1.87 (m, 2H, axial CH_2), 2.00 (s, 3H, C(O)CH_3), 2.61 (s, 3H, SCH_3), 4.03−4.19 (m, 1H, methine-H), 6.95−7.04 (m, 3H, 4-F-Ph and 2-Amino-Pyr), 7.26−7.33 (m, 2H, 4-F-Ph), 8.01 (s, 1H, 2-Amino-Pyr), 8.35−8.38 (m, 2H, 2-Amino-Pyr), 10.62 (s, 1H, exchangeable, NH); IR 1255 cm-1 (C−F); Anal. ($C_{26}H_{32}FN_5OS$) C, H, N.

Ethyl-{4-[5-(4-fluorophenyl)-3-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (15a). Starting from **14a** (1.0 g, 2.8 mmol) the title compound was prepared according to the procedure described for the synthesis of **15b**.

Purification of the crude product by column chromatography yielded 0.67 g (70%) of **15a**: mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, 7.1 Hz, CH_3), 2.70 (s, 3H, SCH_3), 3.23−3.29 (m, 2H, CH_2), 3.47 (s, 3H, NCH_3), 4.59 (t, 1H, 4.5 Hz, exchangeable, NH), 6.26−6.27 (m, 1H, 2-Amino-Pyr), 6.49−6.52 (m, 1H, 2-Amino-Pyr), 6.89−6.98 (m, 2H, 4-F-Ph), 7.46−7.53 (m, 2H, 4-F-Ph), 8.15−8.17 (m, 1H, 2-Amino-Pyr); IR 1221 cm^{-1} (C−F); Anal. ($C_{18}H_{19}FN_4S$) C, H, N.

Ethyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3-propyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (15b). In small portions $LiAlH_4$ (0.5 g, 11.9 mmol) was added to a solution of **14b** (1.0 g, 2.6 mmol) in THF absol (30 mL). The reaction was heated to reflux for 4 h. The slurry was cooled to room temperature, and the reaction was quenched by dropwise addition of H_2O. The aqueous solution was extracted with DCM. The combined organic extract was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography to yield 0.2 g (21%) of **15b**: mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, 7.4 Hz, propyl CH_3), 1.24 (t, 3H, 7.2 Hz, ethyl CH_3), 1.54−1.66 (m, 2H, propyl CH_2), 2.71 (s, 3H, SCH_3), 3.22−3.28 (m, 2H, ethyl CH_2), 3.79 (t, 2H, 7.7 Hz, imidazole-NCH_2), 4.61 (t, 1H, 4.3 Hz, exchangeable, NH), 6.27 (s, 1H, 2-Amino-Pyr), 6.50−6.53 (m, 1H, 2-Amino-Pyr), 6.87−6.98 (m, 2H, 4-F-Ph), 7.43−7.51 (m, 2H, 4-F-Ph), 8.14−8.17 (m, 1H, 2-Amino-Pyr); IR 1219 cm^{-1} (C−F); Anal. ($C_{20}H_{23}FN_4S$) C, H, N.

Ethyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3-(2,2,6,6-tetramethyl-piperidin-4-yl)-3*H*-imidazol-4-yl]pyridin-2-yl}amine (15c). Starting from **14c** (0.1 g, 0.2 mmol), the title compound was prepared according to the procedure described for the synthesis of **15b**. Purification of the crude product by column chromatography yielded 0.03 g (32%) of **15c**: mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 0.90−1.12 (m, 15H, ethyl CH_3 and 4 × CH_3), 1.52−1.59 (m, 2H, equatorial CH_2), 1.91−2.11 (m, 2H, axial CH_2), 2.66 (s, 3H, SCH_3), 3.21−3.27 (m, 2H, ethyl CH_2), 4.14−4.30 (m, 1H, methine-H), 6.37 (s, 1H, 2-Amino-Pyr), 6.41−6.44 (m, 1H, 2-Amino-Pyr), 6.64 (t, 1H, 4.8 Hz, exchangeable, NH), 7.03−7.12 (m, 2H, 4-F-Ph), 7.40−7.47 (m, 2H, 4-F-Ph), 8.07−8.10 (m, 2H, 2-Amino-Pyr); IR 1217 cm^{-1} (C−F); Anal. ($C_{26}H_{34}FN_5S$) C, H, N.

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-propyl-3*H*-imidazol-4-yl]pyridin-2-ylamine (16b). A solution of **14b** (1.0 g, 2.6 mmol) in 10% hydrochloric acid (30 mL) was heated to reflux for 14 h. The reaction was cooled to room temperature and neutralized with an aqueous solution of NaOH (20%). A precipitate formed which was collected by filtration, washed with H_2O, and dried in vacuo. Recrystallization from 2-propanol yielded 0.6 g (67%) of **16b**: mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, 7.4 Hz, CH_3), 1.52−1.63 (m, 2H, CH_2), 2.70 (s, 3H, SCH_3), 3.77 (t, 2H, 7.7 Hz, NCH_2), 4.67 (bs, 2H, exchangeable, NH_2), 6.38 (s, 1H, 2-Amino-Pyr), 6.57−6.60 (m, 1H, 2-Amino-Pyr), 6.87−6.96 (m, 2H, 4-F-Ph), 7.40−7.48 (m, 2H, 4-F-Ph), 8.13−8.15 (m, 2H, 2-Amino-Pyr); IR 1226 cm^{-1} (C−F); Anal. ($C_{18}H_{19}FN_4S$) C, H, N.

{4-[5-(4-Fluorophenyl)-3-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (17a). HPLC (254 nm) 10.5 min (49.9%), 12.2 min (50.1%); Anal. ($C_{24}H_{23}FN_4S$) C, H, N.

Benzyl-{4-[5-(4-fluorophenyl)-3-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (17b) and Dibenzyl-{4-[5-(4-fluorophenyl)-3-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}amine (17d). To a suspension of NaH (50−60%, 0.07 g, approx 1.6 mmol) in DMF absol (15 mL) was added **16a** (0.5 g, 1.6 mmol) in small portions. After the addition was complete, the mixture was stirred at room temperature for 45 min. Benzyl bromide (0.3 g, 1.9 mmol) was added, and the reaction was heated to reflux for 8 h. The reaction was cooled to room temperature and slowly diluted with H_2O. A precipitate formed which was collected by filtration. Both **17b** (0.05 g, 8%) and **17d** (0.25 g, 31%) were isolated from the crude product by column chromatography (SiO_2 60, DCM/ethyl acetate 1+1):

17b: mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H, SCH_3), 3.32 (s, 3H, NCH_3), 4.47 (d, 2H, 5.8 Hz, CH_2), 5.30 (bs, 1H, NH), 6.24 (s, 1H, 2-Amino-Pyr), 6.50−6.53 (m, 1H, 2-Amino-Pyr), 6.86−6.95 (m, 2H, 4-F-Ph), 7.26−7.47 (m, 7H, Ph and 4-F-Ph), 8.12−8.16 (m, 1H, 2-Amino-Pyr); IR 1219 cm^{-1} (C−F); Anal. ($C_{23}H_{21}FN_4S$) C, H, N.

17d: mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, SCH_3), 3.17 (s, 3H, NCH_3), 4.80 (s, 4H, 2 × CH_2), 6.31 (s, 1H, 2-Amino-Pyr), 6.48−6.51 (m, 1H, 2-Amino-Pyr), 6.86−6.95 (m, 2H, 4-F-Ph), 7.19−7.45 (m, 12 H, 2 × Ph and 4-F-Ph), 8.24−8.27 (m, 1H, 2-Amino-Pyr); IR 1219 cm^{-1} (C−F); Anal. ($C_{30}H_{27}FN_4S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-4-methoxybenzamide (17c).** To a solution of **16a** (0.5 g, 1.6 mmol) in THF absol (15 mL) was added triethylamine (0.16 g, 1.6 mmol), and the mixture was cooled in an ice bath. A solution of 4-methoxybenzoyl chloride (0.38 g, 2.2 mmol) was added dropwise. After the addition was complete, the reaction was stirred for 1 h with cooling and for an additional 1 h at room temperature. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to yield 0.11 g (15%) of **17c**: mp 182 °C; ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H, SCH_3), 3.58 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.90−6.95 (m, 5H, 4-MeO-Ph, 4-F-Ph and 2-Amino-Pyr), 7.42−7.49 (m, 2H, 4-F-Ph), 7.89−7.94 (m, 2H, 4-MeO-Ph), 8.28−8.30 (m, 1H, 2-Amino-Pyr), 8.44 (s, 1H, 2-Amino-Pyr), 8.66 (s, 1H, exchangeable, NH); IR 1253 cm^{-1} (C−F); Anal. ($C_{24}H_{21}FN_4O_2S$) C, H, N.

Biological Evaluation: PBMC, Whole Blood, and p38 Assay. Test compounds were assayed in concentrations from 10^{-4} to 10^{-8} M according to the protocols described previously.[23,25]

Cytochrome P450 Assay. The inhibition of cytochrome P450 isoenzymes by selected compounds at a concentration of 10 μM in phosphate buffer (pH 7.4, 0.1% DMSO) was determined as reported.[39,40]

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References

(1) Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. *Nature* **1994**, *372*, 739−746.

(2) Feldmann, M.; Brennan, F. M.; Maini, R. N. Rheumatoid arthritis. *Cell* **1996**, *85*, 307−310.

(3) Feldmann, M. Pathogenesis of arthritis: recent research progress. *Nat. Immunol.* **2001**, *2*, 771−773.

(4) Underwood, D. C.; Osborn, R. R.; Bochnowicz, S.; Webb, E. F.; Rieman, D. J.; Lee, J. C.; Romanic, A. M.; Adams, J. L.; Hay, D. W.; Griswold, D. E. SB 239063, a p38 MAPK inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2000**, *279*, L895−902.

(5) Dean, J. L.; Brook, M.; Clark, A. R.; Saklatvala, J. p38 mitogen-activated protein kinase regulates cyclooxygenase-2 mRNA stability and transcription in lipopolysaccharide-treated human monocytes. *J. Biol. Chem.* **1999**, *274*, 264−269.

(6) Lee, J. C.; Kassis, S.; Kumar, S.; Badger, A.; Adams, J. L. p38 mitogen-activated protein kinase inhibitors—mechanisms and therapeutic potentials. *Pharmacol. Ther.* **1999**, *82*, 389−397.

(7) Foster, M. L.; Halley, F.; Souness, J. E. Potential of p38 inhibitors in the treatment of rheumatoid arthritis. *Drug News Perspect.* **2000**, *13*, 488−497.

(8) Gallagher, T. F.; Seibel, G. L.; Kassis, S.; Laydon, J. T.; Blumenthal, M. J.; Lee, J. C.; Lee, D.; Boehm, J. C.; Fier-Thompson, S. M.; Abt, J. W.; Soreson, M. E.; Smietana, J. M.; Hall, R. F.; Garigipati, R. S.; Bender, P. E.; Erhard, K. F.; Krog, A. J.; Hofmann, G. A.; Sheldrake, P. L.; McDonnell, P. C.; Kumar, S.; Young, P. R.; Adams, J. L. Regulation of stress-induced cytokine production by pyridinylimidazoles; inhibition of CSBP kinase. *Bioorg. Med. Chem.* **1997**, *5*, 49−64.

(9) Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Libby, B. E.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A.; Vacca, J. P.; Varga, S. L.; Agarwal, L.; Dancheck, K.; Forsyth, A. J.; Fletcher, D. S.; Frantz, B.; Hanlon, W. A.; Harper, C. F.; Hofsess, S. J.; Kostura, M.; Lin, J.; Luell, S.; O'Neill, E. A.; Orevillo, C. J.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Visco, D. M.; O'Keefe, S. J. Design and synthesis of potent, selective, and orally bioavailable tetrasubstituted imidazole inhibitors of p38 mitogen-activated protein kinase. *J. Med. Chem.* **1999**, *42*, 2180−2190.

(10) Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. 1-substituted 4-aryl-5-pyridinylimidazoles: a new class of cytokine suppressive drugs with low 5-lipoxygenase and cyclooxygenase inhibitory potency. *J. Med. Chem.* **1996**, *39*, 3929−3937.

(11) Boehm, J. C.; Adams, J. L. New inhibitors of p38 kinase. *Expert Opin. Ther. Pat.* **2000**, *10*, 25−37.

(12) Jackson, P. F.; Bullington, J. L. Pyridinylimidazole Based p38 MAP Kinase Inhibitors. *Curr. Top. Med. Chem.* **2002**, *2*, 1011−1020.

(13) Tong, L.; Pav, S.; White, D. M.; Rogers, S.; Crane, K. M.; Cywin, C. L.; Brown, M. L.; Pargellis, C. A. A highly specific inhibitor of human p38 MAP kinase binds in the ATP pocket. *Nat. Struct. Biol.* **1997**, *4*, 311−316.

(14) Wilson, K. P.; McCaffrey, P. G.; Hsiao, K.; Pazhanisamy, S.; Galullo, V.; Bemis, G. W.; Fitzgibbon, M. J.; Caron, P. R.; Murcko, M. A.; Su, M. S. The structural basis for the specificity of pyridinylimidazole inhibitors of p38 MAP kinase. *Chem. Biol.* **1997**, *4*, 423−431.

(15) Wang, Z.; Canagarajah, B. J.; Boehm, J. C.; Kassisa, S.; Cobb, M. H.; Young, P. R.; Abdel-Meguid, S.; Adams, J. L.; Goldsmith, E. J. Structural basis of inhibitor selectivity in MAP kinases. *Structure* **1998**, *6*, 1117−1128.

(16) Young, P. R.; McLaughlin, M. M.; Kumar, S.; Kassis, S.; Doyle, M. L.; McNulty, D.; Gallagher, T. F.; Fisher, S.; McDonnell, P. C.; Carr, S. A.; Huddleston, M. J.; Seibel, G.; Porter, T. G.; Livi, G. P.; Adams, J. L.; Lee, J. C. Pyridinyl imidazole inhibitors of p38 mitogen-activated protein kinase bind in the ATP site. *J. Biol. Chem.* **1997**, *272*, 12116−12121.

(17) Gum, R. J.; McLaughlin, M. M.; Kumar, S.; Wang, Z.; Bower, M. J.; Lee, J. C.; Adams, J. L.; Livi, G. P.; Goldsmith, E. J.; Young, P. R. Acquisition of sensitivity of stress-activated protein kinases to the p38 inhibitor, SB 203580, by alteration of one or more amino acids within the ATP binding pocket. *J. Biol. Chem.* **1998**, *273*, 15605−15610.

(18) Toledo, L. M.; Lydon, N. B.; Elbaum, D. The structure-based design of ATP-site directed protein kinase inhibitors. *Curr. Med. Chem.* **1999**, *6*, 775−805.

(19) Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. Pyrimidinylimidazole inhibitors of CSBP/p38 kinase demonstrating decreased inhibition of hepatic cytochrome P450 enzymes. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111−3116.

(20) Testa, B.; Jenner, P. Inhibitors of Cytochrome P-450s and their mechanism of action. *Drug. Metab. Rev.* **1981**, *12*, 1−117.

(21) de Laszlo, S. E.; Visco, D.; Agarwal, L.; Chang, L.; Chin, J.; Croft, G.; Forsyth, A.; Fletcher, D.; Frantz, B.; Hacker, C.; Hanlon, W.; Harper, C.; Kostura, M.; Li, B.; Luell, S.; MacCoss, M.; Mantlo, N.; O'Neill, E. A.; Orevillo, C.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Sidler, K.; Widmer, W. R.; O'Keefe, S. J. Pyrroles and other heterocycles as inhibitors of p38 kinase. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2689−2694.

(22) Revesz, L.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Zimmerlin, A. G. SAR of 4-hydroxypiperidine and hydroxyalkyl substituted heterocycles as novel p38 map kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1261−1264.

(23) Laufer, S.; Wagner, G. From Imidazoles to Pyrimidines: New Inhibitors of Cytokine Release. *J. Med. Chem.* **2002**, *45*, 2733−2740.

(24) McIntyre, C. J.; Ponticello, G. S.; Liverton, N.; O'Keefe, S. J.; O'Neill, E. A.; Pang, M.; Schwartz, C. D.; Claremon, D. A. Pyridazine Based Inhibitors of p38 MAPK. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 689−692.

(25) Laufer, S.; Striegel, H.-G.; Wagner, G. Imidazole Inhibitors of Cytokine Release: Probing Substituents in the 2 Position. *J. Med. Chem.* **2002**, *45*, 4695−4705.

(26) Laufer, S.; Wagner, G.; Kotschenreuther, D. Ones, Thiones and *N*-Oxides: An Exercise in Imidazole Chemistry. *Angew. Chem., Int. Ed.* **2002**, *41*, 2290−2293.

(27) Schröter, R. Reduktion von Oximen und Hydroxylaminen. In *Methoden der Organischen Chemie*; 4th ed.; Vol. XI/1b; Müller, E. Ed.; Georg Thieme Verlag: Stuttgart, 1957; pp 495−512.

(28) Lehmann, J. Hydrierung anderer Verbindungen mit N,O−Bindung. In *Methoden der Organischen Chemie*; 4th ed.; Vol. IV/1c; Kropf, H. Ed.; Georg Thieme Verlag: Stuttgart, 1980; pp 537−549.

(29) Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. An efficient synthesis of tetrasubstituted imidazoles from N-(2-oxo)-amides. *Tetrahedron Lett.* **1998**, *39*, 8939−8942.

(30) Armand, J.; Boulares, L. Electrochemical reduction of α-substituted ketones in an aqueous−organic solvent. *Bull. Soc. Chim. Fr.* **1975**, *112*, 711−718.

(31) Wagner, G.; Kotschenreuther, D.; Zimmermann, W.; Laufer, S. Identification of Regioisomers in a Series of N-Substituted Pyridin-4-yl Imidazole Derivatives by Regiospecific Synthesis, GC/MS, and ^{1}H NMR. *J. Org. Chem.* **2003**, *68*, 4527−4530.

(32) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. 6-Amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridine (RWJ 68354): a potent and selective p38 kinase inhibitor. *J. Med. Chem.* **1998**, *41*, 4196−4198.

(33) Boehm, J. C.; Bower, M. J.; Gallagher, T. F.; Kassis, S.; Johnson, S. R.; Adams, J. L. Phenoxypyrimidine inhibitors of p38alpha kinase: synthesis and statistical evaluation of the p38 inhibitory potencies of a series of 1-(piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl) imidazoles. *Bioorg. Med. Chem. Lett* **2001**, *11*, 1123−1126.

(34) The fragment library of Insight II software version 2000 (Accelrys Inc.), running on a SGI Octane workstation, was used to build compound **7g** *in-silico*. The model depicted in Figure 2 was generated with the Discover 3 module of Insight II, starting from the binding geometry seen for SB 203580 in PDB file 1A9U.

(35) Topliss, J. G. Utilization of operational schemes for analogue synthesis in drug design. *J. Med. Chem.* **1972**, *15*, 1006−1011.

(36) Seide, O. α-Amino-γ-picoline and some of its derivatives. *Ber.* **1924**, *57B*, 791−794.

(37) Adger, B. M.; Ayrey, P.; Bannister, R.; Forth, M. A.; Hajikarimian, Y.; Lewis, N. J.; O'Farrell, C.; Owens, N.; Shamji, A. Synthesis of 2-substituted 4-pyridylpropionates. Part 2. Alkylation approach. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2791−2796.

(38) Samanen, J. M.; Brandeis, E. The *p*-(methylsulfinyl)benzyl group: a trifluoroacetic acid (TFA)-stable carboxyl-protecting group readily convertible to a TFA-labile group. *J. Org. Chem.* **1988**, *53*, 561−569.

(39) Crespi, C. L.; Miller, V. P.; Penman, B. W. Microtiter plate assays for inhibition of human, drug-metabolizing cytochromes P450. *Anal. Biochem.* **1997**, *248* (1), 188−190.

(40) Gentest Corporation (Woburn, MA), Technical Bulletin, Version 3, **1998**.

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