Full Paper

A Novel Antifungal Agent with Broad Spectrum: 1-(4-Biphenylyl)-3-(1*H*-imidazol-1-yl)-1-propanone

Gheorghe Roman[1], Mihai Mareş[2], and Valentin Năstasă[2]

[1] Petru Poni Institute of Macromolecular Chemistry, Iaşi, Romania
[2] Ion Ionescu de la Brad University, Laboratory of Antimicrobial Chemotherapy, Iaşi, Romania

A series of (1-substituted aryl)-3-(1*H*-imidazol-1-yl)-1-propanones was synthesized through the *N*-alkylation of imidazole with 3-dimethylamino-1-(substituted aryl)-1-propanone hydrochlorides (ketonic Mannich bases). A second series of N^1-substituted imidazoles was obtained by the reduction of the carbonyl function of the imidazole–ketones in the previous series by means of $NaBH_4$. All of the compounds were evaluated for antifungal activity against 16 strains of *Candida*, and 3-(1*H*-imidazol-1-yl)-1-(4-biphenylyl)-1-propanone emerged as a broad-spectrum antifungal agent. Several 3-(1*H*-imidazol-1-yl)-1-(2′-(substituted benzyl)oxyphenyl)-1-propanones were also active towards *Candida kefyr*.

Keywords: Antifungal activity / Imidazoles / Mannich reaction / *N*-Alkylation

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Introduction

The last half-century has witnessed the increased incidence of fungal infections to the point they have become one of the most common affliction nowadays. Although most human populations affected by mycoses present only topical superficial and cutaneous varieties that are manageable, the number of nosocomial invasive and systemic fungal infections that are associated with considerable morbidity and mortality despite appropriate antifungal therapy has steadily grown, especially in the case of patients at high risk [1]. Some of the most frequent risk factors include the administration of strong antibiotics for a long time [2], or a weakened or compromised immune system due to organ transplant [3], cancer [4], steroid treatments [5, 6], or HIV infections [7]. Among the different pathogens responsible for fungal infections, the yeasts belonging to the *Candida* genus appear to have become the major cause for fungal nosocomial infections worldwide, with *Candida albicans* accounting for the majority of candidiases. The increased incidence of fungal infections is also accompanied by the emergence of strains that are resistant to antifungal treatment [8], which leads to serious limitations in the choice of an available efficient drug. Because transient resistance of *Candida* species to azole-containing antifungals after exposure to fluconazole has rendered the first-line drugs less and less effective, the addition of novel azoles to the antifungal armamentarium is necessary to address these therapeutic issues.

The azole antifungals that are usually used to treat *Candida* infections feature either an imidazole or a 1,2,4-triazole moiety as the pharmacophore. Their mechanism of action relies on the inhibition of the fungal cytochrome P450-dependent 14α-lanosterol demethylase through the binding of the N^3-atom of the azole moiety to iron heme [9, 10]. While the presence of an azole pharmacophore in the structure of an antifungal candidate is crucial, the nature of the substituent at N^1 of the azole moiety is also important for the fine tuning of the candidate's antifungal efficiency. In this respect, a higher affinity of the aromatic moieties of the N^1-substituent for the hydrophobic amino acids within the binding pocket of the enzyme, as well the presence of substituents capable of forming hydrogen bonds within the enzyme's active site, could make the difference between a good and a poor antifungal azole-containing candidate [11].

Many imidazole-containing antifungals in use have a linker of two carbon atoms between the pharmacophore and an aromatic moiety, but only limited information is available on the structure–antifungal activity for analogs

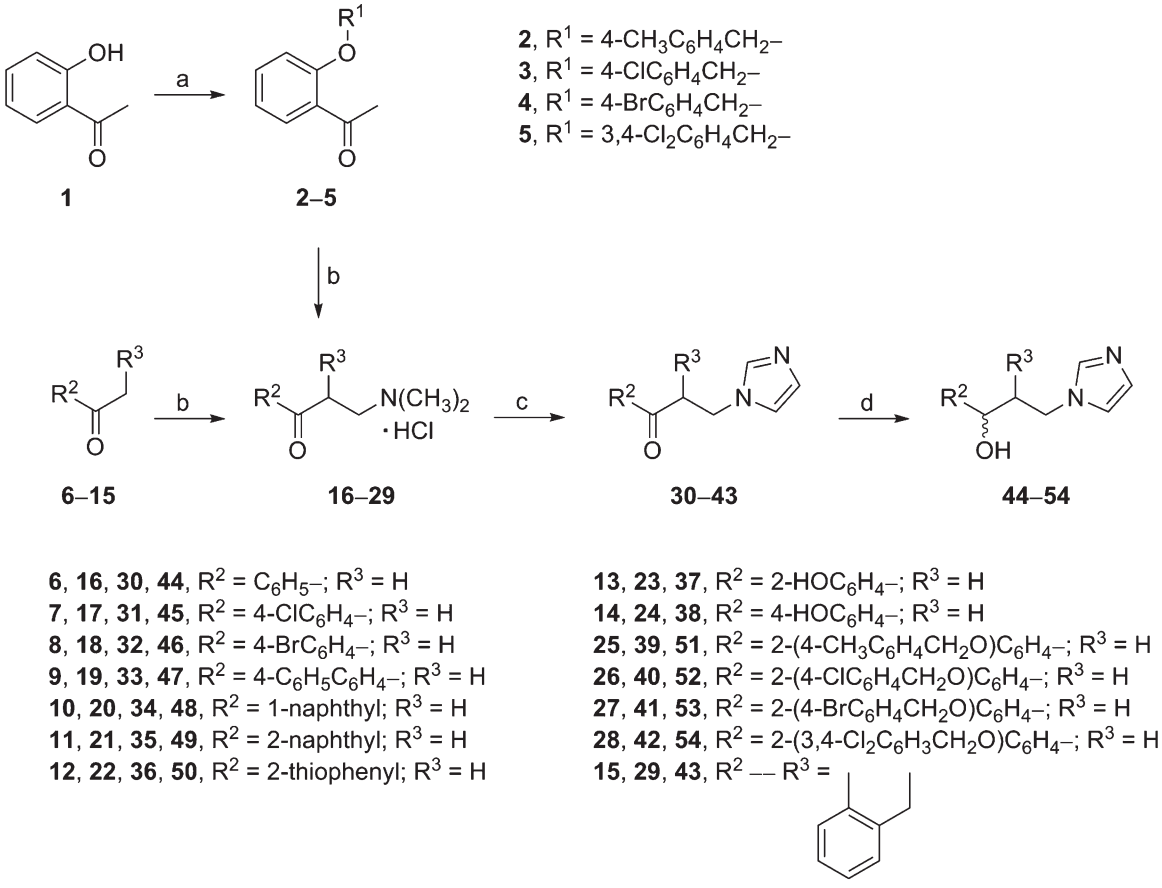
Correspondence: Dr. Gheorghe Roman, Petru Poni Institute of Macromolecular Chemistry, 41A Aleea Gr. Ghica Vodă, Iaşi 700487, Romania.
E-mail: gheorghe.roman@icmpp.ro
Fax: +40 232 211 299

having a three-carbon atom bridge between the pharmacophore and the aromatic moiety. Recently, the evaluation of the antifungal activity of a series of 1-(3-(substituted aryloxy)-3-(substituted aryl)propyl)-1*H*-imidazoles has shown that novel potent antifungal agents active against *C. albicans* could be designed by adept manipulation of the number, nature, and position of substituents in the phenyl ring and phenoxy groups [12, 13]. A few compounds in a small series of esters and tertiary alcohols having a propyl bridge between the imidazole pharmacophore and an unsubstituted phenyl ring possess also a minimal inhibitory concentration (MIC) comparable to that of miconazole or tioconazole [14]. These favorable results encouraged us to undertake the design and synthesis of a collection of 1-(3-(substituted aryl)-3-oxopropyl)-1*H*-imidazoles with the view of exploring the relevance of diverse substitution patterns in the aromatic moiety towards the antifungal activity. In addition, in order to garner insight into the influence of the oxygen-containing function on the propyl bridge on the antifungal activity of these imidazoles, a second library comprising the secondary alcohols corresponding to the compounds in the initial collection was synthesized and evaluated also.

Results and discussion

Chemistry

Four commercially unavailable 2′-benzyloxyacetophenones **2**–**5**, required as starting materials in the preparation of antifungal candidates, have been obtained in good yields through the *O*-alkylation of 2′-hydroxyacetophenone **1** with substituted benzyl halides in ethanol in the presence of sodium ethoxide (Scheme 1). Compounds **2**–**5** and other 11 commercially available ketones **6**–**15** were subjected to aminomethylation in the conditions of the Mannich reaction [15] to afford the ketonic Mannich bases **16**–**29** as hydrochlorides. The aminomethylated ketones **16**–**24** and **29** are known compounds, and their identities have been confirmed by comparing their melting points (see Experimental section) and ^{1}H- and ^{13}C NMR data with the ones reported in the literature. Compounds **25**–**28** are novel, and they have been



Scheme 1. Synthetic pathway for the preparation of imidazole–ketones **30**–**43** and imidazole–alcohols **44**–**54**. Reagents and conditions: (a) substituted benzyl halide, sodium ethoxide, ethanol, reflux, 5 h; (b) dimethylamine hydrochloride, paraformaldehyde, 37% HCl, ethanol, reflux 4–10 h; (c) imidazole, water, reflux, 1 h; (d) $NaBH_4$, methanol, rt, overnight.

fully characterized. *N*-Alkylation of imidazole with the aforementioned Mannich bases proceeded smoothly in water at reflux temperature to yield imidazole–ketones **30–43** as free bases (Scheme 1). With the exception of compounds **33** and **38**, the free bases were converted into the hydrochlorides by treatment of a solution of the crude imidazole–ketone in diethyl ether–2-propanol with ethereal HCl. Reduction of selected compounds from the imidazole–ketone collection by means of $NaBH_4$ in methanol gave imidazole–alcohols **44–54** as racemic mixtures (Scheme 1). The hydrochlorides of imidazole–alcohols **44–46**, **49**, and **54** were obtained in a similar manner as the hydrochlorides of imidazole–ketones.

Evaluation of antifungal activity

Compounds **30–54** were evaluated for their *in vitro* antifungal activity against a series of 16 strains of *Candida* belonging to the species *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. kefyr*, *C. krusei*, *C. parapsilosis*, *C. peliculosa*, and *C. tropicalis*. The antifungal screening of compounds **30–54** was carried out using the broth microdilution technique [16]. The antifungal activity of these compounds was compared to that of the standard antifungal drug fluconazole. Minimum inhibition concentrations (MICs) for the candidates and the standard drug were determined in 96-well tissue culture plates, and are presented in Table 1. Due to its very low solubility in dimethylsulfoxide, compound **38** could not be included in the investigation. One compound from this collection, namely 3-(1*H*-imidazol-1-yl)-1-(4-biphenylyl)-1-propanone **33**, emerged from the antifungal screening as a broad-spectrum antifungal agent. Compound **33** inhibited the growth of all of the strains of *Candida* used in this investigation. This candidate was more potent than fluconazole towards *C. glabrata* and *C. krusei*, and as potent as fluconazole towards *C. tropicalis*. Furthermore, out of the eight species of *Candida* in this study, the strains of *C. kefyr* appear to be sensitive to 13 candidates in this collection in various degrees. Although the antifungal activities of most of these candidates were similar for both strains of *C. kefyr*, the growth of one of these strains (RTCC 1019) was more inhibited by candidates **39–42** and **51–54**. In fact, compound **40** is twofold less potent, whereas compounds **39**, **41**, and **42** are fourfold less potent than the standard drug fluconazole towards this strain. Compounds **30**, **36**, **38**, **44**, **45**, and **48–50** exhibited MIC values higher than 64 mg/L against all of the *Candida* strains investigated in this study.

Structure–activity relationship

This study reports the antifungal activity for two structurally related series of imidazole-containing compounds. One series is comprised of compounds **30–43**, which have a 3-oxo-3-(substituted aryl)propyl moiety attached at N^1 of the imidazole ring, whereas the other series includes candidates

Table 1. Minimal inhibitory concentration values (mg/L) of the synthesized compounds against selected *Candida* strains.

Compound	*C. albicans* RTCC 1003	*C. albicans* RTCC 1024	*C. glabrata* RTCC 1040	*C. glabrata* RTCC 1054	*C. guilliermondii* RTCC 1248	*C. guilliermondii* RTCC 1377	*C. kefyr* RTCC 1019	*C. kefyr* RTCC 1074	*C. krusei* RTCC 1001	*C. krusei* RTCC 1090	*C. parapsilosis* RTCC 1018	*C. parapsilosis* RTCC 1079	*C. peliculosa* RTCC 1029	*C. peliculosa* RTCC 1075	*C. tropicalis* RTCC 1065	*C. tropicalis* RTCC 1095
31	>64	>64	>64	>64	>64	>64	16	8	>64	>64	>64	>64	>64	>64	64	>64
32	>64	>64	64	>64	32	64	4	8	>64	>64	64	64	64	32	>64	>64
33	8	4	4	32	1	4	2	2	8	8	1	8	8	8	2	1
34	>64	>64	64	>64	64	64	>64	64	>64	>64	64	64	>64	64	>64	64
35	>64	>64	64	64	64	64	16	32	>64	16	32	>64	>64	64	>64	8
37	>64	64	>64	>64	>64	>64	>64	64	>64	32	>64	>64	>64	>64	>64	>64
39	>64	>64	64	16	64	64	1	>64	>64	>64	>64	64	64	64	>64	>64
40	64	64	32	4	16	8	0.5	64	64	64	32	64	32	64	64	64
41	>64	>64	64	16	64	16	1	64	>64	>64	64	>64	64	64	>64	64
42	64	64	64	16	32	16	1	16	64	64	32	32	64	16	64	32
43	>64	>64	>64	>64	>64	>64	64	64	64	>64	>64	4	64	16	>64	>64
46	>64	64	64	>64	>64	>64	>64	>64	>64	>64	64	>64	>64	>64	>64	>64
47	>64	64	>64	>64	>64	>64	32	32	>64	>64	>64	64	>64	64	>64	>64
51	>64	>64	>64	>64	>64	>64	16	>64	>64	>64	>64	>64	>64	>64	>64	>64
52	>64	>64	>64	>64	>64	>64	8	>64	>64	>64	>64	>64	>64	>64	>64	>64
53	>64	>64	>64	>64	64	16	2	8	>64	>64	>64	>64	>64	>64	>64	>64
54	>64	32	>64	64	>64	64	4	4	>64	>64	>64	>64	>64	>64	>64	>64
Fluconazole	1	0.5	>64	64	4	0.5	0.25	0.25	32	32	0.25	0.5	2	4	1	1

44–54 featuring a 3-hydroxy-3-(substituted aryl)propyl appendage at N^1 of the imidazole ring. As a general observation, most of the compounds are ineffective towards the strains of *Candida* used in this study (MIC > 64 mg/L), irrespective of the substitution pattern in the aryl moiety, or the nature of the oxygen-containing function on the linker. However, within this collection, a small group consisting of compounds **39–42** and **51–54**, which all share a common 2′-(substituted benzyloxy)phenyl moiety at the end of the linker opposite to the pharmacophore, showed moderate to good activity towards *C. kefyr*. It is noteworthy that the most active candidates in this sub-group, namely compounds **39–42**, have a carbonyl function on the linker, whereas the corresponding alcohols **51–54** are less potent than the parent imidazole–ketones. This suggests that a more hydrophobic carbonyl function on the linker is better tolerated than the hydrophilic secondary alcohol function. Furthermore, it has been previously noted [17, 18] that the number of the chlorine atoms in the aromatic rings in the structure of antifungal candidates is one factor that contributes to the enhancement of the antifungal activity. However, in our hands, only a minor increase could be noticed in the antifungal activity of compound **42** (two chlorine atoms) compared to that of compounds **40** (one chlorine atom) or **39** (no chlorine atom). In the end, the compound that stands out as the most efficient and comprehensive antifungal agent within this collection is candidate **33**, 3-(1*H*-imidazol-1-yl)-1-(4-biphenylyl)-1-propanone. When compared to the analogous imidazole–ketones within this collection of compounds, the hit compound **33** presents an aromatic moiety that is amongst the most hydrophobic. Nevertheless, despite the fact that they also have highly hydrophobic naphthyl residues in their structure, compounds **34** and **35** are not potent antifungal agents. Therefore, we hypothesize that compound **33** owes its unique ability to inhibit broadly the growth of *Candida* yeasts not only to the hydrophobicity of the biphenyl residue, but also to the length of its molecule, which most likely allow compound **33** to interact extensively with hydrophobic amino acid residues within the active site of lanosterol 14-α-demethylase in *Candida*. In addition, compound **33** may exert its antifungal action through a dual mechanism of action, in a manner similar to bifonazole [19], another antifungal agent having a biphenyl moiety in its structure. Also, it appears that the excellent antifungal activity of compound **33** is the result of an unusually particular combination of structural elements, if one takes into consideration the lack of activity of the structurally related imidazole–alcohol **47**. Thus, despite the preservation of all the other structural characteristics, the simple replacement of the carbonyl function in **33** with a secondary alcohol group in **47** results in a compound that is no longer able to inhibit the growth of *Candida* yeasts.

Conclusion

The antifungal evaluation of a small library of novel, easily accessible imidazoles led to the discovery of 3-(1*H*-imidazol-1-yl)-1-(4-biphenylyl)-1-propanone as a broad-spectrum antifungal agent. This hit compound represents a novel and exciting template for future developments of more potent antifungal candidates through rational design that relies on the modifications pertaining to the length of the linker, the nature of the functional groups on the linker, or the substitution pattern of the biphenyl moiety.

Experimental

Materials and methods

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house, on a PerkinElmer 2400 Series II CHNS/O system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to $CDCl_3$ ($\delta = 77.16$ ppm) or d_6-DMSO ($\delta = 39.52$ ppm). High-resolution mass spectra (HRMS) were obtained on an Applied Biosystems/MDS Sciex QSTAR XL spectrometer equipped with an Agilent HP1100 Cap-LC system in electron ionization (EI) mode. A microplate reader model MR-96A (Mindray, China) was used to determine the MIC values.

The ketones **1** and **6–15**, the benzyl halides (4-methylbenzyl bromide, 4-chlorobenzyl bromide, 4-bromobenzyl bromide, 3,4-dichlorobenzyl chloride), paraformaldehyde, dimethylamine hydrochloride, and $NaBH_4$ used as starting materials and reagents in the synthesis were purchased from Sigma–Aldrich. The following ketonic Mannich bases were synthesized from the corresponding ketone through an adaptation of the procedure reported [20] for the direct aminomethylation of acetophenone with paraformaldehyde and dimethylamine hydrochloride: 3-dimethylamino-1-phenyl-1-propanone hydrochloride **16** (mp 153–154°C; lit. mp 153.6–153.7°C [21]), 1-(4-chlorophenyl)-3-dimethylamino-1-propanone hydrochloride **17** (mp 173–174°C; lit. mp 172.5–173.5°C [22]), 1-(4-bromophenyl)-3-dimethylamino-1-propanone hydrochloride **18** (mp 194–195°C; lit. mp 193°C [23]), 1-(4-biphenyl-1-yl)-3-dimethylamino-1-propanone hydrochloride **19** (mp 187–188°C; lit. mp 182–183°C [24]), 3-dimethylamino-1-(naphthalen-1-yl)-1-propanone hydrochloride **20** (mp 156–157°C; lit. mp 157–158°C [25]), 3-dimethylamino-1-(naphthalen-2-yl)-1-propanone hydrochloride **21** (mp 174–175°C; lit. mp 155–157°C [26]), 3-dimethylamino-1-(thiophen-2-yl)-1-propanone hydrochloride **22** (mp 184–185°C; lit. mp 184°C [27]), 3-dimethylamino-1-(2-hydroxyphenyl)-1-propanone hydrochloride **23** (mp 174–175°C; lit. mp 175–176°C [28]), 3-dimethylamino-1-(4-hydroxyphenyl)-1-propanone hydrochloride **24** (mp 199–200°C; lit. mp 192°C [29]), and (±)-2-dimethylaminomethyl-3,4-dihydronaphthalen-1(2*H*)-one hydrochloride **29** (mp 159–160°C; lit. mp: 154–155.5°C [30], 150°C [31], 145°C [32]).

The 16 yeast reference strains belonging to eight species that were used in this study, namely *C. albicans* RTCC 1003 and RTCC 1024, *C. glabrata* RTCC 1040 and RTCC 1054, *C. guilliermondii* RTCC 1248 and RTCC 1377, *C. kefyr* RTCC 1019 and RTCC 1074, *C. krusei*

RTCC 1001 and RTCC 1090, *C. parapsilosis* RTCC 1018 and RTCC 1079, *C. pelliculosa* RTCC 1029 and RTCC 1075, *C. tropicalis* RTCC 1065 and RTCC 1095, were obtained from the Romanian Type Culture Collection, and cultured according to the manufacturer's recommendation. Fluconazole, RPMI-1640 medium, 3-(*N*-morpholino)propanesulfonic acid (MOPS), glucose, and dimethylsulfoxide (DMSO) were obtained from Sigma–Aldrich.

Chemistry

*General procedure for the synthesis of 2′-(substituted-benzyloxy)acetophenones **2–5***

To a solution of sodium ethoxide (prepared by stirring ethanol (20 mL) and metallic sodium (460 mg, 20 g-atoms) at room temperature for 30 min) was added 2′-hydroxyacetophenone **1** (2.72 g, 20 mmol), and the mixture was stirred at room temperature for 5 min. After the substituted benzyl halide (20 mmol) had been added, the mixture was refluxed for 5 h and cooled to room temperature. Addition of water (50 mL) followed by 1% KOH solution (40 mL) resulted in the separation of the benzyloxyacetophenone. The solid compounds **3–5** were filtered, washed with water, and dried. Compound **2**, which separated as an oil, was extracted with ethyl acetate (2× 40 mL), the organic phase was washed with water (30 mL), and brine (30 mL), and then the solvent was removed under reduced pressure to give a residue that crystallized under high vacuum. Recrystallization from the appropriate solvent afforded the pure ketones.

*1-(2′-(4-Methylbenzyloxy)phenyl)ethanone **2***

Colorless crystals, 2.54 g (56%), mp 48–49°C (2-propanol–hexanes); ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.60 (s, 3H), 5.13 (s, 2H), 6.98–7.06 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.41–7.49 (m, 1H), 7.76 (dd, J = 2.0 and 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.3, 32.3, 70.7, 112.9, 120.9, 127.8, 128.8, 129.5, 130.6, 133.3, 133.7, 138.2, 158.2, 200.1; HRMS (EI): Calcd. for $C_{16}H_{16}O_2$: 240.1150 (M^+). Found: 240.1155.

*1-(2′-(4-Chlorobenzyloxy)phenyl)ethanone **3***

Colorless crystals, 3.96 g (74%), mp 74–75°C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 5.13 (s, 2H), 6.96–7.07 (m, 2H), 7.38 (s, 4H), 7.40–7.49 (m, 1H), 7.74 (dd, J = 2.0 and 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.1, 70.0, 112.9, 128.9, 129.0, 130.6, 133.7, 134.2, 134.8, 157.8, 199.9; HRMS (EI): Calcd. for $C_{15}H_{13}ClO_2$: 260.0604 (M^+). Found: 260.0601.

*1-(2′-(4-Bromobenzyloxy)phenyl)ethanone **4***

Colorless crystals, 4.94 g (81%), mp 85–86°C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 5.11 (s, 2H), 6.98 (d, J = 8.4 Hz, 1H), 7.00–7.06 (m, 1H), 7.29–7.35 (m, 2H), 7.41–7.48 (m, 1H), 7.51–7.57 (m, 2H), 7.74 (dd, J = 2.0 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.1, 70.1, 112.9, 121.2, 122.4, 129.0, 129.3, 130.7, 132.0, 133.7, 135.4, 157.8, 199.9; HRMS (EI): Calcd. for $C_{15}H_{13}BrO_2$: 304.0099 (M^+). Found: 304.0103.

*1-(2′-(3,4-Dichlorobenzyloxy)phenyl)ethanone **5***

Colorless crystals, 4.84 g (82%), mp 84–85°C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 3H), 5.11 (s, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.00–7.07 (m, 1H), 7.24–7.32 (m, 1H), 7.40–7.50 (m, 2H), 7.54 (s, 1H), 7.74 (dd, J = 2.0 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.0, 69.4, 112.9, 121.5, 126.8, 129.1, 129.5, 130.7, 130.9, 132.5, 133.1, 133.7, 136.6, 157.5, 199.7; HRMS (EI): Calcd. for $C_{15}H_{12}Cl_2O_2$: 294.0214 (M^+). Found: 294.0218.

General procedure for the synthesis of ketonic Mannich bases as hydrochlorides

A mixture of alkyl aryl ketone **2–15** (20 mmol), paraformaldehyde (1.2 g, 40 mmol), dimethylamine hydrochloride (1.79 g, 22 mmol), and 37% HCl (five drops) either in 2-propanol (10–15 mL) was heated under reflux for 6 h. The mixture was then cooled to approximately 50°C, and acetone (50 mL) was added gradually under efficient stirring. The mixture was kept in a freezer for 24 h, and then the crystals were filtered, washed with acetone, air-dried, and recrystallized from the appropriate solvent.

*3-Dimethylamino-1-(2′-(4-methylbenzyloxy)phenyl)-1-propanone hydrochloride **25***

Colorless crystals, 4.20 g (63%), mp 169–170°C (ethanol); ^{1}H NMR (CD_3OD): δ 2.36 (s, 3H), 2.75 (s, 6H), 3.38–3.50 (m, 4H), 7.02–7.10 (m, 1H), 7.22–7.30 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H), 7.53–7.61 (m, 1H), 7.80 (dd, J = 2.0 and 8.0 Hz, 1H); ^{13}C NMR (CD_3OD): δ 21.2, 39.6, 43.5, 54.3, 72.1, 114.6, 122.0, 127.6, 129.7, 130.5, 131.4, 134.7, 136.1, 139.6, 160.2, 199.0; Anal. calcd. for $C_{19}H_{24}ClNO_2$: C 68.35, H 7.25, N 4.20. Found: C 68.58, H 7.16, N 4.07.

*1-(2′-(4-Chlorobenzyloxy)phenyl)-3-dimethylamino-1-propanone hydrochloride **26***

Colorless crystals, 5.59 g (79%), mp 177–178°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 2.66 (s, 6H), 3.32 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 7.2 Hz, 2H), 5.28 (s, 2H), 7.08 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.54–7.61 (m, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.70 (dd, J = 1.6 and 7.6 Hz, 1H), 10.90 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.2, 42.0, 51.7, 69.3, 113.8, 120.8, 126.7, 128.6, 129.9, 130.0, 132.6, 134.4, 135.4, 157.5, 197.2; Anal. calcd. for $C_{18}H_{21}Cl_2NO_2$: C 61.02, H 5.97, N 3.95. Found: C 61.23, H 6.11, N 3.88.

*1-(2′-(4-Bromobenzyloxy)phenyl)-3-dimethylamino-1-propanone hydrochloride **27***

Colorless crystals, 5.74 g (72%), mp 172–173°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 2.66 (s, 6H), 3.32 (t, J = 7.4 Hz, 2H), 3.51 (t, J = 7.4 Hz, 2H), 5.27 (s, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.53–7.65 (m, 5H), 7.70 (dd, J = 1.6 and 7.6 Hz, 1H), 10.94 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.2, 42.0, 51.7, 69.3, 113.8, 120.8, 121.2, 126.7, 129.9, 130.3, 131.5, 134.4, 135.8, 157.4, 197.2; Anal. calcd. for $C_{18}H_{21}BrClNO_2$: C 54.22, H 5.31, N 3.51. Found: C 54.40, H 5.15, N 3.68.

*1-(2′-(3,4-Dichlorobenzyloxy)phenyl)-3-dimethylamino-1-propanone hydrochloride **28***

Colorless crystals, 5.13 g (66%), mp 159–160°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 2.69 (s, 6H), 3.34 (t, J = 7.4 Hz, 2H), 3.52 (t, J = 7.4 Hz, 2H), 5.29 (s, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.55–7.66 (m, 2H), 7.67–7.74 (m, 2H), 8.78 (d, J = 1.6 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.0, 42.0, 51.7, 68.6, 113.8, 121.0, 126.8, 128.4, 129.9, 130.6, 130.9, 131.1, 134.4, 137.6, 157.2, 197.3; Anal. calcd. for $C_{18}H_{20}Cl_3NO_2$: C 55.62, H 5.19, N 3.60. Found: C 55.43, H 5.04, N 3.79.

General procedure for the N-alkylation of imidazole with ketonic Mannich bases hydrochlorides

A ketonic Mannich base hydrochloride **16**–**29** (4 mmol) and imidazole (272 mg, 4 mmol) were heated under reflux in water (10 mL) for 1 h. The reaction mixture was then stirred in an ice bath until the oil that had initially separated crystallizes, and then the solid was filtered, washed thoroughly with water and air-dried. Alternatively, for compounds that do not become solid after 1 day, the oil was extracted with ethyl acetate (2 × 15 mL), the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. This crude imidazole–ketone was dissolved in a mixture of 2-propanol (4 mL) and diethyl ether (20–30 mL), treated with an excess of ethereal hydrogen chloride, and kept at room temperature overnight. The crystals were filtered, washed with diethyl ether, and recrystallized from the appropriate solvent to yield the imidazole–ketone hydrochloride.

*3-(1H-Imidazol-1-yl)-1-phenyl-1-propanone hydrochloride **30***

Off-white crystals, 570 mg (60%), mp 175–176°C (2-propanol) (lit. mp 174–176°C [33]); ^{1}H NMR (CD_3OD): δ 3.77 (t, J = 6.0 Hz, 2H), 4.69 (t, J = 6.0 Hz, 2H), 7.47–7.56 (m, 3H), 7.59–7.67 (m, 1H), 7.34 (t, J = 1.6 Hz, 1H), 7.97–8.05 (m, 2H), 9.05 (s, 1H); ^{13}C NMR (CD_3OD): δ 39.2, 45.5, 120.9, 123.6, 129.2, 129.9, 134.9, 137.2, 137.4, 198.3; Anal. calcd. for $C_{12}H_{13}ClN_2O$: C 60.89, H 5.54, N 11.84. Found: C 60.56, H 5.73, N 11.61.

*1-(4-Chlorophenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride **31***

Off-white crystals, 630 mg (58%), mp 174–175°C (2-propanol); ^{1}H NMR (CD_3OD): δ 3.73 (t, J = 6.0 Hz, 2H), 4.67 (t, J = 6.0 Hz, 2H), 7.49–7.57 (m, 3H), 7.69 (t, J = 1.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.98 (br s, 1H); ^{13}C NMR (CD_3OD): δ 39.3, 45.4, 120.9, 123.6, 130.1, 130.9, 135.9, 137.2, 141.1, 197.2; Anal. calcd. for $C_{12}H_{12}Cl_2N_2O$: C 53.16, H 4.46, N 10.33. Found: C 52.91, H 4.65, N 10.14.

*1-(4-Bromophenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride **32***

Off-white crystals, 670 mg (53%), mp 173–174°C (2-propanol); ^{1}H NMR (d_6-DMSO): δ 3.80 (t, J = 6.6 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 7.66 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.0, 43.7, 119.5, 122.2, 127.8, 130.0, 131.8, 134.9, 135.5, 196.4; Anal. calcd. for $C_{12}H_{12}BrClN_2O$: C 45.67, H 3.83, N 8.88. Found: C 45.88, H 3.98, N 9.09.

*1-(4-Biphenyl-1-yl)-3-(1H-imidazol-1-yl)-1-propanone **33***

Off-white crystals, 1015 mg (81%), mp 147–148°C (2-propanol) (lit. mp 149–151°C [34]); ^{1}H NMR (d_6-DMSO): δ 3.47 (t, J = 6.6 Hz, 2H), 4.45 (t, J = 6.6 Hz, 2H), 6.99 (s, 1H), 7.05 (s, 1H), 7.37–7.51 (m, 3H), 7.57 (s, 1H), 7.59–7.65 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H); ^{13}C NMR (d_6-DMSO): δ 40.0, 41.6, 119.2, 127.4, 127.5, 128.5, 128.7, 129.1, 129.8, 134.9, 137.6, 139.7, 146.5, 196.3; Anal. calcd. for $C_{18}H_{16}N_2O$: C 78.24, H 5.84, N 10.14. Found: C 78.47, H 5.97, N 10.02.

*3-(1H-Imidazol-1-yl)-1-(naphthalen-1-yl)-1-propanone hydrochloride **34***

Off-white crystals, 640 mg (56%), mp 131–132°C (2-propanol–ethyl acetate); ^{1}H NMR (d_6-DMSO): δ 3.91 (t, J = 6.4 Hz, 2H), 4.63 (t, J = 6.4 Hz, 2H), 7.56–7.67 (m, 3H), 7.68 (s, 1H), 7.89 (s, 1H), 8.03 (dd, J = 1.2 and 8.0 Hz, 1H), 8.15–8.24 (m, 2H), 8.52 (d, J = 8.4 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 40.8, 44.1, 119.6, 122.2, 124.8, 125.1, 126.5, 128.0, 128.6, 129.1, 129.3, 133.3, 133.5, 133.9, 135.6, 200.8; Anal. calcd. for $C_{16}H_{15}ClN_2O$: C 67.02, H 5.27, N 9.77. Found: C 66.79, H 5.46, N 9.96.

*3-(1H-Imidazol-1-yl)-1-(naphthalen-2-yl)-1-propanone hydrochloride **35***

Off-white crystals, 480 mg (42%), mp 185–186°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.95 (t, J = 6.6 Hz, 2H), 4.62 (t, J = 6.6 Hz, 2H), 7.60–7.72 (m, 3H), 7.88 (s, 1H), 7.96–8.07 (m, 3H), 8.13 (d, J = 8.0 Hz, 1H), 8.73 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.1, 44.0, 119.6, 122.2, 123.3, 127.1, 127.7, 128.4, 128.9, 129.6, 130.3, 132.1, 133.2, 135.2, 135.6, 197.1; Anal. calcd. for $C_{16}H_{15}ClN_2O$: C 67.02, H 5.27, N 9.77. Found: C 66.85, H 5.40, N 9.69.

*3-(1H-Imidazol-1-yl)-1-(thiophen-2-yl)-1-propanone hydrochloride **36***

Tan crystals, 515 mg (53%), mp 136–137°C (2-propanol); ^{1}H NMR (d_6-DMSO): δ 3.74 (t, J = 6.6 Hz, 2H), 4.54 (t, J = 6.6 Hz, 2H), 7.27 (dd, J = 4.0 and 4.8 Hz, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.83 (t, J = 1.6 Hz, 1H), 8.02 (dd, J = 1.2 and 4.0 Hz, 1H), 8.06 (dd, J = 1.2 and 4.8 Hz, 1H), 9.25 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.3, 43.8, 119.5, 122.2, 128.9, 134.1, 135.5, 135.6, 142.8, 190.1; Anal. calcd. for $C_{10}H_{11}ClN_2OS$: C 49.48, H 4.57, N 11.54. Found: C 49.75, H 4.79, N 11.29.

*1-(2-Hydroxyphenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride **37***

Colorless crystals, 215 mg (21%), mp 153–154°C (2-propanol); ^{1}H NMR (d_6-DMSO): δ 3.80 (t, J = 6.6 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 6.90–6.97 (m, 1H), 7.06 (dd, J = 0.8 and 8.4 Hz, 1H), 7.46–7.54 (m, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.78–7.86 (m, 2H), 9.23 (s, 1H), 11.47 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 40.2, 43.7, 117.7, 119.2, 119.5, 121.1, 122.2, 130.3, 135.6, 135.9, 160.0, 201.0; Anal. calcd. for $C_{12}H_{13}ClN_2O_2$: C 57.04, H 5.19, N 11.09. Found: C 57.32, H 5.44, N 10.81.

*1-(4-Hydroxyphenyl)-3-(1H-imidazol-1-yl)-1-propanone **38***

Off-white crystals, 750 mg (87%), mp 198–199°C; ^{1}H NMR (d_6-DMSO): δ 3.46 (t, J = 6.8 Hz, 2H), 4.29 (t, J = 6.8 Hz, 2H), 6.81–6.87 (m, 3H), 7.19 (s, 1H), 7.64 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 10.47 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.7, 41.4, 115.2, 119.4, 127.9, 128.2, 130.3, 137.4, 162.3, 195.7; Anal. calcd. for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.96. Found: C 66.39, H 5.81, N 12.65.

*3-(1H-Imidazol-1-yl)-1-(2′-(4-methylbenzyloxy)phenyl)-1-propanone hydrochloride **39***

Colorless crystals, 1025 mg (72%), mp 182–183°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 2.31 (s, 3H), 3.62 (t, J = 6.8 Hz, 2H), 4.47 (t, J = 6.8 Hz, 2H), 5.20 (s, 2H), 7.05 (t, J = 7.4 Hz, 1H), 7.17

(d, J = 7.6 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.53–7.60 (m, 1H), 7.63–7.69 (m, 3H), 9.13 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 20.8, 43.5, 44.0, 70.1, 114.0, 119.5, 120.7, 122.0, 126.7, 128.0, 129.0, 129.8, 133.2, 134.5, 135.4, 137.4, 157.9, 197.7; Anal. calcd. for $C_{20}H_{21}ClN_2O_2$: C 67.32, H 5.93, N 7.85. Found: C 67.11, H 6.03, N 8.02.

1-(2′-(4-Chlorobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride ***40***

Colorless crystals, 1220 mg (81%), mp 177–178°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.64 (t, J = 6.6 Hz, 2H), 4.49 (t, J = 6.6 Hz, 2H), 5.25 (s, 2H), 7.06 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.53–7.60 (m, 1H), 7.64 (t, J = 1.6 Hz, 1H), 7.67 (dd, J = 1.6 and 7.6 Hz, 1H), 7.71 (t, J = 1.6 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 43.3, 44.0, 69.3, 113.9, 119.5, 120.9, 122.0, 126.7, 128.5, 129.7, 129.8, 132.6, 134.4, 135.4, 135.5, 157.5, 197.7; Anal. calcd. for $C_{19}H_{18}Cl_2N_2O_2$: C 60.49, H 4.81, N 7.43. Found: C 60.62, H 4.89, N 7.28.

1-(2′-(4-Bromobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride ***41***

Off-white crystals, 1435 mg (85%), mp 178–179°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.64 (t, J = 6.8 Hz, 2H), 4.49 (t, J = 6.8 Hz, 2H), 5.24 (s, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.53–7.61 (m, 3H), 7.64 (s, 1H), 7.67 (dd, J = 1.6 and 7.6 Hz, 1H), 7.72 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 43.2, 44.0, 69.3, 113.9, 119.5, 120.9, 121.2, 122.0, 126.7, 129.8, 130.0, 131.4, 134.4, 135.5, 135.8, 157.5, 197.7; Anal. calcd. for $C_{19}H_{18}BrClN_2O_2$: C 54.11, H 4.30, N 6.64. Found: C 54.27, H 4.16, N 6.83.

1-(2′-(3,4-Dichlorobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanone hydrochloride ***42***

Colorless crystals, 1270 mg (77%), mp 164–165°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.66 (t, J = 6.8 Hz, 2H), 4.49 (t, J = 6.8 Hz, 2H), 5.27 (s, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 1.6 and 8.0 Hz, 1H), 7.54–7.61 (m, 1H), 7.62–7.67 (m, 2H), 7.69 (dd, J = 1.6 and 7.6 Hz, 1H), 7.73 (s, 1H), 7.78 (d, J = 1.6 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 43.2, 44.0, 68.6, 113.9, 119.5, 121.0, 122.0, 126.7, 128.0, 129.7, 129.9, 130.6, 130.7, 131.1, 134.5, 135.5, 137.6, 157.3, 197.6; Anal. calcd. for $C_{19}H_{17}Cl_3N_2O_2$: C 55.43, H 4.16, N 6.80. Found: C 55.25, H 4.33, N 6.68.

(±)-2-(1H-Imidazol-1-ylmethyl)-3,4-dihydronaphthalen-1(2H)-one hydrochloride ***43***

Off-white crystals, 545 mg (52%), mp 156–157°C (2-propanol); ^{1}H NMR (d_6-DMSO): δ 1.73–1.88 (m, 1H), 1.99–2.09 (m, 1H), 2.92–3.14 (m, 2H), 3.30–3.43 (m, 1H), 4.45 (dd, J = 6.4 and 13.6 Hz, 1H), 4.71 (dd, J = 6.0 and 14.0 Hz, 1H), 7.32–7.40 (m, 2H), 7.54–7.61 (m, 1H), 7.69 (t, J = 1.6 Hz, 1H), 7.79 (t, J = 1.6 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 26.1, 27.9, 46.8, 48.4, 119.6, 122.6, 126.5, 126.7, 129.1, 131.5, 133.9, 135.9, 144.2, 197.1; Anal. calcd. for $C_{14}H_{15}ClN_2O$: C 64.00, H 5.75, N 10.66. Found: C 64.26, H 5.51, N 10.47.

General procedure for the reduction of imidazole–ketones

To the solution of imidazole–ketone (3 mmol) in methanol (20 mL), $NaBH_4$ (342 mg, 9 mmol) was added in small portions, under good stirring, at room temperature. The reaction mixture was then stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between water (30 mL) and ethyl acetate (15 mL). The aqueous phase was further extracted with ethyl acetate (15 mL), the organic phases were combined, washed with water (15 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give a residue. In the case of compounds **47**, **48**, and **50–53**, the residue was crystallized from the appropriate solvent. The other imidazole–alcohols were converted into the corresponding hydrochlorides by treating a solution of the residue in a mixture of 2-propanol (4 mL) and diethyl ether (20–30 mL) with an excess of ethereal hydrogen chloride. After being kept at room temperature overnight, the crystals were filtered, washed with diethyl ether, and recrystallized from the appropriate solvent to yield the imidazole–alcohol hydrochlorides **44–46**, **49**, and **54**.

(±)-3-(1H-Imidazol-1-yl)-1-phenyl-1-propanol hydrochloride ***44***

Off-white crystals, 385 mg (54%), mp 100–101°C (2-propanol–hexanes); ^{1}H NMR (d_6-DMSO): δ 2.03–2.25 (m, 2H), 4.26–4.40 (m, 2H), 4.54 (dd, J = 3.8 and 9.0 Hz, 1H), 5.68 (br s, 1H), 7.19–7.37 (m, 5H), 7.67 (t, J = 1.6 Hz, 1H), 7.83 (t, J = 1.6 Hz, 1H), 9.23 (s, 1H), 14.93 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.8, 46.0, 69.1, 119.6, 122.0, 125.6, 126.9, 128.1, 135.3, 145.1; Anal. calcd. for $C_{12}H_{15}ClN_2O$: C 60.38, H 6.33, N 11.74. Found: C 60.52, H 6.21, N 11.62.

(±)-1-(4-Chlorophenyl)-3-(1H-imidazol-1-yl)-1-propanol hydrochloride ***45***

Colorless crystals, 345 mg (42%), mp 149–150°C (2-propanol–diethyl ether); ^{1}H NMR (d_6-DMSO): δ 2.01–2.13 (m, 1H), 2.13–2.25 (m, 1H), 4.24–4.38 (m, 2H), 4.55 (dd, J = 3.6 and 9.2 Hz, 1H), 5.81 (br s, 1H), 7.37 (s, 4H), 7.67 (s, 1H), 7.83 (s, 1H), 9.23 (s, 1H), 14.91 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.6, 45.9, 68.4, 119.6, 122.1, 127.6, 128.0, 131.4, 135.3, 144.2; Anal. calcd. for $C_{12}H_{14}Cl_2N_2O$: C 52.76, H 5.17, N 10.26. Found: C 52.60, H 5.32, N 10.07.

(±)-1-(4-Bromophenyl)-3-(1H-imidazol-1-yl)-1-propanol hydrochloride ***46***

Off-white crystals, 665 mg (70%), mp 165–166°C (2-propanol–diethyl ether); ^{1}H NMR (d_6-DMSO): δ 2.00–2.13 (m, 1H), 2.13–2.25 (m, 1H), 4.24–4.38 (m, 2H), 4.54 (dd, J = 3.6 and 9.2 Hz, 1H), 5.80 (br s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 1.6 Hz, 1H), 7.83 (t, J = 1.6 Hz, 1H), 9.22 (s, 1H), 14.89 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.6, 45.9, 68.5, 119.6, 119.9, 122.0, 127.9, 131.0, 135.3, 144.6; Anal. calcd. for $C_{12}H_{14}BrClN_2O$: C 45.38, H 4.44, N 8.82. Found: C 45.54, H 4.26, N 9.01.

(±)-1-(4-Biphenyl-1-yl)-3-(1H-imidazol-1-yl)-1-propanol ***47***

Colorless crystals, 590 mg (71%), mp 141–142°C (2-propanol) (lit. mp 144–145°C [34]); ^{1}H NMR ($CDCl_3$): δ 2.04–2.25 (m, 2H), 3.99–4.09 (m, 1H), 4.19–4.29 (m, 1H), 4.53 (dd, J = 3.6 and 8.8 Hz, 1H), 4.58 (br s, 1H), 6.93 (s, 1H), 6.97 (s, 1H), 7.31–7.47 (m, 6H), 7.53–7.60 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 40.0, 43.8, 69.9, 118.9, 126.3, 127.2, 127.4, 127.5, 128.9, 129.3, 137.5, 140.7, 140.8,

143.5; Anal. calcd. for $C_{18}H_{18}N_2O$: C 77.67, H 6.52, N 10.06. Found: C 77.85, H 6.33, N 9.89.

(±)-3-(1H-Imidazol-1-yl)-(naphthalen-1-yl)-1-propanol ***48***

Tan crystals, 535 mg (71%), mp 152–153°C (2-propanol); ^{1}H NMR ($CDCl_3$): δ 2.10–2.35 (m, 2H), 3.99–4.11 (m, 1H), 4.27–4.39 (m, 1H), 4.49 (br s, 1H), 5.20 (dd, J = 3.0 and 9.4 Hz, 1H), 6.92 (s, 1H), 6.97 (s, 1H), 7.35–7.51 (m, 4H), 7.65–7.73 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 39.2, 44.0, 66.9, 118.9, 122.6, 123.0, 125.6, 125.7, 126.3, 128.1, 129.1, 129.5, 130.1, 133.9, 137.8, 140.1; Anal. calcd. for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10. Found: C 76.31, H 6.12, N 11.31.

(±)-3-(1H-Imidazol-1-yl)-(naphthalen-2-yl)-1-propanol hydrochloride ***49***

Colorless crystals, 657 mg (76%), mp 165–166°C (2-propanol); ^{1}H NMR (d_6-DMSO): δ 2.14–2.25 (m, 1H), 2.25–2.36 (m, 1H), 4.28–4.44 (m, 2H), 4.72 (dd, J = 3.6 and 8.8 Hz, 1H), 5.80 (br s, 1H), 7.44–7.55 (m, 3H), 7.67 (t, J = 1.6 Hz, 1H), 7.82–7.92 (m, 5H), 9.23 (s, 1H), 14.82 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 38.6, 46.0, 69.2, 119.6, 122.1, 123.9, 124.3, 125.6, 126.1, 127.5, 127.7, 132.3, 132.8, 135.3, 142.6; Anal. calcd. for $C_{16}H_{17}ClN_2O$: C 66.55, H 5.93, N 9.70. Found: C 66.37, H 6.05, N 9.86.

(±)-3-(1H-Imidazol-1-yl)-1-(thiophen-2-yl)-1-propanol ***50***

Colorless crystals, 410 mg (66%), mp 102–103°C (2-propanol–hexanes); ^{1}H NMR ($CDCl_3$): δ 2.15–2.32 (m, 2H), 4.01–4.09 (m, 1H), 4.20–4.29 (m, 1H), 4.54 (br s, 1H), 4.74 (dd, J = 4.6 Hz and 9.0 Hz, 1H), 6.90–6.97 (m, 3H), 6.98 (s, 1H), 7.23 (dd, J = 1.2 and 4.8 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 40.1, 43.7, 65.8, 119.0, 123.7, 124.7, 126.9, 129.1, 137.5, 148.7; Anal. calcd. for $C_{10}H_{12}N_2OS$: C 57.67, H 5.81, N 13.45. Found: C 57.43, H 5.98, N 13.27.

(±)-3-(1H-Imidazol-1-yl)-1-(2′-(4-methylbenzyloxy)-phenyl)-1-propanol ***51***

Colorless crystals, 665 mg (69%), mp 128–129°C (2-propanol); ^{1}H NMR ($CDCl_3$): δ 2.05–2.28 (m, 2H), 2.37 (s, 3H), 3.74 (br s, 1H), 3.96–4.07 (m, 1H), 4.09–4.20 (m, 1H), 4.82 (dd, J = 3.6 and 9.6 Hz, 1H), 4.98 (dd, J = 11.2 and 19.2 Hz, 2H), 6.76 (s, 1H), 6.89–7.03 (m, 3H), 7.15–7.27 (m, 5H), 7.37 (s, 1H), 7.41 (dd, J = 1.2 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.3, 38.0, 43.9, 66.6, 70.2, 111.9, 118.9, 121.3, 126.7, 127.7, 128.6, 129.3, 129.5, 132.4, 133.6, 137.5, 138.2, 155.5; Anal. calcd. for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69. Found: C 74.34, H 7.03, N 8.54.

(±)-1-(2′-(4-Chlorobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanol ***52***

Colorless crystals, 845 mg (82%), mp 144–145°C (2-propanol); ^{1}H NMR ($CDCl_3$): δ 1.99–2.11 (m, 1H), 2.14–2.25 (m, 1H), 3.94–4.05 (m, 1H), 4.11 (br s, 1H), 4.15–4.26 (m, 1H), 4.83 (dd, J = 3.2 and 9.6 Hz, 1H), 4.95 (dd, J = 11.6 and 26.4 Hz, 2H), 6.77 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.17–7.26 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.48 (dd, J = 1.2 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 37.9, 43.8, 65.7, 69.4, 111.7, 118.9, 121.5, 126.8, 128.6, 128.8, 129.0, 129.2, 132.7, 134.1, 135.2, 137.6, 155.0; Anal. calcd. for $C_{19}H_{19}ClN_2O_2$: C 66.57, H 5.59, N 8.17. Found: C 66.41, H 5.77, N 8.06.

(±)-1-(2′-(4-Bromobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanol ***53***

Colorless crystals, 870 mg (75%), mp 131–132°C (2-propanol); ^{1}H NMR ($CDCl_3$): δ 2.02–2.26 (m, 2H), 3.85 (br s, 1H), 3.97–4.07 (m, 1H), 4.15–4.26 (m, 1H), 4.83 (dd, J = 3.2 and 9.2 Hz, 1H), 4.94 (dd, J = 11.6 and 24.4 Hz, 2H), 6.78 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.21–7.27 (m, 1H), 7.41 (s, 1H), 7.44–7.51 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 38.0, 43.8, 65.9, 69.4, 111.7, 118.9, 121.6, 122.2, 126.8, 128.7, 129.1, 129.2, 132.0, 132.6, 135.7, 137.6, 155.0; Anal. calcd. for $C_{19}H_{19}BrN_2O_2$: C 58.93, H 4.95, N 7.23. Found: C 59.13, H 5.09, N 7.11.

(±)-1-(2′-(3,4-Dichlorobenzyloxy)phenyl)-3-(1H-imidazol-1-yl)-1-propanol hydrochloride ***54***

Colorless crystals, 845 mg (68%), mp 115–116°C (ethanol); ^{1}H NMR (d_6-DMSO): δ 1.95–2.09 (m, 1H), 2.13–2.27 (m, 1H), 4.23–4.43 (m, 2H), 4.86 (dd, J = 2.4 and 8.8 Hz, 1H), 5.11 (dd, J = 13.2 and 14.4 Hz, 2H), 5.55 (br s, 1H), 6.94–7.03 (m, 2H), 7.17–7.25 (m, 1H), 7.35 (dd, J = 1.6 and 8.4 Hz, 1H), 7.47 (dd, J = 1.2 and 7.6 Hz, 1H), 7.61 (s, 1H), 7.65–7.72 (m, 2H), 7.75 (s, 1H), 9.21 (s, 1H), 14.79 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 37.3, 45.9, 63.2, 67.7, 111.8, 119.6, 120.9, 122.0, 126.3, 127.4, 127.9, 129.2, 130.3, 130.8, 131.1, 133.2, 135.4, 138.4, 153.8; Anal. calcd. for $C_{19}H_{19}Cl_3N_2O_2$: C 55.16, H 4.63, N 6.77. Found: C 55.29, H 4.44, N 6.90.

Antifungal evaluation

In vitro antifungal susceptibility was evaluated using the guidelines of EUCAST EDef. 7.1 [35]. Fluconazole was used as positive control. The tests were performed in RPMI-1640 medium buffered with MOPS, and supplemented with 2% glucose. From each compound to be tested, a stock solution containing 12,800 μg/mL was prepared by dissolving 100 mg substance in 7.8 mL DMSO. Fluconazole was dissolved in pure, sterile water. The solutions of the tested compounds were prepared by a serial twofold dilution starting from the stock solutions, with the view to reach the following final concentrations: 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, and 0.125 mg/L. The 96-well microplates containing the solutions of the tested compounds at these concentrations were prepared and stored in a freezer at approximately −20°C until they were used (but no more than 1 month). The final content of the inoculum was adjusted to 10^5 CFU/mL. MIC values were determined spectrophotometrically, by measuring the absorbance at 450 nm using an MR-96A microplate reader after 24 or 48 h (depending on the species) of incubation at 36°C. The MIC endpoint was defined as the lowest concentration of tested compound for which at least a reduction of 50% in growth compared to that of the negative control (no tested compound in the well) was noticed, as reflected by measurements of the optical density.

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