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Synthesis, antimicrobial evaluation and docking study of triazole containing triaryl-1*H*-imidazole

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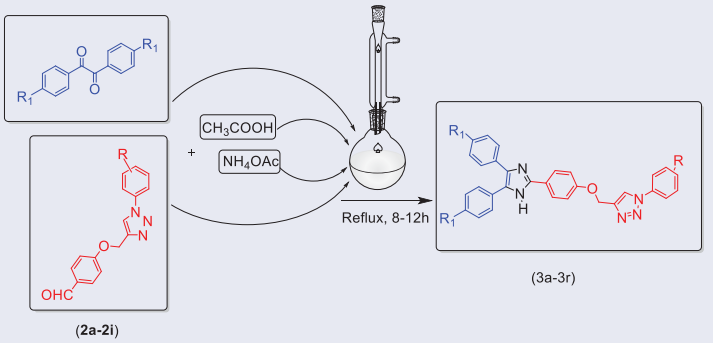
ABSTRACT

An efficient route for the synthesis of triazole containing triaryl-1*H*-imidazole (**3a**–**3r**) was achieved involving multicomponent condensation of triazole aldehydes, ammonium acetate and 1,2-dicarbonyl compounds in glacial acetic acid. The structure of newly synthesized imidazoles was established by the FTIR, HRMS and NMR spectra. All the compounds displayed considerable antimicrobial activity against fungal and bacterial strains. The triazolyl imidazole **3p** was substantially potent against *P. aeruginosa* (0.0113 μmol/mL), *A. niger* (0.0113 μmol/mL) and *C. albicans* (0.0056 μmol/mL) wherein triazolyl imidazoles **3i** was found to be more potent against *B. subtilis* (0.0122 μmol/mL) & *A. niger* (0.0121 μmol/mL); and compound **3r** was also found to be more potent against *S. epidermidis* (0.0117 μmol/mL) & *C. albicans* (0.0058 μmol/mL). As a result of docking studies, the binding affinity of the compound **3o** was –9.6 kcal/mol which was even more in comparison to the binding affinity of co-crystallized ligand CBN (–9.4 kcal/mol).

GRAPHICAL ABSTRACT



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Introduction

Among the variety of five membered-heterocyclic compounds, imidazole possesses widespread range of applications,[1] effective biological activity[2] and synthetic utility.[3] Many compounds having imidazole moiety play vital roles in biochemical processes[4] and exhibits pharmacological properties. Imidazole derivatives demonstrate binding affinity with different metals, which are present in various biological active sites.[5] Imidazole derivatives display good inhibitory activity against tumor & bacteria,[6] inflammation,[4] and show good pesticidal,[7] cytotoxic[8] and antioxidant activity.[9,10]

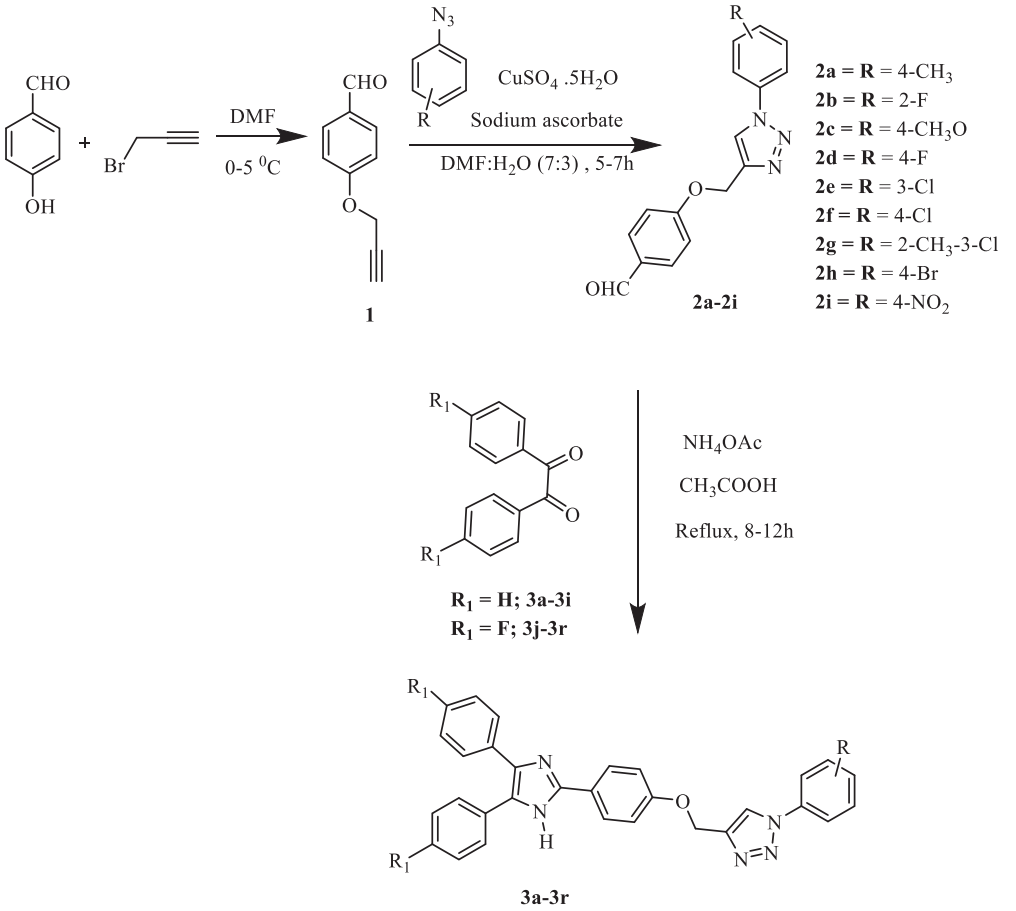
Triazole is also a class of important N-heterocyclic molecules endowed with wide spectrum of bioactivity and display antimicrobial, antiviral, antimalarial and anticancer activities.[11–14] This has attracted the chemist worldwide to design better therapeutic molecules having different azole moieties so that combination of two scaffolds may result in displaying more pharmacological activity. Therefore, we aimed to tether substituted traizoles with suitably functionalized imidazolyl scaffolds via aryloxy methylene spacer to yield synergistic effect on antimicrobial and antifungal activities and their docking study. The structure of these triazolyl imidazoles were established utilizing different spectral techniques (FTIR, 1D-NMR, 2D-NMR and HRMS) and evaluated for antimicrobial activity against gram negative as well as gram positive and two fungal strains.

Results and discussion

Chemistry

The triazole substituted aryl aldehydes[15] (**2a**–**2i**) were obtained in good yield by reacting 4-(prop-2-yn-1-yloxy)benzaldehyde (**1**) with different organic azides in presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate using DMF:H_2O (7:3) as solvent at room temperature for 5–7 h. The resultant triazole aldehydes (**2a**–**2i**) were then reacted with 1,2-dicarbonyl compounds and ammonium acetate under reflux for 8–12 h thus generating 4-((4-(4,5-diaryl-1*H*-imidazol-2-yl)phenoxy)methyl)-1-substituted-1*H*-1,2,3-triazole (**3a**–**3r**) in good yield (Scheme 1). All the synthesized compounds were characterized by analyzing their FTIR, HRMS and NMR spectra.

The structure of compound **3a** was identified by analyzing the FTIR, 1D-NMR (^{1}H, 13C and DEPT-135), 2D-NMR (COSY, ROESY, HSQC, HMBC) and HRMS data. In the FTIR spectrum, the band at 3614 cm^{-1} was due to N–H stretching of imidazole ring and the appearance of band at 3124 cm^{-1} was assigned to C–H stretching of triazole ring. In the ^{1}H NMR spectrum of compound **3a**, two singlets at δ 5.29 ppm (2H) and 8.86 ppm (1H) were assigned to CH_2O and C–H of triazole ring, respectively. A broad singlet at δ 12.70 ppm (1H) was established due to N–H of imidazole ring. The two doublets at δ 7.40 ppm and 7.76 ppm were attributed to $C_{8'}$–H, $C_{10'}$–H and $C_{7'}$–H, $C_{11'}$–H, respectively. Similarly, another phenyl group attached with imidazole ring showed two doublets at δ 8.03 ppm and 7.18 ppm which were attributed to C_8–H, C_{10}–H and C_7–H, C_{11}–H, respectively. A doublet of four protons at δ 7.49 ppm was endorsed to C_{13}–H, C_{17}–H and C_{19}–H, C_{23}–H, respectively. In 13C NMR spectrum of **3a**, peak at δ 123.32 and 144.11 ppm were assigned for tertiary carbon and quaternary



Scheme 1. Synthesis of triazole containing triaryl-1*H*-imidazole (**3a**–**3r**).

carbon of triazole ring, respectively and peak at δ 133.23 ppm was due to quaternary carbon of imidazole ring. In DEPT-135 spectrum of **3a**, there appeared eight carbon signals for methine carbons, one carbon signal of methylene and another carbon signal of methyl group.

The connectivity of all hydrogen atoms in **3a**, through intervening bond was established by COSY (Correlation Spectroscopy) and through space by ROESY (Rotational Frame Overhauser Effect Spectroscopy) techniques. The ^{1}H–^{1}H correlation between vicinal protons of phenyl rings $H_{8'}/H_{10'}$ with $H_{7'}/H_{11'}$ and H_8/H_{10} with H_7/H_{11}, respectively was corroborated through COSY spectrum. In ROESY spectrum, the hydrogen of methylene (CH_2) are found to be near to the hydrogen at position-5′ of triazole ring (Fig. 1).

The carbon-hydrogen correlations were established by analyzing the HSQC (Heteronuclear Single-Quantum Coherence) spectrum of **3a** that revealed the position of carbon signals at δ 21.01 (CH_3), 61.47 (OCH_2), 115.46 (C-8, C-10), 120.56 (C-7′, C-11′), 123.32 (C-5′), 123.53 (C-12, C-18), 127.42 (C-7, C-11), 127.71 (C-15, C-21), 128.25 (C-14, C-16, C-20, C-22), 128.92 (C-13, C-17, C-19, C-23), 130.77 (C-8′, C-10′), 133.23 (C-2, C-4, C-5), 134.70 (C-9′), 139.06 (C-6′), 144.11 (C-1′), 146.1 (C-6), 158.75

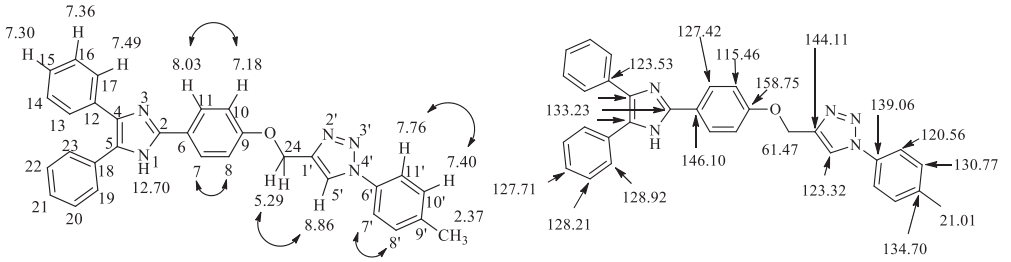


Figure 1. ^{1}H and ^{13}C NMR of compound **3a**.

(C-9) ppm, because the key correlation was δ 2.37→21.01, 5.29→61.47, 7.18→115.46, 7.30→127.71, 7.36→128.21, 7.40→130.77, 7.49→128.92, 7.76→120.56, 8.03→127.42 and 8.86→123.32 ppm.

Heteronuclear Multiple Bond Correlation (HMBC) experiment established the connectivity of hydrogen with other carbons through multiple bond correlation of signals at δ 2.37–130.77 and 134.70, 7.40 to 21.01, 120.56 and 134.70, 5.29 to 123.32, 144.11 and 158.57 ppm. HMBC gives the information of carbon atom having two and three bond coupling with hydrogens. Analysis of spectrum clearly indicated that proton 5′-H attached with carbon C-5′ showed two bond coupling with C-1′ at δ 144.11 ppm and three-bond coupling with CH_2 at δ 61.47 ppm, respectively (Fig. 1). Mass spectrometry also confirmed the structure of **3a** by observing the molecular ion; HRMS (*m/z*) calculated for $C_{31}H_{25}N_5O$: 483.2059. Found $[M+H]^+$: 484.1923. All the other compounds (**3b**–**3r**) were similarly characterized.

Antimicrobial activity

The newly constructed 4-((4-(4,5-diaryl-1*H*-imidazol-2-yl)phenoxy)methyl)-1-substituted-1*H*-1,2,3-triazoles were monitored for *in-vitro* antibacterial activity against bacterial strain (*B. subtilis*, *S. epidermidis, E. coli*, and *P. aeruginosa)* and also monitored for antifungal activity against fungal strains (*C. albicans* and *A. niger*). Sabouraud dextrose broth-I.P. and nutrient broth-I.P. were employed for fungal and bacterial growth, respectively. Minimum Inhibitory Concentrations (MIC in µmol/mL) were scrutinized by serial dilution method[12,13] through a stock solution of 100 µg/mL and values in µmol/mL are presented in Tables 1 and 2. The synthesized compounds exhibited considerable activity against the used strains, where ciprofloxacin and fluconazole were used as reference drugs in case of antibacterial and antifungal activities, respectively.

Antibacterial and antifungal activity

In general, the synthesized 4-((4-(4,5-diaryl-1*H*-imidazol-2-yl)phenoxy)methyl)-1-substituted-1*H*-1,2,3-triazoles displayed MIC value from 0.0513 to 0.0113 µmol/mL as compared to reference drug ciprofloxacin (0.0047 µmol/mL) against antibacterial strains. Among them, **3 h** (0.0114 µmol/mL) and **3p** (0.0113 µmol/mL) were substantially potent against *P. aeruginosa* and **3o** (0.0116 µmol/mL) showed promising activity against *E. coli*. Compounds **3r** (0.0117 µmol/mL) and **3i** (0.0122 µmol/mL) were found to be more potent against *S. epidermidis* and *B. subtilis,* respectively (Table 1). Most of the

Table 1. *In vitro* antibacterial screening of compounds **3a–3r** (MIC in μmol/mL).

Entry	Compounds	R_1	R	*B. subtilis*	*S. epidermidis*	*E. coli*	*P. aeruginosa*
1	**3a**	H	4-CH_3	0.0259	0.0259	0.0259	0.0259
2	**3b**	H	2-F	0.0257	0.0257	0.0257	0.0257
3	**3c**	H	4-CH_3O	0.0250	0.0250	0.0250	0.0250
4	**3d**	H	4-F	0.0257	0.0513	0.0513	0.0513
5	**3e**	H	3-Cl	0.0248	0.0248	0.0248	0.0497
6	**3f**	H	4-Cl	0.0248	0.0497	0.0248	0.0248
7	**3g**	H	2-CH_3–3-Cl	0.0242	0.0483	0.0241	0.0121
8	**3h**	H	4-Br	0.0228	0.0457	0.0228	0.0114
9	**3i**	H	4-NO_2	0.0122	0.0243	0.0243	0.0243
10	**3j**	F	4-CH_3	0.0240	0.0240	0.0240	0.0120
11	**3k**	F	2-F	0.0478	0.0239	0.0239	0.0239
12	**3l**	F	4-NO_2	0.0227	0.0227	0.0227	0.0227
13	**3m**	F	4-F	0.0239	0.0239	0.0239	0.0239
14	**3n**	F	3-Cl	0.0232	0.0232	0.0232	0.0232
15	**3o**	F	4-Cl	0.0232	0.0232	0.0116	0.0464
16	**3p**	F	2-CH_3–3-Cl	0.0452	0.0226	0.0226	0.0113
17	**3q**	F	4-Br	0.0214	0.0214	0.0429	0.0214
18	**3r**	F	4-CH_3O	0.0234	0.0117	0.0467	0.0234
19	Ciprofloxacin	–	–	0.0047	0.0047	0.0047	0.0047

Table 2. *In vitro* antifungal screening of compounds **3a–3r** (MIC in μmol/mL).

Entry	Compounds	R_1	R	*A. niger*	*C. albicans*
1	**3a**	H	4-CH_3	0.0258	0.0129
2	**3b**	H	2-F	0.0257	0.0128
3	**3c**	H	4-CH_3O	0.0125	0.0063
4	**3d**	H	4-F	0.0128	0.0064
5	**3e**	H	3-Cl	0.0248	0.0062
6	**3f**	H	4-Cl	0.0248	0.0062
7	**3g**	H	2-CH_3–3-Cl	0.0242	0.0060
8	**3h**	H	4-Br	0.0114	0.0057
9	**3i**	H	4-NO_2	0.0121	0.0243
10	**3j**	F	4-CH_3	0.0481	0.0060
11	**3k**	F	2-F	0.0478	0.0060
12	**3l**	F	4-NO_2	0.0227	0.0057
13	**3m**	F	4-F	0.0234	0.0060
14	**3n**	F	3-Cl	0.0116	0.0058
15	**3o**	F	4-Cl	0.0227	0.0058
16	**3p**	F	2-CH_3–3-Cl	0.0113	0.0056
17	**3q**	F	4-Br	0.0429	0.0107
18	**3r**	F	4-CH_3O	0.0233	0.0058
19	Fluconazole	–	–	0.0102	0.0051

compounds with fluorine at R_1 position were found to be more active against all the bacterial strain and *C. albicans*. However, in compounds with fluorine at R_1 position, the presence of any substituents (R) at position-2 led to decrease in the activity against *B. subtilis* whereas, the compound having methoxy substituent at position-4 was found to possess increased activity against *S. epidermidis*. In case of gram negative bacteria 4-Cl derivative showed maximum activity while 4-OCH_3 and 4-Br derivative exhibited minimum activity against *E. coli*. The methyl substitution (R) at position-4 led to highest activity of compound against *P. aeruginosa*.

The synthesized compounds showed good to moderate antifungal activity with MIC value from 0.0481 to 0.0056 μmol/mL as compared to reference drug fluconazole against *A. niger* (0.0102 μmol/mL) and *C. albicans* (0.0051 μmol/mL). All compounds were discreetly active against the fungal species and compound **3p** was observed to be more

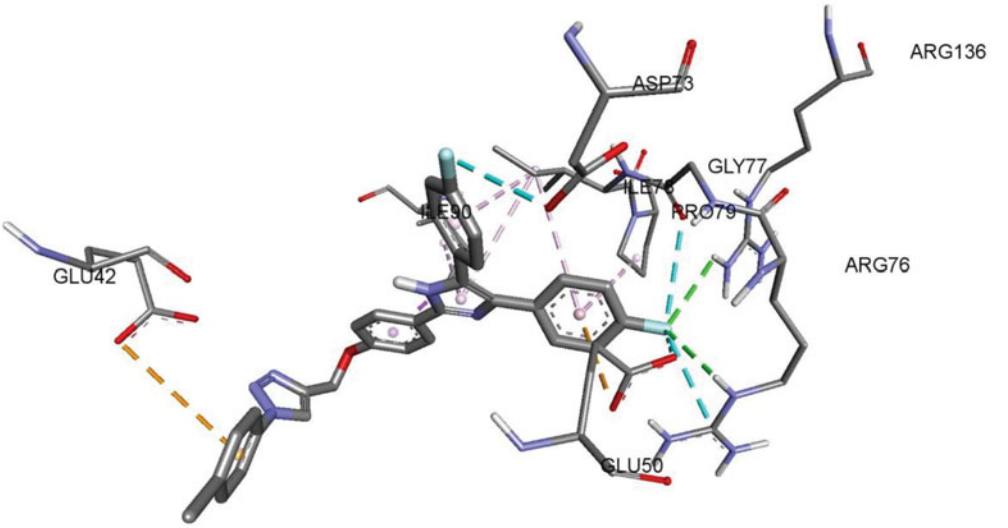


Figure 2. Interactions (dotted lines) of compound **3o** docked in ligand binding region of DNA gyrase topoisomerase II. (Green: hydrogen bond, Cyano: Halogen bond, Yellow: pi-anion, Light pink: Hydrophobic interactions).

effective against *A. niger* (0.0113 µmol/mL) and *C. albicans* (0.0056 µmol/mL). All the compounds except **3i** showed better activity against *C. albicans* (0.0056–0.0243 µmol/mL) than A. *niger* (0.0478–0.0113 µmol/mL), which are given in Table 2. It was also observed that all triazole containing triaryl-1*H*-imidazole compounds (**3a**–**3r**) exhibited better antimicrobial activities as compared to **2a**–**2i**.[16] Further, **3a**–**3r** showed good antifungal activity than **2a**–**2i** against *A. niger* & *C. albicans* and almost comparable antibacterial activity to **2a**–**2i**.

Docking studies

The compound **3o** was observed to be most active against *E. coli*. Therefore, it was docked into the active site region of DNA gyrase of *E. coli* using Autodock Vina docking tool.[17] The x-ray crystal structure of DNA gyrase was acquired from protein data bank (PDB: 1KZN) and the docking protocols were selected were adopted.[18] The results were visualized with Discovery studio visualizer client 2017 R2.[19]

The lowest energy complex of compound **3o** with the active site residues of DNA gyrase is depicted in Fig. 2 that is anchored in the binding site by various types of interactions. Interestingly, fluorine atoms played important role in affixing the molecule. The fluorine atom present at position-4 of phenyl ring attached on imidazole made hydrogen bonds[20] with Arg76 and Arg136 by behaving as acceptor. Further, both fluorine atoms created halogen bonds[21] with Glu50, Asp73, and Gly77. Glu42 built pi-anion contacts[22] with chloro phenyl ring present on triazole. 4-Fluorophenyl rings made pi-anion contacts with Glu50. Imidazole and its substituent aromatic rings were involved in hydrophobic interactions with the active site residues. Moreover, the binding affinity of compound **3o** was −9.6 kcal/mol which was more in comparison to the binding

affinity of co-crystallized ligand CBN (–9.4 kcal/mol). These observations validated that compound **3o** efficiently inhibits the enzyme (Fig. 2).

Conclusion

In conclusion, 4-((4-(4,5-diaryl-1*H*-imidazol-2-yl)phenoxy)methyl)-1-substituted-1*H*-1,2,3-triazoles **(3a–3r)** were synthesized from 1,2-dicarbonyl compounds and triazole substituted aryl aldehydes in the presence of ammonium acetate in good yield. The synthesized compounds were examined for *in-vitro* antimicrobial activity with serial dilution method that showed good to substantial antibacterial and antifungal activity. The compound **3p** was substantially more potent against *P. aeruginosa*, *A. niger* and *C. albicans*, whereas compound **3i was** more potent against *B. subtilis* and **3o** and **3r** were more potent against *E. coli & S. epidermidis*. Docking simulation of compound **3o** was also carried out to study binding mode with drug target.

Experimental

The reagents and chemicals used were procured from Sigma-Aldrich and Himedia. The reaction progress was monitored by TLC and melting points were determined in open capillaries and are uncorrected. IR spectra were obtained in KBr on SHIMAZDU FTIR spectrophotometer. ^{1}H, 13 C, DEPT-135 and 2-D NMR (COSY, ROESY, HSQC and HMBC) spectra were scanned on a Bruker Avance-III 400 MHZ FT-NMR. Chemical shift values are reported in δ (ppm) and coupling constant (J) value are given in Hertz (Hz). HRMS were scanned on SCIEX (LC-MS/MS QTOF-5600+).

Synthesis of 4-((4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1-(p-tolyl)-1H-1,2,3-triazole (3a)

4-(Prop-2-yn-1-yloxy)benzaldehyde (1.0 mmol) was stirred with 4-methylphenylazide (1.0 mmol) in the presence of copper sulfate pentahydrate (0.10 mmol) and sodium ascorbate (0.20 mmol) using DMF:water (7:3) as solvent at 40 °C temperature for 8h.[14] After completion of the reaction, which was monitored through TLC, cold aq. NH_3 solution was added to the reaction mixture and extracted thrice with ethyl acetate. The ethyl acetate layer was dried using anhydrous Na_2SO_4, percolated and dried under vacuum to get *4-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde* (**2a**) in 92% yield that was crystallized from chloroform.

Compound **3a** was synthesized by condensation of triazole substituted aryl aldehydes (**2a**, 1.0 mmol) with benzil (1.0 mmol) and ammonium acetate (10.0 mmol) in glacial acetic acid under reflux condition for 10 h. The reaction mixture was poured with stirring into crushed ice with stirring. After 30 min, the precipitates were filtered, washed twice with distilled water and dried under vacuum.

General procedure of antimicrobial activity

The newly synthesized 4-((4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenoxy)methyl)-1-substituted-1*H*-1,2,3-triazoles were screened for *in-vitro* antibacterial activity against *Bacillus*

subtilis MTCC 441, *Staphylococcus epidermidis* MTCC 6880 (Gram-positive) and *Escherichia coli* MTCC 16521, *pseudomonas aeruginosa* MTCC 424 (Gram-negative) and also screened for antifungal activity against fungal strains (*Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 8189). Sabouraud dextrose broth-I.P. and nutrient broth-I.P. were used for fungal and bacterial growth, respectively. Minimum Inhibitory Concentrations (MIC in μmol/mL) were examined by serial dilution method[12,13] using a stock solution of 100 μg/mL. The synthesized compounds exhibited considerable activity against the used strains where ciprofloxacin and fluconazole were used as reference drugs in case of antibacterial and antifungal activity, respectively. The stock solution of control drug and synthesized compounds were diluted to different concentration of 50, 25, 12.5, 6.25, 3.12 μg/mL. All samples were prepared in dimethylsulfoxide and the tubes-containing bacterial organism were incubated at 37 ± 0.5 °C and the tubes containing fungal organism *C. albicans* were incubated at 30 ± 0.5 °C for 48 h except in case of *A. niger* which is incubated for 7 days and then compared with control drug.

Docking simulations

The procedure for docking simulation was followed according to the protocols reported by Kumar et al.[16,23] The 3D structure of the molecules was made using Marvin Sketch 5.10.[24]

Additional Supporting information may be found online in the supporting information tab for this article.

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