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Synthesis and Anti-Microbial Activity of Novel Substituted Chalcone Derivatives

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Abstract:

Some chalcones derivatives show antimicrobial, anti-fungal and insecticidal activity. All solvents were redistilled before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. All the synthesized compounds were purified by recrystallization. Melting points were determined by using open capillary method. Fine powdered zinc chloride (8.25) was dissolved in glacial acetic acid (18ml) by heating on sand bath then dry resorcinol (appx.5.5 gm) was added with continuous stirring to the mixture at 140^{o}C. The solution was heated until the solution just begins boil and kept it for 20 min at 150^{o}C temperatures. All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by Cup plate Method. Broth double dilution method was use for screening Antifungal activity. Ketoconazole used as standard, was dissolved in sterile DMSO. DMF, DMSO were also test as control. All the compounds C1-C6 were evaluated for antimicrobial activity against gram positive bacteria, *Staphylococcus aureus*, gram negative bacteria *Escherichia coli*, and fungi *Candida albicans*. compounds C3 and C4 have near to activity significant with standard compound amoxiciliine and Compound C1, C3, C5 shown growth of fungus in petridish other compounds shown no growth. According to docking studies compound C1 shown as maximum negative contribution -8.03006 and C6 shown less contribution -7.71101.

Keywords: chalcones, *Staphylococcus aureus, Escherichia coli, Candida albicans,* antimicrobial, 2K35, Docking.

Introduction:

A microorganism or microbe is an organism that is microscopic (usually too small to be seen by the naked human eye). Microorganisms are very diverse; they include bacteria, fungi, archaea, and protists; microscopic plants (green algae) and animals such as plankton the planarian and the amoeba. Robert Koch (1843-1910) defined the principles of infectious diseases, namely, that a microbe causing disease in one animal when transferred to another animal produces the same disease (Koch's postulate). Koch also identified *Mycobacterium tuberculosis* and *Vibrio cholera* [1-2].

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Broadly, all microbes that can grow in the absence of oxygen are called anaerobic bacteria. They include clostridia, a spore-bearing anaerobe, and Gram-negative bacteria like bacteroides and fusobacteria. Microbes that require oxygen to grow are called aerobic bacteria. Those that grow in the presence of some oxygen (but not a lot) are called microaerophilic; they include *E. coli*, *neisseria*, *haemophilus* and others. Gram (1853-1938) classified all bacteria by the colour they take with the Gram's stain. Those that take a blue colour (Gentian violet) are called Gram-positive, and those that take the red stain (eosin) are called Gram-negative [3-4]

Some chalcones derivatives show antimicrobial, anti-fungal and insecticidal activity. Some of chalcones derivatives are isolated with the anticanceractivity [5, 6]. Moreover, chalcones derivatives are also regarded as a new class of effective anti-TB candidates owing to their potential anti-TB activities.

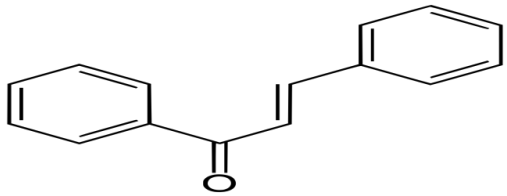

Figure 1: structure of chalcone

Materials and methods:

All chemicals were provided from our college. All solvents were redistilled before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. All the synthesized compounds were purified by recrystallization.Melting points were determined by using open capillary method.Fourier Transform Infra-Red spectra (FTIR) were recorded on Shimadzu FTIR-8400S spectrophotometer using potassium bromide pellets and sodium chloride cell. Nuclear Magnetic Resonance spectra (^{1}H-NMR) were recorded on JEOL-300 MHz spectrophotometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra were recorded on HEWLETT 180017, PACKARD GCD System mass spectrophotometer using electron ionization detector and anticonvulsant activity checked by electroconvulsometer.

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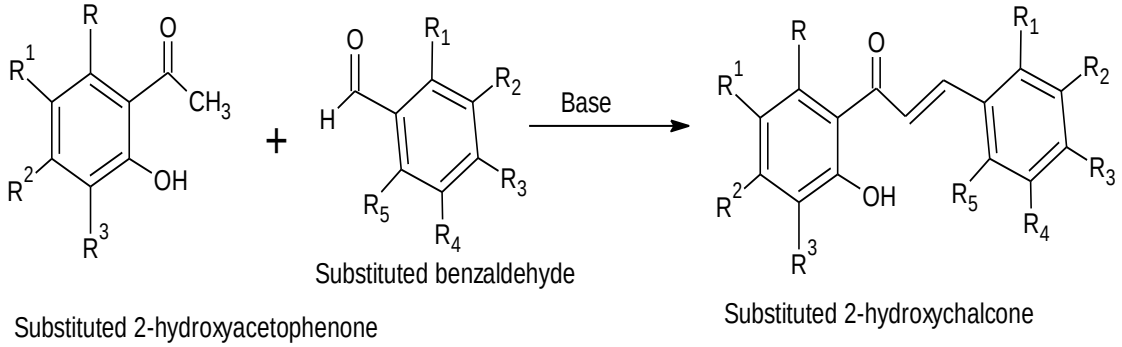
Synthetic scheme:



Methods:

Synthesis of 2,4-dihydroxyacetophenone:

Fine powdered zinc chloride (8.25) was dissolved in glacial acetic acid (18ml) by heating on sand bath then dry resorcinol (appx.5.5 gm) was added with continuous stirring to the mixture at 140^{o}C. The solution was heated until the solution just begins boil and kept it for 20 min at 150^{o}C temperatures. Dilute HCl was added to mixture and cooled at the temperature of 5^{o}C then filter & washed with dil. Hydrochloric acid (1:3) and crystallized from hot water containing a littleHCl [7].

Table 1: Physicochemical characterization of starting materials

Sr. No.	Compound	Mol. Formula	Mol. Weight	M.P./ B.P.
1	2-Hydroxyacetophenone	$C_8H_8O_2$	136.14	213 °C
2	2,4-Dihydroxyacetophenone	$C_8H_8O_3$	152.14	143°C
3	Salicylaldehyde	$C_7H_6O_2$	122.12	-
4	4-Methylbenzaldehyde	$C_8H_8O_2$	120.15	-
5	4-Isopropylbenzaldehyde	$C_{10}H_{12}O$	148.20	235 °C

General procedure for synthesis of chalcone derivatives:

2.5 mmol of the benzaldehyde derivative and 2.5 mmol of the acetophenone derivative were measured accurately and placed in a mortar. To this added 3 pellets of NaOH (7.5 mmole). Mixture was ground for about 5–10 min. The mixture was turned yellow and pasty after a few times of grinding. Grinding was continued until the mixture turn into a solid mass and the solid became powdery. 10 mL of water added to the mortar at the last minute of the

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grinding period. Product was mixed properly with the water using the spatula solid product was dislodged from the mortar's wall andfiltered [8].

Anti-bacterial activity:

All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by Cup plate Method [9]. Antibacterial activities were tested on nutrient medium against, *Staphylococcus aureus* and *Escherchia coli* which are representative types of gram positive and gram negative organisms respectively. The antibacterial activities of the compounds were assessed by disc-diffusion method.

Preparation of nutrient agar media:

Media Composition and Procedure:

The nutrient agar media were prepared by using the following ingredients.

1) Peptone (Bacteriological) 20 gm
2) Beef extract (Bacteriological) 5 gm
3) Sodium chloride 5 gm
4) Agar 20 gm
5) Distilled water up to 1000 ml

Weighed quantities of peptone and beef extract were dissolved in distilled water by gentle warming and then specified amount of agar were dissolve by heating on water bath. Then the pH of the solution was adjusted to7.2 to7.4 by adding the sodium chloride and the volume of the final solution was maked up to 1000 ml with distilled water. Then it was transferred into a suitable container, plugged with non-adsorbent cotton and the media were sterilized in autoclave at 121^{o}C for 20 minutes at 15 lbs pressure [10].

Preparation of test solutions:

10 mg of the compound was dissolved in 10 ml of DMF. From this 1 ml of solution was taken and diluted up to 10 ml with DMF. Now the concentration of the test solution was 100 μg/ml. From the stock solution 1ml of solution was taken and diluted with 1ml of DMF now the concentration was 50μg/ml [11].

Preparation of Standard Antibiotic Solution:

Amoxicillin was used as standard antibiotic for comparison and solution was prepared by using sterile water, as it is water-soluble. The solution was diluted by using sterile water so that the concentrations of the solution were 100 μg/ml and 50 μg/ml [12].

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Preparation of Discs:

Discs of 6-7 mm in diameter were punch from No. 1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 140^0 C for 60 minutes. Then standard and test solutions were added to each disc and discs were air-dried.

Method of Testing:

The sterilize media was cooled to 45^oC with gentle shaking to bring about uniform cooling and then inoculate with 18-24 hrs old culture under aseptic conditions, mix well by gentle shaking. This was poured in to sterile Petri dishes (properly labeled) and allowed the medium to set. After solidification all the Petri dishes were transfer to laminar flow unit. Then the discs, which were previously prepared were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept as it is for one-hour diffusion at room temperature and then for incubation at 37^0 C for 24 hours in an incubator [13].

The diameter of inhibition after 24 hours was measured as the zone of inhibition in milli meters.

Anti-fungal activity:

Broth double dilution method was use for screening Antifungal activity as described below.

Broth double dilution method:

The broth double dilution method was used to evaluate the minimal inhibitory concentration (MIC) of the test compounds. The classical method yields accurate, precise and quantitative results for the amount of antimicrobial agent that is needed to inhibit growth of micro organisms. Determination of minimum inhibitory concentration (MIC) by broth double dilution method:-

A. MIC of the entire test (synthesized compounds) was determined using the said method.
B. following controls was also incorporated :-
    - Drug control- Ketoconazole as reference standard was used.
    - Solvent control – DMF and DMSO was used as solvent controls.
C. Sabourauds Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) was used as nutrient medium for growth of microorganism and MIC determination for *C. albicans.*
D. All the compounds were dissolved in DMF and standard dissolve in DMSO.
E. All the compounds were serially diluted.
F. The test compounds and standard drug solution was diluted using Sabourauds

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Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) so as to get required concentration [13-17].

G. To serially diluted solution, test organisms were added using saline solutions or broth.
H. Then the plates were incubated at 37^0 C for 48 hrs.
I. The growth of Fungus in the test compound solutions and control drug were see after incubation.

Methods Used For Screening:

In screening the test compounds was dissolved in DMF, so as to give 8000μg/ml which was then serially diluted [18]. Ketoconazole used as standard, was dissolved in sterile DMSO. DMF, DMSO were also test as control.

RESULTS:

Table 3: Physical characteristics of substituted chalcone derivatives

Property	**Results**					
Comp. Code	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**
Meltingpoint	89^0C	92^0C	160^0C	190^0C	150^0C	150^0C
Yield	80.4 %	91%	94.20%	90.03%	88.8%	88.8%
Rf value	0.69	0.8	0.73	0.59	0.69	0.69
Molecular formula	$C_{15}H_{12}O_3$	$C_{18}H_{18}O_2$	$C_{16}H_{14}O_2$	$C_{15}H_{12}O_4$	$C_{18}H_{18}O_3$	$C_{16}H_{14}O_3$
Molecular weight	240	266	238	256	282	254

Screening of anti-microbial activity:

Table no. 4: Zone of inhibition of synthesized compounds

Sr.No	Compound code	Concentration μg/ml	*E.coli*	*S.Aureus*
1	C1	50	11	10
2		100	12	11
3	C2	50	11	9
4		100	13	11
5	C3	50	9	10
6		100	11	12
7	C4	50	10	11
8		100	12	14

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9	C5	50	12	13
10		100	14	14
11	C6	50	10	9
12		100	12	10
13	Amoxicilline	50	14	13
14		100	15	14

Note*: Range of Zone of inhibition of synthesized compounds:* ***** 6-8 mm poor activity, 9-11 mm moderate activity, 12-15 above good.

Strain of *E.Coli* Strain of *S. Aureus* **Strain of *E.Coli* Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

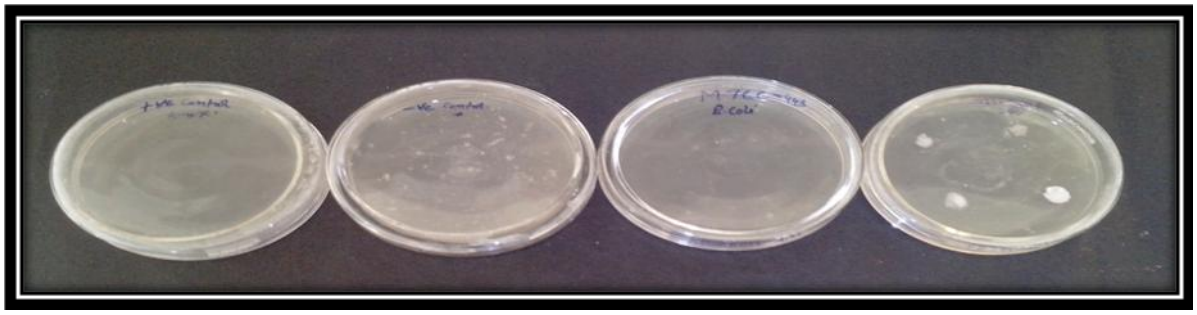

Fig 2: Zone of inhibition of comp C1

Strain of *E. Coli* Strain of *S. Aureus* **Strain of *E. Coli* Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

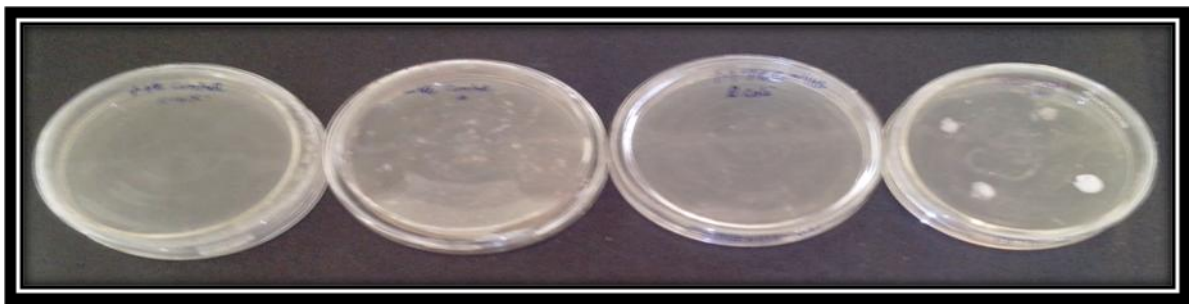

Fig 3: Zone of inhibition of comp C2

Strain of *E.Coli* Strain of *S. Aureus* **Strain of *E.Coli* Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

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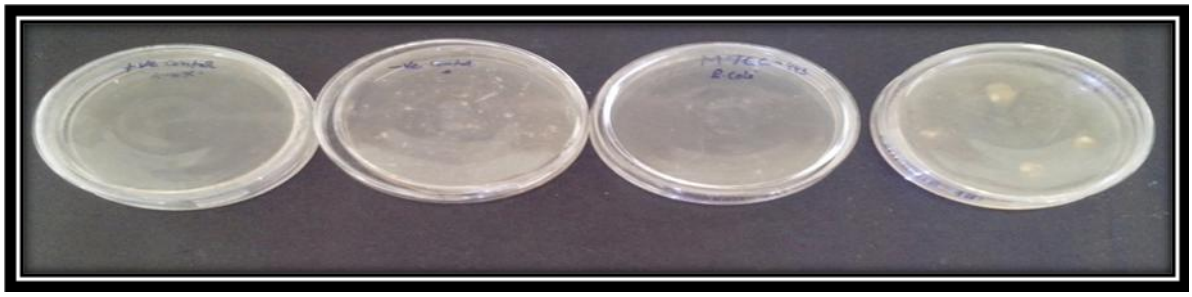

Fig 4: Zone of inhibition of comp C3

Strain of *E.Coli* **Strain of *S. Aureus*** **Strain of *E.Coli*** **Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

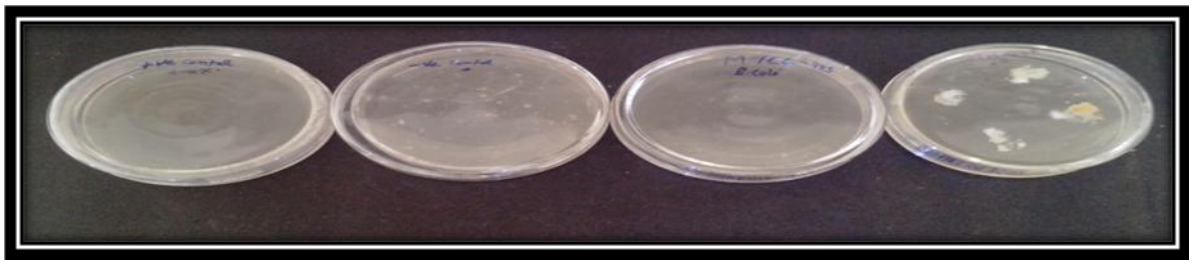

Fig 5: Zone of inhibition of comp C4

Strain of *E. Coli* **Strain of *S. Aureus*** **Strain of *E. Coli*** **Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

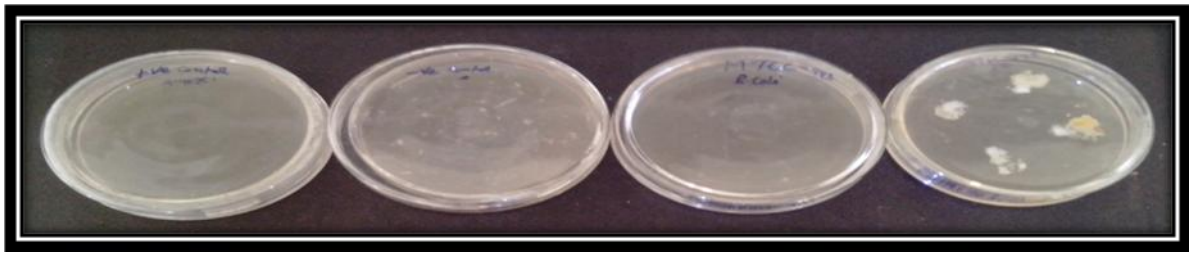

Fig 6: Zone of inhibition of comp C5

Strain of *E. Coli* **Strain of *S. Aureus*** **Strain of *E. Coli*** **Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

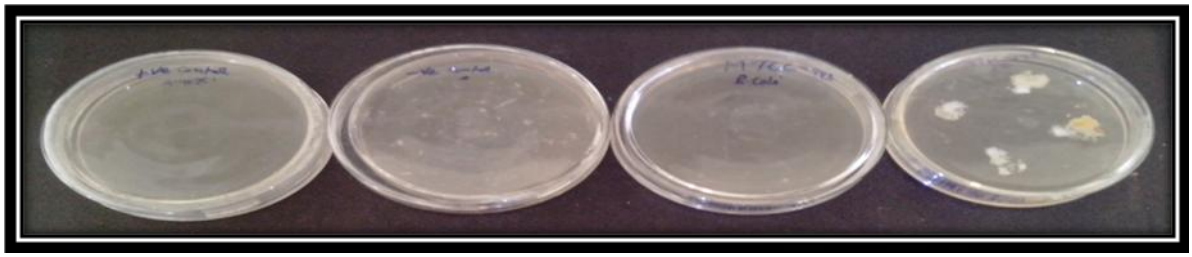

Fig 7: Zone of inhibition of comp C6

Strain of *E. Coli* **Strain of *S. Aureus*** **Strain of *E. Coli*** **Strain of *S. Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

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Fig 8: Zone of inhibition of Amoxicillin (Standard)

Screening of anti-fungal activity:

Table no. 4 MIC of synthesized compounds

Sr.No	Compound	Concentration µg/ml	*Candida albicans*
1	C1	250	-
2		500	-
3	C2	250	+
4		500	-
5	C3	250	-
6		500	-
7	C4	250	+
8		500	-
9	C5	250	+
10		500	-
11	C6	250	-
12		500	+
13	ketaconazole	250	-
14		500	-

(-) No growth, (+) Growth, (Keto) Ketoconazole

Strain of *candida albicans*

CONC. 250µg/ml**&**500µg/ml

Fig 9: Zone of inhibition of comp C1

Strain of *candida albicans*

CONC. 250µg/ml**&**500µg/ml

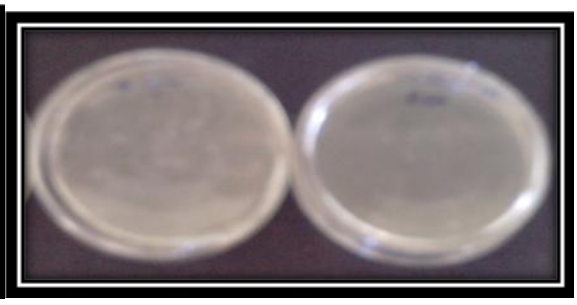

Fig 10: Zone of inhibition of comp C2

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Fig 11: Zone of inhibition of comp C3
Strain of *candida albicans*
CONC. 250µg/ml**&**500µg/ml

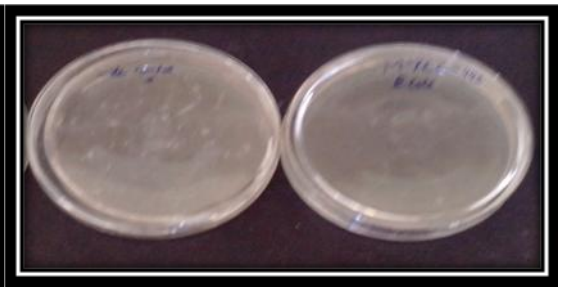

Fig 12: Zone of inhibition of comp C4
Strain of *candida albicans*
CONC. 250µg/ml**&**500µg/ml

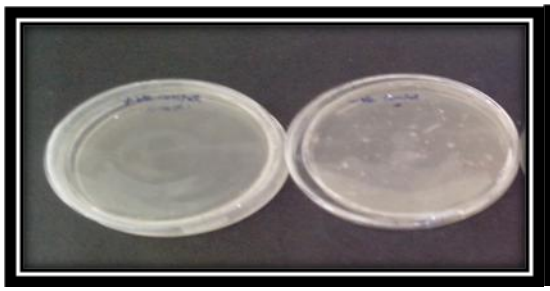

Fig 13: Zone of inhibition of comp C5

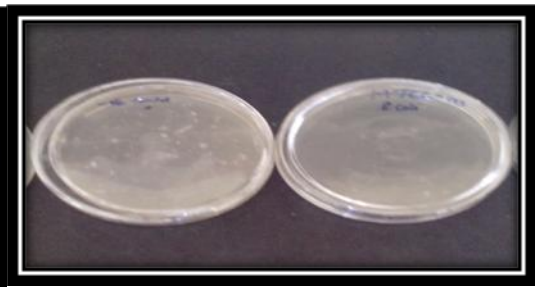

Fig 14: Zone of inhibition of Ketoconazole (standard)

DOCKING Analysis:

Docking analysis is important to study the ligand-enzyme interaction. For Docking analysis all compounds were selected to evaluated anticancer activity as series under consideration. Docking was done using to PDB code 2K35, using Maestro 9.0. The molecular docking tool, GLIDEwas used for ligand docking studies into the EGFR-TK pocket. All designed compounds have good docking score on the PDB as shown in table.

PDB Description: 2K35

The crystal structure of the kinase domain from the epidermal growth factor receptor (EGFRK) including forty amino acids from the carboxyl-terminal tail has been determined to 2.6-A resolution. The EGFR family members are distinguished from all other known receptor tyrosine kinases in possessing constitutive kinase activity without a phosphorylation event within their kinase domains. Despite its lack of phosphorylation, we find that the EGFRK activation loop adopts a conformation similar to that of the phosphorylated active form of the kinase domain from the insulin receptor. Surprisingly, key residues of a putative dimerization motif lying between the EGFRK domain and carboxyl-terminal substrate docking sites are

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found in close contact with the kinase domain. Significant intermolecular contacts involving the carboxyl-terminal tail are discussed with respect to receptor oligomerization.

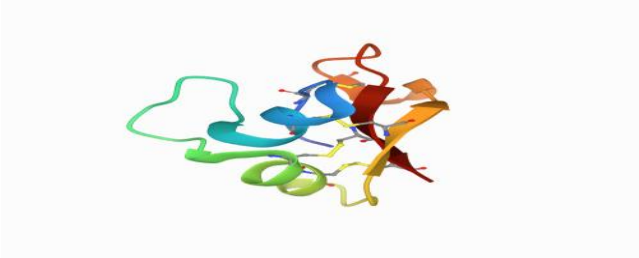

Fig 15: PDB View 2K35

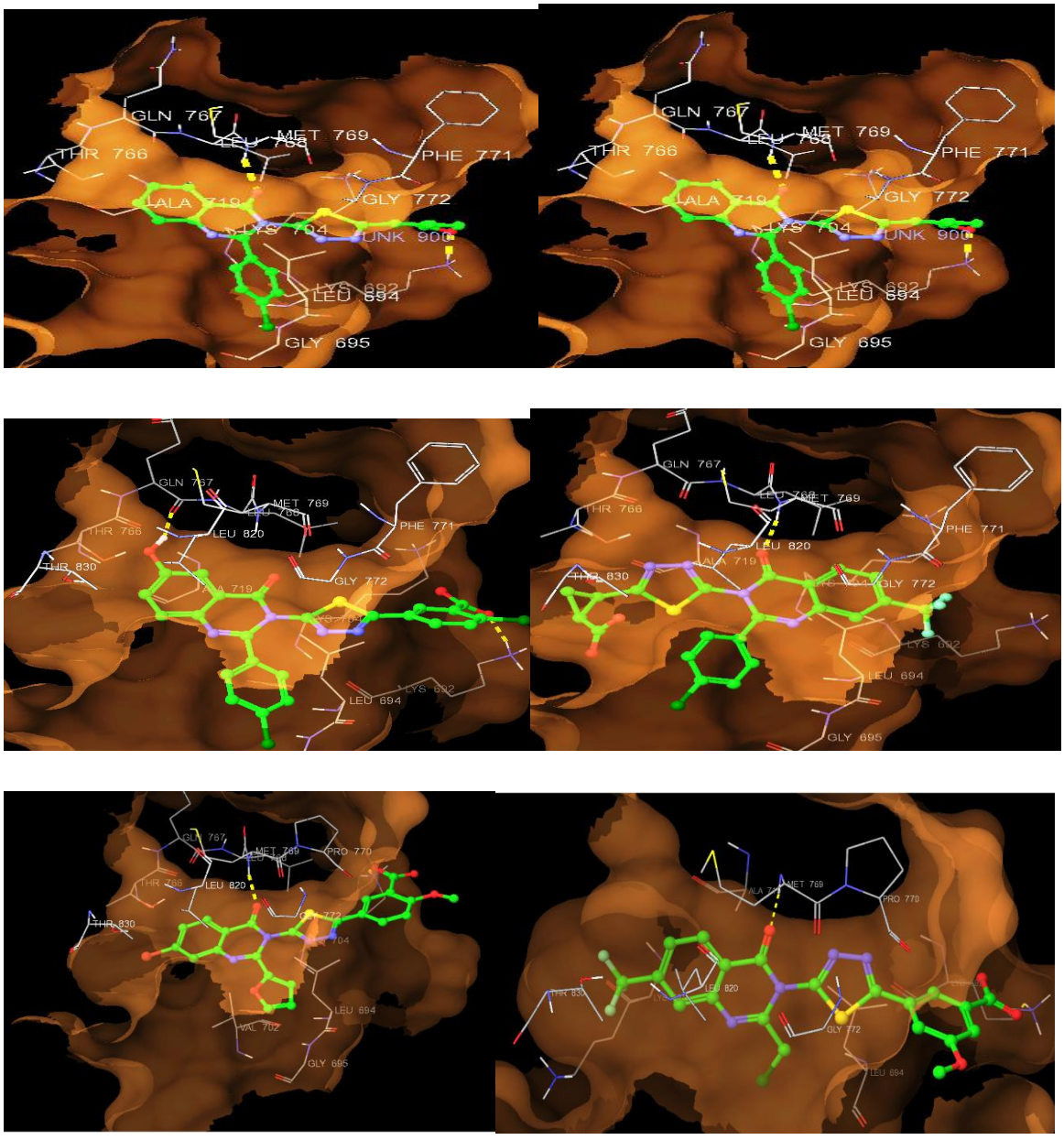

Fig 15: Docking pose of synthesized compounds C1-C6

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Title	RMSD	Docking score	Glide evdw	Glide emodel	Glide energy	Glide einternal	DonorHB	AcceptHB	QPlogPo/w	QPlogS	QPlogHERG	QPsPCaco	QPPMDCK	QPlogKhsa	Percent Human Oral Absorption	Rule of Five
C1	0.028859	-8.03006	-39.9366	-82.9757	-53.7226	8.343221	2	9.5	2.211	-5.292	-4.123	10.832	13.242	-0.221	58.413	0
C2	0.009363	-7.81076	-37.1224	-75.1048	-50.252	3.499143	2	8.75	3.771	-6.706	-4.954	21.093	33.858	0.25	59.768	1
C3	0.008341	-7.80312	-41.4639	-78.679	-51.6437	5.531269	1	8.75	4.541	-7.19	-5.12	59.252	190.55	0.295	72.303	1
C4	0.011714	-7.79771	-37.8445	-77.5613	-50.3613	4.783609	2	8.75	3.895	-6.914	-5.03	19.237	64.199	0.216	59.778	1
C5	0.010529	-7.7112	-43.1603	-80.5693	-52.8868	6.257923	1	8.75	5.263	-8.252	-5.182	57.141	441.692	0.504	63.291	2
C6	0.013159	-7.71107	-44.58	-81.6336	-54.0733	3.10326	1	8	5.153	-7.965	-5.133	60.794	583.095	0.473	63.126	2

Conclusion:

All the compounds C1-C6 were evaluated for antimicrobial activity against gram positive bacteria, *Staphylococcus aureus*, gram negative bacteria *Escherichia coli,* and fungi *Candida albicans*. The results suggested that in the compound C3 presence of electron withdrawing group –CHO, and compound C4 having methyl group $–CH_3$ is important for the antibacterial activity. All three compounds C3 and C4 have near to activity significant with standard compound amoxiciliine, other synthesized compounds were found to be less active than amoxicilline as standard drugs. Compound C1, C3, C5 shown growth of fungus in petridish, other compounds having shown no growth so they possess a capacity of antifungal activity. According to docking studies compound C1 shown as maximum negative contribution -8.03006 and C6 shown less contribution -7.71101, so binding affinity of ligand with protein was highest found in Compound C1.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable.

Competing intrests

Not applicable.

Funding

None.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Author contribution

All the authors have equally contributed to this manuscript.

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