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In-Silico Design, Docking Studies and Synthesis of Some Novel Heterocyclic Compounds

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Abstract: This study, I hoped that these compounds may produce more effective, efficient and potent application for antifungal and antibacterial effects. The purpose of this study is to test the antioxidant, anti-tubercular, and anti-fungal properties of the produced chemicals. One of the main approaches in developing potent drug molecule is based on the structural modification based on docking studies. Nitrogen containing heterocyclic system is indispensable structural unit for both the chemist and biochemist.

Introduction

Drug designing is a process of designing a drug molecule that can interact and bind to a target. Receptors are molecule which can be seen on the surface of the cell which receives signals and can be defined as a molecule which recognizes a small molecule, which on binding triggers a cellular process. In an unbounded state receptor, functionalities of the receptor remain silent.

One of the main approaches in developing potent drug molecule is based on the structural modification based on docking studies. Nitrogen containing heterocyclic system is indispensable structural unit for both the chemist and biochemist.

- Among the various classes of heterocyclic compounds Quinazolinone form an important component of pharmacologically active compounds. The invention concerns certain novel Quinazolinone derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-bacterial and antifungal activity and are accordingly useful in methods of treatment of the human or animal body.
- The invention also concerns processes for the manufacture of said Quinazolinone derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of microbial and fungal disorders in human.
- These potential chemical compounds are used as best therapeutic agents for Human diseases and further research findings.

- Research particularly drug discovery is a continuous process for many reasons like,
- In this research, computational drug discovery is used to identify the lead compound and protein target for the selected human diseases.
- The pathogenic organisms are known to develop resistance gradually against a particular drug; hence the drugs, which are active today, may become inactive after several years. In order to overcome this problem there is a need to replace old drugs by newer ones.
- Though some of the drugs are highly effective they are associated with toxic side effects
- Nature always possess problem to the human races, through new pathogenic bacteria, fungi etc, that cause newer diseases.
- In the course of medicinal chemistry program aimed at discovering new heterocyclic Quinazolineone derivatives induced with different biological activities. I have synthesized ten novel substituted Quinazolineonederivatives and study them for antibacterial and antifungal activities.

All the synthesized compounds were identified by UV, IR, NMR (1H &13C) and MASS spectral analysis.

Quinazolinone derivatives of synthesized compounds are undergone for

- Anti bacterial activity &
- Anti fungal activity.

Drug designing and validation: The potentially identified eighty chemical compound structures were drawn and validated by using Molinspiration and Chemaxon software's in order to perform drug likeness prediction (Lipinski's rule) and verification of the chemical structures.

Molinspiration: Virtual Screening is the computational chemistry technique to assess the large drug databases to identify the new drug molecules. It screens the molecules and provides the bioactivity score between -3 and +3. Molecules with highest bioactivity score will be more biologically active and produces better activity.

Lipinski's rule

Lipinski's rule of five states that, in general, an orally active drug has

- Not more than 5 hydrogen bond donors.
- Not more than 10 hydrogen bond acceptors.
- Molecular weight below 500g/mol.
- Partition co-efficient log P less than 5.
- Molar refractivity values must between 40 -130cm3/mol.

The molecules violating any one of the above rule will not have proper bioavailability.

From the scheme of synthesis eighty compounds chemical structure properties were identified by molinspiration software.

2D to 3D structure prediction: The designed 2D chemical structures were converted in to 3D structures using Online Smiles Translator server.

Molecular docking: The modeled protein and designed chemical 3D structures were docked with the help of advanced molecular docking servers, Patchdock. Out of the eighty compounds, the molinspiration and docking results shown eighteen compounds have high binding energy. Based on the

docking results of the eighteen compounds, I selected ten compounds for synthesis.

Literature Survey

From the literature review, it was concluded that several Quinazolin-4-one derivatives have found to exhibit interesting different biological activities including anti-tubercular and antifungal activities. Some of its derivatives were already in the market and several compounds were found in patented, literature indicating that many of them were undergoing trails for their clinical activity. It was proved from the literature survey revealed that the 2, 3, 7-trisubstituted-4(3H)-1, 3-benzoxazin-4-one and its derivatives were found to possess important biological activities. Keeping this in view, it was synthesized some novel 2, 3, 7-trisubstituted quinazolin-4-ones by conventional method.

- Predicted the biological activities of the number of compounds by Molinspiration and Patchdock computerized programs (Insilico methods).
- From the Molinspiration and Patchdock results selected ten compounds for synthesis.
- Attempted very simple and facile procedures for the synthesis of the quinazolin-4-ones derivative compounds with improved properties and least possible side effects.
- Purified the intermediates and final compounds by appropriate recrystallization and chromatographic techniques.
- Characterized the synthesized compounds by physical, spectral and analytical data's.

Objective of the project

The objectives of this research were:

- In-silico design.
- Docking studies.
- Synthesis of docked compounds and activity.
- The confirmation of compounds will be carried out by using various spectroscopic methods UV, FT-IR, 1H NMR, 13C NMR, MASS and Elemental analysis (CHN) studies.
- To assess the biological activity of selected synthesized compounds.

➢ Antifungal activity of selected organisms
➢ Antibacterial activity

Methodology

The experimental part has been divided into four parts.

1. Insilico drug design
2. Synthetic methodology
3. Analytical techniques
4. Evaluation of biological activity

INSILICO DRUG DESIGN

Data mining: The collection of literature for the human pathogens was done using literature databases like MBGD, Pubmed, OMIM and Pubmed central.

Protein Target identification and Sequence retrieval system: In this research work to be focused on human pathogen *Mycobacterium tuberculosis* and *Candidadubliniensis*. Multi drug resistance gene and protein sequences were retrieved from microbial genome database in order to perform molecular modeling process. Resistance to antimicrobial agents among bacteria and fungi is a persistent problem complicating the management of critically ill patients. To understand the issues involved in resistance in critical care, it is essential to understand the epidemiology and mechanisms of resistance. In this present *insilico* research found that the potential multi drug resistance protein target present in the *Mycobacterium tuberculosis* and *Candida dubliniensis*. Performed a

complete molecular modeling and visualization on the Multidrug Resistance Gene Coded Proteins, emrB (*Mycobacterium tuberculosis*) and MDR1 (*Candida dubliniensis).*

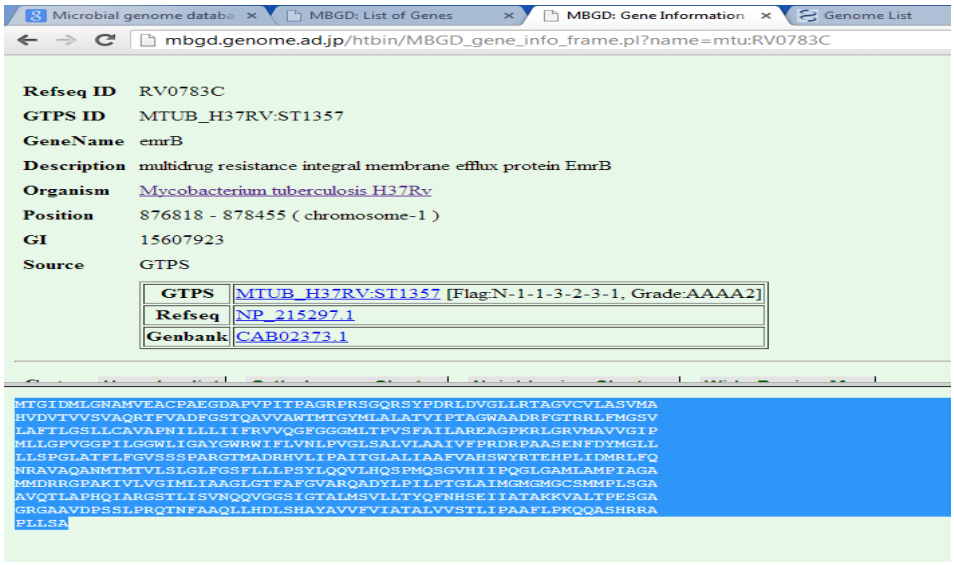


Figure 1: Emrb (Mycobacterium Tuberculosis) Protein Sequence

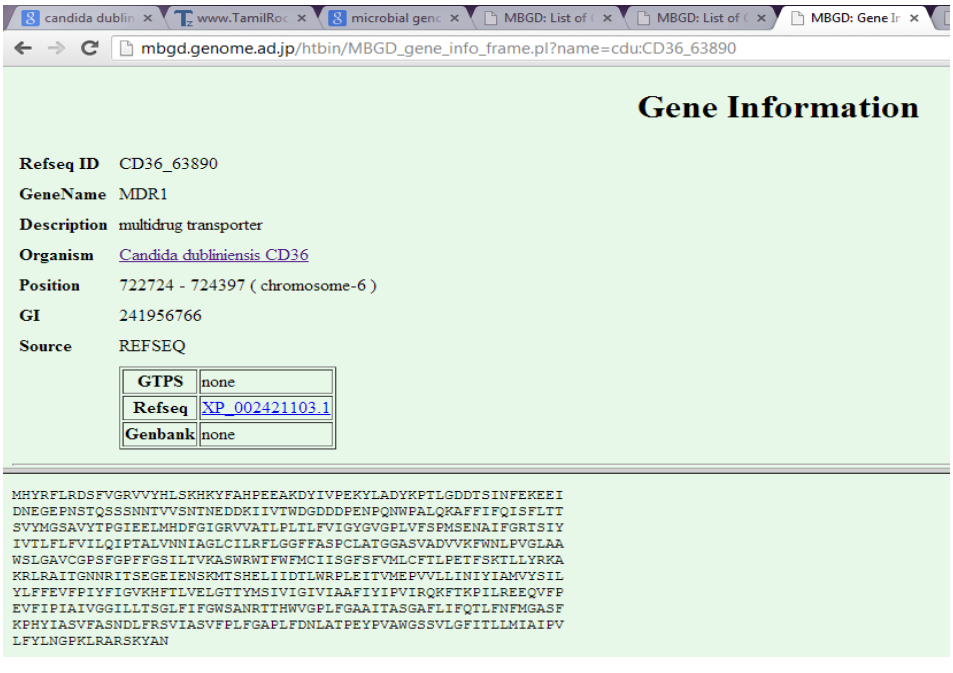


FIGURE 2: MDR1 (Candida dubliniensis) PROTEIN SEQUENCE

Protein modeling: Protein modeling studies were done using CPH 3.0 model server and the modeled proteins (*Mycobacterium tuberculosis*- emrB and *Candida dubliniensis*- MDR1) were

viewed with the help of molecular visualization tools like Discovery studio software, Molsoft and Molegro Molecular viewer software.

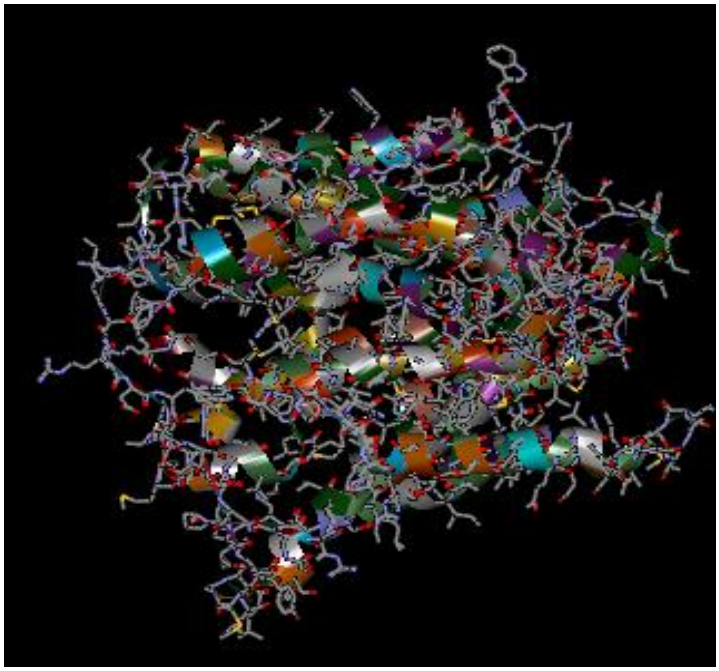


FIGURE 3: emrB (Mycobacterium tuberculosis) PROTEIN STRUCTURE

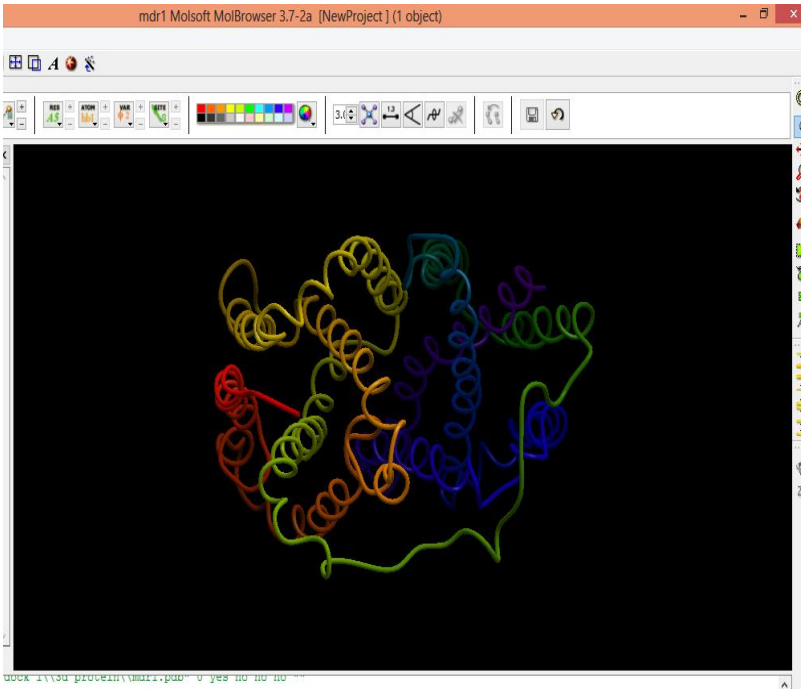
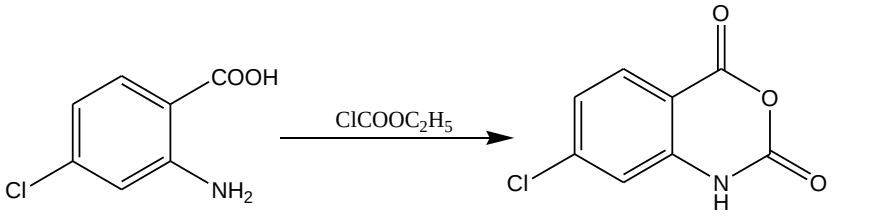


Figure 4: Mdr1 (Candida Dubliniensis) Protein Structure

Cheminformatics: The new potential chemical compounds scheme of synthesis was identified from literature survey and the structures drawn by Molinspiration and converted into 3D models.

SCHEME OF REACTION

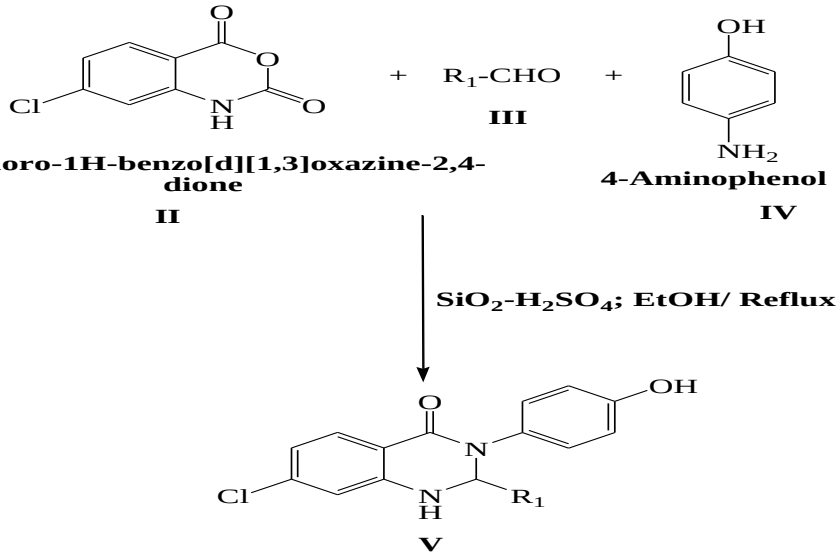
STEP 1



2-amino-4-chlorobenzoic acid — **I**

7-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione — **II**

STEP 2



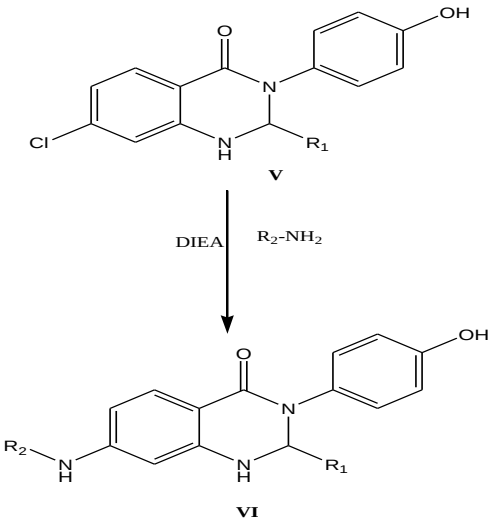
7-Chloro-1H-benzo[d][1,3]oxazine-2,4-dione — **II**

III

4-Aminophenol — **IV**

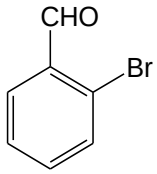
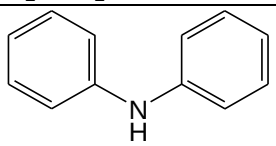
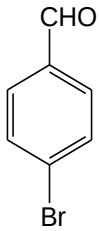
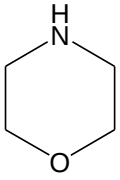
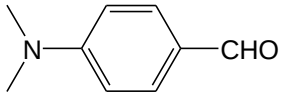
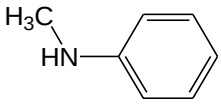
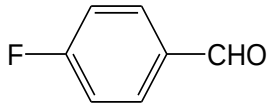
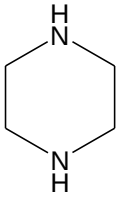
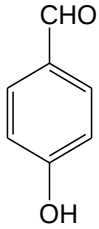
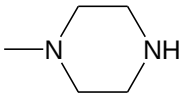
V

STEP 3



VI

TABLE 2: LIST OF CHEMICALS USED IN SCHEME OF REACTION

Sl.NO	**R_1-CHO**	**R_2-NH_2**
1	 2-Bromo benzaldehyde	 Diphenylamine
2	 4-Bromo benzaldehyde	 Morpholine
3	 4- (Dimethyl amino) benzaldehyde	 Methyl phenyl amine
4	 4-Fluoro benzaldehyde	 Piperazine
5	 4-Hydroxy benzaldehyde	 N-Methyl piperazine

From the scheme of synthesis ten different aldehydes and eight different amines were used, to get eighty different compounds. All the eighty compounds were subjected to docking studies.

Results and Discussions

DOCKING STUDIES – PATCHDOCK

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three dimensional structure. Successful docking methods search

high dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings.

Selected target proteins (*Mycobacterium tuberculosis* emrB &*Candida dubliniensis* MDR1) with the molinspiration obeyed compounds undergone for docking studies by using patchdock online software.

The docking studies of selected target proteins (*Mycobacterium tuberculosis* emrB &*dubliniensis* MDR1) with identified lead molecules were done by using patchdock online software.

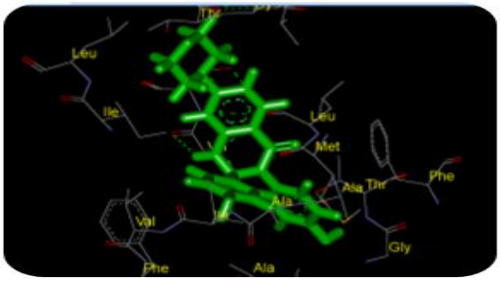


FIGURE 5: DOCKING STUDY OF COMPOUND C1 WITH emrB

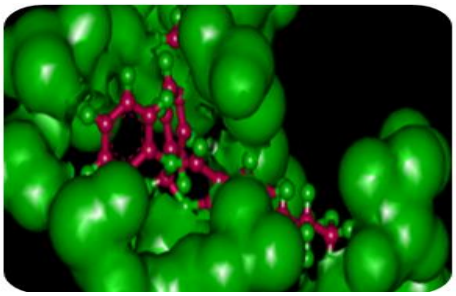


FIGURE 6: DOCKING STUDY OF COMPOUND C2 WITH emrB

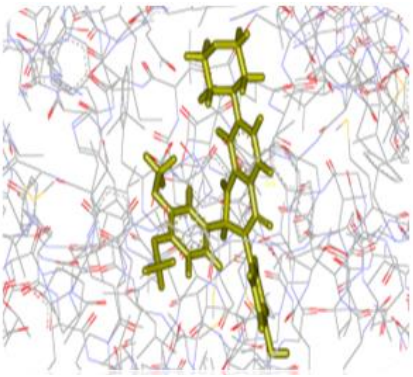


FIGURE 7: DOCKING STUDY OF COMPOUND C3 WITH emrB

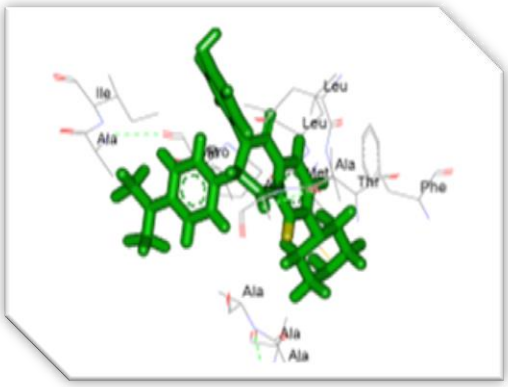


FIGURE 8: DOCKING STUDY OF COMPOUND C5 WITH emrB

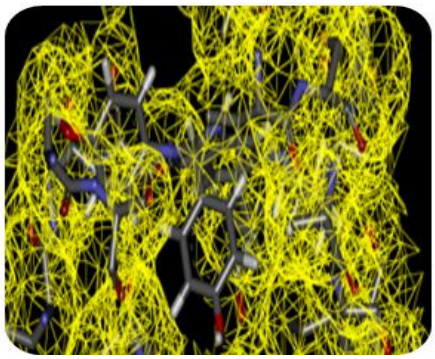


FIGURE 9: DOCKING STUDY OF COMPOUND C6 WITH emrB

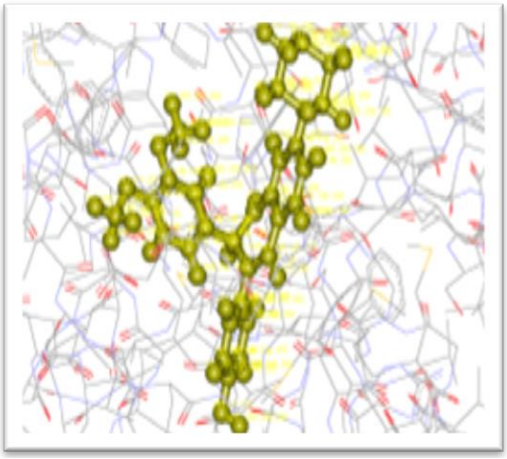
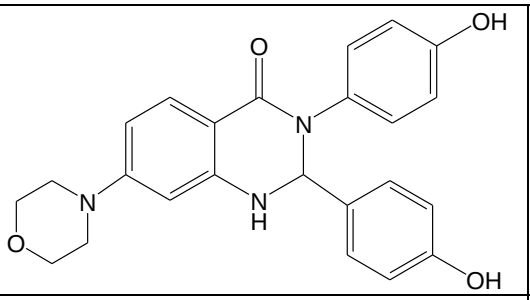
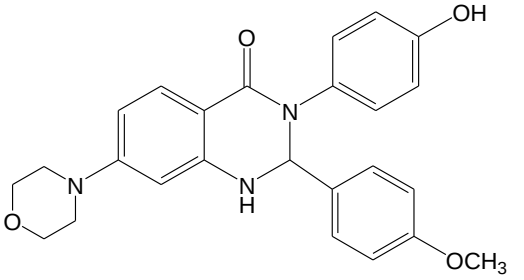
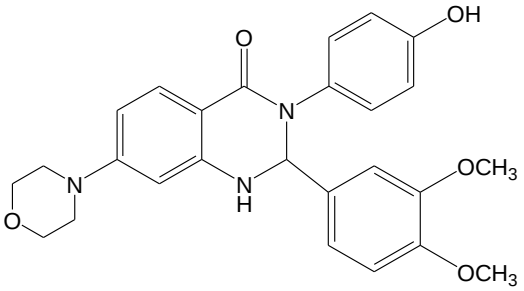
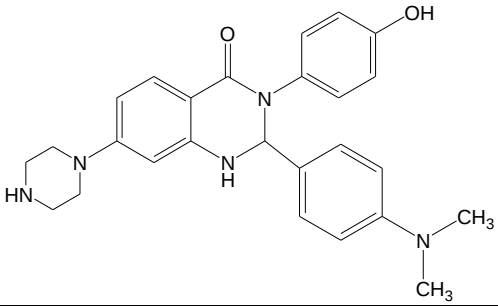
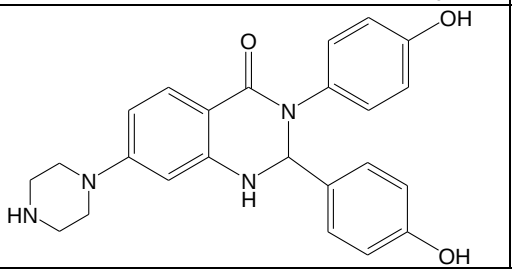


FIGURE 10: DOCKING STUDY OF COMPOUND C7 WITH emrB

TABLE 1: DOCKING RESULTS OF SYNTHESIZED COMPOUNDS

Sl. No.	Cpd. code	Molecular 2D structrure	Binding values-Protein target emrB TB	Binding values-Protein target MDR1 Fungi

1	C1		-494.28	-369.53
2	C2		-503.65	-419.50
3	C3		-528.42	-365.75
4	C5		-464.47	-399.86
5	C6		-466.67	-368.07

The structure of the synthesized compounds was elucidated by physical and spectral analysis like UV, IR, NMR and MASS.

Table 2: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Sl.No	Cpd. Code	Mol. formula	Relative Mol. mass	Appearance	Solubility	Melting point (°C)	R_f value	% Yield
1	C1	$C_{24}H_{23}N_3O_4$	417.46	Brown solid	DMSO	234 - 237	0.72	72
2	C2	$C_{25}H_{25}N_3O_4$	431.48	Brown solid	DMSO	245 - 249	0.76	75
3	C3	$C_{26}H_{27}N_3O_5$	461.51	Brown solid	DMSO	237 - 241	0.71	71
4	C5	$C_{26}H_{29}N_5O_2$	443.54	Brown solid	DMSO	239 - 247	0.79	78
5	C6	$C_{24}H_{24}N_4O_3$	416.47	Brown solid	DMSO	242 – 246	0.67	69
6	C7	$C_{26}H_{28}N_4O_4$	460.52	Brown solid	DMSO	245 -251	0.69	74
7	C8	$C_{25}H_{26}N_4O_4$	446.5	Brown solid	DMSO	227 – 232	0.73	73
8	C16	$C_{25}H_{27}N_3O_3$	417.5	Brown solid	DMSO	248- 252	0.71	78
9	C17	$C_{24}H_{24}N_3O_2F$	405.46	Brown solid	DMSO	236 – 240	0.77	70
10	C18	$C_{25}H_{27}N_3O_3$	417.5	Brown solid	DMSO	241 – 246	0.78	75

Table 3: ELEMENTAL ANALYSIS OF SYNTHESIZED COMPOUNDS

Sl.No	Cpd. Code	Elemental analysis found (calculated) %				
		C	H	N	O	F
1	C1	69.05	5.55	10.07	15.33	-
2	C2	69.59	5.84	9.74	14.83	-
3	C3	67.66	5.90	9.10	17.33	-
4	C5	70.41	6.59	15.79	7.21	-
5	C6	69.21	5.81	13.45	11.52	-
6	C7	67.81	6.13	12.17	13.90	-
7	C8	67.25	5.87	12.55	14.33	-
8	C16	71.92	6.52	10.06	11.50	-
9	C17	71.09	5.97	10.36	7.89	4.69
10	C18	71.92	6.52	10.16	11.50	-

Conclusion

Drug designing is a process of designing a drug molecule that can interact and bind to a target. Receptors are molecule which can be seen on the surface of the cell which receives signals and can be defined as a molecule which recognizes a small molecule, which on binding triggers a

cellular process. In an unbounded state receptor, functionalities of the receptor remain silent.

One of the main approaches in developing potent drug molecule is based on the structural modification based on docking studies. Nitrogen containing heterocyclic system is indispensable structural unit for both the chemist and biochemist. This study, I hoped that these compounds may produce more effective, efficient and potent application for antifungal and antibacterial effects. The purpose of this study is to test the antioxidant, anti-tubercular, and anti-fungal properties of the produced chemicals.

Acknowledgement
The author Dr. D. Jothieswari thanks the University Grants Commission, Minor Research Project Scheme, Government of India, New Delhi (F.No. 4-4/2015-16 (MRP/UGC-SERO/P.No. 2068, Link No.6800 dated 30.06.2017) for its financial support. The authors also thank the Management and Principal of Sri Venkateswara College of Pharmacy for providing facilities towards successful completion of this project.

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