Regiospecific and Highly Flexible Synthesis of 1,4,5-Trisubstituted 2-Sulfanylimidazoles from Structurally Diverse Ethanone Precursors

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Received 4 October 2007; revised 16 October 2007

Abstract: Imidazoles represent important bioactive scaffolds in medicinal chemistry. More than 2,500 structures are listed in drug discovery databases and over 3,000 patents have been claimed for imidazole-based structures. Recent imidazole pharmacophores have targeted various MAP kinases. p38 Mitogen-activated protein (MAP) kinase plays a central role in the signaling network responsible for the upregulation of proinflammatory cytokines like IL-1β and TNFα and offers, therefore, a valid target for small molecule anti-inflammatory drugs. 2-Sulfanylimidazole derivatives offer some advantages over prototype inhibitors (SB203580), e.g. lower cytochrom P450 interactions and better kinetic properties. We report here three novel regioselective and, at the same time, highly flexible synthetic approaches towards 1,4,5-trisubstituted 2-sulfanylimidazoles starting from different ethanone regioisomers allowing maximum variability of all substituents introduced. As a result, a variety of selective and highly potent p38 MAPK inhibitors were prepared and selected for further preclinical development. Synthesis of structurally diverse inhibitor candidates, p38 inhibition data, and selectivity profiling of some selected compounds are specified. Furthermore, the benefits of the useful, brief synthetic sequences are outlined and contrasted with already published multistep routes.

Key words: medicinal chemistry, heterocycles, ring closure, nucleophilic aromatic substitutions, regioselectivity, p38 MAP kinase inhibitors

Imidazoles are widespread scaffolds in highly significant biomolecules exhibiting interesting biological activities.[1] Imidazole derivatives have also been found to possess many pharmacological properties and are largely implicated in biochemical processes.[1] Members of this class of 1,3-diazoles are known to possess NO synthase inhibition, antibiotic, antifungal, and antiulceratice activities and include compounds that are inhibitors of phosphodiesterase (PDE4), 5-lipoxygenase, or substances with VEGF receptor I and II antagonistic activities.[1] In addition, these heterocycles comprise several inhibitors of p38 MAP kinases, a subgroup of mitogen-activated protein kinases, which are thought to be involved in a variety of inflammatory and immunological disorders. To date 3,312 patent files dealing with heterogeneous imidazole structures are registered in the electronical patent document archive DEPATISnet.[2] About 2,500 'imidazole' hits alone could be found in the structure–activity relationship(s) (SAR) database Integrity (Prous Science[3]), an integrated drug discovery portal that is structure and sequence searchable. From these, 165 compounds have been advanced to preclinical development or clinical studies. In particular 18 imidazole derivatives have reached phase I and 12 compounds have entered phase II of the clinical trials, e.g. the prototypical p38 mitogen-activated protein (MAP) kinase inhibitors SB203580,[4] SB242235,[4] L-790070[4] and RWJ67657[4] (Figures 1 and 2) for the potential therapeutic intervention of acute and chronic inflammatory diseases. Protein kinases like p38 are critical enzymes of cellular signal transduction cascades. p38 is a member of the highly conserved serine/threonine protein MAP kinase family mediating fundamental biological cell processes both at the translation and the transcription level and is activated in response to extracellular stress stimuli. Numerous severe diseases, including inflammatory and autoimmune disorders, neurodegenerative conditions, cardiovascular diseases, and cancer are directly linked to dysfunction of protein kinase-mediated cell signaling pathways.[5] Approximately 20–25% of the druggable human genome[6] encodes for kinases, which are involved in signal transduction. Currently almost 200 compounds with kinase inhibitory activity against more than 50 different human kinase targets are in the various stages of preclinical and clinical development. The vast majority of these compounds target the kinase's ATP site, and, because all of the more than 500 protein kinases identified in the human genome[7] have an ATP site, there is great potential for cross-interaction. At present only six kinase inhibitors are used in clinical practice in the field of cancer therapy.[8,9] Several inhibitors of p38 MAP kinase have been demonstrated to reduce efficiently cytokine levels in functional assays as well as in animal tests.[10,11] Many of these ATP mimetics were derived from the prototypical 5-(4-pyridyl)imidazole SB 203580 (Figure 2), and the structural requirements for p38 inhibition have been extensively discussed.[12–17] Despite the fact that a few p38 imidazole-based inhibitor candidates have, meanwhile, reached phase II of clinical development, safety issues appear to represent the main hurdle for successful development. The selectivity profile, i.e. the extent of p38 inhibition versus inhibition of other protein kinases, represents a critical feature. However, exploitation of less-conserved surrounding kinase areas that are not used by ATP can improve the selectivity.[18,19] To date, p38 MAP kinase[20,21] remains one of the most promising small molecule

SYNTHESIS 2008, No. 2, pp 0253–0266
Advanced online publication: 18.12.2007
DOI: 10.1055/s-2007-1000852; Art ID: Z23507SS

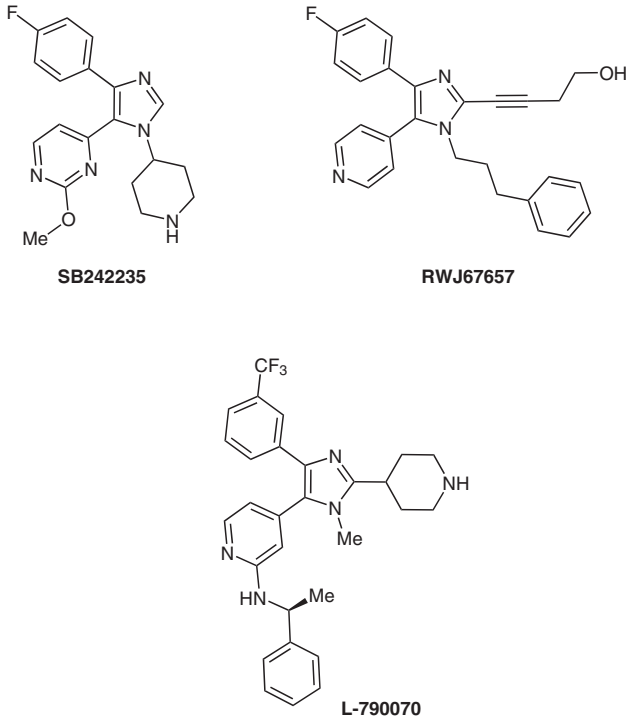


Figure 1 p38 MAP kinase inhibitors that have been advanced to preclinical or clinical studies for therapeutic intervention of acute and chronic inflammatory diseases.

therapeutic targets for treatment of autoimmune and inflammatory diseases.[22]

Although binding at the ATP-binding site, imidazole scaffolds allow the design of selective MAPK inhibitors (e.g., SB202190 or SB203580 vs BIRB796),[23,24] thereby targeting all major interaction regions.[19] Many first generation imidazole-based inhibitors, however, suffer from non-mechanistic side effects [particularly inhibition of cytochrome P-450 enzymes (CYP)] making more structural modification necessary.[25] For this reason newer pyridylimidazole inhibitors have been tried to further optimize by incorporating different substituents on the imidazole core itself and/or by introducing additional (amino)-substituents at the *ortho*-position of the pyridine ring. Especially the nature of the substituents at the imidazole N1 and C2 position has been varied extensively mainly in order to improve physicochemical properties and to reduce toxicity. The different design strategies have led to several inhibitors with high potency and enhanced selectivity among closely related kinases. 2-Sulfanylimidazoles have proved to have decisive advantages over prototype SB203580-like 2-arylimidazoles, e.g. fewer interactions with metabolic enzymes like CYP-450s and better kinetic and metabolic properties.[26] These compounds can be regarded as open-chain analogues of the early lead SK&F 86002 (Figure 2).

The general architecture of the ATP site in protein kinases has been reviewed in recent years.[19,27] Essential interactions of the class of p38 pyridylimidazole inhibitors with the ATP-binding cleft are:[28,29]

(a) Hydrogen donor/acceptor functions of the 2-aminopyridyl residues (mainly gaining activity).

(b) Space-filling lipophilic aryl residues, binding to the hydrophobic back pocket (mainly gaining selectivity).

(c) Interactions of additional substituents at the pyridine C2 position with the hydrophobic front region (gaining both activity and selectivity).

(d) Further interactions with both the sugar pocket and the phosphate binding region by imidazole N1, and C2-S residues, respectively (importance less clear; preferred positions to modify physicochemical properties).

Thus, despite the prejudices (lack of selectivity, CYP-inhibition), imidazoles are still preferred scaffolds for p38 MAPK inhibition for the reasons discussed. Suitable synthetic procedures would make a high chemical diversity possible and at the same time offer a great challenge. As there is still a deficit of promising development candidates, our aim was to develop short syntheses useful for fast and regioselective access to various di- and trisubstituted 2-sulfanylimidazoles. We report here multifunctional synthetic methods allowing flexible and regioselective modification of substituents to yield bioactive (1,)2,4,5-substituted imidazoles starting from structural diverse ethanone scaffolds.

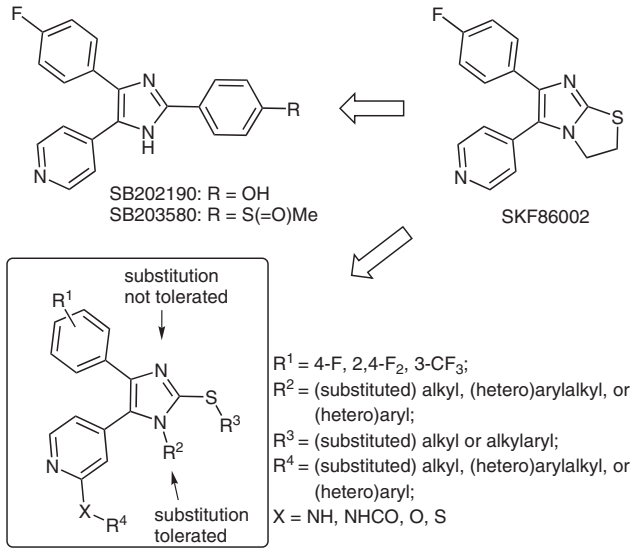
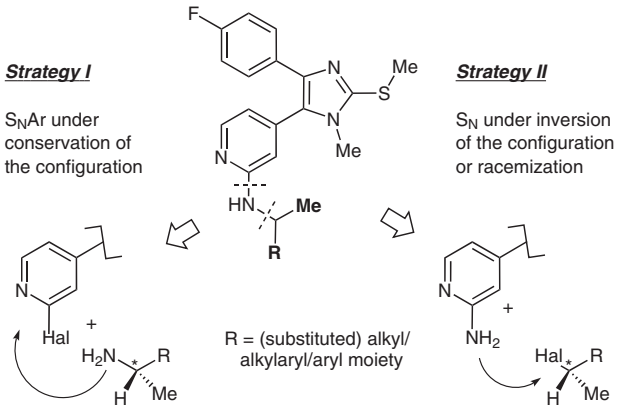


Figure 2 Vicinal aryl-/heteroaryl-substituted imidazoles under investigation for p38 MAP kinase inhibition derived from the early lead SK&F 86002.

State of the art in 2-sulfanylimidazole chemistry: brief synthetic methods for the preparation of highly substituted imidazole cores are rare and generally not practicable under neutral reaction conditions.[30] Moreover, the first synthetic approaches towards 1,4,5-trisubstituted 2-sulfanylimidazoles derived from SK&F86002 (Figure 2) did not allow the introduction of imidazole N1 substituents in a regioselective manner and/or the arrangement of any further substituents at the pyridine moiety.[31–33]

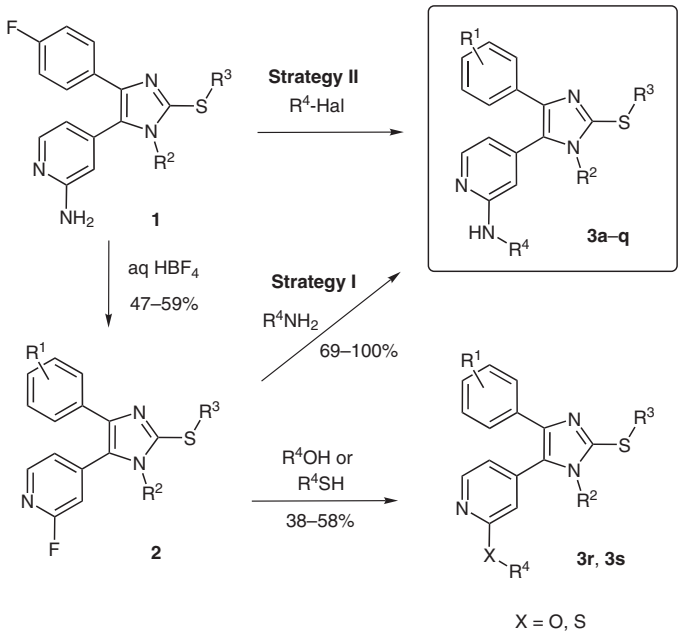
Due to the drastic reaction conditions of the Neber rearrangement (NaOMe) typically used to synthesize the intermediate amino ketones, halogen atoms at C2 of the pyridine ring would also be substituted early in the synthetic sequence by either solvent or base.[32,33] Although the latest published method[34,35] can perform the regioselective construction of a variety of such imidazole scaffolds, the introduction of substituents in the corresponding pyridine position was still limited to nitrogen residues; chiral N-, O- or S-(aryl)alkyl substituents could not be introduced. In addition this multistep reaction sequence suffers from low overall yield and requires repeated protection of the exocyclic NH group. As some substituents that should be varied need to be defined in early reaction steps, the whole process is quite inflexible and time consuming. Therefore, our aim was to develop a novel regioselective, but extremely flexible and short, reaction strategy for rapid access to 1,2,4,5-tetrasubstituted imidazoles.



Scheme 1 Vicinal aryl-/heteroaryl-substituted imidazoles under investigation for p38 MAP kinase inhibition derived from the early lead SK&F 86002.

Retrosynthetic analysis of an exemplary tetrasubstituted target molecule in Scheme 1 demonstrates two principal approaches to arrange substituents at the pyridine bridged by a heteroatom. The starting aminopyridine derivatives exemplified by formula **1** (Scheme 2) used in strategy II can be derived via a previously published multistep method.[26,34] However, the existing route is complicated and needs repeated protection of the exocyclic amino group during the reaction course. Imidazole C4/C5 residues as well as the N1 position need to be defined at a very early stage. Unfortunately, beside the expenditure of time, overall yields of **1** are low. Moreover as a result of the S_N mechanism in strategy II, the configuration of introduced haloalkyl substituents will be inverted or racemized (compounds **3**).

The S_NAr mechanism in strategy I allows the introduction of chiral building blocks (N-, O-, or S-nucleophiles) on the one hand and even tolerates aniline-like substituents (e.g., **3h**) that cannot be coupled by strategy II as well as chiral amines. The commercial availability of various primary or secondary amines allows rapid variation leading to a broad substitution pattern; C2 of the pyridine is activated for S_NAr reactions. Substituents are directed *ortho* (or *para*) by the ^-M effect of the heterocyclic sp^2-N. Additionally the reactivity is enhanced by the high electronegativity of the fluorine, making it the preferred leaving group. Thus, strategy I seems to be more promising and flexible. The starting amino pyridine derivatives **1**, however, are suitable for the simple production of varied (acylamino)pyridyl-substituted imidazoles using acid halides. To obtain the tetrasubstituted imidazole precursors bearing a fluorine atom at the 2-position of the pyridine, compounds **1** were successfully subjected to a mild variant of the Schiemann reaction according to Minor et al.[36] using sodium nitrite in aqueous tetrafluoroboric acid



Scheme 2 Preparation of compounds **2** using a modified Balz–Schiemann fluorination reaction starting from **1** and different coupling reactions at the pyridine moieties via either strategy I or II.

(Scheme 2, Table 1) giving **2** in 47–59% isolated yields depending on N1 residue. Though, under these aqueous conditions side reactions resulting in 2-hydroxypyridine derivatives are likely to take place. For every molecule represented by general formula **2**, fluorination conditions had to be optimized. Moreover the preparation of **2** from **1** requires an additional reaction step in an already laborsome reaction sequence further decreasing the overall yield. Therefore we developed an alternative, much shorter, synthetic strategy and introduced the fluorine in an earlier reaction step.

To avoid repeated protection of the exocyclic amino group, we accomplished the fluorination step first starting from ethanone **4** (Scheme 3, route A). We readily obtained the 1-(2-fluoro-4-pyridyl)ethanone **5** in good yields (<85%) when reacting **4** with sodium nitrite in dry hydrogen fluoride/pyridine consistent with the protocol of Fukuhara et al.[37] The following α-oximination could now be easily performed according to previously reported practices toward 2,4,5-trisubstituted imidazoles in glacial acetic acid with sodium nitrite, yielding **6**.[26] Ring closure with the appropriate triazinane afforded **7** in excellent yields (70–86%). Imidazole *N*-oxides **7** then were converted into imidazole-2-thiones **8** by treatment with a small excess of 2,2,4,4-tetramethylcyclobutane-1,3-dithione at room temperature; yields were approx. 80%. Subsequent alkylation of imidazole-2-thiones **8** was carried out in methanol and in the presence of potassium carbonate at ambient temperature yielding the corresponding 2-(alkylsulfanyl)imidazoles **3** almost quantitatively.[38,39] Other protocols that favor higher temperatures constantly gave elevated amounts of side and decomposition products. In contrast, our mild method was also suitable with arylalkyl- or even polar-substituted alkyl residues, e.g., benzyl or 2,3-dihydroxypropyl, to achieve compounds that potentially interact with the enzyme's phosphate binding region.[19] By this means the production of 1,2,4,5-tetrasubstituted imidazoles **2** was obviously shortened while yields were commonly high. Various aminonucleophiles could be readily introduced at the 2-position of the pyridine using known S_NAr methods (Scheme 2, **3a–q**), and both the substrate **2** as well as the resulting products **3** proved to be surprisingly thermostable. In each case yields were excellent (<100%) and much higher than reported previously for such S_NAr reactions at analogous 2,4,5-trisubstituted derivatives.[26] Moreover, as expected, the 2-fluoro-4-pyridyl intermediate **2** could be also successfully undergo nucleophilic substitution with (ionic) O- and S-nucleophiles (Scheme 2, **3r** and **3s**). However, the multistep production of ethanone **4** was still a limiting factor. As reported earlier **4** could be obtained in low overall yield in four steps starting from 2-aminopicoline.[34] Therefore, we were still required a shorter reaction sequence.

Table 1 Substitution for Compounds **1–3**

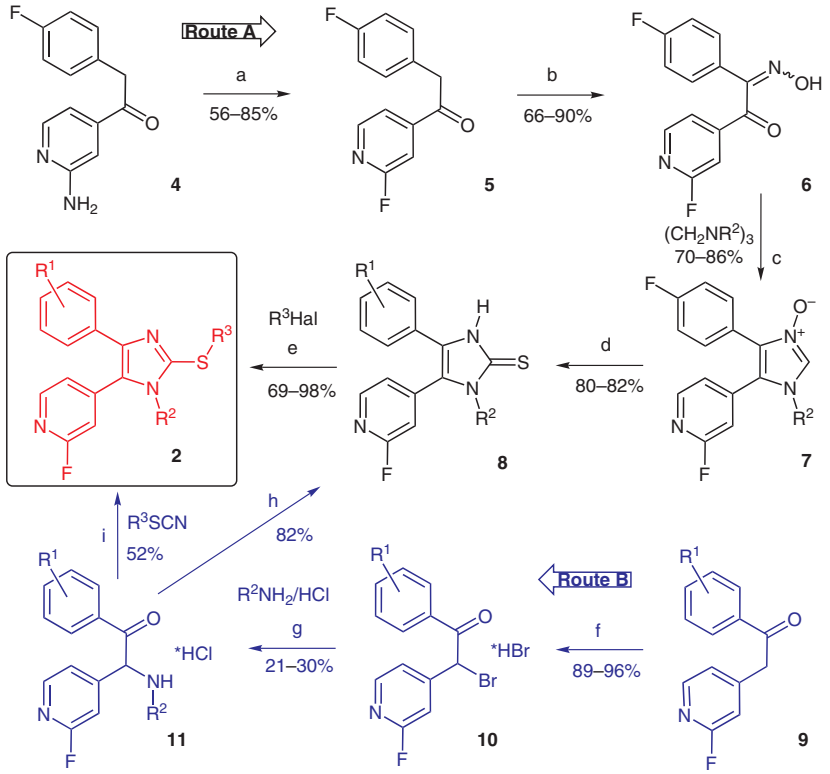
Comp.	R^1	R^2	R^3	NHR^4 or XR^4
1a	–	Me	Me	–
1b	–	$(CH_2)_2OMe$	Me	–
2a	4-F	H	Me	–
2b	4-F	Me	Me	–
2c	4-F	$(CH_2)_2OMe$	Me	–
3a	4-F	Me	Me	(*R*)-CH(Me)Ph
3b	4-F	Me	Me	(*S*)-CH(Me)Ph
3c	4-F	$(CH_2)_2OMe$	Me	(*R*)-CH(Me)Ph
3d	4-F	$(CH_2)_2OMe$	Me	(*S*)-CH(Me)Ph
3e	4-F	$(CH_2)_2OMe$	Me	(*R*/*S*)-CH(Me)CH_2OH
3f	4-F	$(CH_2)_2OMe$	Me	(*R*)-CH(Me)CH_2OH
3g	4-F	$(CH_2)_2OMe$	Me	(*S*)-CH(Me)CH_2OH
3h	4-F	$(CH_2)_2OMe$	Me	Ph
3i	4-F	$(CH_2)_2OMe$	Me	(*R*)-2-hydroxycyclohexyl
3j	4-F	$(CH_2)_2OMe$	Me	*trans*-4-hydroxycyclohexyl
3k	4-F	$(CH_2)_2OMe$	Me	(*R*)-CH(Me)Cy
3l	4-F	$(CH_2)_2OMe$	Me	tetrahydropyran-4-yl
3m	4-F	$(CH_2)_2OMe$	Me	2-hydroxycyclohexylmethyl
3n	4-F	$(CH_2)_2OMe$	Me	$CH_2CH(OH)Me$
3o	4-F	H	Me	tetrahydropyran-4-yl
3p	4-F	H	Me	*trans*-4-hydroxycyclohexyl
3q	4-F	$(CH_2)_2OMe$	Me	Cy
3r	4-F	H	Me	2-thienylmethoxy
3s	4-F	H	Me	SPh

In contrast the regioisomeric ethanone **9** of compound **5** is accessible in only one step in excellent yield. In addition the variation of the aryl moiety is easily possible as the corresponding precursors (acids, esters) are commercially available.[40,41] In either case we directly yielded **9** (84–88%) by reacting 2-halo-4-methylpyridines with substituted benzoic acid esters. However, exercising route A (Scheme 3, Table 2) starting from **9** in order to receive tetrasubstituted imidazole scaffolds specified by the routes discussed would result in the wrong regioisomers with low or no bioactivity.[42] For that reason a third synthetic methodology was investigated, which allows, finally, the most elegant access to key intermediate **2** (Scheme 3, route B). To obtain tetrasubstituted imidazole derivatives of the desired regiochemistry and to diversify substituents at the intended N1 position, we first tried to α-monofunctionalize the ethanones **9** by acid-catalyzed treatment with bromine. The reaction was generally carried out according to Revesz[43] by adding one equivalent of bromine to a solution of **9** in acetic acid at room temperature. The received products **10** were viscous oils that were directly used in the following reaction. Initial attempts to substi-

tute the bromine of **10** with primary (aryl)alkylamines (e.g. methoxyethylamine) failed. Heating **10** with the appropriate amine in ethanol indeed formed the desired product (DC; LC/MS), which was not stable, however, and could not be isolated or successfully further converted with thiocyanic acid ethers in *N*,*N*-dimethylformamide.[32] The procedure was changed as follows. A twofold excess of the amine was dissolved in dichloromethane at 0 °C and a cold solution of **10** in dichloromethane was slowly added. Products **11** precipitated as fine white salts after treating the organic residue with hydrogen chloride saturated ethanol, evaporation of the solvent, and repeated washing with a mixture of Et_2O and acetone (1:1). From these isolated key intermediate salts, compounds **2** could be readily derived by either reacting **11** with different (aryl)alkyl-substituted thiocyanates or with potassium thiocyanate in *N*,*N*-dimethylformamide and subsequent S-alkylation of the resulting 2-sulfanylimidazoles **8** (Scheme 3). Using the first variant gave predominantly **2** (52%) and the second **8** (12%) (when R^1 = 4-F, $R^2 = (CH_2)_2OMe$). The unwanted formation of **8** may be explained by an (acid- or) chloride-catalyzed cleavage of the sulfanyl function during the thermal reaction. With potassium thiocyanate the reactions ran smoothly and **8a–c** were formed in high yields (<82%) as the sole product. The following S-alkylation yielded the desired key intermediates **2** quantitatively, which is in line with the results from route A. Compounds **2** are again well-suited for the synthesis of target compounds **3** upon substitution with all kinds of nucleophiles (Scheme 1). This reaction sequence allows the regioselective introduction and variation of all relevant substituents within only four (to five) steps. Solely production of **11** from the brominated **10** gave 30% maximum yield and requires further optimization. Comparison of analytical data of compounds **3** obtained either by route A or by route B (Scheme 3) confirmed that both routes lead to identical products.

An even more flexible and efficient synthetic variant to provide 1,2,4,5-tetrasubstituted imidazoles is shown in Scheme 4 (Table 3). Initially the pyridine moiety was omitted and should be introduced later. In the procedures presented above the aryl moieties are defined very early in the synthesis. We, therefore, developed an alternative route which allows the introduction of the 5-(hetero)aryl moiety in the final step. We chose a cross-coupling procedure to provide a variety of compounds represented by general structures **2** and **18**.

Compounds **13** were realized by treating fluoro-substituted 1-arylethanones **12** with bromine according to Ridge et al.[44] The less sterically hindered **13** underwent coupling with relevant primary amines by the synthesis described for the preparation of **11** to give the amino hydrochlorides **14** in moderate to high yields (42–76%). The subsequent ring closure was carried out with either potassium thiocyanate or methylrhodanide leading to the imidazole-2-thiones **15** and to the 2-(methylsulfanyl)imidazoles **16**, respectively; alkylation of **15** with iodomethane gave **16**



Scheme 3 Preparation of 2-fluoro-4-pyridyl imidazole scaffolds with fixed regiochemistry using different ethanone precursors: (a) $NaNO_2$, 70% HF–pyridine (Olah's reagent), –15 to –10 °C, then r.t.; (b) $NaNO_2$, glacial AcOH, r.t.; (c) EtOH, reflux; (d) 2,2,4,4-tetramethylcyclobutane-1,3-dithione, CH_2Cl_2, r.t.; (e) K_2CO_3, MeOH, r.t.; (f) Br_2, glacial AcOH, r.t.; (g) initially CH_2Cl_2, –5 to 0 °C, then 1.25 M HCl in EtOH; (h) KSCN, DMF, reflux, (i) DMF, reflux.

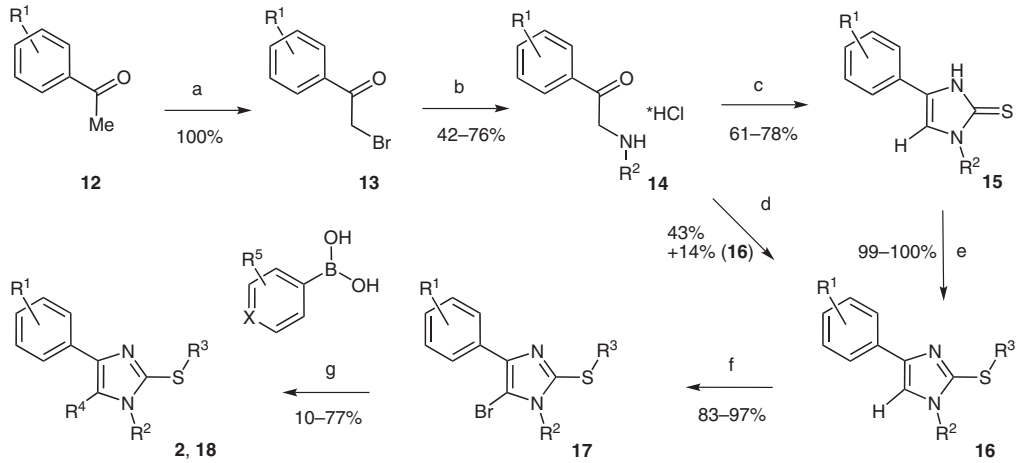
Table 2 Substitution for Compounds **2**, **7–11**

Compound	R^1	R^2	R^3
2b	4-F	Me	Me
2c	4-F	$(CH_2)_2OMe$	Me
2d	4-F	$(CH_2)_2OMe$	Bn
2e	4-F	$(CH_2)_2OMe$	$CH_2CH(OH)CH_2OH$
7a	–	Me	–
7b	–	$(CH_2)_2OMe$	–
8a	4-F	Me	–
8b	4-F	$(CH_2)_2OMe$	–
8c	3-CF_3	$(CH_2)_2OMe$	–
9a	4-F	–	–
9b	3-CF_3	–	–
10a	4-F	–	–
10b	3-CF_3	–	–
11a	4-F	Me	–
11b	4-F	$(CH_2)_2OMe$	–
11c	3-CF_3	$(CH_2)_2OMe$	–

Table 3 Substitution for Compounds **2b**, **12–18**

Compound	R^1	R^2	R^3	R^4
12a, **13a**	H	–		
12b, **13**	4-F	–		
14a, **15a**	H	$(CH_2)_2OMe$		
14b, **15b**	H	Bn		
14c, **15c**	4-F	Me		
14d, **15d**	4-F	$(CH_2)_2OMe$		
16a	H	$(CH_2)_2OMe$	Me	–
16b	H	Bn	Me	–
16c	4-F	Me	Me	–
16d	4-F	$(CH_2)_2OMe$	Me	–
17a	4-F	Me	Me	–
17b	4-F	$(CH_2)_2OMe$	Me	–
18a	4-F	Me	Me	3-Tol
18b	4-F	$(CH_2)_2OMe$	Me	4-Tol
18c	4-F	Me	Me	4-pyridyl
2b	4-F	Me	Me	2-fluoro-4-pyridyl

quantitatively. Compounds **17** were readily obtained by bromination of **16** at the imidazole C5 position using *N*-bromosuccinimide.[45,46] Finally, the 5-(2-fluoro-4-pyridyl)imidazole **2** and analogous products **18** were obtained from **17** in 10–77% yield by the Suzuki–Miyaura coupling[45,47] using different (hetero)aryl boronic acids and dichlorobis(triphenylphoshine)palladium/triphenylphosphine or tetrakis(triphenylphosphine)palladium as a catalyst. The coupling reactions were carried out either in a biphasic toluene/water system or in *N*,*N*-dimethylformamide. Alternatively sodium carbonate or potassium acetate was used as the base. This access to 1,4,5-trisubstituted 2-sulfanylimidazoles combines the advantages of rapid imidazole construction with the regioselective introduction of different N1 residues in good yields. Furthermore, to complete the essential vicinal diaryl system, the



R^1 = H, halogen(alkyl), R^2 = (substituted) alkyl/alkyl(hetero)aryl/(hetero)aryl, R^3 = (substituted) alkyl/alkyl(hetero)aryl, R^4 = (substituted) (hetero)aryl, R^5 = halogen/alkyl, X = C, N

Scheme 4 Synthesis of 1,4,5-trisubstituted 2-sulfanylimidazoles using the Suzuki–Miyaura coupling reaction: (a) Br_2, glacial AcOH, r.t.; (b) R^2NH_2, CH_2Cl_2 (+ MeOH), –5 to 0 °C, 1.25 M HCl in EtOH, acetone–Et_2O (1:1); (c) KSCN, DMF, reflux; (d) MeSCN, DMF, reflux; (e) MeI, K_2CO_3, MeOH, r.t.; (f) NBS, CCl_4, 0 °C then r.t.; (g) $Pd(PPh_3)_4$, argon, 2 M Na_2CO_3, toluene, 120 °C.

C5 position of the imidazole could be varied in a final step, which is in contrast to most existing sulfanylimidazole syntheses.

The above regiospecific synthetic methodologies enabled us to prepare highly diverse substituted imidazole derivatives starting from regioisomeric ethanones. In contrast to an already published multistep method (10 steps), our novel and extremely flexible synthetic approaches towards further substitutable pyridylimidazole intermediates ran with only three to six steps, dependant on the starting ethanone, thereby notably increasing overall yields. All kinds of relevant substituents were tolerated on the defined positions and no protection group was needed for the construction of the imidazole ring. Consequently the brief syntheses described here were more efficient and much less time consuming than earlier procedures. Moreover the fluorine atom at the pyridine moiety allowed the introduction of different (chiral) N-, O-, or S-nucleophiles. As a result both selective and highly potent p38 MAPK inhibitors could be prepared and selected for further development.

All reagents and solvents were of commercial quality and used without further purification. Melting points were determined on a Büchi Melting Point B-545 apparatus and are thermodynamically corrected. ^{1}H and ^{13}C NMR spectra were generally collected on a Bruker Avance 200 at 200 and 50 MHz, respectively, except ^{1}H NMR spectra of **3a**, **3b**, **3d**, **3h**, **3j**, and **7a**, which were collected on a Varian Mercury plus 400 at 400 MHz; TMS was used as internal standard. IR spectra were recorded by ATR technique on a Perkin–Elmer Spectrum One spectrophotometer. 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); He was used as carrier gas, and one of the following temperature programs was employed: (1) initial isothermal period of 1.0 min at 160 °C, then an increase at 10.0 °C/min to 240 °C with an isothermal period of 5 min at 240 °C, then an increase at 10.0 °C/min to 270 °C with an isothermal period of 15 min at 270 °C; or (2) initial isothermal period of 1.0 min at 240 °C, then an increase at 10.0 °C/min to 290 °C with an isothermal period of 20 min at 290 °C. GC data are presented as t_R (min) and MS results as *m/z* ratio and intensity (%) relative to the base peak. MS spectra were recorded on a Thermo Finnigan LCQ Duo Ion Trap System. Purity of compounds was either determined by LC on a GROM-SIL 120 ODS-5 ST column (3 μm, 150 × 2 mm) which was eluted isocratically with a H_2O–MeCN–HCO_2H system at a flow rate of 0.2 mL/min (ESI-MS detection, positive ion mode) or by HPLC (*vide infra*). LC results are given as t_R (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. Purification via preparative TLC was performed on fluorescent silica gel 60 F_{254} plates, 2 mm (Merck Art.-Nr.1.05717.0001).

HPLC apparatus and chromatographic procedure: a HPLC Hewlett-Packard HP 1090 Series II liquid chromatograph equipped with a UV diode array detector (DAD) was used (detection at 230 nm and 254 nm). The chromatographic separation was performed on a Betasil C8 column (150 mm × 4.6 mm i.d., dp = 5 μm, Thermo Fisher Scientific, Waltham, MA, USA) at 35 °C oven temperature. Injection volume was 5 μL. HPLC Gradient (flow: 1.5 mL/min): 0.01 M KH_2PO_4, pH 2.3 (Solvent A),: MeOH (Solvent B): 40% B to 85% B in 8 min, 85% B for 5 min, 85% B to 40% B in 1 min, 40% B for 2 min, stoptime 16 min. HPLC results are presented as t_R (min) and relative chemical purity (%). The Agilent ChemStation software (Version Rev. A.09.03) was used for the instrument control and data analysis.

The following compounds were prepared according to common literature procedures: **10a** and **13b**.[43,44] The syntheses and analytical properties of compounds **1a**, **1b**, **2a**, **4**, **9a**, and **9b** have been reported elsewhere; commercially available **12a**, **12b**, and **13a** were used.

2-Fluoro-4-[4-(4-fluorophenyl)-1-methyl-2-(methylsulfanyl)-1*H*-imidazol-5-yl]pyridine (2b)

Variant 1: To a cooled soln (0 °C) of **1a** (1.73 g, 5.50 mmol) in 50% HBF_4 (6.0 mL) was carefully added $NaNO_2$ (450 mg) in small portions. A little N_2 gas was released and a yellowish green precipitate formed. The mixture was stirred for a short period at 0 °C and then the thermal decomposition of the intermediate diazonium salt was accomplished by warming the mixture to 45 °C where it was aged for 1 h. The mixture then was cooled to –10 °C (acetone and liq N_2 bath) and made alkaline with Na_2CO_3 to pH 8; the precipitate agglutinated. CH_2Cl_2 (70 mL) and H_2O (70 mL) were consecutively poured to the suspension and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were washed with H_2O (2 × 70 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The resulting crude material was purified by column chromatography (silica gel 60, EtOAc) to give **2b** (0.95 g, 54%) as a fine yellowish powder.

Variant 2: Starting from **8a**, the preparation of **2b** was accomplished as follows: **8a** (0.3 g, 1.0 mmol) was suspended in MeOH (6 mL) in a 25-mL round-bottomed flask. K_2CO_3 (0.11 g) was added to the stirred suspension followed by the injection of a soln of MeI (0.23 g, 1.6 mmol) in a little MeOH. The flask was capped with a glass plug and the mixture was stirred at r.t. for 19.5 h. During this time (~1.5 h), the initial suspension changed to give a bright yellow soln. The solvent as well as excess MeI were removed in vacuo and subsequent the solid residue was combined with EtOAc–H_2O (3:2, 12 mL). The organic phase was collected and the aqueous phase again extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and the filtrate was evaporated to dryness; yield: 255 mg (81%). The resulting solid product **2b** is of high analytical purity.

Variant 3: Using the Suzuki–Miyaura coupling, **2b** (25 mg, 12%) was obtained starting from **17a** (0.2 g, 0.66 mmol), 2-fluoro-4-pyridylboronic acid (0.1 g, 0.73 mmol), a catalytical mixture of $PdCl_2(PPh_3)_2$ (0.14 g, 0.20 mmol) and Ph_3P (0.03 g, 0.11 mmol), and KOAc (0.1 g, 1.0 mmol) in DMF (2 mL). The soln was heated to 80 °C for 23 h. Isolation of the product was accomplished by column chromatography (silica gel, EtOAc–hexane, 1:2); mp 147–149 °C.

IR (neat): 3050, 2924, 1612, 1538, 1508, 1477, 1400, 1262, 1222 (C–F), 1192, 1161, 984, 876, 847, 817, 654 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.79 (s, 3 H, SCH_3), 3.53 (s, 3 H, NCH_3), 6.88 (s, 1 H, $H3_{pyridyl}$), 6.93–7.03 (m, 2 H, $H3/H5_{phenyl}$), 7.11 (d, *J* = 5.05 Hz, 1 H, $H5_{pyridyl}$), 7.38–7.45 (m, 2 H, $H2/H6_{phenyl}$), 8.29 (d, *J* = 5.00 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR ($CDCl_3$): δ = 15.9 (s, SCH_3), 32.0 (s, NCH_3), 110.3 (d, *J* = 37.6 Hz, $C3_{pyridyl}$), 115.4 (d, *J* = 21.5 Hz, $C3/C5_{phenyl}$), 122.4 (d, *J* = 4.3 Hz, $C5_{pyridyl}$), 126.2 (d, *J* = 3.6 Hz, $C5_{imidazole}$), 128.9 (s, $C1_{phenyl}$), 129.2 (d, *J* = 8.0 Hz, $C2/C6_{phenyl}$), 139.2 (s, $C4_{imidazole}$), 143.4 (d, *J* = 8.5 Hz, $C4_{pyridyl}$), 145.9 (s, $C2_{imidazole}$), 148.5 (d, *J* = 15.5 Hz, $C6_{pyridyl}$), 162.2 (d, *J* = 245.6 Hz, $C4_{phenyl}$), 164.1 (d, *J* = 238.7 Hz, $C2_{pyridyl}$).

^{1}H NMR (DMSO-d_6): δ = 2.65 (s, 3 H, SCH_3), 3.44 (s, 3 H, NCH_3), 7.07–7.16 (m, 2 H, $H3/H5_{phenyl}$), 7.26–7.41 (m, 4 H, $H3/H5_{pyridyl}$, $H2/H6_{phenyl}$), 8.31 (d, *J* = 5.08 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR (DMSO-d_6): δ = 15.4 (s, SCH_3), 31.9 (s, NCH_3), 110.6 (d, *J* = 38.1 Hz, $C3_{pyridyl}$), 115.5 (d, *J* = 21.4 Hz, $C3/C5_{phenyl}$), 123.4 (d,

J = 4.1 Hz, $C5_{pyridyl}$), 126.8 (d, J = 3.7 Hz, $C5_{imidazole}$), 128.9 (d, J = 8.1 Hz, $C2/C6_{phenyl}$), 130.3 (d, J = 3.1 Hz, $C1_{phenyl}$), 138.3 (s, $C4_{imidazole}$), 143.8 (d, J = 8.8 Hz, $C4_{pyridyl}$), 144.9 (s, $C2_{imidazole}$), 148.6 (d, J = 15.8 Hz, $C6_{pyridyl}$), 161.4 (d, J = 242.5 Hz, $C4_{phenyl}$), 163.7 (d, J = 234.6 Hz, $C2_{pyridyl}$).

GC (conditions 2): t_R = 4.6 min; MS (EI, 70 eV): m/z (%) = 317 (100, M^+), 302 (5, $M^+ - CH_3$), 284 (80), 270 (6), 244 (42), 215 (12), 202 (4), 137 (8), 121 (6), 96 (5, 2-fluoro-4-pyridyl).

LC: t_R = 19.1 min (100.0%); MS: m/z = 318.2 $[M + 1]^+$.

2-Fluoro-4-[4-(4-fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]pyridine (2c)

Variant 1: A soln of **1b** (1.6 g, 4.46 mmol) in 50% HBF_4 (6 mL) under argon was stirred in a 100-mL round-bottom flask. This soln was cooled to 0 °C in an ice bath and $NaNO_2$ (440 mg) were added in small portions over 15 min (diazotization step). The flask was closed each time the addition of a portion of the $NaNO_2$ was complete. The mixture became foamy and a white precipitate developed. Dediazotization was accomplished by stirring the mixture at 45 °C for 1 h. The suspension was cooled to –10 °C (liquid N_2 in acetone bath) and then made alkaline with Na_2CO_3 to pH 7–8; the precipitate agglutinated. CH_2Cl_2 (50 mL) and H_2O (50 mL) were added sequentially, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and then the solvent was removed in vacuo. The yellowish orange semisolid residue was repeatedly concentrated with Et_2O and combined with Et_2O again at 4 °C resulting in a fine yellow precipitation that was filtered off. From this crude product the pure **2c** was either isolated by exhaustive extraction (hot hexane) or by column chromatography (silica gel–EtOAc); in each case a bright yellow and viscous residue of **2c** (0.76 g, 47%) was obtained. Crystallization of the product occurred very slowly.

Variant 2: Following the typical procedure for **2b**, variant 2, using **8b** (2.3 g, 6.6 mmol) and MeI (1.55 g, 10.9 mmol) in MeOH (48 mL) gave **2c** (2.31 g, 97%) as an oily residue, that crystallized subsequent to freezing in liquid N_2, seeding, and storing under vacuum.

Variant 3: A soln of **11b** (0.5 g, 1.5 mmol) with methyl thiocyanate (0.26 g, 3.6 mmol) in DMF (15 mL) was refluxed for 35 min. Addition of ice H_2O to the cooled mixture followed by repeated extraction with EtOAc (3 × 30 mL) and separation of the concentrated organic layer by column column chromatography (silica gel 60, CH_2Cl_2–EtOAc, 1:2) gave **2c**, which was initially isolated in one fraction together with small amounts of the imidazole-2-thione **8b** (GC/MS). Upon treatment of the oily mixture with Et_2O the side product **8b** quantitatively precipitated in white crystals that could be filtered off (60 mg, 12%). Evaporation of the solvent (Et_2O) left the yellowish main product **2c** (275 mg, 52%) as a semisolid, but in good analytical quality that was dried in vacuo over $CaCl_2$; mp 86–88 °C.

IR (neat): 3072, 2932, 2894, 1728, 1608, 1543, 1508, 1400, 1260, 1221 (C-F), 1186, 1157, 1117, 1095, 1015, 880, 840, 815 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.89 (s, 3 H, SCH_3), 3.27 (s, 3 H, OCH_3), 3.57 (t, J = 5.33 Hz, 2 H, CH_2O), 4.09 (t, J = 5.35 Hz, 2 H, NCH_2), 6.93–7.06 (m, 3 H, $H3/H5_{phenyl}$, $H3_{pyridyl}$), 7.19 (dd, J = 1.58/5.00 Hz, 1 H, $H5_{pyridyl}$), 7.40–7.47 (m, 2 H, $H2/H6_{phenyl}$), 8.30 (d, J = 4.98 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR ($CDCl_3$): δ = 17.1 (s, SCH_3), 45.2 (s, NCH_2), 59.0 (s, OCH_3), 70.0 (s, CH_2O), 111.5 (d, J = 37, 9 Hz, $C3_{pyridyl}$), 115.6 (d, J = 21.6 Hz, $C3/C5_{phenyl}$), 123.2 (d, J = 4.3 Hz, $C5_{pyridyl}$), 126.5 (s, $C5_{imidazole}$), 128.6 (d, $C1_{phenyl}$), 129.7 (d, J = 8.2 Hz, $C2/C6_{phenyl}$), 137 (s, $C4_{imidazole}$), 142.4 (d, $C4_{pyridyl}$), 145.4 (s, $C2_{imidazole}$), 148.6 (d, J = 15.3 Hz, $C6_{pyridyl}$), 162.6 (d, J = 247.1 Hz, $C4_{phenyl}$), 164.0 (d, J = 239.3 Hz, $C2_{pyridyl}$).

^{1}H NMR (DMSO-d_6): δ = 2.65 (s, 3 H, SCH_3), 3.08 (s, 3 H, OCH_3), 3.39 (t, J = 5.82 Hz, 2 H, CH_2O), 4.01 (t, J = 5.34 Hz, 2 H, NCH_2), 7.06–7.15 (m, 2 H, $H3/H5_{phenyl}$), 7.31–7.38 (m, 4 H, $H3/H5_{pyridyl}$, $H2/H6_{phenyl}$), 8.33 (d, J = 4.88 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR (DMSO-d_6): δ = 15.5 (s, SCH_3), 44.0 (s, NCH_2), 58.0 (s, OCH_3), 69.7 (s, CH_2O), 111.0 (d, J = 37.9 Hz, $C3_{pyridyl}$), 115.2 (d, J = 21.4 Hz, $C3/C5_{phenyl}$), 123.7 (d, J = 4.1 Hz, $C5_{pyridyl}$), 126.3 (d, J = 4.4 Hz, $C5_{imidazole}$), 128.5 (d, J = 8.0 Hz, $C2/C6_{phenyl}$), 129.9 (d, J = 3.2 Hz, $C1_{phenyl}$), 137.8 (s, $C4_{imidazole}$), 144.0 (d, J = 8.8 Hz, $C4_{pyridyl}$), 144.5 (s, $C2_{imidazole}$), 148.3 (d, J = 15.8 Hz, $C6_{pyridyl}$), 161.1 (d, J = 242.4 Hz, $C4_{phenyl}$), 163.4 (d, J = 234.9 Hz, $C2_{pyridyl}$).

GC (conditions 2): t_R = 5.4 min; MS (EI, 70 eV): m/z (%) = 361 (100, M^+), 346 (4, $M^+ - CH_3$), 330 (24), 316 (15), 303 (23), 288 (5), 270 (81), 243 (12), 230 (8), 215 (10), 182 (7), 167 (9), 121 (22), 101 (4), 59 (8, methoxyethylamino$^+$).

4-[2-(Benzylsulfanyl)-4-(4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl]-2-fluoropyridine (2d)

To a suspension of **8b** (0.3 g, 0.86 mmol) in MeOH (5 mL) in a 25 mL flask was added initially K_2CO_3 (0.09 g) and then BnBr (0.148 g, 0.86 mmol) in MeOH (1 mL) was added by injection and the mixture stirred at r.t. for 22 h (monitored by GC/MS). During this time the initial suspension changed to a brownish soln. The solvent was removed in vacuo and the resulting viscous residue combined with EtOAc–H_2O (3:2). The aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and the filtrate was concentrated to dryness on a rotary evaporator leaving almost pure **2d** as a red to brownish viscous mass. Crystallization of the residue was initiated by evaporating the product several times with Et_2O; yield: 0.37 g (98%); mp 61 °C.

IR (neat): 3063, 2932, 2893, 1609, 1542, 1507, 1453, 1400, 1259, 1220 (C–F), 1185, 1156, 1118, 1015, 879, 839, 815, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.17 (s, 3 H, OCH_3), 3.36 (t, J = 5.51 Hz, 2 H, CH_2O), 3.81 (t, J = 5.52 Hz, 2 H, NCH_2), 4.49 (s, 2 H, CH_2), 6.94–7.03 (m, 3 H, $H3_{pyridyl}$, $H3/H5_{phenyl}$), 7.09–7.13 (m, 1 H, $H5_{pyridyl}$), 7.29–7.47 (m, 7 H, H_{benzyl}, $H2/H6_{phenyl}$), 8.27 (d, J = 5.14 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR ($CDCl_3$): δ = 39.5 (s, SCH_2Ph), 44.5 (s, NCH_2), 58.8 (s, OCH_3), 70.6 (s, CH_2O), 111.2 (d, J = 37.7 Hz, $C3_{pyridyl}$), 115.4 (d, J = 21.5 Hz, $C3/C5_{phenyl}$), 123.1 (d, J = 4.3 Hz, $C5_{pyridyl}$), 126.6 (d, J = 3.6 Hz, $C5_{imidazole}$), 127.6 (s, $C4_{benzyl}$), 128.5 (s, $C2/C6_{benzyl}$), 128.9 (s, $C3/C5_{benzyl}$), 129.1 (d, J = 8.1 Hz, $C2/C6_{phenyl}$), 137.2 (s, $C1_{benzyl}$), 138.9 (s, $C4_{imidazole}$), 143.0 (s, $C2_{imidazole}$), 143.8 (d, J = 7.9 Hz, $C4_{pyridyl}$), 148.3 (d, J = 15.4 Hz, $C6_{pyridyl}$), 162.2 (d, J = 245.9 Hz, $C4_{phenyl}$), 164.0 (d, J = 238.8 Hz, $C2_{pyridyl}$).

GC (conditions 2): t_R = 10.4 min; MS (EI, 70 eV): m/z (%) = 437 (41, M^+), 404 (3), 379 (50), 346 (100, $M^+ - C_7H_7$), 314 (9), 288 (13), 270 (9), 256 (6), 243 (19), 230 (6), 215 (2), 121 (6), 91 (81, tropylium$^+$), 65 (5).

LC: t_R = 19.1 min (94.9%); MS: m/z = 438.3 $[M + 1]^+$.

3-[4-(4-Fluorophenyl)-5-(2-fluoro-4-pyridyl)-1-(2-methoxyethyl)-1*H*-imidazol-2-ylsulfanyl]propane-1,2-diol (2e)

A stirred suspension of **8b** (0.15 g, 0.43 mmol) in MeOH (5 mL) at r.t. was combined with K_2CO_3 (0.01 g). At the same time color changed rapidly from bright to dark yellow. A soln of 3-bromopropane-1,2-diol (0.098 g, 0.63 mmol) in MeOH (1 mL) was immediately injected into the mixture. The initial suspension was aged at r.t. for 20 h thereby changing into a soln. The solvent was evaporated and the residue was separated from unreacted substrate by preparative TLC (silica gel 60 F_{254}, 2 mm; EtOAc, separation from silica gel by extraction with acetone) to give analytical **2e** (125 mg, 69%). The highly viscous product was hygroscopic and therefore could not be durable crystallized. While storing the product it took a glass-like shape.

IR (neat): 3307 (OH), 2929, 2876, 1610, 1543, 1509, 1449, 1400 (OH), 1261 (C–F), 1221 (C–F), 1187, 1158, 1117, 1096, 1035, 1016, 881, 839, 816, 691 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.28 (s, 3 H, OCH_3), 3.41 (d, *J* = 5.50 Hz, 2 H, SCH_2), 3.57 (t, *J* = 5.35 Hz, 2 H, CH_2O), 3.71–3.81 (m, 2 H, CH_2OH), 3.99–4.08 (m, 3 H, C*H*OH, NCH_2), 6.91–7.00 (m, 2 H, $H3/H5_{phenyl}$), 7.05 (s, 1 H, $H3_{pyridyl}$), 7.16–7.20 (m, 1 H, $H5_{pyridyl}$), 7.25–7.32 (m, 2 H, $H2/H6_{phenyl}$), 8.29 (d, *J* = 5.13 Hz, 1 H, $C6_{pyridyl}$), OH signals were not detected.

^{13}C NMR ($CDCl_3$): δ = 36.3 (s, SCH_2), 44.9 (s, NCH_2), 58.9 (s, OCH_3), 64.0 (s, CH_2OH), 70.2 (s, CH_2O), 72.0 (s, CHOH), 111.3 (d, *J* = 37.7 Hz, $C3_{pyridyl}$), 115.6 (d, *J* = 21.5 Hz, $C3/C5_{phenyl}$), 123.2 (d, *J* = 4.4 Hz, $C5_{pyridyl}$), 126.7 (s, $C5_{imidazole}$), 128.4 (d, *J* = 3.3 Hz, $C1_{phenyl}$), 128.8 (d, *J* = 8.1 Hz, $C2/C6_{phenyl}$), 138.4 (s, $C4_{imidazole}$), 143.4 (d, *J* = 8.5 Hz, $C4_{pyridyl}$), 145.6 (s, $C2_{imidazole}$), 148.4 (d, *J* = 15.5 Hz, $C6_{pyridyl}$), 162.2 (d, *J* = 246.1 Hz, $C4_{phenyl}$), 164.0 (*J* = 238.9 Hz, $C2_{pyridyl}$).

LC: t_R = 15.9 min (98.5%); MS: *m*/*z* = 422.2 $[M + 1]^+$.

{4-[4-(4-Fluorophenyl)-1-methyl-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-pyridyl}[(*R*)-1-phenylethyl]amine (3a); Typical Procedure

A mixture of **2b** (500 mg, 1.6 mmol) and (+)-(*R*)-α-methylbenzylamine (1.7 g, 14.0 mmol) was stirred at 165 °C for 17 h. The amine was removed in vacuum and residue taken up in a mixture of H_2O, sat. $NaHCO_3$, and EtOAc. The phases were separated and the organic phase washed with H_2O and brine, dried, and evaporated; yield: 520 mg (80%).

HPLC: t_R = 6.67 min; purity: 99.8% (λ = 254 nm).

IR (neat): 1219 (C–F) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.41 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.62 (s, 3 H, SCH_3), 3.30 (s, 3 H, NCH_3), 4.99 (q, *J* = 6.8 Hz, 1 H, CH), 6.40 (s, 1 H, $H3_{pyridyl}$), 6.42 (d, *J* = 5.2 Hz, 1 H, $H5_{pyridyl}$), 7.05–7.42 (m, 9 H, H_{phenyl}), 8.01 (d, *J* = 5.2 Hz, 1 H, $H6_{pyridyl}$).

2-{4-[4-(4-Fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-pyridylamino}propan-1-ol (3e); Typical Procedure

Compound **2c** (0.25 g, 0.7 mmol) and 2-aminopropan-1-ol (0.52 g, 6.9 mmol) were combined and stirred under argon at 155 °C for 19 h (monitored by TLC). The mixture was allowed to cool to r.t. and EtOAc (60 mL) was added. The organic soln was washed with H_2O (6 × 20 mL) to quantitatively separate excess amino alcohol and then it was dried (Na_2SO_4). After removal of the solvent, the resulting yellow, viscous residue was repeatedly evaporated with Et_2O to yield pure **3e** (287 mg, 100%) as an amorphous product that, however, was hygroscopic and, therefore, shortly merged into a glass-like consistence; mp 87 °C.

IR (neat): 3307 (OH), 2928, 1606, 1547, 1503, 1480, 1445, 1354 (OH), 1220 (C–F), 1157, 1118, 1094, 1050, 975, 840, 812 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.72 Hz, 3 H, CH_3), 2.71 (s, 3 H, SCH_3), 3.28 (s, 3 H, OCH_3), 3.46–3.78 (m, 4 H, CH_2O, CH_2OH), 3.96–4.06 (m, 3 H, CH, NCH_2), 4.74 (d, exchangeable, *J* = 5.68 Hz, 1 H, NH), 6.45 (s, 1 H, $H3_{pyridyl}$), 6.55 (dd, *J* = 1.37/5.32 Hz, 1 H, $H5_{pyridyl}$), 6.89–6.98 (m, 2 H, $H3/H5_{phenyl}$), 7.42–7.49 (m, 2 H, $H2/H6_{phenyl}$), 8.06 (dd, *J* = 0.61/5.31 Hz, 1 H, $H6_{pyridyl}$).

^{13}C NMR ($CDCl_3$): δ = 16.3 (s, SCH_3), 17.7 (s, CH_3), 44.1 (s, NCH_2), 50.3 (s, CH), 58.9 (s, OCH_3), 68.4 (s, CH_2OH), 70.6 (s, CH_2O), 109.8 (s, $C3_{pyridyl}$), 114.7 (s, $C5_{pyridyl}$), 115.0 (d, *J* = 21.3 Hz, $C3/C5_{phenyl}$), 127.8 (s, $C5_{imidazole}$), 128.6 (d, *J* = 8.0 Hz, $C2/C6_{phenyl}$), 129.9 (d, *J* = 3.2 Hz, $C1_{phenyl}$), 138.3 (s, $C4_{pyridyl}$), 140.5 (s, $C4_{imidazole}$), 144.3 (s, $C2_{imidazole}$), 147.7 (s, $C6_{pyridyl}$), 158.7 (s, $C2_{pyridyl}$), 161.8 (d, *J* = 244.5 Hz, $C4_{phenyl}$).

GC (conditions 2): t_R = 11.6 min; MS: *m*/*z* (%) = 416 (29, M^+), 401 (1, $M^+ - CH_3$), 385 (100), 357 (7, $M^+ - C_3H_7O$), 341 (1), 327 (7), 311 (6), 293 (13), 192 (4), 146 (5), 121 (3), 59 (2).

{4-[4-(4-Fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-pyridyl}phenylamine (3h); Typical Procedure

NaH (55–65%, 170 mg, 3.9 mmol) and aniline (280 mg, 3.0 mmol) in diglyme (3 mL) were heated to 70 °C while stirring. When gas evolution ceased a soln of **2c** (361 mg, 1 mmol) in diglyme was added and the mixture was further stirred (monitored by TLC). The mixture then was cooled to r.t. and CH_2Cl_2 (40 mL) added. The organic phase was washed with H_2O (6 × 25 mL), dried (Na_2SO_4), and rotary evaporated. The oily residue was purified by column chromatography (silica gel, EtOAc–hexane, 3:7); yield: 275 mg (65%); mp 107.6 °C.

HPLC: t_R = 7.79 min; purity: 99.9% (λ = 254 nm).

IR (neat): 1219 (C–F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.71 (s, 3 H, SCH_3), 3.20 (s, 3 H, OCH_3), 3.51 (t, *J* = 6.0 Hz, 2 H, CH_2O), 4.04 (t, *J* = 6.0 Hz, 2 H, 2 H, NCH_2), 6.76–7.47 (m, 11 H, $H3/H5_{pyridyl}$, H_{phenyl}), 8.23 (d, *J* = 6.0 Hz, 1 H, $H6_{pyridyl}$).

4-{4-[4-(4-Fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-pyridylamino}cyclohexanol (3j); Typical Procedure

Compound **2c** (1.45 g, 4.0 mmol) and *trans*-4-aminocyclohexanol (2.32 g, 19.8 mmol) were combined and stirred at 140 °C in a sealed tube for 14 h. After cooling the mixture was taken up in a mixture of H_2O and EtOAc. The organic layer was separated and washed with H_2O (4 ×), dried (anhyd Na_2SO_4), and evaporated in vacuo; yield: 1.75 g (97%).

HPLC: t_R = 4.33 min; purity: 98.1% (λ = 254 nm).

IR (ATR): 3319 (OH), 2928, 2856, 1604, 1546, 1501, 1448, 1219 (C–F), 1117, 839, 812 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.26–1.39 (m, 4 H, $H_{cyclohexyl}$), 1.98–2.07 (m, 4 H, $H_{cyclohexyl}$), 2.73 (s, 3 H, SCH_3), 3.28 (s, 3 H, OCH_3), 3.38–3.46 (m, 1 H, $H1_{cyclohexyl}$), 3.56 (t, *J* = 5.80 Hz, 2 H, $NCH_2CH_2OCH_3$), 3.65–3.72 (m, 1 H, $H4_{cyclohexyl}$), 4.05 (t, *J* = 5.60 Hz, 2 H, $NCH_2CH_2OCH_3$), 6.42 (s, 1 H, $H3_{pyridyl}$), 6.56 (dd, *J* = 1.4/5.40 Hz, 1 H, $H5_{pyridyl}$), 6.92–6.96 (m, 2 H, $H3/H5_{phenyl}$), 7.44–7.47 (m, 2 H, $H2/H6_{phenyl}$), 8.05 (d, *J* = 6.40 Hz, 1 H, $H6_{pyridyl}$).

^1H NMR (DMSO-d_6): δ =1.13–1.28 (m, 4 H, $H_{cyclohexyl}$), 1.80–1.93 (m, 4 H, $H_{cyclohexyl}$), 2.63 (s, 3 H, SCH_3), 3.12 (s, 3 H, OCH_3), 3.47–3.42 (t, *J* = 5.62 Hz, 3 H, $NCH_2CH_2OCH_3$, $H1_{cyclohexyl}$), 3.57 (s, 1 H, $H4_{cyclohexyl}$), 3.95 (t, *J* = 5.60 Hz, 1 H, $NCH_2CH_2OCH_3$), 4.52 (d, *J* = 4.40 Hz, 1 H, OH), 6.37 (s, 1 H, $H3_{pyridyl}$), 6.45 (m, 2 H, $H5_{pyridyl}$, NH), 7.07–7.12 (m, 2 H, $H3/H5_{phenyl}$), 7.40–7.44 (m, 2 H, $H2/H6_{phenyl}$), 8.06 (d, *J* = 5.20 Hz, 1 H, $H6_{pyridyl}$).

{4-[4-(4-Fluorophenyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-pyridyl}(tetrahydro-2*H*-pyran-4-yl)amine (3o); Typical Procedure

Compound **2a** (0.3 g, 1 mmol) and tetrahydropyran-4-ylamine (0.9 g, 8.9 mmol) were combined and stirred under argon at 155 °C for 18 h (monitored by TLC). The brown mixture was allowed to cool to r.t. and was taken up in 10% citric acid (adjusted to pH 4–5 with NaOH, 15 mL). The resulting suspension was extracted with EtOAc (4 × 40–50 mL) and the aqueous phase was discarded. Upon concentrating the combined organic layers pure **3o** was obtained after twofold preparative TLC [(1) silica gel 60 F_{254}, 2 mm, acetone; (2) silica gel 60, F_{254}, 2 mm, EtOAc; relevant fractions were extracted with acetone]. After filtration from silica gel and removal of the solvent, the oily residue was solidified by evaporation with Et_2O to give amorphous **3o**; yield: 85 mg (22%); mp 99 °C.

IR (neat): 2927, 2847, 1606, 1548, 1519, 1502, 1433, 1366, 1292, 1220 (C–F), 1157, 1137, 1086, 980, 839, 814 cm^{-1}.

^1H NMR (CD_3OD): δ = 1.38–1.57 (m, 2 H, H3/H5$_{tetrahydropyranyl}$), 1.86–1.93 (m, 2 H, H3/H5$_{tetrahydropyranyl}$), 2.62 (s, 3 H, SCH_3), 3.42–3.53 (m, 2 H, H2/H4$_{tetrahydropyranyl}$), 3.65–3.76 (m, 1 H, CH), 3.91–3.97 (m, 2 H, H2/H6$_{tetrahydropyranyl}$), 6.55–6.57 (m, 2 H, H3/H5$_{pyridyl}$), 7.10–7.19 (m, 2 H, H3/H5$_{phenyl}$), 7.43–7.49 (m, 2 H, H2/H6$_{phenyl}$), 7.83 (d, *J* = 5.83 Hz, 1 H, H6$_{pyridyl}$).

^{13}C NMR (CD_3OD): δ = 16.9 (s, SCH_3), 34.3 (s, C3/C5$_{tetrahydropyranyl}$), 48.4 (s, CH), 68.0 (s, C2/C6$_{tetrahydropyranyl}$), 107.4 (s, C3$_{pyridyl}$), 111.8 (s, C5$_{pyridyl}$), 116.7 (d, *J* = 21.8 Hz, C3/C5$_{phenyl}$), 131.8 (d, *J* = 8.2 Hz, C2/C6$_{phenyl}$), 144.6, 148.3 (s, C6$_{pyridyl}$), 159.7 (s, C2$_{pyridyl}$), 164.1 (d, *J* = 244.8 Hz, C4$_{phenyl}$).

GC: t_R = 16.4 min; MS *m/z* (%) = 384 (76, M^+), 369 (10, $M^+ - CH_3$), 355 (10), 339 (19), 327 (79), 312 (20), 299 (100, M^+ – tetrahydropyranyl), 285 (16), 267 (32), 252 (9), 227 (9), 207 (7), 170 (8), 146 (19), 121 (7), 100 (5, tetrahydropyran-4-ylamino$^+$), 55 (7).

4-[4-(4-Fluorophenyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-(2-thienylmethoxy)pyridine (3r); Typical Procedure

For the initial deprotonation step, a suspension of NaH (55–65%, 0.3 g, 6.9 mmol) in DMF (3 mL) was treated dropwise with thiophene-2-methanol (0.75 g, 6.6 mmol) and the mixture stirred at r.t. until H_2 evolution ceased (~1 h). Compound **2a** (0.2 g, 0.7 mmol) was added in 1 portion and the mixture was stirred at 155–160 °C for 5.5 h under argon. The mixture was allowed to cool to r.t. and was combined with H_2O (30 mL) and extracted with EtOAc (5 × 30 mL). The combined organic extracts were washed with 10% citric acid (pH 4–5), 10% Na_2CO_3, and brine; the solvent was evaporated and the oily residue purified by flash chromatography (Combi Flash Retrieve: silica gel, CH_2Cl_2–EtOAc gradient). The isolated product fraction was concentrated and the residue evaporated with Et_2O to yield crystalline **3r** (0.1 g, 38%); mp 124 °C.

IR (neat): 2927, 2855, 1606, 1542, 1505, 1412, 1364, 1308, 1220 (C–F), 1157, 1021, 971, 834, 814, 699 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.61 (s, 3 H, atropisomers 'A' + 'B', SCH_3), 5.49 (s, 1 H 'A', OCH_2), 5.52 (s, 1 H 'B', OCH_2), 6.83 (s, 1 H 'A', H3$_{pyridyl}$), 6.83 (s, 1 H 'B', H3$_{pyridyl}$), 6.91 (dd, *J* = 1.33/5.49 Hz, 1 H 'B', H5$_{pyridyl}$), 6.99–7.03 (m, 2 H 'A' + 1 H 'B', H5$_{pyridyl}$ 'A', H4$_{thienyl}$ 'A' + 'B'), 7.17–7.36 (m, 3 H, 'A' + 'B', H3$_{thienyl}$, H3/H5$_{phenyl}$), 7.45–7.55 (m, 3 H, 'A' + 'B', H5$_{thienyl}$, H2/H6$_{phenyl}$), 8.06 (d, *J* = 5.38 Hz, 1 H 'A', H6$_{pyridyl}$), 8.12 (d, *J* = 5.26 Hz, 1 H 'B', H6$_{pyridyl}$), 12.73 (br s, 1 H 'A' + 'B', exchangeable, NH$_{imidazole}$).

^1H NMR (CD_3OD): δ = 2.62 (s, 3 H, SCH_3), 5.48 (s, 2 H, OCH_2), 6.85 (br s, 1 H, H3$_{pyridyl}$), 6.95–6.99 (m, 2 H, H5$_{pyridyl}$, H4$_{thienyl}$), 7.10–7.15 (m, 3 H, H3$_{thienyl}$, H3/H5$_{phenyl}$), 7.35–7.45 (m, 3 H, H5$_{thienyl}$, H2/H6$_{phenyl}$), 8.02 (d, *J* = 5.38 Hz, 1 H, H6$_{pyridyl}$).

GC (conditions 2): t_R = 10.8 min; MS: *m/z* (%) = 397 (66, M^+), 382 [1 (!), $M^+ - CH_3$], 300 (7, M^+ – 2-thienylmethyl), 285 (51), 207 (3), 172 (4), 121 (2), 97 (100, 2-thienylmethyl$^+$), 53 (4).

4-[4-(4-Fluorophenyl)-2-(methylsulfanyl)-1*H*-imidazol-5-yl]-2-(phenylsulfanyl)pyridine (3s); Typical Procedure

Following the typical procedure for **3r** using NaH (55–65%, 0.6 g, 13.8 mmol), thiophenol (1.45 g, 13.2 mmol), and **2a** (0.4 g, 1.3 mmol) in abs DMF (5 mL) the product formed after 7 h at 155–160 °C. Ice H_2O (100 mL) was added to the cold mixture followed by acidification with 20% HCl to pH 3–4. Extraction with EtOAc (4 × 50 mL), evaporation of the organic solvent in vacuo, and repeated separation on preparative TLC led to the desired product that, however, could not be isolated absolutely pure. Solidification of the resulting oily residue was achieved by treatment with Et_2O to give **3s** (0.3 g, 58%) as an amorphous foam; mp 215 °C.

IR (neat): 3052 (aryl-H), 2926 (CH_3), 1586, 1515, 1503, 1475, 1439, 1386, 1221 (C–F), 1158, 1132, 991, 837, 783, 748, 690 cm^{-1}.

^1H NMR (CD_3OD): δ = 2.58 (s, 3 H, SCH_3), 6.77 (br s, 1 H, H3$_{pyridyl}$), 7.06–7.41 (m, 10 H, H$_{phenyl}$, H5$_{pyridyl}$), 8.28 (d, *J* = 5.26 Hz, 1 H, H6$_{pyridyl}$).

GC (conditions 2): t_R = 18.9 min; MS: *m/z* (%) = 392 (100, [M – 1]$^+$), 376 (11), 360 (3), 344 (5), 319 (8), 211 (7), 179 (12), 121 (3), 109 [1 (!), PhS^+], 95 (2, 4-fluorophenyl$^+$), 77 (2), 51 (1).

2-(4-Fluorophenyl)-1-(2-fluoro-4-pyridyl)ethanone (5); Typical Procedure

In a 100-mL flask p. f. FEP (perfluoroethylenepropylene) with a screw cap was provided Olah's reagent (70% HF in pyridine, 39 g). The stirred soln was cooled to –15 °C in an ice/NaCl bath and subsequently combined in some portions with **4** (10.0 g, 43.4 mmol). After 45 min, anhyd $NaNO_2$ (4.89 g, 0.07 mol) was added portionwise to the orange mixture; the flask was closed after each addition of $NaNO_2$. N_2 as well as little amounts of NOx were released whenever the flask was opened again. After complete addition of $NaNO_2$ the initial cloudy mixture gradually changed to a soln that was stirred at –15 to 0 °C for 1 h and at r.t. for 1 h. The mixture was then rapidly poured into ice H_2O (150 mL) immediately followed by the addition of CH_2Cl_2 (90 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were washed with 5% Na_2CO_3 (1 × 100 mL) and H_2O (1 × 100 mL), dried (Na_2SO_4), and the solvent removed in vacuo. Purification could be afforded by repeatedly extracting the oily residue with hot hexane (7 × 30 mL). Pure **5** crystallized from the cooled hexane extracts in fluffy needles and could be filtered and dried in an evacuated desiccator; yield: 5.90 g (58%); mp 58–66 °C.

IR (neat): 3067, 1702 (C=O), 1607, 1564, 1512, 1480, 1403, 1338, 1268 (C–F), 1221 (C–F), 1160, 1016, 866, 846, 825, 791, 662 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.49 (s, 2 H, CH_2), 7.12–7.21 (m, 2 H, H3/H5$_{phenyl}$), 7.27–7.34 (m, 2 H, H2/H6$_{phenyl}$), 7.72–7.74 (m, 1 H, H3$_{pyridyl}$), 7.84–7.87 (m, 1 H, H5$_{pyridyl}$), 8.47–8.50 (m, 1 H, H6$_{pyridyl}$).

^{13}C NMR (DMSO-d_6): δ = 44.1 (s, CH_2), 108.1 (d, *J* = 38.6 Hz, C3$_{pyridyl}$)), 115.0 (d, *J* = 21.1 Hz, C3/C5$_{phenyl}$), 119.8 (d, *J* = 4.4 Hz, C5$_{pyridyl}$), 130.1 (d, *J* = 3.1 Hz, C1$_{phenyl}$), 131.8 (d, *J* = 8.1 Hz, C2/C6$_{phenyl}$), 148.4 (d, *J* = 6.9 Hz, C4$_{pyridyl}$), 148.9 (d, *J* = 14.5 Hz, C6$_{pyridyl}$), 161.1 (d, *J* = 241.0 Hz, C4$_{phenyl}$), 163.7 (d, *J* = 235.5 Hz, C2$_{pyridyl}$), 196.3 (dd, *J* = 1.1/3.1 Hz, C=O).

GC (conditions 1): t_R = 5.2 min; MS (EI, 70 eV): *m/z* (%) = 233 (26, M^+), 205 (66), 124 (69, M^+ – fluorobenzyl), 109 (100, 4-fluorobenzyl$^+$), 96 (33, 2-fluoro-4-pyridyl$^+$), 83 (31), 69 (12), 57 (8).

1-(4-Fluorophenyl)-2-(2-fluoro-4-pyridyl)ethane-1,2-dione 1-Oxime (6); Typical Procedure

A soln of $NaNO_2$ (4.72 g, 68.4 mmol) in H_2O (15 mL) was added dropwise over 8 min to a cooled (10 °C) soln of **5** (5.5 g, 23.6 mmol) in glacial AcOH (110 mL). The visible release of N_2 gas thereby initiated the reaction. After complete addition, cooling was removed and the mixture stirred at r.t. for 1.5 h. Subsequently as much cold H_2O (~140 mL) as necessary to produce a fine growing suspension was added. The mixture was stirred at r.t. for 5 h to quantify the precipitation and then the white solid product was gathered by filtration and dried in vacuo over $CaCl_2$ to give analytically pure **6**; yield: 4.1 g (66%); mp 168 °C.

IR (neat): 3156, 3006, 2843, 1673 (C=O), 1615, 1510, 1462, 1399, 1321, 1263 (C–F), 1225 (C–F), 1163, 1030, 1004, 820, 805, 678 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.27–7.36 (m, 2 H, H3/H5$_{phenyl}$), 7.53–7.60 (m, 3 H, H2/H6$_{phenyl}$, H3$_{pyridyl}$), 7.67–7.70 (m, 1 H, H5$_{pyridyl}$), 8.41 (d, *J* = 5.04 Hz, 1 H, H6$_{pyridyl}$), 13.12 (s, 1 H, NOH).

^{13}C NMR (DMSO-d_6): δ = 109.4 (d, J = 39.3 Hz, $C3_{pyridyl)}$), 114.7 (d, J = 21.5 Hz, $C3/C5_{phenyl}$), 121.3 (d, J = 4.2 Hz, $C5_{pyridyl}$), 125.1 (d, J = 3.4 Hz, $C1_{phenyl}$), 132.0 (d, J = 8.4 Hz, $C2/C6_{phenyl}$), 147.7 (d, J = 14.6 Hz, $C6_{pyridyl}$), 151.1 (d, J = 7.4 Hz, $C4_{pyridyl}$), 153.7 (s, C=NOH), 162.2 (d, J = 25.9 Hz, $C4_{phenyl}$), 162.6 (d, J = 234.6 Hz, $C2_{pyridyl}$), 190.0 (d, J = 3.3 Hz, C=O).

2-Fluoro-4-[4-(4-fluorophenyl)-1-(2-methoxyethyl)-3-oxido-1*H*-imidazol-5-yl]pyridine (7b); Typical Procedure

Compound **6** (3.94 g, 15.0 mmol) was suspended in EtOH (68 mL) at r.t. To the stirred suspension, a soln of 1,3,5-tris(2-methoxyethyl)-1,3,5-triazinane (1.92 g, 7.3 mmol) in EtOH (8 mL) was added under argon and the mixture was refluxed for 20 h. The solvent was removed in vacuo and the resulting oily residue cooled in an ice bath and taken up in Et_2O (40 mL). The mixture was stored in a refrigerator overnight, and the crystalline product was filtered off and washed (Et_2O); yield: 3.46 g (70%); mp 167 °C.

IR (neat): 3056, 2894, 2828, 1607, 1547, 1514, 1436, 1379, 1352, 1241 (C–F), 1202, 1161, 1124, 1093, 1058, 898, 867, 827, 807, 690 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.17 (s, 3 H, OCH_3), 3.50 (t, J = 4.96 Hz, 2 H, CH_2O), 4.06 (t, J = 4.92 Hz, 2 H, NCH_2), 7.12–7.21 (m, 2 H, $H3/H5_{phenyl}$), 7.26–7.31 (m, 2 H, $H3/H5_{pyridyl}$), 7.46–7.53 (m, 2 H, $H2/H6_{phenyl}$), 8.31 (d, J = 5.13 Hz, 1 H, $H6_{pyridyl}$), 8.59 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 45.5 (s, NCH_2), 58.0 (s, OCH_3), 70.0 (s, CH_2O), 111.2 (d, J = 38.7 Hz, $C3_{pyridyl)}$), 114.9 (d, J = 21.5 Hz, $C3/C5_{phenyl}$), 122.7 (d, J = 3.8 Hz, $C5_{imidazole}$), 123.1 (d, J = 3.3 Hz, $C1_{phenyl}$), 123.6 (d, J = 4.3 Hz, $C5_{pyridyl}$), 127.1 (s, $C2_{imidazole}$), 128.9 (s, $C4_{imidazole}$), 131.6 (d, J = 8.3 Hz, $C2/C6_{phenyl}$), 141.1 (d, J = 8.9 Hz, $C4_{pyridyl}$), 148.4 (d, J = 15.6 Hz, $C6_{pyridyl}$), 161.6 (d, J = 244.4 Hz, $C4_{phenyl}$), 163.1 (d, J = 234.8 Hz, $C2_{pyridyl}$).

4-(4-Fluorophenyl)-5-(2-fluoro-4-pyridyl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazole-2-thione (8b); Typical Procedure

Variant 1: A soln of **7b** (3.2 g, 9.7 mmol) in CH_2Cl_2 (40 mL) was slowly combined with an equimolar amount of 2,2,4,4-tetramethylcyclobutane-1,3-dithione in a small amount of pyridine. The mixture was stirred at r.t. for 2 h, after which the fine white to yellowish product **8b** began to precipitate. To quantify precipitation, the suspension was stirred for a further 30 min and finally the solid phase was filtered off and dried on the air. From the orange filtrate further **8b** could be obtained by evaporating to half its volume followed by addition of an equivalent volume of Et_2O; yield: 2.76 g (82%).

Variant 2: The title compound could be also obtained by refluxing **11b** (1.48 g, 4.3 mmol) and KSCN (0.78 g, 8.0 mmol) in DMF (38 mL) for 40 min under argon. Precipitation and isolation of the product from the cold organic soln was conducted by stepwise addition of ice cold H_2O (75 mL) and subsequent filtration. The sandy raw product was washed with a small volume of H_2O and Et_2O (2 ×) to give very pure **8b**; yield: 1.23 g (82%).

Variant 3: Compound **8b** could also be isolated via column chromatography as a single side product in the synthesis of **2c** from the reaction of **11b** with MeSCN; yield: 60 mg (12%); mp 229 °C.

IR (neat): 3070, 2902, 1609, 1548, 1494, 1474, 1408, 1395, 1254, 1224 (C–F), 1186, 1165, 1120, 1098, 982, 882, 845, 815 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.26 (s, 3 H, SCH_3), 3.79 (t, J = 4.95 Hz, 2 H, CH_2O), 4.18 (t, J = 4.99 Hz, 2 H, NCH_2), 6.97–7.16 (m, 3 H, $H3/H5_{phenyl}$, $H3_{pyridyl}$), 7.21–7.28 (m, 3 H, $H2/H6_{phenyl}$, $H5_{pyridyl}$; signal group superposed by the $CHCl_3$ peak), 8.30 (d, J = 5.14 Hz, 1 H, $H6_{pyridyl}$), 12.22 (br s, 1 H, exchangeable, NH).

^{13}C NMR ($CDCl_3$): δ = 45.4 (s, NCH_2), 58.7 (s, OCH_3), 69.0 (s, CH_2O), 111.8 (d, J = 38.2 Hz, $C3_{pyridyl)}$), 116.3 (d, J = 21.9 Hz, $C3/C5_{phenyl}$), 117.8, 123.3 (d, J = 4.3 Hz, $C5_{pyridyl}$), 124.4, 125.0, 129.3 (d, J = 8.3 Hz, $C2/C6_{phenyl}$), 141.8 (d, J = 9.1 Hz $C4_{pyridyl}$), 148.5 (d, J = 15.4 Hz, $C6_{pyridyl}$), 161.6 (s, $C2_{imidazole}$), 162.8 (d, J = 249.1 Hz, $C4_{phenyl}$), 163.9 (d, J = 234.0 Hz, $C2_{pyridyl}$).

GC (conditions 2): t_R = 7.7 min; MS (EI, 70 eV): m/z (%) = 347 (24, M^+), 315 (4), 289 (100), 255 (5), 230 (6), 202 (4), 122 (6), 95 (3, 4-fluorophenyl$^+$), 58 (2).

2-Bromo-2-(2-fluoro-4-pyridyl)-1-[3-(trifluoromethyl)phenyl]ethanone Hydrobromide (10b); Typical Procedure

Compound **9b** (5.0 g, 17.7 mmol) was dissolved in glacial AcOH (90 mL) and treated dropwise with Br_2 (2.83 g, 17.7 mmol) in AcOH (14 mL) at r.t.. The mixture was aged at r.t. for 1 h and then the light brown soln was rotary evaporated to dryness. The crude oily product **10b** was used without further purification in the following reaction step; yield: 7.24 g (93%).

IR (neat): 3073, 1698 (C=O), 1611, 1412, 1328, 1203, 1168, 1126 (CF_3), 1072, 1001, 818, 760, 691 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.23 (s, 1 H, CH), 7.37 (s, 1 H, $H3_{pyridyl}$), 7.51–7.58 (m, 1 H, $H5_{pyridyl}$), 7.84 (t, J = 7.92 Hz, 1 H, $H5_{phenyl}$), 8.07 (d, J = 8.33 Hz, 1 H, $H4_{phenyl}$), 8.29–8.39 (m, 3 H, $H6_{pyridyl}$, $H2/H6_{phenyl}$).

1-(4-Fluorophenyl)-2-(2-fluoro-4-pyridyl)-2-[(2-methoxyethyl)amino]ethanone Hydrochloride (11b); Typical Procedure

To a cooled soln of 2-methoxyethylamine (6.64 g, 88.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 45 min under argon a soln of **10a** (6.95 g, 17.7 mmol) in CH_2Cl_2 (20 mL). The yellow to brownish mixture was stirred at –5 to 0 °C for 50 min and it was then poured into ice H_2O (80 mL). The phases were separated and the organic layer was washed with ice H_2O (2 × 70–80 mL). Subsequently the aqueous layers were extracted with CH_2Cl_2 (2 × 25 mL) and finally all organic phases were combined and dried (Na_2SO_4). 1.25 M HCl in EtOH (15 mL) was added rapidly to the still cold organic soln; the solvent was removed in vacuo at 40 °C. The resulting (viscous) residue was stirred with Et_2O–acetone (1:1) and a fine bright beige product salt separated. The product salt was filtered off and dried in vacuo over $CaCl_2$. From the mother liquor further product precipitated; yield: 1.79 g (30%); mp 160–173 °C.

IR (neat): 2944, 2641 (NH_2^+), 1687 (C=O), 1611, 1596, 1568, 1531, 1509, 1457, 1413, 1274 (C–F), 1234 (C–F), 1162, 1129, 1100, 931, 859, 848, 802, 725 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.92–3.05 (m, 2 H, NCH_2), 3.21 (s, 3 H, OCH_3), 3.66 (t, J = 4.82 Hz, 2 H, CH_2O), 6.67 (br s, 1 H, CH), 7.37–7.46 (m, 2 H, $H3/H5_{phenyl}$), 7.58–7.61 (m, 2 H, $H3/H5_{pyridyl}$), 8.15–8.22 (m, 2 H, $H2/H6_{phenyl}$), 8.36 (d, J = 5.10 Hz, 1 H, $H6_{pyridyl}$), 9.94–10.31 (br d, exchangeable, J = 43.02 Hz, 2 H, NH_2^+).

^{13}C NMR (DMSO-d_6): δ = 45.2 (s, NCH_2), 57.9 (s, OCH_3), 62.7 (s, CH), 66.9 (s, CH_2O), 110.5 (d, J = 38.4 Hz, $C3_{pyridyl)}$), 116.4 (d, J = 22.1 Hz, $C3/C5_{phenyl}$), 122.1 (s, $C5_{pyridyl}$), 129.4 (s, $C1_{phenyl}$), 132.2 (d, J = 9.6 Hz, $C2/C6_{phenyl}$), 144.8 (d, J = 8.8 Hz, $C4_{pyridyl}$), 149.1 (d, J = 14.9 Hz, $C6_{pyridyl}$), 163.3, 165.4, 190.0 (s, C=O).

LC: t_R = 9.9 (10.7) min, 87.4%; MS: m/z = 307.0 [M + 1]$^+$ (base).

2-(2-Fluoro-4-pyridyl)-2-(2-methoxyethylamino)-1-[3-(trifluoromethyl)phenyl]ethanone Hydrochloride (11c); Typical Procedure

Following the typical procedure for **11b** reacting **10b** (7.0 g, 15.8 mmol) and 2-methoxyethylamine (5.9 g, 78.6 mmol) in CH_2Cl_2 (35 mL) for 45 min, gave **11c**; yield: 1.33 g (21%); mp 168 °C.

IR (neat): 2920, 2741, 2498 (NH_2^+), 1698 (C=O), 1609, 1451, 1415, 1331, 1242, 1205, 1160, 1128 (CF_3), 1100, 1072, 1044, 931, 798, 678 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.90–3.05 (m, 2 H, NCH_2), 3.19 (s, 3 H, OCH_3), 3.66 (t, J = 4.73 Hz, 2 H, CH_2O), 6.80 (s, 1 H, CH), 7.57–7.62 (m, 2 H, $H3/H5_{pyridyl}$), 7.80 (t, J = 8.15 Hz, 1 H, $H5_{phenyl}$), 8.06

(d, J = 7.72 Hz, 1 H, $H4_{phenyl}$), 8.32–8.35 (m, 3 H, $H6_{pyridyl}$, H2/$H6_{phenyl}$), 10.22 (br s, 2 H, exchangeable, NH_2^+).

^{13}C NMR (DMSO-d_6): δ = 45.2 (s, NCH_2), 57.8 (s, OCH_3), 62.8 (s, CH), 66.9 (s, CH_2O), 110.6 (d, J = 39.1 Hz, $C3_{pyridyl}$), 122.3 (d, J = 4.1 Hz, $C5_{pyridyl}$), 123.4 (q, J = 270.8 Hz, CF_3), 125.3 (s, $C2_{phenyl}$), 129.8 (q, J = 32.5 Hz, $C3_{phenyl}$), 130.2, 130.5, 131.1, 132.9, 133.6, 144.7 (d, J = 9.9 Hz, $C4_{pyridyl}$), 149.1 (d, J = 15.2 Hz, $C6_{pyridyl}$), 163.1 (d, J = 238.8 Hz, $C2_{pyridyl}$), 190.6 (s, C=O).

LC: t_R = 12.8 min, 96.5%; MS: m/z = 357.1 $[M + 1]^+$ (base).

1-(4-Fluorophenyl)-2-(methylamino)ethanone Hydrochloride (14c)

A soln of **13b** (5.0 g, 23.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 45 min to a stirred soln of ethanolic $MeNH_2$ (5.37 g, corresponding to 57.1 mmol $MeNH_2$) in CH_2Cl_2 (10 mL) at –5 °C and under argon. A slight white precipitate was formed after 10 min that was slowly intensified during the reaction. The mixture was stirred at 0 °C for a further 95 min and then poured into ice H_2O (50 mL). The phases were separated and the organic layer was again washed with ice H_2O (50 mL). The aqueous phases were extracted with CH_2Cl_2 (2 × 20 mL) and all organic phases were combined and dried (Na_2SO_4). Finally the still cold organic soln was treated with 1.25 M HCl in EtOH (20 mL) and the color changed to intensive red. The solvent was evaporated in vacuo to give a viscous dark green product, this was repeatedly stirred with acetone to separate **14c** as pure white crystals. The product salt was filtered off and dried in an evacuated desiccator over $CaCl_2$. From the mother liquor further product precipitated upon storage overnight; yield: 1.98 g (42%); mp 222 °C.

IR (neat): 2932, 2771, 2703, 2419, 1680 (C=O), 1600, 1510, 1470, 1417, 1401, 1364, 1251, 1237 (C–F), 1167, 1012, 942, 837 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.60 (s, 3 H, CH_3), 4.74 (s, 2 H, CH_2), 7.38–7.50 (m, 2 H, H3/$H5_{phenyl}$), 8.03–8.13 (m, 2 H, H2/$H6_{phenyl}$), 9.40 (br s, 2 H, exchangeable, NH_2^+).

^{13}C NMR (DMSO-d_6): δ = 32.6 (s, NCH_3), 53.4 (s, CH_2), 116.1 (d, J = 22.0 Hz, C3/$C5_{phenyl}$), 130.4 (d, J = 2.9 Hz, $C1_{phenyl}$), 131.2 (d, J = 9.8 Hz, C2/$C6_{phenyl}$), 165.6 (d, J = 252.2 Hz, $C4_{phenyl}$), 190.9 (s, C=O).

LC: t_R = 3.4 min, 99.9%; MS: m/z = 168.0 $[M + 1]^+$ (base).

4-(4-Fluorophenyl)-1-methyl-1,3-dihydro-2*H*-imidazole-2-thione (15c)

A soln of **14c** (1.8 g, 8.8 mmol) and KSCN (1.71 g, 17.6 mmol) in DMF (75 mL) was refluxed for 45 min under argon and then was allowed to cool to r.t. Precipitation of the product was initiated by the addition of ice-cold H_2O (160 mL) to the cold organic mixture. The fine sandy-like (orange to red) crystals were filtered off, washed with H_2O and dried in vacuo over $CaCl_2$. Further purification was not necessary; yield: 1.12 g (61%); mp 234 °C.

IR (neat): 3069, 2915, 1588, 1508, 1474, 1387, 1231 (C–F), 1204, 1159, 1134, 946, 837, 813, 756, 725, 677 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.47 (s, 3 H, NCH_3), 7.18–7.30 (m, 2 H, H3/$H5_{phenyl}$), 7.55 (d, J = 2.26 Hz, 1 H, CH), 7.63–7.71 (m, 2 H, H2/$H6_{phenyl}$), 12.64 (br s, 1 H, exchangeable, NH).

^{13}C NMR (DMSO-d_6): δ = 33.5 (s, NCH_3), 115.8 (d, J = 21.7 Hz, C3/$C5_{phenyl}$), 115.8 (d, J = 1.5 Hz, $C5_{imidazole}$), 124.7 (d, J = 3.1 Hz, $C1_{phenyl}$), 125.9 (d, J = 8.1 Hz, C2/$C6_{phenyl}$), 126.3 (s, $C4_{imidazole}$), 161.3 (d, J = 243.4 Hz, $C4_{phenyl}$), 162.2 (s, $C2_{imidazole}$).

LC: t_R = 14.8 min, 100.0%; MS: m/z = 209.2 $[M + 1]^+$.

4-(4-Fluorophenyl)-1-methyl-2-(methylsulfanyl)-1*H*-imidazole (16c)

Compound **15c** (1.0 g, 4.8 mmol) was dissolved in MeOH (28 mL) and K_2CO_3 (0.52 g, 3.8 mmol) and MeI (1.11 g, 7.8 mmol) in MeOH (5 mL) were added successively. The mixture was stirred at r.t. for 36 h and afterwards poured into EtOAc–H_2O (3:2, 90 mL). The aqueous phase was washed with EtOAc (30 mL) and finally the combined organic layers were dried (Na_2SO_4). The organic soln was concentrated in vacuo to give pure **16c** as an oily residue that completely crystallized after seeding and cooling (bright yellow solid product); yield: 1.07 g (100%); mp 71 °C.

IR (neat): 2935, 1665, 1560, 1497, 1457, 1431, 1386, 1310, 1213 (C–F), 1199, 1153, 1136, 1091, 943, 842, 813, 757, 730, 691 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.65 (s, 3 H, SCH_3), 3.64 (s, 3 H, NCH_3), 6.98–7.13 (m, 3 H, H3/$H5_{phenyl}$, CH), 7.67–7.75 (m, 2 H, H2/$H6_{phenyl}$).

^{13}C NMR ($CDCl_3$): δ = 16.6 (s, SCH_3), 33.1 (s, NCH_3), 115.3 (d, J = 21.4 Hz, C3/$C5_{phenyl}$), 117.3 (s, $C5_{imidazole}$, CH), 126.2 (d, J = 7.9 Hz, C2/$C6_{phenyl}$), 129.9 (d, J = 3.4 Hz, $C1_{phenyl}$), 140.7 (s, $C4_{imidazole}$), 143.3 (s, $C2_{imidazole}$), 161.8 (d, J = 243.7 Hz, $C4_{phenyl}$).

LC: t_R = 11.0 min, 100.0%; MS: m/z = 323.1 $[M + 1]^+$.

5-Bromo-4-(4-fluorophenyl)-1-methyl-2-(methylsulfanyl)-1*H*-imidazole (17a)

To a cooled soln (ice bath) of **16c** (0.9 g, 4.0 mmol) in CCl_4 (15 mL) was added NBS (0.79 g, 4.4 mmol). The cloudy, yellowish mixture was stirred at 0 °C for 10 min and was then allowed to come up to r.t. where it was stirred for 18 h (TLC monitoring). Undiluted components were separated by filtration (glass frit por. 3) and the purified filtrate was concentrated to dryness by rotary evaporation. Upon treatment with liquid N_2 the resulting oily residue was obtained as a crystalline solid; yield: 1.18 g (97%); mp 63 °C.

IR (neat): 2926, 1713, 1542, 1489, 1460, 1434, 1372, 1310, 1216 (C–F), 1158, 1126, 1076, 953, 833, 813, 744, 720, 685 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.67 (s, 3 H, SCH_3), 3.63 (s, 3 H, NCH_3), 7.04–7.14 (m, 2 H, H3/$H5_{phenyl}$), 7.88–7.97 (m, 2 H, H2/$H6_{phenyl}$).

^{13}C NMR ($CDCl_3$): δ = 16.5 (s, SCH_3), 32.7 (s, NCH_3), 101.0 (s, $C5_{imidazole}$ (CH)), 115.2 (d, J = 21.5 Hz, C3/$C5_{phenyl}$), 128.0 (d, $C1_{phenyl}$), 128.5 (d, J = 8.1 Hz, C2/$C6_{phenyl}$), 137.4 (s, $C4_{imidazole}$), 143.7 (s, $C2_{imidazole}$), 162.2 (d, J = 245.5 Hz, $C4_{phenyl}$).

LC: t_R = 22.7 min, 100.0%; MS: m/z = 301.1 $[M]^+$, 303.1 $[M + 2]^+$.

4-(4-Fluorophenyl)-1-methyl-2-(methylsulfanyl)-5-(3-tolyl)-1*H*-imidazole (18a)

To a stirred soln of **17a** (0.2 g, 0.66 mmol), 3-tolylboronic acid (0.14 g, 1.03 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in toluene (4 mL) was added 2 M Na_2CO_3 (0.7 mL). The mixture was heated to 120 °C under argon and stirred for 6 h (monitored by TLC and GC/MS). After complete conversion of the starting material the soln was cooled to r.t. and combined with H_2O (5 mL). The phases were separated and the organic layer was dried (Na_2SO_4). The solvent was rotary evaporated and the resulting organic residue purified by preparative TLC (silica gel 60 F_{254}, CH_2Cl_2, isolation from silica gel by extraction with acetone, 3 × 40 mL). Upon removing the solvent, a yellow oil was obtained that slowly crystallized after treatment with liquid N_2; yield: 0.16 g (77%); mp 87 °C.

IR (neat): 2928, 1608, 1561, 1507, 1456, 1376, 1316, 1218 (C–F), 1156, 1130, 969, 837, 793, 701 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.39 (s, 3 H, $C_6H_4CH_3$), 2.76 (s, 3 H, SCH_3), 3.43 (s, 3 H, NCH_3), 6.85–6.94 (m, 2 H, H3/$H5_{phenyl}$), 7.09–7.13 (m, 2 H, H2/$H4_{3\text{-tolyl}}$), 7.24–7.40 (m, 2 H, H5/$H6_{3\text{-tolyl}}$; superposed by CD_3OD signal), 7.44–7.51 (m, 2 H, H2/$H6_{phenyl}$).

^{13}C NMR ($CDCl_3$): δ = 16.3 (s, SCH_3), 21.3 (s, CH_3), 31.5 (s, NCH_3), 114.8 (d, J = 21.3 Hz, C3/$C5_{phenyl}$), 126.3, 127.6 (s, $C6_{3\text{-tolyl}}$), 128.2 (d, J = 7.9 Hz, C2/$C6_{phenyl}$), 128.9 (s, $C_{3\text{-tolyl}}$), 129.5 (s, $C_{3\text{-tolyl}}$), 130.1, 130.4 (d, J = 4.1 Hz, $C1_{phenyl}$), 131.0 (s, $C_{3\text{-tolyl}}$), 136.8 (s, $C1_{3\text{-tolyl}}$), 138.8 (s, $C3_{3\text{-tolyl}}$), 142.7 (s, $C2_{imidazole}$), 161.6 (d, J = 243.7 Hz, $C4_{phenyl}$).

GC (conditions 2): t_R = 4.7 min; MS (EI, 70 eV): m/z (%) = 312 (100, M^+), 297 (5, $M^+ - CH_3$), 296 (5), 279 (91), 265 (5), 239 (63), 210 (11), 197 (5), 183 (6), 148 (4), 132 (15), 121 (7), 117 (8), 91 (10, tropylium$^+$), 65 (4).

Supporting information for this article is available from the corresponding author. p38 inhibition data and selectivity profiling of selected compounds; detailed synthetic procedures, relevant analytical data and ^{1}H NMR spectra of all target compounds and intermediates.

Acknowledgment

This work was financially supported by the ratiopharm group and Fonds der Chemischen Industrie. We thank Dr. S. Linsenmaier, S. Luik and K. Bauer for the assistance in biological testing. Dr. H. Scheible is friendly acknowledged for generating LC/MS data. We are also thankful to R. Selig for arranging the Suzuki-coupling conditions for the preparation of compound **2b** according to the synthesis described in Scheme 4.

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