UNIVERSITY GRANT COMMISSION

MAJOR RESEARCH PROJECT

Final Report

Design, Synthesis and Pharmacological Evaluation of Novel Structural Hybrids (Mannich Bases) as Antitubercular / Antibacterial Agents

(MRP-MAJOR-PHAR-2013-30864)

Principal Investigator

Dr. S S Pekamwar
Professor, School of Pharmacy
Swami Ramanand Teerth Marathwada University
Vishnupuri, Nanded 431606 (MS)
sspekamwar@gmail.com

C O N T E N T S

"Design, Synthesis and Pharmacological Evaluation of Novel Structural Hybrids (Mannich Bases) As Antitubercular/ Antibacterial Agents.

Since 1993, when the World Health Organization (WHO) declared tuberculosis (TB) as a global emergency and there has been tremendous progress in the fight against the disease. Directly observed therapy short-course (DOTS), the recognized case management approach for TB, has been implemented throughout the world, because of which, global burden of TB is falling slowly. Despite this progress, Tuberculosis (TB) remains an urgent global health issue. Although TB is curable and preventable, one in three people in the world is currently infected with the TB bacterium, and the active form of the disease kills 1.8 million peoples annually. Co-infection with TB and HIV (TB/HIV) and a surge in multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are threatening to disrupt recent global successes in TB control.

In India, TB kills two persons per three minutes and almost 1000 deaths every day. So, the ultimate detection, identification and total cure of TB are of extreme importance in India.

We have chosen to synthesize the compounds with possible antitubercular activity because; Tuberculosis (TB) remains the only infectious disease to cause serious health damage of human being, especially in Indian subcontinent. Tuberculosis approximately causes three million deaths annually and about five deaths every minute. So, the ultimate detection, identification and total cure of TB are of extreme importance in India. Unfortunate to say but it is the fact that, every fifth person dies due to TB in the world is an Indian**,** that's why Indian government have decided to eradicate the tuberculosis from India; for the same government is ready for providing all types of support and motivations

Need for Newer Antibacterial Agents:

In addition to the emergence of multidrug-resistance, list of side effects and reoccurrence of illness after removal therapy are the two another serious limitations associated with present antibacterial. In addition to these problems, the pharmaceutical pipeline for getting newer antibacterial agent act by novel mechanism of action is getting drying up. Within five years from 1983 to 1987 about 16 antibiotics were approved, but for next five year not a single antibiotic was approved and condition become more serious after 1992 to onwards. Recently from 2003 to 2007 only five antibiotics have been approved. The condition is even more serious in case of drugs acting against gram negative bacterial,

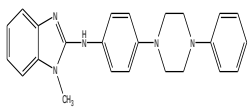
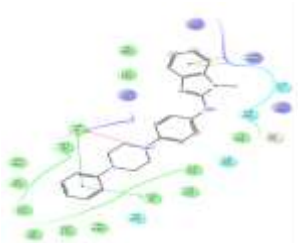
especially in case of countries like China, where the drug resistance is as high as up to 70%. If this rate of emergence of resistance remains continued for next few years then surely one day, we should have to face conditions like “Dooms Day”, ‘The day on which it becomes impossible to treat most of the microbial infections due to antimicrobial resistance’. So, to solve this complex problem of resistance, sincere efforts are strictly needed so as to find out alternative to present drugs.

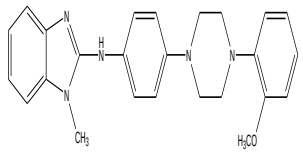
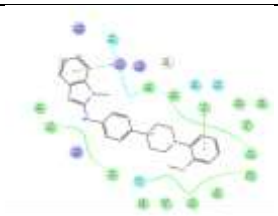
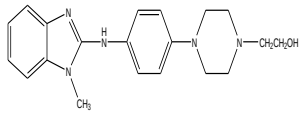
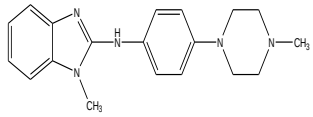
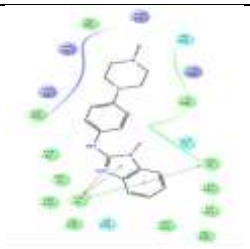
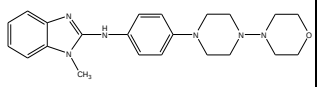
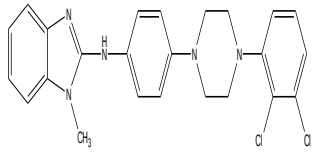
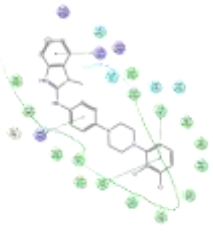
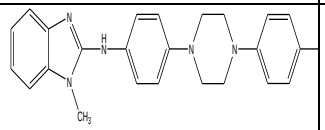
With this background problems are defined and work undertook and completed. In this work molecules are designed, synthesized and evaluated for pharmacological profile. Work done is briefly explained below.

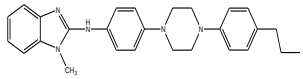
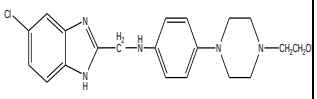
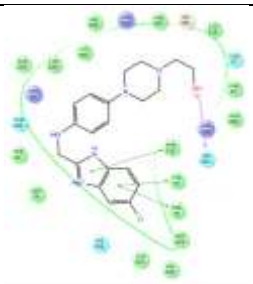
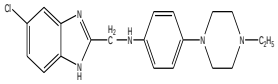
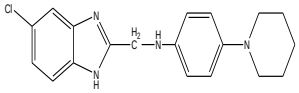
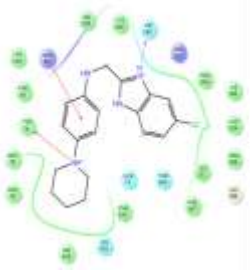
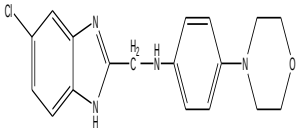
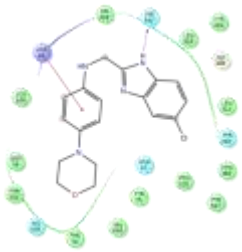
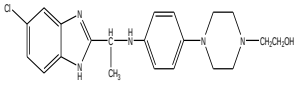
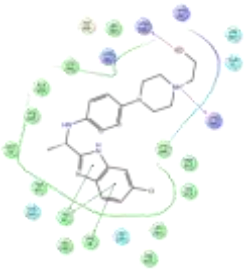
1. Design and synthesis of Benzimidazole derivatives for Anti TB / Antibacterial activity.

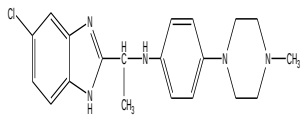
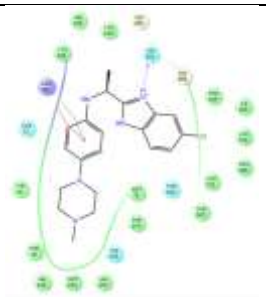
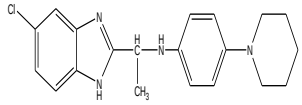
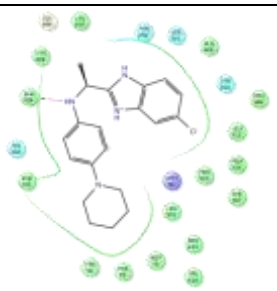
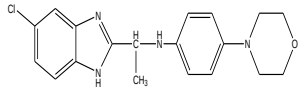
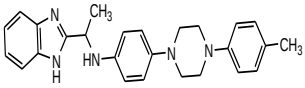
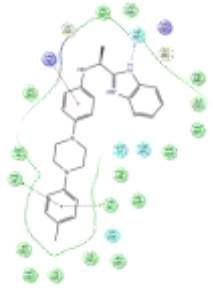
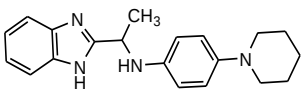
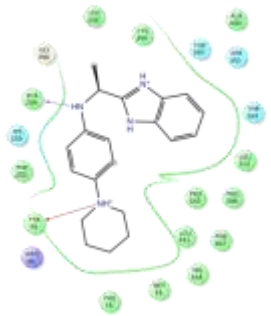
Wagh et al. have synthesized series of 2-substituted benzimidazole derivatives and screened for antifungal activity. This series of benzimidazole derivatives with their MIC values (0.007-0.625 µm/ml) was available for docking study. This series was docked on cytochrome P 450 of M. tuberculosis (PDB code 1EA1) at Glide module of Schrödinger drug design software. Docking environment was maintained as per below conditions

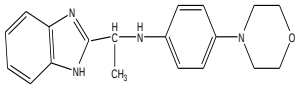
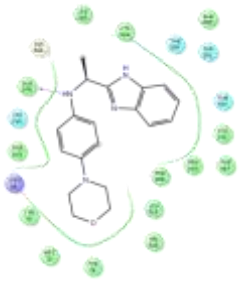
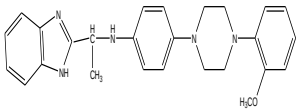
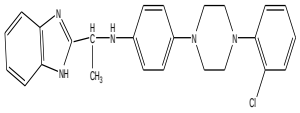
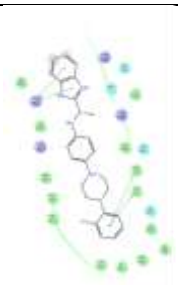
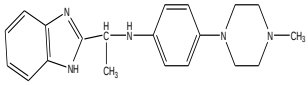
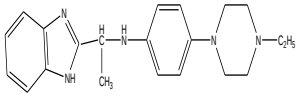
1. pH 7,
2. Force field OPLS3,
3. Only water molecules having 3 bonds with non-water molecules within the range of 5 A^o from binding site. The results of docking study is shown in table 1

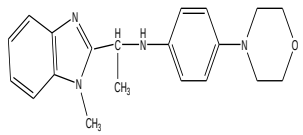
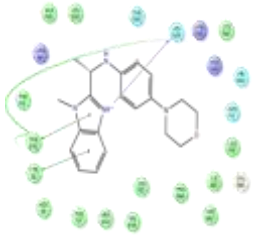
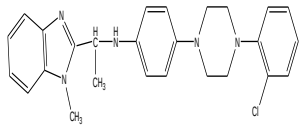
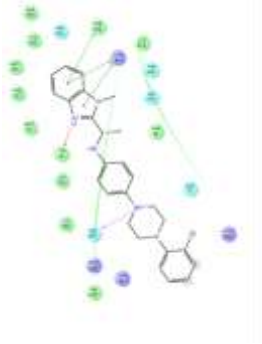
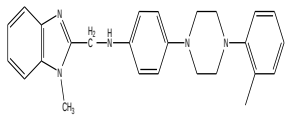
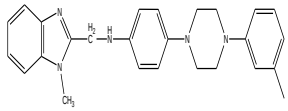
Sr. no.	Structure	MW	Dock score	Image	Binding Amino acids (Within 5^0A)
1.		383.49	-6.825		TYR 76 PHE 70 ARG 95

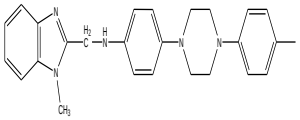
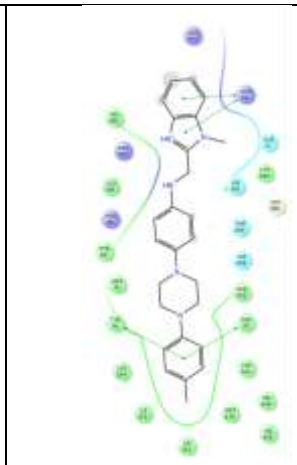
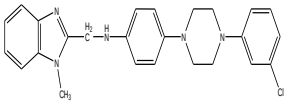
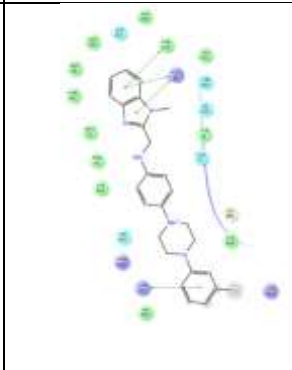
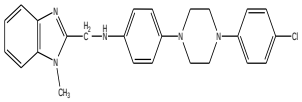
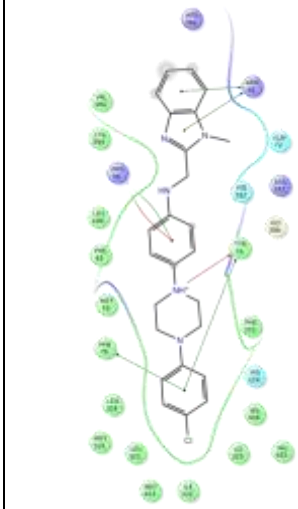
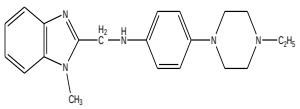
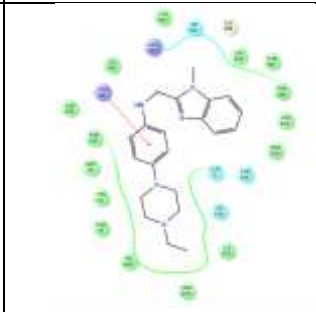
2.		413.51	-7.368		ARG 95 TYR38
3.		351.45	-6.915		ARG 95 ARG 96 MET 433 HIE 392
4.		321.42	-6.198		PHE78 TYR76
5.		392.5	-6.089		ARG95 ARG96 MET433 HIE392
6.		452.38	-7.175		ARG95 ARG96 PHE18 TYR78
7.		401.48	-7.077		ARG95 ARG96 PHE18 TYR78

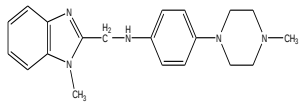
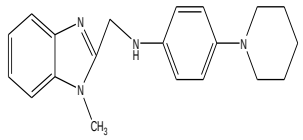
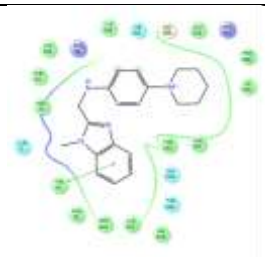
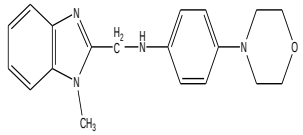
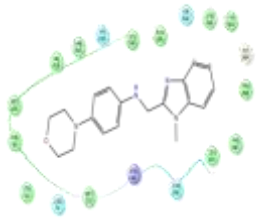
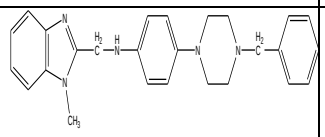
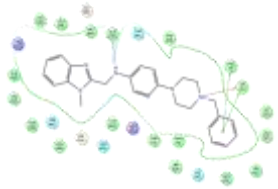
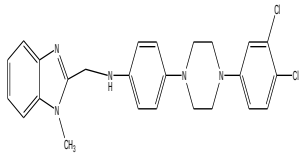
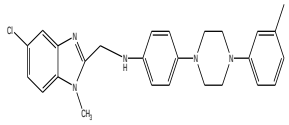
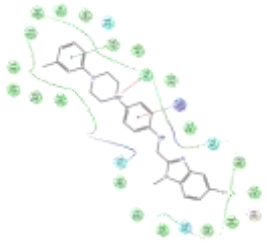
8.		425.73	-	No good pose	
9.		385.89	-8.728		ARG326 PHE255 TYR76 PHE78
10		369.89	-6.739		ARG96 TYR76 HIE392
11		340.85	-8.13		ARG96 HIE392 TYR76
12		342.82	-7.311		ARG96 HIE392
13		399.92	-7.989		TYR76 PHE78 ARG391 ARG393

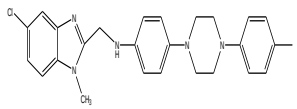
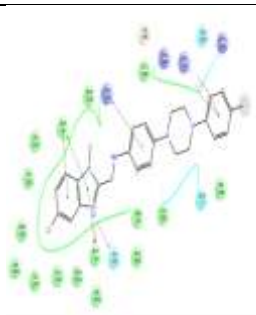
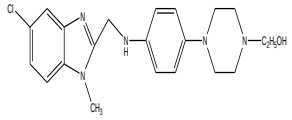
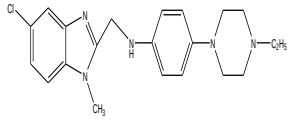
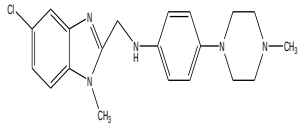
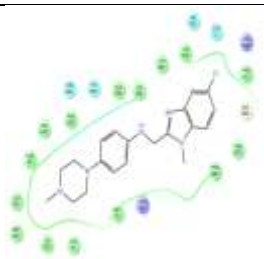
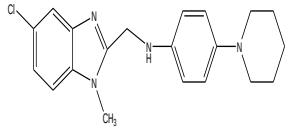
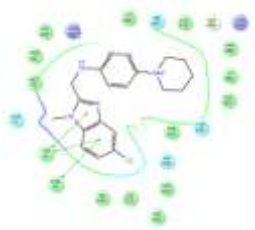
14		389.89	-7.418		ARG96 HIE392
15		354.88	-7.373		ALA256
16		356.85	-6.364		ARG96
17		411.54	-7.201		ARG96 PHE78 TYR76
18		320.43	-8.147		ALA256 TYR76

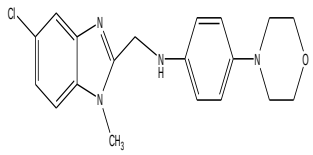
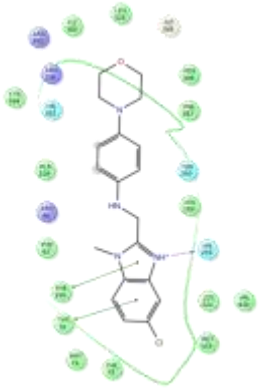
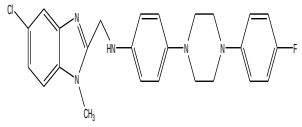
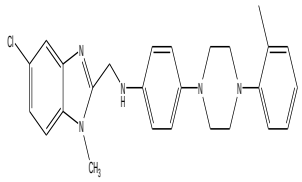
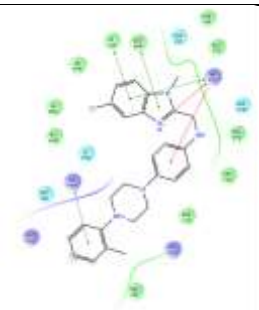
19		338.45	-8.127		ALA256
20		443.58	-7.468		ARG95 TYR76 PHE78 HIS259
21		448	-8.484		PHE38 TYR39 ARG96
22		351.49	-7.235		TYR76 HIS259 PHE255
23		365.52	-6.465		PHE255 TYR76 HIS259

24		352.47	-8.443		HIS259 PHE255 TYR76
25		462.03	-7.292		PHE255 ARG96 TYR76 HIE292
26		411.54	-8.228		ARG95 ARG393 PHE78
27		411.54	-6.679		ARG96 AGR95 PHE73 TYR76

28		411.54	-7.371		ARG95 PHE78 TYR76
29		431.96	-7.165		PHE255 ARG96 ARG95
30		431.96	-7.333		PHE78 TYR76 ARG96 ARG95
31		349.47	-8.135		ARG96

32		335.45	-7.225		ARG96
33		320.43	-8.597		TYR76
34		322.4	-7.406		
35		411.54	-10.549		ALA256 TYR36 PHE38
36		466.41	-7.601		PHE255 TYR76 ARG95
37		445.99	-6.776		PHE78 TYR76 ARG96

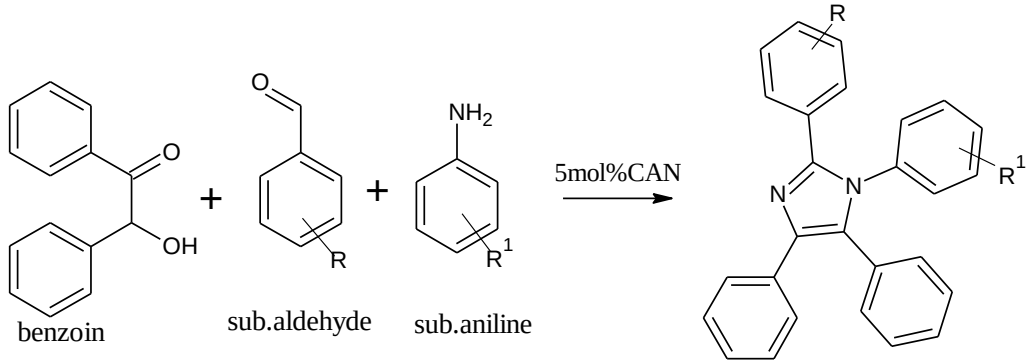
38		445.99	-7.183		PHE78 TYR76 HIS259
39		400.92	-8.687		ARG96 TYR76 ILE323
40		383.92	-7.04		
41		369.89	-8.084		
42		354.88	-6.707		TYR76 PHE78

43		356.85	-6.783		PHE255 TYR76 HIS259
44		449.95	-7.24		ARG96 PHE255 TYR76
45		445.99	-8.367		ARG96 PHE255 TYR76 ARG95

Benzimidazole derivatives are showing good poses except compound no. 8 and dock well into the binding pocket and shows good binding with the nearby amino acids within 5^0A region as mentioned against their image. The derivatives 9, 21, 24, 33, 35, and 39 are showing highest docking score hence recommended for synthesis.

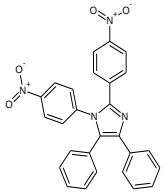
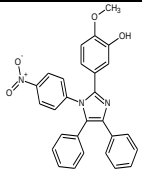
2. Design, Synthesis andBiological Evaluation of Some Novel Imidazole Derivatives

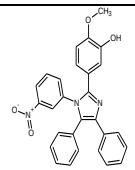
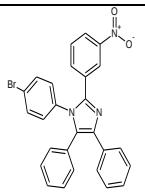
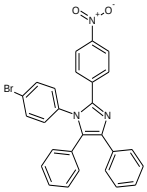
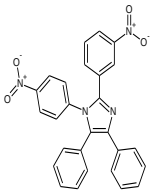
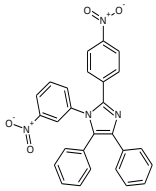
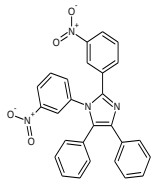
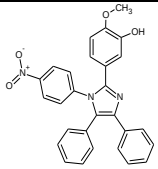
Rajanarendaretal. had introduced the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles. Considering this as lead nucleus various analogues are designed (1A to 1O). Designed analogues were subjected for ADME property calculations at QIKPROP module of Schrodinger drug design software. Results are shown in table 2.

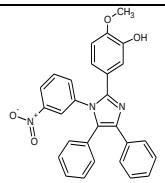
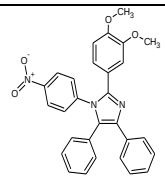
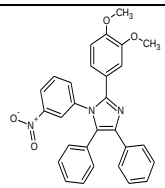
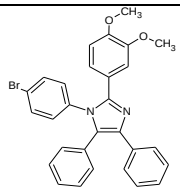
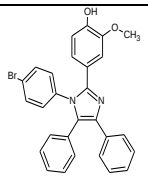
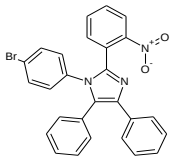


1, 2, 3, 4 -tetraarylimidazole

Table No 2:

Code No.	Molecule	Mol.wt.	MP	Donor HB	Accept. HB	Qlog Pw/o	Qlog Po/w	HO	%HOA	Rule Of 5	Rule Of 3
2A		462g	66^0c	0	3.5	9.408	5.493	1	81.119	1	1
2B		463g	70^0c	1	4	10.538	5.577	1	90.383	1	1

2C		463g	76^0c	1	4	10.462	5.618	1	92.276	1	1
2D		451g	68^0c	0	2.5	8.265	7.174	1	100	1	1
2E		496g	70^0c	0	2.5	8.341	7.145	1	100	1	1
2F		462g	66^0c	0	3.5	9.612	5.835	1	86.602	1	1
2G		462g	78^0c	0	3.5	9.646	5.827	1	85.878	1	1
2H		462g	66^0c	0	3.5	9.562	5.852	1	87.462	1	1
2I		463g	76^0c	1	4	10.813	5.972	1	95.069	1	1

2J		463g	80^0c	0	2.5	7.81	6.931	1	100	1	1
2K		477g	78^0c	0	4	9.15	6.754	1	100	1	1
2L		477g	68^0c	0	4	9.083	6.767	1	100	1	1
2M		511g	80^0c	0	3	7.804	8.097	1	100	2	1
2N		497g	78^0c	0	4	8.56	6.31	1	100	1	1
2O		496g	80^0c	1	3	9.173	6.814	1	100	1	1
Code No.	Molecule	Mol.wt.	MP	Donor HB	Accept. HB	Qlog Pw/o	Qlog Po/w	HO	%HOA	Rule Of 5	Rule Of 3

From the literature survey, novel substituted imidazole derivatives were designed and synthesized. Yields of compounds are in the range of 80-90%. Structures are confirmed by physicochemical parameters and spectral study. Novelty of this work is the fully substituted imidazole derivatives are synthesized by using cerric ammonium nitrate (CAN) catalyst.

Advantage of CAN is that it is useful as an oxidant, possess excellent solubility profile and it is non-toxic.

Designed compounds are subjected for PASS analysis. From ADME properties all fifteen derivatives fulfill the Molecular weight < 500 Da; logP*w/oct*< 5; with not more than 5 hydrogen bond donors and not more than 10 hydrogen bond acceptors, with best % Human Oral Absorption about 25% and all synthesized derivatives passes Lipinski Rule.

All the synthesized compounds are successfully screened for anti-bacterial and anti-fungal activities against *E.coli* and *Candida albicans, Aspirgillusniger, Microsporescanis respectively*. Cefexime and fluconazole are used as a standard.

The screening study shows that Compound 2A, 2B (zone of inhibition 6.2mm) have good activity as anti-bacterial(*E.coli*) as compared to standard Cefexime (6.7mm).

Compound 2A, 2D (zone of inhibition 6.5mm) have good activity as anti-fungal (*Candida alabicans*) as compared to standard Fluconazole (7mm). Compound 2A (8mm), 2B (7.9mm) have good activity as anti-fungal (*Aspergillus niger*) as compared to standard Fluconazole (8mm). Compound 2A, 2B, 2E, 2F, 2G, 2I (9mm) have good activity as anti-fungal (*Aspergillus niger*) as compared to standard Fluconazole (9.5mm).

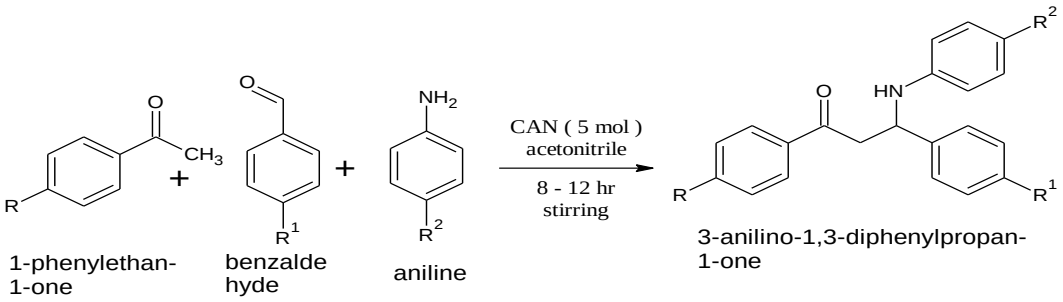
3 Design, Synthesis and Biological Evaluation of Beta Amino Carbonyl Compounds by Using Cerric Ammonium Nitrate (CAN).

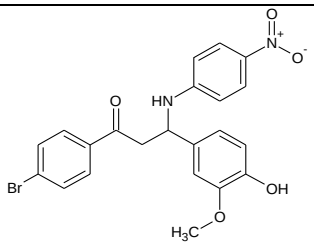
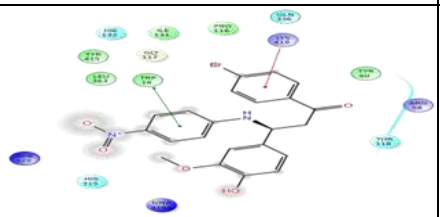
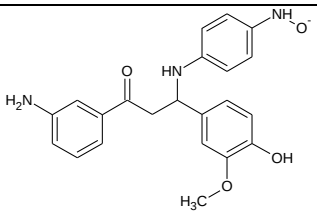
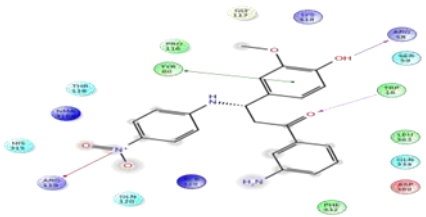
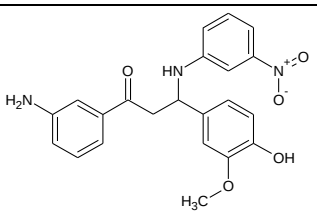
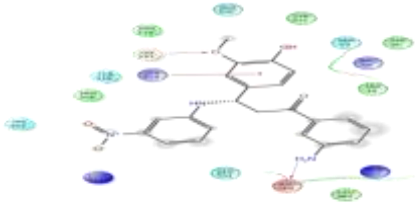
The Mannich reaction is known for the preparation of secondary and tertiary amine derivatives (Mannich Bases) using an acid or base catalyst. The products of Mannich reaction are mainly β-amino carbonyl compounds and its derivatives, which are used for synthesis of amino alcohols, peptides and lactums. Kidwai and coauthors have reported one pot, three component Mannich reactions of acetophenone, aromatic aldehydes and aromatic amines using Cerric Ammonium Nitrate (CAN) as an efficient catalyst. Considering this as lead nucleus various analogues are designed and synthesized. The series of Beta amino carbonyl compound were docked on 3-deoxy-D-arabino-heptulosonate 7-phosphate synthase of M. tuberculosis (PDB code 4PFA) at glide module of Schrodinger drug design software. Docking environment was maintained as per below the conditions

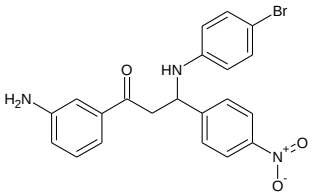
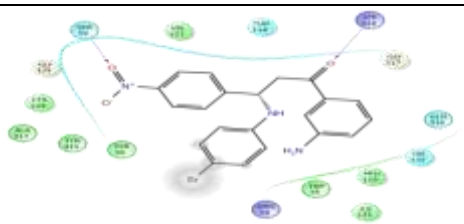
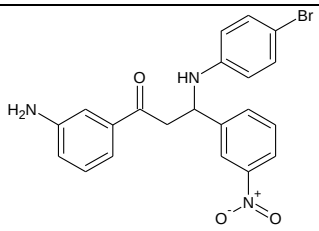
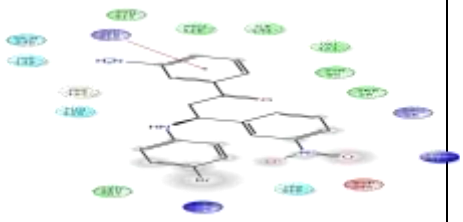
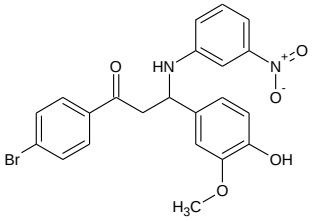
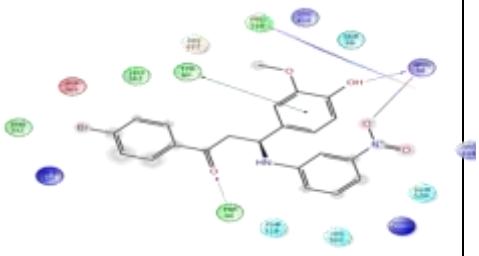
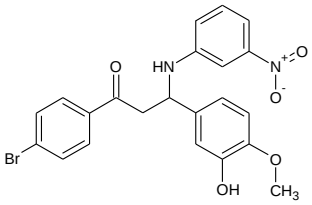
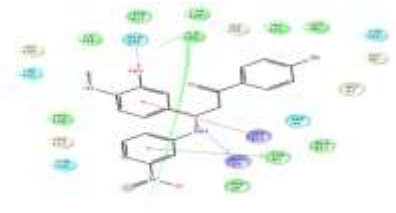
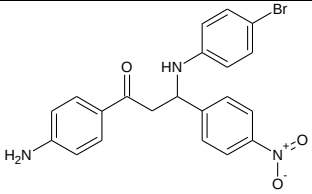
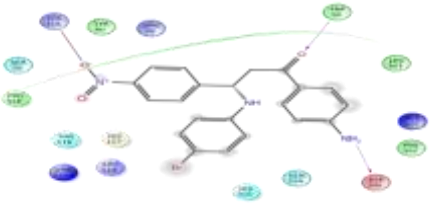
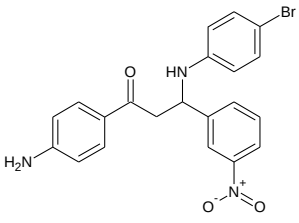
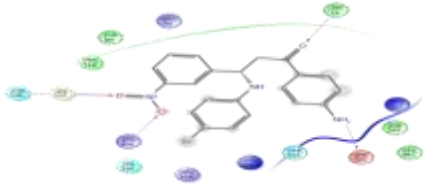
- At pH 7
- Force field OPLS3
- Only water molecules having 3 bonds with non-water molecules

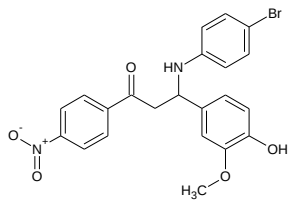
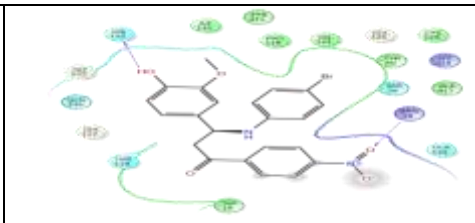
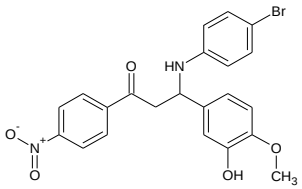
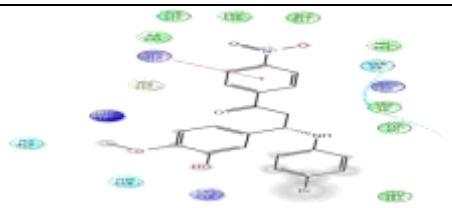
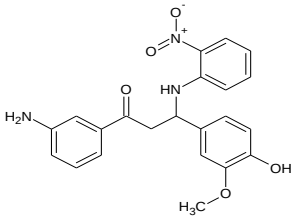
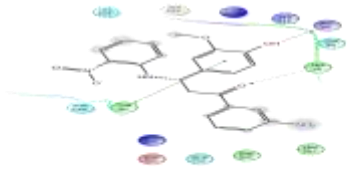
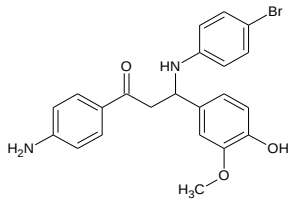
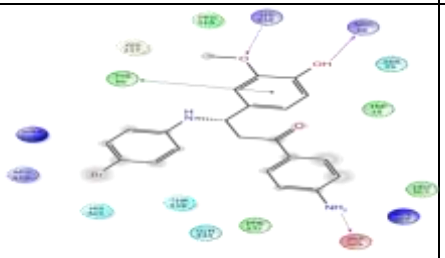
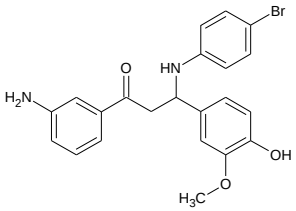
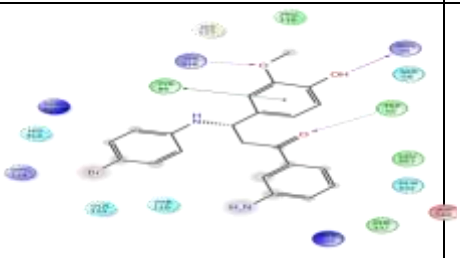
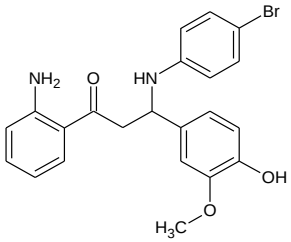
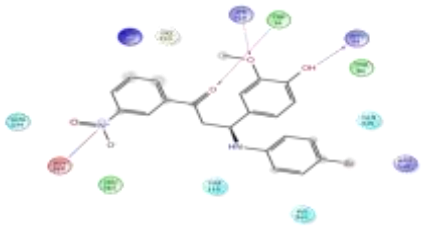
The results of docking study are shown in below table 3.

Table 3



Sr No	Structure	MW	Dock score	Docking Image	Binding amino acid
1		471.30	-5.58		TRP 16 LYS 418
2		407.42	-5.215		TYR 60 TRP 16 ARG 58 ARG 119
3		407.42	-5.782		GLY 117 LYS 418 ASP 389

4		440.29	-6.052		LYS 418 SER 59
5		440.29	-4.605		LYS 418
6		471.30	-5.022		ARG 58 TRP 16 TRY 60
7		471.30	-9.336		GLN 336 TRY 60 LYS 418 ARG 58
8		440.29	-5.54		LYS 418 ASP 389 TRP 16
9		440.29	-5.966		GLY 117 THR 118 LYS 418 ASP 389 TRP 16

10		471.06	-5.195		HIE 132 ARG 58
11		471.30	-5.962		LYS 418
12		471.30	-5.749		ARG 58 TRY 60
13		407.42	-6.606		TRY 60 ARG 58 ASP 389
14		441.32	-5.64		LYS 418 TRP 16 TRY 60 ARG 58
15		441.32	-5.463		LYS 418 TRP 16 ARG 58 ASP 389

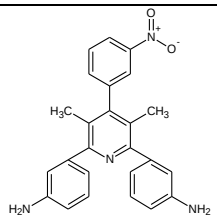
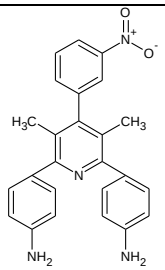
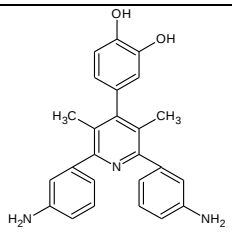
Mannich derivatives are showing good poses and dock well into the binding pocket and showgood binding with the nearby amino acids within 5^0A region as mentioned against their image. The derivatives 4,7,9,11,12,13are showing highest docking score. Novelty of this work is the substituted β-amino carbonyl a compound was synthesized by ceric ammonium nitrate (CAN). Other catalysts for Mannich reaction include SSA, $CeCl_3$, MgO/ZrO_2, lanthanide triflate in solvents like dichloromethane and silica supported $AlCl_3$. They often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product separation, less product yield long process of purification. Ceric (IV) ammonium nitrate has emerged as an important reagent for the construction of carbon–carbon and carbon– heteroatom bonds via radical intermediate. In addition, many advantages such as excellent solubility in water, inexpensiveness, eco-friendly nature, uncomplicated handling, high reactivity, fast conversions and convenient work up procedures make CAN a potent catalyst in organic synthesis. A designed molecule was subjected for PASS study. This study show that all compounds have Pa value less than 0.5 for anti-tuberculosis, anti-fungal and antibacterial agent. The compound has more than 0.5 Pa value are compound 9 (0.504) for anti-tuberculosis, compound 2 (0.581) for antibacterial, compound 5 (0.596) for antifungal. From result of docking study, it was concluded that all compounds have a number of good contacts with the crystal structure of epidermal growth factor receptor 3-deoxy-D-arabino-heptulosonate 7-phosphate synthase (4PFA). Compound from molecular docking study, 8(-9.336), 5(-6.052) molecules show good poses and fit into binding pocket and also good contacts with (2VKZ) and (1H3D) for antifungal and antibacterial target of Inhibition of ATP Phosphoribosyltransferase. Compound from molecular docking study, 13(-4.802), 5(-4.789) and 12 (-8.256), 3 (-8.146). From ADME properties all compounds follow the Lipinski rule of five. Log P value is less than 5. All compounds have Hydrogen acceptor less than 10 and donor lessthan 5. All compounds have good dipole moment and human oral absorption is greater than 25%. All synthesized derivatives were evaluated for antibacterial and antifungal activities by well diffusion method against bacterial strain E. coli and fungi A. niger, Candida albicans &Microsporous Canis Cefexine and Fluconazole were used as standard for antimicrobial study. Compound 4 (zone of inhibition, 7.7 mm) and compound 16 (zone of inhibition, 8.7mm) of this series had emerged as moderate antibacterial agent against Escherichia coli as compared to standard Cefexine (8.8 mm). Compound 7 (6.8 mm) and compound 10 (6.8 mm) of this series had shown potent antifungal activity against A. niger compared to standard Fluconazole (7 mm). Compound 6 (7.8 mm) of this series had shown potent antifungal activity against C. albicans compared to standard Fluconazole (8 mm).

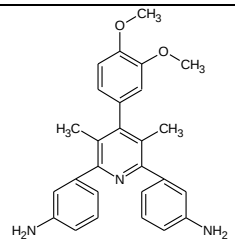
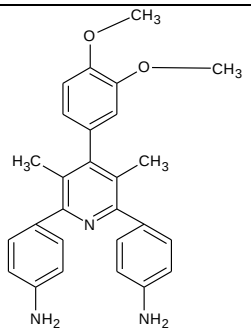
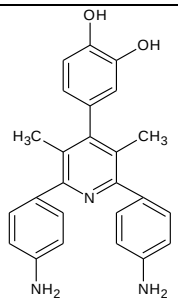
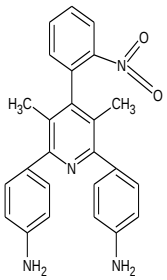
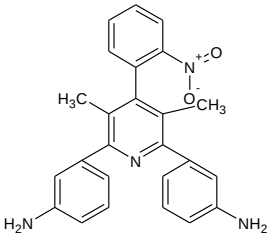
Compound 5 (8.3 mm), compound 13(8.7 mm) and compound 14 (8.7 mm) of this series had shown potent antifungal activity against Microsporous Canis compared to standard Fluconazole (9.0 mm) Overall it is an attempt to design, synthesize and perform biological evaluation of substituted β-amino carbonyl compound derivatives.

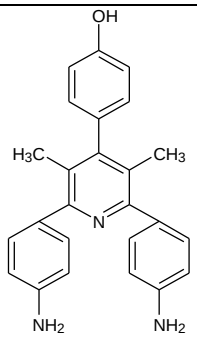
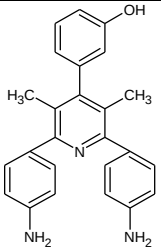
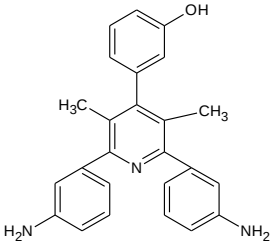
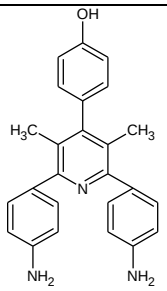
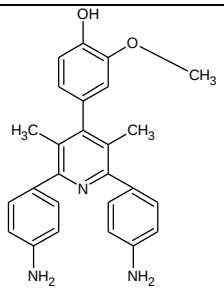
4. Design, Synthesis and Biological Evaluation of Pyridine Derivatives By Using Cerric Ammonium Nitrate (CAN)

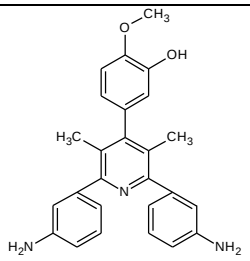
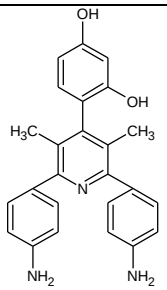
Tapasavi etal (2011) have reported the synthesis of 2,3,4,5,6-pentasubstituted pyridines via three component condensation of aromatic aldehydes, ammonium acetate and acetophenone derivatives. Considering this as lead nucleus various analogues are designed (1to 15). Designed analogues were subjected for ADME property calculations at QIKPROP module of Schrodinger drug design software. Results are shown in below mentioned table 4.

Table No. 4:

Sr. No.	Code no.	Molecule	MW	MP	Donor HB	Accept. HB	Qlog Pw/o	%HOA	Rule of 5
1	1		410	97-99	3	4	12.796	82.97	0
2	2		410	98-100	3	4	12.798	82.97	0
3	3		397	122-125	5	4.5	15.818	64.941	1

4	4		425	135-137	3	4.5	12.076	100	0
5	5		425	134-136	3	4.5	12.061	100	0
6	6		397	120-123	5	4.5	15.809	64.828	1
7	7		410	88-90	3	4	12.578	89.578	0
8	8		410	89-91	3	4	12.579	89.578	0

9	9		381	177-180	3	4	13.732	89.58	0
10	10		381	173-175	4	3.75	13.732	89.972	0
11	11		381	175-177	4	3.75	13.726	90.046	0
12	12		381	180-183	4	3.75	13.732	90.075	0
13	13		411	147-150	4	4.5	13.969	91.143	0

14	14		411	150-152	4	4.5	14.012	90.367	0
15	15		397	180-182	5	4.5	3.308	67.53	1

Novelty of this work is the fully substituted pyridine derivatives were synthesized by ceric ammonium nitrate (CAN). Advantage CAN is useful as an oxidant. Designed molecules were subjected for PASS study. This study show that all compounds have Pa value less than 0.5 for anti-tuberculosis, anti-fungal and anti-bacterial agent.

From result of docking study, it is concluded that all compounds have a number of good contacts with Crystal Structure of Cytochrome P450 ALPHA-STEROL DEMETHYLASE (CYP51). Compound from molecular docking study, 5(-7.765), 12(-7.495), 10(-7.378), 9(-7.127) molecules show good poses and fit into binding pocket.

From ADME properties all compounds follow the Lipinski rule of five. Log P value is less than 5. All compounds have Hydrogen acceptor less than 10 and donor less than 5. All compounds have good dipole moment and human oral absorption is greater than 25%.

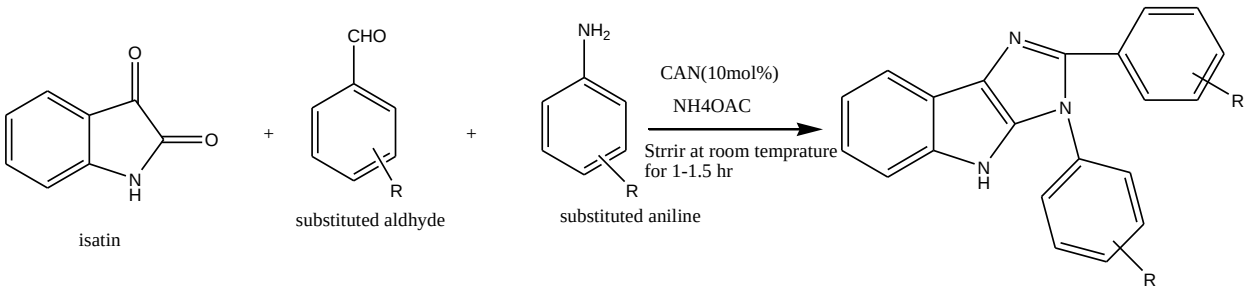
All synthesized derivatives were evaluated for antibacterial and antifungal activities by well diffusion method against bacterial strain *E. coli* and fungi *A. niger*, *Candida albicans* &*Trchophytum rubrum.* Cefexime and Fluconazole were used as standard for antimicrobial study.

Compound 11 (zone of inhibition, 7.5 mm) of this series had emerged as moderate antibacterial agent against *Escherichia coli* as compared to standard Cefexim (8.6 mm). Compound 3 (8.6 mm) and compound 8 (8.6mm) of this series had shown potent antifungal activity against *A. niger* compared to standard Fluconazole (9.7 mm). Compound 14 (7.9mm) of this series had shown potent antifungal activity against *C. albicans* compared to standard

Fluconazole (8.7 mm). Compound 2(7.0mm) of this series had shown potent antifungal activity against *Trychophytum rubrum* compared to standard Fluconazole (8.5 mm)

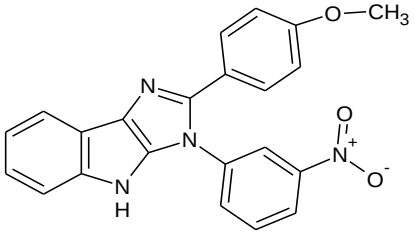
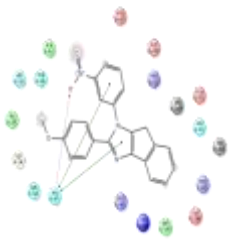
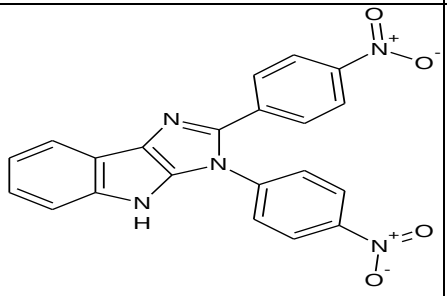
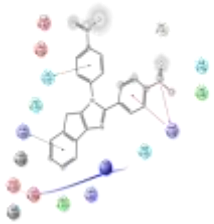
5. Design, Synthesis and Biological Evaluation of Imidazole Derivatives

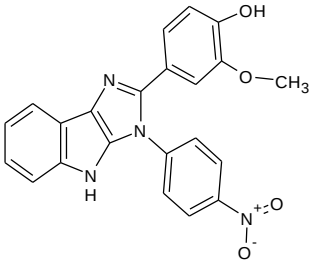
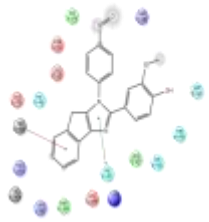
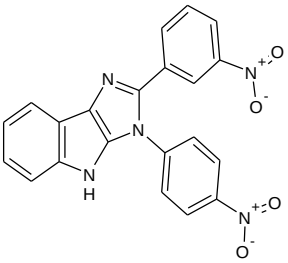
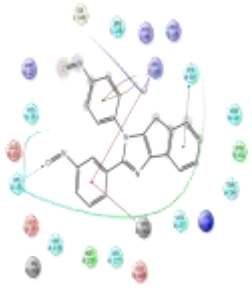
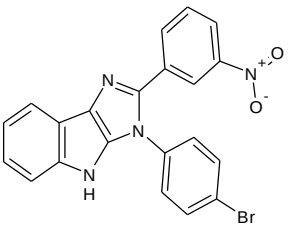
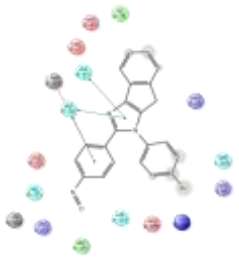
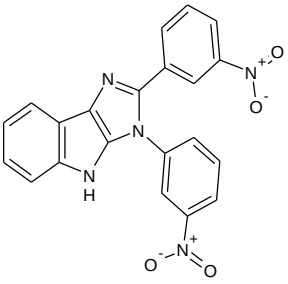
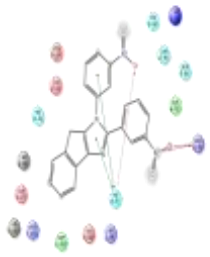
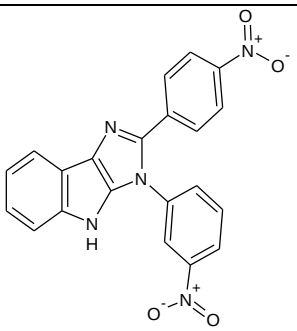
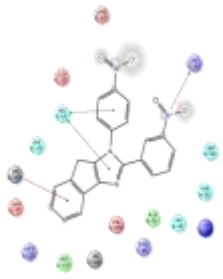
Rajanarendra and colleagues et.al. have reported the synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives. Considering this as lead nucleus isatin based analogues of imidazole derivatives were designed and synthesized as per below mentioned scheme. This series was docked on imidazole glycerol phosphate dehydratase of M.tuberculosis (pdb code 4LOM) at Glide molecule of Schrödinger drug design software. The results of docking study are shown in table

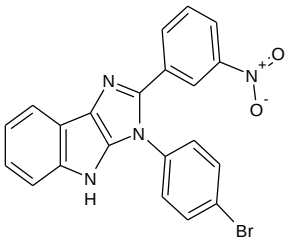
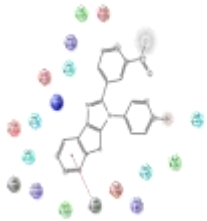
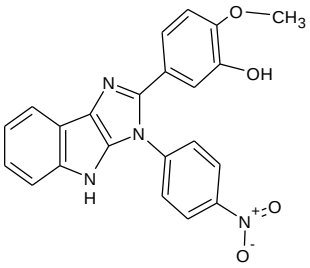
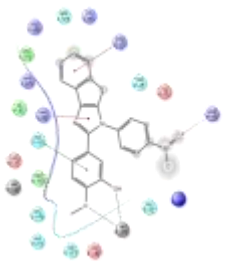
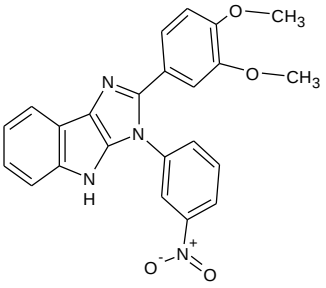
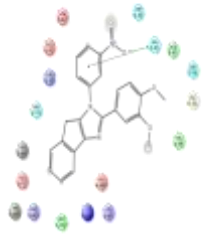
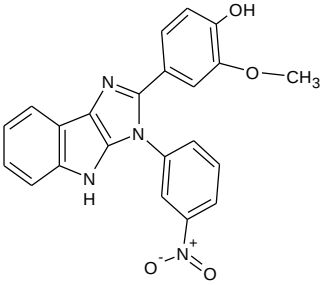
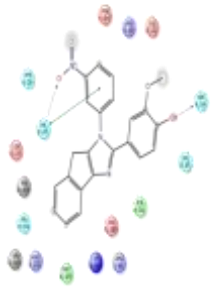
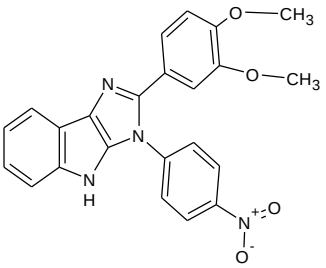
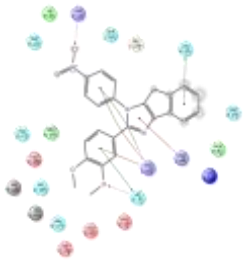


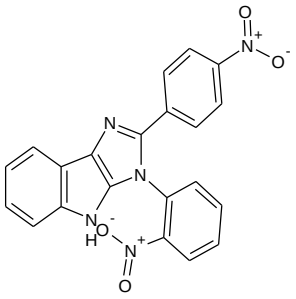
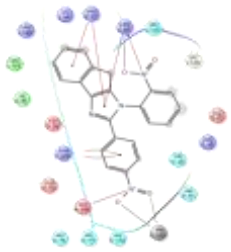
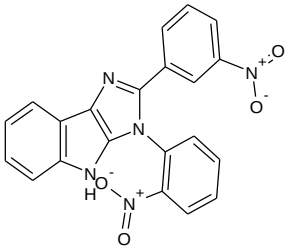
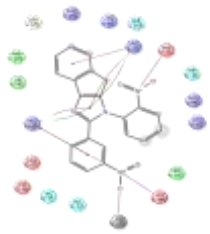
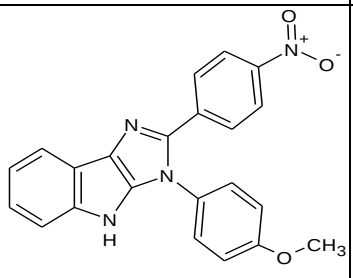
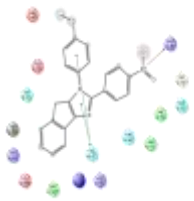
isatin substituted aldhyde substituted aniline imidazole derivative

Docking study result table 5

Sr. No.	Structure	MW	Dock Score	Image	Binding aminoacids
1		383.406	-4.576		HISA:47
2		398.377	-3.499		HISA:47 ARGJ:121 ARG0.20

3		383.406	-3.27		HISA:47 MNA:303
4		366.378	-3.202		HISO:74 HISA:55 ARGJ:121 MN A:303
5		416.276	-3.174		HISO:74 HISA:55 MN A:303
6		398.377	-3.101		HISA:47 ARGO:20
7		398.377	-3.06		HIS A:47 ARG O:20 MN A:303

8		432.275	-2.812		MN A:303
9		399.405	-2.77		HIS O.74 ARGO:17 ARG O:20 ARG J:99 MN A:303
10		413.432	-2.467		HIS A:47
11		399.405	-2.286		HIS A:47 SERA:54
12.		413.432	-3.292		ARGO:17 ARG J:121 HIS0:74 HISO:55 ARGJ:99

13.		398.377	-2.744		ARGO:17 ARG J:121 ARG J:99 MN A:303 GLU A:180
14		398.377	-2.157		ARGO:17 ARG J:121 MN A:303 GLU A:180 GLU O:21
15.		383.406	-3.499		HISA:47 ARGO:20

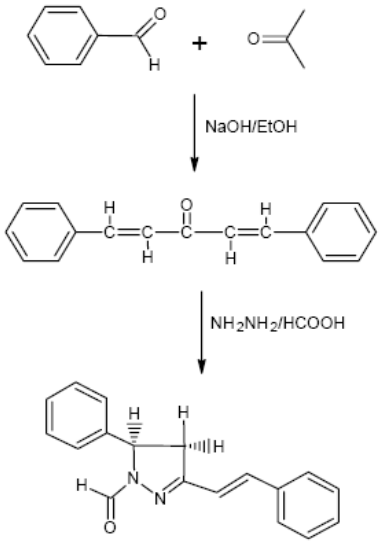
Isatin based imidazole derivatives are showing good poses and dock well into the binding pocket and show good binding with the nearby amino acids within 5^0A region as mentioned against their image. The derivatives 1,2,3,12 and15 are showing highest docking score. Total fifteen derivatives with substitution on aniline and benzaldehyde ring had been synthesized using halogens and nitro groups as substituent. All synthesized compounds had been characterized by melting point, thin layer chromatography, also by spectral analysis and their structures were confirmed.

All the proposed derivatives of substituted imidazole were docked by using Schrodinger glide software. PDB id 4LOM was used to dock all the proposed derivatives. Their ligand interaction was taken. And also, ADME prediction of synthesized compounds was done by using Quick prop module (Schrödinger 9.0).

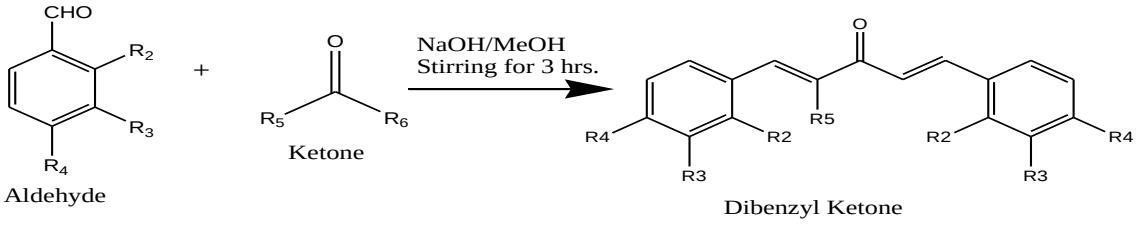
The synthesized imidazole derivatives were evaluated for their possible in vitro antibacterial and antifungal activity by well diffusion method with the help of different bacterial strain like E. coli and fungal strain like *Aspergillus niger, Trichophyllum rubrum and Candidaalbicans.*

6. Design, Synthesis and Biological Evaluation of Dibenzyl Ketone Derivatives.

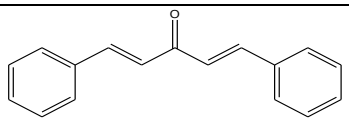
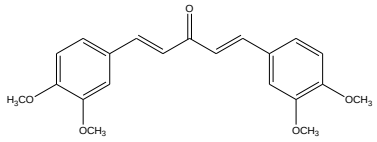
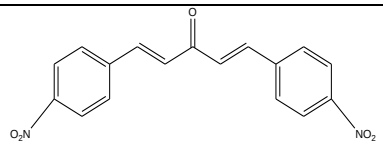
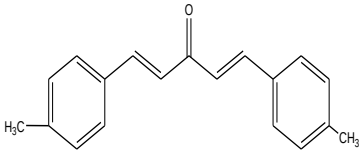
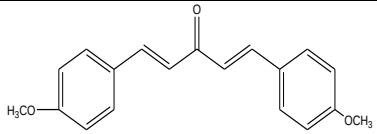
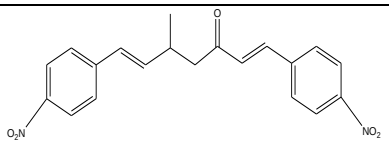
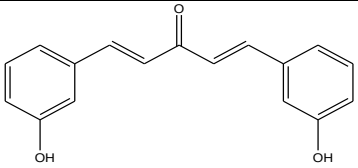
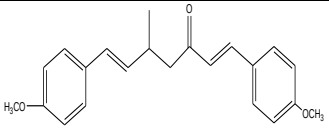
Pramod Singh etal have reported the synthesis and characterisation of novel 2-pyrazoline derivative as per below mentioned scheme.

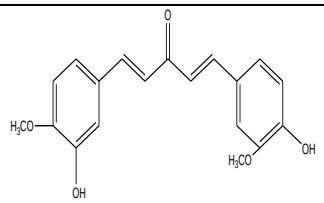
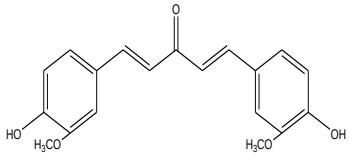
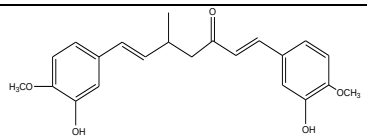
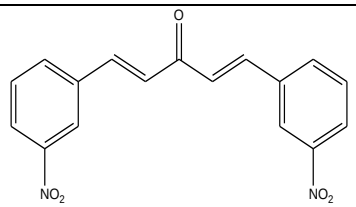
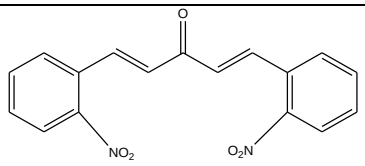
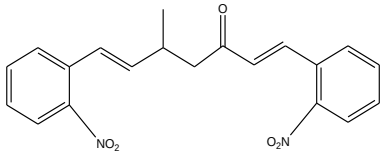
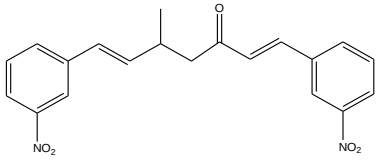


Product of step 1 (Dibenzal acetone dvt) and step 2 (Pyrazoline dvt) were subjected for PASS (online prediction of activity using structure). PASS results of various dibenzylketone derivatives shows promising activity spectra. By considering this dibenzalketone nucleus is considered as lead nucleus for design. Various analogues were designed and synthesised as per below mentioned scheme. These analogues were docked into Mycobacterium tuberculosis lipoprotein LprG (pdb id 4ZRA). Docking images and dock score are shown in below table. Compounds GD-102 (-4.794), GD-103 (-4.335), GD-105 (-4.743), GD-109 (-5.128) and GD-110 (-4.463) are showing good poses and highest dock score. These molecules will be subjected for in vivo study (Antimycobacterial activity).

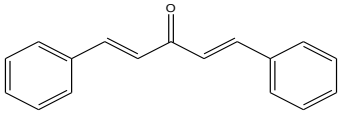


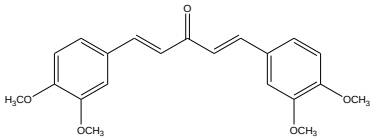
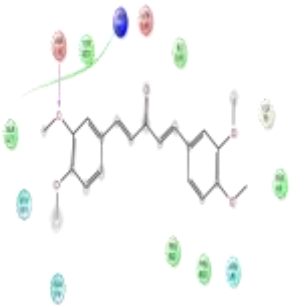
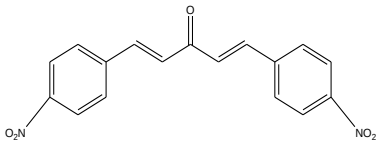
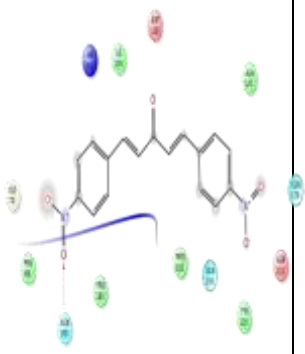
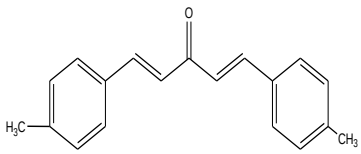
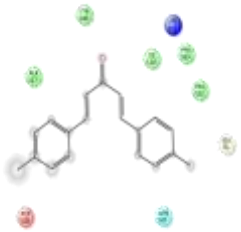
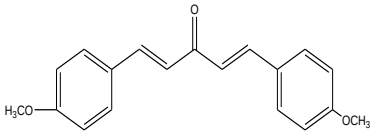
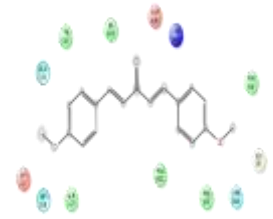
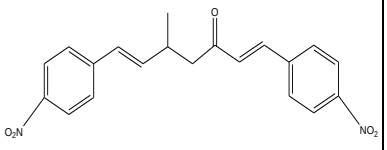
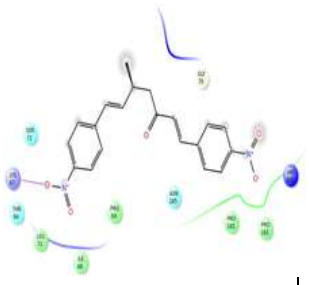
PASS score for Dibenzyl ketone analogues table 6

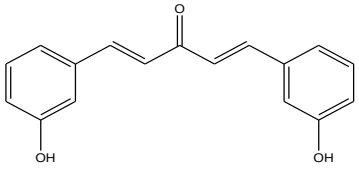
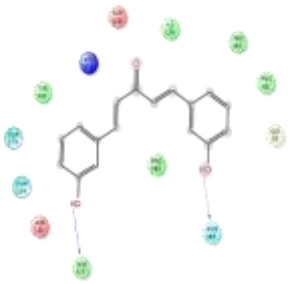
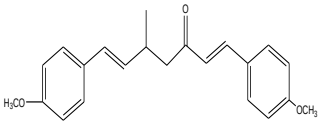
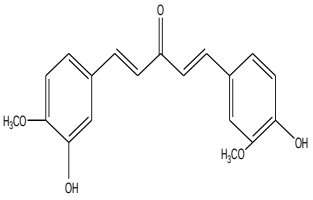
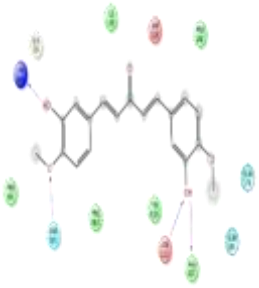
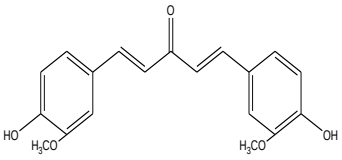
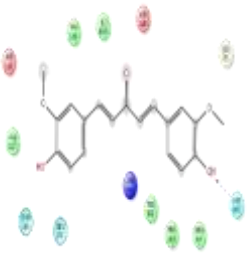
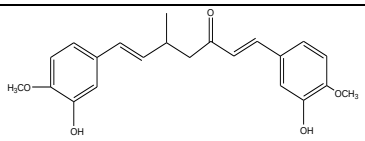
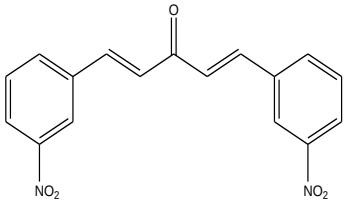
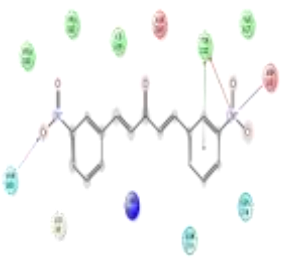
Sr. No.	Comp. Code	Sructure	Pass anti-tuberculosis activity
1	GD-101		0.497
2	GD-102		0.512
3	GD-103		0.632
4	GD-104		0.503
5	GD-105		0.503
6	GD-106		0.521
7	GD-107		0.516
8	GD-108		0.499

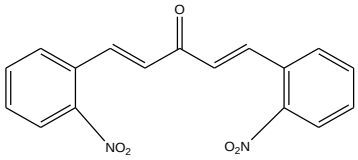
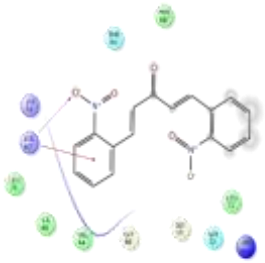
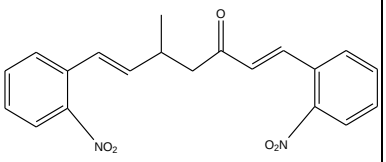
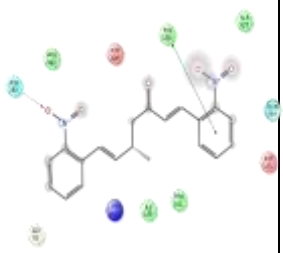
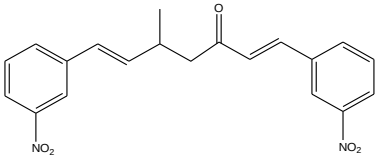
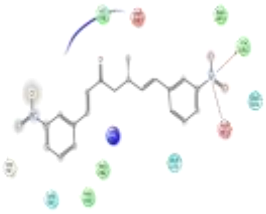
9	GD-109		0.558
10	GD-110		0.558
11	GD-111		0.456
12	GD-112		0.628
13	GD-113		0.523
14	GD-114		0.543
15	GD-115		0.519

Docking into Mycobacterium tuberculosis lipoprotein LprG (4ZRA)

Sr. No.	Comp. Code	Structure	MW	Dockscore	Image	Amino acid binding
1	GD-101		234.297		No good pose	

2	GD-102		354.402	-4.794		ASP 131
3	GD-103		324.292	-4.335		ASN 185
4	GD-104		262.351	-2.527		
5	GD-105		294.349	-4.743		
6	GD-106		366.373	-4.141		

7	GD-107		266.296	-5.682		ALA 127 ASN 185
8	GD-108		336.430	-4.004		LYS 67 GLY 70 ASN 185
9	GD-109		326.348	-5.128		4RF 301 ASN 185 ASP 131 ALA 127
10	GD-110		326.348	-4.463		ASN 185
11	GD-111		368.429	---	No good pose	
12	GD-112		324.292	-4.837		ASN 185 TYR 130 ASP 131

13	GD-113		324.292	-3.221		LYS 67
14	GD-114		366.373	-3.977		ASN 185 TYR 130
15	GD-115		366.373	-4.339		ASP 131 TYR 130

In the present study, on literature survey dibenzyl ketone derivatives were designed. It is found that this dibenzyl ketone nucleus is yet to fully explore for its biological potential. So, this nucleus is selected for the research work.

The compounds had been synthesized with an attempt to potentiate them by fulfilling the structural requirement for special biological activities. Total fifteen derivatives have been synthesized by using various aldehydes and ketones in alkaline medium.

Compounds were characterized by thin layer chromatography, infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectroscopy for their structural conformation. All the synthesized derivatives are polar molecule.

These molecules were subjected for docking study at different targets like tuberculosis, bacteria and fungi at Schrodinger software. Their ADME properties were also predicted by using Quick pro module of Schrodinger. From the docking study, some compounds are showing good poses and hence fitted into the binding pocket and showing good binding with the nearby amino acid. All the compounds follow the Lipinski rules of five.

All the synthesized compounds were screened for their possible in vitro antibacterial and antifungal activity by well diffusion method with the help of different bacterial strain like *E. coli* and *S. aureus* and fungal strain like *Aspergillus niger, Trichophytumrubrum* and *Candida albicans*.

2. Details of workshop conducted

Swami Ramanand Teerth Marathwada University, Nanded
School of Pharmacy

One Day Workshop on Advances in Computer Aided Drug Design and Discovery

Report on
One Day Workshop on Advances in Computer Aided Drug Design and Discovery

School of Pharmacy, SRTM University, Nanded was organised on 16 September 2016. This one day hands on workshop on 'Advances in Computer Aided Drug Design and Discovery' was , jointly organized by School of Pharmacy of this University with Schrödinger Ltd. , Banglore , saw participation from different department of School Viz: Pharmaceutical Chemistry, Pharmaceutics, Pharmacology and Quality Assurance. It included talks and discussions by eminent speakers in the morning and a hands-on session post lunch on Computer Aided Drug design and Discovery and QSAR.

During the inaugural function, Prof. Dr. S.G. Gattani, Director, SOP gave a genesis of the workshop and expressed the importance of *in-silico* approaches in drug design and discovery. He also expressed his appreciation and gratitude to Schrödinger Ltd. while speaking on the occasion congratulated on this venture. He further mentioned on how interdisciplinary education helps the society.

Dr. S.S. Pekamwar, HOD of Pharmaceutical Chemistry officially inaugurated the workshop using an in - silico approach and gave a brief account of the participants extended a cordial welcome to all and emphasized the need for generating trained human resource in this niche area and also congratulated the industry partner.

After the inauguration, Dr. Ravi Kumar spoke on the 'Basics of molecular modelling Molecular mechanics, Optimization and Conformation Analysis'. The fundamental concepts of some of the key initiation steps of any molecular modelling exercise were covered. These included basics of different methods of geometry optimization, force field or molecular mechanics, conformation generation and analysis and descriptors. Further, the basic approaches of any Computer Aided Drug Design (CADD) work in terms of Structure and

Ligand Based Drug Design (SBDD and LBDD respectively) with details of each of these approaches were covered with an emphasis on utilizing both approaches in any CADD work to try to arrive at a meaningful consensus for realistic and practical solutions.

This was followed by the lecture of Dr. S.R. Butle discussed the importance of 'CADD in New Drug Discovery'.

It was stated that new drug discovery is an intellectual, time consuming and expensive process. A typical drug discovery cycle, from lead to pharmacy shelf, can take about 14 years with the cost of ~ 800 million US dollars. In time, a new paradigm in drug discovery emerged, which includes early assessment of activity and selectivity of lead molecules, as well as their potential pharmacokinetics, ADME/Tox liabilities. This helps to reduce costly late-stage failures and reduce the time for successful development of new chemical entities (NCE's). CADD now plays vital role in the search for NCEs. Currently the main focus is on management of data sources and to improve design methodologies, computer programs to generate big libraries of compounds with desired pharmacological interest, development of new computational models to assess the potency and selectivity of lead candidates and to identify potential ADME Tox liabilities. In the centre of this paradigm shift is the application of computational techniques to ease the discovery of NCEs.

Post lunch, detailed hands -on session was carried out with participants on the fundamental initial steps of any molecular modeling work using Schrödinger Ltd S flagship suite of modelling program of Schrödinger Ltd Technologies, Bangalore- India. The topics covered were drawing a molecule, energy minimization(optimization) of both small molecules/legends as well as proteins, studying structure and bonding parameters of molecules, calculation of descriptors of molecules and generation and analysis of conformation of molecules.

Dr. Ravi Kumar
Sr. Application Scientist
(Schrodinger)

Dr. S.S. Pekamwar
Convener
(HOD, Pharm. Chemistry)

Sanjay Pekamwar
Professor
School of Pharmacy
SRTM University, Nanded

Dr. S.G. Gattani
Director
(School of Pharmacy)

संचालक
औषधनिर्माणशास्त्र संकुल
स्वा.रा.ती.म.विद्यापीठ,
नांदेड-४३१६०६ (भारत)

Brief CV of Dr M.Ravikumar

Dr. Ravi received his Ph.D. from the Osmania University, Hyderabad. He worked as a R.A in School of Chemistry, University of Hyderabad (from 2003 to 2005) under Dr. Goutham Desiraju; where he worked on the discovery of inhibitors against multi drug resistant *Mycobacterium tuberculosis* studied using Bioinformatics, Cheminformatics and Computational approaches. From 2005– 2009, he served at GVK BioSciences, Hyderabad and worked in various research areas including discovery of novel compounds against cancer, inflammation, diabetes and bacterial infections using Computer-Aided Drug Design methods. From 2009 onwards, he is working as Applications Scientist in Schrodinger, GmbH, Bangalore, conducting training to the clients, providing technical support and working on the drug discovery projects

Dr. Ravi's research interests are in the discovery of novel compounds for critical human diseases such as tuberculosis, diabetes, AIDS and cancer using Bioinformatics, Cheminformatics, Structural Biology. Dr. M. Ravikumar is an author of over 50 scientific publications, many of them are in European Journal of Medicinal Chemistry, Journal of Medicinal Chemistry, Journal of Chemical Information and Modeling etc. .

Swami Ramanand Teerth Marathwada University, Nanded
School of Pharmacy

Date: 16-09-2016

One Day Workshop on Advances in Computer Aided Drug Design and Discovery

Attendance of Participants

Sr.No.	Name of Participants	Department	Signature		
			Morning	Afternoon	
1	Pilaji Payal G.	M Pharm II (P'chemistry)			
2.	Unnati U. Lokulwar	Pharmacology			
3)	Pathare Savita D.	Pharm chemistry			
4)	Bhise Ashwini P.	pharmachemistry			
5)	Patel Swati D.	Pharmacology			
6)	Pathade Neha N.	P'chemistry			
7)	Pople Shraddha S.	P'chemistry			
8)	Rathod Santosh G.	P'cology			
9]	Ippar Nitin A.	P'chemistry			
[10]	Choudhari Gaurav G.	P'chemistry			
11)	Marwade Hrishikesh Shivaji	Pharmaceutics			
12)	Buktare Rutuja Pandurang	P'chem			
13)	Shaikh H Ali M.	P'cology			
14)	Kanthale Sangam	Quality Assurance			
15)	Shyam Shelke	P'chemistry			
16)	Mr. R.S. Sakhare	quality ass.			
17)	Mr. Gahodge Bhimrao	pharmacology			
18)	Kulkarni Rutuja S.	P'chemistry			
19)	Wagh Sharayu S.	P'cology			
20)	Gaikwad Shital K.	QA			
21)	Songule Ambika V.	QA			
22)	Nidhi Kasbe	QA			
23)	Vandana Singh	P'cology			
24)	Anagha G. Sujalegaonkar	P'chemistry			
25)	~~Gahodge Bhimrao M.~~ Shrayu Vaidya	~~P'cology~~ P'cology			

Sr No.	Name of Participant	Dept	Signature		certificate Received
			Morning	After noon	
1	Dr. A. D. Kshirsagar	Pharmacology			
2	Dr. S. J. Wadher	P'chemistry			
3	Jamkhande PG	pharmacology			
4	Dhawale S.C.	-u-			
5	R. V. Kshirsagar	Pharmaceutics			
6.	T. M. Kalyankar	P. chemistry			
7	Navghare Vijay V.	P cology			
8	Wankhade P. P.	P'cology			
9	Ipper Nitin A.	P. chemistry			
10	Mansure Hirakant Suraj	P'ceutics			
11	Shyam Shelke	P'chemistry			
12	Kasbe Nidhi	Q. A.			

स्कुल ऑफ फार्मसी

SOP/704
22/09/16

SOP /2016-17/235

दिनांक :20/09/2016

VICE-CHANCELLOR'S SECRETARIAT
S.R.T.M.U. Nanded-431606
Inward No. 1898
Dt.of Receipt 21/9/16
Time

मा.कुलगुरू महोदय यांना सादर

विषय: प्रस्तुत संकुलात दि.१६/९/२०१६ रोजी संपन्न झालेल्या "Advances in Computer Aided Drug Design and Discovery" या एक दिवसीय कार्यशाळे बाबत.

प्रस्तुत संकुलात शुक्रवार दि. १६/९/२०१६ रोजी प्रस्तुत संकुल व Schrodinger Port land USA यांच्या संयुक्त विद्यनाने वरिल उल्लेखीत विषयावर एक दिवशीय कार्यशाळेचे आयोजन करण्यात आले होते.

या कार्यशाळेत संकुलातील शिक्षक व संशोधक आणि विद्यार्थ्यांनी (एकुण संख्या ५०) सहभाग नोदविला होता, या कार्यशाळेच्या यशस्वीतेसाठी संकुलस्तरावर छोटेखानी आयोजन समिती खालील प्रमाणे गठीत करण्यात आली होती.

1. Dr. S.G. Gattani Director
2. Dr. S. S. Pekamwar Convener
3. Dr. S. R. Butle Membar
4. Dr. A.D. Kshirsagar Membar
5. Mr.R.S. Sakhare Membar

सदरील कार्यशाळेत संकुलातील प्राध्यापकांनी व डॉ. रविकुमार Sr. Application Scientist Schrodinger यांनी मार्गदर्शन केले.

कार्यशाळेसाठी खालील प्रमाणे खर्च झालेला आहे.

अ.क्र.	विवरण	रक्कम
१	प्रमाणपत्र छपाई	५००.००
२	हॉस्पीटेलिटी (चही,नास्ता,जेवण)	६००.००

सदरील खर्च हा डॉ एस.एस. पेकमवार यांनी केला आहे, संकुलाच्या चालू अर्थसंकल्पात परिषद व चर्चासत्र आयोजन या अर्थशीर्षा खाली रू १००,०००ची तरतुद आहे. सदर कार्यशाळेचे आयोजन तातडीने करण्यात आल्यामुळे आपली पुर्वपरवानगी घेणे शक्य झाले नाही.

तरी सदरील कार्यशाळेच्या आयोजनास,गठीत केलेल्या समितीस व कार्यशाळेसाठी झालेल्या खर्चास व खर्चाची रक्कम डॉ एस.एस. पेकमवार यांना देण्यास कार्योत्तर प्रशासकीय व वित्तीय मान्यता मिळणेस्तव सादर.

20.9.16
Director
School of Pharmacy
S.R.T.M.University,
NANDED - 431606 (INDIA)

21/9/16

Future Journal of Pharmaceutical Sciences

Design, synthesis and biological evaluation of novel dibenzyl ketone derivatives for antimicrobial activity

--Manuscript Draft--

Manuscript Number:	FJPS-D-21-00092
Full Title:	Design, synthesis and biological evaluation of novel dibenzyl ketone derivatives for antimicrobial activity
Article Type:	Research
Funding Information:	University Grants Commission (IN) (43-498/2014(SR) dated 30 Oct 2015) — Dr. Sanjay Pekamwar
Abstract:	In an effort to improve biological activity, a series of Dibenzyl Ketone derivatives were synthesized by using various ketones and aldehydes in alkaline medium through conventional methods. Their chemical structures were confirmed by spectral analysis like FT-IR, 1 H NMR and Mass spectrum. Such synthesized molecules were subjected for docking study at different targets at Schrodinger software. Their ADME properties were also predicted by using Quick pro module of Schrodinger. From the docking study, it is predicted that compounds have good biological activity. All the synthesized compounds were screened for their possible in vitro antibacterial and antifungal activity by well diffusion method. Biological evaluation results reveals that synthesized compounds have good biological activity when compared with standard drug.
Corresponding Author:	Sanjay Pekamwar, Ph.D School of Pharmacy, SRTM University, Nanded Nanded, Maharashtra INDIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	School of Pharmacy, SRTM University, Nanded
Corresponding Author's Secondary Institution:	
First Author:	Sanjay Pekamwar, Ph.D
First Author Secondary Information:	
Order of Authors:	Sanjay Pekamwar, Ph.D Gaurav Chaudhari, M. Pharmacy Deepak Kulkarni
Order of Authors Secondary Information:	
Opposed Reviewers:	
Additional Information:	
Question	**Response**
Is this study a clinical trial? *A clinical trial is defined by the World Health Organisation as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.*	No

Design, synthesis and biological evaluation of novel dibenzyl ketone derivatives for antimicrobial activity

Sanjay Pekamwar*[1], Gaurav Choudhari[1] and Deepak Kulkarni[1]

[1]School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

*** Correspondence** (Author 1)

Prof. Sanjay Pekamwar

School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

Email id: sspekam@rediffmail.com

Contact no. +91 8888981273

Author 2

Mr. Gaurav Chaudhari

School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

Email id: cgaurav865@gmail.com

Author 3

Mr. Deepak Kulkarni

School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

Email id: deepakkulkarni68@gmail.com

Orcid id: https://orcid.org/0000-0001-5992-5903

Cover letter

January 25, 2021

Editor in Chief,

Future Journal of Pharmaceutical Sciences

Subject: Submission of manuscript for research paper

Dear Editor in Chief,

With reference to the subject cited above, I would like to submit my manuscript entitled, "**Design, synthesis and biological evaluation of novel dibenzyl ketone derivatives for antimicrobial activity"** for publication in Future Journal of Pharmaceutical Sciences.

In an effort to improve biological activity, a series of Dibenzyl Ketone derivatives were synthesized by using various ketones and aldehydes in alkaline medium through conventional methods. Their chemical structures were confirmed by spectral analysis like FT-IR, ^{1}H NMR and Mass spectrum. Such synthesized molecules were subjected for docking study at different targets at Schrodinger software. Their ADME properties were also predicted by using Quick pro module of Schrodinger. From the docking study, it is predicted that compounds have good biological activity. All the synthesized compounds were screened for their possible in vitro antibacterial and antifungal activity by well diffusion method. Biological evaluation results reveals that synthesized compounds have good biological activity when compared with standard drug.

I confirm that all authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be submitted. I further confirm that the manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

Thereby, we request you to consider this manuscript for Future Journal of Pharmaceutical Sciences

Regards.

Yours Sincerely,

Prof. Sanjay Pekamwar

School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

sspekam@rediffmail.com

+91 8888981273

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The data or analysis during the current study will be made available on request by corresponding author.

Conflict of interest

The authors don't have any conflict of interest.

Funding

The authors are thankful to University Grants Commission, New Delhi for providing financial support under major research project scheme.

Authors' contributions

SP guided for the work analyzed results. DK contributed in preparation of manuscript. GC designed and performed complete experimental part. All the authors approved and submitted the manuscript.

Acknowledgements

The authors are thankful to University Grants Commission, New Delhi for providing financial support under major research project scheme.

Author details

Sanjay Pekamwar*[1], Gaurav Choudhari[1] and Deepak Kulkarni[1]

[1]School of Pharmacy, S.R.T.M. University, Vishnupuri, Nanded, (M.S.), 431606, India.

Design, synthesis and biological evaluation of novel dibenzyl ketone derivatives for antimicrobial activity

Abstract:

In an effort to improve biological activity, a series of Dibenzyl Ketone derivatives were synthesized by using various ketones and aldehydes in alkaline medium through conventional methods. Their chemical structures were confirmed by spectral analysis like FT-IR, ^{1}H NMR and Mass spectrum. Such synthesized molecules were subjected for docking study at different targets at Schrodinger software. Their ADME properties were also predicted by using Quick pro module of Schrodinger. From the docking study, it is predicted that compounds have good biological activity. All the synthesized compounds were screened for their possible in vitro antibacterial and antifungal activity by well diffusion method. Biological evaluation results reveals that synthesized compounds have good biological activity when compared with standard drug.

Keywords: Dibenzyl ketone, Spectral analysis, Antibacterial activity, Antifungal activity.

1. Introduction:

Microbial infections are still the issue of concern due to microbial resistance. Antibiotics and other antimicrobials are consistently used over last 6-7 decades for the treatment of microbial infections [1]. The continuous and irrational use of these antimicrobial agents potentiates the pathogens and boost up the microbial resistance. This threat of microbial resistance give rise to need of novel antimicrobial agents [2].

Increasing numbers of fungal strains are becoming resistant to the current antifungal drugs (fortunately, drug resistance is not transferable in fungi), and toxicity and low efficacy also contribute to the need for better antifungal drugs [3]. Many antifungal agents are quite toxic, and when systemic therapy is required these agents must often be used under strict medical supervision [4].

Computer Aided Drug Design (CADD) is the best trending approach for the development of novel derivatives. The computational molecular docking provide brief idea of docking and ultimately in vivo binding of novel derivatives to the receptors [5]. The structure based virtual screening provides multiple hypothetical interaction and provide an optimistic approach for lab scale and large scale synthesis of novel structural hybrids [6].

In the present study dibenzyl ketone derivatives were designed. It is found that this dibenzyl ketone nucleus is yet to fully explore for its biological potential so, this nucleus is selected for the research work. Dibenzyl ketone, or 1, 3-diphenylacetone, composed of two benzyl groups attached to a central carbonyl moiety [7]. The central carbonyl carbon atom is electrophilic and the two adjacent carbon atoms are slightly nucleophilic. This property of dibenzyl ketone is useful in an aldol condensation reaction with benzil [8]. In former research studies this reactive property of ketone derivatives is found to be useful for the development antioxidant compounds [9]. Polyimide-silver composites were also found to be synthesized with the inclusion of dibenzalacetone moiety in the main chain [10].

2. Material and Method:

2.1 General:

Chemicals and solvents were procured from commercial units, Aldrich India Ltd., E. Merck India Ltd. These solvents and reagents were of LR grade and if necessary purified before use. Thin-layer chromatography (TLC) was carried out on aluminium- supported silica gel plates (Merck 60 F254) with visualization of components by UV light (254 nm). 1H NMR spectra was recorded at 500 MHz using a Bruker AV 500 spectrometer (Bruker CO., Chennai) in CDCl3 and DMSO-d6 solution with tetramethylsilane as the internal standard, and chemical shift values (d) were given in ppm. Melting points were determined on an electrothermal melting point apparatus (Stuart-SMP30) in open capillary tubes. IR spectra were recorded with an FT-IR spectrophotometer (Schimandzu FTIR-00722). Compounds were analysed by KBr disc method and mmax is expressed in cm_1; Mass spectra (ESI–MS) were recorded on Schimadzu MS/ESI mass spectrometer.

2.2 Experimental

General procedure for synthesis of (1E, 4E)-1,5-diphenylpenta-1,4-diene-3-one derivatives

In this synthesis, substituted benzaldehyde (30 mmol) react with substituted ketone (15 mmol) with continuous stirring for 3 hrs. During the reaction, simultaneous addition of sodium hydroxide and methanol mixture for 3 hrs. drop by drop. Then, the resultant mixture left for 2 hrs. The precipitate was crystallized from methanol [11].

2.3 Molecular Docking:

In this study, molecules are docked in schrodinger platform (Version 2016.3) for different targets like *E.coli* and *Candida albicans*. Maestro is used as graphical user interface. Protein is prepared using protein preparation wizard [12]. The prepared protein is loaded into maestro environment and the active site is defined. Grid centre is defined for the active site and box sizes are set. The next step is to generate glide grid. After successful generation of the grids, prepared ligands are loaded into maestro [13]. Ligands are kept flexible, while the protein is rigid and docking started with extra precision mode (XP mode). The docking calculation generated few poses for each ligand. The selection of the best pose was done on the interaction energy between the ligand and the protein as well as on the interactions the ligand shows with experimentally proved important residues [14].

2.4 Biological Evaluation:

2.4.1 Antibacterial and antifungal activity:

The antibacterial activity of synthesized compounds were determined by screening them against the *E. coli and S. aureus* [15]. The antifungal activity of synthesized compound were determined against the *Aspergillus niger, Trichophytum rubrum and Candida ablicans* [16]. The basic principle of antibacterial and antifungal assay lies in the comparison of inhibition of growth of microorganism produced by the known concentration of antibacterial and antifungal agents to be tested with that produced by known concentration of standard antifungal agent having known activity (Table 1) [17].

3. Result and discussion:

In the present study, dibenzyl ketone derivatives were synthesized as scheme depicted in Figure 1. Computational studies and virtual screening provided an idea about molecular docking and ADME properties of novel structural hybrids.

3.1 Structure of synthesized compounds Dibenzyl ketone derivatives

Total fifteen novel derivatives synthesized from a scheme only with changing the substitutions at R1, R2, R3, R4 and R5 (Table 2). The highest yield was obtain with compound GD-108 i.e. 82.66% and the lowest yield was obtained for compound GD-115 i.e. 67.89%.

3.2 Molecular Docking of molecule:

The organism which is taken in consideration for molecular docking for antibacterial study was *E. coli* and for antifungal study was *Candida albicans*.

3.2.1 Antibacterial activity

(PDB Code: 5FX3; Organism-*E.coli*;)

In molecular docking for antibacterial activity the results for compounds GD-101 (-3.364), GD-108 (-3.063), GD-109 (-3.057), GD-112 (-3.187) and GD-113 (-3.105) showed good results with docking study (Table 3 and 4).

3.2.3 Antifungal activity

Docking molecule images: (PDB Code: 5HW6; Organism-*candida albicans*)

From the docking study it was observed that compound GD-101 (-3.441), GD-103 (-2.962), GD-107 (-3.906), GD-109 (-3.875) and GD-111 (-3.419) are showing good poses and hence fitted into the binding pocket and showing good binding with the nearby amino acid (Table 5 and 6).

3.3 ADME properties of molecule

The data of Lipinski rule of five for all the compounds is illustrated in Table no 7. Data in the table clearly demonstrates that the compound follows Lipinski rules of five. Molecular properties including human absorption were found to be promising for pharmacological application (Table 8)

3.4 Pharmacological activity evaluation

Antibacterial and antifungal activity of synthesized dibenzyl ketone derivatives.

The compound which have been synthesized were subjected to in vitro biological screening for the study of anti-bacterial and anti-fungal activity with the help of different bacterial strain like *E. coli* and *S. aureus* and fungal strain like *Aspergillus niger*, *Trichophytum* and *Candida albicans*. From the biological screening study the zone of inhibitions of microorganism was measured and compared with standard drug (Table 9 and 10). Both the activities were found to be satisfactory.

3.5 Spectral Studies

(1E,4E)-1,5-diphenylpenta-1,4-diene-3-one **(GD-101)**

IR(KBr):v cm-1 3022(C-H stretching aromatic), 1647.87(C=O stretching), 1623.36(C=C stretching), 1445.68(C-H stretching aliphatic); ^{1}H NMR (500MHz,$CDCl_3$) δ: 7.758-7.726(m, 2H, Ar-H), 7.628-7.613(m, 3H, Ar-H), 7.438-7.410(m, 3H, Ar-H), 7.374(S, 1H, Ar-H), 7.256(m, 2H, C-H), 7.104-7.072(m, 2H, C-H); Mass spectrum shows the formation of molecular ion peak at m/z=234.29.

(1E,4E)-1,5-bis(3,4-dimethoxyphenyl)penta-1,4-diene-3-one **(GD-102)**

IR(KBr): cm-1 2831 (C-H stretching aromatic), 1617.38 (C=O stretching), 1577.06(C=C stretching), 1463.08 (C-H stretching aliphatic), 1257.42 (C-O stretching); ^{1}H NMR (500MHz,$CDCl_3$) δ: 6.827-6.800 (m, 2H, Ar-H), 6.782 (s, 1H, Ar-H), 6.732 (s, 1H, Ar-H), 6.710 (s, 1H, Ar-H), 6.695-6.622 (m, 2H, C-H), 6.590-6.427 (m, 2H, C-H), 3.064 (s, 1H, C-H), 2.371 (s, 1H, C-H), ; Mass spectrum shows the formation of molecular ion peak at m/z=354.40.

(1E,4E)-1,5-bis(4-nitrophenyl)penta-1,4-diene-3-one **(GD-103)**

IR(KBr): cm-1 3362.07 (C-H stretching aromatic), 1650.05 (C=O stretching), 1597.97 (C=C stretching), 1445.68 (C-H stretching aliphatic), 1516.25 (N=O stretching); ^{1}H NMR (500MHz,$CDCl_3$) δ: 7.758-7.726 (m, 2H, Ar-H), 7.628-7.613 (m, 3H, Ar-H), 7.438-7.410 (m, 3H, Ar-H), 7.374 (S, 1H, Ar-H), 7.256 (m, 2H, C-H), 7.104-7.072 (m, 2H, C-H); Mass spectrum shows the formation of molecular ion peak at m/z=324.29.

(1E,4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-diene-3-one **(GD-109)**

IR(KBr): cm-1 2992.12 (C-H stretching aromatic), 1615.21(C=O stretching), 1559.59 (C=C stretching), 1493.30 (C-H stretching aliphatic), 1256.29 (C-O stretching), 1102.60 (O-H stretching); ^{1}H NMR (500MHz,$CDCl_3$) δ: 7.659-7.627 (m, 2H, Ar-H), 7.154 (s, 1H, Ar-H), 7.051 (s, 1H, Ar-H), 6.946 (S, 1H, Ar-H), 6.641-6.609 (m, 2H, C-H), 6.270-6.245 (m, 2H, C-H), 2.174 (s, 1H, O-H), 1.649 (s, 1H, C-H); Mass spectrum shows the formation of molecular ion peak at m/z=326.34.

4. Discussion:

After performing computational molecular docking the compounds with good docking score were noticed and considered to be have good in vivo receptor binding ability [18]. The molecular docking provided a hypothetical evidence about better in vivo binding of compound for antibacterial and antifungal activity [19]. Compounds GD-101 (-3.364), GD-108 (-3.063), GD-109 (-3.057), GD-112 (-3.187) and GD-113 (-3.105) were convincing where the molecules were showing good poses and fitting into the binding pocket and good binding with the nearby amino acid. In antiviral activity screening also compound GD-101 (-3.441), GD-103 (-2.962), GD-107 (-3.906), GD-109 (-3.875) and GD-111 (-3.419) showed good fitting in binding pocket along with good poses [20]. This observation from molecular docking endorse the good binding abilities this molecules and promises suitability for pharmacological application.

All the compounds follows the Lipinski rules of five. No violations of rule were seen with any of the compounds. All the compounds has good dipole moment and are polar molecule. All the compounds has greater than 25% human oral absorption and ultimately good bioavailability [21]. All the compounds has good serum protein binding.

In vitro antibacterial and antifungal activity study provided the quantitative data about zone of inhibition of all the compounds for bacterial and fungal strain [22]. Compound GD-103, compound GD-104, compound GD-106, compound GD-109, compound GD-115 having good anti-bacterial activity and compound GD-103, compound GD-106, compound GD-108, compound GD-110, compound GD-115 having good anti-fungal activity.

5. Conclusion:

In the present study dibenzyl ketone derivatives were designed. It is found that this dibenzyl ketone nucleus is yet to fully explore for its biological potential so, this nucleus is selected for the research work.

The compounds had been synthesized with an attempt to potentiate them by fulfilling the structural requirement for special biological activities. Total fifteen derivatives have been synthesized by using various aldehydes and ketones in alkaline medium. Compounds were characterized by thin layer chromatography, infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectroscopy for their structural conformation. All the synthesized derivatives are polar molecule. These molecules were subjected for docking study at different targets like tuberculosis, bacteria and fungi at Schrodinger software. Their ADME properties were also predicted by using Quick

pro module of Schrodinger. From the docking study, some compounds are showing good poses and hence fitted into the binding pocket and showing good binding with the nearby amino acid. All the compounds follows the Lipinski rules of five.

All the synthesized compounds were screened for their possible in vitro antibacterial and antifungal activity by well diffusion method with the help of different bacterial strain like *E. coli* and *S. aureus* and fungal strain like *Aspergillus niger*, *Trichophytum rubrum* and *Candida albicans*.

List of abbreviations:

FTIR: Fourier Transform Infrared; NMR: Nuclear Magnetic Resonance; ADME: Absorption, Distribution, Metabolism, Excretion; MS: Mass Spectroscopy

References:

1. Frieri M, Kumar K, Boutin A (2017) Antibiotic resistance. J Infect Public Health 10(4):369–78.
2. Gajdács M, Albericio F (2019) Antibiotic resistance: from the bench to patients. Antibiotics 8(3):8–11.
3. Wiederhold NP (2017) Antifungal resistance: current trends and future strategies to combat. Infect Drug Resist 10:249–59.
4. Girois SB, Chapuis F, Decullier E, Revol BGP (2006) Erratum: Adverse effects of antifungal therapies in invasive fungal infections: Review and meta-analysis. Eur J Clin Microbiol Infect Dis 25(2):138–49.
5. Yu W, Mackerell AD (2017) Docking and scoring in virtual screening for drug discovery. Methods Mol Biol 1520:85–106.
6. Lill M. (2013) Virtual screening in drug design. Methods Mol Biol 993:1–12.
7. Noh T, Step E, Turro NJ (1993) Singlet state photochemistry of dibenzyl ketone and its o-tolyl derivatives. J Photochem Photobiol A Chem 72(2):133–45.

8. Mandal S, Mandal S, Ghosh SK, Ghosh A, Saha R, Banerjee S (2016) Review of the aldol reaction. Synth Commun 46(16):1327–42.

9. Handani S, Indyah Sulistyo A (2008) Synthesis of Hydroxyl Radical Scavengers from Benzalacetone and its Derivatives. J Phys Sci 19(2):61–8.

10. Faghihi K, Hajibeygi M (2013) Synthesis and properties of polyimide/silver nanocomposite containing dibenzalacetone moiety in the main chain. J Saudi Chem Soc 17(4):419–23.

11. Singh P, Negi JS, Pant GJN, Rawat MSM, Budakoti A (2009) Synthesis and characterization of a novel 2-pyrazoline. Molbank 3:1–4.

12. Madhavi Sastry G, Adzhigirey M, Day T, Annabhimoju R, Sherman W (2013) Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. J Comput Aided Mol Des 27(3):221–34.

13. Elokely KM, Doerksen RJ (2013) Docking challenge: Protein sampling and molecular docking performance. J Chem Inf Model 53(8):1934–45.

14. Acharya R, Chacko S, Bose P, Lapenna A, Pattanayak SP (2019) Structure Based Multitargeted Molecular Docking Analysis of Selected Furanocoumarins against Breast Cancer. Sci Rep 9(1):1–13.

15. Mummed B, Abraha A, Feyera T, Nigusse A, Assefa S (2018) In Vitro Antibacterial Activity of Selected Medicinal Plants in the Traditional Treatment of Skin and Wound Infections in Eastern Ethiopia. Biomed Res Int 2018:1-8.

16. Martins FJ, Caneschi CA, Senra MP, Carvalho GSG, Da Silva AD, Raposo NRB (2017) In Vitro Antifungal Activity of Hexahydropyrimidine Derivatives against the Causative Agents of Dermatomycosis. Sci World J 2017:1-8.

17. Schoenknecht FD, Washington JA, Gavan TL, Thornsberry C (1980) Rapid determination of minimum inhibitory concentrations of antimicrobial agents by the Autobac method: A collaborative study. Antimicrob Agents Chemother 17(5):824–33.

18. Meng XY, Zhang HX, Mezei M, Cui M (2011) Molecular docking: a powerful approach for structure-based drug discovery. Current computer-aided drug design. Curr Comput

Aided Drug Des 7(2):146–57.

19. Jia B, Ma YM, Liu B, Chen P, Hu Y, Zhang R (2019) Synthesis, Antimicrobial Activity, Structure-Activity Relationship, and Molecular Docking Studies of Indole Diketopiperazine Alkaloids. Front Chem. 7:1–13.

20. Patel MM, Patel LJ (2014) Design, synthesis, molecular docking, and antibacterial evaluation of some novel flouroquinolone derivatives as potent antibacterial agent. Sci World J 2014:1-10.

21. Mullard A (2018) Re-assessing the rule of 5, two decades on. Nat Rev Drug Discov 17(11):777.

22. Shakhatreh MAK, Al-Smadi ML, Khabour OF, Shuaibu FA, Hussein EI, Alzoubi KH (2016) Study of the antibacterial and antifungal activities of synthetic benzyl bromides, ketones, and corresponding chalcone derivatives. Drug Des Devel Ther 10:3653–60.

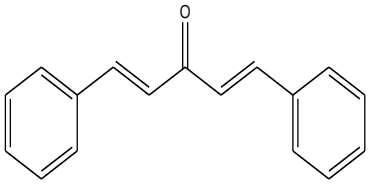
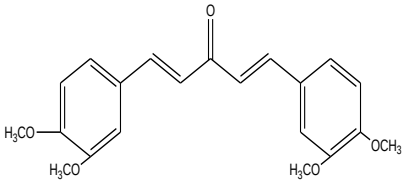
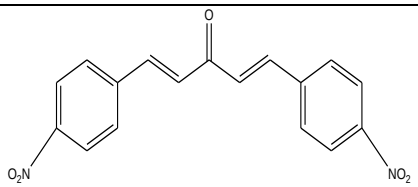
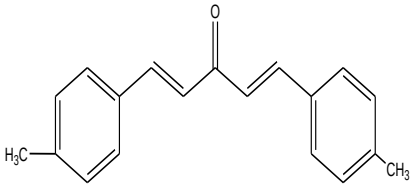
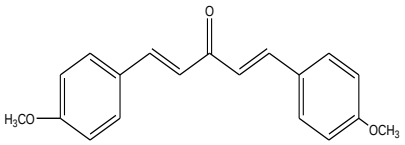
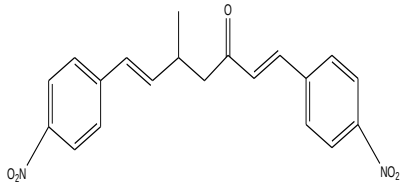
Figure legends

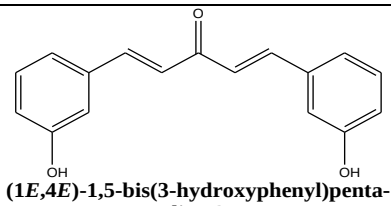
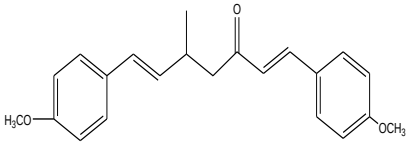
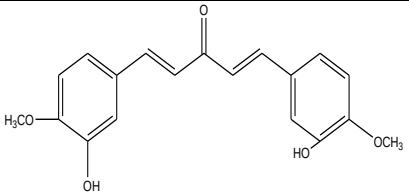
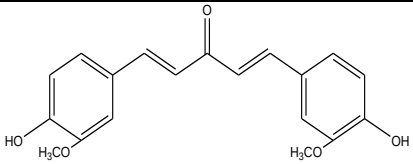
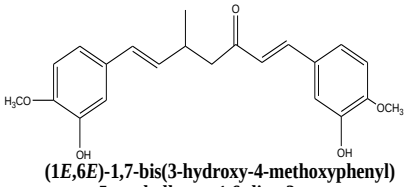
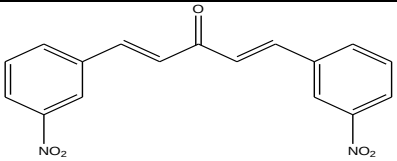
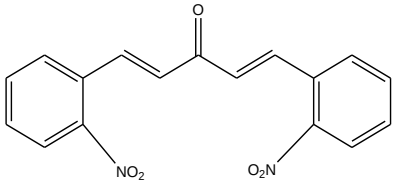
Fig.1: Scheme for synthesis

Table 1: Antibacterial and antifungal activity testing parameters

Parameter	Anti-bacterial activity	Anti-fungal activity
Method	Well Diffusion Method	Well Diffusion Method
Medium	Nutrient agar	Potato dextrose agar
Organism used	Gram positives- *S. aureus,* Gram negative- *E. coli*	*Aspergillus niger, Trichophytum rubrum and Candida albicans.*
Stock solution	Prepared in dimethyl sulphoxide for both synthesized compound and standard compounds	Prepared in dimethyl sulphoxide for both synthesized compound and standard compounds
Incubation time	24 hours	48hours
Incubation temperature	37ºC	37ºC
Dose of compound	1%	1%
Well size	6 mm	6 mm

Table 2: Structures of synthesized compounds Dibenzyl ketone derivatives

Sr. No.	Comp. Code	Structure and IUPAC Name	Molecular Weight (g/mol)	Melting point	Rf value	% Yield (w/w)
1	GD-101	 **(1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one**	234.297	126^{0}c	0.46	68.27
2	GD-102	 **(1*E*,4*E*)-1,5-bis(3,4-dimethoxyphenyl)penta-1,4-dien-3-one**	354.402	130^{0}C	0.50	71.31
3	GD-103	 **(1*E*,4*E*)-1,5-bis(4-nitrophenyl)penta-1,4-dien-3-one**	324.292	131^{0}C	0.46	72.87
4	GD-104	 **(1*E*,4*E*)-1,5-di*p*-tolylpenta-1,4-dien-3-one**	262.351	134^{0}C	0.51	70.32
5	GD-105	 **(1*E*,4*E*)-1,5-bis(4-methoxyphenyl)penta-1,4-dien-3-one**	294.349	132^{0}C	0.53	74.12
6	GD-106	 **(1*E*,6*E*)-5-methyl-1,7-bis(4-nitrophenyl) hepta-1,6-dien-3-one**	366.373	128^{O}C	0.40	78.23

7	GD-107	 **(1*E*,4*E*)-1,5-bis(3-hydroxyphenyl)penta-1,4-dien-3-one**	266.296	130^{O}C	0.43	75.56
8	GD-108	 **(1*E*,6*E*)-1,7-bis(4-methoxyphenyl)-5-methylhepta-1,6-dien-3-one**	336.430	133^{0}C	0.43	82.66
9	GD-109	 **(1*E*,4*E*)-1,5-bis(3-hydroxy-4-methoxyphenyl) penta-1,4-dien-3-one**	326.348	127^{0}C	0.45	73.16
10	GD-110	 **(1*E*,4*E*)-1,5-bis(4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3-one**	326.348	128^{0}C	0.46	79.24
11	GD-111	 **(1*E*,6*E*)-1,7-bis(3-hydroxy-4-methoxyphenyl) -5-methylhepta-1,6-dien-3-one**	368.429	136^{0}C	0.58	71.34
12	GD-112	 **(1*E*,4*E*)-1,5-bis(3-nitrophenyl) penta-1,4-dien-3-one**	324.292	133^{0}C	0.53	75.55
13	GD-113	 **(1*E*,4*E*)-1,5-bis(2-nitrophenyl) penta-1,4-dien-3-one**	324.292	134^{0}C	0.60	80.67

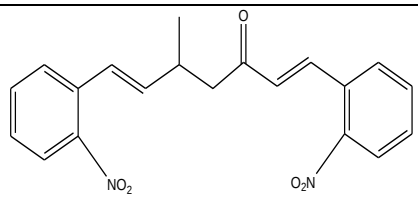
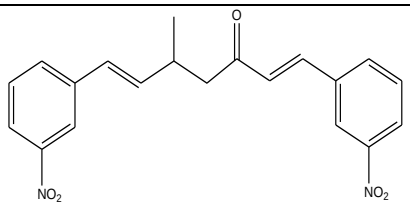
14	GD-114	 **(1*E*,6*E*)-5-methyl-1,7-bis(2-nitrophenyl) hepta-1,6-dien-3-one**	366.373	136^{0}C	0.50	78.65
15	GD-115	 **(1*E*,6*E*)-5-methyl-1,7-bis(3-nitrophenyl) hepta-1,6-dien-3-one**	366.373	138^{0}C	0.50	67.89

Table 3: Molecular docking for antibacterial activity (PDB Code: 5FX3; Organism-*E.coli*; Enzyme-Tyrosine)

Sr. No.	Comp. code	Docking score	Glide g score	Glide e model	Potential energy-OPLS-2005	Amino acid binding
1	GD-101	-3.364	-3.364	-22.355	65.002	TYR 53
2	GD-102	-2.762	-2.762	-25.323	157.312	TYR 53
3	GD-103	-2.201	-2.201	-22.354	82.948	ASN 96
4	GD-104	-2.527	-2.527	-22.665	64.727	ASN 96
5	GD-105	-2.466	-2.466	-20.083	94.104	ASN 96
6	GD-106	-2.629	-2.629	-26.291	81.390	
7	GD-107	-3.877	-3.877	-28.834	62.131	PRO 49 GLU 50
8	GD-108	-3.063	-3.063	-27.655	92.614	TYR 55
9	GD-109	-3.057	-3.057	-29.216	126.028	PRO 49 TYR 53 GLU 50
10	GD-110	-2.940	-3.226	-28.429	88.600	ASN 136 TYR 53
11	GD-111	-	-	-	-	
12	GD-112	-3.187	-3.187	-29.475	81.382	GLU 50 THR 53 TYR 55
13	GD-113	-3.105	-3.105	-26.441	125.976	ASN 96 THR 53
14	GD-114	-2.539	-2.539	-28.285	129.877	ASN 96
15	GD-115	-2.704	-2.704	-31.317	79.795	ASN 96

Table 4: Structures of compounds with good molecular docking results for antibacterial activity

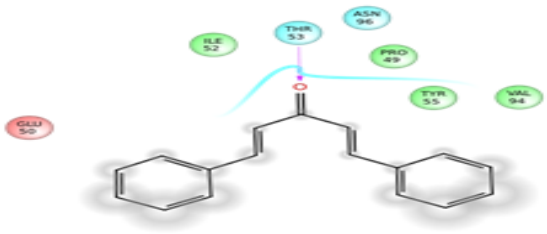
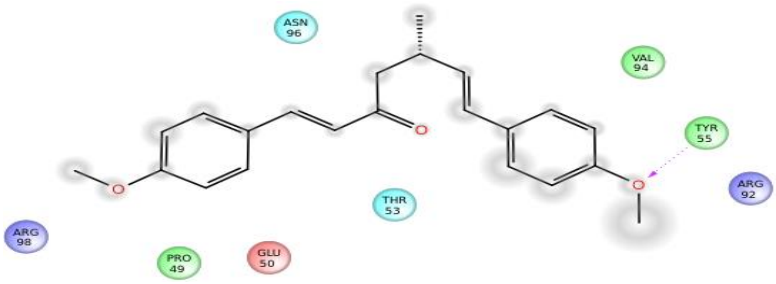
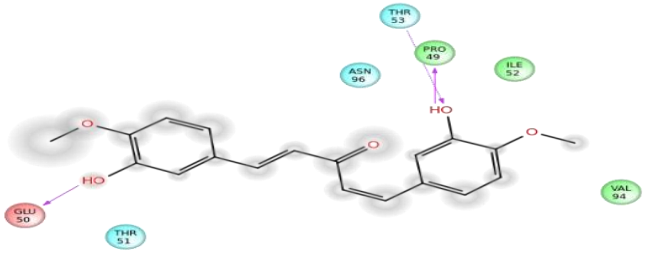
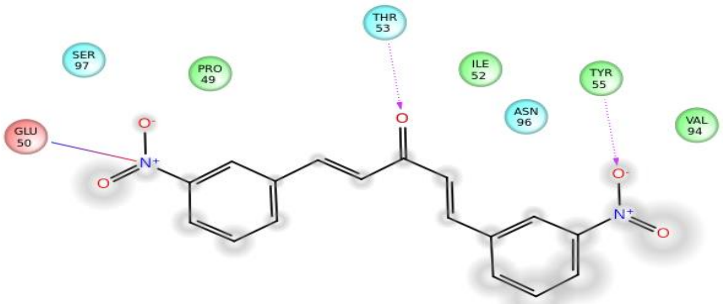
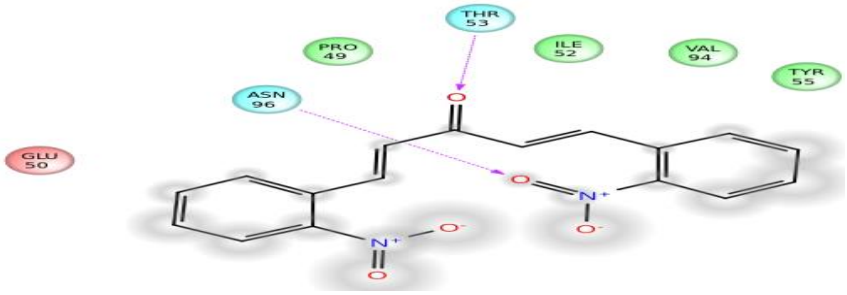
Compound code	Structure
GD-101 (-3.364)	
GD-108 (-3.063)	
GD-109 (-3.057)	
GD-112 (-3.187)	
GD-113 (-3.105)	

Table 5: Molecular docking for antifungal activity (PDB Code: 5HW6 Organism-candida albicans Enzyme-FKBP12 Apo protein)

Sr. No.	**Comp. code**	**Docking score**	**Glide emodel**	**Potential energy-OPLS-2005**	**Amino acid binding**
1	GD-101	-3.441	-28.188	65.002	LYS 61
2	GD-102	-2.945	-31.054	157.312	
3	GD-103	-2.962	-32.297	82.948	LYS 61 LYS 73 TYR 71
4	GD-104	-2.732	-26.425	64.727	LYS 73 TYR 71
5	GD-105	-2.566	-27.795	94.104	TYR 71
6	GD-106	-2.608	-34.496	81.390	LYS 61
7	GD-107	-3.906	-34.191	62.131	LYS 61 GLU 3
8	GD-108	-2.341	-30.665	92.614	LYS 73
9	GD-109	-3.875	-38.772	126.028	LYS 61 GLU 3
10	GD-110	-2.756	-33.053	88.600	LYS 61 GLU 3 VAL 59
11	GD-111	-3.419	-38.099	87.270	ACT 201 GLY 55
12	GD-112	-2.743	-30.449	81.382	LYS 73 GLU 4 TYR 71
13	GD-113	-2.823	-28.993	125.976	LYS 73 GLU 3
14	GD-114	-2.272	-29.460	129.877	LYS 73 GLU 3
15	GD-115	-2.742	-34.434	79.795	LYS 73 GLU 4

Table 6: Structures of compounds with good molecular docking results for antifungal activity

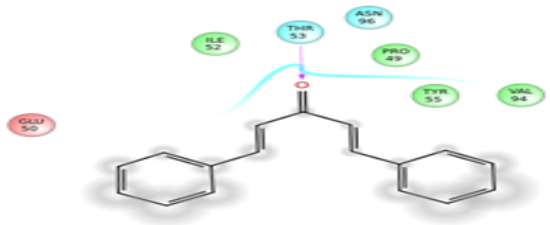
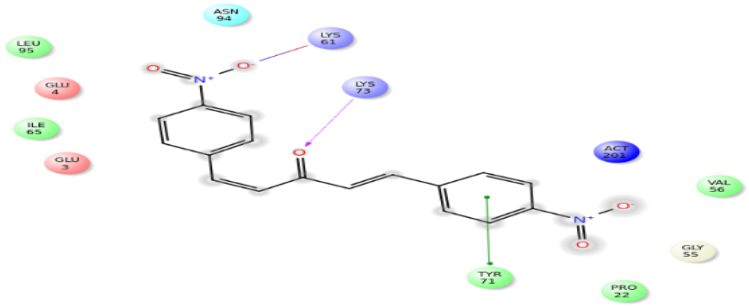
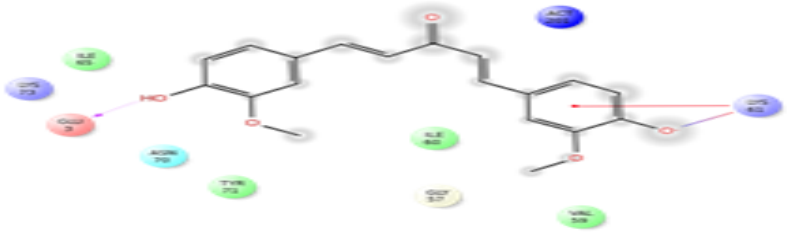
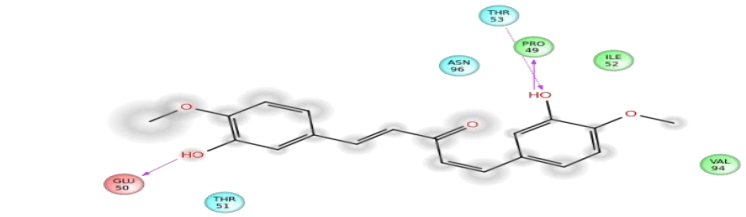
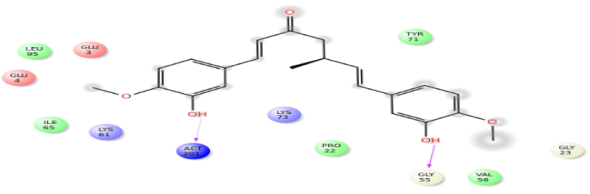
Compound code	Structure
GD-101 (-3.364)	
GD-103 (-2.962)	
GD-107 (-3.906)	
GD-109 (-3.057)	
GD-111 (-3.419)	

Table 7: Lipinski Rules of Five parameters for all compounds

Sr. no.	Comp. code	Lipinski Rules of Five				
		log P	Molecular Weight (g/mol)	H acceptors	H donors	No. of violations
1	GD-101	4.18	234.297	2	0	0
2	GD-102	3.48	354.402	5	0	0
3	GD-103	4.10	324.292	4	0	0
4	GD-104	5.08	262.351	2	0	0
5	GD-105	4.30	294.349	3.5	0	0
6	GD-106	5.12	366.373	4	0	0
7	GD-107	3.18	266.296	3.5	2	0
8	GD-108	5.32	336.43	3.5	0	0
9	GD-109	2.86	326.348	5	2	0
10	GD-110	2.86	326.348	5	2	0
11	GD-111	3.88	368.429	5	2	0
12	GD-112	4.05	324.292	4	0	0
13	GD-113	3.65	324.292	4	0	0
14	GD-114	4.66	366.373	4	0	0
15	GD-115	5.07	366.373	4	0	0

Table 8: Molecular properties of synthesized compounds

Sr. no.	**Comp. code**	**Dipole moment**	**%Human Oral Absorption in GI (+-20%) <25% is poor**	**QP logK hsa serum protein binding**
1	GD-101	3.383	100	0.399
2	GD-102	0.524	100	0.229
3	GD-103	6.202	71.963	0.256
4	GD-104	3.882	100	0.741
5	GD-105	5.357	100	0.306
6	GD-106	15.556	76.828	0.523
7	GD-107	2.436	88.304	0.06
8	GD-108	5.358	100	0.733
9	GD-109	0.311	90.487	0.086
10	GD-110	0.056	89.448	0.096
11	GD-111	5.671	100	0.443
12	GD-112	13.754	71.963	0.256
13	GD-113	17.869	77.655	0.164
14	GD-114	17.514	86.505	0.573
15	GD-115	10.447	80.114	0.555

Table 9: Antibacterial activity of synthesized Dibenzyl ketone derivatives

Sr. No.	**Comp. No.**	**Compound Code**	**Zone of Inhibition(mm)**	
			Staphylococcus aureus	***Escherichia coli***
1	1	GD-101	3	5
2	2	GD-102	4	3
3	3	GD-103	9	5
4	4	GD-104	3	6
5	5	GD-106	5	4
6	6	GD-108	3	2
7	7	GD-109	6	5
8	8	GD-110	4	5
9	9	GD-111	3	4
10	10	GD-115	7	6
11	-ve control	DMSO	--	--
12	+ve control	Cefexime	7	5

Table 10: Antifungal activity of synthesized Dibenzyl ketone derivatives

Sr. No.	**Comp. No.**	**Compound Code**	***Zone of Inhibition(mm)***		
			Aspergillus niger	***Trichophytum rubrum***	***Candida albicans***
1	1	GD-101	6	--	--
2	2	GD-102	5	4	4
3	3	GD-103	8	8	3
4	4	GD-104	4	6	7
5	5	GD-106	6	10	6
6	6	GD-108	7	6	8
7	7	GD-109	5	8	4
8	8	GD-110	7	6	4
9	9	GD-111	6	10	6
10	10	GD-115	5	6	5
11	-ve control	DMSO	--	--	--
12	+ve control	Ketoconazole	6	6	6

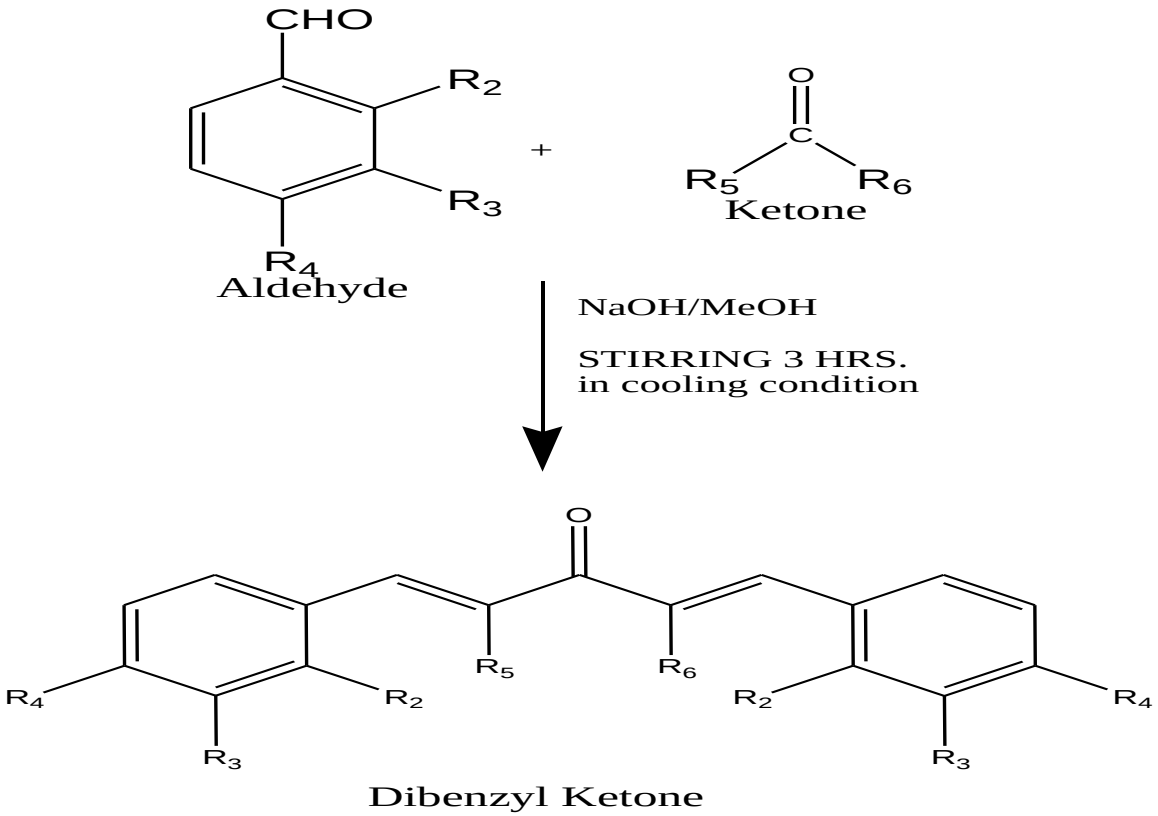


Fig.1: Scheme for synthesis

ACKNOWLEDGEMENT

I, Sanjay S Pekamwar as a principal investigator (PI) thankful to University Grants Commission, New Delhi for sanctioning the major research project giving an opportunity to work in contemporary research area.

I am grateful Hon. Vice- Chancellor of the University for promoting research activities and providing an opportunity to do the work.

I am thankful to Director of School of Pharmacy for providing all necessary facility and extending administrative support for completition of the project.

Last but not least, I am thankful to all those who contributed directly and indirectly for successful completition of the project

Date: 25/01/2021

Sanjay Pekamwar

Sanjay Pekamwar
Professor
School of Pharmacy
SRTM University, Nanded