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Potent, orally available, selective COX-2 inhibitors based on 2-imidazoline core

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ABSTRACT

A novel series of compounds containing a polar, non-flat 2-imidazoline core was designed based on the SAR information available for aromatic azole cyclooxygenase-2 inhibitors. While the majority of the compounds prepared using an earlier developed imidazoline *N*-arylation methodology turned out to be inferior to the known COX-2 inhibitors, one lead compound displayed potency (300 nM) comparable to clinically used Celecoxib and was shown to be more selective. The series represents the first example of selective COX-2 inhibitors built around a distinctly polar core, contradicting an earlier accepted view that a lipophilic scaffold is required for high inhibitor potency. The lead compound demonstrated very good oral bioavailability in mice, slow metabolic degradation, modest distribution into the brain and a remarkable anti-inflammatory efficacy in carrageenan-induced mouse paw edema model. A foundation has therefore been laid for a chemically novel series of COX-2 inhibitors that has a potential for diverse therapeutic applications in inflammatory disease area.

1. Introduction

The last decade of 20th century was marked by the advent of a new generation of non-steroidal anti-inflammatory drugs (NSAIDs) with selective inhibition of cyclooxygenase-2 (COX-2) as the principal mode of action [1]. Examples of drugs belonging to this class (so-called coxibs) include Merck's Rofecoxib (Vioxx) [2] and Pfizer's Celecoxib (Celebrex) [3] both of which were markedly successful commercially at the start of this century [4]. In addition, there are many other known coxibs at various stages of drug development cycle, all of which are based on a common pharmacophore (derived from the prototypical compound DuP697) [5], namely, an almost predominantly five-membered cyclic core (with some examples of six-membered counterparts) decorated with two adjacently placed aromatic groups, one of which contains a sulfonyl or a primary sulfamide group (as well as some known bioisosteres thereof [6]) in position 4, a substitution pattern required for selective COX-2 inhibition (Fig. 1) [7].

The development of this exciting area of anti-inflammatory pharmacology was severely hampered by the emerging serious cardiovascular liabilities associated with some of the approved drugs – leading, most notably, to the voluntary withdrawal of Vioxx (by Merck in 2004) and Bextra (by Pfizer in 2005) from the market. Moreover, the entire field of selective COX-2 inhibitors has been tarnished by the potential side-effect risks [8]; a view of COX-2 inhibition being innately linked to adverse effects on vasoconstriction, platelet aggregation XZ and thrombosis appeared to be convincingly supported by the thorough analysis of the perturbations in prostaglandin synthesis introduced by coxib treatment [9].

However, this clinically validated area of chemotherapeutic treatment and prevention may see a renaissance in the upcoming years as potential use of COX-2 inhibitors in the areas other than the traditional systemic treatment of inflammatory conditions (such as

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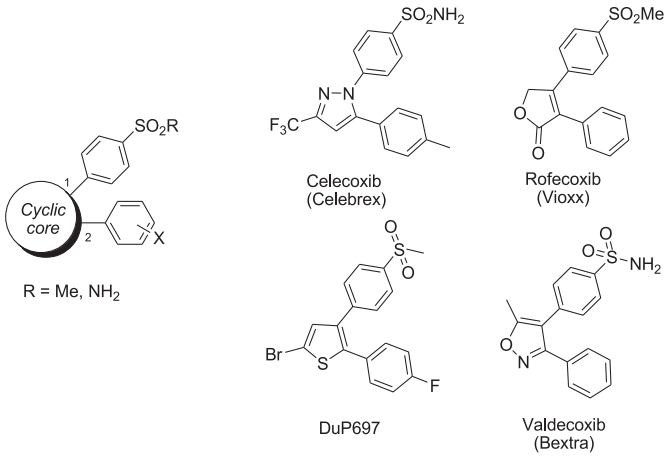
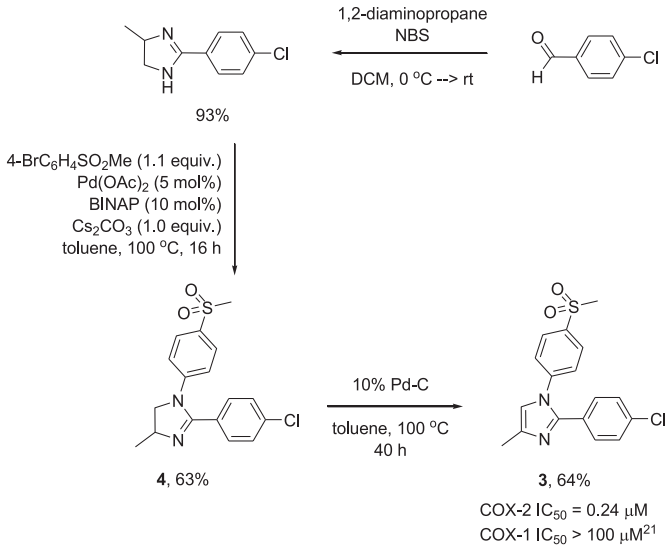


Fig. 1. Common pharmacophore and representative examples of selective COX-2 inhibitors.



Scheme 1. Synthesis of known imidazole-based selective COX-2 inhibitor **3**.

rheumatoid arthritis) is supported by the scientific evidence. In particular, selective inhibition of this enzyme in central nervous system has been suggested as a novel therapeutic approach to such conditions as Parkinson's disease [10] or ischemic brain injury [11]. More recently, selective COX-2 inhibitors have been also found effective in treating inflammatory neurodegeneration and therefore implicated as potential treatments for major depressive disorders and schizophrenia [12]. Additionally, COX-2 inhibition has been shown to slow down neuroblastoma growth [13,14] and retard the onset of Alzheimer's Disease [15].

As the majority of new therapeutic applications for COX-2 inhibitors are envisioned in central nervous system disease area, development of structurally novel series of inhibitors, with the emphasis on blood–brain barrier permeability and elimination of structural motifs that could be responsible for the unwanted side-effects, is likely to be needed. The central core (scaffold) of the known selective COX-2 inhibitors appears to contribute little to the interaction with the amino acid residues of the enzyme's active site and is mainly responsible for projecting the two pharmacophoric aromatic rings in correct orientation for the efficient binding. Moreover, a dogma was introduced stating that, due to the high lipophilicity of the enzyme's active site, in order for a compound to exert COX-2 inhibitory activity, its scaffold should too be relatively lipophilic [16]. This notion is a likely reason for the vast majority of known COX-2 inhibitors being designed with a flat aromatic heterocycle (most prominently, an azole) at their core. In fact, only a small number of examples (Fig. 2) of non-flat COX-2 inhibitor scaffolds can be found in the literature (including, interestingly, Rofecoxib, its lactam analog Imrecoxib [17], Searle's 1,2-diarylcyclopentene SC-57666 (**1**) [18], and non-selective pyrazoline-based COX-1/2 inhibitor **2** [19]). This seeming requirement for the high degree of unsaturation can, in fact, be a limiting factor for the development and subsequent clinical use of these compounds as drugs. Indeed, according to the recent observation by a Wyeth team [20], the average degree of saturation (or fraction of sp^3-hybridized carbons, F_{sp3}) increases for the clinical candidates and approved drugs compared to early pre-clinical research compounds. This general trend suggests potential advantages of front-loading this requirement in compound's development life-cycle and perhaps introducing it as early as the lead generation stage.

Earlier, we described [21] a concise synthesis of Searle's imidazole-based selective COX-2 inhibitor **3** [22] employing Pd-catalyzed *N*-arylation of 2-imidazolines (Scheme 1) [23]. In the course of development of this synthetic strategy, a somewhat sluggish aromatization of the intermediate 2-imidazolines **4** upon treatment with Pd/C [24] was noted. This stability of **4** toward the conversion into the known, flat, aromatic imidazoles gave us an idea to consider **4** as a novel (and, surprisingly, hitherto unexplored) chemotype for the design of potential selective COX-2 inhibitors that would also be sufficiently stable toward potential cytochrome-mediated aromatization [25] *in vivo* (in analogy with other imidazoline-based drugs, such as moxonidine [26] that is a clinically used antihypertensive drug). In addition to its novelty, the 2-imidazoline scaffold, if validated as the basis for COX-2 inhibitor design, promised to offer certain advantages from the standpoint of prospective drug development. Firstly, it is a non-flat, non-aromatic core, which is an attractive feature according to Wyeth's 'flatland' dogma (*vide supra*). Further, 2-imidazoline is a markedly polar motif and its suitability for COX-2 inhibitor design would contrast the lipophilic scaffolds used earlier. Should the chemical nature of the clinically used coxibs be responsible for the observed adverse

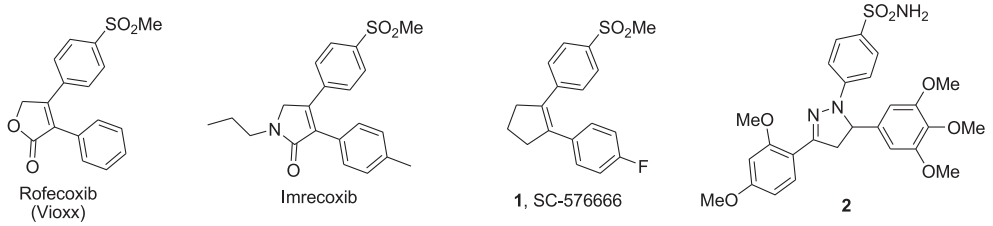


Fig. 2. Examples on coxibs based on a non-flat heterocyclic scaffold.

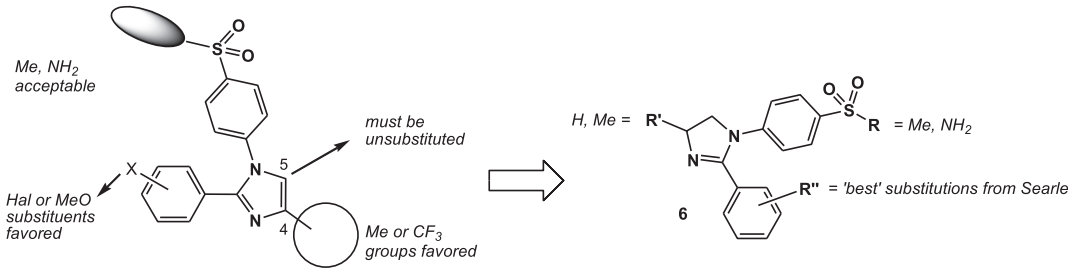


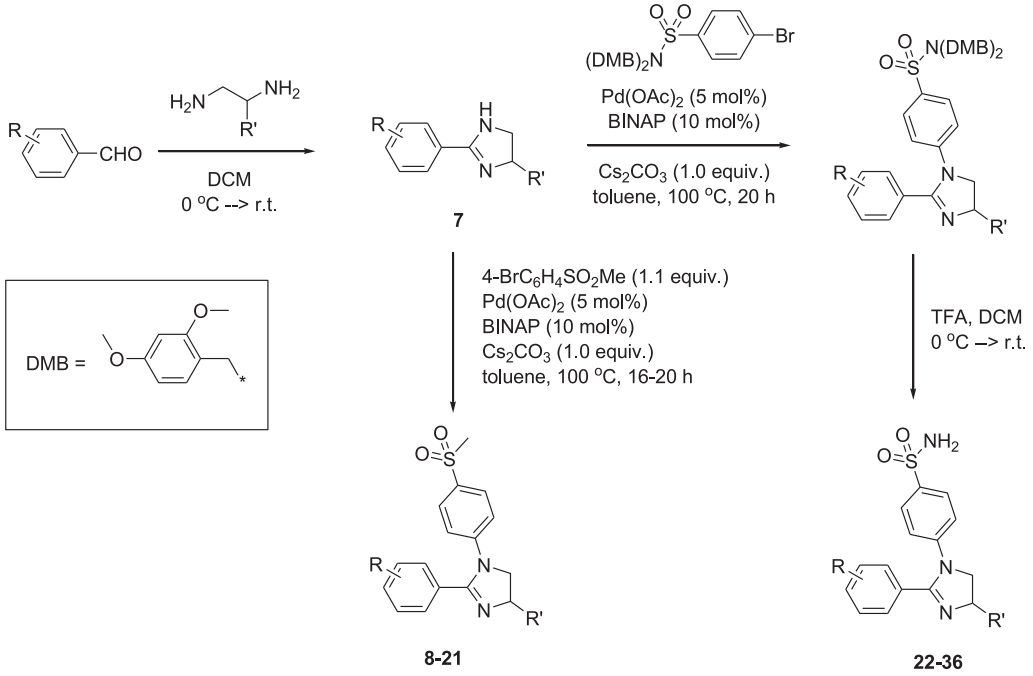
Fig. 3. Analysis of the SAR for Searle's imidazolines and our design of the pilot 2-imidazoline-based library (**6**).

effects, 2-imidazoline-based inhibitors would occupy a drastically different chemical space which may help avoid compounds' unwanted liabilities. Finally, the high basicity of 2-imidazolines (somewhat attenuated by the electron-withdrawing group in the *para*-position of the N^1-aryl substituent [27]) may ensure not only the high solubility of these compounds in the aqueous medium due to protonation but also their permeability with respect to the blood–brain barrier or BBB (in analogy to Astra Zeneca's cyclic amidine BACE-1 inhibitors reported recently [28]) and even potential propensity to active transport across the BBB by the organic cation transport system [29]. Herein, we report the results of our studies toward novel selective COX-2 inhibitors based on 2-imidazoline core.

2. Results

In order to establish whether the remarkably polar and basic 2-imidazoline scaffold could indeed serve as a scaffold for selective COX-2 inhibitor assembly, a relatively small pilot library was envisioned. As 2-imidazolines were expected to be drastically different in their physicochemical nature from other scaffolds explored to-date in this area of medicinal chemistry, we could, in principle, base our design on any available structure–activity relationship information. Considering the wealth of biological data available for Searle's (now Pfizer's) imidazole inhibitors similar to **3** [22,30], we chose to base our pilot library design on that foundation.

Analysis of the COX inhibition data from Searle available in the literature [22,30] revealed certain generalizations that could be made regarding the structural features of imidazoles that are favorable for selective COX-2 blockage. In particular, suitability of both methylsulfonyl and (even more so) primary sulfonamide substituents in position 4 of N^1-Ph group was evident, so was the favorable influence on the biological activity of halogen or methoxy groups in the second peripheral aromatic group. Furthermore, imidazole's inhibitory potency appeared particularly sensitive to any substitutions in position 4, which led to the loss of activity, while small substituents like methyl or trifluoromethyl enhanced COX-2 inhibition. On the basis of these observations, we designed a series of 2-imidazolines containing substituted phenyl groups in positions 1 and 2 of the imidazoline core. The prospective set of compounds was to include both 4-$MeSO_2$- and 4-H_2NSO_2-substituted compounds with 2-imidazoline core left unsubstituted or containing 4-methyl substitutent (in case the SAR available for imidazoles turns out to be not transferrable to imidazolines). The choice of substitutions for the aromatic ring at position 2 of imidazoline was also dictated by the favorable SAR disclosed by Searle (Fig. 3). With such a design in mind, we set off to synthesize a pilot



Scheme 2. Synthesis of 2-imidazolines compounds **4**, **8**–**36** studied in this work.

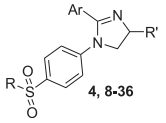
set of 30 compounds for biological testing. It is noteworthy that we had found this library size to be optimal for identifying biological activities for newly designed chemotypes, similarly to the NIH Roadmap Molecular Libraries Program's guidelines for pilot-scale libraries intended for biological screening [31].

The synthesis of the compounds in the methylsulfone series was achieved in a similar fashion to our synthesis of **4**. However, direct arylation of the imidazoline core with unprotected 4-bromophenylsulfonamide was not feasible and led to *N*-arylation of the sulfonamide functionality instead (i.e. homocoupling). Therefore, the primary sulfonamide function was protected with 2,4-dimethoxybenzyl (DMB) groups [32] prior to imidazoline *N*-arylation. Efficient removal of DMB groups was achieved on treatment with TFA [33]. Notably, in both cases, the arylation of methyl-substituted imidazolines proceeded in highly regiospecific fashion, at the less sterically hindered nitrogen atom (according to NOESY data), in line with our earlier observations (Scheme 2) [21].

The 30 compounds thus prepared (**4**, **8**–**36**) were tested for inhibition of COX-2 and COX-1 using indomethacin and celecoxib as reference standards. None of the compounds studied inhibited COX-1 significantly at 100 μM. A half of the compounds investigated also showed no appreciable inhibition (IC_{50} > 10 μM) of COX-2. A number of compounds displayed a full inhibition of the target enzyme with potencies in the single-digit micromolar range. To our outmost delight, however, one compound (**35**) displayed a sub-micromolar inhibition of COX-2 (IC_{50} = 300 nM), i.e. was found to be nearly equipotent not only to Searle's imidazoles like **4** but also similar in activity to the clinically used celecoxib – and remarkably more selective than the latter (celecoxib's COX-2 IC_{50} = 91 nM and COX-1 IC_{50} = 2.8 μM as measured in PGE2 production assay in human dermal fibroblasts and lymphoma cell, respectively [34]). In general, the primary sulfonamide subset of COX-2 inhibitors was more potent compared to the methylsulfonyl one (Table 1). However, the compounds containing methyl substituent in position 4 of the imidazoline core were all inactive and less potent compared to their non-methylated counterparts. This is in sharp contrast to the SAR established for Searle's imidazoles and may possibly suggest a different binding mode for the newly discovered series of COX-2 inhibitors.

We performed a docking study of the lead compound (**35**) using the available X-ray crystallographic data for COX-2 with a known inhibitor (4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide) [7]. The docking algorithm was validated by de-novo docking of the same compound into the active site of the enzyme that led to a full superposition of the co-crystallized and docked structures (Fig. 4). Docking of compound **35** (Fig. 5) revealed that the binding mode of this compound is identical to that of the pyrazole (and, by analogy, of the imidazole) inhibitors. This supports the similar trend in biological activity observed for the methylsulfone compounds compared to primary sulfonamides. In order to rationalize the complete loss of activity for the methyl-substituted imidazolines, we scrutinized the vicinity of the pocket formed by Arg120, Tyr355 and Ala516. It was observed that, unlike the flat aromatic imidazoles [22,30], ring-methylated imidazolines, that exist as a racemic mixture of two enantiomers, can experience steric clashes with specific amino acid residues of the protein backbone: more specifically, with Arg120 in case of (*R*)-**35** and with Leu379 and Val349 in case of (*S*)-**35**. Finally, we were curious to see why 3,4-dichloro substitution of the phenyl ring in **35** leads to the observed pronounced increase in potency compared to both 4-chloro (**23**) and 3-chloro (**29**) counterparts (IC_{50} of 3.4 μM and 2.5 μM, respectively). The 3-Cl substituent was found to be involved in dipole–dipole interaction with the OH group of Tyr385 while 4-Cl substituent appears to completely fill the shared van-der-Waals (VDW) cavity formed by Tyr385, Trp387 and Phe518. In our opinion, this convincingly explains the observed additive effect of the two substituents.

Table 1
COX inhibition data for compounds **4**, **8**–**36** investigated in this work.



Compound	Ar	*R*	*R*′	Yield (%)	COX-1 % inh at 100 μM	COX-2 IC_{50}, μM
Indomethacin					73.5	87 %[a]
Celecoxib					21.7	98 %[a]
4	4-ClC_6H_4	Me	Me	52	−5.2	>10
8	4-FC_6H_4	Me	H	83	12.6	>10
9	4-FC_6H_4	Me	Me	62	6.3	>10
10	4-ClC_6H_4	Me	H	59	3.2	7.1
11	3-BrC_6H_4	Me	H	31	12.6	6.8
12	3-BrC_6H_4	Me	Me	24	11.1	>10
13	3-FC_6H_4	Me	H	25	0.7	>10
14	3-ClC_6H_4	Me	H	47	1.4	8.1
15	3-MeC_6H_4	Me	H	77	6.0	>10
16	3-F,4-$MeOC_6H_3$	Me	H	53	−1.6	>10
17	4-F,3-$MeOC_6H_3$	Me	H	52	−4.3	>10
18	3-Cl,4-$MeOC_6H_3$	Me	H	58	1.2	>10
19	3,4-diFC_6H_3	Me	H	49	9.2	>10
20	3,4-diClC_6H_3	Me	H	41	1.9	2.1
21	4-Cl,3-$F_3CC_6H_3$	Me	H	24	4.7	3.6
22	4-FC_6H_4	NH_2	H	73	11.4	6.9
23	4-FC_6H_4	NH_2	Me	36	5.5	>10
24	4-ClC_6H_4	NH_2	H	66	0.4	3.4
25	4-ClC_6H_4	NH_2	Me	51	3.2	>10
26	3-BrC_6H_4	NH_2	H	36	12.9	2.9
27	3-BrC_6H_4	NH_2	Me	64	20.2	>10
28	3-FC_6H_4	NH_2	H	61	−1.4	7.2
29	3-ClC_6H_4	NH_2	H	79	−8.0	2.5
30	3-MeC_6H_4	NH_2	H	37	1.5	>10
31	3-F,4-$MeOC_6H_3$	NH_2	H	68	−5.5	9.5
32	4-F,3-$MeOC_6H_3$	NH_2	H	66	−13.0	>10
33	3-Cl,4-$MeOC_6H_3$	NH_2	H	63	3.0	6.2
34	3,4-diFC_6H_3	NH_2	H	46	6.6	6.7
35	3,4-diClC_6H_3	NH_2	H	80	8.7	0.3
36	4-Cl,3-$F_3CC_6H_3$	NH_2	H	24	2.7	1.8

[a] % inhibition at the highest concentration tested (10 mM).

Since the level of COX-2 inhibition by the lead compound (**35**) was comparable to the clinically used compounds, we undertook no further optimization at this point and proceeded to investigate the pharmacokinetic profile of this compound. Pharmacokinetic assessment of compound **35** in mice at 10 mg/kg p.o. confirmed that for this compound, sufficiently high plasma levels (C_{max} = 16.6 μM corresponding to approximately 55 × its *in vitro* IC_{50}) can be achieved at that dosing [35]. Plasma volume of distribution of **35** was 1220 mL/kg, which corresponds to approximately 1.7 volume of the total body water and suggests broad distribution to extravascular liquids without significant tissue binding or deep penetration.

Mindful of the recent results that justify the need for brain-penetrating selective COX-2 inhibitors [10–15] we also performed assessment of the pharmacokinetic profile of compound **35** in brain tissue. The plasma and brain PK data are presented in Table 2. Apparently, the distribution into the brain for **35** is relatively low (only 4%). This is in accordance with the general wisdom with regard to the range of calculated properties that make BBB crossing more favorable [36]. Indeed, the molecular parameters critical for a good distribution into the brain appear to be borderline with respect to that range for compound **35** (Table 4) [37]. However, the C_{max} that was achieved on 10 mg/kg p.o. dosing corresponds to ~2×

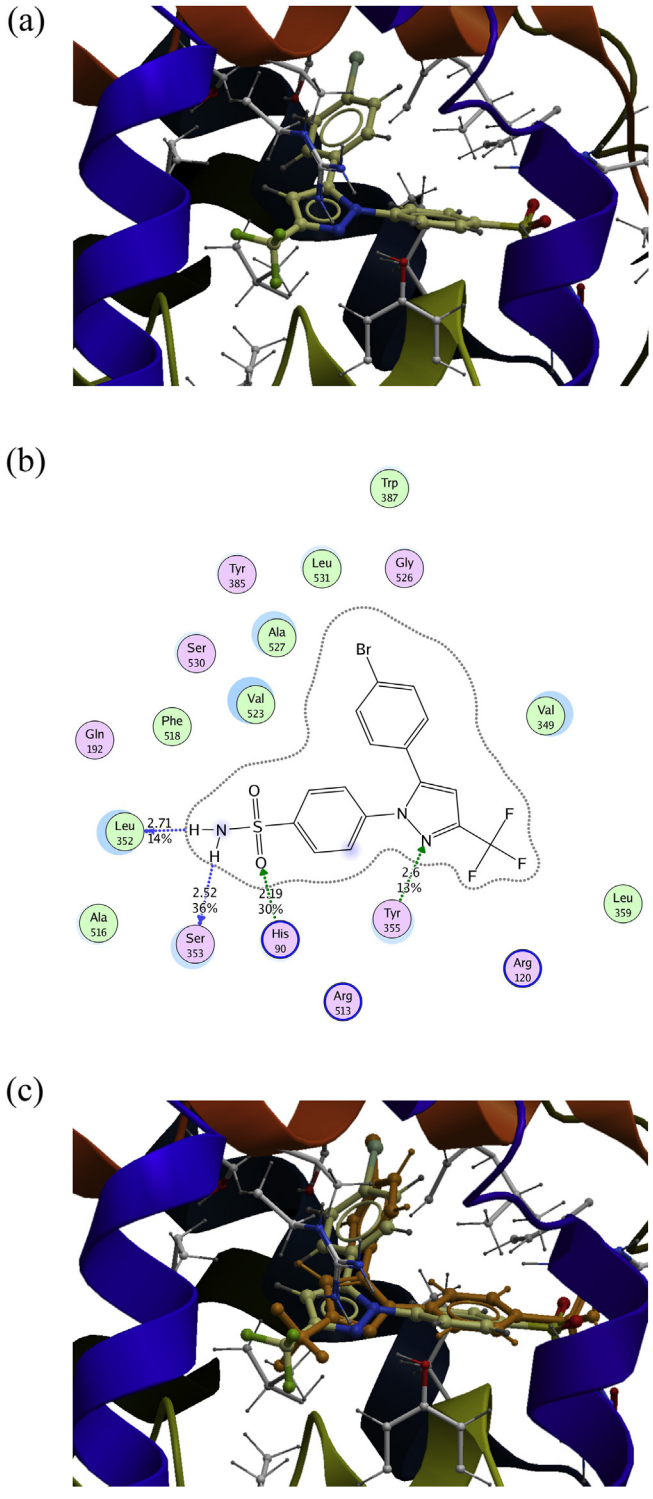


Fig. 4. Available crystal structure of COX-2 with a pyrazole inhibitor (a), key amino acid interactions (b), superposition (RMSD = 0.1) of co-crystallized (orange) and docked structures in COX-2 active site (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

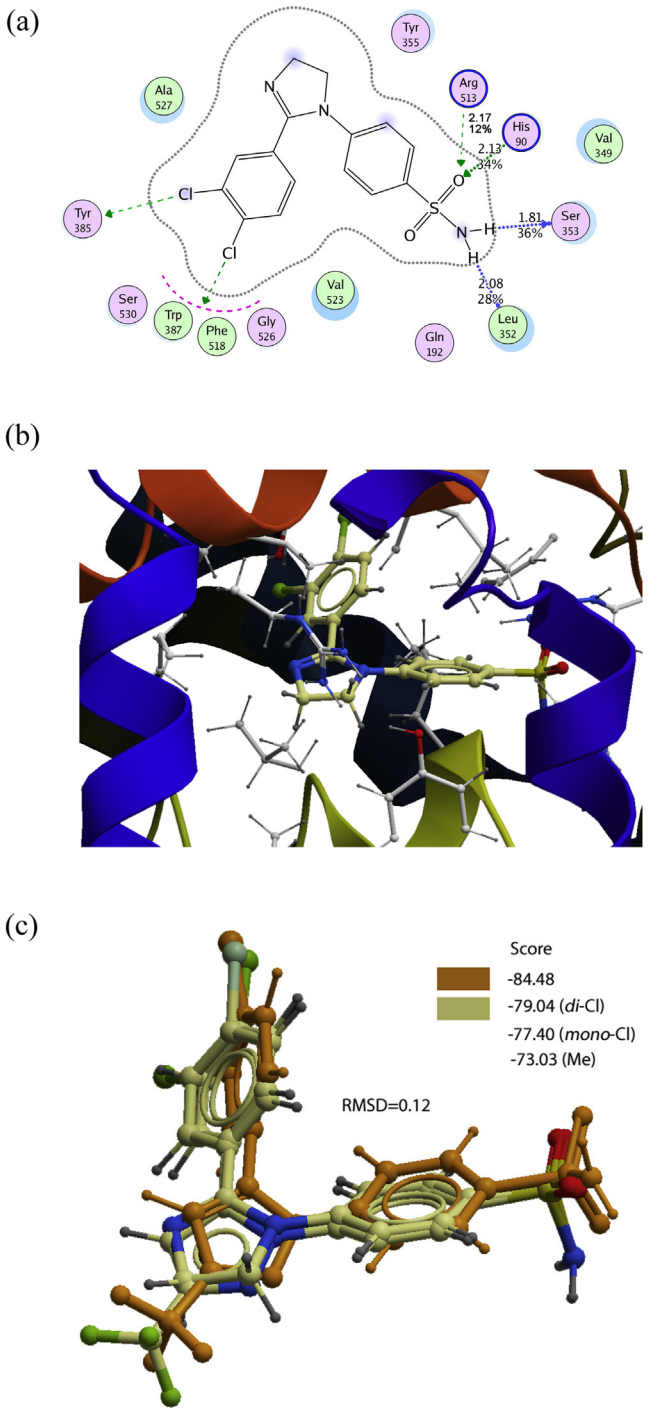


Fig. 5. Docking of compound **35** in the crystal structure of COX-2: contributing interactions with the key amino acid residues in 2D and 3D (a and b, respectively), superposition of compounds **35**, **29**, methylated analog of **35** (not prepared) and the reference pyrazole compound (orange) in COX-2 active site. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in vitro IC_{50} for this compound. Therefore, this compound can be viewed as a starting point for developing more advanced compounds for studying the effects of COX-2 inhibition in CNS, possibly at higher dosing. Low brain penetration, however, is traditionally considered an advantageous pharmacokinetic aspect as far as systemic anti-inflammatory applications are concerned [38]. Therefore, **35** can be considered as a new lead for COX-2 inhibitors that are based on a non-flat, polar heterocyclic core and that may serve as an effective substitute or follow-on to the existing systemically acting anti-inflammatory agents.

Table 2
Pharmacokinetic parameters of compound **35** determined in male C57Bl mice (10 mg/kg p.o.) in plasma and brain tissue.

	T_{max} (min)	C_{max} (ng/mL)	$AUC_{0\rightarrow240\ min}$ (ng min/mL)	$AUC_{0\rightarrow\infty}$ (ng min/mL)	$T_{1/2}$ (min)	V_d (mL/kg)	CL (mL/min/kg)
Plasma	5	6138	704,258	762,758	65	1220	13
Brain	30	267	29,471	31,489	58	nd	nd

The pharmacokinetic profile of compound **35** suggests its fairly slow systemic elimination (considering both the $T_{1/2}$ and CL values). In order to determine if potential cytochrome-mediated aromatization [25] of *in vivo* of this lead compound could be a contributing factor, we monitored the levels of a $[M-2]^+$ metabolite (i. e. the respective imidazole) in the same tissues. The PK profile of a putative imidazole metabolite is presented in Table 3. While the 'dehydroimidazoline' metabolite was indeed observable, it accumulation does not appear to be predominant and the majority of **35** survives the first-pass metabolic events and remains intact for exerting its COX-2 inhibitory effects, particularly in the first 2 h post dosing (i. e. until C_{max} for the imidazole metabolite is achieved).

While pharmacodynamic readouts and animal disease models relevant to COX-2 inhibition in the central nervous system remain to be established, assessment of systemic effects of COX-2 inhibition is a relatively routine undertaking [39]. In order to assess systemic anti-inflammatory effects of compound **35** *in vivo*, the carrageenan-induced mouse paw edema model was used. Intraperitoneal injection of 3.7 mg/kg of **35** in a vehicle led to a pronounced, statistically significant volume reduction of the inflamed mouse paw (56%), compared to the no-treatment control group (Figs. 5 and 6). Indomethacin that was used as an efficacy standard in this experiment provided 47% reduction at an equivalent dose.

3. Conclusions

While developing an alternative synthesis of a known imidazole-based selective COX-2 inhibitor [21], we became interested in exploring the potential of 2-imidazoline scaffold (which, in our approach, was an intermediate en route to imidazoles) for design of novel inhibitors of this clinically validated enzyme target. 2-Imidazolines, in particular, appeared as a daring addition to the existing COX-2 inhibitor space considering the widely accepted dogma that a non-polar, lipophilic core is required for COX-2 inhibitory potency [16]. Very few non-flat, non-aromatic cores have been studied so far in a similar context. Moreover, 2-imidazolines were expected to invigorate the field due to their basic character (and, hence, improved aqueous solubility) and a potential to cross the blood–brain barrier (similarly to AstraZeneca's amidine-based BACE-1 inhibitors [28]). A library of 30 2-imidazoline compounds was designed, synthesized and tested for COX inhibition. A lead compound (**35**) that displayed potency comparable to and selectivity superior to the clinically used NSAIDs was identified. It demonstrated a very good plasma pharmacokinetic profile in mice but only a modest distribution into the brain (4%). We have shown the metabolic conversion of our lead compound (presumably, to the corresponding imidazole) to be slow, thereby alleviating concerns of a fast CYP-mediated aromatization [25] of our inhibitors being a liability. The lead compound demonstrated a remarkable efficacy in reducing carrageenan-induced mouse paw edema. In conclusion, we have validated 2-imidazolines as a suitable, novel, polar, non-flat scaffold for the design of orally available, efficacious anti-inflammatory COX-2 inhibitors. The lead compound demonstrated some (though clearly not pronounced) potential for entering the CNS from the blood stream. The series will be developed and evaluated further in the context of novel therapeutic applications. In addition to that, potential cardiotoxicity of our new lead will be evaluated in cellular models, in comparison to the known cardiotoxic coxibs. The results of these studies will be reported in due course.

4. Experimental section

4.1. Cyclooxygenase inhibition assay

Inhibition by test compounds **4**, **8**–**36** of ovine COX-1 and human recombinant COX-2 (% inhibition at 100 μM and IC_{50} values (μM), respectively) was assessed using a COX Fluorescent Inhibitor Screening Assay Kit (catalog number 700100, Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. Stock solutions of test compounds were prepared in a minimum volume of DMSO. Briefly, to a series of supplied reaction buffer solutions (150 μl, 100 mM Tris–HCl, pH 8.0) with either COX-1 or COX-2 (10 μl) enzyme in the presence of Heme (10 μl) and fluorometric substrate (10 μl) were added 10 μl of various concentrations of the test compound solutions ($[I]_{final}$ between 0.01 and 100 μM). The reactions were initiated by quickly adding 10 μl of arachidonic acid solution and then incubated for 2 min at room temperature. Fluorescence of resorufin that is produced by the reaction between PGG_2 and the fluorometric substrate, ADHP (10-acetyl-3,7-dihydroxyphenoxazine) was read with an excitation wavelength of 535 nm and an emission wavelength of 590 nm. The intensity of this fluorescence is proportional to the amount of resorufin, which is proportional to the amount of PGG_2 present in the well during the incubation. Percent inhibition was calculated by comparison from the 100% initial activity sample value (no inhibitor). The concentration of the test compound causing 50% inhibition of COX-2 (IC_{50}, μM) was calculated from the concentration-inhibition response curve (triplicate determinations).

4.2. Pharmacokinetic experiments

Male C57Bl mice (~2 months old, body weight 18.1–23.6 g and average body weight across all groups – 20.7 g) were used in this study. The animals were randomly assigned to the treatment groups before the pharmacokinetic study; all animals were fasted overnight before dosing. Each of the treatment groups included 4 animals; there was also one plasma control group of 4 non-dosed animals. Dosing was done by peroral gavage. Animals were sacrificed by cervical dislocation and blood samples were withdrawn by

Table 3
Pharmacokinetic parameters of a putative aromatization metabolite corresponding to compound **35** in plasma and brain tissue.

	T_{max} (min)	C_{max} (ng/mL)	$AUC_{0\rightarrow240\ min}$ (ng min/mL)	$AUC_{0\rightarrow\infty}$ (ng min/mL)	$T_{1/2}$ (min)	CL (mL/min/kg)
Plasma	120	735	145,573	364,739	279	27
Brain	120	33	5969	8533	112	nd

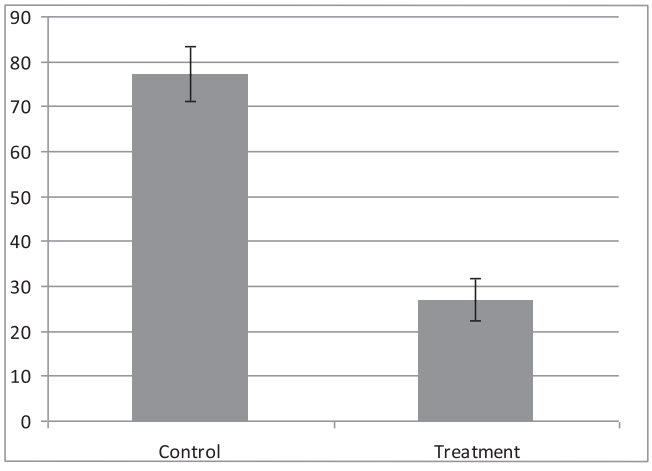
Table 4
Molecular parameters of **35** vs. the favorable range for high blood–brain barrier permeability.

Parameter	The target range	Compound **35**
PSA, Å^2	<90	84
HBD	<3	2
clog*P*	2–5	1.95
Mol. weight	450	370

intra-cardiac puncture. Blood samples were collected in EDTA tubes at pre-dose and 5, 15, 30, 60, 120 and 240 min post-dose. Plasma and whole brain samples were immediately prepared and stored frozen at −80 °C until further processing and bioanalysis.

Analyses of plasma and brain samples were conducted by high performance liquid chromatography-mass spectrometry (HPLC-MS) method. The LC system comprised a Shimadzu liquid chromatograph equipped with isocratic pumps (Shimadzu LC-10ADvp), an autosampler (Shimadzu SIL-HTc), a switching valve (FCV-14AH) and a degasser (Shimadzu DGU-14A). Mass spectrometric analysis was performed using an API 3000 (triple-quadrupole) instrument from AB Sciex (USA) with an electro-spray (ESI) interface. The data acquisition and system control was performed using Analyst 1.5.2 software from AB Sciex. Accessory equipment used: Mixer Lab Dancer (IKA, Germany); BMT-20-S tubes with stainless steel balls and ULTRA-TURRAX Tube Drive (IKA, Germany); Eppendorf 5417R centrifuge (USA), Sigma 4–15C centrifuge (USA), Barnstead NANOpure Diamond ultrapure-water generating system.

Plasma samples (0.050 mL) were transferred to 1.3 mL tube, mixed with 200 μl of the IS solutions (400 ng/ml). After mixing by pipetting five times and centrifuging for 5 min at 6000 rpm, 3 μl of each supernatant was injected into LC-MS system. Weighted brain samples (about 0.4 g) were placed into BMT-20-S tubes, five stainless steel balls (5 mm diameter) and 5 mL of homogenization solvent (67% methanol) were added to each tube. Following solvent addition, samples were homogenized using an ULTRA-TURRAX Tube Drive for 2 min at the speed set up to position 6. Thereafter, 0.75 mL of the homogenate was centrifuged for 5 min at 5 °C and 14,000 rpm (20,817 rcf); 500 μl of the supernatants obtained were mixed in microtubes with 20 μl of the IS solution (5000 ng/ml in 67% methanol) by pipetting up and down 5 times. To construct calibration curve, 500 μl aliquots of the supernatant of a blank brain were mixed with 20 μl of corresponding working standard solution and 20 μl of the IS solution.



[a] Expressed in CPE% values calculated as described in Experimental Section

Fig. 6. Carrageenan-induced mouse paw edema reduction[a] achieved by administration of **35** (3.7 mg/kg i.p.).

4.3. Carrageenan-Induced Mouse Paw Edema Model [40]

Edema was induced in the right hind paw of mice (AKR) by the intradermal injection of 0.05 mL of 2% carrageenan in water. Both sexes were used, but pregnant females were excluded. Each group was composed of 6–10 animals. The animals, which have been bred in our laboratory, were housed under standard conditions and received a diet of commercial food pellets and water ad libitum prior to experimentation, but they were fasted during the experimental period. The tested compounds (0.01 mmol/kg body weight) were suspended in water with a few drops of Tween-80 and ground in a mortar before use and were given intraperitoneally simultaneously with the carrageenan injection. The mice were euthanized 3.5 h after the carrageenin injection. The difference between the weight of the injected and uninjected paws was calculated for each animal. It was compared with that in control animals (treated with water) and expressed as a percent inhibition of the edema CPE% values. Each experiment was performed in duplicate, and the standard deviation was less than 10%.

4.4. Docking studies

3D Molecular docking study was performed in ICM Pro Software [41] on the basis of X-Ray data obtained for COX-2/1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole complex (PDB ID - 6COX) [7]. The model was properly *self*- and *cross*-validated using analogues structures (PDB ID – 3NTG, 6COX, 1CX2) and indomethacin (PDB ID – 6COX). Other reference compounds have been docked successfully as well, with high similarity to the available X-Ray data. Internal Coordinate Mechanics (ICM) was used for modeling. A rigid ICM model of the protein was constructed on the basis of PDB standard coordinates using the ICM conversion procedure. The resulting 3D map was calculated with a grid size of 0.5 Å, step of 0.5 Å, and size of 119,756.

The potential fit of compounds into the active site of COX-2 was then assessed using the constructed model. For each molecule, at least ten different conformations were generated in ICM-Pro. All conformations from the output were within a particular range around the minimum of the potential energy. For assessment we used internal "*score*" functions calculated automatically in ICM-Pro. Generally, a score of −30 or lower was considered good, depending on the receptor (e.g., exposed pockets or pockets with metal ions may give scores higher than −30). All scores generated were thoroughly analyzed and of these values, we have selected the best score for the conformation that is most closely related to the template supramolecular interface was selected.

4.5. Chemistry general procedures

All chemicals and solvents were used as received from the suppliers. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets. Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Varian Unity INOVA 500 MHz spectrometer. Chemical shifts for nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm, δ) using the residual solvent peak(s) as internal standard. Splitting patterns are described as singlet (s), doublet (d),

triplet (t), quartet (q), multiplet (m), broad (br), doublets of doublet (dd). High resolution mass spectra (HRMS) were acquired using a Fourier Transform Ion Cyclotron Resonance spectrometer fitted with an electrospray source and operating in positive ion mode.

4.5.1. General procedure 1

Ethylenediamine (10.5 mmol) was added to a stirred solution of aldehyde (10.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the resulting solution was stirred for 20 min. *N*-bromosuccinimide (10.5 mmol) was then added in portions over 10 min. The reaction mixture was warmed to room temperature and stirred for an additional 12 h, during which time a precipitate formed. A solution of KOH (1 M, 50 mL, 50 mmol) was added causing the precipitate to disappear and a clear biphasic solution was formed. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure to afford the crude product. The analytically pure imidazolines **7** were obtained by a brief crystallization from EtOAc/hexane. All imidazolines **7** used in subsequent Pd-catalyzed *N*-arylation are known compounds except for **7a**–**c**.

4.5.2. General procedure 2

A thick-glass screw-capped pressure tube (50 mL) was charged with a suspension of starting imidazoline (3.0 mmol), 1-bromo-4-(methylsulfonyl)benzene or 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide [21] (3.0 mmol), Cs_2CO_3 (3.0 mmol), and toluene (15 mL). $Pd(OAc)_2$ (0.12 mmol) and BINAP (0.24 mmol) were weighed as solids into a 10 mL screw-capped vial and toluene (8 mL) was added. The resulting suspension was heated at 110 °C until a clear purple solution was obtained. The latter was rapidly transferred, while still hot, to the screw-capped pressure tube using a Pasteur pipette. The reaction vessel was filled with argon, sealed, and the reaction mixture was vigorously stirred at 110 °C for 20 h. The reaction mixture was cooled to ambient temperature and filtered through a Celite pad. The latter was washed with copious amounts of EtOAc, and the combined filtrate and washings were evaporated to dryness. The crude material was briefly fractionated on silica (CH_2Cl_2:MeOH, 95:5) and the fractions containing the *N*-aryl 2-imidazolines were collected and evaporated to dryness. The residue was either purified further by chromatography under the same conditions (methylsulfone compounds **8**–**21**) or taken forward to the next step without further purification.

4.5.3. General procedure 3

A 0 °C solution of DMB-protected sulphonamides obtained according to General Procedure 2 in CH_2Cl_2 (10 mL) was treated with dropwise addition of neat TFA (3 mL) at 0 °C. The stirring continued at the same temperature for 30–60 min. The excess TFA was neutralized with sat. aq. $NaHCO_3$, the organic layer was separated and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica using an appropriate gradient of MeOH in CH_2Cl_2 as eluent to provide sulfonamide products **22**–**36**.

4.5.4. 2-(3-Fluoro-4-methoxyphenyl)-4,5-dihydro-1H-imidazole (**7a**)

Prepared according to General procedure 1 commencing with 3-fluoro-4-methoxybenzaldehyde. Yellow solid was obtained.

Yield 1.22 g (63%). MP 148–150 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64–7.59 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.58 (s, 4H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 150.8 (d, $J_{C\text{-}F}$ = 243.7 Hz), 148.6 (d, $J_{C\text{-}F}$ = 10.7 Hz), 123.8 (d, $J_{C\text{-}F}$ = 4.0 Hz), 123.4 (d, $J_{C\text{-}F}$ = 6.7 Hz), 114.4 (d, $J_{C\text{-}F}$ = 18.9 Hz), 113.2 (d, $J_{C\text{-}F}$ = 1.7 Hz), 56.0, 49.5.

4.5.5. 2-(3,4-Dichlorophenyl)-4,5-dihydro-1H-imidazole (**7b**)

Prepared according to General Procedure 1 commencing with 3,4-dichlorobenzaldehyde. White solid was obtained.

Yield 946 mg (44%). MP 125–127 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 8.3, 2.0 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 3.80 (s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 134.5, 131.6, 131.1, 129.4, 128.6 (q, $J_{C\text{-}F}$ = 31.8 Hz), 126.2 (q, $J_{C\text{-}F}$ = 5.3 Hz), 122.5 (q, $J_{C\text{-}F}$ = 273.6 Hz), 50.4.

4.5.6. 2-[4-Chloro-3-(trifluoromethyl)phenyl]-4,5-dihydro-1H-imidazole (**7c**)

Prepared according to General Procedure 1 commencing with 4-chloro-3-(trifluoromethyl)benzaldehyde. White solid was obtained.

Yield 1.32 g (53%). MP 116–118 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.10 (br s, 1H), 3.62 (s, 4H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 161.5, 132.7, 131.02, 130.98, 130.5, 128.7, 127.1, 49.6.

4.5.7. 2-(4-Chlorophenyl)-4-methyl-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-imidazole (**4**)

Prepared as according to General Procedure 2 starting from 2-(4-chlorophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [42] and 1-bromo-4-(methylsulfonyl)benzene a yellow oil was obtained.

Yield 544 mg (52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.39–4.32 (m, 1H), 4.20 (t, J = 9.2 Hz, 1H), 3.70 (dd, J = 9.2, 7.9 Hz, 1H), 3.01 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 146.8, 136.7, 133.2, 129.9, 129.1, 128.9, 128.3, 120.2, 60.0, 59.9, 44.6, 21.8.

HRMS *m/z* calcd for $C_{17}H_{18}ClN_2O_2S$ $(M+H)^+$ 349.0772 found 349.0768.

4.5.8. 2-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**8**)

Prepared as according to General Procedure 2 starting from 2-(4-fluorophenyl)-4,5-dihydro-1*H*-imidazole [43] and 1-bromo-4-(methylsulfonyl)benzene. A yellow oil was obtained.

Yield 792 mg (83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.51–7.43 (m, 2H), 7.07–7.00 (m, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.15–4.03 (m, 3H), 2.99 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (d, $J_{C\text{-}F}$ = 251.4 Hz), 159.8, 146.8, 133.1, 130.5 (d, $J_{C\text{-}F}$ = 8.6 Hz), 128.7, 128.2, 127.9, 126.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 126.7, 120.3, 117.9, 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 53.1, 53.0, 44.5.

HRMS *m/z* calcd for $C_{16}H_{16}FN_2O_2S$ $(M+H)^+$ 319.0911 found 319.0977.

4.5.9. 2-(4-Fluorophenyl)-4-methyl-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**9**)

Prepared as according to General Procedure 2 starting from 2-(4-fluorophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [44] and 1-bromo-4-(methylsulfonyl)benzene. A white solid was obtained.

Yield 619 mg (62%). MP = 63–65 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.48 (dd, J = 8.6, 5.5 Hz, 2H), 7.04 (dd, J = 8.6, 5.5 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.37–4.28 (m, 1H), 4.19 (t, J = 9.2 Hz, 1H), 3.70 (dd, J = 9.2, 7.9 Hz, 1H), 3.00 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (d, $J_{C\text{-}F}$ = 251.4 Hz), 158.5, 146.9, 133.1, 130.7 (d, $J_{C\text{-}F}$ = 8.6 Hz), 128.3, 126.8, 120.2, 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 59.9, 59.8, 44.6, 21.8.

HRMS *m/z* calcd for $C_{17}H_{18}FN_2O_2S$ $(M + H)^+$ 333.1068 found 333.1063.

4.5.10. 2-(4-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**10**)

Prepared as according to General Procedure 2 starting from 2-(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole [45] and 1-bromo-4-(methylsulfonyl)benzene. A yellow oil was obtained.

Yield 593 mg (59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 4.17–4.01 (m, 4H), 3.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 146.8, 136.6, 133.3, 129.8, 129.2, 128.9, 128.3, 120.3, 53.2, 53.0, 44.5.

HRMS *m/z* calcd for $C_{16}H_{16}ClN_2O_2S$ $(M+H)^+$ 335.0916 found 335.0611.

4.5.11. 2-(3-Bromophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**11**)

Prepared as according to General Procedure 2 starting from 2-(3-bromophenyl)-4,5-dihydro-1*H*-imidazole [46] and 1-bromo-4-(methylsulfonyl)benzene. A light yellow solid was obtained.

Yield 352 mg, 31%; MP = 66–68 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.68 (m, 3H), 7.61–7.54 (m, 1H), 7.35–7.30 (m, 1H), 7.21 (t, J = 7.9 HZ, 1H), 6.79 (d, J = 8.2 Hz, 2H), 4.18–4.02 (m, 4H), 3.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 146.6, 133.6, 133.4, 132.8, 131.4, 130.1, 128.4, 127.0, 122.7, 120.3, 53.3, 53.0, 44.6.

HRMS *m/z* calcd for $C_{16}H_{16}BrN_2O_2S$ $(M + H)^+$ 379.0110 found 379.0105.

4.5.12. 2-(3-Bromophenyl)-4-methyl-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**12**)

Prepared as according to General Procedure 2 starting from 2-(3-bromophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [47] and 1-bromo-4-(methylsulfonyl)benzene. A white solid was obtained.

Yield 283 mg (24%); MP = 118–120 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.58–7.54 (m, 1H), 7.34–7.30 (m, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 8.6 Hz, 2H), 4.42–4.33 (m, 1H), 4.20 (t, J = 9.2 Hz, 1H), 3.70 (dd, J = 9.2, 8.0 Hz, 1H), 3.01 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 146.7, 133.6, 133.3, 132.8, 131.5, 130.1, 128.3, 127.1, 122.8, 120.1, 60.1, 59.8, 44.6, 21.8.

HRMS *m/z* calcd for $C_{17}H_{18}BrN_2O_2S$ $(M + H)^+$ 393.0267 found 393.0261.

4.5.13. 2-(3-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**13**)

Prepared as according to General Procedure 2 starting from 2-(3-flurophenyl)-4,5-dihydro-1*H*-imidazole [48] and 1-bromo-4-(methylsulfonyl)benzene. A light yellow solid was obtained.

Yield 239 mg (25%); MP = 119–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 2H), 7.36–7.29 (m, 1H), 7.25–7.19 (m, 2H), 7.16–7.10 (m, 1H), 6.78 (d, J = 7.7 Hz, 2H), 4.17–4.05 (m, 4H), 3.00 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}F}$ = 247.6 Hz), 159.7, 146.7, 133.3, 132.9 (d, $J_{C\text{-}F}$ = 7.8 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.3, 124.2 (d, $J_{C\text{-}F}$ = 3.2 Hz), 120.3, 117.6 (d, $J_{C\text{-}F}$ = 21.2 Hz), 115.6 (d, $J_{C\text{-}F}$ = 23.2 Hz), 53.3, 53.0, 44.6.

HRMS *m/z* calcd for $C_{16}H_{16}FN_2O_2S$ $(M + H)^+$ 319.0911 found 319.0903.

4.5.14. 2-(3-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**14**)

Prepared as according to General Procedure 2 starting from 2-(3-chlorophenyl)-4,5-dihydro-1*H*-imidazole [49] and 1-bromo-4-(methylsulfonyl)benzene. A light orange solid was obtained.

Yield 471 mg (47%); MP = 131–133 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8 Hz, 2H), 7.56 (s, 1H), 7.44–7.40 (m, 1H), 7.32–7.26 (m, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.18–4.07 (m, 4H), 3.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 146.6, 134.7, 133.3, 132.6, 130.6, 129.8, 128.5, 128.3, 126.5, 120.2, 53.2, 53.0, 44.6.

HRMS *m/z* calcd for $C_{16}H_{16}ClN_2O_2S$ $(M + H)^+$ 335.0616 found 335.0607.

4.5.15. 1-(4-(Methylsulfonyl)phenyl)-2-m-tolyl-4,5-dihydro-1H-imidazole (**15**)

Prepared as according to General Procedure 2 starting from 2-(*m*-tolyl)-4,5-dihydro-1*H*-imidazole [50] and 1-bromo-4-(methylsulfonyl)benzene. A yellow solid was obtained.

Yield 725 mg (77%); MP = 74–74 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, 2H), 7.40 (s, 1H), 7.28–7.15 (m, 3H), 6.81 (d, J = 8.8 Hz, 2H), 4.17–4.06 (m, 4H), 3.01 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 146.7, 138.6, 131.3, 128.9, 128.8, 128.4, 128.1, 128.1, 125.4, 120.1, 52.8, 52.7, 44.5, 21.2.

HRMS *m/z* calcd for $C_{17}H_{19}N_2O_2S$ $(M + H)^+$ 315.1162 found 315.1154.

4.5.16. 2-(3-Fluoro-4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**16**)

Prepared as according to General Procedure 2 starting from 2-(3-fluoro-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole (**7a**) and 1-bromo-4-(methylsulfonyl)benzene. A yellow oil was obtained.

Yield 556 mg (53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.9 Hz, 2H), 7.27–7.18 (m, 2H), 6.94–6.90 (m, 1H), 6.82 (d, J = 8.9 Hz, 2H), 4.15–4.03 (m, 4H), 3.92 (s, 3H), 3.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 151.8 (d, $J_{C\text{-}F}$ = 247.6 Hz), 149.6, 149.5, 147.1, 133.2, 128.2, 125.0 (d, $J_{C\text{-}F}$ = 3.7 Hz), 123.3, 120.4, 116.3 (d, $J_{C\text{-}F}$ = 19.9 Hz), 113.1, 113.0, 56.2, 43.1, 43.2, 44.6.

HRMS *m/z* calcd for $C_{17}H_{18}FN_2O_3S$ $(M + H)^+$ 349.1017 found 349.1007.

4.5.17. 2-(4-Fluoro-3-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**17**)

Prepared as according to General Procedure 2 starting from 2-(*4-fluoro-3-methoxyphenyl*)-4,5-dihydro-1*H*-imidazole [44] and 1-bromo-4-(methylsulfonyl)benzene. A light yellow oil was obtained.

Yield 543 mg (52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.23–7.17 (m, 1H), 7.03–6.96 (m, 1H), 6.92–6.86 (m, 1H), 6.79 (d, J = 8.8 Hz, 2H), 4.14–4.03 (m, 4H), 3.82 (s, 3H), 2.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 153.6 (d, $J_{C\text{-}F}$ = 251.3 Hz), 147.8 (d, $J_{C\text{-}F}$ = 10.9 Hz), 146.9, 133.2, 128.2, 127.0 (d, $J_{C\text{-}F}$ = 4.4 Hz), 121.4 (d, $J_{C\text{-}F}$ = 7.2 Hz), 120.4, 116.1 (d, $J_{C\text{-}F}$ = 19 Hz), 113.6 (d, $J_{C\text{-}F}$ = 2.1 Hz), 56.2, 53.1, 53.0, 44.5.

HRMS *m/z* calcd for $C_{17}H_{18}FN_2O_3S$ $(M + H)^+$ 349.1017 found 349.1008.

4.5.18. 2-(3-Chloro-4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**18**)

Prepared as according to General Procedure 2 starting from 2-(*3-chloro-4-methoxyphenyl*)-4,5-dihydro-1*H*-imidazole [23] and 1-bromo-4-(methylsulfonyl)benzene. A yellow oil was obtained.

Yield 633 mg (58%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 2.1 Hz, 1H), 7.29 (dd, J = 8.5, 2.1 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.15–4.03 (m 4H), 3.93 (s, 3H), 3.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 147.1, 133.2, 130.4, 128.3, 128.2, 123.7, 122.8, 120.4, 111.6, 56.2, 53.1, 53.0, 44.6.

HRMS *m/z* calcd for $C_{17}H_{18}ClN_2O_3S$ $(M + H)^+$ 365.0721 found 365.0712.

4.5.19. 2-(3,4-Difluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**19**)

Prepared as according to General Procedure 2 starting from 2-(*3,4-difluorophenyl*)-4,5-dihydro-1*H*-imidazole [48] and 1-bromo-4-(methylsulfonyl)benzene. A light yellow solid was obtained.

Yield 494 mg (49%); MP = 125–126 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 2H), 7.40–7.33 (m, 1H), 7.24–7.18 (m, 1H), 7.16–7.10 (m, 1H), 6.80 (d, J = 8.8 Hz, 2H), 4.16–4.04 (m, 4H), 3.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 151.7 (dd, $J_{C\text{-}F}$ = 253.7, 12.5 Hz), 150.2 (dd, $J_{C\text{-}F}$ = 250.4, 12.9 Hz), 146.7, 133.6, 128.4, 127.7 (dd, $J_{C\text{-}F}$ = 6.0, 3.9 Hz), 125.1 (dd, $J_{C\text{-}F}$ = 6.8, 3.8 Hz), 120.5, 117.8 (dd, $J_{C\text{-}F}$ = 20.3, 18.3 Hz), 53.3, 53.2, 44.6.

HRMS *m/z* calcd for $C_{16}H_{15}F_2N_2O_2S$ $(M + H)^+$ 337.0817 found 337.0808.

4.5.20. 2-(3,4-Dichlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**20**)

Prepared as according to General Procedure 2 starting from 2-(3,4-dichlorophenyl)-4,5-dihydro-1*H*-imidazole (**7b**) and 1-bromo-4-(methylsulfonyl)benzene. A light yellow solid was obtained.

Yield 453 mg (41%); MP = 158–160 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 1.7, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 1.7, 1H), 6.80 (d, J = 8.3 Hz, 2H), 4.16–4.05 (m, 4H), 3.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 146.6, 134.9, 133.7, 133.1, 130.7, 130.6, 130.4, 128.4, 127.5, 120.5, 53.4, 53.2, 44.6.

HRMS *m/z* calcd for $C_{16}H_{15}Cl_2N_2O_2S$ $(M + H)^+$ 369.0226 found 369.0216.

4.5.21. 2-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (**21**)

Prepared as according to General Procedure 2 starting from 2-[4-chloro-3-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-imidazole (**7c**) and 1-bromo-4-(methylsulfonyl)-benzene. A light yellow solid was obtained.

Yield 289 mg (24%); MP = 153–155 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.52–7.45 (m, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.18–4.06 (m. 4H), 3.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 146.6, 134.6, 134.1, 132.5, 131.7, 129.6, 129.0 (q, $J_{C\text{-}F}$ = 31.8 Hz), 128.5, 127.9 (q, $J_{C\text{-}F}$ = 5.3 Hz), 122.3 (q, $J_{C\text{-}F}$ = 273.6 Hz), 120.8, 53.4, 53.3, 44.6.

HRMS *m/z* calcd for $C_{17}H_{15}ClF_3N_2O_2S$ $(M + H)^+$ 403.0489 found 403.0478.

4.5.22. 4-(2-(4-Fluorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**22**)

Prepared as according to General Procedures 2 and 3 starting from 2-(4-fluorophenyl)-4,5-dihydro-1*H*-imidazole [43] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A light yellow solid was obtained.

Yield 700 mg (73%); MP = 94–96 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, 2H), 7.50–7.45 (m, 2H), 7.07–7.02 (m, 2H), 6.75 (d, J = 8.8 Hz, 2H), 4.91 (br s, 2H), 4.15–4.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (d, $J_{C\text{-}F}$ = 251.4 Hz), 160.1, 146.2, 134.9, 130.6 (d, $J_{C\text{-}F}$ = 8.6 Hz), 127.4, 126.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 120.5, 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 53.13, 53.11.

HRMS *m/z* calcd for $C_{15}H_{15}FN_3O_2S$ $(M + H)^+$ 320.0864 found 320.0860.

4.5.23. 4-(2-(4-Fluorophenyl)-4-methyl-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**23**)

Prepared as according to General Procedures 2 and 3 starting from 2-(4-fluorophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [44] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)-benzenesulfonamide. A yellow solid was obtained.

Yield 360 mg (36%); MP = 157–159 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.86–7.82 (m, 2H), 7.57–7.53 (m, 2H), 7.26–7.19 (m, 4H), 4.63–4.53 (m 2H), 4.14–4.06 (m 1H), 1.56–1.51 (m, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 166.7 (d, $J_{C\text{-}F}$ = 254.0 Hz), 164.2, 143.3, 142.8, 133.1 (d, $J_{C\text{-}F}$ = 9.4 Hz), 128.6, 125.5, 117.5 (d, $J_{C\text{-}F}$ = 22.6 Hz), 61.3, 55.8, 20.9.

HRMS *m/z* calcd for $C_{16}H_{17}FN_3O_2S$ $(M + H)^+$ 334.1020 found 334.1016.

4.5.24. 4-(2-(4-Chlorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**24**)

Prepared as according to General Procedures 2 and 3 starting from 2-(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole [45] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A yellow solid was obtained.

Yield 663 mg (66%); MP = 141–143 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.81 (d, J = 8.8 Hz, 2H), 7.54–7.46 (m, 4H), 7.08 (d, J = 8.8 Hz, 2H), 4.36 (t, J = 9.9 Hz, 2H), 4.14 (t, J = 9.9 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 163.9, 145.0, 140.7, 1387, 131.5, 130.1, 128.4, 128.3, 123.7, 54.3, 51.1.

HRMS *m/z* calcd for $C_{15}H_{15}ClN_3O_2S$ $(M + H)^+$ 336.0568 found 336.0564.

4.5.25. 4-(2-(4-Chlorophenyl)-4-methyl-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**25**)

Prepared as according to General Procedures 2 and 3 starting from 2-(4-chlorophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [42] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)-benzenesulfonamide. A light brown solid was obtained.

Yield 534 mg (51%); MP = 160–162 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.85 (d, J = 8.7 Hz, 2H), 7.53–7.47 (m, 4H), 7.26 (d, J = 8.7 Hz, 2H), 4.67–4.58 (m, 2H), 4.17–4.09 (m, 1H), 1.58–1.50 (m, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 164.3, 143.5, 142.5, 140.5, 132.0, 130.6, 128.6, 125.7, 124.5, 61.3, 55.6, 20.8.

HRMS *m/z* calcd for $C_{16}H_{17}ClN_3O_2S$ $(M + H)^+$ 350.0724 found 350.0719.

4.5.26. 4-(2-(3-Bromophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**26**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-bromophenyl)-4,5-dihydro-1*H*-imidazole [46] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A white solid was obtained.

Yield 409 mg (36%); MP = 194–194 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 8.8 Hz, 2H), 7.68–7.64 (m, 2H), 7.40–7.36 (m, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 4.20 (td, J = 9.3, 1.2 Hz, 2H), 4.05 (td, J = 9.3, 1.2 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 162.6, 146.2, 139.4, 134.8, 134.0, 132.3, 131.5, 128.5, 128.1, 123.5, 122.6, 54.1, 53.3.

HRMS *m/z* calcd for $C_{15}H_{15}BrN_3O_2S$ $(M + H)^+$ 380.0063 found 380.0057.

4.5.27. 4-(2-(3-Bromophenyl)-4-methyl-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**27**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-bromophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole [47] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)-benzenesulfonamide. A white solid was obtained.

Yield 755 mg (64%); MP = 180 °C (decomp.)

^{1}H NMR (500 MHz, CD_3OD) δ 7.91 (d, J = 8.7 Hz, 2H), 7.86–7.83 (m, 1H), 7.81–7.78 (m, 1H), 7.48–7.37 (m, 4H), 4.75–4.68 (m, 2H), 4.32–4.24 (m, 1H), 1.63–1.60 (m, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 164.7, 145.1, 141.0, 138.0, 133.2, 132.2, 129.3, 128.8, 126.7, 125.9, 124.0, 51.5, 54.0, 20.4.

HRMS *m/z* calcd for $C_{16}H_{17}BrN_3O_2S$ $(M + H)^+$ 394.0219 found 394.0214.

4.5.28. 4-(2-(3-Fluorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**28**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-fluorophenyl)-4,5-dihydro-1*H*-imidazole [48] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A white solid was obtained.

Yield 584 mg (61%); MP = 225–227 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.77–7.75 (m, 2H), 7.48–7.44 (m, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 6.97–6.96 (m, 2H), 4.24 (t, J = 9.6 Hz, 2H), 4.09 (t, J = 9.6 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 164.7 (d, $J_{C\text{-}F}$ = 244.6 Hz), 163.6, 147.1, 140.2, 134.9 (d, $J_{C\text{-}F}$ = 7.8 Hz), 132.6 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.9, 126.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 123.5, 117.4 (d, $J_{C\text{-}F}$ = 23.1 Hz), 119.4 (d, $J_{C\text{-}F}$ = 21.1 Hz), 54.9, 54.2.

HRMS *m/z* calcd for $C_{15}H_{15}FN_3O_2S$ $(M + H)^+$ 320.0864 found 320.0854.

4.5.29. 4-(2-(3-Chlorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**29**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-chlorophenyl)-4,5-dihydro-1*H*-imidazole [49] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A white solid was obtained.

Yield 794 mg (79%); MP = 188–190 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.76 (m, 2H), 7.54–7.56 (m, 2H), 7.44–7.38 (m, 2H), 6.98–6.96 (m, 2H), 4.25 (t, J = 9.4 Hz, 2H), 4.10 (t, J = 9.7 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 163.5, 147.1, 140.2, 136.5, 134.7, 132.6, 132.2, 130.5, 129.0, 128.9, 123.5, 55.0, 54.2.

HRMS *m/z* calcd for $C_{15}H_{15}ClN_3O_2S$ $(M + H)^+$ 336.0568 found 336.0560.

4.5.30. 4-(2-m-Tolyl-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**30**)

Prepared as according to General Procedures 2 and 3 starting from 2-(*m*-tolyl)-4,5-dihydro-1*H*-imidazole [50] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfonamide. A cream solid was obtained.

Yield 350 mg (37%); MP = 244–246 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 8.8 Hz, 2H), 7.37–7.26 (m, 3H), 7.22–7.18 (m, 1H), 6.99 (d, J = 8.8 Hz, 2H), 4.28 (t, J = 10.3 Hz, 2H), 4.07 (t, J = 10.3 Hz, 2H), 2.33 (s, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 164.7, 145.5, 140.1, 140.0, 133.1, 130.3, 130.2, 129.8, 128.1, 126.9, 123.1, 54.1, 51.4, 21.3.

HRMS *m/z* calcd for $C_{16}H_{18}N_3O_2S$ $(M + H)^+$ 316.1114 found 316.1107.

4.5.31. 4-(2-(3-Fluoro-4-methoxyphenyl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**31**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-Fluoro-4-methoxyphenyl)-4,5-dihydro-1H-imidazole (**7a**) and 4-bromo-*N,N-bis*(2,4-dimethoxy-benzyl)benzenesulfonamide. A yellow solid was obtained.

Yield 712 mg (68%); MP = 195–197 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.76 (m, 2H), 7.25 (t, J = 7.3 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.00–6.98 (m, 2H), 4.22 (t, J = 9.6 Hz, 2H), 4.06 (t, J = 9.6 Hz, 2H), 3.95 (s, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 163.6, 153.9 (d, $J_{C\text{-}F}$ = 245.3 Hz), 152.0 (d, $J_{C\text{-}F}$ = 10.6 Hz), 147.5, 140.1, 128.9, 127.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 124.8 (d, $J_{C\text{-}F}$ = 7.0 Hz), 123.7, 118.1 (d, $J_{C\text{-}F}$ = 20.0 Hz), 115.3, 57.6, 55.1, 53.8.

HRMS *m/z* calcd for $C_{16}H_{17}FN_3O_3S$ $(M + H)^+$ 350.0969 found 350.0960.

4.5.32. 4-(2-(4-Fluoro-3-methoxyphenyl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**32**)

Prepared as according to General Procedures 2 and 3 starting from 2-(4-Fluoro-3-methoxyphenyl)-4,5-dihydro-1H-imidazole [44] and 4-bromo-*N,N-bis*(2,4-dimethoxy-benzyl)benzenesulfonamide. A white solid was obtained.

Yield 691 mg (66%); MP = 248–249 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.79–7.76(m, 2H), 7.24 (dd, J = 8.1, 1.8 Hz, 1H), 7.14 (dd, J = 13.7, 8.3 Hz, 1H), 7.01–7.04 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 4.25 (t, J = 9.4 Hz, 2H), 4.09 (t, J = 10.3 Hz, 2H), 3.83 (s, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 164.1, 155.8 (d, $J_{C\text{-}F}$ = 249.1 Hz), 150.0 (d, $J_{C\text{-}F}$ = 11.3 Hz), 147.3, 140.1, 130.7, 128.8, 123.7, 123.6, 118.0 (d, $J_{C\text{-}F}$ = 19.0 Hz), 116.2 (d, $J_{C\text{-}F}$ = 1.8 Hz), 57.6, 54.9, 53.8.

HRMS *m/z* calcd for $C_{16}H_{17}FN_3O_3S$ $(M+H)^+$ 350.09693 found 350.0960.

4.5.33. 4-(2-(3-Chloro-4-methoxyphenyl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**33**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3-chloro-4-methoxyphenyl)-4,5-dihydro-1H-imidazole [23] and 4-bromo-*N,N-bis*(2,4-dimethoxy-benzyl)benzenesulfonamide. A white solid was obtained.

Yield 712 mg (63%); MP = 255–257 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, J = 8.6 Hz, 2H), 7.55 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 4.23 (t, J = 9.6 Hz, 2H), 4.06 (t, J = 9.2 Hz, 2H), 3.97 (s, 3H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 163.5, 159.3, 147.5, 140.1, 132.3, 130.8, 129.0, 125.4, 124.6, 123.6, 114.0, 57.7, 55.1, 53.8.

HRMS *m/z* calcd for $C_{16}H_{17}ClN_3O_3S$ $(M+H)^+$ 366.0674 found 366.0664.

4.5.34. 4-(2-(3,4-Difluorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**34**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3,4-difluorophenyl)-4,5-dihydro-1H-imidazole [48] and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfon-amide. A white solid was obtained.

Yield 465 mg (46%); MP = 177–179 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, J = 7.9 Hz, 2H), 7.46–7.44 (dd, J = 10.6, 8.9 Hz, 1H), 7.38–7.30 (m, 2H), 6.98 (d, J = 8.0 Hz, 2H), 4.24 (t, J = 9.8 Hz, 2H), 4.09 (t, J = 9.7 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 162.9, 153.8 (dd, $J_{C\text{-}F}$ = 251.8, 12.5 Hz), 152.2 (dd, $J_{C\text{-}F}$ = 248.6, 12.8 Hz), 147.1, 140.3, 129.8 (dd, $J_{C\text{-}F}$ = 6.3, 4.2 Hz), 129.0, 127.7 (dd, $J_{C\text{-}F}$ = 6.7, 3.7 Hz), 123.7, 119.9 (d, $J_{C\text{-}F}$ = 19.0 Hz), 119.7 (d, $J_{C\text{-}F}$ = 18.0 Hz), 55.1, 54.2.

HRMS *m/z* calcd for $C_{15}H_{14}F_2N_3O_2S$ $(M+H)^+$ 338.0769 found 338.0760.

4.5.35. 4-(2-(3,4-Dichlorophenyl)-4,5-dihydroimidazol-1-yl) benzenesulfonamide (**35**)

Prepared as according to General Procedures 2 and 3 starting from 2-(3,4-dichlorophenyl)-4,5-dihydro-1H-imidazole (**7b**) and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfon-amide. A white solid was obtained.

Yield 886 mg (80%); MP = 232–234 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.79–7.78 (m, 2H), 7.70 (s, 1H), 7.59–7.58 (m, 1H), 7.36–7.38 (m, 1H), 6.99–6.98 (m, 2H), 4.29–4.19 (m, 2H), 4.15–4.03 (m, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 155.8, 147.0, 140.5, 136.7, 134.7, 133.0, 132.8, 132.6, 130.3, 129.1, 123.7, 55.2, 54.3.

HRMS *m/z* calcd for $C_{15}H_{14}Cl_2N_3O_2S$ $(M+H)^+$ 370.0178 found 370.0169.

4.5.36. 4-(2-(4-Chloro-3-(trifluoromethyl)phenyl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**36**)

Prepared as according to General Procedures 2 and 3 starting from 2-[4-chloro-3-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-imidazole (**7c**) and 4-bromo-*N,N-bis*(2,4-dimethoxybenzyl)benzenesulfon-amide. A white solid was obtained.

Yield 786 mg (65%); MP = 215–217 °C.

^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (s, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.66–7.58 (m, 2H), 7.00 (d, J = 8.6 Hz, 2H), 4.27 (t, J = 9.7 Hz, 2H), 4.12 (t, J = 9.6 Hz, 2H), NH_2 protons in exchange.

^{13}C NMR (125 MHz, CD_3OD) δ 162.7, 147.0, 140.7, 136.2 (unresolved q, $J_{C\text{-}F}$ = 1.9 Hz), 135.5, 133.9, 132.1, 130.5 (q, $J_{C\text{-}F}$ = 31.8 Hz), 130.0 (q, $J_{C\text{-}F}$ = 5.1 Hz), 129.1, 124.7 (q, $J_{C\text{-}F}$ = 271.1 Hz), 123.9, 55.2, 54.4.

HRMS *m/z* calcd for $C_{16}H_{14}ClF_3N_3O_2S$ $(M + H)^+$ 404.0442 found 404.0431.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.07.023.

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