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DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF N-PHENYLACETYLAMIDO DERIVATIVES OF HETEROCYCLIC COMPOUNDS

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ABSTRACT

Microbial infections pose a continuing and serious threat to human health. The intrinsic resistance has been observed in many genera of bacteria and fungi. Many infections are caused by opportunistic pathogens that may be endogenous. So, new chemical entities are needed to combat various microbial infections. In the present study, design, synthesis and evaluation of antibacterial and antifungal activities of simple N-phenylacetylamide derivatives of benzothiazole/ benzimidazole/ morpholine moieties are reported. Design of antibacterial and antifungal activities was carried out by performing docking studies using *Glide* module of the molecular modelling software *Maestro 10.5* from Schrödinger, USA. A cubing receptor grid was centered around the co-crystallized ligand. Validation of ligands was carried out by dedocking and redocking the inhibitor. The SP (standard precision) scoring function was used. The compounds showing good G-scores were synthesized and their structures were confirmed by physical and spectral studies. The synthesized compounds were screened for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and for antifungal activity against *Aspergillus niger*. Synthesized compounds exhibited significant antimicrobial activity and can certainly hold greater promise in discovering new antimicrobial entities.

KEYWORDS: Benzothiazole, benzimidazole, morpholine, antimicrobial activity, molecular docking.

1. INTRODUCTION

Microbial infections, including communicable infections ranging from common cold, cough, malaria, typhoid, cholera to even some severe disease conditions like tuberculosis, are becoming the most important issue for global health and economy. Aspergillosis encompasses infections that range from superficial, such as oral thrush and vaginitis, to systemic and potentially life-threatening diseases, particularly in patients undergoing anticancer chemotherapy, organ transplants, or long treatment with antimicrobial agents and in patients with AIDS, because of immune system suppression.[1,2] Such a broad range of infections and development of resistance to currently available antimicrobial agents require an equally broad range of diagnostic and therapeutic strategies. The present study is undertaken to develop new antimicrobials with heterocyclic moieties like benzothiazole, benzimidazole and morpholine. Benzothiazole is an aromatic heterocyclic compound, which represents an extensive group of compounds having a thiazole ring fused with benzene ring. Benzothiazole is reported to possess various pharmacological activities of clinical importance.[1] Benzothiazole derivatives possess a wide spectrum of biological applications such as antimicrobial, anticancer, anthelmintic, antidiabetic, antituberculosis, antitumor, antitrypanosomal, antiviral, antibacterial, antioxidant, antiglutamate and antiparkinsonism, analgesic, anti-inflammatory, antifungal, anti-leishmanial and anticonvulsant activities.[1,3] Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. Benzimidazole and its derivatives have a long history as antimicrobial agents. Several thousands of benzimidazole analogs have been synthesized and screened for pharmacological activities. They are of wide interest because of their diverse biological activities and clinical applications. These heterocyclic systems have different activities such as bacteriostatic or bactericidal, as well as fungicidal and they are present in numerous antiparasitic, antitumoral and antiviral drugs.[4] Morpholine derivatives are very essential in the drug discovery process and stimulate research in broad spectrum of biological activity study. This class of heterocyclic compounds have found great significance in modern years due to their variety of pharmacological activities including analgesic, anti-inflammatory, anticancer, antidepressant, HIV-protease inhibition, appetite suppression, local anaesthetic, antiplatelet, selective inhibition of protein kinase C, antitumor, neuroprotective, antifungal, anti-tuberculosis,

anti-parasitic, anti-malarial, hypolipidemic and hypocholesterolemic activities.

Initial step of our research was the *in silico* screening for possible potential molecules. Molecular docking is frequently used to predict the binding orientation of drug candidates to their protein targets, to predict their affinity for targets and their activity. Docking is an important process in the rational design of drugs. Docking studies were carried out using *Glide* module of the molecular modelling software *Maestro 10.5* from Schrödinger, USA. The benzothiazole and benzimidazole derivatives are from the fastest growing antimicrobial class in terms of global revenue, increasingly being used in both the hospital and community sectors to treat broad range of infections.[5,7] At the beginning of this century, neither the causative agents nor the active ingredients used to cure infections, could be identified. The scientific practice of organic chemistry and the rational application of microbiology resulted in the birth of various antimicrobial substances. This observation prompted us to design, synthesize and study the antimicrobial activity of benzothiazole, benzimidazole and morpholine derivatives.

2. MATERIALS AND METHODS

2.1. *IN SILICO* MOLECULAR MODELLING

2.1.1. Ligand preparation

The ligand molecules were drawn using Chem Sketch program. A single low-energy 3D structure was generated for each ligand using the program *LigPrep* (*Maestro 10.5* from Schrödinger, USA).

2.1.2. Receptor grid generation

The receptor site was identified using the receptor grid generation panel in *Glide* and was defined by identifying the co-crystallized active ligand molecule on the enzyme so that it could be excluded from the grid generation.

2.1.3. Protein preparation

After conducting adequate literature review, *biotin carboxylase* (PDB entry code 3JZI) in bacteria and s*terol -14-alpha demethylase* (PDB entry code 3GW9) in fungi a were selected as the targets for the current study. The X-ray crystal structures of the above targets were obtained from Protein Data Bank (PDB) and saved in standard 3D coordinate format.

2.1.4. Molecular docking

Molecular docking is a well-established technique to determine the interaction of ligand and receptor and to find the best orientation of a ligand which would form a complex with the receptor with minimum energy. Molecular docking studies were carried out in order to provide understandable evidence for the observed antibacterial and antifungal activities of all the synthesized compounds. The antibacterial and antifungal potencies of all newly synthesized compounds (3a-3g, 4a-4c) were explored by studying their binding patterns against *biotin carboxylase complexed with 7-amino-2-[(2-chlorobenzyl)amino]-1-{[(1S,2S)- 2-hydroxycycloheptyl]methyl}-1H-benzimidazole- 5-carboxamide* (PDB ID: 3JZI) and *sterol -14-alpha demethylase complexed with N-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide* (PDB ID: 3GW9) using the program *Glide.* A cubing receptor grid was centered around the co-crystallized ligand, where the active binding site is present. The SP (standard precision) scoring function was used. Validation of ligands was carried out by de-docking and redocking the inhibitor.

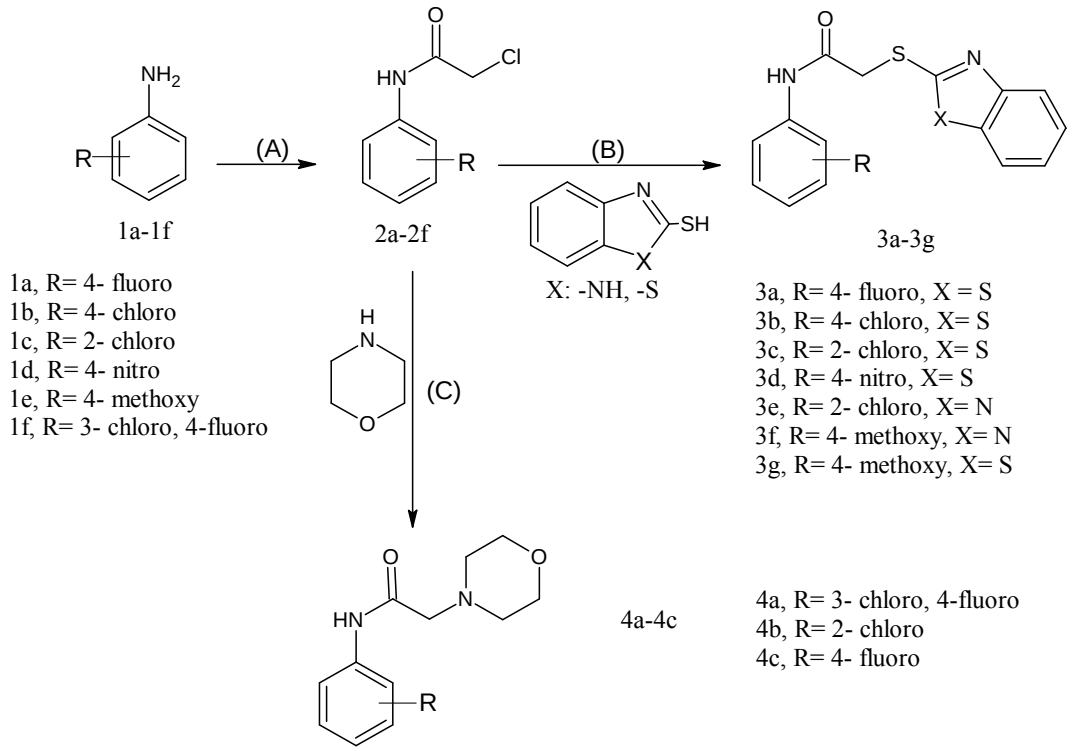
The process involved following steps:

a) Importing a ligand/protein co-crystallized structure from the Protein Data Bank.
b) Preprocessing the protein structure (assigning the bond order, adding or deleting hydrogens, finding overlaps, deleting water molecules in 5 Å).
c) Inspecting the structure and deleting unwanted chains.

The acting force of this binding mode mainly depends on hydrogen bonding, electrostatic forces, van-der Waal forces and hydrophobic interaction due to non-polar residue interaction and water structure effect alteration.[6,8]

2.2. GENERAL INTRODUCTION

Compounds showing G-scores of about 6.00 or more than 6.00 were synthesized in the laboratory (Table 1) as per the chemical reactions shown in Fig 1. All the chemicals and reagents used in current study were of Analytical (AR) and Laboratory (LR) grades. All synthesized compounds were characterized from melting point, TLC and FTIR, ^{1}H-NMR and Mass spectra. All the reactions were monitored using aluminium-supported precoated thin layer chromatography (TLC), silica gel 60G F_{254} plates (Mercks), with a hexane: ethylacetate solvent system (7:3). The spots were visualized using an ultraviolet (UV) lamp (254 nm). Melting points of the compounds were determined by using an electrothermal melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using appropriate deuterated solvents. The chemical shifts are expressed in δ ppm and splitting patterns are designated as s: singlet; d: doublet; q: quartet and m: multiplet. The FTIR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The mass spectra were recorded on Waters-Q-TOF Micromass (ESI-MS) spectrometer.



Reagents and conditions: (A) 2-chloroacetyl chloride, CH_2Cl_2, K_2CO_3, 0-5 ^oC, constant stirring
(B) THF, Et_3N, RT, 8-16 h, constant stirring
(C) THF, Et_3N, RT, 2-5 h, constant stirring

Fig 1: Synthetic route for synthesis of compounds 3a-3g and 4a-4c.

2.3. SYNTHETIC PROCEDURES AND SPECTRAL ANALYSIS

2.3.1. General Procedures for synthesis of compounds 2a-2f

Compounds 2a-2f were prepared following the literature procedure.[9,10] 2-Chloroacetylchloride (0.01mol) was added drop wise to a mixture of a substituted aniline (1a-1f) (0.01mol) and K_2CO_3 (0.01mol) in dichloromethane at 0-5^{o}C, with constant stirring. After removal of dichloromethane and vacuum filtration, the solid was washed with water and dried under vacuum at 25-30^{o}C. The compounds obtained were purified by recrystallization with petroleum ether/ ethyl acetate.

2.3.2. General procedure for synthesis of compounds 3a-3g

Compounds 3a-3g were synthesized according to the procedure obtained from literature[9,11], with few modifications. Briefly, 2-mercaptobenzothiazole / 2-mercaptobenzimidazole was added to a mixture of an amine [(1a-1f) (0.01mol)] and triethylamine (0.01mol) in tetrahydrofuran at room temperature with constant stirring for 8-16 h. The precipitate obtained was collected by filtration and washed with ice-cold water to yield the crude product. The purification was carried out by column chromatography on silica gel using petroleum ether/ ethyl acetate as a mobile phase.

2.3.3. Spectral analysis of compounds 3a-3g

2-(1,3-Benzothiazol-2-ylsulfanyl)-N-(4-fluorophenyl) acetamide (3a) (Fig 2)

Yield: 50%; mp: 120-125^{o}C; FTIR (KBr, cm^{-1}); 3668-3285 (N-H), 3068-2821 (C-H), 1680 (C=O), 1618 (C=N), 1558-1428 (C=C), 1216-1131 (C-S), 1100 (C-F). ^{1}H-NMR (DMSO, ppm); 4.05 (s, 2H, -CH_2), 7.00 (t, 2H, Ar-H), 7.40 (t, 1H, Ar-H), 7.45 (m, 3H, Ar-H), 7.81 (d, 1H, Ar-H), 7.95 (d, 1H, Ar-H), 10.09 (s, 1H, NH). ESI-MS (M+1, *m/z*): 319.04

2-(1,3-Benzothiazol-2-ylsulfanyl)-*N*-(4-chlorophenyl) acetamide (3b)

Yield: 45%; mp: 80-85^{o}C FTIR (KBr, cm^{-1}); 3414 (N-H), 2998-2831 (C-H), 1681 (C=O), 1617 (C=N), 1610-1401 (C=C), 1097 (C-S), 615 (C-Cl). ^{1}H-NMR (DMSO, ppm); 3.97 (s, 2H, -CH_2), 7.17 (d, 2H, Ar-H), 7.31 (t, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.87 (d, 1H, Ar-H), 10.11 (s, 1H, NH). ESI-MS (M^+, *m/z*): 335.05

2-(1,3-Benzothiazol-2-ylsulfanyl)-*N*-(2-chlorophenyl) acetamide (3c)

Yield: 55%; mp: 120-125^{o}C. FTIR (KBr, cm^{-1}); 3287-3668 (N-H), 3008-2853 (C-H), 1692 (C=O), 1691 (C=N), 1500-1428 (C=C), 1208-1124 (C-S), 693 (C-Cl). ^{1}H-NMR (DMSO, ppm); 4.12 (s, 2H, -CH_2), 6.95 (t, 1H, Ar-H), 7.28 (m, 2H, Ar-H), 7.40 (t, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 7.87 (d, 1H, Ar-H), 8.27 (d, 1H, Ar-H), 9.55 (s, 1H, NH). ESI-MS (M^+, *m/z*): 335.05

2-(1,3-Benzothiazol-2-ylsulfanyl)-*N*-(4-nitrophenyl) acetamide (3d)
Yield: 57%; mp: 115-120°C. FTIR (KBr, cm^{-1}); 3267 (N-H), 3010-3082 (C-H), 1705-1783 (C=O), 1616 (C=N), 1452-1596 (C=C), 1015 (C-S), 1308 and 1508 (O=N=O). ^{1}H-NMR (DMSO, ppm); 4.02 (s, 2H, -CH2), 8.14 (d, 2H, Ar-H), 7.90 (d, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 7.62 (d, 2H, Ar-H), 7.50 (t, 1H, Ar-H), 7.37 (t, 1H, Ar-H), 10.75 (s, 1H, NH). ESI-MS (M+1, *m/z*): 346.11

2-(1*H*-Benzimidazol-2-ylsulfanyl)-*N*-(2-chlorophenyl) acetamide (3e) (Fig 2)
Yield: 65%; mp: 155-160°C; FTIR (KBr, cm^{-1}); 3228 (N-H), 3000 (C-H; aromatic), 2800 (C-H, aliphatic), 1659-1618 (C=O), 1450 (C=C), 1262-1102 (C-N), 1100 (C-S), 696 (C-Cl). ^{1}H-NMR (DMSO, ppm); 4.11 (s, 2H, -CH_2), 7.01 (dd, 1H, Ar-H) 7.07 (dd, 2H, Ar-H), 7.18 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.39 (s, 2H, Ar-H), 8.08 (1H, Ar-H), 10.40 (s, 1H, -NH), 12.57 (s, 1H, -NH imidazole). ESI-MS (M^+, *m/z*): 318.04

2-(1*H*-Benzimidazol-2-ylsulfanyl)-*N*-(4-methoxyphenyl) acetamide (3f)
Yield: 68%; mp: 148-150°C; FTIR (KBr, cm^{-1}); 3340 (N-H), 2892 (C-H; aromatic), 2800 (C-H, aliphatic), 1655 (C=O), 1453 (C=C), 1110 (C-N), 1100 (C-S), 1090 (C-O). ^{1}H-NMR (DMSO, ppm); 3.85 (s, 3H, -OCH_3), 3.78 (s, 2H, -CH_2), 6.66 (d, 1H, Ar-H), 6.99 (dd, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.60 (d, 1H, Ar-H), 8.58 (s, 1H, N-H), 9.24 (s, 1H, N-H).

2-(1,3-Benzothiazol-2-ylsulfanyl)-*N*-(4-methoxyphenyl) acetamide (3g)
Yield: 71%; mp: 165-173°C; FTIR (KBr, cm^{-1}); 3235 (N-H), 2899 (C-H; aromatic), 2810 (C-H, aliphatic), 1637 (C=O), 1456-1501 (C=C), 1132 (C-N), 1148 (C-S), 1107 (C-O). ^{1}H-NMR (DMSO, ppm); 4.17 (s, 2H, -CH_2), 3.79 (s, 3H, -OCH_3), 7.45 (d, 2H, Ar-H), 7.41 (d, 1H, Ar-H), 7.28 (m, 3H, Ar-H), 6.90 (d, 2H, Ar-H).

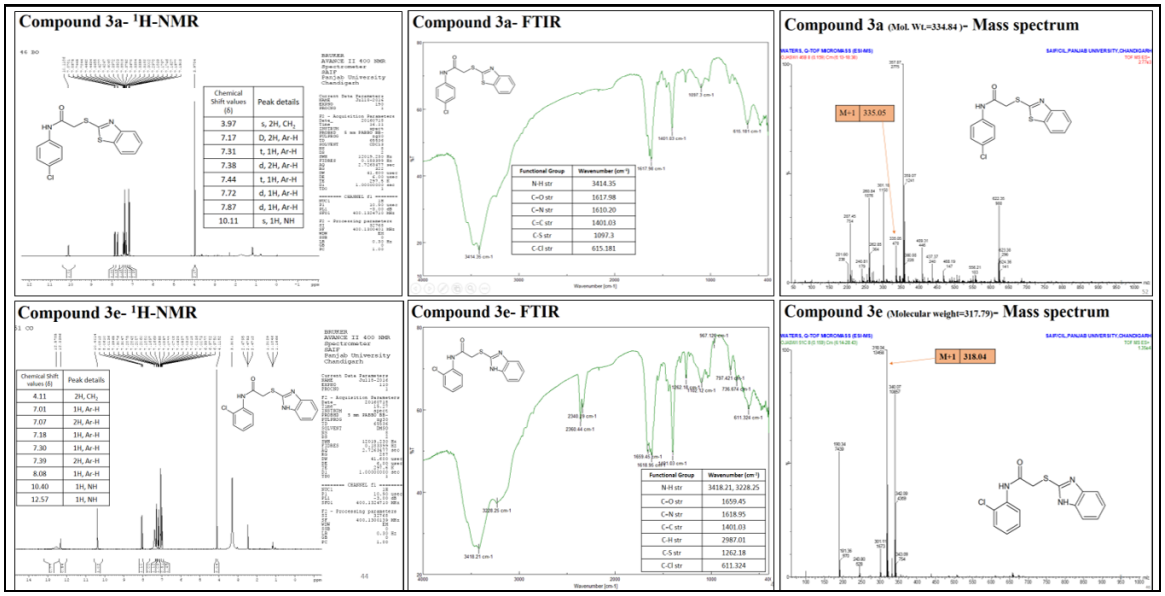


Fig 2: Spectral analysis of compounds 3a and 3e.

2.3.4. General procedure for synthesis of compounds 4a-4c

Compounds 4a-4c were synthesized by modifying the procedure reported in the literature[9,11], with few modifications. Briefly, morpholine was added to a mixture of an amine [(1a-1d) (0.01mol) and triethylamine (0.01mol) in tetrahydrofuran at room temperature with constant stirring for 3-4 h. The precipitate obtained was collected by filtration and washed with ice-cold water to yield the crude product. Purification was done by recrystallization from ethanol.

2.3.5. Spectral analysis of compounds 4a-4c

***N*-(3-chloro-4-fluorophenyl)-2-(morpholin-4-yl) acetamide (4a)**
Yield: 50%; mp: 80-85°C; FTIR (KBr, cm^{-1}); 3417 (N-H), 2990 (C-H; aromatic), 3031 (C-H, aliphatic), 1659 (C=O), 1450-1540 (C=C), 1122 (C-N), 1100 (C-F), 686 (C-Cl). ^{1}H-NMR (DMSO, ppm); 2.6196-2.6428 (t, 4H, 2 x CH_2), 3.1486 (s, 2H, -CH_2), 3.79 (t, 4H, 2 x CH_2), 7.12 (t, 1H, Ar-H), 7.42 (m, 1H, Ar-H), 7.74 (dd, 1H, Ar-H), 9.08 (s, 1H, N-H). ESI-MS (M-1, *m/z*): 272.93

***N*-(2-chlorophenyl)-2-(morpholin-4-yl) acetamide (4b)**
Yield: 55%; mp: 100-105°C; FTIR (KBr, cm^{-1}); 3416 (N-H), 2960-3031 (C-H; aromatic), 3000 (C-H, aliphatic), 1609 (C=O), 1485-1570 (C=C), 1102 (C-N), 1100 (C-O), 696 (C-Cl). ^{1}H-NMR (DMSO, ppm); 2.58 (t, 4H, 2 x CH_2), 3.09 (s, 2H, -CH_2), 3.72 (t, 4H, 2 x CH_2), 6.97 (t, 1H, Ar-H), 7.21 (d, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 8.34 (d, 1H, Ar-H), 9.85 (s, 1H, N-H). ESI-MS (M-1, *m/z*): 254.86.

***N*-(4-fluorophenyl)-2-(morpholin-4-yl) acetamide (4c)**
Yield: 60%; mp: 95-100°C; FTIR (KBr, cm^{-1}); 3417 (N-H), 2804-3054 (C-H; aromatic), 2890 (C-H, aliphatic),

1654 (C=O), 1485-1570 (C=C), 1212 (C-N), 1143 (C-O), 1111 (C-F). ^{1}H-NMR (DMSO, ppm); 2.56 (t, 4H, 2 x CH_2), 3.07 (s, 2H, -CH_2), 3.72 (t, 4H, 2 x CH_2), 6.98 (t, 2H, Ar-H), 7.48 (dd, 2H, Ar-H), 8.95 (s, 1H, N-H). ESI-MS (M-1, *m/z*): 238.81.

Table 1: G-Score and physiochemical properties of compounds 3a-3g and 4a-4c.

Compound Code	G-Score (3JZI) *Biotin carboxylase*	G-Score (3GW9) *Sterol 14-alpha demethylase*	Molecular formula	Molecular weight	Melting Point (mp) (^{o}C)	Yield (%)
3a	-6.983	-8.843	$C_{15}H_{11}FN_2OS_2$	318	120-125	50
3b	-6.901	-8.68	$C_{15}H_{11}ClN_2OS_2$	335	80-85	45
3c	-6.843	-8.592	$C_{15}H_{11}ClN_2OS_2$	335	120-125	55
3d	-6.991	-8.489	$C_{15}H_{11}N_3O_3S_2$	345	115-120	57
3e	-7.448	-8.782	$C_{15}H_{12}ClN_3OS$	318	155-160	65
3f	-7.38	-8.70	$C_{16}H_{15}N_3O_2S$	313	148-150	68
3g	-7.31	-8.69	$C_{16}H_{14}N_2O_2S_2$	330	165-173	71
4a	-6.002	-8.152	$C_{12}H_{14}ClFN_2O_2$	273	80-85	50
4b	-5.994	-8.033	$C_{12}H_{15}ClN_2O_2$	255	100-105	55
4c	-5.958	-7.903	$C_{12}H_{15}FN_2O_2$	239	95-100	60
Co-crystallized ligand*	-11.933	_	-	-	-	-
Co-crystallized ligand#	_	-10.238	-	-	-	-

* *7-amino-2-[(2-chlorobenzyl)amino]-1-{[(1S,2S)- 2-hydroxycycloheptyl]methyl}-1H-benzimidazole- 5-carboxamide* (inhibitor complexed in *Biotin carboxylase*, PDB ID: 3JZI).
#N-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide (inhibitor complexed in *Sterol 14-alpha demethylase*, PDB ID: 3GW9).

3. Evaluation of antimicrobial activity

Antibacterial activity of the synthesized compounds was tested against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* using nutrient agar medium. The antifungal activity of the compounds was tested against *Aspergillus niger* using Sabouraud dextrose agar medium.

3.1 Agar diffusion method

All compounds were screened *in vitro* for their antimicrobial activity, by agar diffusion method. Bacterial suspension of the organisms was added to sterile nutrient agar media and fungal suspension was added to Sabouraud dextrose agar medium, at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Cups of 10 mm diameter were made using a cork borer. An amount of 0.1 ml (concentration of 25, 50, 75, 100, 125, 150 µg/ml) of the synthesized compounds was poured inside the cups. A cup filled with DMF was used as a control. The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects of variation in time between the applications of different solutions. The plates were then incubated at 37°C for 24 h and observed for antimicrobial activity.[12] The diameters of zone of inhibition were measured and compared with that of the standard. Ofloxacin (100 µg/ml) was used as a standard for antibacterial activity and Fluconazole (100 µg/ml) was used as a standard for antifungal activity. The observed zones of inhibition are presented in Table 2.

4. RESULTS AND DISCUSSION

4.1. *In silico* molecular docking

The X-ray crystal structure of *biotin carboxylase* from *E. coli* with resolution of 1.87 A^o corresponding to PDB ID 3JZI was downloaded from the Protein Data Bank (PDB) data base. The enzyme *biotin carboxylase* is complexed with *7-amino-2-[(2-chlorobenzyl)amino]-1-{[(1S,2S)- 2-hydroxycycloheptyl]methyl}-1H-benzimidazole- 5-carboxamide* Docking score of the complexed inhibitor was found to be -11.939, with RMSD of 1.96.

Crystal structure of *sterol 14-alpha-demethylase from Trypanosoma brucei* with resolution of 2.31 A^o corresponding to PDB ID 3GW9 was downloaded from Protein Data Bank (PDB) data base. The enzyme *sterol 14-alpha-demethylase* is complexed with inhibitor N-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide. Docking score of the complexed inhibitor was found to be -10.238, with RMSD of 0.6176.

Compound 3e showed the highest G score (-7.448) against the target 3JZI and compound 3a showed the highest G score (-8.843) against the target 3GW9. Thus, on analyzing the docking scores, it was observed that the compounds 3a and 3e gave comparatively good interaction with the selected targets, 3JZI and 3GW9. The binding mode of compounds 3a and 3e in ATP binding sites of targets 3GW9 and 3JZI and their interaction with various amino acids is shown in Figures

3 and 4, respectively. Docking sores of all the 10 synthesized compounds are listed in Table 1.

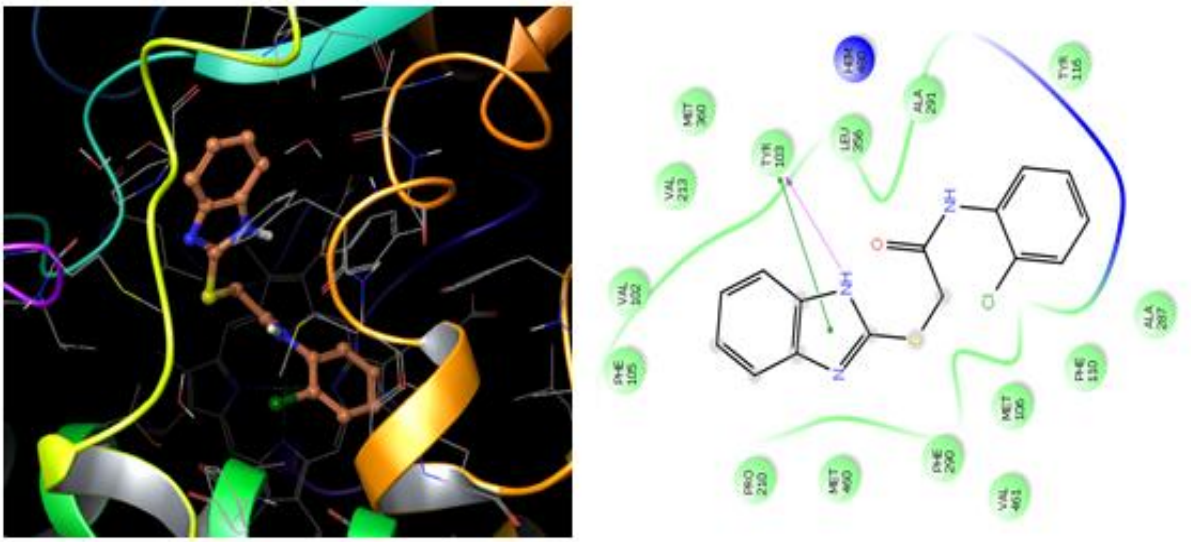


Fig. 3: Binding mode of compound 3e in ATP binding site of 3JZI (*biotin carboxylase*) and its interaction with various amino acids.

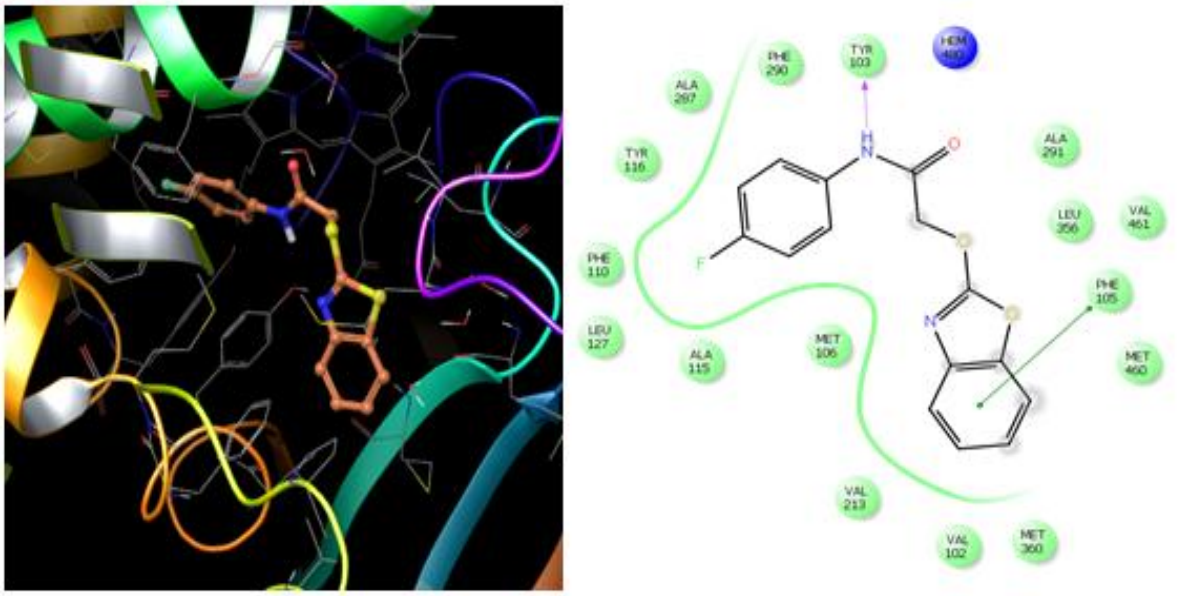


Fig. 4: Binding mode of compound 3a in ATP binding site of 3GW9 (*sterol 14-alpha demethylase*) and its interaction with various amino acids.

4.2 Antimicrobial activity

The results mentioned in Table 2 indicate that there is a variable inhibitory effect on the growth of bacterial and fungal strains. Compound 3a showed good antibacterial activity against both *E. coli* and *S. aureus* strains. Compound 3e showed good antifungal activity against *A. niger* strain. It should also be noted that antifungal activity increased when benzothiazole moiety of the N-phenylacetylamide derivatives was replaced with benzimidazole and morpholine, as compounds containing benzimidazole **(3e, 3f)** and morpholine **(4a-4c)** exhibited good zones of inhibition.

Table 2: Antibacterial and antifungal activities of the newly synthesized compounds indicated by zones of inhibition.

Compound code	*S. aureus*	*E. coli*	*A. niger*
	Zone of Inhibition (mm) at 100 µg/ml	Zone of Inhibition (mm) at 100 µg/ml	Zone of Inhibition (mm) at 100 µg/ml
3a	14	13	10
3b	10	10	9
3c	11	8	10
3d	9	7	9
3e	12	10	15
3f	10	7	13
3g	10	10	8
4a	8	8	11
4b	7	9	10
4c	7	8	10
Ofloxacin	18	18	_
Fluconazole	_	_	17

5. CONCLUSION

Drug discovery is a challenging process due to complexity of biological systems. Synthesis of new molecules containing active moieties can be a promising approach to improve therapeutic properties. N-phenylacetylamide derivatives containing benzothiazole/ benzimidazole/ morpholine moieties were subjected to *in silico* molecular modelling. The binding mode of these compounds with different antimicrobial targets was found out using *Glide* module of the molecular modelling software *Maestro 10.5* from Schrödinger, USA. The docking results for antimicrobial activity were in good correlation with the results obtained by agar diffusion assay method. Among the synthesized compounds, compound 3a and 3e had good G score values and exhibited promising antibacterial and antifungal activities. The ligands in this study can be used for further studies to develop molecules with more potent antimicrobial activity.

6. ACKNOWLEDGEMENT

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