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Docking, Synthesis and Antifungal Activity of 2-Phenyl Benzimidazole Derivatives

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Review Article

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ABSTRACT

Benzimidazole nucleus is a component of many bioactive heterocyclic compounds that are of wide interest because of their diverse biological activity. Benzimidazole derivatives are structure isosteres of naturally occurring nucleotides which allows them to interact easily with biopolymers of the living system. Benzimidazole and its derivatives docked with ID 4P80 protein. According to hypothesis there derivatives will show good antifungal activity. Benzimidazole inhibits microgramtubule synthesis by binding with beta-tubulin and inhibition of mitochondrial reductase causes reduced glucose transport for developing new antimicrogrambial agents. In the present work, Benzimidazole and 2-phenylbenzimidazole derivatives were synthesized and evaluated for antifungal activity against Candida albicans. The structure of the synthesized compounds was confirmed by infrared spectroscopy, proton nuclear magnetic resonance and mass spectroscopy and biological activity. Antifungal activity of all the Compounds N3, N5, N8, N9 and Compound N12 showed better antifungal activity against Candida Robusta as compared to benzimidazole, 2-phenylbenzimidazole and Griseofulvin.

INTRODUCTION

In the last few years, peoples are infected and around 10,000 deaths are reported in the tropical regions every year because of bacterial infection. Antimicrobial chemotherapy has been the mainstay of medical intervention against infectious diseases caused by various pathogens. Infectious microbial diseases remain pressing problems world- wide, because resistance to a number of antimicrobial agents (β- lactams antibiotics, Macrolide, Quinolones and Vancomycin)

among variety of clinically significant species of microorganisms has become an important global health problem. Benzimidazole contain a phenyl ring fused to an imidazole ring and compounds having benzimidazole as a structural motif have been widely used in medicinal chemistry and Drug development, and show a variety of different pharmacological activities like Antimicrobial, Antifungal, Neuroleptic, Anti-HIV, Antihelmintic, Antihistaminic and Antiulcer [1]. Benzimidazole inhibits microtubule synthesis by binding with Beta-tubulin and inhibition of mitochondrial reductase causes reduced glucose transport for developing new Antimicrobial agents [2]. In the present work, we have synthesized 2-Phenylbenzimidazole derivative and evaluated Antimicrobial activity against E.coli (Escherichia coli), Staphylococcus aureus, and Candida albicans.

LITERATURE REVIEW

Docking

Molecular docking by gold docking wizard: Docking study of designed compounds was performed with Gold suite 5.0 software. GOLD (Genetic Optimisation for Ligand Docking) is a genetic algorithm for docking flexible ligand into protein binding sites. The Desired protein mol file was loaded in Gold Wizard hydrogen atoms were added and water molecules deleted. Then ligand to be docked was added and docking was performed by choosing gold score as scoring function. Gold was run and viewed gold solution [3,4].

Docking is a computer algorithm that determines how a ligand will bind in its active site.

It is one of the most accurate methods for predicting whether a particular compound will be a good inhibitor of a particular protein. Two main components of docking are searching and scoring algorithm. It involves following steps:

Ligand preparation, Protein preparation, Protein ligand docking

Ligand preparation: Ligands were drawn in Chem draw Ultra 8.0 and energy was minimized in Chem Bio 3D (three dimensions). The desired protein file was downloaded from RCSB protein data bank and the protein was prepared in Chimera. The PDB ID (Protein data bank identification) of CA (carbonic anhydrase) isoforms are: *Candida Robusta*: 1S4N Docking was performed with GOLD (Genetic Optimisation for Ligand Docking)software. Binding site was defined by using co-crystallized ligands. The results were validated by determine RMSD (Root Mean Square Deviation) which shall be <2 Å (ångström) [5-9].

Protein preparation: Protein were downloaded from RCSB Protein data bank, and prepared by using UCSF (University of California, San Francisco) Chimera Software 1.7s by, selecting in suitable chain, removal of water molecules, and addition of hydrogen and saved in mole 2 format (Figure 1).

Docking using gold docking wizard: The desired protein mol file was loaded in gold wizard and hydrogen atoms were added. The binding site was defined for:

1S4N at X=10.973, Y=1.673, Z=3.283

Then ligand to be docked was added and docking was performed by choosing gold score as scoring function. Gold was run and gold solution was viewed 002E (Table 1).

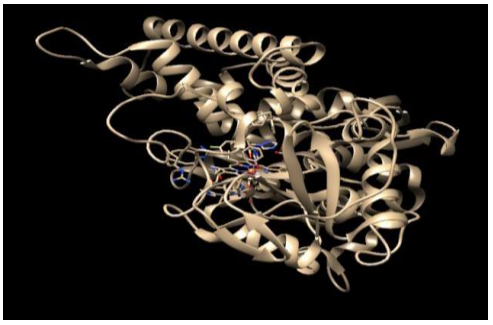

Figure 1. Protein Preparation.

Table 1. Docking score of synthesized compounds (N1-N12).

Compound code	R1	R2	R3	R4	Molecular formula
N1	H	NH_2	H	H	$C_{13}H_{11}N_3$
N2	H	Cl	Cl	H	$C_{13}H_8Cl_2N_2$
N3	Cl	H	H	NO_2	$C_{13}H_8ClN_3O_2$
N4	OH	H	H	H	$C_{13}H_{10}N_2O$
N5	H	H	NH_2	H	$C_{13}H_{11}N_3$
N6	H	H	NO_2	H	$C_{13}H_9N_3O_2$
N7	H	OH	OH	H	$C_{13}H_{10}N_2O_2$
N8	Cl	H	Cl	H	$C_{13}H_8N_2Cl_2$
N9	H	Cl	H	H	$C_{13}H_9N_2Cl$
N10	H			H	$C_{14}H_{12}N_2O$
N11	H	H	F	H	$C_{13}H_9N_2F$
N12	H	NH_2	NH_2	H	$C_{12}H_{11}N_4$

Docking score of synthesized compounds (N1-N12)

Chemistry: Present study was undertaken to synthesize some Benzimidazole derivatives and investigate their probable

Antibacterial and Antifungal effects. All reagents were used as purchased from commercial suppliers (Merck, Lobachemie or Sigma-Aldrich) without further purification, melting points (m p) were determined by capillary tube method. During the synthesis, the compounds were routinely checked for purity by TLC using pre coated aluminum sheets with GF-254 (Fluorescence indicator green 254 nm) silica gel and mobile phase Ethyl acetate: n- hexane: methanol (3:2:1) (Figure 2).

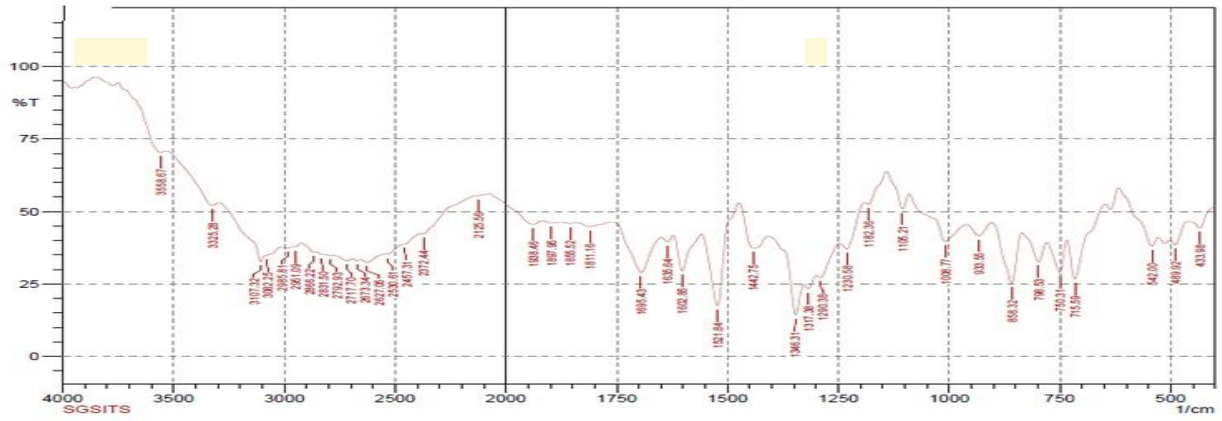

Figure 2. IR spectra of compound N5.

The sports were visualized in UV (Ultraviolet) light chamber. The λ_{max} (nanometer) of the synthesized compounds was determined by Shimadzu 1700 UV- Visible Spectrophotometer. The FTIR spectra of the synthesized compounds were recorded on FTIR alpha Bruker by KBr disc in the range of 4000-400 cm^{-1} (centimetre power–1). The proton (^{1}H NMR) spectra were recorded using Bruker advance ii 400 NMR (Nuclear Magnetic Resonance) Spectrometer. The Mass Spectra (MS) of synthesized compound were recorded using CIF mass facility IISAR Bhopal. A series of twelve synthesized compound at position 2- substituted Phenylbenzimidazole (N1-N12) (Table 2).

Table 2. Antifungal activity results.

Compound code	R1	R2	R3	R4	Fungal (1S4N)
N1	H	NH_2	H	H	30.623
N2	H	Cl	Cl	H	33.803
N3	Cl	H	H	NO_2	28.198
N4	OH	H	H	H	29.995
N5	H	H	NH_2	H	36.036
N6	H	H	NO_2	H	31.010

N7	H	OH	OH	H	32.521
N8	Cl	H	Cl	H	27.849
N9	H	Cl	H	H	26.543
N10	H	OCH_3	H	H	28.591
N11	H	H	F	H	34.209
N12	H	NH_2	NH_2	H	27.591
GRISEOFULVIN					29.054

General procedure for Synthesis of 2-phenyl benzimidazole

A mixture of Orthophenylenediamine 12mmol (1.29 gram) and substituted benzoic acid (36mmol, 4.97 gram) was taken in 250 ml (mililiter) round bottom flask (RBF) and 4N (40 ml) of HCl was added slowly to this mixture with continuous stirring and refluxed for 4 hours at 25^0 C (degree Celsius) temperature. The reaction mixture was filtered and residue so obtained was dissolved in warm water, filtered and Precipitate was collected and dried. The product was further recrystallized from ethanol. The structure of the obtained compounds was elucidated by spectral data. Significant stretching bands in the IR spectra were observed at expected regions [10-14]. All of the aromatic and aliphatic protons in the 500 MHz (megahertz) ^{1}H NMR spectra were also recorded at estimated areas (Table 3).

Table 3. Interpretation of mass spectra.

Compound code	Exact mass	Position of ion peak M^+
N1	209.25	210.23 (M+1)
N2	263.12	263.3 (M^+)
N3	273.67	274.0 (M+1)
N4	210.23	211.1 (M+1)
N5	239.23	239.2(M^+)
N6	209.25	207.5M-2)
N7	226.07	226.3 (M+1)
N8	263.12	263.0 (M^+)
N9	228.68	228.1 (M^+)
N10	224.26	223.2 (M-1)
N11	212.22	213.3 (M+1)
N12	211.24	201.0 (M+10)

RESULTS AND DISCUSSION

In the present study 2-phenyl benzimidazole derivatives were synthesized. The synthesis of these compounds involves ring closer reaction between o-phenylenediamine and substituted benzoic acid to form the corresponding substituted 2-phenylbenzimidazole. The structure of all synthesized compounds confirmed by FTIR, ^{1}H NMR and Mass Spectroscopy. The result showed that all compounds were screened for antifungal activity against C. albicans (MTCC 227). The compounds were dissolved in chloroform and antifungal activity was determined using the broth dilution method. Griseofulvin was taken as the standard drug. Compound N3, N5, N8, N9 and N12 showed better antifungal activity as compared to benzimidazole [15-17]. The result of the antifungal screening is summarized in (Table 4).

Table 4. Antifungal activity of synthesized compounds n1- n12.

		Fungal strain
Code	**Molecular formula**	***Candida robusta* MTCC 227**
N1	$C_{13}H_{11}N_3$	250
N2	$C_{13}H_8Cl_2N_2$	250
N3	$C_{13}H_8ClN_3O_2$	500
N4	$C_{13}H_{10}N_2O$	250
N5	$C_{13}H_{11}N_3$	500
N6	$C_{13}H_9N_3O_2$	250
N7	$C_{13}H_{10}N_2O_2$	250
N8	$C_{13}H_8N_2Cl_2$	500
N9	$C_{13}H_9N_2Cl$	500
N10	$C_{14}H_{12}N_2O$	1000
N11	$C_{13}H_9N_2F$	250
N12	$C_{12}H_{11}N_4$	500
Griseofulvin	-	500

CONCLUSION

In the present work N-2 of benzimidazole derivative was synthesized. Substitution by $–NH_2$ group at para position in benzoic acid moiety at N-2 position of benzimidazole increase antifungal activity against *Candida albicans*.

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