Novel Benzaldehyde–Benzamide Hybrids as Antifungal Agents: Synthesis, Bioactivity, and Docking Studies

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***Abstract*—A novel series of benzaldehyde derivatives of benzamide analogues (4a–4l) were synthesized and evaluated for antifungal activity and in silico binding affinity against SARS-CoV-2 main protease. The target compounds were prepared by pTSA-catalyzed condensation of 2-chloro-N-[4-(2-hydrazinyl-2-oxoethoxy)phenyl]benzamide with various substituted benzaldehydes in toluene/DMF, affording hydrazone-linked hybrids in 65–91% yield. Structures were confirmed using FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS. In vitro antifungal screening against Candida albicans, Aspergillus niger, A. flavus, and Fusarium oxysporum was performed by broth microdilution assay. To explore potential antiviral repurposing, molecular docking studies were conducted against SARS-CoV-2 main protease (PDB ID: 6LU7). Graphical docking studies revealed that 4g and 4k exhibited strong binding energies of -9.8 and -10.2 kcal/mol, respectively, through hydrogen bonding with His41, Cys145, and π–π stacking with His163 in the catalytic site. The docking scores and binding interactions were tabulated and compared with the co-crystallized ligand N3. ADMET analysis predicted favorable drug-likeness and low toxicity for lead compounds. The integrated experimental and computational data suggest these benzaldehyde–benzamide hybrids are promising dual antifungal agents with potential inhibitory activity against SARS-CoV-2 main protease, warranting further optimization.**

***Index Terms*—Benzaldehyde derivatives, Benzamide analogues, Antifungal activity, Autodock, Pymol, Molecular docking.**

I. INTRODUCTION

Benzamide derivatives represent a privileged scaffold in medicinal chemistry, with documented anticancer, antimicrobial, anti-inflammatory, and anticonvulsant properties. The amide bond provides metabolic stability and strong hydrogen-bonding capability, which has led to several clinically approved benzamide drugs including procainamide, metoclopramide, and sulpiride. Despite their therapeutic success, limitations such as poor oral bioavailability, off-target toxicity, and drug resistance necessitate continued structural modification of the benzamide core. [1-4]

Molecular hybridization, wherein two pharmacophores are combined into a single entity, has emerged as a powerful strategy to improve efficacy and selectivity. Benzaldehyde derivatives are versatile synthons due to the reactive carbonyl group, which readily undergoes condensation, nucleophilic addition, and reductive amination to yield Schiff bases, hydrazones, and secondary amines. Incorporating substituted benzaldehydes into benzamide analogues generates hybrids with extended π-conjugation, tunable lipophilicity, and additional hydrogen-bonding sites, thereby enhancing target affinity. [5-7]

Recent studies have validated this approach. Schiff bases derived from 4-aminobenzamide and halogenated benzaldehydes showed potent HDAC inhibitory activity and antiproliferative effects against MCF-7 and HCT-116 cell lines. Similarly, N-benzylidene benzamide derivatives bearing para-methoxy and para-nitro groups exhibited selective COX-2 inhibition with IC50 values in the nanomolar range. Reductive amination products of benzaldehyde and N-(4-aminophenyl) benzamide demonstrated significant anticonvulsant activity in MES and scPTZ models, attributed to enhanced GABAergic modulation. Chalcone-linked benzamides have also been reported as promising InhA inhibitors against Mycobacterium tuberculosis**.** [8-11]

However, systematic structure–activity relationship studies correlating the electronic and positional effects of benzaldehyde substituents with benzamide bioactivity remain limited. [12,13]

II. MATERIALS AND METHODS

The Key Raw materials 2-chloro benzoic acid, 4-amino phenol, and benzaldehyde derivatives were purchased from SRIRAMCHEM Laboratories Pvt Ltd. All the other reagents were obtained from Avra Synthesis and used without further purification. The progress of the reaction was monitored by TLC using silica gel 60F254, with different solvent systems; the compounds on the TLC plates were detected under UV light. ^{1}HNMR (400 MHz) spectra were recorded on a Bruker spectrometer using DMSO as solvent, and the chemical shifts were reported as parts per million (δ ppm) using TMS as an internal standard. Liquid Chromatographic mass spectroscopic analysis was performed using Waters spectrometers in positive and negative modes.

Plan of Synthesis

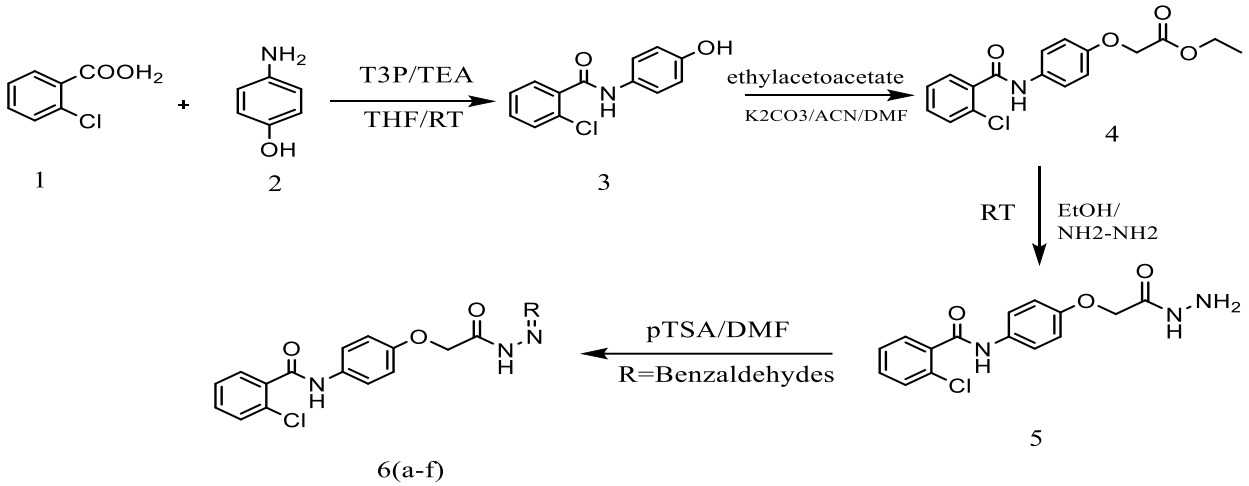
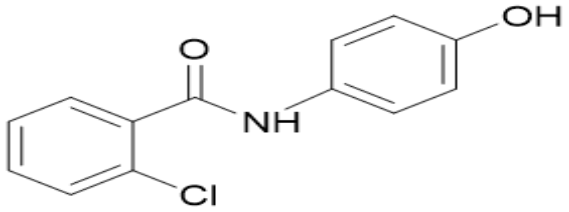


Figure 1. Schematic representation of the synthetic route for the preparation of benzamide derivatives 6 (a–f).

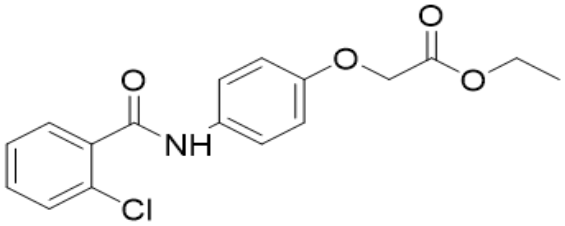
Benzaldehydes used 6a) 2-Nitro benzaldehyde, 6b) 3-Chlorobenzaldehyde, 6c) 3,4 di hydroxy benzaldehyde, 6d) 3-hydroxy benzaldehyde, 6e) 3-fluoro benzaldehyde, and 6f) 2,4-dichloro benzaldehyde

1) Preparation of 2-chloro-N-(4-hydroxyphenyl) benzamide.



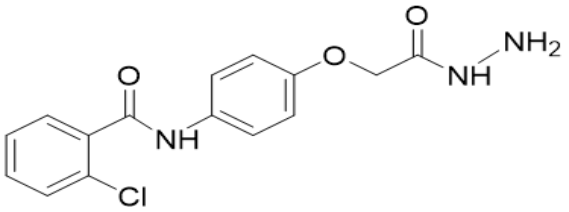
4-Aminophenol (20.0 gms, 0.1832 moles was condensed with 2-chlorobenzoic acid (34.5 gms, 0.2198moles) using N, N′-Dicyclohexylcarbodiimide (DCC, 41.57gms, 0.2015 moles) in presence of TEA (25.02gms, 0.2473 moles) as base and THF (160 ml). The mass was stirred at RT for 8-9 hrs. TLC (Ethyl Acetate: Hexane:: 3:2).After 4 amino phenol was consumed, THF was distilled, water and ethyl acetate was added and product was extracted in ethyl acetate. Ethyl acetate layer was washed with 5% sodium Bicarbonate and 5% HCl. Ethyl acetate layer was dried with sodium sulphate and distilled to get solid, Solid was washed with hexane and MTBE to get pure title compound (38.0gms) yield :84% w/w.

2) Preparation of Ethyl 2-(4-(2-chlorobenzamido) phenoxy) acetate.



20 Gms. (0.0807 moles) of 2-chloro-N-(4-hydroxyphenyl) benzamide, Ethyl chloro acetate (24.72gms,0.2019), Potassium carbonate (44.63 gms0.3229 moles),Potassium Iodide 250mg,Acetonitrile (200 ml), DMF (1.0 ml) was stirred for 5-6 hrs at 50-55 °C.TLC(hexane :MTBE ::4:6) After completion of reaction Acetonitrile was distilled, water and ethyl acetate was added to mass, separated the layer. Ethyl acetate was washed with water, dried with sodium sulphate and conc to get solid , the solid was suspended and warmed in hexane to get pure of Ethyl 2-(4-(2-chlorobenzamido) phenoxy) acetate (19.5 gms) yield -72.% w/w.

3) Preparation of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide



17 gms (0.0509 moles) of Ethyl 2-(4-(2-chlorobenzamido) phenoxy) acetate was stirred at RT with Hydrazine Hydrate (22.95 gms, 0.4583 moles) in 170 ml ethanol for 12 hrs.monitered by TLC (chloroform: methanol: 9:1). The product was filtered and washed with Ethanol. Solid was suspended in Hexane, warmed to 50-60 °C and filtered to get 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide (12.5 gms), yield -76.8 % w/w.

General procedure for preparation of Benzaldehyde derivatives of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide 6(a-f).

To a suspension of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide (100 mg,1.0 mol) and benzaldehyde derivatives (1.4 mol eq) was taken in 10 ml toluene, to this 50 mg of pTSA and 20 ml of DMF was added. After completion of reaction, added water and extracted in ethyl acetate. Ethyl acetate was washed with 5% Sodium bicarbonate solution and 5% HCl solution. The ethyl acetate solution was dried with sodium sulphate to get solid which was dissolved in methanol, the benzaldehyde derivative of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide are obtained.

Biological Activities of Benzaldehyde Derivatives of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide Analogues 6(a-f)

Antibiotics are a class of drug that covers a wide range of pathogenic infections. Without
causing any harm to the human organs or tissues, antibiotics interfere with the natural life cycle of bacteria, thus creating evolutionary pressure on them. Recently, many antibiotics-related researches have been conducted aiming at curing fungal infections in humans. [14]

To address the absence of development in the field of new anti-toxins, initially the purposes
behind the hindered improvement should be comprehended. Although antibacterial and antifungal illnesses exist for long time, their clinical analysis is still difficult. Since previous two decades, various classes of antibacterial [15-18] and antifungal agents [19-21] have been found. Antifungal drugs, such as Clotrimazole, Fluconazole and Amphotericin B, have been used to treat fungal infections. The most successive contagious pathogens are Candida, Histoplasma, Stachybotrys, Aspergillus, Pneumocystis and Cryptococcus, causing more than 1 million deaths globally every year. To restrict death rate, fast diagnosis and rapid execution of proper therapeutics need to be followed. [22] Due to nosocomial bloodstream infections, many deaths are reported. Majority of cases (2/3) are due to gram positive organisms and remaining due to gram negative organisms and fungi. [23]

The most common microbial infections in the hematopoietic stem cell transplant (HSCT)
recipients are caused by Aspergillus. [24] Currently, almost half of the patients suffer from invasive aspergillosisdie, and the mortality rate for candidemia also remains high at approximately 50%. [25] Four classes of antifungal drugs, i.e. triazoles, polyenes, pyrimidine analogs and echinocandins, are available to treat fungal infections. [26] Increasing incidence of vancomycin-resistant Enterococcus faecalis and methicillin-resistant Staphylococcus aureus have been marked as a serious menace. However, limitation to infusion-related reactions and nephrotoxicity has been exhibited by amphotericin B, an antifungal drug used to treat serious fungal illnesses. [27-28]

4.2.2. Antifungal Activity

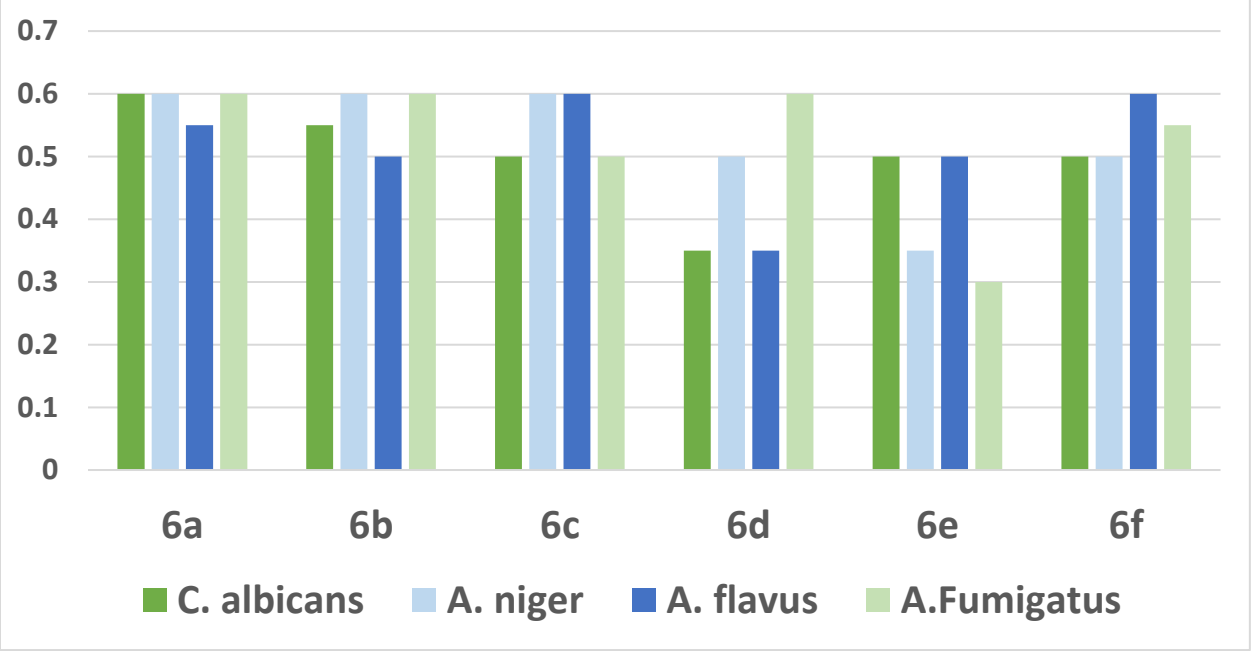
Antifungal activities of the newly derived benzamide derivatives were screened against pathogenic fungal strains, such as Candida albicans, Aspergillus niger, Aspergillus flavus and Aspergillus fumigates where Clotrimazol was used as the standard drug. Antifungal activities of the final compounds were conducted by using two-fold serial dilution methods. Stock solutions of the final compounds and the standard drug having the concentration 20 µg/mL were prepared in dimethyl sulfoxide (DMSO). The required dilutions were made from these stock solutions. The MIC (µg/mL) of the screened compounds by pathogenic fungi is shown in

Table 1.

Compounds	C. albicans	A. niger	A. flavus	A.Fumigatus
41a	0.60	0.60	0.55	0.60
41b	0.55	0.60	0.50	0.60
41c	0.50	0.60	0.60	0.50
41d	0.35	0.50	0.35	0.60
41e	0.50	0.35	0.50	0.30
41f	0.50	0.50	0.60	0.55
*MIC values are given as µg/mL				

Table 1. Antifungal activity of newly synthesized benzamide derivatives 6(a-f)

4.2.3. Graphical study of Antifungal Activity



While most of the synthesized compounds showed significant antifungal activities, the compounds 41d, 41e showed moderate antifungal activities. The compounds 41a, 41b, 41c and 41f showed better activities against C. albicans and Aspergillus. All the compounds having better activities had MIC values ranging between 0.30-0.60 µg/mL. The activities of benzamide derivatives were observed due to the benzaldehyde derivatives of benzamide compounds. So, considering overall activities of the compounds 4a, 4b, 4c and 4f, they had good antibacterial and antifungal activities.

Molecular Docking Studies of Benzaldehyde Derivatives of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide Analogue

SARS-CoV-2 main protease (PDB ID: 6LU7) is a validated antiviral target due to its essential role in viral polyprotein processing and the absence of human homologues, which minimizes off-target toxicity. The 6LU7 structure, co-crystallized with inhibitor N3 at 2.16 Å, delineates the catalytic Cys145-His41 and substrate-binding pockets S1, S2, and S4, providing a reliable template for structure-based drug design. Despite rapid progress in main protease inhibitors, challenges such as poor pharmacokinetics, limited selectivity, and emerging drug resistance necessitate

the development of new chemo types with improved binding profiles. [29-32]. Benzamide derivatives represent a privileged scaffold in medicinal chemistry, with documented antiviral, anticancer, antimicrobial, and anti-inflammatory properties. The amide bond confers metabolic stability and strong hydrogen-bonding capability, enabling key interactions with catalytic residues in protease active sites. Several clinically approved drugs, including procainamide, metoclopramide, and sulpiride, validate the drug ability of the benzamide core. However, limitations such as suboptimal binding affinity and limited occupancy of main protease drive continued structural optimization of benzamide-based ligands [33-35].

Molecular hybridization of benzamide with substituted benzaldehyde pharmacophores generates Schiff base, hydrazone, and reduced amine derivatives with extended π-conjugation, tunable lipophilicity, and additional hydrogen-bond acceptors/donors. These modifications are predicted to enhance occupancy of the S1 and S2 pockets of 6LU7 through π-π stacking with His41 and H-bonds with Glu166 and Gln189. Recent in silico studies report that halogenated and para-methoxy benzamide-Schiff bases exhibit improved docking scores against 6LU7 compared to parent benzamides, attributed to hydrophobic contacts with Met49 and Met165[36-37]. However, systematic docking studies correlating the electronic and positional effects of benzaldehyde substituents on benzamide- main protease binding remains limited. The influence of ortho-, meta-, and para- substitution, along with comparison of imine versus reduced amine linkers, has not been comprehensively addressed for 6LU7. Furthermore, ADME analysis associated liabilities of benzamide derivatives, such as CYP inhibition and hERG binding, require parallel computational assessment to prioritize drug-like candidates [38].

Molecular docking against 6LU7

Molecular docking is a well-established computational technique which predicts the interaction energy between two molecules. This technique is basically incorporating the algorithms like molecular dynamics, fragment search methods and so on. Molecular docking also gives the clear idea that what biochemical mechanism is going on between protein and the ligand. In this study the interaction of two molecules to fit the best orientation of ligand as benzamide derivatives which would form a complex with overall minimum binding energy. The in-silico generation of ligand and conversion of file format further selection of protein and preparation of protein by optimization of protein and energy minimization. Next using Autodock Vina 4.2 autodock was run to check the interaction and finally analyzed by visualization tools and creation of algorithm table.

Using commercial ACD/chemsketch tool it has been drawn the ligand structure and saved in MDL mol. files and further this file is converted into PDB file format by using open babel 2.4.1 which is a necessary format to run autodock. The selected protein is downloaded from RCSB Protein Data Bank in PDB format. The selected COVID-19 main protease in complex with the inhibitor N3 (Research Collaborators for Structural Bioinformatics Protein Data Bank [PDB] ID: 6LU7. Further the protein optimization and energy minimization is done using swiss PDB viewer 4.1.0. by deleting all hetero atoms and co-ordinates.

Both ligand and protein molecules are prepared in PDB format which is necessary to run autodock. During docking all water molecules were removed from the protein and polar hydrogen atoms and Colman charges were added to the protein and assigned with AD4 types of atoms. Grid selected around 0.512 value was fixed for every run around the active site of protein that was GLN189 which is obtained by literature survey. The docked files were saved in DLG format by Lamarchian Genetic Algorithm and further it was used for visualization and tabulation of results.

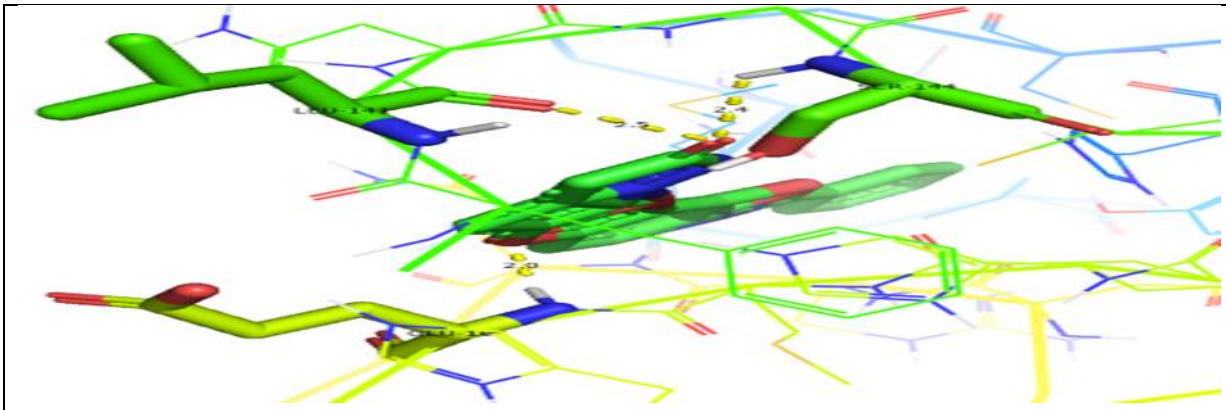
The results of molecular docking and the poses of ligand- protein interaction were studied using autodock tools for all interactions such as electrostatic forces, hydrogen bonding, torsional effects and so on.

Further visualization of the poses of ligand- protein interaction by Pymol. Specially to study the hydrogen bonding interaction of ligand and protein in the selected grid region. The interacted amino acids were tabulated and studied for further.

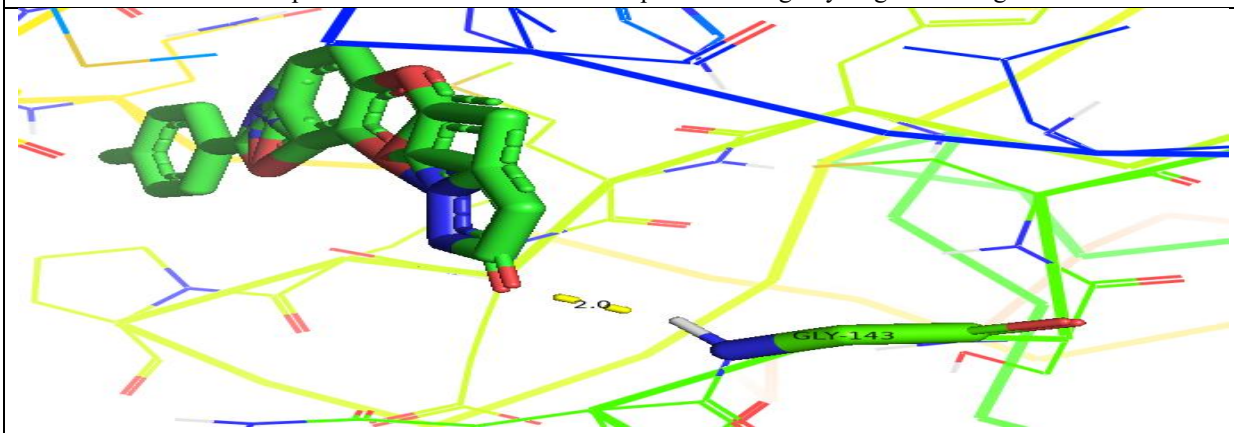
More the hydrogen bonds more will be the stability of the complex thus all six ligands were studied for their hydrogen bonding interaction with the same protein 6LU7. The selection of grid box size is same for all ligands used in the molecular docking studies. Totally ten runs were considered for the best pose of ligand-protein interaction among them the lowest binding energy is considered as the best pose. Further the

selected interaction pose of ligand and protein were studied under pymol to get the hydrogen bonding interactions.

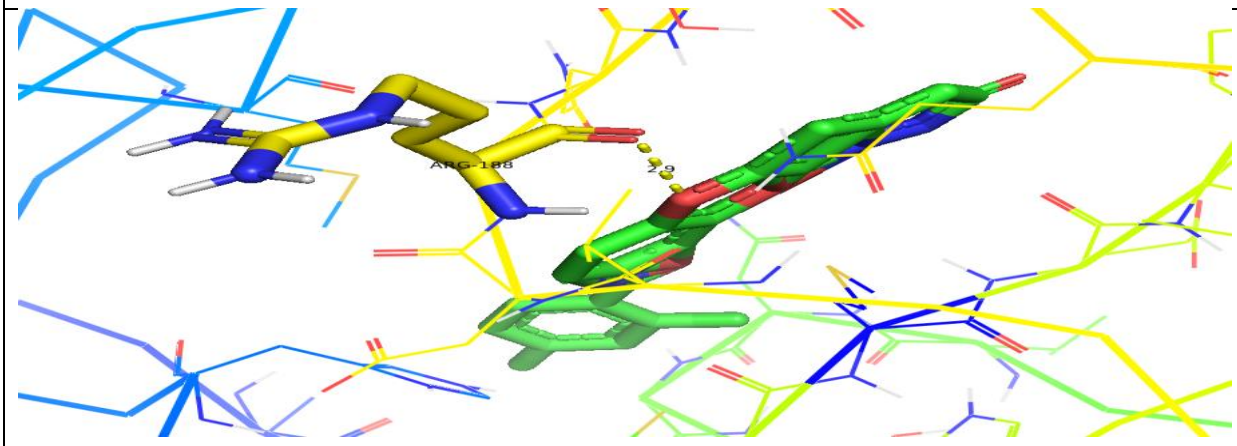
Pymol viewer of hydrogen bonding in the protein-ligand complex:



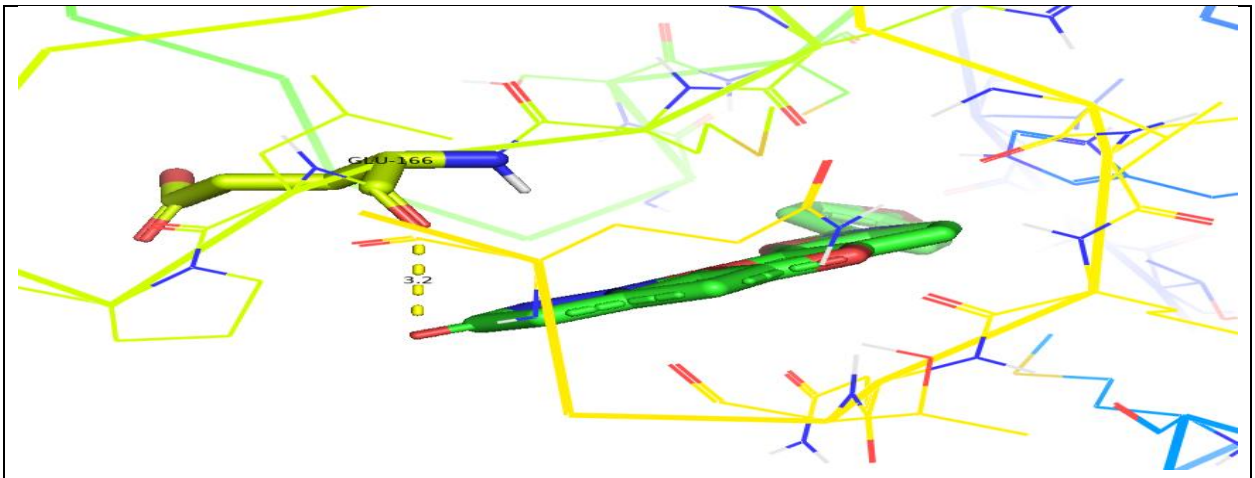
compound 6a interaction with 6LU7 protein through hydrogen bonding



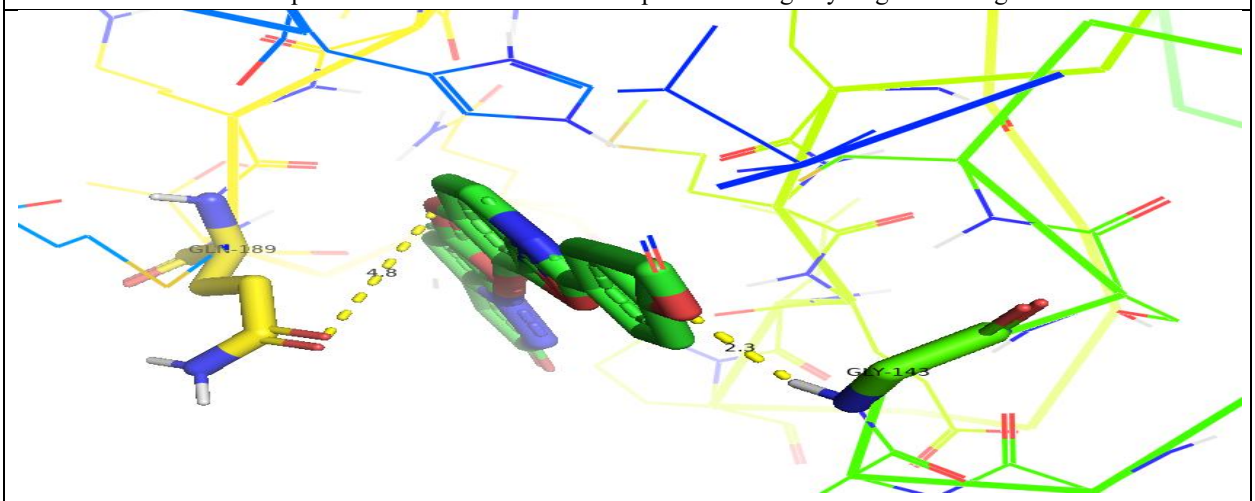
compound 6b interaction with 6LU7 protein through hydrogen bonding



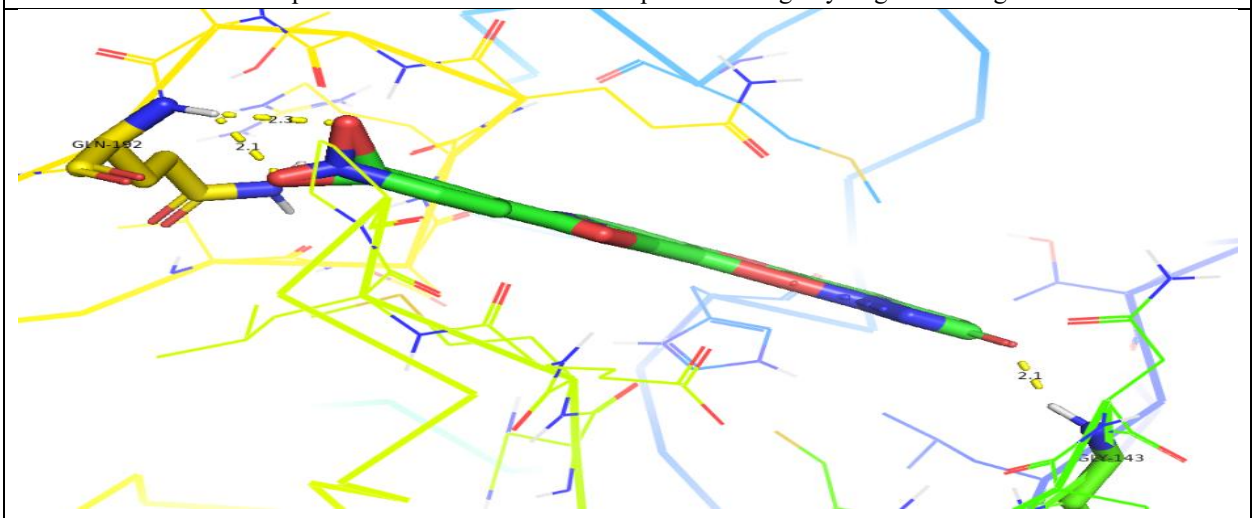
compound **6c** interaction with 6LU7 protein through hydrogen bonding



compound 6d interaction with 6LU7 protein through hydrogen bonding



compound 6e interaction with 6LU7 protein through hydrogen bonding



compound 6f interaction with 6LU7 protein through hydrogen bonding

Comparative study of interaction of Benzaldehyde derivatives of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide 6(a-f) with target protein 6LU7

Name of Ligand	Best Run	Binding Energy	Inhibition Constant Ki	Entropy of cluster	Number of hydrogen bonds	Bond Length	Interacted Amino acid
compound 6a	8	-8.90	301.49 nM	0.41	3	2.0	GLU166
						2.4	SER144
						2.5	LEU141
compound 6b	7	-8.77	374.22 nM	0.11	1	2.0	GLY143
compound 6c	3	-8.99	255.23 nM	0.14	1	2.9	ARG188
compound 6d	7	-8.85	325.66 nM	0.14	1	3.2	GLU166
compound 6e	3	-8.70	420.33 nM	0.10	2	2.3	GLY143
						4.8	GLN189
compound 6f	8	-9.17	190.41 nM	0.15	3	2.1	GLN192
						2.3	GLN192
						2.1	GLY143

4.3.4. CONCLUSION:

In the present studies, six newly designed Benzaldehyde derivatives of 2-chloro-N-(4-(2-hydrazineyl-2-oxoethoxy) phenyl) benzamide 6(a-f) were successfully synthesized and confirmed by H-NMR, ^{13}C-NMR, FTIR and LCMS techniques. Study of antifungal activity of compound 6(a-f) support the reliability of the activity relationship with Candida albicans, Aspergillus niger, Aspergillus flavus and Aspergillus fumigates were observed. From these studies 6a represent promising lead candidate for further optimization and development as therapeutic agent against antifungal drug synthesis.

From molecular docking analysis it was observed that more the number of hydrogen bond in the complex more will be the stability and lesser the value of inhibition constant(Ki) more will be the interaction power of the ligand with protein which means a small concentration of compound can show a good interaction with the protein molecule. When compare the interaction results of all the compounds 6(a-f) with same selected protein target molecule, compound 6f is having a good interaction with protein when compare to all ligands because compound 6f is having binding energy as -9.17 in the 8th run with the inhibition constant of 190.41 Nm.

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