Full Paper

Synthesis of Imidazole Derivatives with Antimycobacterial Activity

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4-Substituted 1-(*p*-methoxybenzyl)imidazoles were designed and synthesized in order to mimic parts of the structure of highly potent antimycobacterial 6-aryl-9-(*p*-methoxybenzyl)purines. 4-Haloimidazoles were subjected to Pd-catalyzed cross-coupling in order to introduce a (hetero)-aryl group, or they were converted to Grignard reagents and reacted with (hetero)arylaldehydes. Further transformations of the adducts gave a variety of potential antimycobacterials with different "spacers" between the imidazole and (hetero)aryl group. The adduct from furfural was rearranged to a cyclopentenone derivative when treated with methanol under acidic conditions. Several target compounds exhibited antimycobacterial activity *in vitro* (IC_{90} 13 μg/mL for the best inhibitors), but they were not as active as the most potent purines and pyrimidines synthesized before.

Keywords: Antimycobacterial activity / Cross-coupling / Imidazole / Metallation

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Introduction

We have previously reported that certain 6,9-disubstituted purines are potent inhibitors of *Mycobacterium tuberculosis* (*Mtb*) *in vitro* [1–5]. These compounds display several properties which make them highly interesting as potential drugs against tuberculosis: high selectivity towards *Mtb* compared to other microorganisms, activity against several drug-resistant strains of *Mtb*, generally low toxicity towards mammalian cells, and ability to affect *Mtb* inside macrophages. A summary of the current SAR knowledge as well as the structures of some of the most active compounds identified in this series is shown in Fig. 1.

It has been estimated that approximately 30 million people will die from tuberculosis in about ten years. Agents that reduce the duration and complexity of the current therapy would have a major impact on the overall cure rate, meaning, there is an urgent need for new antimycobacterials [6–10]. After exploring the SAR of intact purines (Fig. 1), we now focus on non-purine analogs [11, 12], and recently reported high antimycobacterial activities *in vitro* for certain 5-formylamino-4-(2-furyl)-pyrimidines (Fig. 2) [12]. Herein, we report the synthesis and antimycobacterial activities for imidazole analogs of antimycobacterial purines. A general structure is shown in Fig. 2.

Results and discussion

Imidazoles can be conveniently *N*-alkylated when treated with base followed by an alkyl halide or sulfonate [13–20]. However, *N*-alkylation of 4(5)-substituted imidazoles gives both regioisomers in most cases. The ratio of isomers is difficult to predict, as the regiochemical outcome generally is dependent on the structure of both imidazole and alkylating agent as well as the exact reaction conditions used [15–20]. However, some 1,4-disubstituted imidazoles are available in high yields when the parent imidazole is alkylated in the presence of base and alkylating agent followed by an alkyl-halide-induced isomerization of the 1,5- to 1,4-disubstituted isomer [21]. This strategy was attempted for the synthesis of the 1,4-

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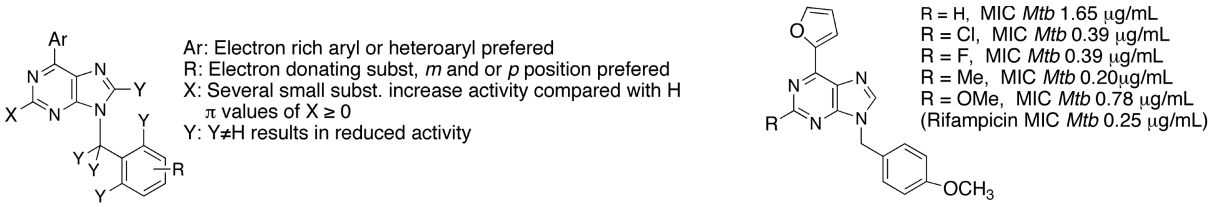


Figure 1. SAR summary for antimycobacterial purines and structures of some of the most active compounds.

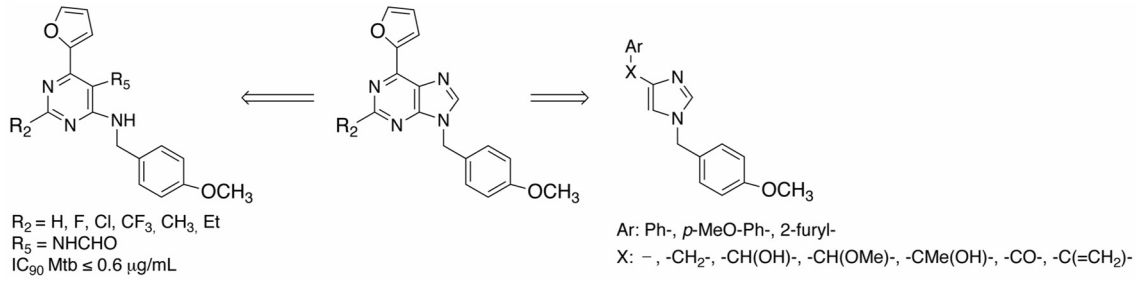
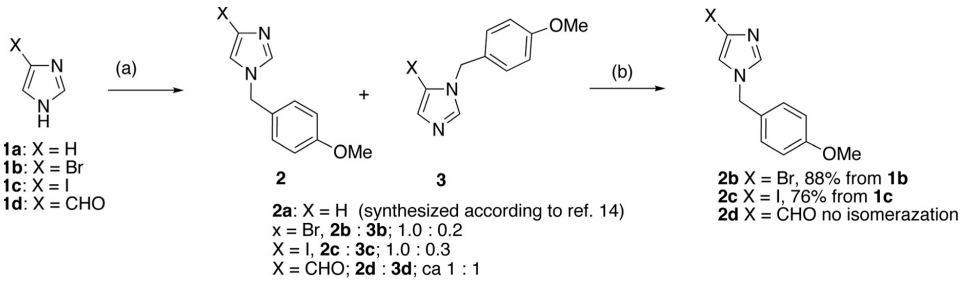


Figure 2. General structure of recently reported antimycobacterial pyrimidines and general structure of the target imidazoles in this study.



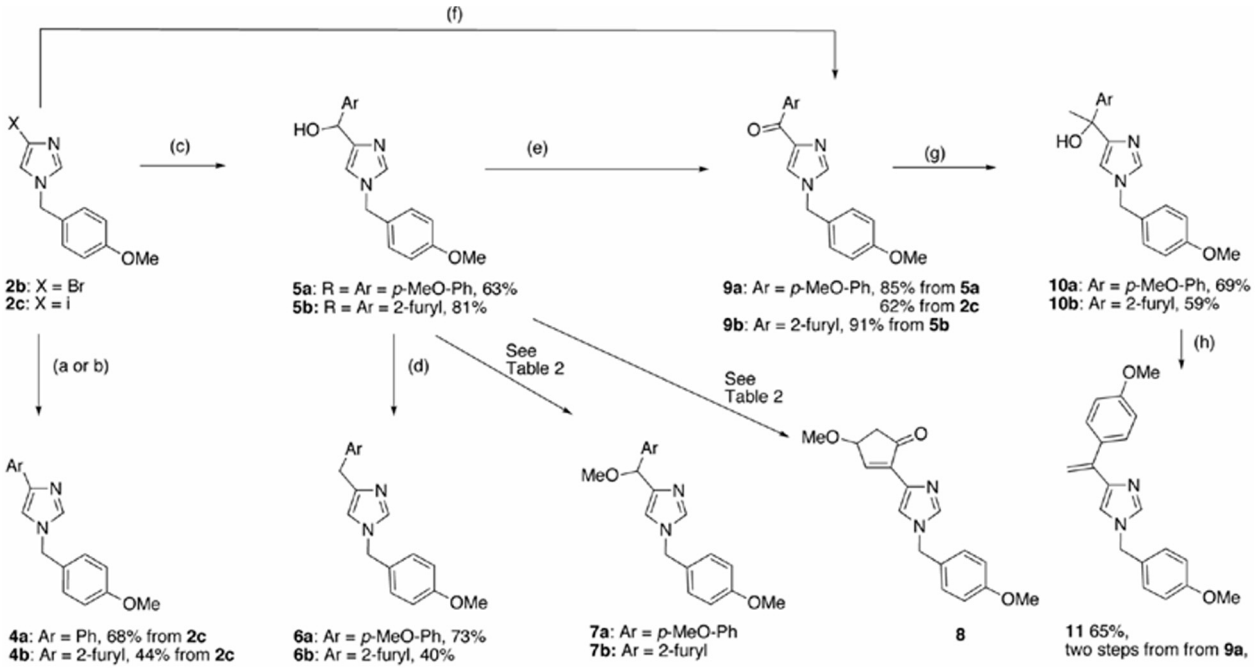
Reactions and conditions: (a) *p*-MeO-C_6H_4-CH_2Cl, NaH, DMF, 0°C to r.t.; (b) *p*-MeO-C_6H_4-CH_2Cl (10%), DMF, 75°C.

Scheme 1. Synthesis of compounds **1a–d** and **2a–d**.

disubstituted imidazoles **2b–2d**, whereas compound **2a** was synthesized as described before (Scheme 1) [14]. *N*-Alkylation of the haloimidazoles **1b** and **1c**, gave the 1,4-substituted regioisomer **2b** and **2c** as the major product and these were present as the only isomers after the alkyl-halide-catalyzed isomerization. *N*-Alkylation of the formylimidazole **1d**, on the other hand, resulted in a 1:1 mixture of the regioisomers **2d** and **3d**, and no isomerization took place when the mixture was treated with a catalytic amount of the benzylic chloride at 75°C for 24 h.

Aryl groups could be introduced directly in the imidazole 4-position, by Pd-catalyzed coupling reactions on 4-iodoimidazole **2c**. Different strategies were applicable as illustrated by the formation of the phenylimidazole **4a** by coupling between phenyl iodide and zincated imidazole, and the synthesis of the 4-(2-furyl)imidazole by Stille coupling on iodo compound **2c** (Scheme 2). The reactive catalyst $[(2\text{-furyl})_3P]_4Pd$ and a relatively high temperature (90°C) are the requirements for the Stille coupling in order to obtain product **2b** in a reasonable yield.

In the parent purines (Fig. 1), the furyl group is separated from the imidazole part of the purine by one carbon (the purine C-6); this led us to synthesize the imidazole derivatives **5–11** (Scheme 2). Synthesis of compounds **6** by Pd-catalyzed coupling reactions on the haloimidazoles **2** met with little success. Instead, compounds **6** were synthesized via the alcohols **5**. 4(5)-Bromoimidazole **1b** has been effectively lithiated by treatment with *t*-BuLi and subsequently trapped with aldehydes [22–23]. Having the desired substitution pattern in the *N*-alkylated 4-halopurines **2b** and **2c**, we preferred to metallate these compounds, and various conditions were tried



Reactions and conditions: (a) 1.) MeMgI, 2.) $ZnCl_2$, 3.) PhI, $Pd(PPh_3)_4$, THF, Δ; (b) (2-Furyl)$SnBu_3$, $[(2\text{-furyl})_3P]_4Pd$, DMF, 90°C; (c) 1.) MeMgI, CH_2Cl_2, 2.) ArCHO; (d) Et_3SiH, TFA, CH_2Cl_2; (e) MnO_2, CH_2Cl_2; (f) 1.) MeMgI, CH_2Cl_2, 2.) excess ArCHO; (g) MeMgI, THF; (h) 10% HCl (aq), 70°C.

Scheme 2. Synthesis of compounds **4a–b**, **5a–b**, **6a–b**, **7a–b**, **9a–b**, **10a–b**, and **11**.

Table 1. Metallation conditions employed in the synthesis of compounds **5** from compounds **2**.

Starting materia Compound 2	RMet	ArCHO	Yield (%) Compound 5	Recovered starting material (%) Compound 2
2b	*t*-BuLi	(*p*-MeO-C_6H_4)CHO	–	70
2b	EtMgBr	(*p*-MeO-C_6H_4)CHO	–	63
2b	MeMgI	(*p*-MeO-C_6H_4)CHO	–	82
2c	EtMgBr	(*p*-MeO-C_6H_4)CHO	–	76
2c	MeMgI	(*p*-MeO-C_6H_4)CHO	63, **5a**	–
2c	MeMgI	(2-Furyl)CHO	81, **5b**	–

Table 2. Reaction conditions employed in the synthesis of compounds **7** from compounds **5**.

Ar	Reagents	Solvent	Yield (%) Compound 7	Yield (%) Compound 9
p-MeO-C_6H_4-	NaH, MeI	DMF	–	59, **9a**
2-Furyl-	NaH, MeI	DMF	–	56, **9b**
p-MeO-C_6H_4-	NaH, MeI	THF	–	70, **9a**
2-Furyl-	NaH, MeI	THF	52, **7b**	–
p-MeO-C_6H_4-	NaH, MeI	THF-DMF (2:1)	39, **7a**	–
2-Furyl-	NaH, MeI	THF-DMF (2:1)	51, **7b**	–
p-MeO-C_6H_4-	Ag_2O, MeI	CH_2Cl_2	_	68, **9a**
2-Furyl-	Ag_2O, MeI	CH_2Cl_2	_	88, **9b**
p-MeO-C_6H_4-	HCl (aq)	MeOH	33	–
2-Furyl-	HCl (aq)	MeOH	– [a]	–

[a] Compound **8** (48%) was isolated.

(Table 1). Metallation with *t*-BuLi failed. It was also previously reported that the protocol is only applicable for imidazoles, which are not *N*-alkylated [22]. *N*-Trityl protected 4-iodoimidazole successfully underwent metal-halogen exchange when treated with EtMgBr [24–26], but, in our hands, compounds **5** were only formed when the iodoimidazole **2c** was metallated with MeMgI. Imidazolylcarbinols related to compounds **5** have also been prepared by addition of organometallic compounds to *N*-trityl-4-formylimidazole [27], but synthesis of compounds **5** from the formylimidazole **2d** was not attempted since the latter compound was not easily available in pure form (Scheme 1).

The alcohols **5** were subsequently reduced by Et_3SiH to give the imidazoles **6** carrying benzylic substituents in the 4-position. The exact amount of TFA (trifluoroacetic acid) required for each substrate was fine-tuned in order to facilitate the desired reduction, and not oxidation to ketones **9**. Compound **6a** has previously been synthetized by a *N*-alkylation of *N*-protected (SEM-protection) 5-(*p*-methoxybenzyl)-1*H*-imidazole [28] or in several steps from tyrosine [29].

O-Methylation of the alcohols **5** employing MeI/NaH was sensitive to the solvent used. When the reaction was carried out in DMF, only the ketones **9** could be isolated (Table 2). Both methoxy ethers **7** were formed in a mixture of DMF and THF, and the furylalcohol **5b** could also

Table 3. Antibacterial activity against *M. tuberculosis* compounds **2** and **4–11**.[a)]

Compound	Ar-	-X-	IC_{90} *M. tuberculosis* H37Rv (μg/mL)[a)]	IC_{50} *M. tuberculosis* H37Rv (μg/mL)[b)]
2a	_	H-	n.d.[d)]	n.d.[d)]
2b	_	Br-	>100	99
2c	_	I-	>100	89
4a	Ph-	_	13	7.8
4b	2-Furyl-	_	>100	48
5a	*p*-MeO-C_4H_6-	-CH(OH)-	16	11
5b	2-Furyl-	-CH(OH)-	28	24
6a	*p*-MeO-C_4H_6-	-CH_2-	13	12
6b	2-Furyl-	-CH_2-	36	21
7a	*p*-MeO-C_4H_6-	-CH(OMe)-	27	18
7b	2-Furyl-	-CH(OMe)-	76	53
8		–[e)]	>50	>50
9a	*p*-MeO-C_4H_6-	-CO-	46	29
9b	2-Furyl-	-CO-	>50	>50
10a	*p*-MeO-C_4H_6-	-CMe(OH)-	14	12
10b	2-Furyl-	-CMe(OH)-	32	16
11	*p*-MeO-C_4H_6-	-(C=CH_2)-	>100	>100

a) For a general structure of compounds **2–11**, see Fig. 2 and Scheme 2.
b) IC_{90} amicain 0.13 μg/mL.
c) IC_{50} amicain 0.07.
d) 0% inhibition at 6.25 μg/mL.
e) For detailed structure, see Scheme 2.

be *O*-methylated in pure THF. *O*-Metylation with MeI in the presence of Ag_2O afforded only the ketones **9** when employed on alcohols **5**. Reaction between the compounds **5** and methanol in the presence of acid was also attempted. Ether **9a** was isolated in a moderate yield, but the acid-labile furan derivative rearranged to compound **8**. Related formation of 4-methoxy-cyclopent-2-en-1-ones from furylcarbinols has been reported, but not in one single step [30].

Alcohols **5** were oxidized by MnO_2 to give ketones **9** in high yields. One-step formation of the ketones **9** was also attempted employing Magnesium-Oppenauer oxidation [31] of alcohols **5** formed *in situ*. Compound **9a** was available by this route, whereas in similar attempts to prepare compound **9b**, only carbinol **5b** was isolated (80%).

Methylene derivatives **11** were formed directly from ketones **9** under Wittig conditions, but the complete separation of the products from triphenylphosphine oxide was not achieved. Also, reaction of ketones **9** with the Petasis reagent (Cp_2TiMe_2) was attempted, but in these cases no desired products were observed. Instead a two-step strategy for the formation of compounds **11** was employed. Both ketones reacted readily with MeMgI to give the tertiary carbinols **10**. Elimination of water to give compound **11** was achieved when the adduct formed by reaction of MeMgI with ketone **9a**, was heated directly with dilute acid. Several other attempts to form the corresponding methylene compound from the furylketone **9b** in pure form failed as well due to severe instability of the product.

The target compounds **2** and **4–11** were screened for antibacterial activity against *M. tuberculosis* H37Rv and the results are presented in Table 3. *N*-(*p*-Methoxybenzyl) imidazole **2a** itself and the 4-halo derivatives **2b** and **2c** were without any significant activity. However, attaching a phenyl group in the imidazole 4-position had a profound positive effect and compound **4a** were among the most active compounds examined in this study (IC_{90} 13 μg/mL and IC_{50} 7.8 μg/mL) and significantly more active than the corresponding 4-furylimidazole **4b**. Compounds **5–7** and **9–11** were designed with different "spacers" (X in the general structure in Fig. 2) between the imidazole and the (hetero)aryl rings. In all cases examined, the compounds with the *p*-methoxyphenyl groups were more active than the 2-furyl derivatives when compounds with identical spacers were compared. This is in contrast to what we have previously observed in the purine series [4]. The -CH_2- (compounds **6**), -CH(OH)- (compounds **5**), and -CMe(OH)- (compounds **10**) spacers resulted in the most active compounds, IC_{90}: 13-16 μg/mL in the *p*-methoxyphenyl series and IC_{90}: 28–36 μg/mL in the 2-furyl series.

In summary, 4-substituted 1-(*p*-methoxybenzyl)imidazoles were designed and synthesized in order to mimic parts of the structure of highly potent antimycobacterial 6-aryl-9-(*p*-methoxybenzyl)purines. Several of the imidazoles exhibited antimycobacterial activity, but they

were not as active as the most potent purines and pyrimidines synthesized before.

Experimental

General

The ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument (Bruker, Bioscience). The decoupled ^{13}C-NMR spectra were recorded at 75 or 50 MHz using instruments mentioned above. Mass spectra under electron-impact conditions were recorded with a VG Prospec instrument (Fison Instruments) at 70 eV ionizing voltage, and are presented as *m*/*z* (% rel. int.). Elemental analyses were performed by the School of Chemistry, University of Birmingham, UK. Melting points were determined with a C. Reichert melting point apparatus (C. Reichert, Vienna, Austria) or a Büchi Melting Point B-545 apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. DMF was distilled from BaO, CH_2Cl_2 from CaH_2, and THF from Na/benzophenone. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). All other reagents were commercially available and used as received. Compounds synthesized by literature procedures: 4(5)-iodoimidazole **1c** [27] and 1-(4-methoxybenzyl)-1*H*-imidazole **2a** [14].

Chemistry

*4-Bromo-1-(4-methoxybenzyl)-1H-imidazole **2b***

4-Bromoimidazole **1b** (100 mg, 0.680 mmol) was dissolved in dry DMF (6 mL) under an Argon atmosphere. The mixture was cooled to 0°C before NaH (41 mg, ca. 60% in mineral oil, ca. 1.0 mmol) was added. After stirring for 30 min., 4-methoxybenzyl chloride (46 μL, 0.34 mmol) was added, the mixture was allowed to warm to ambient temperature and was then stirred for 18 h. After quenching with a small amount of water, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), and washed with H_2O (10 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The ratio between isomers **2b** and **3b** was 1.0:0.2 according to ^{1}H-NMR (CH_2 in **2b** 4.95 ppm, CH_2 in **3b** 5.03 ppm). A mixture of **2b** and **3b** (190 mg, 0.600 mmol) was dissolved in dry DMF (3 mL), 4-methoxybenzyl chloride (8 μL, 0.06 mmol) was added and the resulting mixture was heated at 75°C for 24 h. After cooling, a small amount of water was added and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (8:2); yield: 80 mg (88%), pale yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.34 (d, *J* = 1.3 Hz, 1H, H-2), 7.06 (d, *J* = 8.7 Hz, 2H, Ar), 6.78–6.87 (m, 3H, 2H in Ar and H-5), 4.95 (s, 2H, CH_2), 3.76 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.2 (C-4 in Ar), 137.1 (C-2), 129.6 (CH in Ar), 127.6 (C-1 in Ar), 118.7 (C-5), 115.8 (C-4), 114.9 (CH in Ar), 55.7 (CH_3), 51.4 (CH_2); MS EI *m*/*z* (rel.%): 268/266 (5/5) [M^+], 122 (9), 121 (100), 106 (1), 91 (3), 90 (2), 89 (2), 78 (8), 77 (6). HRMS calcd. for $C_{11}H_{11}BrN_2O$: 266.0055. Found: 266.0058.

*4-Iodo-1-(4-methoxybenzyl)-1H-imidazole **2c***

The title compound was prepared from 4-iodoimidazole **1c** (1.20 g, 6.19 mmol) and 4-methoxybenzyl chloride as described for compound **2b** above. The product was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (1:1); yield: 740 mg (76%), colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.38 (br s, 1H, H-2), 7.08 (d, *J* = 8.6 Hz, 2H, Ar), 6.84 (d, *J* = 8.6 Hz, 2H, Ar), 6.80 (s, 1H, H-5), 4.96 (s, 2H, CH_2), 3.75 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.2 (C-4 in Ar), 139.1 (C-2), 129.6 (CH in Ar), 127.5 (C-1 in Ar), 125.1 (C-5), 114.9 (CH in Ar), 82.3 (C, C-4), 55.8 (CH_3), 51.2 (CH_2); MS EI *m*/*z* (rel.%): 314 (20) [M^+], 121 (100), 78 (5). HRMS calcd. for $C_{11}H_{11}N_2IO$: 313.9916. Found: 313.9907. Anal. calc. for $C_{11}H_{11}N_2IO$: C, 42.06; H, 3.53; N, 8.92. Found: C, 42.24; H, 3.43; N, 8.66.

*1-(4-Methoxybenzyl)-4-phenyl-1H-imidazole **4a** [32]*

Methylmagnesium iodide (0.20 mL, 0.61 mmol, 3.0 M in Et_2O) was added to a solution of **2c** (160 mg, 0.51 mmol) in dry THF (5 mL) at 0°C under argon (Ar) atmosphere. The reaction was stirred at ambient temperature for 30 min, before $ZnCl_2$ (139 mg, 1.02 mmol) was added. The mixture was stirred for an additional 1 h, before iodobenzene (70 μL, 0.61 mmol) followed by $Pd(PPh_3)_4$ (29 mg, 0.03 mmol) were added. The reaction mixture was heated at reflux for 16 h. After cooling, the mixture was quenched with sat. aq. NH_4Cl (20 mL), the phases were separated, and the organic phase was washed with water (20 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (1:1); yield: 90 mg (68%), yellow solid. M.p.: 121–124°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, *J* = 7.3 Hz, 2H, Ph), 7.68 (br s, 1H, H-2), 7.33 (d, *J* = 7.3 Hz, 2H, Ph), 7.21 (br s, 1H, H-5), 7.18–7.13 (m, 3H, 1H in Ph and 2H in Ar), 6.88 (d, *J* = 8.7 Hz, 2H, Ar), 5.06 (s, 2H, CH_2), 3.78 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.1 (C-4 in Ar), 142.3 (C-4), 137.6 (C-2), 133.8 (C-1 in Ph), 129.4 (CH in Ar), 129.0 (CH in Ph), 128.0 (C-1 in Ar), 127.4 (C-4 in Ph), 125.2 (CH in Ph), 115.3 (C-5), 114.8 (CH in Ar), 55.7 (CH_3), 51.2 (CH_2); MS EI *m*/*z* (rel.%): 264 (31) [M^+], 122 (10), 121 (100), 77 (5). HRMS calcd. for $C_{17}H_{16}N_2O$: 264.1263. Found: 264.1259.

*4-(2-Furyl)-1-(4-methoxybenzyl)-1H-imidazole **4b***

A solution of $Pd[P(2\text{-furyl})_3]_4$ [generated *in situ* from $Pd(dba)_3$ (13 mg, 0.013 mmol) and tri(2-furyl)phosphine (31 mg, 0.14 mmol) in dry DMF (2 mL)] was added to a stirring solution of **2c** (140 mg, 0.45 mmol) in dry DMF (4 mL) at ambient temperature under N_2. Subsequently, (2-furyl)tributyltin (0.25 mL, 0.68 mmol) was added and the mixture was stirred at 90°C under nitrogen for 18 h, and evaporated *in vacuo*. The residue was dissolved in sat. KF in MeOH (10 mL), stirred at ambient temperature for 16 h, and evaporated *in vacuo* together with a small amount of SiO_2. The residue was placed on top of a flash chromatography column and the product was eluted with EtOAc; yield: 50 mg (44%), oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.51 (s, 1H, H-2), 7.31 (br s, 1H, H-5 in furyl), 7.12 (d, *J* = 8.6 Hz, 2H, Ar), 7.08 (s, 1H, H-5), 6.85 (d, *J* = 8.6 Hz, 2H, Ar), 6.60 (br d, *J* = 3.3 Hz, 1H, H-3 in furyl), 6.39 (dd, *J* = 3.3 and 1.8 Hz, 1H, H-4 in furyl), 5.02 (s, 2H, CH_2), 3.78 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.1 (C-4 in Ar), 150.3 (C-2 in furyl), 141.2 (C-5 in furyl), 137.7 (C-2), 135.4 (C-4), 129.4 (CH in Ar), 128.0 (C-1 in Ar), 115.1 (C-5), 114.8 (CH in Ar), 111.6 (C-4 in furyl), 104.6 (C-3 in furyl), 55.8 (CH_3), 51.0 (CH_2); MS EI *m*/*z* (rel.%): 254 (35) [M^+], 122 (9), 121 (100), 78 (6). HRMS calcd. for $C_{15}H_{14}N_2O_2$: 254.1055. Found: 254.1055.

*[1-(4-Methoxybenzyl)-1H-imidazol-4-yl](4-methoxyphenyl)methanol **5a***

MeMgI in Et_2O (0.13 mL, 0.38 mmol, 3.0 M in Et_2O) was added to a solution of **2c** (100 mg, 0.318 mmol) in dry CH_2Cl_2 (1 mL) under Ar atmosphere at ambient temperature, and the resulting mix-

ture was stirred for 5 h, before anisaldehyde (40 µL, 0.38 mmol) was added. The reaction mixture was stirred for 18 h, quenched by the addition of sat. aq. NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/EtOAc (1:19); yield: 63 mg, (63%), colorless solid. M.p.: 134–136°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.47 (br s, 1H, H-2), 7.34 (d, *J* = 8.7 Hz, 2H, Ar), 7.05 (d, *J* = 8.7 Hz, 2H, Ar), 6.84 (d, *J* = 8.7 Hz, 2H, Ar), 6.83 (d, *J* = 8.7 Hz, 2H, Ar), 6.49 (br s, 1H, H-5), 5.72 (s, 1H, C*H*OH), 4.91 (s, 2H, CH_2), 4.02 (br s, 1H, OH), 3.77 (s, 6H, 2 × CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.0 (C-4 in Ar), 159.4 (C-4 in Ar), 146.6 (C-4), 137.3 (C-2), 135.5 (C-1 in Ar), 129.4 (CH in Ar), 128.3 (CH in Ar), 128.1 (C-1 in Ar), 116.4 (C-5), 114.8 (CH in Ar), 114.1 (CH in Ar), 70.6 (CHOH), 55.7 (2 × CH_3), 50.9 (CH_2); MS EI *m/z* (rel.%): 324 (24) [M$^+$], 216 (6), 203 (15), 188 (10), 122 (9), 121 (100), 77 (6). HRMS calcd. for $C_{19}H_{20}N_2O_3$: 324.1474. Found: 324.1472. Anal. calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.61, H, 6.44; N, 8.36.

(2-Furyl)[1-(4-methoxybenzyl)-1H-imidazol-4-yl]methanol ***5b***

The title compound was prepared from **2c** (750 mg, 2.39 mmol), MeMgI (1.0 mL, 3.0 mmol, 3.0 M in Et_2O) and furfural (0.25 mL, 2.9 mmol) as described for the synthesis of **5a**; yield: 550 mg (81%), oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.40 (br s, 1H, H-2), 7.32 (br s, 1H, H-5 in furyl), 7.05 (d, *J* = 8.7 Hz, 2H, Ar), 6.82 (d, *J* = 8.7 Hz, 2H, Ar), 6.75 (br s, 1H, H-5), 6.28–6.23 (m, 2H, H-4 and H-3 in furyl), 5.75 (s, 1H, C*H*OH), 4.92 (s, 2H, CH_2), 4.71 (s, 1H, OH), 3.75 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.5 (C-4 in Ar), 156.5 (C-2 in furyl), 143.9 (C-4), 142.9 (C-5 in furyl), 137.7 (C-2), 129.9 (CH in Ar), 128.6 (C-1 in Ar), 117.3 (C-5), 115.3 (CH in Ar), 111.1 (C-4 in furyl), 107.9 (C-3 in furyl), 65.3 (CHOH), 56.2 (CH_3), 51.4 (CH_2); MS EI *m/z* (rel.%): 284 (40) [M$^+$], 122 (10), 121 (100), 78 (5). HRMS calcd. for $C_{16}H_{16}N_2O_3$: 284.1161. Found: 284.1165. Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.76; H, 5.77; N, 9.62.

1,4-Bis(4-methoxybenzyl)-1H-imidazole ***6a***

Triethylsilane (0.32 mL, 2.0 mmol) and trifluoroacetic acid (0.15 mL, 2.0 mmol) were added to a stirred solution of **5a** (120 mg, 0.403 mmol) in CH_2Cl_2 (5 mL) at 0°C under N_2. The solution was stirred for 3 h at ambient temperature and quenched by the addition of sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc; yield: 90 mg (73%), yellow solid. M.p.: 87–90°C (Lit. [29]: 83.5–86°C). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.42 (br s, 1H, H-2), 7.16 (d, *J* = 8.7 Hz, 2H, Ar), 7.05 (d, *J* = 8.7 Hz, 2H, Ar), 6.83 (d, *J* = 8.7 Hz, 2H, Ar), 6.79 (d, *J* = 8.7 Hz, 2H, Ar), 6.46 (br s, 1H, H-5), 4.91 (s, 2H, CH_2N), 3.82 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.74 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.9 (C-4 in Ar), 158.3 (C-4 in Ar), 143.6 (C-4), 137.0 (C-2), 132.8 (C-1 in Ar), 130.2 (CH in Ar), 129.2 (CH in Ar), 128.6 (C-1 in Ar), 116.3 (C-5), 114.7 (CH in Ar), 114.2 (CH in Ar), 55.7 (2 × CH_3), 50.7 (CH_2N), 34.6 (CH_2); MS EI *m/z* (rel.%): 308 (43) [M$^+$], 187 (9), 122 (10), 121 (100). HRMS calcd. for $C_{19}H_{20}N_2O_2$: 308.1525. Found: 308.1518. Anal. calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00, H, 6.54; N, 9.08. Found: C, 74.07; H, 6.49; N, 9.09.

4-(2-Furylmethyl)-1-(4-methoxybenzyl)-1H-imidazole ***6b***

Triethylsilane (0.70 mL, 4.2 mmol) and trifluoroacetic acid (1.3 mL, 17 mmol) were added to a stirred solution of **5b** (150 mg, 0.528 mmol) in CH_2Cl_2 (10 mL) at 0°C under N_2. The solution was stirred for 12 h at ambient temperature and quenched by the addition of water (10 mL) followed by Na_2CO_3 (s) to basic pH. The layers were separated and the organic layer was washed with brine (5 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc; yield: 57 mg (40%), oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.42 (br s, 1H, H-2), 7.28 (br s, 1H, H-5 in furyl), 7.06 (d, *J* = 8.7 Hz, 2H, Ar), 6.84 (d, *J* = 8.7 Hz, 2H, Ar), 6.62 (br s, 1H, H-5), 6.24 (dd, *J* = 3.1 and 1.8 Hz, 1H, H-4 in furyl), 6.04 (br d, *J* = 3.1, 1H, H-3 in furyl), 4.92 (s, 2H, CH_2N), 3.89 (s, 2H, CH_2), 3.76 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.9 (C-4 in Ar), 154.1 (C-2 in furyl), 141.6 (C-5 in furyl), 139.9 (C-4), 137.0 (C-2), 129.3 (CH in Ar), 128.6 (C-1 in Ar), 116.6 (C-5), 114.7 (CH in Ar), 110.7 (C-4 in furyl), 106.4 (C-3 in furyl), 55.7 (CH_3), 50.8 (CH_2N), 28.2 (CH_2); MS EI *m/z* (rel.%): 268 (26) [M$^+$], 121 (100), 122 (8), 78 (6); HRMS calcd. for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1217. Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62, H, 6.01; N, 10.44. Found: C, 71.38; H, 6.09; N, 10.22.

1-(4-Methoxybenzyl)-4-[methoxy(4-methoxyphenyl)methyl]-1H-imidazole ***7a***

Imidazole **5a** (160 mg, 0.537 mmol) was dissolved in a mixture of THF (4 mL) and DMF (2 mL) and stirred under N_2 at 0°C, before NaH (32 mg, ca. 0.81 mmol, ca. 60% in oil) was added. After 15 min, MeI (37 µL, 0.64 mmol) was added, and the resulting mixture was stirred for 1 h at 0°C. The reaction mixture was quenched by the addition of water (2 mL), and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc; yield: 70 mg (39%), yellow solid. M.p.: 62–65°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.42 (br s, 1H, H-2), 7.30 (d, *J* = 8.7 Hz, 2H, Ar), 7.05 (d, *J* = 8.7 Hz, 2H, Ar), 6.85 (d, *J* = 8.7 Hz, 2H, Ar), 6.82 (d, *J* = 8.7 Hz, 2H, Ar), 6.59 (br s, 1H, H-5), 5.19 (s, 1H, C*H*OCH$_3$), 4.91 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.32 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.9 (C-4 in Ar), 159.5 (C-4 in Ar), 144.8 (C-4), 137.2 (C-2), 133.3 (C-1 in Ar), 129.3 (CH in Ar), 128.8 (CH in Ar), 128.2 (C-1 in Ar), 117.0 (C-5), 114.7 (CH in Ar), 114.1 (CH in Ar), 80.6 (*C*HOCH$_3$), 57.1 (CH_3), 55.7 (2 × CH_3), 50.8 (CH_2); MS EI *m/z* (rel.%): 338 (11) [M$^+$], 308 (24), 307 (62), 187 (16), 122 (10), 121 (100). HRMS calcd. for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1634. Anal. calcd. for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.12, H, 6.54; N, 8.20.

4-[2-Furyl(methoxy)methyl]-1-(4-methoxybenzyl)-1H-imidazole ***7b***

The title compound was prepared from **5b** (110 mg, 0.390 mmol), NaH (24 mg, ca. 0.59 mmol, ca. 60% in oil), and MeI (27 µL, 0.43 mmol) in dry THF (4 mL) as described for the synthesis of compound **7a**; yield: 60 mg (52%), oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.43 (br s, 1H, H-2), 7.37 (br d, *J* = 1.3 Hz, 1H, H-5 in furyl), 7.09 (d, *J* = 8.7 Hz, 2H, Ar), 6.89 (br s, 1H, H-5), 6.84 (d, *J* = 8.7 Hz, 2H, Ar), 6.31 (m, 2H, H-4 and H-3 in furyl), 5.31 (s, 1H, C*H*OCH$_3$), 4.97 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.34 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.0 (C-4 in Ar), 153.6 (C-2 in furyl), 142.9 (C-5 in furyl), 141.4 (C-4), 137.2 (C-2), 129.4 (CH in Ar), 128.2 (C-1 in Ar), 117.7 (C-5), 114.8 (CH in Ar), 110.5 (C-4 in furyl), 109.1 (C-3 in furyl), 74.3

($CHOCH_3$), 57.0 (CH_3), 55.8 (CH_3), 50.9 (CH_2); MS EI *m/z* (rel.%): 298 (10) [M^+], 267 (42), 121 (100). HRMS calcd. for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1322. Anal. calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44, H, 6.08; N, 9.32. Found: C, 68.45; H, 5.80; N, 9.62.

4-Methoxy-2-[1-(4-methoxybenzyl)-1H-imidazol-4-yl] cyclopent-2-enone ***8***

A mixture of **5b** (400 mg, 1.41 mmol), MeOH (25 mL), and conc. HCl (aq) (10 drops) was heated under reflux for 20 h under N_2 atmosphere and evaporated *in vacuo*. The residue was partitioned between water (20 mL) and EtOAc (40 mL). The aqueous layer was basified with NaOH (s), the phases were separated and the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc; yield: 190 mg (45%), yellow solid. M.p.: 90–92°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 2.5 Hz, 1H, H-3 in *c*-pent), 7.63 (br s, 1H, H-2), 7.48 (br s, 1H, H-5), 7.07 (d, *J* = 8.6 Hz, 2H, Ar), 6.82 (d, *J* = 8.6 Hz, 2H, Ar), 4.99 (s, 2H, CH_2), 4.57 (m, 1H, H-4 in *c*-pent), 3.75 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 2.84–2.72 (dd, *J* = 18.4 and 5.9 Hz, 1H, H-5_A in *c*-pent), 2.45–2.35 (dd, *J* = 18.4 and 2.1 Hz, 1H, H-5_B in *c*-pent); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 204.0 (C=O), 160.0 (C-4 in Ar), 150.4 (C-3 in *c*-pent), 139.8 (C-2 in *c*-pent), 137.8 (C-5), 133.0 (C-4), 129.3 (CH in Ar), 128.0 (C-1 in Ar), 120.4 (C-2), 114.8 (CH in Ar), 77.1 (C-4 in *c*-pent), 57.0 (CH_3), 55.7 (CH_3), 51.0 (CH_2), 42.9 (C-5 in *c*-pent); MS EI *m/z* (rel.%): 298 (24) [M^+], 177 (12), 122 (10), 121 (100). HRMS calcd. for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1317. Anal. calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.25, H, 5.98; N, 9.35.

[1-(4-Methoxybenzyl)-1H-imidazol-4-yl](4-methoxyphenyl)methanone ***9a***

Method A

A mixture of **5a** (50 mg, 0.15 mmol) and MnO_2 (23 mg, 0.26 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 18 h at ambient temperature under Ar atmosphere. The solution was filtered through a pad of Celite and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (9:1); yield: 42 mg (85%), pale yellow solid. M.p.: 100–103°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.29 (d, *J* = 8.8 Hz, 2H, Ar), 7.67 (br s, 1H, H-2), 7.61 (br s, 1H, H-5), 7.15 (d, *J* = 8.6 Hz, 2H, Ar), 6.93 (d, *J* = 8.8 Hz, 2H, Ar), 6.88 (d, *J* = 8.6 Hz, 2H, Ar), 5.08 (s, 2H, CH_2), 3.84 (s, 3H, CH_3), 3.78 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 186.1 (C=O), 163.0 (C-4 in Ar), 159.9 (C-4 in Ar), 142.3 (C-4), 137.3 (C-5), 132.6 (CH in Ar), 130.5 (C-1 in Ar), 129.9 (CH in Ar), 126.9 (C-1 in Ar), 126.0 (C-2), 114.6 (CH in Ar), 113.4 (CH in Ar), 55.4 (2 × CH_3), 51.0 (CH_2); MS EI *m/z* (rel.%): 322 (29) [M^+], 175 (14), 122 (9), 121 (100), 77 (6). HRMS calcd. for $C_{19}H_{18}N_2O_3$: 322.1317. Found: 322.1318. Anal. calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.50, H, 5.48; N, 8.71.

Method B

MeMgI in Et_2O (0.90 mL, 2.7 mmol, 3.0 M in Et_2O) was added to a solution of **2c** (700 mg, 2.26 mmol) in dry CH_2Cl_2 (20 mL) under Ar atmosphere at ambient temperature, and the resulting mixture was stirred for 5 h, before anisaldehyde (2.7 mL, 23 mmol) was added. The reaction was stirred for 18 h, quenched by the addition of sat. aq. NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (9:1); yield: 450 mg (62%).

(2-Furyl)[1-(4-methoxybenzyl)-1H-imidazol-4-yl] methanone ***9b***

The title compound was prepared from **5b** (220 mg, 0.70 mmol) and MnO_2 (103 mg, 1.19 mmol) as described for the synthesis of **9a** (method A). EtOAc/hexane (8:2) was used as eluent for flash chromatography; yield 190 mg (91%), yellow solid. M.p.: 126–128°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, *J* = 3.5 Hz, 1H, H-5 in furyl), 7.77 (br s, 1H, H-2), 7.59 (br s, 1H, H-3 in furyl), 7.55 (br s, 1H, H-5), 7.11 (d, *J* = 8.7 Hz, 2H, Ar), 6.82 (d, *J* = 8.7 Hz, 2H, Ar), 6.50 (dd, *J* = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 5.04 (br s, 2H, CH_2), 3.73 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 175.0 (C=O), 160.7 (C-4 in Ar), 152.7 (C-2 in furyl), 147.4 (C-3 in furyl), 141.6 (C-4), 138.5 (C-5), 130.1 (CH in Ar), 127.7 (C-2), 126.9 (C-1 in Ar), 121.9 (C-5 in furyl), 115.4 (CH in Ar), 113.0 (C-4 in furyl), 56.2 (CH_2), 51.8 (CH_3); MS EI *m/z* (rel.%): 282 (23) [M^+], 122 (8), 121 (100), 78 (6). HRMS calcd. for $C_{16}H_{14}N_2O_3$: 282.1004. Found: 282.1007. Anal. calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92%. Found: C, 68.88, H, 5.07; N, 9.62.

1-[1-(4-Methoxybenzyl)-1H-imidazol-4-yl]-1-(4-methoxyphenyl)ethanol ***10a***

MeMgI (0.8 mL, 2.5 mmol, 3 M in Et_2O) was added to a solution of **9a** (360 mg, 1.12 mmol) in dry THF (12 mL) at 0°C under Ar atmosphere. The reaction was stirred at ambient temperature for 30 min and quenched with water. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/EtOAc (1:9); yield: 269 mg (69%), colorless solid. M.p.: 97–100°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.52 (br s, 1H, H-2), 7.35 (d, *J* = 8.7 Hz, 2H, Ar), 7.10 (d, *J* = 8.7 Hz, 2H, Ar), 6.85 (d, *J* = 8.7 Hz, 2H, Ar), 6.80 (d, *J* = 8.7 Hz, 2H, Ar), 6.64 (br s, 1H, H-5), 4.96 (s, 2H, CH_2), 3.78 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 1.80 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.0 (C-4 in Ar), 158.8 (C-4 in Ar), 149.6 (C-4), 139.9 (C-1 in Ar), 136.9 (C-2), 129.4 (CH in Ar), 127.9 (C-1 in Ar), 127.0 (CH in Ar), 115.4 (C-5), 114.8 (CH in Ar), 113.7 (CH in Ar), 72.7 (COH), 55.7 (2 × OCH_3), 51.1 (CH_2), 30.5 (CH_3); MS EI *m/z* (rel.%): 338 (8) [M^+], 323 (24), 320 (100), 122 (10), 121 (100). HRMS calcd. for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1633.

1-(2-Furyl)-1-[1-(4-methoxybenzyl)-1H-imidazol-4-yl] ethanol ***10b***

The title compound was prepared from **9b** (200 mg, 0.708 mmol) and MeMgI (0.3 mL, 0.9 mmol, 3 M in Et_2O) as described for the synthesis of **10a**; yield: 125 mg (59%), oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.43 (br s, 1H, H-2), 7.29 (br s, 1H, H-5 in furyl), 7.08 (d, *J* = 8.7 Hz, 2H, Ar), 6.84 (d, *J* = 8.7 Hz, 2H, Ar), 6.72 (br s, 1H, H-5), 6.24 (dd, *J* = 3.1 and 1.8 Hz, 1H, H-4 furyl), 6.17 (br d, *J* = 3.1 Hz, 1H, H-3 in furyl), 4.94 (s, 2H, CH_2), 3.92 (br s, 1H, OH), 3.76 (s, 3H, OCH_3), 1.83 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.0 (C-4 in Ar), 159.3 (C-2 in furyl), 147.4 (C-4), 142.0 (C-5 in furyl), 136.8 (C-2), 129.4 (CH in Ar), 128.0 (C-1 in Ar), 115.2 (C-5), 114.8 (CH in Ar), 110.5 (C-4 in furyl), 105.7 (C-3 in furyl), 69.7 (COH), 55.7 (OCH_3), 50.9 (CH_2), 27.3 (CH_3); MS EI *m/z* (rel.%): 298 (4) [M^+], 280 (44), 230 (8), 121 (100). HRMS calcd. for $C_{17}H_{18}N_2O_3$: 298.1317. Found:

298.1310. Anal. calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44, H, 6.08; N, 9.39. Found: C, 68.33; H, 6.38; N, 9.33.

*1-(4-Methoxybenzyl)-4-[1-(4-methoxyphenyl)vinyl]-1H-imidazole **11***

MeMgI (0.4 mL, 1.2 mmol, 3 M in Et_2O) was added to a solution of **9a** (190 mg, 0.589 mmol) in dry THF (6 mL) at 0°C under Ar atmosphere. The reaction was stirred at ambient temperature for 30 min and 10% aq. HCl (5 drops) were added. The resulting mixture was heated at 70°C for 12 h and quenched by the addition of sat. aq. $NaHCO_3$ (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/hexane (6:4); yield: 120 mg (65%), yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.50 (d, *J* = 1.2 Hz, 1H, H-2), 7.34 (d, *J* = 8.7 Hz, 2H, Ar), 7.05 (d, *J* = 8.7 Hz, 2H, Ar), 6.84 (d, *J* = 8.7 Hz, 2H, Ar), 6.80 (d, *J* = 8.7 Hz, 2H, Ar), 6.67 (d, *J* = 1.2 Hz, 1H, H-5), 5.84 (d, *J* = 1.8 Hz, 1H, H_A in $=CH_2$), 5.11 (d, *J* = 1.8 Hz, 1H, H_B in $=CH_2$), 4.94 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.75 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.4 (C-4 in Ar), 159.0 (C-4 in Ar), 142.6 (C-4), 141.5 (C=), 137.2 (C-2), 133.5 (C-1 in Ar), 129.1 (CH in Ar), 128.6 (CH in Ar), 127.8 (C-1 in Ar), 117.7 (C-5), 114.2 (CH in Ar), 113.4 (CH in Ar), 110.9 ($=CH_2$), 55.2 ($2 \times CH_3$), 50.3 (CH_2); MS EI *m/z* (rel.%): 320 (40) [M^+], 122 (9), 121 (100). HRMS calcd. for $C_{20}H_{20}N_2O_2$: 320.1525. Found: 320.1529. Anal. calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98, H, 6.29; N, 8.74. Found: C, 74.58; H, 6.17; N, 8.94.

Antimicrobial testing

Activities against *M. tuberculosis* were determined as reported before [12]. For testing see also Collins and Franzblau [33].

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