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

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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 cytochrome 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.2 Members of this class of 1,3-diazoles are known to possess NO synthase inhibition, antibiotic, antifungal, and anticancer activities and include compounds that are inhibitors of phosphodiesterase (PDE4), 5-lipoxygenase, or substances with VEGF receptor I and II antagonistic activities.3 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.4 About 2,500 ‘imidazole’ hits alone could be found in the structure–activity relationship(s) (SAR) database Integrity (Prous Science5), 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 SB203580,6 SB242235,7 L-7900708 and RWJ676579 (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.10 Approximately 20–25% of the druggable human genome11 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 genome12 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.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 kinase20,21 remains one of the most promising small molecule...
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-Sulfonylimidazoles 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-sulfonylimidazoles. 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.
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. Although the latest published method 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.

Retrosynthetic analysis of an exemplary tetrasubstituted target molecule in Scheme I demonstrates two principal approaches to arrange substituents at the pyridine bridged by a heteroatom. The starting aminopyridine derivatives exemplified by formula 1 (Scheme II) can be derived via a previously published multistep method. 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 SN mechanism in strategy II, the configuration of introduced haloalkyl substituents will be inverted or racemized (compounds 3).

The SNAr mechanism in strategy I allows the introduction of chiral building blocks (N-, O-, or S-nucleophiles) on one hand and 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 SNAr reactions. Substituents are directed ortho (or para) by the –M effect of the heterocyclic sp²-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. using sodium nitrite in aqueous tetrafluoroboric acid.
(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 labor-some reaction sequence further decreasing the overall yield. Therefore we developed an alternative, much short-er, synthetic strategy and introduced the fluorine in an ear-lier 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 ob-tained the 1-(2-fluoro-4-pyridyl)ethanone 5 in good yields (<85%) when reacting 4 with sodium nitrite in dry hydro-gen fluoride/pyridine consistent with the protocol of Fukuhara et al.37 The following α-oximation 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 triazinanone afforded 7 in excellent yields (70–86%). Imidazole N-oxides 7 then were con-verted into imidazole-2-thiones 8 by treatment with a small excess of 2,2,4,4-tetramethylcyclobutane-1,3-di-thione at room temperature; yields were approx. 80%. Subsequent alkylation of imidazole-2-thiones 8 was car-ried out in methanol and in the presence of potassium car-bonate at ambient temperature yielding the corresponding 2-(alkylsulfanyl)imidazoles 9 almost quantitatively.38 Other protocols that favor higher temperatures constantly gave elevated amounts of side and decomposition prod-ucts. In contrast, our mild method was also suitable with aroylalkyl- or even polar-substituted alkyl residues, e.g., benzyl or 2,3-dihydroxpropyl, 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 aminonucleo-philes could be readily introduced at the 2-position of the pyridine using known SNAr 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 re-ported previously for such SNAr reactions at analogous 2,4,5-trisubstituted derivatives.26 Moreover, as expected, the 2-fluoro-4-pyridyl intermediate 2 could be also suc-cessfully 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 se-quence.

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 substi-tuted 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-monofunc-tionalize the ethanones 9 by acid-catalyzed treatment with bromine. The reaction was generally carried out according to Revesz43 by adding one equivalent of bromine to a so-lution of 9 in acetic acid at room temperature. The re-ceived 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 Et2O 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 R1 = 4-F, R2 = (CH2)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.
Compounds 17 were readily obtained by bromination of 16 at the imidazole C5 position using N-bromosuccinimide. 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 using different (hetero)aryl boronic acids and dichlorobis(triphenylphosphine)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

Table 2  Substitution for Compounds 2, 7–11

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Table 3  Substitution for Compounds 2b, 12–18

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Scheme 4  Synthesis of 1,4,5-trisubstituted 2-sulfanylimidazoles using the Suzuki–Miyaura coupling reaction: (a) Br₂, glacial AcOH, r.t.; (b) R²NH₂, CH₂Cl₂ (+ MeOH), –5 to 0 °C, 1.25 M HCl in EtOH, acetone–Et₂O (1:1); (c) KSCN, DMF, reflux; (d) MeSCN, DMF, reflux; (e) MeI, K₂CO₃, MeOH, r.t.; (f) NBS, CCl₄, 0 °C then r.t.; (g) Pd(PPh₃)₄, argon, 2 M Na₂CO₃, 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 regioselective 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 over 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. 1H and 13C NMR spectra were generally collected on a Bruker Avance 200 at 200 and 50 MHz, respectively, except 1H NMR spectra of 3a, 3b, 3d, 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 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 R (min) and relative purity (%). TLC analyses were recorded on a Thermo Finnigan LCQ Duo Ion Trap System. Purity of compounds was either determined by HPLC (vide infra) or by HPLC (positive ion mode) or by HPLC (vide infra) or by HPLC (positive ion mode) or by HPLC (positive ion mode).

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H NMR (DMSO-d$_6$): $\delta = 2.65$ (s, 3 H, SCH$_2$), 3.08 (s, 3 H, OCH$_3$), 3.39 (t, $J = 5.82$ Hz, 2 H, CH$_2$O), 4.01 (t, $J = 5.34$ Hz, 2 H, NCH$_2$), 7.06–7.15 (m, 2 H, H$_3$/H$_5$ phenyl), 7.31–7.38 (m, 4 H, H$_3$/H$_5$ pyridyl-H$_2$/H$_6$ phenyl), 8.33 (d, $J = 4.88$ Hz, 1 H, H$_6$ pyridyl).

$^1$C NMR (DMSO-d$_6$): $\delta = 15.5$ (s, SCH$_2$), 44.0 (s, NCH$_2$), 58.0 (s, OCH$_3$), 69.7 (s, CH$_2$O), 111.0 (d, $J = 37.9$ Hz, C$_3$/C$_5$ phenyl), 115.2 (d, $J = 21.4$ Hz, C$_3$/C$_5$ phenyl), 123.7 (d, $J = 4.1$ Hz, C$_2$ pyridyl), 126.3 (d, $J = 4.4$ Hz, C$_5$ imidazolyl), 128.5 (d, $J = 8.0$ Hz, C$_2$ phenyl), 129.9 (d, $J = 3.2$ Hz, C$_1$ phenyl), 137.8 (s, C$_2$ imidazolyl), 144.0 (d, $J = 8.8$ Hz, C$_4$ pyridyl), 144.5 (s, C$_2$ imidazolyl), 148.3 (d, $J = 15.8$ Hz, C$_6$ pyridyl), 161.1 (d, $J = 242.4$ Hz, C$_4$ phenyl), 163.4 (d, $J = 234.9$ Hz, C$_5$ pyridyl).

GC (conditions 2): $t_g = 5.4$ min; MS (EI, 70 eV): m/z (% = 361 (100, M$^+$)), 346 (4, M$^+$ – CH$_3$), 324 (20), 316 (15), 303 (23), 288 (5), 270 (8), 243 (12), 230 (8), 215 (10), 182 (7), 169 (12), 211 (4), 59 (8, methoxyethylamine).

4-[2-(Benzylsulfanyl)-4-(4-fluorophenyl)-1-(2-methoxyethyl)-1H-imidazol-5-yl]pyridine (2f)

To a suspension of 8b (0.3 g, 0.86 mmol) in MeOH (5 mL) in a 25 mL flask was added initially K$_2$CO$_3$ (0.09 g) and then BrNMe$_2$ (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$_2$O (3:2). The aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na$_2$SO$_4$) and the filtrate was concentrated to dryness on a rotary evaporator leaving almost pure 2f as a red to brownish viscous mass. Crystallization of the residue was initiated by evaporating the product several times with EtOAc; yield: 0.37 g (98%); mp 61 °C.

IR (neat): 3063, 2932, 2893, 1609, 1542, 1453, 1400, 1259, 1185, 1105, 1015, 879, 839, 815, 698 cm$^{-1}$.

1H NMR (CDCl$_3$): $\delta = 3.17$ (s, 3 H, OCH$_3$), 3.36 (t, $J = 5.52$ Hz, 2 H, CH$_2$O), 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, H$_3$/H$_5$ pyridyl, H$_3$/H$_5$ phenyl), 7.09–7.13 (m, 1 H, H$_5$ pyridyl), 7.79–7.47 (m, 7 H, H$_3$/H$_5$ pyridyl, H$_2$/H$_6$ phenyl), 8.27 (d, $J = 5.14$ Hz, 1 H, H$_6$ pyridyl).

1C NMR (CDCl$_3$): $\delta = 39.5$ (s, SCH$_2$Ph), 44.5 (s, NCH$_2$), 58.8 (s, OCH$_3$), 70.6 (s, CH$_2$O), 111.2 (d, $J = 37.7$ Hz, C$_3$/C$_5$ phenyl), 115.4 (d, $J = 21.5$ Hz, C$_3$/C$_5$ phenyl), 123.1 (d, $J = 4.3$ Hz, C$_3$/C$_5$ phenyl), 126.6 (d, $J = 3.6$ Hz, C$_5$ imidazolyl), 127.6 (s, C$_4$/C$_6$ phenyl), 128.5 (d, $J = 2.8$ Hz, C$_5$/C$_6$ phenyl), 129.8 (s, C$_3$/C$_5$ phenyl), 129.1 (d, $J = 8.1$ Hz, C$_2$/C$_6$ phenyl), 137.2 (s, C$_1$ imidazolyl), 138.9 (s, C$_4$ imidazolyl), 143.0 (s, C$_2$ imidazolyl), 143.8 (d, $J = 7.9$ Hz, C$_4$/C$_6$ phenyl), 148.3 (s, $J = 15.4$ Hz, C$_6$ pyridyl), 162.2 (d, $J = 245.9$ Hz, C$_4$/C$_6$ phenyl), 164.0 (d, $J = 238.8$ Hz, C$_2$/C$_6$ pyridyl).

GC (conditions 2): $t_g = 10.4$ min; MS (EI, 70 eV): m/z (% = 437 (41, M$^+$), 404 (3), 379 (50), 346 (100, M$^+$ – CH$_3$), 314 (9), 288 (13), 270 (9), 256 (6), 243 (19), 230 (6), 215 (2), 121 (6), 91 (81, tropylidinyl), 65 (5).

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

3-[4-(4-Fluorophenyl)-5-(2-fluoro-4-pyridyl)-1-(2-methoxethyl)-1H-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$_2$CO$_3$ (0.01 g). At the same time color changed rapidly from bright to dark yellow. A soln of 3-bromopropene-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.
amine (1.7 g, 14.0 mmol) was stirred at 165 °C for 17 h. The amine
H5pyridyl), 6.89–6.98 (m, 2 H, H3/H5 phenyl), 7.42–7.49 (m, 2 H, H2/
C2pyridyl), 161.8 (d, J = 244.5 Hz, C4phenyl). GC (conditions 2): τf = 11.6 min; MS: m/z (%) = 416 (29, M1), 401 (1, M1 – CH3), 385 (100, 357 (M1 – C2H5O), 341 (1), 327 (7), 311 (6), 293 (13), 192 (4), 146 (5), 121 (3), 59 (2).

{[4-(4-Fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1H-imidazol-5-yl]-2-pyridyl}phenylamine (3b): 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 2e (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 CH2Cl2 (40 mL) added. The organic phase was washed with H2O (6 × 25 mL), dried (Na2SO4) 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: τf = 7.79 min; purity: 99.9% (λ = 254 nm).

IR (neat): 1219 (C–F) cm–1.

H NMR (CDCl3): δ = 2.71 (s, 3 H, SCH3), 3.20 (s, 3 H, OCH3), 3.51 (t, J = 6.0 Hz, 2 H, CH2O), 4.04 (t, J = 6.0 Hz, 2 H, NCH2), 6.76–7.47 (m, 11 H, H3/H5pyridyl, Hphenyl), 8.23 (d, J = 6.0 Hz, 1 H, H3pyridyl).

{[4-(4-Fluorophenyl)-1-(2-methoxyethyl)-2-(methylsulfanyl)-1H-imidazol-5-yl]-2-pyridyl}cyclohexanol (3j): Typical Procedure
Compound 2e (1.45 g, 4.0 mmol) and trans-4-amincyclohexanol (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 H2O and EtOAc. The organic layer was separated and washed with H2O (4 ×), dried (anhyd Na2SO4), and evaporated in vacuo; yield: 1.75 g (97%).

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

IR (ATR): 3319 (OH), 2928, 2856, 1604, 1541, 1448, 1219 (C–F), 1117, 839, 812 cm–1.

H NMR (CDCl3): δ = 1.26–1.39 (m, 4 H, H1/2phenyl), 1.98–2.07 (m, 4 H, H3/cyclohexyl), 2.73 (s, 3 H, SCH3), 3.28 (s, 3 H, OCH3), 3.38–3.46 (m, 1 H, H1/cyclohexyl), 3.56 (t, J = 5.80 Hz, 2 H, NCH2CH2OCH3), 3.65–3.72 (m, 1 H, H4/cyclohexyl), 4.05 (t, J = 5.60 Hz, 2 H, NCH2CH2OCH3), 6.42 (s, 1 H, H3phenyl), 6.56 (dd, J = 1.45/50 Hz, 1 H, H5phenyl), 6.92–6.96 (m, 2 H, H3/H5phenyl), 7.44–7.47 (m, 2 H, H2/H5phenyl), 8.05 (d, J = 6.40 Hz, 1 H, H3pyridyl).

H NMR (DMSO-d6): δ = 1.13–1.28 (m, 4 H, H1/2phenyl), 1.80–1.93 (m, 4 H, H3/cyclohexyl), 2.63 (s, 3 H, SCH3), 3.12 (s, 3 H, OCH3), 3.47–3.42 (t, J = 5.62 Hz, 3 H, NCH2CH2OCH3), 3.57 (s, 1 H, H1/cyclohexyl), 3.95 (s, J = 5.60 Hz, 1 H, NCH2CH2OCH3), 4.52 (d, J = 4.40 Hz, 1 H, H3phenyl), 6.73 (s, 1 H, H3phenyl), 6.85 (4 mg, 2 H, H2phenyl), 8.06 (d, J = 5.20 Hz, 1 H, H3pyridyl).

{[4-(4-Fluorophenyl)-2-(methylsulfanyl)-1H-imidazol-5-yl]-2-pyridyl}(tetrahydro-2H-pyran-4-yl)amine (3o): Typical Procedure
Compound 2a (0.3 g, 1 mmol) and tetrahydroprop-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 F254, 2 mm, acetone; (2 silica gel 60, F254, 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 Et2O to give amorphous 3o; yield: 85 mg (22%); mp 99 °C.

IR (neat): 2927, 2847, 1595, 1579, 1549, 1503, 1479, 1461, 1449, 1439, 1386, 1221 (C–F), 1157, 1137, 1086, 980, 839, 814 cm⁻¹.

'H NMR (CD3OD): δ = 1.38–1.57 (m, 2 H, H3/H5 Hernandez); 1.86–1.93 (m, 2 H, H3/H5 Hernandez); 2.62 (s, 3 H, SCH3); 3.42–3.53 (m, 2 H, H2/H4 Hernandez); 3.65–3.76 (m, 1 H, CH); 3.91–3.97 (m, 2 H, H2/H6 Hernandez); 5.65–5.67 (m, 2 H, H3/H5 Hernandez); 7.10–7.19 (m, 2 H, H3/H5 Hernandez); 7.43–7.49 (m, 2 H, H2/H6 Hernandez); 7.83 (d, J = 5.83 Hz, 1 H, H6 Hernandez).

'13C NMR (CD3OD): δ = 26.19 (s, SCH3), 34.3 (s, C3/H5 Hernandez), 48.4 (s, CH), 68.0 (s, C2/H2 Hernandez), 107.4 (s, C3/H3 Hernandez), 111.8 (s, C5/H5 Hernandez), 116.7 (d, J = 21.8 Hz, C3/H3 Hernandez), 131.8 (d, J = 8.2 Hz, C2/H6 Hernandez), 144.6, 148.3 (s, C6/H6 Hernandez), 159.7 (s, C2/H2 Hernandez), 164.1 (d, J = 244.8 Hz, C4/H4 Hernandez).

GC (conditions 2): tR = 16.4 min; MS: m/z (%): 384 (76, M⁺), 369 (10, M⁺ – CH3), 355 (10), 393 (279), 327 (32), 299 (100, M⁺ – tetrahydro- pyranyl), 285 (16), 267 (32), 252 (9), 227 (9), 207 (7), 170 (8), 146 (19), 121 (100), 75 (5, tetrahydropropyran-4-ylmethyl), 55 (7).

2-(4-Fluorophenyl)-1-(2-fluoro-4-pyridyl)ethane (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 NaNO3 (4.89 g, 0.07 mol) was added portion-wise to the orange mixture; the flask was closed after each addition of NaNO3, N2 as well as liquid amounts of NOX were released whenever the flask was opened again. After complete addition of NaNO3, 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 H2O (150 mL) immediately followed by the addition of CH2Cl2 (90 mL). The organic layer was separated and the aqueous phase extracted with CH2Cl2 (4 × 50 mL) and H2O (1 × 100 mL), dried (Na2SO4), and the solvent removed in vacuo. Purification could be afforded by repeatedly extracting the oily residue with hot hexane (7 × 30 mL). Pure 5 crystalized 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 (CeO), 1607, 1564, 1512, 1480, 1403, 1338, 1268 (C–F), 1211 (C–F), 1160, 1016, 866, 846, 825, 791, 662 cm⁻¹.

'H NMR (CD3OD): δ = 4.49 (s, 2 H, CH2), 7.12–7.21 (m, 2 H, H3/H5 Hernandez), 7.27–7.34 (m, 2 H, H2/H6 Hernandez), 7.72–7.74 (m, 1 H, H3 Hernandez), 8.14–8.15 (m, 1 H, H5 Hernandez), 8.87–8.85 (m, 1 H, H6 Hernandez).

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

A soln of NaNO2 (4.72 g, 68.4 mmol) in H2O (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 N2 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 H2O (~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 CaCl2 to give analytically pure 6; yield: 4.1 g (66%); mp 168 °C.

IR (neat): 3156, 3006, 2843, 1673 (CeO), 1615, 1510, 1462, 1399, 1321, 1263 (C–F), 1225 (C–F), 1163, 1030, 1004, 820, 805, 678 cm⁻¹.

'H NMR (CD3OD): δ = 7.27–7.36 (m, 2 H, H3/H5 Hernandez), 7.53–7.60 (m, 3 H, H2/H6 Hernandez, H3 Hernandez), 7.67–7.70 (m, 1 H, H5 Hernandez), 8.41 (d, J = 5.04 Hz, 1 H, H6 Hernandez).

GC (conditions 2): tR = 10.8 min; MS: m/z (%): 392 (100, [M – 1]⁺), 376 (11), 360 (3), 344 (5), 319 (8), 211 (7), 179 (12), 123 (1), 109 [1 (Ph)⁺], 95 (2, 4-fluorophenyl), 77 (2), 51 (1).

IR (neat): 3052 (aryl-H), 2926 (CH2), 1586, 1515, 1503, 1475, 1439, 1386, 1221 (C–F), 1158, 1132, 991, 837, 783, 748, 690 cm⁻¹.

'H NMR (CD3OD): δ = 2.58 (s, 3 H, SCH3), 6.77 (br s, 1 H, H3 Hernandez), 7.06–7.41 (m, 10 H, H Hernandez), 8.28 (d, J = 5.26 Hz, 1 H, H Hernandez).

GC (conditions 2): tR = 18.9 min; MS: m/z (%): 392 (100, [M – 1]⁺), 376 (11), 360 (3), 344 (5), 319 (8), 211 (7), 179 (12), 123 (1), 109 [1 (Ph)⁺], 95 (2, 4-fluorophenyl), 77 (2), 51 (1).
2-Fluoro-4-[4-(4-fluorophenyl)-1-(2-methoxyethyl)-3-oxido-1H-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, 1,3,5-tris(2-methoxyethyl)-1,3,5-triazinane (1.92 g, 7.3 mmol) in EtOH (8 mL) was added under argon. Precipitation and isolation of the product was washed with a small volume of H2O and Et2O (2 × 25 mL) for 40 min under argon. The mixture was stirred at r.t. for 2 h, after which the fine white to yellowish product was washed with a small volume of H2O and Et2O (2 × 25 mL) for 40 min under argon. The mixture was stored in a refrigerator overnight, and the crystalline product was filtered off and washed (Et2O); yield: 3.46 g (70%); mp 167 °C.

IR (neat): 3070, 2902, 1609, 1548, 1494, 1474, 1408, 1395, 1274 (C–F), 1202, 1161, 1124, 1093, 882, 845, 815 cm–1.

1H NMR (DMSO-d6): δ = 3.17 (s, 3 H, OCH3), 7.64–7.69 (m, 2 H, H5/H6imidazole), 7.51–7.58 (m, 1 H, H2/imidazole), 7.54 (d, J = 8.4 Hz, H2imidazole), 7.51 (d, J = 7.3 Hz, H4imidazole), 7.42 (d, J = 8.2 Hz, H3imidazole), 7.37 (d, J = 7.9 Hz, H6imidazole), 7.35 (d, J = 8.4 Hz, H2imidazole), 7.28 (m, 1 H, H2imidazole), 7.26 (d, J = 8.1 Hz, H2imidazole), 7.25 (d, J = 7.9 Hz, H6imidazole), 7.17 (d, J = 7.3 Hz, H4imidazole), 6.32 (t, J = 4.8 Hz, 2 H, NH2), 4.18 (t, J = 4.9 Hz, 2 H, NCH2), 3.19 (s, 3 H, OCH3), 2.93 (s, 3 H, CH3), 1.98 (s, 3 H, OCH3), 1.69 (s, 3 H, OCH3), 1.64 (d, J = 3.4 Hz, C2pyridyl), 1.48 (s, 3 H, OCH3), 1.24 (s, 3 H, OCH3), 0.91 (s, 3 H, OCH3), 0.88 (s, 3 H, OCH3).

13C NMR (DMSO-d6): δ = 152.0 (d, J = 23.4 Hz, C7imidazole), 151.2 (d, J = 23.3 Hz, C7imidazole), 147.7 (d, J = 14.6 Hz, C6imidazole), 141.1 (d, J = 21.9 Hz, C5imidazole), 131.3 (d, J = 21.5 Hz, C5imidazole), 125.1 (t, J = 7.4 Hz, C4imidazole), 121.3 (d, J = 21.5 Hz, C3imidazole), 116.3 (d, J = 3.3 Hz, C2imidazole), 116.3 (d, J = 3.3 Hz, C2imidazole), 114.9 (d, J = 7.4 Hz, C3imidazole), 114.9 (d, J = 7.4 Hz, C3imidazole), 113.3 (t, J = 7.4 Hz, C7imidazole), 113.3 (t, J = 7.4 Hz, C7imidazole), 112.1 (d, J = 3.3 Hz, C1imidazole), 112.1 (d, J = 3.3 Hz, C1imidazole), 109.5 (s, 1 H, CH), 108.9 (s, 1 H, CH), 102.0 (s, 1 H, CH).
the addition of ice-cold H\textsubscript{2}O (160 mL) to the cold organic mixture. DMF (75 mL) was refluxed for 45 min under argon and then was
A soln of LC:

1159, 1134, 946, 837, 813, 756, 725, 677 cm\textsuperscript{–1}. IR (neat):

3069, 2915, 1588, 1508, 1474, 1387, 1231 (C–F), 1204, 1133, 1447 (d, J = 9.9 Hz, C\textsubscript{4}(pyridyl)), 149.1 (d, J = 15.2 Hz, C\textsubscript{6}(pyridyl)), 163.1 (d, J = 238.8 Hz, C\textsubscript{2}(pyridyl)), 190.6 (s, C=O). LC: \textit{t}\textsc{f} = 12.8 min, 96.5%; MS: \textit{m/z} = 357.1 [M + 1]\textsuperscript{+} (base).

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

A soln of 13b (5.0 g, 23.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) was added dropwise over 45 min to a stirred soln of ethanolic MeNH\textsubscript{2} (5.37 g, corresponding to 57.1 mmol MeNH\textsubscript{2}) in CH\textsubscript{2}Cl\textsubscript{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\textsubscript{2}O (50 mL). The phases were separated and the organic layer was again washed with ice H\textsubscript{2}O (50 mL). The aqueous phases were extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 20 mL) and all organic phases were combined and dried (Na\textsubscript{2}SO\textsubscript{4}). Finally the still cold organic solution 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 Ca\textsubscript{O}. From the mother liquor further product precipitated upon storage overnight; yield: 1.18 g (97%); mp 63 °C.

IR (neat): 2942, 2931, 2862, 1713, 1608, 1561, 1447, 1437, 1387, 1376, 1316, 1218 (C–F), 1123, 1107, 1067, 953, 833, 813, 744, 720, 685 cm\textsuperscript{–1}.

1H NMR (CDCl\textsubscript{3}):

2.76 (s, 3 H, NCH\textsubscript{3}), 2.73 (s, 3 H, SCH\textsubscript{3}), 3.61 (s, 3 H, NCH\textsubscript{3}), 115.3 (d, J = 16.5 Hz, C\textsubscript{6}H\textsubscript{4}C\textsubscript{4}imidazole), 110.1 (s, C\textsubscript{5}imidazole), 115.2 (d, J = 21.5 Hz, C\textsubscript{4}imidazole), 128.0 (d, C\textsubscript{1}phenyl), 128.5 (d, J = 8.1 Hz, C\textsubscript{2}(phenyl)), 137.4 (s, C\textsubscript{4}imidazole), 143.7 (s, C\textsubscript{2}imidazole), 162.2 (d, J = 245.5 Hz, C\textsubscript{4}phenyl). LC: \textit{t}\textsc{f} = 22.7 min, 100.0%; MS: \textit{m/z} = 301.1 [M]\textsuperscript{+}, 303.1 [M + 2]\textsuperscript{+}.

4-(Fluorophenyl)-1-methyl-2-(methylsulfanyl)-1H-imidazole (17a)

To a cooled soin (ice bath) of 16c (0.9 g, 4.0 mmol) in CCl\textsubscript{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 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\textsubscript{2} the resulting oily residue was obtained as a crystalline solid; yield: 1.18 g (97%); mp 63 °C.

IR (neat): 2926, 2971, 2934, 2862, 1713, 1608, 1561, 1447, 1437, 1387, 1376, 1316, 1218 (C–F), 1123, 1107, 1067, 953, 833, 813, 744, 720, 685 cm\textsuperscript{–1}.

1H NMR (CDCl\textsubscript{3}):

2.76 (s, 3 H, NCH\textsubscript{3}), 7.17–7.30 (m, 2 H, H\textsubscript{3}/H\textsubscript{5} phenyl), 7.67–7.75 (m, 2 H, H\textsubscript{2}/H\textsubscript{6} phenyl). LC: \textit{t}\textsc{f} = 11.0 min, 100.0%; MS: \textit{m/z} = 323.1 [M + 1]\textsuperscript{+}.
$^{13}$C NMR (CDCl$_3$): $\delta = 16.3$ (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/C8$_{phenyl}$), 128.2 (d, $J = 7.9$ Hz, C2/C8$_{phenyl}$), 128.9 (s, C1$_{tolyl}$), 129.5 (s, C5$_{tolyl}$), 130.1, 130.4 (d, $J = 4.1$ Hz, C1$_{phenyl}$), 131.0 (s, C4$_{imidazole}$), 136.8 (s, C2$_{imidazole}$), 138.8 (s, C3$_{tolyl}$), 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), 75 (23), 69 (100, M$^+$).

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.

References