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Imidazoles from nitroallylic acetates and α-bromonitroalkenes with amidines: synthesis and trypanocidal activity studies†

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Cascade reactions of amidines with nitroallylic acetates and α-bromonitroalkenes provide potentially bioactive imidazoles in good to excellent yields in most cases. While 2,4-disubstituted imidazol-5-yl acetates are formed in the first case, 2,4-disubstituted imidazoles, bearing no substituent at position 5, are the products in the second case. These two series of imidazoles, *viz*. 2,4,5-trisubstituted and 2,4-disubstituted, were screened for their activity against the protozoan parasite *Trypanosoma cruzi* which is responsible for Chagas disease. As many as three compounds were as active as the standard benznidazole and two others were 2–3-fold more active highlighting the potential of substituted imidazoles, easily accessible from nitroalkenes, as possible anti-parasitic agents.

Introduction

Several imidazole containing compounds exhibit activity against *Trypanosoma cruzi*, a parasite that causes Chagas disease.[1] Synthesis and detailed evaluation of such anti-parasitic activity of imidazoles, including studies on their mechanism of action, have been reported in the recent literature.[2] Other biological properties of imidazoles and their applications for the treatment of various diseases have also been well documented (Fig. 1).[3] The presence of imidazoles in bioactive compounds, including natural products,[4] for instance, marine alkaloids,[5] have received considerable attention. Potential applications of imidazoles in coordination chemistry[6] and as precursors to ionic liquids[7] and stable carbenes[8] are also noteworthy.

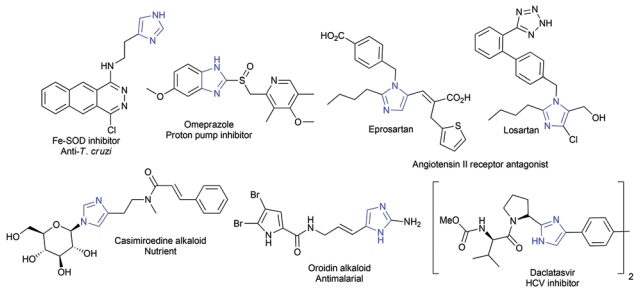

Fig. 1 Selected examples of bioactive imidazoles.

Many new multi-component[9] and metal-mediated[10–12] approaches have appeared in the literature for the synthesis of imidazoles. However, the three component reaction of 1,2-dicarbonyl compound, aldehyde and ammonia,[13] and the reaction of (α-halo)ketones or diketones with formamide/amines[14] or amidines[15] are the classical ones. Reactions of amidines with acetylenes[11] and nitroalkenes[12] also lead to substituted imidazoles.

In essence, functionalized and fused imidazoles are attractive targets for synthetic chemists due to their diverse applications in chemistry and biology.[16]

From another perspective, the reactivity of conjugated nitroalkenes as substrates in reactions as diverse as Michael addition, Diels–Alder reaction, 1,3-dipolar cycloaddition and Morita–Baylis–Hillman reaction has been amply demonstrated.[17] In particular, the Morita–Baylis–Hillman (MBH)[18] reaction of nitroalkenes has emerged as a convenient means of synthesizing α-functionalized nitroalkenes which could in turn serve as excellent substrates for the synthesis of complex molecules.[19–22] Several carbocycles[20] and heterocycles[21,22] have been synthesized exploiting the 1,2 or 1,3-bi-electrophilic character of the nitroallylic acetates through a cascade S_N2 or S_N2' reaction of a binucleophile followed by an intramolecular Michael addition.

Among nitroalkenes, α-bromonitroalkenes, by virtue of their 1,2-bielectrophilic character, are capable of taking part in

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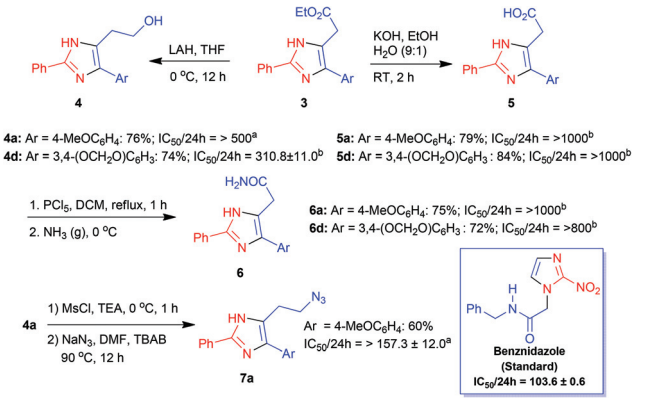
cascade reactions with various binucleophiles. Their reaction with 1,3-dicarbonyl compounds,[23] enamines,[24] and other miscellaneous binucleophiles[25] provided various functionalized heterocycles such as furans, pyrroles, pyrazoles, and triazoles among others. However, to our knowledge, there is no report on the reaction of α-bromonitroalkenes with amidines for the synthesis of functionalized imidazoles.

This work describes the full version of our studies on the synthesis of imidazoles by treating amidines with nitroallylic acetates and α-bromonitroalkenes and studies on their trypanocidal activity.[26]

Results and discussion

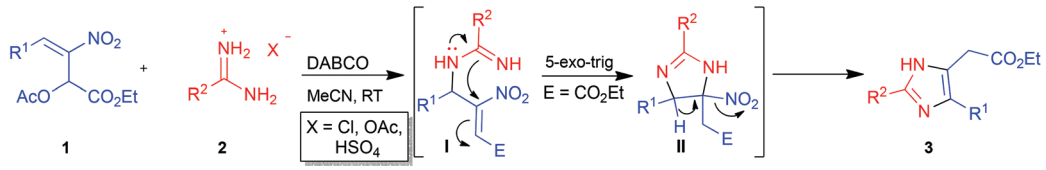
In our recent communication,[26] we reported the synthesis of imidazole esters **3** from nitroallylic acetates **1** and amidines **2** through a one-pot cascade intermolecular aza-S_N2' reaction–intramolecular aza-Michael addition (Table 1). Selected imidazole esters **3** were transformed to alcohols **4**, acids **5** and then to amides **6** (Scheme 1). Many of these imidazoles were screened for their activity against the protozoan parasite *T. cruzi*, the etiological agent of Chagas disease. In particular, the activity of imidazole esters **3a** and **3b** was comparable to that of the standard benznidazole. More importantly, imidazole ester **3e** exhibited activity twice that of benznidazole thus prompting us to synthesize and screen more imidazoles in this series and also those with other substitution patterns.

At the outset, imidazoles **3h**, **3o** and **3p** (Table 1, entries 8, 15 and 16) and **4d**, **5a**, **5d**, **6a** and **6d** (Scheme 1) which were reported in our previous communication,[26] but could not be screened earlier were later evaluated for their activity. Unfortu-



Scheme 1 Synthesis of derivatives of selected imidazole esters **3a** and **3d** and their activity against *T. cruzi* trypomastigotes. IC_{50}/24 h reported in μM. [a]New compound. [b]IC_{50}/24 h was not reported in ref. 26.

Table 1 Synthesis of imidazoles **3** from nitroallylic acetates **1** and amidines **2** and their activity against *T. cruzi* trypomastigotes



Entry	1, R^1	2, R^2	Time (h)	3	% Yield[a]	IC_{50}/24 h (μM)[b,c]
1	**1a**, 4-$MeOC_6H_4$	C_6H_5	3	**3a**	92	111.9 ± 15.4
2	**1b**, 2,4-$(MeO)_2C_6H_3$	C_6H_5	4	**3b**	68	102.0 ± 10.3
3	**1c**, 3,4-$(MeO)_2C_6H_3$	C_6H_5	3	**3c**	86	236.2 ± 16.4
4	**1d**, 5-Benzo[*d*][1,3]dioxole	C_6H_5	2	**3d**	91	193.0 ± 08.6
5	**1e**, 4-MeC_6H_4	C_6H_5	3	**3e**	91	51.1 ± 04.3
6	**1f**, C_6H_5	C_6H_5	4	**3f**	89	561.7 ± 56.6
7	**1g**, 4-FC_6H_4	C_6H_5	2	**3g**	68	256.6 ± 21.9
8	**1h**, 4-ClC_6H_4	C_6H_5	0.5	**3h**	67	213.9 ± 22.8[d]
9	**1i**, 3-BrC_6H_4	C_6H_5	0.5	**3i**	65	187.5 ± 05.5
10	**1j**, 1-Naphthyl	C_6H_5	4	**3j**	67	190.8 ± 02.3
11	**1k**, 2-Furyl	C_6H_5	7	**3k**	74	1002.6 ± 76.8
12	**1l**, 2-Thienyl	C_6H_5	2	**3l**	62	734.9 ± 41.8
13	**1m**, $C_6H_5CH{=}CH$	C_6H_5	1.5	**3m**	58	382.2 ± 46.7
14	**1n**, Cyclohexyl	C_6H_5	1	**3n**	67	172.0 ± 00.8
15	**1o**, C_6H_5	4-MeC_6H_4	2	**3o**	69	192.7 ± 21.6[d]
16	**1p**, C_6H_5	4-ClC_6H_4	1.5	**3p**	54	194.5 ± 14.4[d]
17	**1q**, C_6H_5	3-ClC_6H_4	1	**3q**	88	221.2 ± 28.2
18	**1r**, C_6H_5	CH_3	1	**3r**	62	946.7 ± 12.2
19	**1s**, C_6H_5	CH_3S	1.5	**3s**	32	1402.3 ± 260
20	**1t**, 3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	2.5	**3t**	63	>600[e]
21	**1u**, 3,4-$(MeO)_2C_6H_3$	3-ClC_6H_4	1	**3u**	67	>600[e]
22	**1v**, 3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4	2.5	**3v**	63	>1000[e]

[a] After purification by column chromatography. [b] Mean ± SD of at least 3 independent experiments. [c] Positive control: benznidazole IC_{50} 103.6 ± 0.6. [d] IC_{50}/24 h was not reported in ref. 26. [e] New compound.

nately, none of them yielded positive results. While **3h**, **3o** and **3p** showed activity approximately half (IC_{50}/24 h in the range of 190–214 μM) of that of the standard, benznidazole (IC_{50}/24 h 103.6 μM), the other derivatives **4d**, **5a**, **5d**, **6a** and **6d** did not show any activity at all (IC_{50}/24 h > 300 μM).

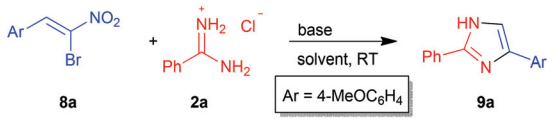
In view of the above, imidazole esters **3t–v** were synthesized following the general procedure reported by us earlier (Table 1, entries 20–22). Additionally, imidazole ester **3a** was transformed to alcohol **4a** using LAH in 76% yield and alcohol **4a**, in turn, was converted to azide **7a** in 60% yield (Scheme 1). Subsequently, esters **3t–v**, alcohol **4a** and azide **5a** were subjected to trypanocidal activity studies as reported before. However, while esters **3t–v** and alcohol **4a** were inactive, azide **7a** showed only moderate activity (IC_{50}/24 h 157.3 μM). It is worth mentioning the potential of the clickable imidazole **7a** that can be considered as an important intermediate in click chemistry reactions for the synthesis of hybrid compounds.

In the above scenario, we decided to explore the possibility of synthesizing imidazoles with different substitution patterns by our own methodology and screen them for their trypanocidal activity. Interestingly, although synthesis of imidazoles of type **9** *via* various miscellaneous methods is known in the literature,[27–36] the reaction of amidines **2** with α-bromonitroalkenes **8** has not been employed for such purposes. At the outset, amidine **2a** and α-bromonitroalkene **8a** were chosen as model substrates in order to establish the optimal conditions (Table 2).

There was no appreciable conversion when 1 equiv. of Cs_2CO_3 was employed as a base in THF at room temperature even after 24 h (entry 1). However, upon increasing the loading of Cs_2CO_3 to 2 and 3 equiv., there was a dramatic rise in the product yields to 55% and 85% as well as an improvement in the reaction rate to 18 h and 12 h, respectively (entries 2 and 3). While K_2CO_3 also gave comparable yields (80%) of the product **9a** (entry 4), amine bases such as DMAP, DABCO and Et_3N were less effective (entries 5–7) under otherwise identical conditions. Finally, changing solvent to CH_3CN enabled us to improve the yield further to 93% and considerably reduce the reaction time to 3 h (entry 8) though the yield was much lower (75%) in a hydrocarbon solvent such as toluene (entry 9).

The above optimized conditions were successfully employed for the synthesis of a variety of 2,5-disubstituted imidazoles **9** and **10** (Tables 3 and 4). Initially, benzamidine **2a** was treated with bromonitroalkenes **8** bearing various substituents at the β-position to afford imidazoles **9** (Table 3). In particular,

Table 2 Optimization studies for the synthesis of imidazole **9a** from α-bromonitroalkene **8a** and amidine **2a**



8a **2a** **9a**

Entry	Base (equiv.)	Solvent	Time (h)	% Yield[a]
1	Cs_2CO_3 (1)	THF	24	—[b]
2	Cs_2CO_3 (2)	THF	18	55
3	Cs_2CO_3 (3)	THF	12	85
4	K_2CO_3 (3)	THF	12	80
5	DMAP (3)	THF	12	56
6	DABCO (3)	THF	12	61
7	NEt_3 (3)	THF	12	49
8	**Cs_2CO_3 (3)**	**CH_3CN**	**3**	**93**
9	Cs_2CO_3 (3)	Toluene	5	75

[a] After silica gel column chromatography. [b] No reaction.

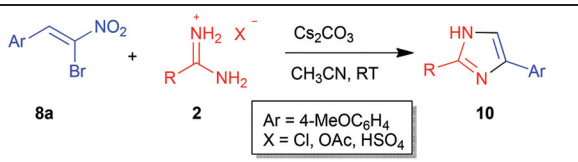
Table 3 Synthesis of imidazoles **9** from α-bromonitroalkenes **8** and amidine **2a**

8 **2a** **9**

Entry	8	R	Time (h)	9	% Yield[a]	IC_{50}/24 h (μM)[b,c]
1	**8a**	4-$MeOC_6H_4$	3.0	**9a**	93	177.2 ± 20.7
2	**8b**	3,4-$(MeO)_2C_6H_3$	3.0	**9b**	92	372.5 ± 29.9
3	**8c**	5-Benzo[*d*][1,3]dioxole	3.0	**9c**	90	194.5 ± 14.2
4	**8d**	C_6H_5	3.0	**9d**	88	377.2 ± 37.6
5	**8e**	4-MeC_6H_4	3.0	**9e**	92	240.6 ± 32.9
6	**8f**	4-$MeSC_6H_4$	6.0	**9f**	84	256.2 ± 9.8
7	**8g**	4-ClC_6H_4	4.5	**9g**	86	332.2 ± 41.9
8	**8h**	4-FC_6H_4	4.5	**9h**	76	329.8 ± 33.1
9	**8i**	3-BrC_6H_4	4.0	**9i**	74	339.4 ± 16.5
10	**8j**	2-$O_2NC_6H_4$	5.0	**9j**	85	395.2 ± 5.3
11	**8k**	2-Thienyl	4.5	**9k**	85	352.1 ± 16.5
12	**8l**	3-Thienyl	5.0	**9l**	71	355.3 ± 3.0
13	**8m**	1-Naphthyl	5.5	**9m**	81	35.5 ± 4.3
14	**8n**	$C_6H_5CH{=}CH$	6.0	**9n**	67	157.8 ± 23.6
15	**8o**	Cyclohexyl	5.0	**9o**	85	99.6 ± 5.2
16	**8p**	*n*-Butyl	5.0	**9p**	75	151.1 ± 3.2

[a] After silica gel column chromatography. [b] Mean ± SD of at least 3 independent experiments. [c] Positive control: benznidazole IC_{50} 103.6 ± 0.6.

Table 4 Synthesis of imidazoles **10** from α-bromonitroalkene **8a** and amidines **2**



8a **2** **10**

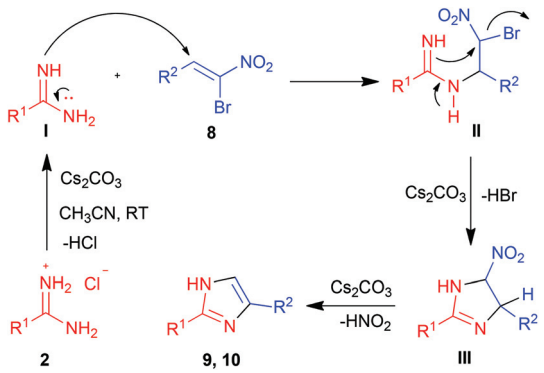
Entry	2	R	Time (h)	10	% Yield[a]	IC_{50}/24 h (μM)[b,c]
1	**2b**	4-MeC_6H_4	3.5	**10b**	87	123.0 ± 13.9
2	**2c**	4-ClC_6H_4	4.0	**10c**	79	182.6 ± 16.5
3	**2d**	3-ClC_6H_4	3.5	**10d**	83	184.4 ± 7.1
4	**2e**	MeS	5.0	**10e**	55	213.8 ± 14.6
5	**2f**	NH_2	2.0	**10f**	—[d]	—
6	**2g**	H	3.0	**10g**	—[d]	—

[a] After silica gel column chromatography. [b] Mean ± SD of at least 3 independent experiments. [c] Positive control: benznidazole IC_{50} 103.6 ± 0.6. [d] Complex mixture.

bromonitroalkenes bearing electron rich aryl groups at the β-position **8a–c** and **8e** provided the products **9a–c** and **9e**, respectively, in excellent yield (>90%, entries 1–3 and 5). The only exception among nitroalkenes bearing an electron rich aryl group was **8f** which afforded the product **9f** in a slightly lower yield (84%) and a longer reaction time (6 h, entry 6). The yields of imidazoles derived from nitroalkenes bearing parent phenyl **8d**, electron deficient aryls **8g–j** and a fused aryl **8m** at the β-position were in the range of 74–88% (entries 4, 7–10 and 13). Heteroaryl substituted bromonitroalkenes **8k–l** also delivered the corresponding imidazoles **9k–l** in good to high yield (71–85%, entries 11 and 12). While bromonitrodiene **8n** afforded the product **9n** in moderate yield (67%, entry 14), β-alkylated nitroalkenes **8o** and **p** were better substrates and provided the desired imidazoles **9o–p** in 75–85% yield (entries 15 and 16).

Having demonstrated the wide scope of bromonitroalkenes **8** in the reaction with amidine **2a**, the scope of amidines **2** was investigated by taking bromonitroalkene **8a** as the representative substrate (Table 4). The reaction of **8a** proceeded well with various arylamidines **2b–d** to afford the products **10b–d** in high yield (79–87%, entries 1–3). However, lower yield of imidazole **10e** was encountered with thioamidine **2e** (55%, entry 4). Guanidine **2f** and formamidine **2g** were not suitable substrates for the synthesis of imidazoles **10f–g** as complex mixtures were isolated under our experimental conditions (entries 5 and 6).

The structure and regiochemistry of imidazoles **9** and **10** were confirmed by comparison of their spectral data with those reported in the literature. In the proposed mechanism, the free amidine **I** derived from the neutralization of amidinium hydrochloride **2** by a base adds to bromonitroalkene **8** in a Michael fashion to afford intermediate **II**. Intramolecular nucleophilic substitution of bromide in **II** in a 5-*exo*-tet fashion provides the cyclized intermediate nitroimidazoline **III** which then undergoes base mediated elimination of HNO_2 to give the product 2,5-disubstituted imidazole **9** or **10** (Scheme 2).



Scheme 2 Possible mechanism for formation of imidazoles **9** and **10** *via* [3 + 2] cycloaddition of amidines **2** with bromonitroalkenes **8**.

Trypanocidal activity studies

In the case of imidazoles **3–7** derived from nitroallylic acetates **1**, the most active compound was imidazole ester **3e** (2-fold more potent than the current drug benznidazole) followed by esters **3b** and then **3a**, presenting IC_{50}/24 h values of 51.1, 102.0 and 111.9 μM, respectively. These three imidazoles possess a phenyl group at position 2 and an aryl group at position 5 bearing weakly or strongly electron donating substituent(s) at the *ortho*/*para* position(s). The presence of groups such as CH_2CO_2H, CH_2CONH_2, CH_2CH_2OH, and $CH_2CH_2N_3$ at position 5 did not improve the activity as compared to CH_2CO_2Et (Scheme 1 and Table 1). This was also a motivating factor to synthesize imidazoles of types **9** and **10** wherein there is no substituent at position 5. The evaluation of the IC_{50} values of imidazoles **9** and **10** in Tables 3 and 4 reveal that imidazole **9m** bearing a phenyl group at position 2 and a naphthyl group at position 4 is 3-fold more active (IC_{50}/24 h = 35.5 μM, Table 3, entry 13) than the standard benznidazole. This is followed by **9o** with a phenyl group at position 2 and a cyclohexyl group at position 4 (IC_{50}/24 h = 99.6 μM, Table 3, entry 15) which is as active as benznidazole. Imidazole **10b** with a *p*-tolyl group at position 2 and a *p*-anisyl group at position 4 (IC_{50}/24 h = 123.0 μM, Table 4, entry 1) is marginally less active than benznidazole. Other analogs that show appreciable activity which is attributable to the substituents at positions 2 and 4 are **9p** (Ph, *n*-Bu, IC_{50}/24 h = 151.1 μM, Table 3, entry 16), **9n** (Ph, styrenyl, IC_{50}/24 h = 157.8 μM, Table 3, entry 14), **9a** (Ph, *p*-anisyl, IC_{50}/24 h = 177.2 μM, Table 3, entry 1), **10c** (*p*-anisyl, *p*-ClC_6H_4, IC_{50}/24 h = 182.6 μM, Table 4, entry 2), **10d** (*p*-anisyl, *m*-ClC_6H_4, IC_{50}/24 h = 184.4 μM, Table 4, entry 3) and **9c** (Ph, benzo[*d*][1,3]dioxole, IC_{50}/24 h 194.5 μM, Table 3, entry 3).

In general, our compounds possess low molecular weight, partition coefficient and polar surface area values adhering to the Lipinski's rules. For the compounds described herein, the hydrophobicity appears sufficient for penetrating the biological membranes of the parasite, as determined by Lipinski's rule of 5 (clog P < 5, molecular weight ≤500, and PSA ≤ 140 Å^2, number of hydrogen bond acceptors <10 and donors <5).[37] Finally, a chemical informatics approach[38] was used to calculate the octanol–water partition coefficient (clog P value) and molecular polar surface area (PSA) for the most active compounds **3a**, **3b**, **3e**, **9m**, **9o** and **10b**, with IC_{50}/24 h in the range of 35.5 to 123 μM. The clog P and PSA values were in the range of 4.16–4.87 and 28.68–73.46, respectively.

Conclusions

Substituted imidazoles have been synthesized using amidines *via* a cascade S_N2'-intramolecular aza-Michael addition–elimination with nitroallylic acetates and *via* a cascade Michael addition-intramolecular S_N2 reaction with α-bromonitroalkenes. Imidazoles belonging to both the series have been screened against *T. cruzi* bloodstream trypomastigotes, an infective form of the protozoa that causes Chagas disease.

While three of the imidazoles exhibited activity comparable to the effect of the standard compound benznidazole, the activity of two others was two- and three-fold that of the current drug, suggesting possible application of such imidazoles as effective anti-*T. cruzi* agents.

Experimental section

General

The melting points recorded are uncorrected. NMR spectra (^{1}H, ^{1}H decoupled ^{13}C, ^{13}C-APT and ^{1}H–^{1}H COSY) were recorded with TMS as the internal standard. The coupling constants (*J* values) are given in Hz. High resolution mass spectra were recorded under ESI Q-TOF conditions. Amidinium salt **2a** was purchased from Sigma-Aldrich and others **2b–d** were prepared by following published procedures.[36] The MBH alcohols and their acetates **1** were prepared by following reported procedures.[39] Bromonitroalkenes **8** were prepared by following literature methods.[40] Experimental data for compounds **3a–s**, **4d**, **5a**, **5d**, **6a**, **6d** and **7a** were reported in our preliminary communication.[26]

Trypanocidal assay

Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.4%. Preliminary experiments showed that DMSO has no deleterious effect on the parasites when its concentration is up to 4%. *T. cruzi* bloodstream trypomastigotes (Y strain) were obtained at the peak of parasitaemia from infected albino mice, purified by differential centrifugation and resuspended in RPMI to a parasite concentration of 10^7 cells per mL in the presence of 10% of mouse blood. This suspension (100 μL) was added into the same volume of each compound previously prepared at twice the desired final concentrations for 24 h at 4 °C. Cell quantification was performed in a Neubauer chamber and the trypanocidal activity was expressed as IC_{50}/24 h, corresponding to the concentration that leads to the lysis of 50% of the parasites. The activity of standard benznidazole was reported earlier.[41] It is different from that reported by Moraes *et al.*[42] due to different experimental conditions.

General procedure for the synthesis of imidazoles from nitroallylic acetates

To a stirred solution of amidine **2** (0.24 mmol) and DABCO (61 mg, 0.5 mmol) in acetonitrile (2 mL), MBH acetate **1** (0.2 mmol) was added. After the completion of the reaction, monitored by TLC, the solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography by gradient elution with pet. ether/ethyl acetate (20–70%).

Ethyl 2-(2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1*H*-imidazol-5-yl)acetate (3t). Yellow solid; 63%, 50 mg; mp 128 °C; IR (KBr, cm^{-1}) 2963 (m), 2934 (m), 1730 (vs), 1667 (m), 1613 (m), 1593 (m), 1510 (vs), 1481 (s), 1465 (s), 1442 (s), 1254 (vs), 1228 (s), 1176 (s), 1143 (s), 1093 (m), 1027 (vs), 836 (m), 811 (m), 765 (m), 736 (vs); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 1.8 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 149.1, 148.6, 144.7, 134.5, 129.0, 128.3, 126.7, 124.7, 119.8, 111.3, 110.9, 61.6, 56.0, 55.9, 32.7, 14.3; MS (ES$^+$, Ar) *m*/*z* (rel. intensity) 403 ([MH + 2]$^+$, 33), 401 (M$^+$, 100), 248 (15), 110 (25); HRMS (ES$^+$, Ar) calcd for $C_{21}H_{22}ClN_2O_4$ (MH$^+$) 401.1263, found 401.1269.

Ethyl 2-(2-(3-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1*H*-imidazol-5-yl)acetate (3u). Yellow solid; yield 67%, 54 mg; mp 126 °C; IR (KBr, cm^{-1}) 2961 (w), 2935 (w), 2838 (w), 1732 (s), 1593 (m), 1510 (s), 1465 (s), 1453 (m), 1320 (w), 1254 (vs), 1227 (s), 1175 (s), 1142 (s), 1026 (s), 865 (w), 737 (vs); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (s, 1H), 7.67 (td, *J* = 4.4, 1.6 Hz, 1H), 7.23–7.26 (m, 2H), 7.11 (d, *J* = 1.6 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 149.1, 148.6, 144.3, 134.9, 131.5, 130.2, 128.7, 125.4, 123.5, 119.8, 111.3, 110.8, 61.7, 56.0, 56.0, 32.7, 14.3; MS (ES$^+$, Ar) *m*/*z* (rel. intensity) 403 ([MH + 2]$^+$, 33), 401 (MH$^+$, 100), HRMS (ES$^+$, Ar) calcd for $C_{21}H_{22}ClN_2O_4$ (MH$^+$) 401.1263, found 401.1261.

Ethyl 2-(4-(3,4-dimethoxyphenyl)-2-*p*-tolyl-1*H*-imidazol-5-yl)-acetate (3v). Light yellow liquid; yield 63%, 48 mg; IR (neat, cm^{-1}) 2957 (m), 2925 (m), 2853 (w), 1732 (vs), 1614 (m), 1596 (m), 1514 (s), 1464 (m), 1300 (m), 1255 (vs), 1229 (s), 1174 (m), 1142 (m), 1026 (vs), 825 (m), 733 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 1.9 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.04 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (s, 2H), 2.34 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 149.2, 148.5, 145.9, 138.8, 129.7, 127.2, 125.4, 119.8, 111.4, 111.0, 61.5, 56.1, 56.0, 32.5, 21.5, 14.3; MS (ES$^+$, Ar) *m*/*z* (rel. intensity) 381 (MH$^+$, 100), 349 (5), 320 (10), 301 (8); HRMS (ES$^+$, Ar) calcd for $C_{22}H_{25}N_2O_4$ (MH$^+$) 381.1809, found 381.1810.

2-(4-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazol-5-yl)ethan-1-ol (4a). To a stirred suspension of LAH (16 mg, 0.4 mmol) in THF (3 mL) at 0 °C, was added slowly a solution of ester **3** (70 mg, 0.2 mmol) in THF (1 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 12 h. After the completion of the reaction (monitored by TLC), a saturated solution of NH_4Cl (5 mL) was added, the resulting mixture was filtered through a pad of celite and the filtrate was concentrated. To the aqueous layer was added ethyl acetate (10 mL), the layers were separated and the organic phase was washed with brine (3 × 5 mL) and water (3 × 5 mL) and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated *in vacuo* and the residue was subjected to silica gel column chromatography (72% EtOAc/pet. ether). Colorless solid; yield 76%, 45 mg; mp 196–198 °C; IR (KBr, cm^{-1}) 3397 (br vs), 2925 (w), 1613 (m), 1508 (s), 1463 (m), 1248 (vs), 1177 (m), 1032 (s), 831 (w), 757 (w), 696 (w); ^{1}H NMR ($CDCl_3$ + MeOH 3 : 1, 400 MHz) δ 7.78 (d, *J* = 7.9 Hz, 2H),

7.39 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.23–7.27 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 3.75–3.75 (m, 2H), 3.74 (s, 3H), 2.87 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$ + MeOH 3 : 1, 100 MHz) δ 158.9, 145.2, 133.0, 130.0, 129.4, 128.8 (×2), 125.4, 124.6, 114.1, 61.8, 55.3, 28.9; MS (ES^+, Ar) m/z (rel. intensity) 317 (MNa^+, 50), 295 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{18}H_{19}N_2O_2$ (MH^+) 295.1441, found 295.1441.

5-(2-Azidoethyl)-4-(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (7a). To a stirred solution of imidazolyl alcohol **4a** (147 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL) triethylamine (0.21 mL, 152 mg, 1.5 mmol, 3 equiv.) was added at 0 °C, followed by mesyl chloride (0.12 mL, 172 mg, 1.5 mmol, 3 equiv.). The resulting reaction mixture was stirred for 1 h at 0 °C and then for an additional 2 h at room temperature. After the completion of the reaction, the reaction mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were thoroughly washed with water (3 × 10 mL) to remove the excess mesyl chloride followed by saturated $NaHCO_3$ (3 × 10 mL) and 5% dil. HCl (3 × 10 mL). The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude mesylate was suspended in DMF (8 mL) to which NaN_3 (130 mg, 2 mmol, 4 equiv.) was added followed by TBAB (16 mg, 0.05 mmol, 10 mol%). Then the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica gel column chromatography to afford diazide **7a** as colorless oil; yield 60%, 95 mg; IR (neat, cm^{-1}) 2933 (br m), 2101 (m), 1616 (w), 1507 (s), 1462 (m), 1286 (m), 1250 (vs), 1177 (m), 1029 (w), 912 (w), 835 (m), 735 (m); ^{1}H NMR ($CDCl_3$ + MeOH, 500 MHz) δ 7.83 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.29–7.36 (m, 3H), 6.90 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.52 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 145.9, 130.2, 128.9 (×2), 128.7, 125.4, 114.3, 55.5, 51.1, 26.7; MS (ES^+, Ar) m/z (rel. intensity) 320 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{18}H_{18}N_5O$ (MH^+) 320.1506, found 320.1515.

General procedure for the synthesis of imidazoles 9 and 10 from α-bromonitroalkenes 8 and amidines 2

To a stirred solution of α-bromonitroalkene **8** (0.2 mmol) in CH_3CN (3 mL), was added benzamidine hydrochloride **2** (0.2 mmol) followed by Cs_2CO_3 (195 mg, 0.6 mmol) at room temperature. The stirring was continued at room temperature and the completion of the reaction was monitored by TLC analysis. The crude reaction mixture was directly subjected to silica gel column chromatography by eluting with 15–50% EtOAc–pet. ether (gradient elution).

4-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazole (9a).[27] White solid; Yield 93%, 47 mg; mp 175–177 °C (lit[27] 178–179 °C); IR (KBr, cm^{-1}) 3161 (w), 2928 (w), 2836 (w), 1607 (w), 1500 (s), 1462 (w), 1249 (vs), 1180 (m), 1030 (m), 835 (m), 694 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 7.1 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.47–7.45 (m, 2H), 7.37–7.35 (m, 1H), 6.97 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.2, 138.6, 130.1, 128.9, 128.7, 126.5, 125.7, 125.3, 117.3, 114.3, 55.4; MS (ES^+, Ar) m/z (rel. intensity) 273 (MNa^+, 14), 251 (MH^+, 100), 132 (10); HRMS (ES^+, Ar) calcd for $C_{16}H_{15}N_2O$ (MH^+) 251.1179, found 251.1180. The experimental data are consistent with those reported in the literature.[27]

4-(3,4-Dimethoxyphenyl)-2-phenyl-1*H*-imidazole (9b).[28] Off white solid; Yield 92%, 52 mg; mp 89–91 °C; IR (neat, cm^{-1}) 3320 (w), 2933 (w), 2837 (w), 1591 (w), 1528 (w), 1506 (vs), 1464 (m), 1252 (vs), 1223 (m), 1142 (m), 1025 (s), 856 (w), 765 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.4, 2.8 Hz, 2H), 7.35 (s, 1H), 7.21–7.28 (m, 5H), 6.81 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.2, 147.4, 138.9, 130.2, 128.8, 128.7, 125.8, 125.7, 117.7, 117.5, 111.6, 108.7, 55.9, 55.7; MS (ES^+, Ar) m/z (rel. intensity) 303 (MNa^+, 08), 282 (14), 281 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{17}H_{17}N_2O_2$ (MH^+) 281.1285, found 281.1287. Reported only in the patent literature.[28] No experimental data are available.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenyl-1*H*-imidazole (9c).[28] White solid; Yield 90%, 48 mg; mp 156–158 °C; IR (KBr, cm^{-1}) 3402 (br, m), 2892 (w), 1644 (m), 1486 (s), 1233 (vs), 1111 (w), 1039 (s), 936 (w); ^{1}H NMR (500 MHz, CD_3CN) δ 7.94 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.39–7.37 (m, 2H), 7.35–7.32 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 5.98 (s, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 149.1, 147.6, 147.4, 140.8, 131.5, 129.8, 129.4, 129.2, 126.2, 119.2, 116.5, 109.4, 106.3, 102.3; MS (ES^+, Ar) m/z (rel. intensity) 287 (MNa^+, 08), 265 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{16}H_{13}N_2O_2$ (MH^+) 265.0972, found 265.0973. Reported only in the patent literature.[28] No experimental data are available.

2,4-Diphenyl-1*H*-imidazole (9d).[27a] White solid; Yield 88%, 39 mg; mp 275–277 °C (lit[27a] 274–275 °C); IR (KBr, cm^{-1}) 3378 (vs), 2923 (vw), 1640 (s), 1490 (vw), 1460 (vw), 1020 (w), 756 (w), 693 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (br s, 1H), 7.79–7.84 (m, 2H), 7.69 (d, J = 7.4 Hz, 2H), 7.35–7.31 (m, 2H), 7.21–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 138.9, 132.4, 129.8, 129.0, 128.9, 128.8, 127.3, 125.8, 125.2, 118.0; MS (ES^+, Ar) m/z (rel. intensity) 243 (MNa^+, 31), 221 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{15}H_{13}N_2$ (MH^+) 221.1073, found 221.1080. The experimental data are consistent with those reported in the literature.[27a]

2-Phenyl-4-(*p*-tolyl)-1*H*-imidazole (9e).[29] White solid; Yield 92%, 43 mg; mp 156–159 °C; IR (KBr, cm^{-1}) 3190 (vs), 2920 (m), 2855 (m), 1729 (m), 1661 (w), 1607 (w), 1501 (m), 1460 (s), 1265 (m), 1139 (m), 1020 (w), 953 (w), 821 (s), 775 (s), 694 (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.60 (br s, 1H), 8.03 (d, J = 7.0 Hz, 2H), 7.75 (d, J = 7.0 Hz, 2H), 7.65 (s, 1H), 7.47 (t, J = 7.1 Hz, 2H), 7.35 (t, J = 7.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.1, 139.7, 135.7, 131.0, 130.7, 129.3, 128.9, 128.3, 125.1, 124.6, 116.2, 20.9; MS (ES^+, Ar) m/z (rel. intensity) 235 (MH^+, 100), 121 (3); HRMS (ES^+, Ar) calcd for $C_{16}H_{15}N_2$ (MH^+) 235.1230, found 235.1231. No experimental data are available.[29]

4-(4-(Methylthio)phenyl)-2-phenyl-1*H*-imidazole (9f).[30] White solid; Yield 84%, 45 mg; mp 158–160 °C; IR (KBr, cm^{-1}) 3145 (br, vs), 2916 (br m), 1681 (br m), 1604 (m), 1489 (vs), 1460 (s), 1411 (m), 1297 (w), 1105 (m), 953 (m), 824 (m), 775 (m),

708 (s), 693 (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.65 (br s, 1H), 8.04 (d, J = 6.9 Hz, 2H), 7.82 (d, J = 7.4 Hz, 2H), 7.71 (s, 1H), 7.48 (t, J = 6.9 Hz, 2H), 7.38 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 7.4 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.0, 135.6, 130.6, 128.7, 128.1, 126.3, 124.9, 15.0; MS (ES^+, Ar) m/z (rel. intensity) 289 (MNa^+, 87), 267 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{16}H_{15}N_2S$ (MH^+) 267.0950, found 267.0950.

4-(4-Chlorophenyl)-2-phenyl-1*H*-imidazole (9g).[27] White solid; Yield 86%, 44 mg; mp 273–275 °C (lit[27] 277–280 °C); IR (KBr, cm^{-1}) 3413 (m), 2923 (w), 2852 (w), 1643 (m), 1488 (vs), 1461 (s), 1412 (w), 1265 (m), 1092 (m), 833 (s), 776 (m), 693 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.75–7.85 (m, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.40–7.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 139.3, 138.9, 132.7, 131.5, 129.9, 129.1, 129.0, 126.4, 125.8, 117.1; MS (ES^+, Ar) m/z (rel. intensity) 257 (36), 256 (19), 255 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{15}H_{12}N_2Cl$ (MH^+) 255.0684, found 255.0683. The experimental data are consistent with those reported in the literature.[27]

4-(4-Fluorophenyl)-2-phenyl-1*H*-imidazole (9h).[31] Pale pink solid; Yield 76%, 36 mg; mp 163–165 °C (lit[31] 167–168 °C); IR (KBr, cm^{-1}) 3412 (br w), 3069 (br s), 2807 (br m), 1607 (vw), 1497 (s), 1462 (m), 1296 (w), 1231 (s), 1156 (m), 1083 (w), 954 (w), 838 (m), 774 (m), 693 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.86 (m, 2H), 7.70 (dd, J = 7.7, 5.6 Hz, 2H), 7.33–7.38 (m, 3H), 7.26 (s, 1H), 7.05 (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 246.5 Hz), 147.5, 139.3, 130.0, 129.2 (d, J = 3.0 Hz), 129.1, 129.0, 126.9 (d, J = 8.0 Hz), 125.7, 116.1, 115.7 (d, J = 21.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −119.2; MS (ES^+, Ar) m/z (rel. intensity) 261 (MNa^+, 7), 240 ($[M + 2]^+$, 15), 239 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{15}H_{12}FN_2$ (MH^+) 239.0979, found 239.0979. The experimental data are consistent with those reported in the literature.[31]

4-(3-Bromophenyl)-2-phenyl-1*H*-imidazole (9i). Greenish liquid; Yield 74%, 44 mg; IR (neat, cm^{-1}) 3063 (br m), 2961 (br m), 2834 (br m), 1604 (w), 1493 (s), 1464 (m), 1247 (vs), 1179 (m), 1080 (w), 1031 (m), 834 (m), 768 (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 8.08 (s, 1H), 8.02 (d, J = 6.4 Hz, 2H), 7.85–7.90 (m, 2H), 7.48 (t, J = 5.9 Hz, 2H), 7.42–7.32 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.4, 139.5, 137.1, 130.6, 130.4, 128.8, 128.7, 128.3, 126.8, 125.1, 123.3, 122.1, 115.4; MS (ES^+, Ar) m/z (rel. intensity) 301 ($[M + 2]^+$, 98), 299 (MH^+, 100), 251 (53), 185 (25), 153 (29), 129 (47); HRMS (ES^+, Ar) calcd for $C_{15}H_{12}BrN_2$ (MH^+) 299.0178, found 299.0191.

4-(2-Nitrophenyl)-2-phenyl-1*H*-imidazole (9j).[32] Yellow solid; Yield 85%, 45 mg; mp 157–159 °C; IR (KBr, cm^{-1}) 3247 (br s), 1612 (vw), 1526 (vs), 1485 (w), 1460 (w), 1366 (s), 1093 (br w), 780 (m), 748 (w), 694 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 7.93–7.89 (unresolved m, 1H), 7.83 (d, J = 7.7 Hz, 2H), 7.72 (br d, J = 6.7 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43–7.36 (m, 4H), 7.31 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.2, 146.3, 136.3, 131.6, 130.2, 129.2, 128.8, 128.5, 127.5, 127.1, 125.0, 123.3, 116.6; MS (ES^+, Ar) m/z (rel. intensity) 288 (MNa^+, 54), 267 ($[M + 2]^+$, 15), 266 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{15}H_{12}N_3O_2$ (MH^+) 266.0924, found 266.0926. Reported only in the patent literature.[32] No experimental data are available.

2-Phenyl-4-(thiophen-2-yl)-1*H*-imidazole (9k).[33] Greenish liquid; Yield 85%, 38 mg; IR (neat, cm^{-1}) 3067 (br, m), 2894 (m), 1606 (vw), 1486 (vs), 1343 (vw), 1234 (vs), 1110 (w), 1039 (s), 935 (m), 813 (m), 775 (m), 695 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.75 (unresolved m, 2H), 7.35–7.27 (unresolved m, 4H), 7.26 (s, 1H), 7.20–7.17 (m, 1H), 7.04–7.00 (unresolved m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5, 136.4, 135.2, 129.9, 129.0, 129.0, 127.8, 125.8, 123.8, 122.8, 116.4; MS (ES^+, Ar) m/z (rel. intensity) 249 (MNa^+, 100), 235 (14), 227 (8); HRMS (ES^+, Ar) calcd for $C_{13}H_{10}N_2SNa$ (MNa^+) 249.0457, found 249.0456. Experimental data are not available in the literature.

2-Phenyl-4-(thiophen-3-yl)-1*H*-imidazole (9l).[34] Off white solid; Yield 71%, 32 mg; mp 146–148 °C (lit[34] 151–153 °C); IR (KBr, cm^{-1}) 3067 (br, vs), 2911 (m), 1459 (m), 1423 (m), 1404 (m), 1267 (w), 1212 (w), 1137 (m), 1031 (w), 846 (m), 775 (m), 693 (vs), 667 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.3 Hz, 2H), 7.67 (s, 1H), 7.48–7.43 (m, 3H), 7.39 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.3, 134.5, 134.2, 130.0, 128.7, 128.4, 128.2, 127.0, 125.2, 117.2, 105.2; MS (ES^+, Ar) m/z (rel. intensity) 249 (MNa^+, 9), 241 (13), 227 (MH^+, 100), 139 (4); HRMS (ES^+, Ar) calcd for $C_{13}H_{11}N_2S$ (MH^+) 227.0637, found 227.0637. Only mp and CHN data are reported in the literature.[34]

4-(Naphthalen-1-yl)-2-phenyl-1*H*-imidazole (9m). Off white solid; Yield 81%, 44 mg; mp 159–161 °C; IR (KBr, cm^{-1}) 3063 (br, vs), 2918 (s), 1499 (m), 1461 (s), 1414 (w), 1265 (m), 1142 (w), 954 (w), 822 (s), 775 (m), 737 (m), 693 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34–8.32 (m, 1H), 7.90–7.87 (m, 3H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.53–7.45 (m, 3H), 7.40–7.38 (m, 2H), 7.36–7.33 (m, 1H), 7.31 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.8, 138.2, 133.7, 130.9, 130.7, 130.3, 128.9, 128.4, 128.3, 127.5, 126.3, 126.2, 126.1, 125.8, 125.6, 125.2, 119.8; MS (ES^+, Ar) m/z (rel. intensity) 309 (MK^+, 26), 293 (MNa^+, 72), 271 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{19}H_{15}N_2$ (MH^+) 271.1230, found 271.1225.

(*E*)-2-Phenyl-4-styryl-1*H*-imidazole (9n). Yellow oily liquid; Yield 67%, 33 mg; IR (neat, cm^{-1}) 3203 (br, m), 3066 (m), 2954 (vs), 2926 (vs), 1600 (w), 1485 (m), 1463 (s), 1378 (vw), 1248 (s), 1026 (w), 754 (s), 706 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 7.92 (d, J = 6.6 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.33–7.25 (m, 5H), 7.16–7.23 (m, 2H), 7.11, 6.98 (ABq, J = 16.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 137.4, 136.1, 129.9, 129.0, 129.0, 128.8, 127.5, 127.5, 126.3, 125.9, 122.7, 117.7; MS (ES^+, Ar) m/z (rel. intensity) 269 (MNa^+, 20), 247 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{17}H_{15}N_2$ (MH^+) 247.1230, found 247.1230.

4-Cyclohexyl-2-phenyl-1*H*-imidazole (9o).[35] Colorless liquid; Yield 85%, 38 mg; IR (neat, cm^{-1}) 3401 (br, m), 2925 (s), 2852 (m), 1644 (w), 1463 (w), 1412 (w), 1266 (w), 1092 (w), 773 (w), 709 (w), 694 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.32–7.25 (m, 3H), 6.78 (s, 1H), 2.62–2.55 (m, 1H), 2.04–1.97 (m, 2H), 1.78–1.72 (m, 2H), 1.71–1.64 (m, 1H), 1.42–1.16 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 142.8, 129.8, 129.0, 128.8, 125.6, 118.1, 36.0, 33.1, 26.3, 26.2; MS (ES^+, Ar) m/z (rel. intensity) 228 ($[M + 2]^+$, 15), 227 (MH^+, 100);

HRMS (ES^+, Ar) calcd for $C_{15}H_{19}N_2$ (MH^+) 227.1543, found 227.1542. No experimental data are available.[35]

4-Butyl-2-phenyl-1*H*-imidazole (9p). Colorless liquid; Yield 75%, 30 mg; IR (neat, cm^{-1}) 3088 (br w), 2900 (w), 1499 (m), 1485 (s), 1460 (m), 1234 (vs), 1127 (m), 1034 (s), 936 (m), 694 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 2.59 (t, J = 7.6 Hz, 2H), 1.59 (quint, J = 7.6 Hz, 2H), 1.33 (sextet, J = 7.6 Hz, 2H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 137.9, 130.3, 129.0, 128.5, 125.4, 119.7, 31.6, 26.4, 22.5, 14.0; MS (ES^+, Ar) m/z (rel. intensity) 202 ($[M + 2]^+$, 11), 201 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{13}H_{17}N_2$ (MH^+) 201.1386, found 201.1385.

4-(4-Methoxyphenyl)-2-(*p*-tolyl)-1*H*-imidazole (10b). Colorless solid; Yield 87%, 46 mg; mp 116–118 °C; IR (KBr, cm^{-1}) 3401 (m), 2928 (s), 2854 (m), 1505 (m), 1441 (m), 1247 (s), 1175 (m), 1143 (m), 1088 (m), 1027 (s), 834 (m), 739 (m); ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.52 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 3.75 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 145.9, 137.4, 129.3, 128.0, 125.7, 124.9, 114.0, 55.1, 20.9; MS (ES^+, Ar) m/z (rel. intensity) 287 (MNa^+, 49), 265 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{17}H_{17}N_2O$ (MH^+) 265.1335, found 265.1333.

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (10c).[15b] Pale yellow solid; Yield 79%, 45 mg; mp 149–151 °C (lit[15b] 233–235 °C); IR (KBr, cm^{-1}) 2897 (br s), 1433 (s), 1245 (vs), 1142 (br s), 1026 (s), 835 (m), 738 (s); ^1H NMR (500 MHz, acetone-d_6) δ 8.07 (d, J = 8.5 Hz, 2H), 8.02 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.53 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.8, 145.1, 133.2, 129.9, 128.8, 126.6, 125.9, 113.9, 54.6; MS (ES^+, Ar) m/z (rel. intensity) 307 (MNa^+, 22), 287 ($[M + 2]^+$, 29), 285 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{16}H_{14}ClN_2O$ (MH^+) 285.0789, found 285.0788. The experimental data are consistent with those reported in the literature.[15b]

2-(3-Chlorophenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (10d). Greenish liquid; Yield 83%, 47 mg; IR (neat, cm^{-1}) 3374 (br s), 2834 (m), 1616 (m), 1508 (s), 1393 (vw), 1248 (vs), 1179 (m), 1031 (m), 834 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (br s, 1H), 7.76 (s, 1H), 7.67–7.65 (m, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.26 (s, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 145.9, 139.1, 134.8, 131.7, 130.1, 128.6, 126.6, 125.8, 124.9, 123.8, 117.7, 114.3, 55.5; MS (ES^+, Ar) m/z (rel. intensity) 286 ($[M + 2]^+$, 34), 285 (MH^+, 100), 129 (41); HRMS (ES^+, Ar) calcd for $C_{16}H_{14}ClN_2O$ (MH^+) 285.0789, found 285.0798.

4-(4-Methoxyphenyl)-2-(methylthio)-1*H*-imidazole (10e). Yellow oily liquid; Yield 55%, 24 mg; IR (neat, cm^{-1}) 3160 (br m), 2955 (br w), 2839 (br m), 1652 (w), 1602 (m), 1507 (m), 1464 (w), 1302 (w), 1250 (vs), 1181 (m), 1030 (m), 834 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.21 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 141.9, 139.3, 126.3, 125.2, 117.4, 114.3, 55.4, 17.5; MS (ES^+, Ar) m/z (rel. intensity) 237 ($[MH + H_2O]^+$, 15), 221 (MH^+, 100); HRMS (ES^+, Ar) calcd for $C_{11}H_{13}N_2OS$ (MH^+) 221.0743, found 221.0743.

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