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Antimicrobial and Docking Studies of Pyrazole tethered 1,2,4-Trisubstituted and 2,4-Disubstituted Imidazole Hybrids

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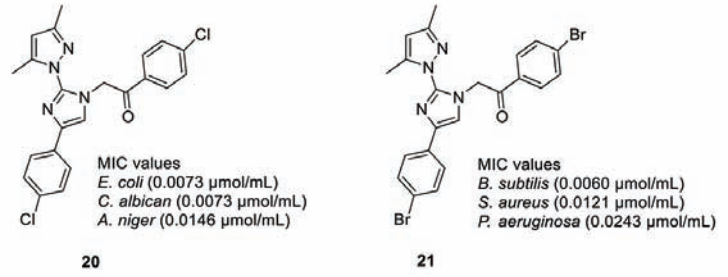
ABSTRACT A series of imidazole hybrids was screened for *in vitro* antimicrobial activities against four bacterial strains *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus* and two fungal strains *Candida* albicans and *Aspergillus niger.* Compounds **10-21, 22-25** exhibited good to moderate activity against bacterial and fungal strains ranging from 0.0060 to 0.0650 µmol/ml and 0.0073–0.0978 µmol/ml, respectively. Among them, compound **21** was found to be most active against *B. subtilis*, *S. aureus*, and *P. aeruginosa*, while compound **20**, against *E. coli*, *C. albicans*, and *A. niger.* The active compound **20** was docked with *E. coli* DNA gyrase B protein (PDB:1KZN) and the target protein 1EA1 selected for *C. albicans*.



KEYWORDS Antimicrobial, Docking, Imidazole, Pyrazole.

INTRODUCTION

Azoles have attracted significant attention, as they constitute immensely important members of aromatic heterocyclic compounds present in more than 80% drugs. Among them, imidazole is one of important element in medicinal chemistry. It is one of the important constituents of ionic liquids and natural products such as histidine Vitamin B12, histamine, nucleic acid bases, biotin, and pilocarpine alkaloids.[1] Several drug candidates having potent biological activity against convulsions, tumor, bacteria, migraines, microbes, arrhythmias, and viral infections contain an imidazole moiety.[2] Moreover, imidazole and its derivatives are widely applied as fungicides for plants.[3] High therapeutic value of imidazole containing compounds encourages the chemists to synthesize imidazole containing chemotherapeutic agents. Medicinal properties include 0-HETE synthase inhibitors,[4] heme oxygenase inhibitors,[5] anticancer,[6] carboxypeptidase inhibitors,[7] β-lactamase inhibitors,[8] antiaging agents,[9] anticoagulants,[10] anti-inflammatory,[11] antidiabetic[12] antibacterial,[13] antifungal,[14] antiviral,[15] antimalarial,[16] and antitubercular,[17] all are unique characteristics known for imidazole derivatives. In addition, pharmacological

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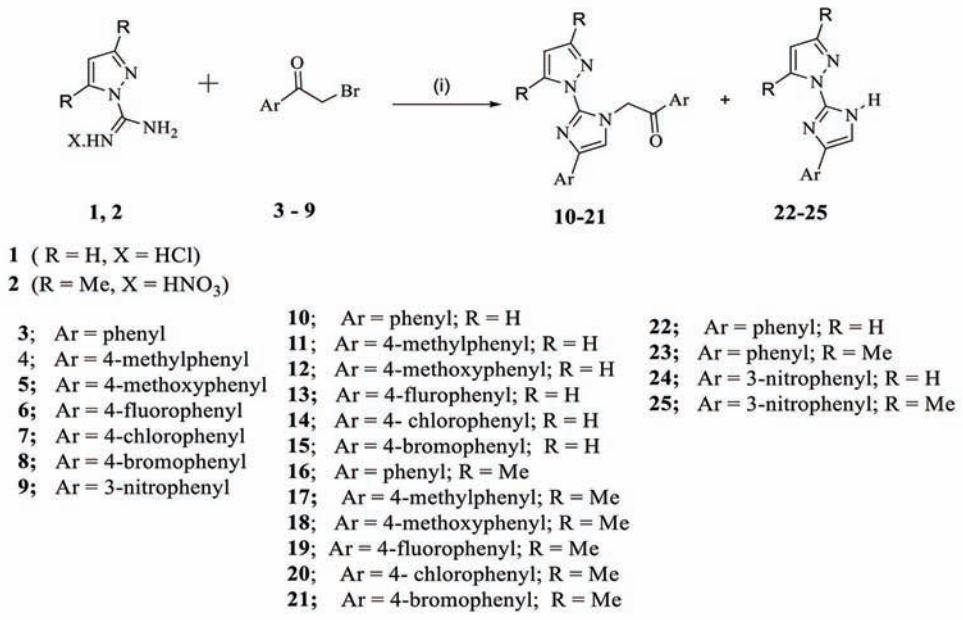
attributes of pyrazole containing compounds include anticonvulsant, antiviral, analgesic, and anti-inflammatory, fungistatic, anticancer, and antibacterial.[18-22] Pyrazofurin (a natural pyrazole C-glycoside) exhibits a broad range of antimicrobial activities. Some synthetic imidazole-pyrazole hybrids and related fused drugs have been attracting the attention of the medicinal chemists due to their considerable biological and pharmacological activities.[23] Prompted by the importance of imidazole and pyrazole compounds, antimicrobial evaluation of pyrazole tethered 1,2,4-trisubstituted, and 2,4-disubstituted imidazole was carried out. Further, the docking of the most active compound was carried out against *Escherichia coli* and *Candida albicans*.

RESULTS AND DISCUSSION

1,2,4-Trisubstituted imidazole hybrids **10-21** and 2,4-disubstituted imidazole hybrids **22-25** were obtained in good yield by refluxing 1*H*-pyrazole-1-carboximidamide hydrochloride (**1**)/3,5-dimethyl-1*H*-pyrazole-1-carboximida mide nitrate **(2)** with phenacyl bromide **3-9** in the presence of potassium carbonate using tetrahydrofuran (THF) and water as a solvent in the ratio of (5:1) (**Scheme 1**) according to literature procedure.[24] When 1.2 equivalent of phenacyl bromide (**3**) was reacted with 1.0 equivalent of **1/2**, N-H imidazoles, **22,23** were isolated, whereas reaction with 2.5 equivalent (one equivalent added after 36 h) of corresponding phenacyl bromide (**3**) furnished N-alkylated imidazoles **10,16**. Phenacyl bromides (1.2 or 2.5 equivalent) **4-8** gave N-alkylated products mainly (**11-15, 17-21**) by reacting with **1/2**. N-Alkylated product was not obtained with phenacyl bromide containing a strong electron-withdrawing nitro group (**9**) even with 2.5 equivalent.

Antibacterial activity

All the synthesized imidazole hybrids were screened for *in vitro* antimicrobial activity against two Gram-positive bacterial strains, namely, *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 3160), and two Gram-negative bacterial strains, namely, *E. coli* (MTCC 1652) and *Pseudomonas aeruginosa* (MTCC 424). Results of antibacterial activity as minimum inhibitory concentrations (MIC in µmol/mL) are presented in **Table 1**. In general, the synthesized pyrazole tethered imidazole hybrids showed MIC from 0.0060 to 0.0650 µmol/mL as compared to reference drug ciprofloxacin (0.0047 µmol/mL). The compound **14 (**0.0078 µmol/mL), **15 (**0.0064 µmol/mL), **20 (**0.0073 µmol/mL), and **2l** (0.0060 µmol/mL) was substantially potent against *B. subtilis* and **15 (**0.0073 µmol/mL), **20 (**0.0064 µmol/mL), and **21 (**0.0120 µmol/mL) showed promising activity against *E. coli*. The compounds **20** and **21** were moderately active against *S. aureus* with MIC 0.0121 and 0.0146 µmol/mL, respectively, while compounds **15 (**0.0243 µmol/mL), **20 (**0.0292 µmol/mL), and **21 (**0.0256 µmol/mL) were active against *P. aeruginosa*. Among the synthesized derivatives, compound **21** showed the highest activity against the tested bacterial strains, namely, *B. subtilis* (0.0060 µmol/ml), *E. coli* (0.0120 µmol/ml), *S. aureus* (0.0121 µmol/ml), and *P. aeruginosa* (0.0243 µmol/ml). The pyrazole tethered imidazole showed significant activity toward *B. Subtilis* and *E. coli* in comparison to the reference drug. Among the N-alkylated derivatives **(10-21)**, halogen-containing compounds such as F, Cl, Br showed higher activity than compounds having electron-donating groups CH_3 and OMe against most of the tested bacterial strains. However, a reverse trend was observed in non-alkylated compounds. The compounds with a methyl group at pyrazole ring **(16-2l, 23, and 25)** were found more active against the tested bacterial strains in comparison to the unsubstituted



Scheme 1: (i) Tetrahydrofuran: H_2O (5:1). Synthesis of pyrazole tethered 1,2,4-trisubstituted and 2,4-disubstituted imidazole hybrids.

Table 1: Antibacterial evaluation of compound 10–25 (MIC µmol/mL)

Compound	R	Ar	*B. subtilis* MTCC 441	*E. coli* MTCC1652	*S. aureus* MTCC3160	*P. aeruginosa* MTCC 424
10	H	phenyl	0.0190	0.0190	0.0380	0.0380
11	H	4-methylphenyl	0.0350	0.0350	0.0700	0.0350
12	H	4-methoxyphenyl	0.0320	0.0320	0.0640	0.0320
13	H	4-fluorophenyl	0.0170	0.0170	0.0340	0.0340
14	H	4-chlorophenyl	0.0078	0.0156	0.0624	0.0312
15	H	4-bromophenyl	0.0064	0.0124	0.0256	0.0256
16	Me	phenyl	0.0174	0.0174	0.0350	0.0350
17	Me	4-methylphenyl	0.0325	0.0325	0.0650	0.0650
18	Me	4-methoxyphenyl	0.0300	0.0300	0.0600	0.0600
19	Me	4-fluorophenyl	0.0158	0.0158	0.0316	0.0316
20	Me	4-chlorophenyl	0.0073	0.0073	0.0146	0.0292
21	Me	4-bromophenyl	0.0060	0.0120	0.0121	0.0243
22	H	phenyl	0.0296	0.0592	0.0296	0.0592
23	Me	phenyl	0.0262	0.0262	0.0524	0.0524
24	H	3-nitrophenyl	0.0244	0.0244	0.0488	0.0488
25	Me	3-nitophenyl	0.0220	0.0880	0.0880	0.0440
Ciprofloxacin	-	-	0.0047	0.0047	0.0047	0.0047

E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa, B. subtilis: Bacillus subtilis, S. aureus: Staphylococcus aureus, MIC: Minimum inhibitory concentration

pyrazole ring. Further, N-alkylation of imidazole enhanced the antibacterial activity.

Antifungal activity

All the tested compounds showed considerable activity (MIC in µmol/mL) toward two fungal strains, *C. albicans* (MTCC 227 and *Aspergillus niger* (MTCC 8189) (**Table 2**). Among the synthesized imidazole hybrids, the compounds **12 (**0.0079 µmol/ml), **14 (**0.0080 µmol/ml), **18(**0.0075 µmol/ml), and **20(**0.0073 µmol/ml) were discretely active against *C. albicans* as compared to reference drug fluconazole (0.0051 µmol/ml). The compound **18** and **20** displayed MIC value 0.0150 and 0.0146 µmol/ml, respectively, against *A. niger* in comparison to fluconazole (0.0102 µmol/ml). The pyrazole tethered imidazole showed significant activity toward *C. albicans* than *E. coli* in comparison to the reference drug. Among the N-alkylated derivatives **(10-21)**, the compounds containing chlorine methoxy group on para position of phenyl ring of N-substituted imidazole derivatives are more active than the other compounds. The compounds with a methyl group at pyrazole ring **(10-2l, 23,** and **25)** were found more potent against the tested antifungal strains in comparison to the unsubstituted pyrazole ring. Further, N-alkylation (**10** and **16)** of imidazole decreased the antifungal activity in respect to NH hybrids (**22** and **25**).

Molecular docking analysis

E. coli

The docking studies revealed that compound **20** shows best binding interactions with *E. coli* DNA gyrase B protein (PDB:1KZN) exhibited various hydrophobic and one electrostatic interaction as presented in **Figure 1**. The methyl group of 3,5-dimethyl substituted pyrazole exhibited two alkyl interactions with Pro:79 and Ile:78 amino acid residues with bond lengths of 4.95 Å and 4.51 Å, respectively. The chlorine of imidazole linked *para* chloro substituted phenyl ring established three alkyl interactions with Val:167, Val:43, and Val:71 amino acid residues with bond lengths of 4.10Å, 4.70Å, and 4.36Å, respectively. The imidazole linked *para* chloro substituted phenyl ring formed pi sigma interaction with Thr:165 (3.96Å) amino acid residue and was also found to be engaged in forming pi-alkyl interaction with Ala:47 (5.35Å) amino acid residue. One pi-alkyl interaction was also observed between imidazole ring and Ile:78 amino acid residue having an interaction distance of 4.44Å and was also involved in pi donor interaction with Asn:46 (4.09Å) amino acid residue. Ile:90 amino acid residue showed pi sigma interaction with ethanone linked para chloro substituted phenyl ring at a distance of 3.72Å. 3,5-Dimethyl substituted pyrazole ring was involved in electrostatic interaction (pi anion) with Glu:50 amino acid residue at a distance of 3.78Å.

C. albicans

The most active compound **20** shows electrostatic and hydrophobic interactions with active site residues of target protein (1EA1), as presented in **Figure 2**. Ethanone linked para chloro substituted phenyl ring displayed pi-pi T shaped interaction with Phe:78 amino acid residues with bond length of 5.16Å. The chlorine of ethanone linked para chloro substituted phenyl ring exhibited two alkyl interactions with Leu:321 (4.37 Å) and Ile:323 (5.48Å) active site residues while chlorine of imidazole linked para chloro substituted phenyl ring shows interaction with Leu:234 (4.45Å) amino acid residue. One methyl of 3,5-dimethyl substituted pyrazole ring established alkyl interaction with Leu:321 (4.42Å)

Table 2: Antifungal evaluation of compounds 10–25 (MIC µmol/mL)

Compound	R	Ar	*C. albicans* MTCC 227	*A. niger* MTCC282
10	H	phenyl	0.0380	0.0380
11	H	4-methylphenyl	0.0175	0.0175
12	H	4-methoxyphenyl	0.0080	0.0160
13	H	4-fluorophenyl	0.0172	0.0172
14	H	4-chlorophenyl	0.0079	0.0158
15	H	4-bromophenyl	0.0128	0.0512
16	Me	phenyl	0.0350	0.0350
17	Me	4-methylphenyl	0.0162	0.0324
18	Me	4-methoxyphenyl	0.0075	0.0150
19	Me	4-fluorophenyl	0.0159	0.0636
20	Me	4-chlorophenyl	0.0073	0.0146
21	Me	4-bromophenyl	0.0243	0.0486
22	H	phenyl	0.0149	0.0298
23	Me	phenyl	0.0131	0.0262
24	H	3-nitrophenyl	0.0978	0.0978
25	Me	3-nitophenyl	0.0882	0.0882
Fluconazole	-	-	0.0051	0.0102

C. albicans: Candida albicans, A. niger: Aspergillus niger, MIC: Minimum inhibitory concentration

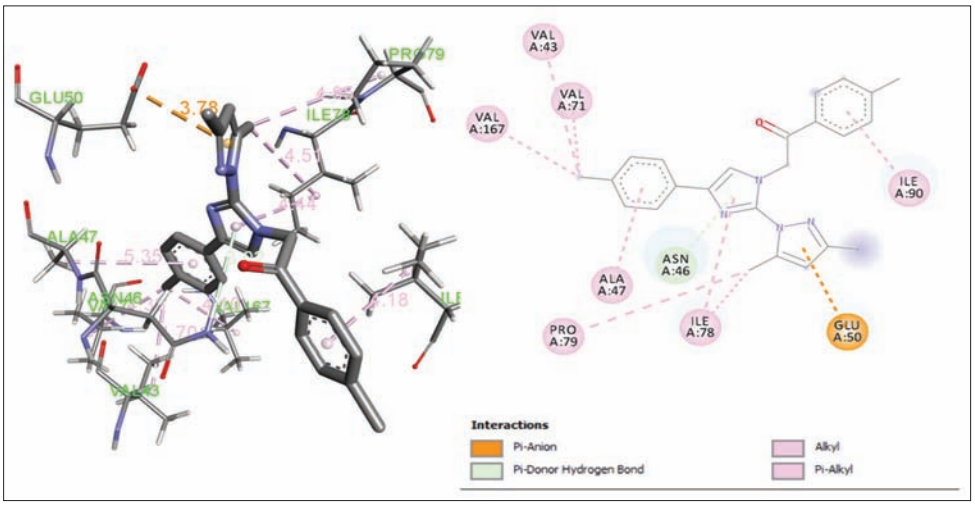


Figure 1: Three dimensional and two dimensional binding conformation of compound 20 with active site residues of *Escherichia coli* DNA gyrase B protein (PDB:1KZN)

residue, whereas another methyl was involved in alkyl interaction with Ala:256 (3.93 Å) amino acid residue. The pyrazole ring established pi-alkyl interaction with Ala:256 amino acid residues with a bond length of 4.75Å while methyl of 3,5-dimethyl substituted pyrazole ring showed two pi-alkyl interactions with Phe:255 and Phe:83 amino acid residues with bond lengths of 4.93Å and 5.28Å, respectively. Leu: 321 amino acid residues were engaged in pi-alkyl interaction with ethanone linked para chloro substituted phenyl ring and pi-sigma interaction with imidazole ring. Pi-sigma interactions were also formed by imidazole linked para chloro substituted ring with Leu:324 (3.84Å) active site residue and by CH_2 of ethanone with Tyr:76 residue (4.00Å). The chlorine of imidazole linked para chloro substituted phenyl ring displayed pi-alkyl interaction with Phe:63 active site residue with a bond length of 4.00Å. One electrostatic interaction was also observed between the imidazole ring and Arg:96 amino acid residue at a distance of 4.78Å.

EXPERIMENTAL

General procedure for synthesis of 10-21

1/2 (1 mmol) in10 ml of THF: H_2O (5:1) solvent was taken in a two necked 100 ml round bottom flask. The slow and portion-wise addition of K_2CO_3 (2.5 mmol) with vigorous refluxing was carried out followed by drop-wise addition of a solution of phenacyl bromide (2.2 mmol) in THF *via* pressure-equalizing funnel over a period of 20 min with refluxing. The progress of the reaction was monitored by thin-layer chromatography and after completion of the reaction,

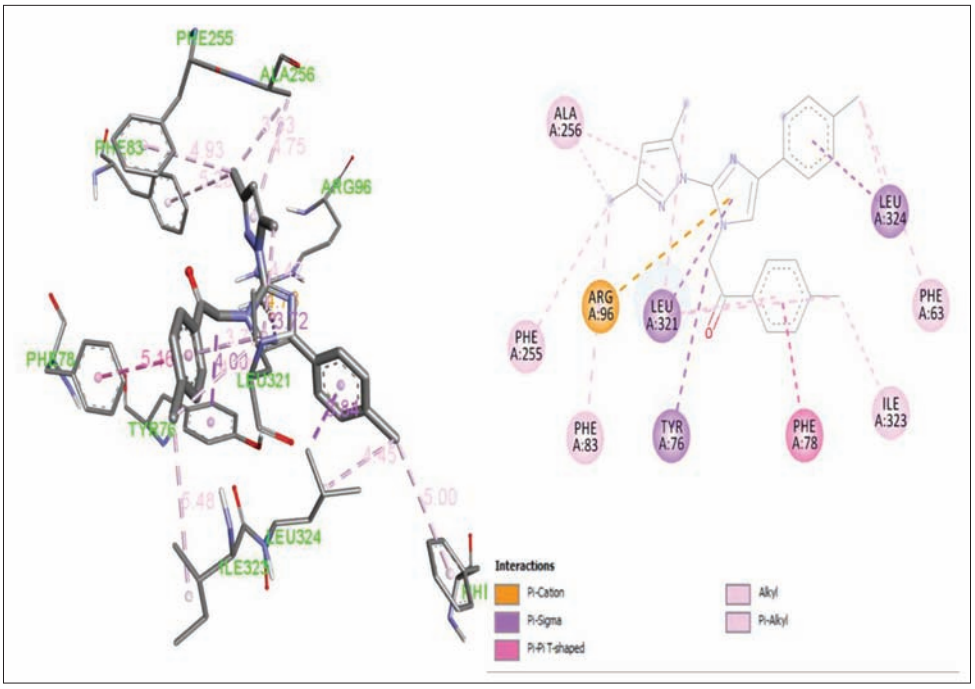


Figure 2: Three dimensional and two dimensional binding conformation of compound 20 with active site residues of fungal target protein (PDB:1EA1)

THF was removed under reduced pressure using a rotatory evaporator. The crude product was filtered and purified by column chromatography over silica gel (60–120 mesh) using 10% hexane from petroleum-ethyl acetate to afford **10-21**.

In vitro antimicrobial activity

The newly constructed imidazole hybrid compounds were evaluated for *in vitro* antibacterial activity against the bacterial strain (*B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*) and also examined 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. MICs (in µmol/mL) were determined by serial dilution method,[25] through a stock solution of 100 µg/mL. From this solution, through serial dilution technique concentration of 50–3.12 µg/mL was obtained in other test tubes. After that 0.1 ml of respective microorganism in sterile saline solution was inoculated in each test tube and then incubated at 37 ± 1°C for 24 h (Bacteria) and 48 h (*C. albicans*) and 25 ± 1°C for 7 days (*A. niger*). The ciprofloxacin and fluconazole were used as reference drugs for antibacterial and antifungal strains, respectively.

Experimental protocol for molecular docking

Ligand molecules were prepared as previously reported methods using MarvinSketch and AutoDock tools.[26] AutoDock Vina, the advanced docking program, was used to evaluate the binding properties of synthesized compounds into the active sites of target proteins. The X-ray crystallographic structure of *E. coli* DNA gyrase B protein (PDB: 1KZN)[27] and cytochrome P450 14 alpha-sterol demethylase (CYP51) from *Mycobacterium tuberculosis* in complex with fluconazole were retrieved from the protein data bank. Due to homology between 14-DM from *M. tuberculosis* and 14-DM *Candida* species PDB:1EA1 is used for antifungal activity as reported in the previous study.[28]

Polar hydrogen atoms were added and all water molecules and internal ligands were removed. Docking studies were carried out as reported in our previous study and literature using AutoDock Vina program.[26,27,29] The docking studies were performed according to specified conditions of grid box by AutoDock tools. The search grid was identified as center_x = 19.1474427293, center_y = 28.3592144362, and center_z = 36.8274474404 for bacterial protein (1KZN) and center_x = −16.172, center_y = −5.396, and center_z = 62.468 for fungal protein (1EA1) with dimension size_x = 40, size_y = 40, and size_z= 40. The exhaustiveness was set to be 8. The results were visualized using PyMol and Discovery Studio visualizer.[30]

CONCLUSION

The previously synthesized new imidazole derivatives **10-21, 22-25** were assessed against four bacterial strains and two fungal strains and exhibited good to moderate activity against bacterial and fungal strains ranging from 0.0060 to 0.0650 µmol/ml and 0.0073–0.0978 µmol/ml, respectively. The hybrids with a methyl group at pyrazole ring **(16-21, 23, and 25)** were found more potent than unsubstituted pyrazole ring and **3l** was found to be most active against *B. subtilis*, *S. aureus*, and *P. aeruginosa* while compound **20**, against *E. coli*, *C. albicans*, and *A. niger.* As a result of docking studies, compound **20** shows the binding affinity of 9.1 and 10.5 kcal/mol with *E. coli* DNA gyrase B protein (PDB:1KZN) and the target protein 1EA1 selected for *C. albicans*.

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