Original article

CAN catalyzed one-pot synthesis and docking study of some novel substituted imidazole coupled 1,2,4-triazole-5-carboxylic acids as antifungal agents

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A B S T R A C T

The present work describes a facile, one-pot three component synthesis of a series of 3-[(4,5-diphenyl-2-substituted aryl/heteryl)-1*H*-imidazol-1-yl]-1*H*-1,2,4-triazole-5-carboxylic acid derivatives **M(1–15)**. Benzil, aromatic aldehydes and 3-amino-1,2,4-triazole-5-carboxylic acid was refluxed in ethanol using cerric ammonium nitrate (CAN) as a catalyst to give the title compounds in good yields. The compounds were evaluated for their *in vitro* antifungal and antibacterial activity. Compounds **M1**, **M9**, and **M15** were found to be equipotent against *Candida albicans* when compared with fluconazole. Compounds **M2**, **M5**, and **M14** showed higher activity against *Streptococcus pneumoniae*, *Escherichia coli* and *Streptococcus pyogenes*, respectively, compared with ampicillin. Docking study of the newly synthesized compounds was performed, and the results showed good binding mode in the active sites of *C. albicans* enzyme cytochrome P450 lanosterol 14α-demethylase. The results of *in vitro* antifungal activity and docking study showed that synthesized compounds had potential antifungal activity and can be further optimized and developed as a lead compound.

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1. Introduction

Multicomponent reactions (MCRs) are powerful synthetic tools which have modified the landscape of organic and medicinal chemistry because of environmental concerns by reducing the number of synthetic steps, waste production and energy consumption. MCRs offer the advantage of simplicity in synthetic work up and efficiency over conventional chemical reactions. This necessitates search and discovery for newer MCRs. Imidazole nucleus has been reported to exhibit variety of biological activities [1–3].

The incidences of systemic fungal infections are increasing dramatically due to an increase in the number of patients undergoing organ transplants, anticancer chemotherapy and patients with AIDS. Commonly used azole antifungal agents are fluconazole, itraconazole, miconazole and voriconazole and have broad-spectrum antifungal activity. These antifungal drugs act by inhibiting CYP51 in the process of biosynthesis of ergosterols through a mechanism in which the heterocyclic nitrogen atom binds to the heme iron atom. However, the increased use of these antifungal drugs has led to the development of resistance to these drugs. Thus, there is an urgent need for development of antifungal agents [4].

Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Imidazole possesses various medicinal properties that include anticancer [5], anticoagulants [6], anti-inflammatory [7,8], antibacterial and antifungal [9–12], antiviral [13], anti tubercular [14,15]. Thus, the high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. 1, 2, 4-Triazole ring has drawn great attention to medicinal chemists due to its wide variety of activities including antibacterial [16–18] and antifungal [19–22], anticancer [23,24] and antioxidant [25,26]. These two heterocyclic moities are important core for antifungal activity. In the present work, our objective was to design (Fig. 1) and synthesize new compounds having imidazole moiety coupled with 1, 2, 4-triazole ring with the hope to get enhanced antifungal activity.

Several methods have been reported for the synthesis of poly substituted imidazoles using variety of catalysts like tandem three-component reaction of hydroxylamines, aldehydes and 2-azido acrylates [27]. Various catalysts like BiCl₃ [28] and Alumina [29]
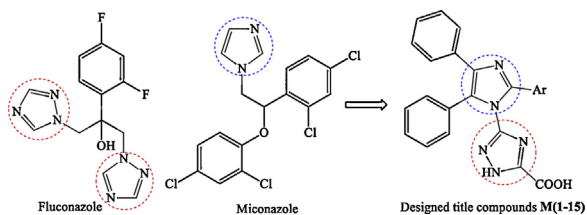
Fig. 1. Designing protocol for target compound.

have been reported for synthesis of tetra substituted imidazoles from benzyl, amines and aldehydes. Ceric (IV) ammonium nitrate (CAN) is a convenient and widely used catalyst for affecting a wide array of synthetic transformations due to its many advantages such as solubility in organic solvents, low toxicity, high reactivity and ease of handling [30]. Due to our increased interest for search of new antifungal agents having imidazole ring coupled with 1,2,4-triazol, here we report a facile one-pot three component synthesis of novel 3-[(4,5-diphenyl-2-substituted aryl/heteryl)-1H-imidazol-1-yl]-1H-1,2,4-triazole-5-carboxylic acids M(1–15) using ceric ammonium nitrate (CAN) as a catalyst, in good yield as antifungal agent. The activity result and docking study revealed that compounds could be exploited as an antifungal drug.

2. Experimental

2.1. Chemistry

All the chemicals used for synthesis were of Merck, Sigma, Research lab, Qualigens and Hi media. Infrared (IR), proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds on JASCO FTIR (PS 4000) using KBr pallet, Brucker Avance II (400 MHz) instruments and AVANCE 300 MHz, respectively. Chemical shifts are reported in parts per million (ppm), using TMS as an internal standard. The mass spectra were recorded on 410 Prostar Binary LC with 500 MS IT PDA Detectors. Elemental analyses (C, H, and N) were undertaken with a Shimadzu's FLASHEA112 analyzer and all analyses were consistent with theoretical values (within ±0.4%), unless indicated. The synthetic protocol employed for the synthesis of 3-[(4,5-diphenyl-2-substituted aryl/heteryl)-1H-imidazol-1-yl]-1H-1,2,4-triazole-5-carboxylic acid is presented in Scheme 1. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes and are uncorrected. The physical characterization data of the synthesized compounds are presented in Table 1.

General procedure for the synthesis of 3-[(4,5-diphenyl-2-substituted aryl/heteryl)-1H-imidazol-1-yl]-1H-1,2,4-triazole-5-carboxylic acid M(1–15): A mixture of benzil (0.01 mol), aldehydes

(0.01 mol), 3-amino-1,2,4-triazole-5-carboxylic acid (0.01 mol), ammonium acetate (0.01 mol) and ceric ammonium nitrate (15 mol%) as a catalyst were refluxed in ethanol (15 mL) for about 3–4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature. The solid formed was filtered and dried. The crude products were recrystallized by ethanol.

2.2. Biological activity

The antifungal activity was evaluated against human pathogenic fungal strains, such as *Candida albicans* (MTCC 227), *Aspergillus clavatus* (MTCC 1323), *Aspergillus niger* (MTCC 282), which are often encountered clinically and were compared with standard drugs like fluconazole and miconazole. From the series of synthesized compounds M(1–15), we have also performed antibacterial activity of 10 selected compounds like M1, M2, M3, M5, M8, M9, M10, M11, M14 and M15. The antibacterial activity was evaluated against strains such as *Escherichia coli* (MTCC 443), *Streptococcus pneumoniae* (MTCC 109), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442) and were compared with standard ampicillin. Minimum inhibitory concentration (MIC) values were determined using standard agar method [31].
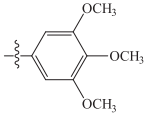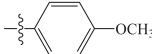
2.3. Docking study
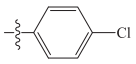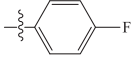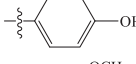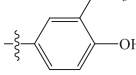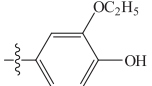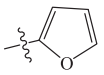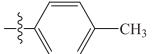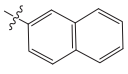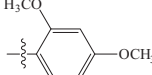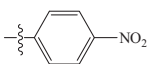
Homology modeling: The 3D model structure of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* was built using homology modeling with the help of VLifeMDS 4.3 ProModel as reported by Sangshetti *et al.* [32]. Amino acid sequence of enzyme was obtained from the Universal Protein Resource (http://www.uniprot.org/) (Accession Code: P10613) and sequence homologous was obtained from Protein Data Bank (PDB) using Blast search. Based on the result of blast search, we used the crystal structure of human lanosterol 14α-demethylase (CYP51) with azole as a template for homology modeling (PDB ID: 3LD6) [33]. The alignment of amino acid sequence of CA-CYP51 (P10613) and human CYP51 (3LD6_B) is given in Fig. S1 (Supporting information). The quality of generated *C. albicans* lanosterol 14α-demethylase model was assessed by using the well-validated program likes PROCHECK [34] and its structural validation is shown in Fig. S2 (Supporting information).

Docking of ligands: The synthesized compounds M(1–15) and standard drug fluconazole and miconazole were docked with the target protein. The 2D structures of synthesized compounds and standard drugs were drawn using VLife2Draw 1.0 and converted to 3D confirmations. The conformers thus obtained, were optimized (MMFF) till they reached a rms gradient energy of 0.001 kcal/(mol Å). The docking of the conformers of


Where Ar = 1) Aromatic

R = OCH$_3$, OH, Cl, F, OC$_2$H$_5$, CH$_3$, NO$_2$

2) Heteryl
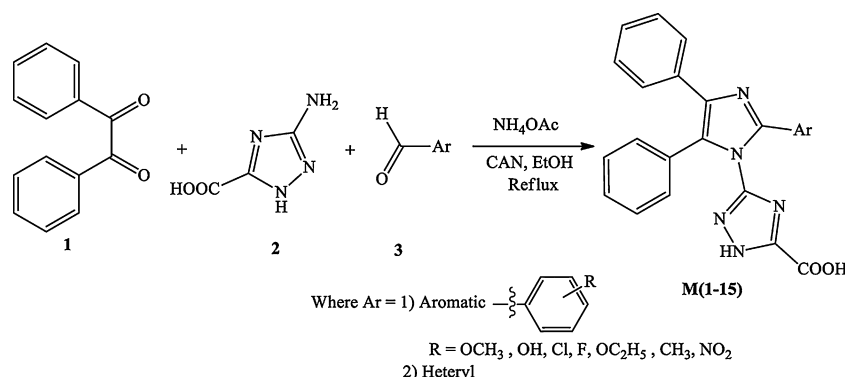
Scheme 1. Synthetic route for a target compounds M(1–15).

Table 1
Physical characterization of the synthesized compounds **M (1–15)**.

Compd.	Ar	Mol. formula (mol. weight)	Yield (%)	Mp (°C)[a]	R_f value
M1	(3,4,5-tri-OCH₃-phenyl)	$C_{27}H_{23}N_5O_5$ (497.50)	79	200–202	0.75
M2	(phenyl)	$C_{24}H_{17}N_5O_2$ (407.42)	77.88	118–120	0.55
M3	(2-HO-phenyl)	$C_{24}H_{17}N_5O_3$ (423.42)	79.66	109–110	0.62
M4	(4-OCH₃-phenyl)	$C_{25}H_{19}N_5O_3$ (437.45)	72.08	238–240	0.42
M5	(4-Cl-phenyl)	$C_{24}H_{16}ClN_5O_2$ (441.87)	66.43	140–143	0.58
M6	(4-F-phenyl)	$C_{24}H_{16}FN_5O_2$ (425.41)	72.70	198–200	0.78
M7	(4-OH-phenyl)	$C_{24}H_{17}N_5O_3$ (423.42)	81.56	130–131	0.52
M8	(2-OCH₃-4-OH-phenyl)	$C_{25}H_{19}N_5O_4$ (453.45)	77.48	138–140	0.70
M9	(3-OC₂H₅-4-OH-phenyl)	$C_{26}H_{21}N_5O_4$ (467.48)	90.36	120–121	0.69
M10	(furan-2-yl)	$C_{22}H_{15}N_5O_3$ (397.39)	81.86	136–138	0.83
M11	(4-CH₃-phenyl)	$C_{25}H_{19}N_5O_2$ (421.45)	70.30	153–155	0.64
M12	(CH₃)	$C_{19}H_{15}N_5O_2$ (345.35)	88.69	98–100	0.65
M13	(naphthyl)	$C_{28}H_{19}N_5O_2$ (457.48)	92.99	158–160	0.77
M14	(3,4-di-OCH₃-phenyl)	$C_{26}H_{21}N_5O_4$ (467.48)	75.76	118–120	0.65
M15	(4-NO₂-phenyl)	$C_{24}H_{16}N_6O_4$ (452.42)	69.91	168–170	0.55

[a] Mp was uncorrected; solvent system chosen for R_f value determination was n-hexane: ethyl acetate (4:1).

each molecule, into the lanosterol 14α-demethylase (CYP51) modeled protein was done by positioning with the active site of cavity 1. The complexes were then minimized using the MMFF method, till they reached an rms gradient of 0.1 kcal/(mol Å). The above procedures were performed using the VLife MDS 4.3 package [35].

3. Results and discussion

3.1. Chemistry

All the titled compounds **M(1–15)** were synthesized as per the synthetic protocol presented in Scheme 1. Initially, benzil (0.01 mol), benzaldehyde (0.01 mol), 3-amino-1,2,4-triazole-5-carboxylic acid (0.01 mol) and ammonium acetate (0.01 mol) were employed as reactants for the model reaction to synthesize compound **M2**. For the optimization of the reaction conditions, we evaluated the effect of different catalysts for model reaction using ethanol as solvent. A wide variety of catalysts (15 mol%) including oxalic acid, sulphamic acid, boric acid, oxalic acid, ZnO and ceric ammonium nitrate (CAN) were used to test their efficacy for the synthesis of model compound **M2**. Among the results, best yield was obtained for CAN (92% yield) compared with other catalysts (Table S1, Supporting information).

After deciding the catalyst, the synthetic protocol was extended for synthesis of 3-[(4,5-diphenyl-2-substituted aryl/heteryl)-1H-imidazol-1-yl]-1H-1,2,4-triazole-5-carboxylic acids **M(1–15)**. Benzil, various aldehydes, 3-amino-1,2,4-triazole-5-arboxylic acid and ammonium acetate was refluxed in ethanol using CAN (15 mol%) as a catalyst for about 3–4 h. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes melting point apparatus and are uncorrected. The physical data of the synthesized compounds are presented in Table 1. The data obtained from ¹H NMR, ¹³C NMR, mass and elemental analysis confirmed the proposed structures (spectral data results are provided in Supporting information). The products were obtained in good yield (80%–93%).

3.2. In vitro antifungal activity

The results of in vitro antifungal activity (Table 2) showed that all the compounds exhibited good to moderate antifungal activity. Amongst the synthesized series some derivatives were found to have moderate activity against C. albicans, A. niger, and A. clavatus as compared with fluconazole. Compounds **M9** and **M15** showed highest activity against C. albicans when compared with miconazole. The compounds **M1**, **M8** and **M10** (MIC = 500 μg/mL against C. albicans) were equipotent when compared with miconazole. The compounds **M2**, **M11** and **M14** (MIC = 250 μg/mL against A. niger and A. clavatus) were equipotent when compared with standard drugs.

From the antifungal activity data in Table 2, it is observed that scaffolds 1, 2, 4-triazole and various substituents at aromatic ring were responsible for antifungal activity. Substitution on aromatic aldehyde by 4-OH and 3-OC₂H₅ as in compound **M9** and 4-NO₂ group in the compound **M15** enhances the antifungal activity.

3.3. In vitro antibacterial activity

The result of in vitro antibacterial activity (Table 3) showed that all the compounds (MIC range = 62.5–500 μg/mL) possess moderate antibacterial activity when compared with ampicillin (MIC range = 100–250 μg/mL). From the series, compound **M5** showed higher activity (MIC = 62.5 μg/mL against E. coli), **M2** (MIC = 62.5 μg/mL against S. pneumoniae) and **M14** (MIC = 62.5 μg/mL against S. pyogenes) when compared with ampicillin. Compound **M14** showed higher activity (MIC = 100 μg/mL against S. aureus) when compared with ampicillin.

From the antibacterial activity data, phenyl **(M2)**, 4-Cl-pheny **(M5)** and 4-OCH₃-phenyl were more active than other derivatives.

3.4. Docking study

The synthesized compounds **M(1–15)** and standard drugs (fluconazole and miconazole) were docked into the active site of cytochrome P450 lanosterol 14α-demethylase of C. albicans

Table 2
In vitro antifungal evaluation of the synthesized compounds **M(1–15)**.

| Entry | Antifungal activity (MIC values in µg/mL)[a] | | | Docking result | |
	C. albicans	*A. niger*	*A. clavatus*	H-interaction	Binding energy (kcal/mol)
M1	500	500	500	PRO498-NH of triazole ring; LEU412-C=O of triazole ring; LEU412-OH of COOH	−67.79
M2	1000	250	250	TYR168-NH of triazoles; TYR168-4N of triazole ring	−52.47
M3	>1000	>1000	>1000	TYR168-OH of phenyl ring; LEU412-C=O of triazole ring; LEU412-OH of COOH of triazole ring	−54.54
M4	>1000	>1000	>1000	SER414-NH of triazole ring; SER414-OH of COOH	−53.23
M5	>1000	>1000	>1000	TYR168-NH of triazole ring	−57.38
M6	1000	1000	1000	TYR168-NH of triazole ring	−57.50
M7	500	1000	1000	TYR168-NH of triazole ring	−58.45
M8	500	1000	1000	LEU412-NH of triazoles	−62.17
M9	250	500	500	LEU412-C=O of COOH; LEU412-OH of COOH	−71.66
M10	500	1000	1000	GLY339-OH of COOH; CYS506-O of furan ring	−64.18
M11	>1000	250	250	–	−59.83
M12	>1000	>1000	>1000	**–**	−59.01
M13	1000	1000	1000	GLY339-OH of COOH	−70.28
M14	1000	250	250	PRO498-NH of triazole ring; LEU412-C=O of triazole ring; LEU412-OH of COOH	−54.97
M15	250	1000	1000	TYR168-C=O of COOH; GLY500-N of NO₂-phenyl	−77.02
STD1	100	100	100	TYR168-F of phenyl	−67.00
STD2	500	100	100	–	−60.12

^a Data represents the mean values of three replicates; STD 1 = Fluconazole; STD 2 = Miconazole.

Table 3
In vitro antibacterial evaluation of synthesized compounds **M(1–15)**.

| Compd. | Antibacterial activity (MIC values in µg/mL)[a] | | | |
	E. coli	*S. pneumoniae*	*S. aureus*	*S. pyogenes*
M1	250	125	250	250
M2	100	62.5	250	250
M3	200	125	500	250
M5	62.5	100	500	100
M8	125	125	250	100
M9	250	200	200	200
M10	250	100	250	250
M11	100	100	200	200
M14	100	500	100	62.5
M15	200	250	250	250
Ampicillin	100	100	250	100

^a Data represents the mean values of three replicates.

using VLifeMDS 4.3 software package to understand the binding interactions. The docking calculation and hydrogen bond interactions data obtained are presented in Table 2. The interaction energy of the synthesized compounds and their antifungal activity showed the corresponding results. The active compounds **M9** and **M15** showed lowest binding interaction energy, *i.e.* −71.66 and −77.02 kcal/mol, respectively. The docking result indicated that synthesized compounds were held in the active pocket by forming combination of hydrogen bonds, hydrophobic bonds and van der Waals interactions with the enzyme. The docking study also revealed that only triazole ring had formed various hydrogen bonding interactions with enzyme suggesting that triazole ring is more important for inhibiting the 14α-demethylase of *C. albicans* when in combination with imidazole ring. The –COOH group of triazole ring had formed the various hydrogen bonds with amino acids residue like TYR168, GLY339, LEU412, and SER414. Thus, suggesting that –COOH group is important for antifungal activity. The interactions of compound **M15** and fluconazole are shown in Fig. 2. In case of compound **M15**, amino acids TYR168 and GLY500 had formed hydrogen bonds with O=C of –COOH and nitrogen of –NO₂, respectively. On the basis of activity data and docking results, it was found that the compound **M15** had potential to inhibit 14α-demethylase of *C. albicans*.
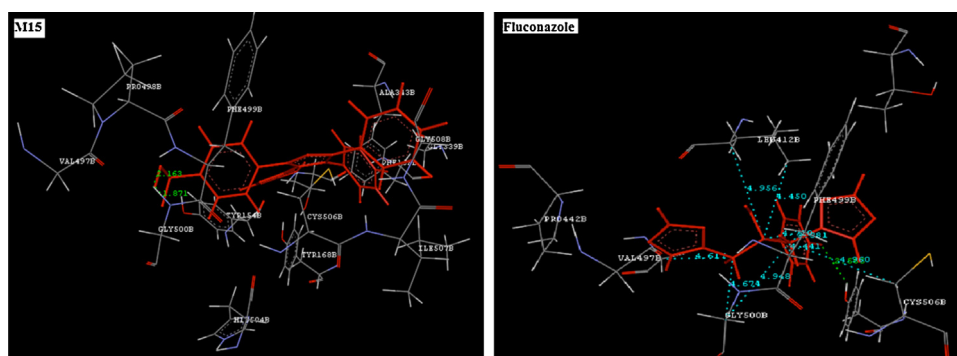

Fig. 2. Docking of compound **M15** and fluconazole. Ligands are shown in red color. Hydrogen bonds are shown in green color. Hydrophobic bonds are shown in sky blue color.

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4. Conclusion

In conclusion, a novel imidazole coupled 1,2,4-triazole-5-carboxylic acid derivatives **M(1–15)** were synthesized using CAN as a catalyst and were evaluated for their antifungal and antimicrobial activity. Use of CAN as a catalyst in ethanol under reflux helped in synthesis of expected derivatives in good yields proving its better use. Based on the antifungal activity data, it is observed that compounds **M9** (MIC = 250 μg/mL) and **M15** (MIC = 250 μg/mL) were more potent against *C. albicans* when compared with miconazole (MIC = 500 μg/mL). Thus, suggesting that 3-ethoxy-4-hydroxyphenyl and 4-nitrophenyl at 2nd position of imidazole ring is favorable for potent antifungal activity. For antibacterial activity, compounds **M2** (Ar = phenyl) and **M5** (Ar = *p*-Cl-phenyl) were more potent against *S. pneumoniae* (MIC = 62.5 μg/mL) and *E. coli* (MIC = 62.5 μg/mL), respectively, when compared with ampicillin (MIC = 100 μg/mL). The compound **M14** (Ar = 2,4-dimethoxyphenyl) have shown potent activity against *S. aureus* (MIC = 100 μg/mL) and *S. pyogenes* (MIC = 62.5 μg/mL) when compared with ampicillin. Further, the docking studies of synthesized compounds with lanosterol 14α-demethylase (CYP51) modeled protein showed good binding interactions and formed various hydrophobic interactions with active site residues. Thus, suggesting that the compounds from the present series **M9** and **M15** (antifungal activity), **M2**, **M5**, and **M14** (antibacterial activity) can be further optimized and can be developed as a lead molecule.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.10.020.

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