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Novel Imidazole Compounds as a New Series of Potent, Orally Active Inhibitors of 5-Lipoxygenase

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Abstract—Replacement of the dihydroquinolinone pharmacophore of Zeneca's ZD2138 by ionizable imidazolylphenyl moiety has lead to the discovery of a novel series of potent and orally active 5-lipoxygenase (5-LO) inhibitors. The synthesis and structure–activity relationship (SAR) of this series of compounds are described herein.

Introduction

Leukotrienes (LTs) have been implicated in a number of human disease states including asthma, rheumatoid arthritis, inflammatory bowel diseases and psoriasis. Accordingly, any agent that controls the release or actions of the LTs is expected to be of considerable therapeutic value for the treatment of acute and chronic inflammatory conditions.[1] ICI (ZENECA) has reported on methyl ether compounds as potent, selective and non-redox 5-LO inhibitors,[2] and in 1992 D2138 (ZD2138) entered phase II studies for asthma and rheumatoid arthritis.[3] While ZD2138 exhibited good activities in animal models of asthma and inflammation, the compound was not well orally absorbed and modifications to improve oral bioavailability by increasing solubility have been reported.[4–6] Herein, we present work on the development of ionizable imidazolylphenyl analogues which led to the identification of CJ-12,918 (**1g**), potent and orally active 5-LO inhibitor.

Results and Discussion

Compounds **1a**–**o** were obtained from phenols **3a**,**b**[3a] by condensation with the requisite benzyl alcohols under Mitsunobu reaction conditions (method A) or by alkylation with the appropriate benzyl chlorides using potassium carbonate in dimethylformamide (DMF) (method B) as shown in Scheme 1 and Table 1. Benzyl alcohols **2a**–**c**,**f** were prepared according to the literature.[7,8] Substituted imidazole benzyl alcohols **2e**,**i**,**k**–**o** were prepared by coupling the appropriate imidazole derivatives with ethyl 4-fluorobenzoate or with 4-fluorobenzonitrile followed by reduction to the corresponding benzyl alcohols (Scheme 2). Alcohol **2d** and **2h** were prepared from ethyl 4-(1*H*-imidazol-2-yl)benzoate by the selective methylation, and 4-(1*H*-imidazol-1-yl)-benzonitrile, respectively, by trifluoromethylation followed by reduction (Schemes 3 and 4).[9–11] For pharmacological evaluation all compounds, except **1i** and **1n**, were submitted as solids, free base or hydrochloride salt thereof.

The inhibitory activities of the compounds for 5-LO, 12-LO, and cyclooxygenase were routinely evaluated in vitro using heparinized human whole blood (HWB) quantitating LTB_4 as well as 5-HETE (5-hydroxyeicosa-6,8,11,14-tetraenoic acid), 12-HETE (12-hydroxyeicosa-5,8,10,14-tetraenoic acid) and HHT (12-hydroxy-heptadeca-5,8,10-trienoic acid), respectively.[12] The in vivo potency after orally administration of compounds to mice was determined by PAF (platelet activating factor)-induced thrombosis assay.[13] For selected compounds, inhibition of yeast-induced edema in rats was determined.[14]

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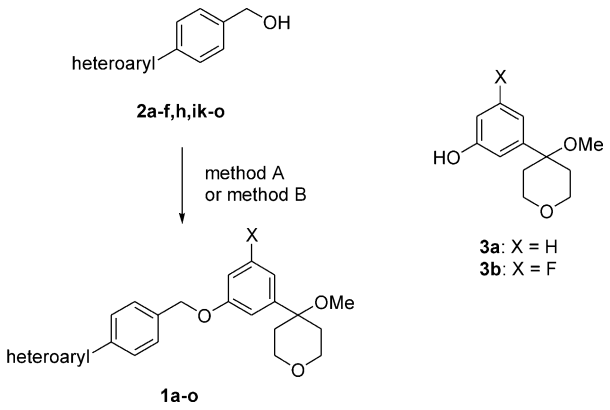
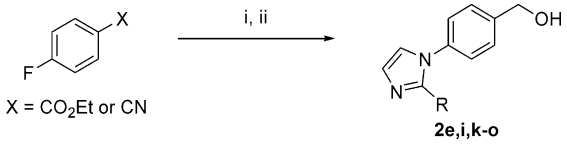
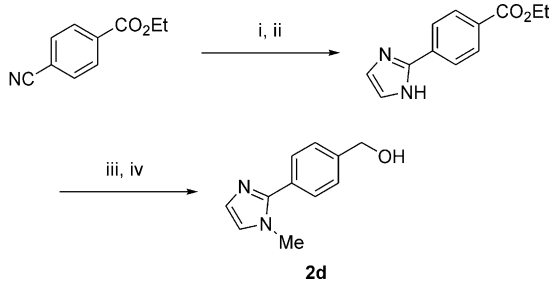


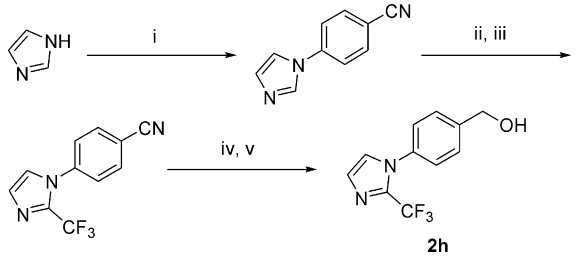
Scheme 1. Method A: **3a** or **3b**, DEAD, TEA, THF; Method B: (i) $SOCl_2$; (ii) **3b**, K_2CO_3, DMF. Generic groups presented as heteroaryl are defined in Table 1.



Scheme 2. (i) 2-R-1*H*-imidazole, base; (ii) Dibal-H, THF or Dibal-H, CH_2Cl_2 then $NaBH_4$, EtOH.

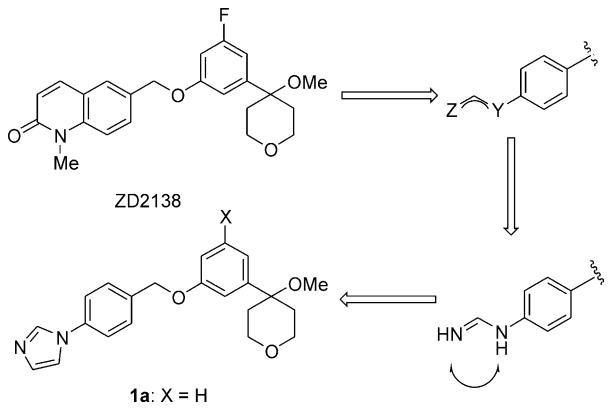


Scheme 3. (i) $NH_2CH_2CH_2NH_3^+$ 4-$MePhSO_3^-$; (ii) $BaMnO_4$; (iii) $MeOCOCO_2Me$, K_2CO_3; (iv) Dibal-H, CH_2Cl_2.



Scheme 4. (i) 4-fluorobenzonitrile, K_2CO_3, DMSO; (ii) *n*-BuLi, THF; (iii) TMS-CF_3, CuI, KF, DMF, 1-methyl-2-pyrrolidone; (iv) Dibal-H, CH_2Cl_2; (v) $NaBH_4$, EtOH.

The physicochemical profile of a drug, including solubility and permeability, inherently affects pharmacokinetics and structure–activity relationships (SAR).[15] When a drug is administered orally as solid, disintegration and dissolution of the drug in the gastrointestinal fluid are the initial steps in drug absorption, followed by absorption of the drug through the gastrointestinal tract. It has been reported that bioavailability of ZD2138 could be improved by enhancing aqueous solubility, viz., by reducing lipophilicity (log *P*) of compounds,[5,6] since high lipophilicity was thought to cause low aqueous solubility.[16] Since ZD2138 is structurally non-ionizable in the physiological pH range, (i.e., pH 1.4–8[17]) our strategy was to enhance aqueous solubility by incorporating an ionizable functional group into the drug molecule.[4]



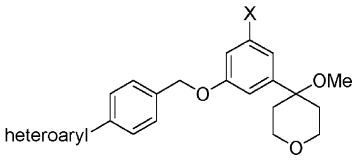
Scheme 5. Evolution of imidazole 5-LOI from ZD2138.

It has been reported that the position of the amidic fragment in the dihydroquinolinone ring of ZD2138, and analogues, is important for in vitro potency.[3a] We speculated that imidazol-1-yl would mimic the amide function of ZD2138 and introduce a basic ionizable center (Scheme 5). Imidazole **1a** was synthesized and, as anticipated, found to exhibit 5-LO inhibitor activity (HWB with an IC_{50} of 0.91 μM). To further test this hypothesis pyrrol-1-yl (**1b**), 1,2-pyrazol-1-yl (**1c**) and 1-methylimidazol-2-ly (**1d**) analogues were synthesized (Table 2). While **1b** ($IC_{50} = 1.7$ mM) had comparable in vitro activity to **1a**, the other compounds did not exhibit meaningful inhibitory activity (**1c**, 8% inhibition (5–11%, $n = 2$) at 1 μM; **1d**, 1% inhibition at 0.3 μM). On the other hand, while **1a** protected mice from PAF-induced thrombosis on oral dosing ($ED_{50} = 7$ mg/kg), **1b** was inactive at 30 mg/kg. Based on these findings, SAR studies around 1*H*-imidazol-1-yl compound **1a** were further pursued (Table 3).

Initial SAR was focused on potentiation of intrinsic inhibitory activity as assessed in the HWB assay. Two-substituted imidazole analogues showed 2–9-fold higher in vitro potency than **1a**, as exemplified by **1e**, **1i**, **1m**, **1n**, and **1o**. While small alkyl group (e.g., **1e** or **1i)** retained oral activities, those compounds with steric demanding substituent at position 2 (**1m**, **1n**, and **1o**) were inactive at the highest dose tested (30 mg/kg). Four-substituted imidazole analogues as exemplified by the 4-methyl regioisomer **1f** had significantly reduced in vitro potency (41% inhibition at 10 μM). In order to evaluate the effect of a fluorine atom (i.e., X = F in Table 2), which was reported to be important with ZD2138 and its analogues,[3a] we prepared fluoro derivatives (**1g**,**h**,**j**–**l**) but found that the fluorine substituent had only a marginal effect on potency (e.g., **1e** and **1i** with **1g** and **1j**, respectively).

Since **1g** (CJ-12,918) was one of the most potent compounds (HWB, LTB_4 $IC_{50} = 0.068 \pm 0.019$ μM, $n = 5$;

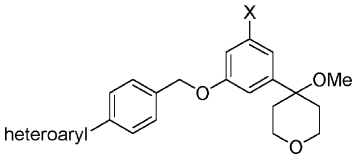
Table 1. Synthetic data for **1a–o**



No.	Heteroaryl[a]	Substituent[b]	X	2[c]	3[d]	Method[e]
1a	1-Im	—	H	**2a**	**3a**	A
1b	1-Pyrrolyl	—	H	**2b**	**3a**	A
1c	1-Pyrazolyl	—	H	**2c**	**3a**	A
1d	2-Im	1-Me	F	**2d**	**3b**	B
1e	1-Im	2-Me	H	**2e**	**3a**	A
1f	1-Im	4-Me	H	**2f**	**3a**	A
1g	1-Im	2-Me	F	**2e**	**3b**	B
1g HCl	1-Im	2-Me	F	**2e**	**3b**	B
1h	1-Im	2-CF_3	F	**2h**	**3b**	B
1i	1-Im	2-Et	H	**2i**	**3a**	A
1j HCl[f]	1-Im	2-Et	F	**2i**	**3b**	A
1k HCl[f]	1-Im	2-(1-Pr)	F	**2k**	**3b**	B
1l HCl[f]	1-Im	2-(2-Pr)	F	**2l**	**3b**	B
1m	1-Im	2-Ph	H	**2m**	**3a**	A
1n	1-Im	2-Bn	H	**2n**	**3a**	A
1o	1-Im	2-(2-Py)	H	**2o**	**3a**	A

[a]1-Im = 1*H*-imidazol-1-yl; 2-Im = 1*H*-imidazol-2-yl.
[b]Numbers hyphened to acronyms for substiutents indicate substitution position on heteroaryls.
[c]Syntheses are described in text.
[d]Structures are described in Scheme 1.
[e]Methods A and B are indicated in Scheme 1.
[f]Hydrochloride salt was the sole final form provided for biological evaluation.

Table 2. 5-LO Inhibitory activities for evolving azole series[a]



No.	Heteroaryl	X	HWB IC_{50} (μM) LTB_4[a]	PAF ED_{50} (mg/kg)[a]
1a		H	0.91	7
1b		H	1.7	>30
1c		H	(5, 10% inh. at 1 μM)	NT[b]
1d		F	(1% inh. at 0.3 μM)	>30

[a]Number of determinations was one otherwise mentioned.
[b]Not tested.

PAF-induced thrombosis, $ED_{50} = 4.3 \pm 0.9$ mg/kg, $n = 3, \pm$SD), it was selected for further characterization as the hydrochloride salt. No inhibition of 12-HETE or HHT was observed with **1g** HCl at the highest concentration (3 μM) tested, which corresponds to higher than 50-fold selectivity ratios for 5-LO compared to 12-LO and cyclooxygenase (Fig. 1). The in vitro activity was found to be comparable to that of ZD2138 (HWB, LTB_4 $IC_{50} = 0.047 \pm 0.09$ μM, no inhibition of 12-HETE or HHT at 3 μM, $n = 6$). Figure 2 shows the oral activity of **1g** HCl with an ED_{50} of 2.0 ± 1.0 mg/kg ($n = 3, \pm$SD) or 1.8 ± 0.9 mgA/mL (mgA indicates the weight in mg of **1g** calculated as free base) in the PAF-induced thrombosis model in mice. Furthermore, **1g** HCl inhibited yeast-induced foot edema formation in rats with an ED_{40} of 5 ± 2 mgA/kg po ($n = 3$, $\pm$SD), compared with 11 ± 3 mg/kg for ZD2138. Thus the elicited pharmacological activity suggested that **1g** would heal or alleviate inflammatory diseases mediated by 5-LO products.

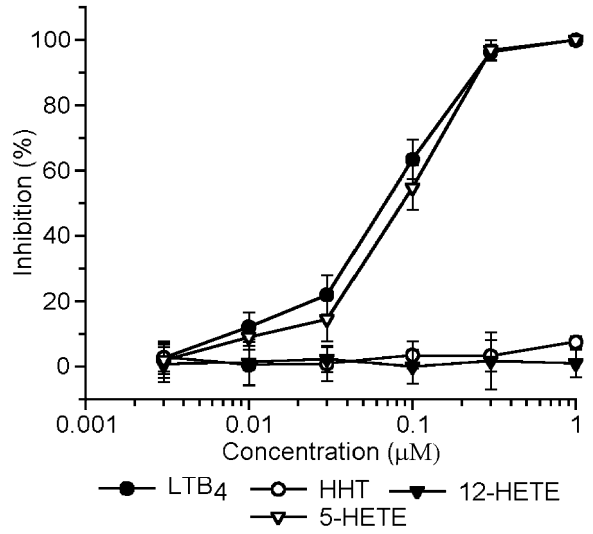


Figure 1. In vitro potency and selectivity of 1g HCl on production of 5-LO metabolites, LTB_4 and 5-HETE, cyclooxygenase and 12-LO metabolites, HHT and 12-HETE, respectively, in human whole blood stimulated with A23187. Each point represents the mean ± SEM ($n = 3$).

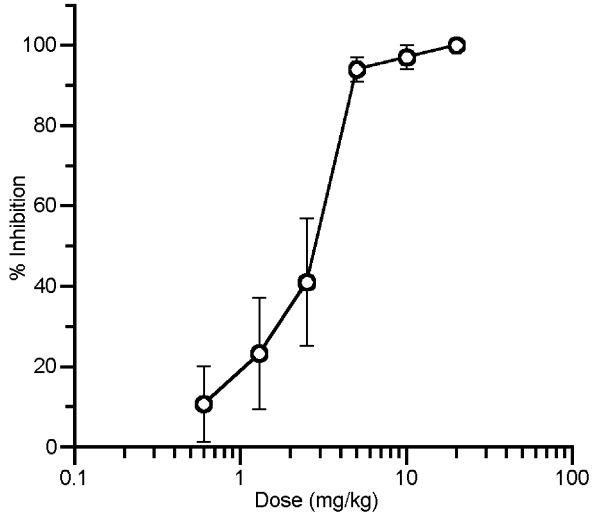


Figure 2. The effect of **1g** HCl inhibition on PAF-induced thrombosis in mice. The compound was perorally administered 45 min prior to PAF challenge. Each point represents the mean ± SEM ($n = 3$).

In Zeneca's publications they discussed the aqueous solubility issue of ZD2138 and its analogues, estimating the solubility of ZD2138 to be 1.5 μg/mL, which is close

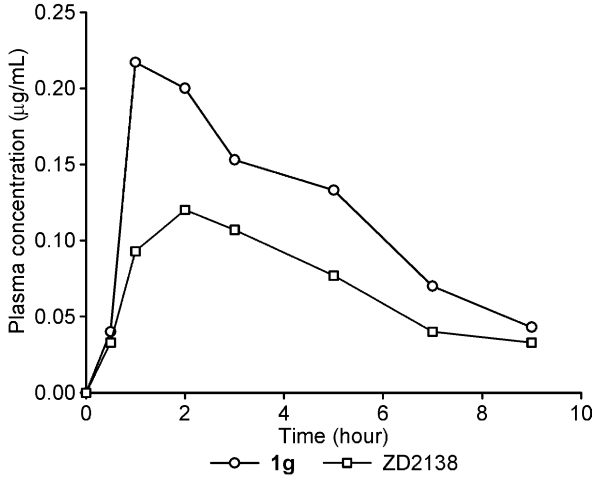
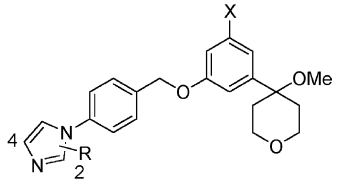


Figure 3. Mean serum concentration of **1g** HCl and ZD2138 in three male monkeys following oral administration (5 mgA/kg).

enough to the experimental data the authors obtained as shown in Table 4.[3] ZD2138, a neutral compound, was expected to show identical solubility throughout the physiologic pH range. In contrast, the solubilities of **1g** HCl were measured to be 4.2 mgA/mL and 1.8 μgA/mL in USP simulated gastric fluid without enzyme (pH 1.2) and in phosphate buffered saline (PBS) at pH 6.5, respectively. Since **1g** was basic enough with a pK_a of 6.9 to form hydrochloride salt, its solubility is suppose to be enhanced.[18] Furthermore, in order to assess the solubilization effects of bile salts and phospholilids, the solubility of **1g** HCl in sodium taurocholate (3 mM)/1-palmitoyl-2-oleoyl-L-α-phosphatidylcholine (0.75 mM) in PBS at pH 6.5 was measured to be 6.6 μgA/mL and found to be higher than that of ZD2138 (4.2 μgA/mL). Thus, our approach for improving solubility by incorporating an ionizable group was successful and was supposed to increase in vivo solubility of the series of compounds. The oral bioavailability in male cynomolgus monkeys of **1g** HCl was determined to be 13.0±4.1% ($n=3$, ±SD) from oral and iv studies at 5 mgA/kg po and 3 mgA/kg iv, compared to 8.60±1.20% for ZD2138 (Fig. 3 and Table 5).

Table 3. Substitution effect of imidazole ring on 5-LO inhibitory activity



no.	R[a]	X	HWB IC_{50} (μM) LTB_4[b]	PAF ED_{50} (mg/kg)[b]
1e	2-Me	H	0.13±0.02 (6)	7
1f	4-Me	H	41% inh. at 10 mM	>30
1g	2-Me	F	0.068±0.019 (5)	4.5±1.5 (4)
1g HCl	2-Me	F	0.060±0.017 (3)	2.0±1.0 (3)
1h	2-CF_3	F	0.83, 0.13	13
1i	2-Et	H	0.12	5
1j HCl	2-Et	F	0.050	5
1k HCl	2-(1-Pr)	F	0.085	9
1l HCl	2-(2-Pr)	F	0.12	10
1m	2-Ph	H	0.12	>30
1n	2-Bn	H	0.11	>30
1o	2-(2-Py)	H	0.40	>30

[a]Numbers hyphened to acronyms for R indicate substitution position on imidazole.
[b]IC_{50}'s and ED_{50}'s are shown with ±SD (number of determinations), where more than three determinations were made. Otherwise results based on single or two determinations are given.

Table 4. Comparison of Physicochemical Properties of CJ-12,918 hydrochloride (**1g** HCl) and ZD2138

	pK_a	log P	Solubility (mgA/mL)		
			pH 1.2[a]	pH 6.5[b]	NaTC/POPC[c]
1g HCl	6.9	3.7	4.2	0.0018	0.0066
ZD2138	—[d]	2.8[e]	0.0013	0.0012	0.0042

[a]Simulated gastric fluid (USP) without enzyme.
[b]Phosphate buffered saline (PBS).
[c]Sodium taurocholate (3 mM) and 1-palmitoyl-2-oleoyl-L-α-phosphatidylcholine (0.75 mM) in PBS at pH 6.5.
[d]Not exist in physiological pH range.
[e]Predicted with *ACD/LogP DB*, version 5.16; Advanced Chemistry Development Inc.: Toronto, Ontario, Canada, 2001.

Table 5. Comparison of Pharmacokinetic Parameters in Male Cynomolgus Monkeys of CJ-12,918 hydrochloride (**1g** HCl) and ZD2138 at 5 mgA/kg[a]

	C_{max} (μgA/mL)	AUC_{0-7} (μgAh/mL)	BA (%)[b]
1g HCl	0.22±0.12	0.84±0.29	13.0±4.1
ZD2138	0.12±0.00	0.56±0.05	8.60±1.20

[a]Mean±SD ($n=3$).
[b]5 mgA/kg po versus 3 mgA/kg iv.

Conclusion

Aiming improvement of oral absorption, incorporation of ionizable group into the known 5-LO inhibitor ZD2138 led to a novel series of imidazole compounds. From the series, CJ-12,918 (**1g** HCl) was discovered as an orally active 5-LO inhibitor, selective over 12-LO and cyclooxygenase and which was more soluble in the physiologic pH range than ZD2138. Compared to ZD2138, CJ-12,918 elicited comparable inhibitory potency in the in vitro HWB assay, and demonstrated improved activity in the in vivo rat foot edema test and superior pharmacokinetic parameters (bioavailability, C_{max}) in monkeys. CJ-12,918 was selected for development into clinical trials, however, was discontinued due to preclinical animal test, **1g** HCl toxicology findings.[19] SAR developed to circumvent these findings is the topic of a separate publication.[20]

Experimental

Biology. In vitro assay using heparinised human whole blood (HWB)

Inhibition has been demonstrated in vitro using heparinized human whole blood, which determines the inhibitory effect of compounds on 5-LO metabolism of arachidonic acid. Aliquots of heparinized human whole

blood (1 mL) from healthy donors were preincubated with drugs dissolved in DMSO (final concentration, 0.1%) for 10 min at 37 °C, then calcium ionophore A23187 (60 μL) and Heparapid (2.5%, Sekisui Chemical Co. LTD., Japan) were added. Incubation was then continued for a further 30 min. Reactions were terminated by rapid cooling in an ice bath. Blood-clots induced by the Heparapid were removed by centrifugation. CH_3CN (1.5 mL) and PGB_2 (500 ng, as an internal standard) were added to the supernatants. Samples were mixed by a Vortex mixer, and precipitated proteins were removed by centrifugation. Supernatants were diluted with water (7 mL) and were loaded onto a pre-washed Sep-Pak C_{18} cartridge (Waters Associates, Milford, MS, USA) and arachidonate metabolites were eluted with 70% methanol (4 mL). Methanolic extract was evaporated and the residue was then reconstituted in 100 μL of 50% aqueous ethanol.

Preconstituents (40 μL) were injected onto a reversed phase C_{18} column (Wakosil $5C_{18}$, 4.6×150 mm, Wako Pure Chemical Industries LTD, Japan). The column temperature was 40 °C. HPLC analysis was performed by Hewlett Packard model 1090HPLC. The chromatography was achieved using two different mobile phases as a gradient program (mobile A consisted of 10% acetonitrile, 0.1% trifluoroacetic acid and 0.5% triethylamine; mobile B consisted of 80% acetonitrile, 0.1% trifluoroacetic acid and 0.5% triethylamine). Each mobile phase was continuously sparged with helium. The HPLC gradient was programmed as follows: mobile phase A increased linearly from 35 to 100% at a flow rate of 1 mL/min over 9.7 min (where A + B = 100%). Peaks of eluting products were quantitated by UV absorbance (LTB_4 and PGB_2 at 275 nm; HHT and 5-HETE at 235 nm) and were corrected by PGB_2 recovery. Sigmoid regression was used to estimate IC_{50} values.

In vivo platelet activating factor (PAF) thrombosis assay in mice

The in vivo potency after oral administration of compounds to IRC mice (male) was determined using a PAF thrombosis assay in a manner similar to that described by J. M. Young et al.[13] PAF was dissolved at a concentration of 1.2 in 0.05 mg/mL propranolol-saline containing 0.25% bovine serum albumin (BSA) and injected intravenously into mice at a dose of 12 mg/kg. The mortality rate was determined 1 h after PAF injection. To investigate the effect(s) of LO inhibitors, compounds were dissolved in 5% Tween 80, 5% EtOH-saline, and the solutions were administered orally (10 mL/kg) 45 min prior to PAF injection.

In vivo yeast-induced foot edema assay in rats

Female rats (5 weeks old), weighting 100–130 g body weight, were fasted overnight. Food edema was induced by subplantar injection of 0.1 mL of 3% Brewer's yeast (Sigma) suspended in saline. Foot volume was measured by water displacement using a plenthysmometer before and 1.5 h after the yeast injection. The compound suspended in 0.1% methylcellulose was administered perorally at a volume of 2.5 mL per 100-g body weight 1 h prior to the yeast injection. The ED_{40} value was calculated from the equation for the log-linear regression line of dose versus percent inhibition by the least squares method.

Chemistry

Proton magnetic resonance (^{1}H NMR) spectra were measured on a Joel FX270 spectrophotometer and proton chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Melting points were determined on either a Büchi 535 or on a Yanagimoto micro-melting-point apparatus and were uncorrected. IR spectra and mass spectra were recorded on a Shimadzu IR-440 spectrometer and a Micromass Quattro II specrtometer, respectively. The results of elemental analyses were within 0.4% of the theoretical values, and are reported only with symbols. Chromatography was performed on silica gel (E. Merck, 70–230 mesh).

4-[3-[4-(1*H*-Imidazol-1-yl)benzyloxy]phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1a). To a stirred solution of 4-(1*H*-imidazol-1-yl)benzyloxy alcohol (**2a**, 0.87 g, 5.0 mmol), 4-(3-hydroxyphenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (**3a**, 1.03 g, 4.9 mmol) and triphenylphosphine (1.55 g, 5.9 mmol) in THF (30 mL) cooled to 0 °C was added dropwise a solution of diethyl azodicarboxylate (DEAD) (1.03 g, 12.0 mmol) in THF (10 mL) over 20 min under a nitrogen atmosphere. After completion of addition, the mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature, and then volatiles were removed under reduced pressure. Chromatographic purification of the residue (gradient elution, 15–30% acetone in dichloromethane) provided 0.27 g of the title compound as a gum, which solidified on standing at room temperature. Fractions contaminated with triphenylphosphine oxide were combined, concentrated to dryness, solidified by triturating with diisopropyl ether/ethyl acetate to provide 0.16 g of the title compound. Combined solids were further purified by recrystallization from diisopropyl ether–ethyl acetate afforded the title compound as tiny colorless needles (0.30 g, 17%): mp = 129–131 °C; ^{1}H NMR ($CDCl_3$) 7.78 (t, 1H, J = 1 Hz), 7.56 (d, 2H, J = 8 Hz), 7.43 (d, 2H, J = 8 Hz), 7.32 (t, 1H, J = 8 Hz), 7.28 (dd, 1H, J = 8, 1 Hz), 7.22 (t, 1H, J = 1 Hz), 7.08–6.98 (m, 2H), 6.94–6.88 (m, 1H), 5.12 (s, 2H), 3.92–3.81 (m, 4H), 2.98 (s, 3H), 2.10–1.92 (m, 4H); MS (ESI+) m/e 365 $(M+H)^+$. Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

The following compounds were prepared from appropriate alcohols and phenols according to a similar procedure to that of **1a** (method A).

4-Methoxy-4-[3-[4-(1*H*-pyrrol-1-yl)benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1b). Mp = 112.5–113 °C;

^{1}H NMR ($CDCl_3$) 7.50 (d, 2H, J=9 Hz), 7.42 (d, 2H, J=9 Hz), 7.40–7.30 (m, 1H), 7.10 (t, 2H, J=2 Hz), 7.06–6.89 (m, 2H), 6.94–6.88 (m, 1H), 6.36 (t, 2H, J=2 Hz), 5.09 (s, 2H), 3.92–3.80 (m, 4H), 3.00 (s, 3H), 2.09–1.91 (m, 4H); MS (ESI+) m/e 332 $(M–OCH_3)^+$. Anal. ($C_{23}H_{25}NO_3$) C, H, N.

4-Methoxy-4-[3-[4-(1*H*-pyrazol-1-yl)benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1c). Mp = 91–92 °C; ^{1}H NMR ($CDCl_3$) 7.94 (dd, 1H, J=2, 1 Hz), 7.75–7.23 (m, 3H), 7.54 (d, 2H, J=8 Hz), 7.34–7.27 (m, 1H), 7.07–6.98 (m, 2H), 6.94–6.89 (m, 1H), 6.48 (dd, 1H, J=3, 2 Hz), 5.11 (s, 2H), 3.92–3.77 (m, 4H), 2.98 (s, 3H), 2.10–1.92 (m, 4H); MS (ESI+) m/e 333 $(M–OCH_3)^+$. Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

4-Methoxy-4-[3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1e). Mp = 135–137 °C; ^{1}H NMR ($CDCl_3$) 7.57 (d, 2H, J=8 Hz), 7.36–7.30 (m, 3H), 7.07–7.00 (m, 4H), 6.93 (ddd, 1H, J=8, 3, 1 Hz), 5.14 (s, 2H), 3.91–3.82 (m, 4H), 2.98 (s, 3H), 2.38 (s, 3H), 2.09–1.92 (m, 4H); MS (ESI+) m/e 379 $(M+H)^+$. Anal. ($C_{23}H_{26}N_2O_3$·0.1H_2O) C, H, N.

4-Methoxy-4-[3-[4-(4-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1f). Mp = 120–121 °C; ^{1}H NMR ($CDCl_3$) 7.76 (d, 1H, J=1 Hz), 7.55 (d, 2H, J=9 Hz), 7.39 (d, 2H, J=9 Hz), 7.32 (t, 1H, J=8 Hz), 7.26–7.00 (m, 3H), 6.91 (dd, 1H, J=8 and 2 Hz), 5.11 (s, 2H), 3.87–3.82 (m, 4H), 2.98 (s, 3H), 2.31 (s, 3H), 2.04–1.92 (m, 4H); MS (ESI+) m/e 379 $(M+H)^+$. Anal. ($C_{23}H_{26}N_2O_3$) C, H, N.

4-[3-[4-(2-Ethyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1i). Oil; ^{1}H NMR ($CDCl_3$) 7.57 (d, 2H, J=8 Hz), 7.33 (dd, 1H, J=8, 8 Hz), 7.32 (d, 2H, J=8 Hz), 7.07 (d, 1H, J=1 Hz), 7.06 (d, 1H, J=3 Hz), 7.02 (d, 1H, J=8 Hz), 6.98 (d, 1H, J=1 Hz), 6.93 (ddd, 1H, J=8, 3, 1 Hz), 5.14 (s, 2H), 3.88–3.82 (m, 4H), 2.98 (s, 3H), 2.67 (q, 2H, J=8 Hz), 2.09–1.92 (m, 4H), 1.26 (t, 3H, J=8 Hz); MS (ESI+) m/e 393 $(M+H)^+$. Anal. ($C_{24}H_{28}N_2O_3$·0.2H_2O) C, H, N.

4-[3-[4-(2-Ethyl-1*H*-imidazol-1-yl)benzyloxy]-5-fluoro-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (1j). Mp = 210–211 °C; ^{1}H NMR ($CDCl_3$) 7.71 (d, 2H, J=8 Hz), 7.47 (d, 1H, J=2 Hz), 7.42 (d, 2H, J=8 Hz), 7.15 (d, 1H, J=2 Hz), 6.85 (brs, 1H), 6.77 (ddd, 1H, J=10, 2, 2 Hz), 6.33 (ddd, 1H, J=10, 2, 2), 5.17 (s, 2H), 3.9–3.8 (m, 4H), 3.06 (q, 2H, J=8 Hz), 3.01 (s, 3H), 2.00–1.90 (m, 4H), 1.41 (t, 3H, J=8 Hz); MS (ESI+) m/e 411 $(M+H)^+$. Anal. ($C_{24}H_{27}FN_2O_3$·HCl) C, H, N.

4-Methoxy-4-[3-[4-(4-phenyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1m). Mp = 117–117.5 °C; ^{1}H NMR ($CDCl_3$) 7.49 (d, 2H, J=9 Hz), 7.42–7.38 (m, 2H), 7.32 (t, 1H, J=8 Hz), 7.30–7.23 (m, 6H), 7.16 (d, 1H, J=1 Hz), 7.05–7.00 (m, 2H), 6.91 (dd, 1H, J=9, 2 Hz), 5.21 (s, 2H), 3.91–3.82 (m, 4H), 2.98 (s, 3H), 2.09–1.92 (m, 4H); MS (ESI+) m/e 441 $(M+H)^+$. Anal. ($C_{28}H_{28}N_2O_3$) C, H, N.

4-[3-[4-(2-Benzyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1n). Oil; ^{1}H NMR ($CDCl_3$) 7.74–6.85 (m, 15H), 5.12 (s, 2H), 4.03 (s, 2H), 3.94–3.76 (m, 4H), 2.98 (s, 3H), 2.10–1.89 (m, 4H); MS (ESI+) m/e 455 $(M+H)^+$. Anal. ($C_{29}H_{30}N_2O_3$·0.9H_2O) C, H; N, calcd, 5.95; found 5.41.

4-Methoxy-4-[3-[4-[2-(pyridin-2-yl)-1*H*-imidazol-1-yl]-benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1o). 103–105 °C; ^{1}H NMR ($CDCl_3$) 8.32 (d, 1H, J=4 Hz), 7.92 (d, 1H, J=8 Hz), 7.70 (dd, 1H, J=8, 2 Hz), 7.47 (d, 2H, J=8 Hz), 7.39–7.24 (m, 4H), 7.21–7.11 (m, 2H), 7.08–6.98 (m, 2H), 6.96–6.87 (m, 1H), 5.12 (s, 2H), 3.94–3.77 (m, 4H), 2.98 (s, 3H), 2.10–1.90 (m, 4H); MS (ESI+) m/e 442 $(M + H)^+$. Anal. ($C_{27}H_{27}N_3O_3$·H_2O) C, H, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1g) and the hydrochloride salt (1g HCl). Step 1: 4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1g). 4-(2-Methyl-1*H*-imidazol-1-yl)benzyl alcohol (**2e**, 1.28 g, 6.8 mmol) in thionyl chloride (5 mL) was stirred at the ambient temperature for 30 min and then volatiles were removed under reduced pressure. The resultant crude product was washed with minimal dry Et_2O and dried in vacuo to afford 4-(2-methylimidazol-1-yl)benzylchloride hydrochloride (1.65 g) as white solids.

A mixture of 4-(5-fluoro-3-hydroxyphenyl)-4-benzylxy-3,4,5,6-terahydro-2*H*-pyran (**3b**, 1.4 g, 6.8 mmol), 4-(2-methyl-1*H*-imidazol-1-yl)benzylchloride hydrochloride (1.65 g, 6.8 mmol) and potassium carbonate (7.2 g, 68 mmol) in dry DMF (10 mL) was stirred at 120 °C for 2 h. The mixture was poured into water (100 mL) and extracted with ethyl acetate–benzene (300 mL, 2:1 v/v). The organic phase was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated. Purification of the residual yellow solids by column chromatography on silica gel (100 g) eluting with dichloromethane/methanol 10:1 and recrystallization from ethyl acetate–*n*-hexane gave 4-[5-fluoro-3-[4-(2-mthyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran as off-white solids (1.9 g, 39%)): mp = 168–168.5 °C; ^{1}H NMR ($CDCl_3$) 7.56 (d, 2H, J=8 Hz), 7.34 (d, 2H, J=8 Hz), 7.04 (d, 1H, J=1 Hz), 7.01 (d, 1H, J=1 Hz), 6.83 (br s, 1H), 7.75 (ddd, 1H, J=10, 2 and 2 Hz), 6.64 (ddd, 1H, J=10, 2 and 2 Hz), 5.11 (s, 2H), 3.86–3.81 (m, 4H), 2.99 (s, 3H), 2.38 (s, 3H), 1.99–1.88 (m, 4H); MS (ESI+) m/e 397 $(M+H)^+$. Anal. ($C_{23}H_{25}FN_2O_3$) C, H, N.

Step 2: 4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (1g HCl). To a stirred solution of 4-[5-fluoro-3-[4-(2-mthyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (0.5 g, 1.3 mmol) in dry dichloromethane (5 mL) was added 'Hydrogen Chloride; Methanol Reagent 10' (4 mL, Tokyo Chemical Industries) at ambient temperature. After being stirred for 10 min, volatiles were removed under reduced pressure. The crude product was recrys-

tallized from isopropyl alcohol/ethanol (4:3) to give the title compound **1i** (0.3 g, 55%) as white solids: mp = 233–234 °C (decomposition); ^{1}H NMR ($CDCl_3$) 7.71 (d, 2H, J = 8 Hz), 7.43 (d, 2H, J = 2 Hz), 7.72 (d, 2H, J = 8 Hz), 7.19 (d, 1H, J = 2 Hz), 6.84 (br s, 1H), 6.77 (ddd, 1H, J = 10, 2 and 2 Hz), 6.62 (ddd, 1H, J = 10, 2 and 2 Hz), 5.16 (s, 2H), 3.9–3.8 (m, 4H), 3.00 (s, 3H), 2.77 (s, 3H), 2.0–1.8 (m, 4H). Anal. ($C_{23}H_{25}FN_2O_3$·HCl) C, H, Cl, F, N.

The following compounds were prepared from appropriate benzyl alcohols and phenol **3b** according to a similar procedure to that of **1g** and **1g** HCl.

4-[5-Fluoro-3-[4-(1-methyl-1*H*-imidazol-2-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1d). Mp = 160–161 °C; ^{1}H NMR ($CDCl_3$) 7.68 (d, 2H, J = 8 Hz), 7.52 (d, 2H, J = 8 Hz), 7.13 (d, 1H, J = 1 Hz), 6.98 (d, 1H, J = 1 Hz), 6.86–6.81 (m, 1H), 6.73 (ddd, 1H, J = 10, 2 and 1 Hz), 6.64 (ddd, 1H, J = 10, 3 and 2 Hz), 5.11 (s, 2H), 3.91–3.78 (m, 4H), 3.77 (s, 3H), 2.98 (s, 3H), 2.08–1.83 (m, 4H); MS (ESI+) m/e 397 $(M+H)^+$. Anal. ($C_{23}H_{25}FN_2O_3$·0.4H_2O) C, H, N.

4-[3-Fluoro-5-[4-(2-trifluoromethyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (1h). Mp = 96–98 °C; ^{1}H NMR ($CDCl_3$) 7.57 (d, 2H, J = 8 Hz), 7.41 (d, 2H, J = 8 Hz), 7.24 (d, 1H, J = 2 Hz), 7.16 (d, 1H, J = 1 Hz), 6.85–6.60 (m, 3H), 5.14 (s, 2H), 3.90–3.80 (m, 4H), 2.98 (s, 3H), 2.05–1.85 (m, 4H); MS (ESI+) m/e 451 $(M+H)^+$. Anal. ($C_{23}H_{22}F_4N_2O_3$) C, H, N.

The following hydrochloride salt compounds were prepared from appropriate benzyl alcohols and phenol **3b** according to a similar procedure to that of **1g** HCl.

4-[3-Fluoro-5-[4-(2-propyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2H-pyran hydrochloride (1k HCl). Mp = 142–146 °C; ^{1}H NMR (DMSO-d_6) 7.89 (d, 1H, J = 2 Hz), 7.82 (d, 1H, J = 2 Hz), 7.88–7.63 (m, 4H), 6.95–6.77 (m, 3H), 5.27 (s, 2H), 3.77–3.59 (m, 4H), 2.89 (s, 3H), 2.86 (t, 2H, J = 8 Hz), 2.00–1.80 (m, 4H), 1.70–1.52(m, 2H), 0.79 (t, 3H, J = 7.3 Hz); MS (ESI+) m/e 425 $(M+H)^+$. Anal. ($C_{25}H_{29}N_2O_3$·HCl·0.5H_2O) C, H, N.

4-[3-Fluoro-5-[4-(2-isopropyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-4-methoxy-3,4,5,6-tetrahydro-2H-pyran hydrochloride (1l HCl). Mp = 140–143 °C; ^{1}H NMR (DMSO-d_6) 7.86 (d, 1H, J = 2 Hz), 7.83 (d, 1H, J = 2 Hz), 7.74 (d, 2H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 6.95–6.77 (m, 3H), 5.28 (s, 2H), 3.78–3.59 (m, 4H), 3.15–3.00 (m, 1H), 2.89 (s, 3H), 2.00–1.80 (m, 4H), 1.31 (d, 6H, J = 7 Hz); MS (ESI+) m/e 425 $(M+H)^+$. Anal. ($C_{25}H_{29}N_2O_3$·HCl·0.3H_2O) C, H, N.

4-(4-Methyl-1*H*-imidazol-1-yl)benzyl alcohol (2f). To a suspension of NaH (0.82 g, 20.5 mmol: 60% suspension on mineral oil) in dry DMF (20 mL) cooled to 0 °C was added a solution of 4-methylimidazole (1.64 g, 20 mmol) in DMF (10 mL) under a nitrogen atmosphere, and the mixture was stirred for 20 min at room temperature. 4-Fluorobenzaldehyde (2.54 g, 20.5 mmol) was added to the reaction mixture, and the resulting solution was stirred for 60 h. The reaction mixture was poured into an ice-cooled saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant residue was purified by column chromatography (5% methanol in ethyl acetate) to give crude 4-(4-methyl-1*H*-imidazol-1-yl)benzaldehyde (3.0 g) as oil, which was contaminated with unknown impurities and used without further purification.

To a stirred solution of the crude 4-(4-methyl-1*H*-imidazol-1-yl)benzaldehyde (3.0 g) in methanol (20 mL) cooled to 0 °C was added $NaBH_4$ (0.352 g, 8.7 mmol) in portions over 15 min and the whole stirred for 1 h. A saturated aqueous NH_4Cl solution (50 mL) was added to the reaction mixture and methanol was evaporated off. The resultant aqueous mixture was extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$), and solvent removed under reduced pressure. The crude product was recrystallized from isopropyl alcohol–isopropyl ether to give **2f** (0.51 g, 21% by 2 steps) as a white amorphous solid: mp 138–141 °C; ^{1}H NMR ($CDCl_3$) 7.65 (br, 1H), 7.5–7.3 (m, 4H), 7.0 (br, 1H), 4.8 (s, 2H), 2.3 (s, 3H); MS (ESI+) m/e 189 $(M+H)^+$. Anal. ($C_{11}H_{12}N_2O$) C, H, N.

4-(2-Methyl-1*H*-imidazol-1-yl)benzyl alcohol (2e). Step 1: Ethyl 4-(2-methyl-1*H*-imidazol-1-yl)benzoate. A mixture of 2-methyl-1*H*-imidazole (50 g, 0.6 mol), ethyl 4-fluorobenzoate (100 g, 0.6 mol) and potassium carbonate (415 g, 3 mol) in dry DMSO (1.5 L) was heated at 120 °C for 66 h under a nitrogen atmosphere. After cooling to room temperature, the mixture was poured into ice water (1 L), and extracted with Et_2O (2×750 mL). The combined organic phases were washed with water (500 mL) and then with brine (500 mL), dried ($MgSO_4$) and evaporated. The residual solid was recrystallized from ethyl acetate–*n*-hexane to give ethyl 4-(2-methyl-1*H*-imidazol-1-yl)benzoate (47 g, 33%) as yellow needles: mp 72–73 °C; ^{1}H NMR ($CDCl_3$) 8.22–8.12 (m, 2H), 7.43–7.33 (m, 2H), 7.10–6.99 (m, 2H), 4.42 (q, 2H, J = 7 Hz), 2.42 (s, 3H), 1.43 (t, 3H, J = 7 Hz); IR (KBr) 1720 cm^{-1}. Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

Step 2: 4-(2-Methyl-1*H*-imidazol-1-yl)benzyl alcohol (2e). To a solution of ethyl 4-(2-methyl-1*H*-imidazol-1-yl)-benzoate (46 g, 0.20 mol) in dry dichloromethane (1 L) cooled to −75 °C under a nitrogen atmosphere was added di-*iso*-butylaluminum hydride in *n*-hexane (0.93 M, 540 mL, 0.50 mol) carefully over 30 min and then the mixture allowed to warm slowly to room temperature. After stirring for 5 h, the reaction mixture was cooled in an ice-bath, after which methanol (30 mL) was carefully added. A 30% aqueous solution of Rochelle salt (500 mL) was then added, and the mixture was stirred at room temperature for 16 h. Insolubles were collected by filtration, and the organic phase was separated, washed with water (500 mL) and dried ($MgSO_4$). The solvents were evaporated to yield a second solid. The combined solids were recrystallized from ethanol

(ca. 300 mL) to afford 4-(2-methyl-1*H*-imidazol-1-yl)-benzyl alcohol (35.6 g, 95%) as white needles: mp 167–168 °C; ^{1}H NMR (DMSO-d_6) 7.50–7.33 (m, 4H), 7.25 (d, 1H, J = 2 Hz), 6.90 (d, 1H, J = 2 Hz), 5.33 (t, 1H, J = 6 Hz), 4.56 (d, 2H, J = 6 Hz), 2.27 (s, 3H); IR (KBr) 3200 cm^{-1}. Anal. ($C_{11}H_{12}N_2O$) C, H, N.

The following benzyl alcohols were synthesized from appropriate imidazoles and the corresponding ethyl 4-fluorobenzoates in a similar manner to that described for **2e**.

4 - (2 - Ethyl - 1*H* - imidazol - 1 - yl)benzyl alcohol (2i). Mp = 104–105 °C; ^{1}H NMR ($CDCl_3$) 7.50 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 7.02 (d, 1H, J = 1 Hz), 6.97 (d, 1H, J = 1 Hz), 4.80 (s, 2H), 2.63 (dq, 2H, J = 1 and 8 Hz), 1.23 (dt, 3H, J = 3 and 8 Hz); MS (ESI+) m/e 203 $(M+H)^+$. Anal. ($C_{12}H_{14}N_2O$) C, H, N.

4 - (2 - Propyl - 1*H* - imidazol - 1 - yl)benzyl alcohol (2k). Mp = 78–79 °C; ^{1}H NMR ($CDCl_3$) 7.60–6.80 (m, 6H), 4.80 (s, 2H), 2.70–2.45 (m, 2H), 2.00–1.50 (m, 3H), 1.00–0.70 (m, 3H); MS (ESI+) m/e 217 $(M+H)^+$. Anal. ($C_{13}H_{16}N_2O$) C, H, N.

4 - (2 - Isopropyl - 1*H* - imidazol - 1 - yl)benzyl alcohol (2l). Mp = 165–166 °C; ^{1}H NMR ($CDCl_3$) 7.55–6.80 (m, 6H), 4.79 (s, 2H), 3.07–2.85 (m, 1H), 2.37 (br s, 1H), 1.24 (d, 6H, J = 6.9 Hz); MS (ESI+) m/e 217 $(M+H)^+$. Anal. ($C_{13}H_{16}N_2O$) C, H, N.

4 - (2 - Benzyl - 1*H* - imidazol - 1 - yl)benzyl alcohol (2n). Mp = 131–132 °C; ^{1}H NMR ($CDCl_3$) 7.45–7.37 (m, 2H), 7.28–7.10 (m, 8H), 7.00 (d, 1H, J = 1 Hz), 4.77 (d, 2H, J = 4 Hz), 4.02 (s, 2H), 2.20–2.07 (br, 1H); MS (ESI+) m/e 265 $(M+H)^+$. Anal. ($C_{17}H_{16}N_2O$) C, H.

4-(2-Phenyl-1*H*-imidazol-1-yl)benzyl alcohol (2m). To a solution of 4-(2-phenyl-1*H*-imidazol-1-yl)benzonitrile[9] (3.2 g, 13 mmol) in dichloromethane (30 mL) and toluene (20 mL) cooled to −78 °C was added dropwise diisobutylalminum hydride in toluene (1.02 M, 13 mL, 13 mmol) under a nitrogen atmosphere and the whole stirred at this temperature for 1.5 h. Saturated aqueous NH_4Cl solution (20 mL) was then added carefully to the reaction mixture, and the whole allowed to warm to room temperature. The resulting gelatinous mixture was washed with 0.3 N HCl solution (100 mL), water (200 mL) and brine (100 mL), and the organic layer dried ($MgSO_4$). Removal of solvent under reduced pressure provided crude product (2.5 g), which was dissolved in methanol (30 mL) and cooled to 0 °C. $NaBH_4$ (0.3 g, 8 mmol) was added in portions and the reaction mixture and the whole extracted three times with ethyl acetate (20 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and solvent removed under reduced pressure. The resultant crude product was washed with ethyl acetate (35 mL) to give **2m** (0.81 g, 25%) as a white powder: mp = 176–178 °C; ^{1}H NMR ($CDCl_3$) 7.41–7.34 (m, 4H), 7.29–7.18 (m, 6H), 7.15 (t, 1H, J = 1 Hz), 4.75 (s, 2H), 2.6 (br, 1H); MS (ESI+) m/e 251 $(M+H)^+$. Anal. ($C_{16}H_{14}N_2O$) C, H, N.

4-[2-(2-Pyridyl)-1*H*-imidazol-1-yl]benzyl alcohol (2o). Benzyl alcohol **2o** was prepared from 2-(2-pyridyl)-1*H*-imidazole and 4-fluorobenzonitrile as a white solid according to the procedure described as step 2 for **2m**: mp = 147–148 °C; ^{1}H NMR ($CDCl_3$) 8.36–8.27 (m, 1H), 7.89 (d, 1H, J = 8 Hz), 7.70 (dd, 1H, J = 8 and 2 Hz), 7.39 (d, 2H, J = 9 Hz), 7.30–7.07 (m, 5H), 4.76 (d, 2H, J = 5 Hz), 2.07 (br s, 1H); MS (ESI+) m/e 252 $(M+H)^+$. Anal. ($C_{15}H_{13}N_3O$) C, H, N.

4-(1-Methyl-1*H*-imidazol-2-yl)benzyl alcohol (2d).[21] Step 1: Ethyl 4-(1*H*-imidazol-2-yl)benzoate. Ethyl 4-(1*H*-imidazol-2-yl)benzoate was prepared from ethyl 4-(1*H*-4,5-dihydroimidazol-2-yl)benzoate[22] as a yellow solid (32%) according to the literature procedure:[23] ^{1}H NMR ($CDCl_3$) 8.19–7.61 (m, 4H), 7.16 (s, 2H), 5.31 (s, 1H), 4.39 (q, 2H, J = 7 Hz), 1.41 (t, 3H, J = 7 Hz).

Step 2: Methyl 4-(1-methyl-1*H*-imidazol-2-yl)benzoate. A mixture of ethyl 4-(-1*H*-imidazol-2-yl)benzoate (1.54 g, 7.1 mmol), potassium carbonate (1.13 g, 11 mmol), 18-crown-6 (26 mg, 0.1 mmol) and dimethyl carbonate (2.45 g, 25 mmol) was heated at 100 °C under a nitrogen atmosphere. After 44 h, the mixture was concentrated to dryness, the residue was covered with water and the whole was extracted with dichloromethane. The organic layer was washed with water (100 mL), dried ($MgSO_4$) and concentrated to dryness. Column chromatographic purification (3% methanol in dichloromethane) yielded methyl 4-(1-methyl-1*H*-imidazol-2-yl)benzoate (0.65 g, 42%).

Step 3: 4-(1-Methyl-1*H*-imidazol-2-yl)benzyl alcohol (2d).[21] Benzyl alcohol **2d** was prepared from methyl 4-(1-methyl-1*H*-imidazol-2-yl)benzoate as a yellow oil according to the procedure described as step 2 for **2e**: ^{1}H NMR ($CDCl_3$) 7.53 (d, 2H, J = 8 Hz), 7.37 (d, 2H, J = 8 Hz), 7.12 (d, 1H, J = 1 Hz), 6.96 (d, 1H, J = 1 Hz), 4.72 (s, 2H), 3.72 (s, 3H).

4-(2-Trifluoromethyl-1*H*-imidazol-1-yl)benzyl alcohol (2h). Step 1: 4-(2-Iodo-1*H*-imidazol-1-yl)benzonitrile. To a solution of 4-(1*H*-imidazol-1-yl)benzonitrile[9b] (5.08 g, 30 mmol) stirred at −78 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium in *n*-hexane (1.61 M, 20 mL, 33 mmol). After 30 min at −78 °C, iodine (9.1 g, 36 mmol) was added, the resultant mixture allowed to warm to room temperature. After stirred at room temperature for 2 h, the mixture was poured into water (100 mL) and the whole extracted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried ($MgSO_4$). Removal of solvent afforded 5.20 g of yellow solid, which was recrystallized from *n*-hexane–ethyl acetate to yield 1.06 g of 4-(2-iodo-1*H*-imidazol-1-yl)benzonitrile as a yellow solid. The filtrate was concentrated to dryness and purified by column chromatography (methanol/dichloromethane) to give another 1.66 g of 4-(2-iodo-1*H*-imidazol-1-yl)benzonitrile (total, 35%): mp = 194–198 °C; ^{1}H NMR ($CDCl_3$) 7.84 (d, 2H, J = 9 Hz), 7.54 (d, 2H, J = 9 Hz), 7.30–7.20 (m, 2H); MS (ESI+) m/e 296 $(M+H)^+$. Anal. ($C_{10}H_6N_3I$) C, H, N.

Step 2: 4-(2-Trifluoromethyl-1*H*-imidazol-1-yl)benzonitrile. A stainless tube was charged with 4-(2-iodo-1*H*-imidazol-1-yl)benzonitrile (2.74, 9.27 mmol), trimethylsilyltrifluoromethane (1.98 g, 13.9 mmol), cuprous iodide (3.52 g, 13.9 mmol), potassium fluoride (0.807 g, 13.9 mmol), DMF (20 mL) and 1-methyl-2-pyrrolidone (20 mL) was sealed and heated to 80 °C. After 41 h, the reaction mixture was poured into a mixture of ethyl acetate/benzene (2:1, 300 mL) and water (200 mL). Precipitates were filtered off and the organic layer was separated, washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to dryness. Recrystallization of the residue from Et_2O afforded 4-(2-trifluoromethyl-1*H*-imidazol-1-yl)benzonitrile (0.820 g, 37%) as a yellow solid: mp = 123–124 °C; ^{1}H NMR ($CDCl_3$) 7.84 (d, 2H, J = 8 Hz), 7.53 (d, 2H, J = 8 Hz), 7.29 (d, 1H, J = 1 Hz), 7.19 (s, 1H, J = 1 Hz); MS (ESI+) m/e 238 $(M+H)^+$. Anal. ($C_{11}H_6N_3F_3$) C, H, N.

Step 3: 4-(2-Trifluoromethyl-1*H*-imidazol-1-yl)benzyl alcohol (2h). Benzyl alcohol **2h** was prepared as a white solid from 4-(2-trifluoromethyl-1*H*-imidazol-1-yl)benzonitrile according to the procedure described for 4-(2-phenyl-1*H*-imidazol-1-yl)benzyl alcohol (**2m**): mp = 112–114 °C ^{1}H NMR ($CDCl_3$) 7.55–7.05 (m, 6H), 4.08 (d, 2H, J = 2 Hz), 1.95 (t, 1H, J = 2 Hz); MS (ESI+) m/e 243 $(M+H)^+$. Anal. ($C_{11}H_9N_2F_3O$) C, H, N.

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