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BIOLIFE ORIGINAL ARTICLE

Docking study of Novel peptide Derivatives of 2- Hydroxy Quinoline-4-Carboxylic Acid as Potential Anti Tuberculosis and Anti-microbial agents

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ABSTRACT

Mycobacterium tuberculosis is the causative agent of the disease tuberculosis. The latest world health organisation survey estimates that close to 2 million deaths occur every year and over 50% of deaths among HIV-infected patients results from co-infection with Mycobacterium Tuberculosis. TB can be treated and even cured with chemotherapy but the current treatment is lengthy and the strain of Mycobacterium Tuberculosis have developed not only multidrug resistant (MDR), but have become extensively drug resistant (XDR). Hence, there is an immense need to develop new TB drugs with rapid bactericidal and potent sterilized activity to enable permeant cure to be achieved in a shorter period, the objective of new drug devolvement is to shorten the duration and lower dose in frequency and active against MDR and XDR to wards to TB causative strain. It makes the discovery of new molecular scaffolds and even necessitates the re-engineering and repositioning of some old drug families. Quinoline is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities by the large number of drugs in the market. The important pharmacological applications and essential quinoline ring system has sparked more interest in preparing new quinoline peptide conjugates. Hence The diversity of chemical structures of the quinoline nucleus and their useful biological activities made these compounds attractive targets in synthetic organic chemistry. Hence in view of the remarkable importance from pharmacological, industrial and the synthetic point of view, Docking Study of (new chemical entities (NCEs) structures) five peptide derivatives of 2-Hydroxy Quinoline-4-Carboxylic acid was done at the active site of InhA protein of MTb, DNA gyrase B protein of Staphylococcus aureus, (Gram positive bacterium) and DHFR of Candida Albicans protein.Key words: Environment attitude, teaching practices, secondary school teachers.

Keywords: Docking Study, Candida Albicans protein, 2-Hydroxy Quinoline -4-Carboxylic acid, Peptide conjugates. Anti-bacterial activity, Anti-fungal activity.

INTRODUCTION

The foundation for life is defined by the functions of biopolymers, such as proteins and nucleic acids. The nucleic acids carry the hereditary information, while proteins are responsible for an extensive range of functions, such as catalysis, tight and specific binding, and others which are very essential to life. The peptides and proteins are generated from 20 proteinogenic amino acids, during the ribosomal biosynthesis. Peptides open up new perspectives in drug design by providing an entire range of highly selective and nontoxic pharmaceuticals. With growing applications of their synthesis and bioactivity, considerable attention has been focused on the research of peptide-based derivatives.

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Kandukuri Usha Rani (2021). Docking study of Novel peptide Derivatives of 2- Hydroxy Quinoline -4-Carboxylic Acid as Potential Anti Tuberculosis and Anti-microbial agents. *Biolife*. 9(3), 7-16.
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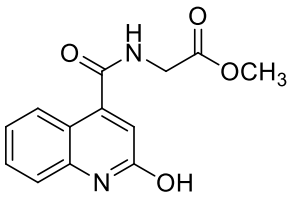
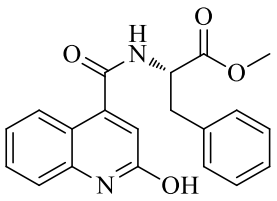
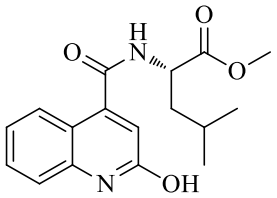
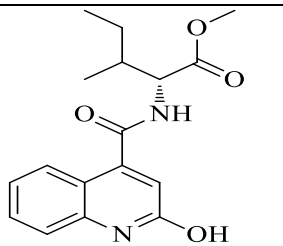
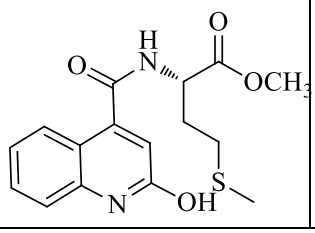
Table-1. Chem Draw structures and IUPAC Nomenclatures

Sl.No	Compound Name	Chemical Structure	IUPAC Nomenclatures
1	Cpd 1		Methyl 2-(2-hydroxyquinoline-4-carboxamido)acetate Chemical Formula: $C_{13}H_{12}N_2O_4$ Exact Mass: 260.08 Molecular Weight: 260.25
2	Cpd 2		(S)-methyl 2-(2-hydroxyquinoline-4-carboxamido) -3-phenylpropanoate Chemical Formula: C20H18N2O4 Exact Mass: 350.13 Molecular Weight: 350.37
3	Cpd 3		(S)-methyl 2-(2-hydroxyquinoline-4-carboxamido) -4-methylpentanoate Chemical Formula: C17H20N2O4 Exact Mass: 316.14 Molecular Weight: 316.35
4	Cpd 4		(2R)-methyl 2-(2-hydroxyquinoline-4-carboxamido) 3-methylpentanoate Chemical Formula: $C_{17}H_{20}N_2O_4$ Exact Mass:316.14 Molecular Weight: 316.35
5	Cpd 5		(S)-methyl 2-(2-hydroxyquinoline-4-carboxamido) -4-(methylthio)butanoate Chemical Formula: $C_{16}H_{18}N_2O_4S$ Exact Mass: 334.10 Molecular Weight: 334.39

Recently, bioactive peptides have received close scientific attention for their broad scope of bioactivities, mainly including antioxidation, antihypertensive, anticancer, and antimicrobial properties. Peptides open up new perspectives in drug design by providing an entire range of highly selective and nontoxic pharmaceuticals. Over 70% of bacterial infections are resistant to one or more of the antibiotics that are generally used to eradicate the infection2. Hence growing applications of Peptides synthesis and bioactivity, considerable attention has been focused on the research of peptide-based derivatives3.
The interaction of peptides and nano particles with DNA constitutes a significant area of research which has attracted considerable attention from biochemists: studies have shown that they are related to the development of new DNA reagents for biotechnology and medicine4,5, 6.

Quinoline is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities such as anti-inflammatory7, antimalarial8, antimicrobial9, anticonvulsant10, antineoplastic11, vasorelaxing12, proliferative13 and platelet derived growth factor receptor tyrosine kinase inhibiting agents14 which can be well illustrated by the large number of drugs in the market.
The important pharmacological applications and essential quinoline ring system has sparked more interest in preparing new quinoline peptide conjugates. Hence The diversity of chemical structures of the quinoline nucleus and their useful biological activities made these compounds attractive targets in synthetic organic chemistry.

Hence In view of the remarkable importance from pharmacological, industrial, and synthetic points of view, we have designed following new peptide derivatives (Cpd 1 to Cpd 5) and carried out docking study (Molecular Modelling programme) using Gold version 5.1

METHODOLOGY

Ligand Preparation

Five peptide derivatives of 2-Hydroxy Quinoline-4-Carboxylic acid (Cpd 1–Cpd 5) were designed using ChemDraw and their IUPAC names, molecular weights, and exact masses were determined. The ligands were optimized for physicochemical properties and drug-likeness using **Lipinski's Rule of Five** to ensure suitability for biological evaluation.

Protein Selection

Three target proteins were chosen based on their relevance to tuberculosis and antimicrobial activity:

- InhA protein of *Mycobacterium tuberculosis* (PDB ID: 2CIG, resolution 1.9 Å)
- DNA gyrase B protein of *Staphylococcus aureus* (PDB ID: 3G75, resolution 2.3 Å)
- Dihydrofolate reductase (DHFR) of *Candida albicans* (PDB ID: IM78, resolution 1.7 Å)

Crystal structures were retrieved from the Protein Data Bank and prepared for docking by removing water molecules, adding hydrogen atoms, and optimizing side chains.

Docking Procedure

Molecular docking was performed using GOLD version 5.1. Each ligand was docked into the active site of the selected proteins. The docking run generated ten poses per compound, and the best pose was selected based on the GOLD fitness score, which integrates hydrogen bonding, van der Waals interactions, intramolecular hydrophobic interactions, and torsional strain.

Docking study of the new five peptide derivatives of 2-Hydroxy Quinoline-4-Carboxylic acid (Cpd 1 to Cpd 5) was done at the active site of InhA protein of MTb, DNA gyrase B protein of Staphylococcus aureus, (Gram positive bacterium) and DHFR of Candida Albicans protein

Scoring Function

The GOLD fitness function was applied:

$$Fitness = S(hb\_ext) + 1.375 \times S(vdw\_ext) + S(hb\_int) + S(int)$$

where *S(hb_ext)* represents protein–ligand hydrogen bonding, *S(vdw_ext)* van der Waals interactions, *S(hb_int)* intramolecular hydrophobic interactions, and *S(int)* intramolecular strain.

Interaction Analysis

The binding modes of each compound were visualized to identify hydrogen bonds, hydrophobic contacts, and π–π interactions with active site residues. Key amino acids involved in stabilization were recorded, and comparative docking scores were tabulated for each protein target.

BIOLOGICAL EVALUATION

Antimicrobial Activity

Using zone of inhibition method, antibacterial and antifungal activities are investigated.

Zone of Inhibition Method:

Well plate method was followed for both antibacterial and antifungal activities for measuring the zone of inhibition by compounds against pathogenic microorganisms. Such as two gram positive Staphylococcus aureu (MTCC3160) s, Bacillus subtilis (MTCC736), threegram negative Klebsiella pneumonia (MTCC 39), Salmonella typhi (98), Escherichia coli (40) and fungal Candida albicans (MTCC1637), strains were used for determination of antimicrobial activity. Initially all bacterial strains were grown in nutrient broth for 24 h at 37 °C and fungal strains were grown in Czapekdox broth. Allthe synthesized compounds were diluted with DMSO to get final concentration of 1mg /ml. Medium and the Petri plates were initially sterilized at 121°C for 15 min. Under sterilized environment, the agar medium poured into Petri plates. After solidification, 50µl of test inoculum was spread on plates using sterilized spreader. Wells were made with sterile cork borer and in each well exactly 100 µl of sample were loaded. Control and standard were also placed in separate wells in each plate. The plates were first incubated for 20-30 min at 4 °C to allow the compounds diffuse into the agar, and then subsequently incubated for 24h at 37°C for antibacterial and 48 h for antifungal activity. Zone of inhibition were expressed in mm using calibrated scale. Experiment was performed in triplicate and average values were reported to minimize the deviations.

. RESULTS

Molecular docking studies of synthesized compounds 1 to 5 along with the protein receptors was carried out to find the binding affinities and key interactions between protein (InhA protein of MTb,/DNA gyrase B protein of Staphylococcus aureus, (Gram positive bacterium) /and DHFR of Candida Albicans) and Synthetic derivatives using GOLD. Two important parameters have been considered for selecting potential compounds among the given input: (i) prediction of binding energy of the best docked pose using scores calculated by GOLD scoring function and (ii) Hydrogen bond details of the top-ranked pose. The docking run generated 10 different poses for each of the compound and the corresponding GOLD fitness scores were generated. Higher the fitness score of the ligand pose was better because it was calculated

Figure-1. The three proteins of DNA gyrase B protein of Staphylococcus aureus, (Gram positive bacterium) is presented here

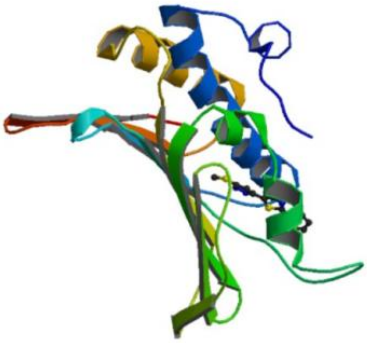
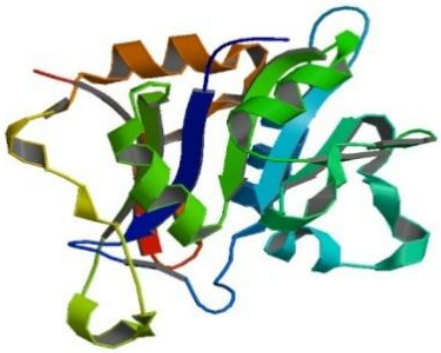
		
Fig.:1a Crystal structure of MTB InhA complexed with acyclic 4R isomer of Inh-NADP a derivative of the prodrug isoniazid (PDB ID: 2CIG with a resolution of 1.9 Å).	Fig.:1b Crystal structure of *Staphylococcus aureus* DNA Gyrase B co-complexed with thiaozle inhibitor (3G75). (PDB ID: 3G75 with a resolution of 2.3 Å)	Fig.:1c the crystal structure of Candida albicans dihydrofolate reductase {DHFR) complexed with dihydro-nicotinamide-adenine-dinucleotide phosphate (nadph) and 5-chloryl-2,4,6-quinazolinetriamine (gw1225) PDBID IM78 with a resolution of 1.7 Å)

Table-2. Docking scores of the compounds with the MTB InhA (PDB ID: 2CIG with a resolution of 1.9 Å)

Ligand name	S(hb_ext)	S(vdw_ext)	S (hb int)	S(int)	Fitness (Docking score)
1	4.49	44.79	0.00	-11.04	38.77
2	5.07	29.5	0.00	-6.86	60.05
3	1.44	46.13	0.00	-4.83	54.67
4	1.3	42.26	0.00	-4.32	55.04
5	0.74	44.66	0.00	-7.48	55.09

based on the negative of the sum of the component energy terms. The fitness function was first optimized for the prediction of ligand binding position. The well orientated ligand poses have lowest energy with average Gold fitness scores were enumerated. So, the above pre-validated analysis was used to sort out the retrieved hit molecules and then those are further validated by using the visualization method to find the suitable binding mode of the inhibitors based on the critical interactions with the active site residues reported as GOLD fitness score.
Gold Score is similar to molecular mechanics like function and has been optimized for the calculation of binding positions of ligand. It considers four terms:

Fitness = S(hb ext) + 1.3750 × S(vdw ext) + S(hb int) + 1.000 × S(int)

and S(int) = S(vdw ext) + S(tors)

Where Shb_ext is the protein-ligand hydrogen bonding and Svdw_ext are the van der waals interactions between protein and ligand. Shb_int are the intramolecular hydrophobic interactions whereas S(int) is the contribution due to intramolecular strain in the ligand Svdw_int and S(tors) the torsional strain.

The Summary of docking information of the top ranked poses was tabulated in respective tables.

DOCKING STUDY OF PEPTIDE DERIVATIVES (Compound 1 to Compound 5) WITH INHA PROTEIN OF MTB (PDB ID: 2CIG)

We took Ligand –based CADD to identify the potent ligands that binds to the active site of the mycobacterial InhA protein domain. Docking study of these compounds was done at the active site of InhA to understand their binding mode with the aim of getting insights into the structural basis of activity for MTB InhA inhibition study. InhA, the enoyl acyl carrier protein reductase of mycobacterium tuberculosis (MTB) is an attractive target for developing novel anti tubercular agents. As a template

Figure-1. The binding modes of the compounds 1 to 5 in the active site of MTB InhA (PDB ID: 2CIG with a resolution of 1.9 Å)

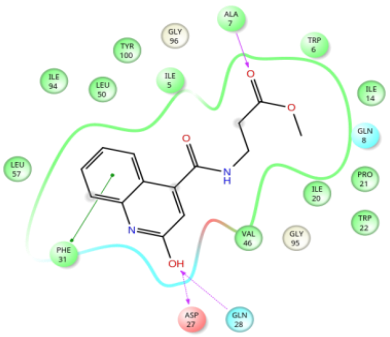


Fig 1d - Compound **1**
Docking score 38.77

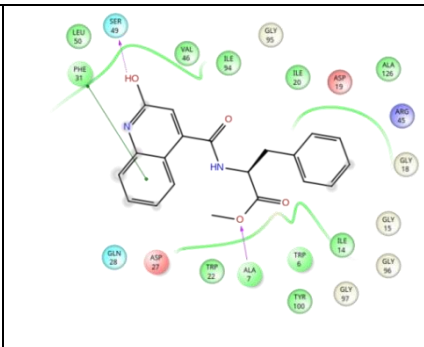


Fig 1e- Compound 2
Docking score 60.05

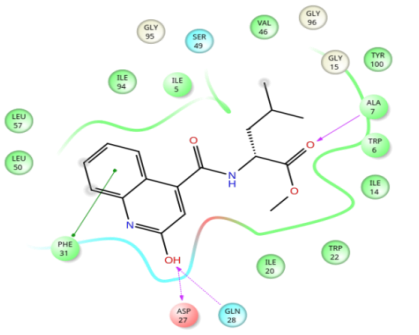


Fig1 f- Compound 3
Docking score 54.67

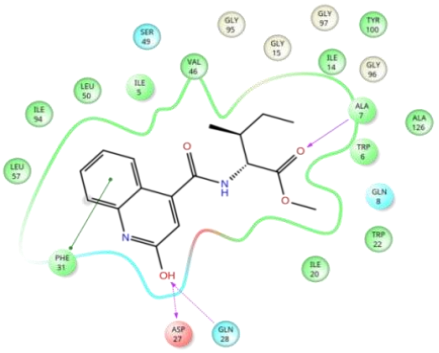


Fig 1g- Compound 4
Docking score 55.04

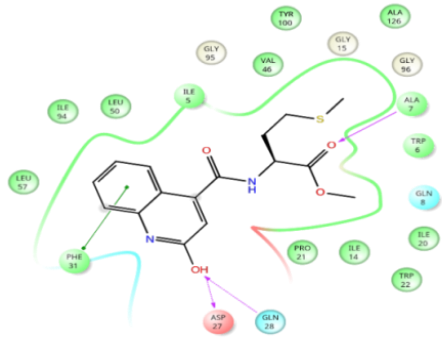


Fig1 h- Compound **5**
Docking score 55.09

we used the crystal structure of MTB InhA complexed with acyclic 4R isomer of Inh-NADP a derivative of the prodrug isoniazid (PDB ID: 2CIG with a resolution of 1.9 Å) was downloaded and docking was carried out using GOLD, version 5.1

These ligands are constructed in order to enrich these ligands with certain desirable physicochemical properties suitable for the target interest. Drug likeness is commonly evaluated using Lipinski's rule of five.

COMPOUND 1: The binding orientation of compound 1 within the InhA binding pocket is represented in the FIG 1d. The predicted bound conformation of the compound showed that the carbonyl oxygen atom of ester group (attached to NH group through -CH2-CH2-) formed a hydrogen bond with side chain of ALA7.The OH group attaché to the quinoline ring formed hydrogen bonding interaction with the ASP 27 and GLN 28. And the compound further stabilized by the strong pi-pi interaction with PHE 31 amino acid residue. This compound was fitted in the hydrophobic pocket within the vicinity of ALA7, TRP6, TRP22, ILE 14, ILE5, ILE20, PRO21, LEU50, VAL46, respectively. Thus, the compound was fit into the active site cavity of protein with a docking score of 38.77.

COMPOUND 2: The binding orientation of compound 2 within the InhA binding pocket is represented in the FIG 1e. The predicted bound conformation of the compound showed that the carbonyl oxygen atom of ester group (attached to NH group through -CH2-CH2-) chain ,formed a hydrogen bond with side chain of ALA7.The OH group attaché to the quinoline ring formed hydrogen bonding interaction with the SER49.Andthe compound further stabilized by the strong pi -pi interaction with PHE 31 amino acid residue .This compound was fitted in the hydrophobic pocket within the vicinity of ALA7, TRP6, TRP22, ILE 14, ILE94, PHE31, LEU50, VAL46 respectively.Thus the compound was fit into the active site cavity of protein with a docking score of 60.05.

COMPOUND 3: In Fig 1f Binding orientation of compound 3 is represented with a docking score of 54.67. A closer analysis revealed that the hydrogen bonding interaction of carbonyl oxygen atom of ester group (attached to NH group through CH2-CH2 chain) with the side chain of ALA 7. The OH group attached to the quinoline ring formed two hydrogen bonding interactions with ASP27and GLN 28. Compound makes the strong pi-pi interaction with PHE 31 amino acid residue. This compound was fitted in the hydrophobic pocket within the vicinity of ALA7, TRP22, TRP100, ILE5, ILE14, ILE20, ILE94, EU50, LEU57, VAL46 respectively.

Table-2. Fitness Score. Docking Results Peptide Derivatives with Staphylococcus aureus Gyrase B (3G75) Protein

Compound No	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)	Fitness Score
Cpd 1	11.69	24.89	0.00	-10.67	35.25
Cpd 2	8.00	35	0.00	-7.76	45.93
Cpd 3	12.70	26.46	0.00	-9.82	39.27
Cpd 4	11.18	26.85	0.00	-15.54	32.56
Cpd 5	7.00	30.23	0.00	-6.76	44.93

Table-3. Ligand Interactions Data of PEPTIDE DERIVATIVES Docking results

S.No	Name	Interacting amino acids	Interacting atoms	H-distance
1	Cpd 1	Arg84, Asp81, Ser55 Ile86, Ileu175,Glu58	Arg84:N-----O18 Arg84:N-----N10 Asp81:OD1---HO18 Asp81:OD1----HN12 Ser55:OG----O16	2.598 2.848 1.943 1.946 2.871
2	Cpd 2	Arg84, Asp81, Ser55 Ile86, Ileu175,Glu58	Ser55:N----O19 Asp81:OD1---HN12	3.060 1.363
3	Cpd 3	Arg84, Asp81, Ser55 Ile86, Ileu175,Glu58	Arg84:N------N10 Arg84:N-----O17 Asp81:OD1---HN12	3.316 2.737 1.864
4	Cpd 4	Arg84, Asp81, Ser55 Ile86, Ileu175,Glu58	Arg84:N-----N10 Arg84:N-----O17 Asp81:OD1---HN12 Ileu175:N----O18	38 2.817 1.141 3.466
5	Cpd 5	Arg84, Asp81, Ser55 Ile86, Ileu175,Glu58	Asp81:OD1---HN12 Asp81:N------H41N25 Arg84:N-----N10 Arg84:N-----O17 Asp81:OD2-----HO17 Arg84:CB------H27	2.120 1.861 2.987 39 1.835 2.957

COMPOUND 4: In Fig 1g Binding orientation of compound 4 is represented with a docking score of 55.04. A closer analysis revealed that the hydrogen bonding interaction of carbonyl oxygen atom of ester group (attached to NH group through -CH2-CH2-chain) with the side chain of ALA 7. The OH group attached to the quinoline ring formed two hydrogen bonding interactions with ASP27 and GLN 28. The compound makes the strong pi-pi interaction with PHE 31 amino acid residue. This compound was fitted in the hydrophobic pocket within the vicinity of ALA7, TRP6, TRP22, ILE5, ILE 14, ILE 20, ILE94, PHE31, LEU50, LEU57, VAL46 respectively.

COMPOUND 5: The docking orientation of the compound 5 is represented in Fig 1h, where the following interactions are observed at the InhA binding site. The compound was found placed proximal to various hydrophobic amino acids such asALA7, ILE5, TRP6 14, ILE20, ILE94, PRO21, LEU50, LEU57, VAL 46 and hence exhibited hydrophobic interactions. And a closer look in to the interaction profile of these molecule revealed hydrogen bonding interaction of carbonyl oxygen atom of ester group (attached to NH group through -CH2-CH2- chain) with the side chain of ALA 7. And the OH group attached to the quinoline ring formed two hydrogen bonding interactions with ASP27and GLN 28. One pi -pi interaction is observed with PHE 31.

Figure-2. The binding modes of the compounds 1 to 5 in the active site of Staphylococcus aureus Gyrase B (3G75)

Fig. 2a Compound 1
Docking score 35.25

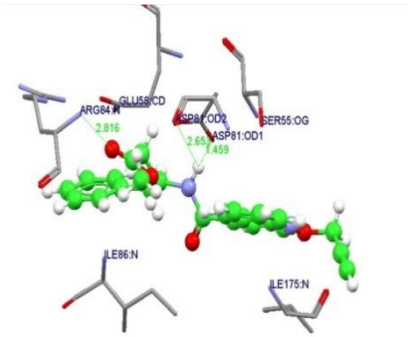


Fig. 2b Compound 2
Docking score 45.93

Fig. 2c Compound 3
Docking score 39.27

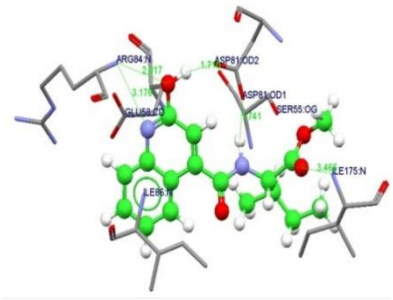


Fig. 2d Compound 4
Docking score 32.56

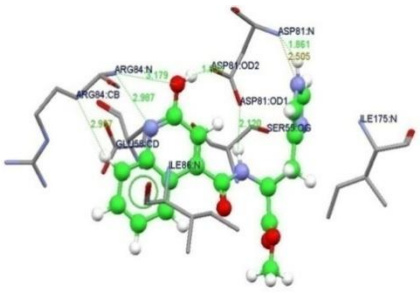


Fig. 2e Compound 5
Docking score 44.93

Thus, this compound fit in to the active site of the protein with the docking score 55.09.

DOCKING STUDY OF PEPTIDE DERIVATIVES (Compound 1 to Compound 5) AS POTENTIAL ANTI MICROBIAL AGENTS

The increasing incidence of bacterial resistance to antibiotics and antimicrobial agents poses a tremendous threat to the human race, and a continued search for new chemotherapeutic agents is vital to combat this threat. A significant amount of attention has been directed towards the development of novel classes of biocides. To this end, one of the best ways to design new biocidal agents is to synthesize hybrid molecules by combining two or more bioactive moieties in a single molecular scaffold.

Hence a series of 2- Hydroxy Quinoline -4-Carboxylic Acid peptide derivatives are synthesized that have been proved to possess antibacterial and antifungal activities aiming to synergize the antimicrobial activity. The newly synthesized derivatives were then evaluated for their antimicrobial activity against different gram-positive, gram-negative bacteria and fungi.

DOCKING STUDY OF PEPTIDE DERIVATIVES (Compound 1 to Compound 5) WITH STAPHYLOCOCCUS AUREUS GYRASE B PROTEIN(3G75)

In the present study 2- Hydroxy Quinoline -4- Carboxylic Acid Peptide derivatives were synthesized as potent anti-bacterial/DNA gyrase inhibitors. And the molecular docking study of all Optimized compounds was performed in order to evaluate their affinity to DNA gyrase B protein of Staphylococcus aureus, a Gram-positive bacterium. Subsequently, the antimicrobial activities were evaluated to ensure the maximum potent antimicrobial agents among 2- Hydroxy Quinoline -4- Carboxylic Acid peptide derivatives.

COMPOUND 1 was showing reasonably good activity with protein 3G75active site. It showed docking score of 35.25. Arg84, Asp81, Ser55, of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Asp81:OD1---HO18: of the Compound with distsnce1.943 is observed. The active site of the 3G75protein is stabilized by, Ile86, Ileu175, through hydrophobic interactions (Fig. 2a).

COMPOUND 2 was showing reasonably good activity with protein 3G75active site. It showed good docking score of 45.93. Ser 55, Asp81 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Asp81:OD1---HN12 of the

Table-3. Docking Results of Candida albicans DHFR (PDB id IM78) Protein:

Docking Score of with 1M78						
S.No	Compound	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)	Fitness score
1	Cpd 1	5.71	31.53	0.00	-7.70	41.72
2	Cpd 2	1.89	41.44	0.00	-11.01	45.34
3	Cpd 3	1.07	38.97	0.00	-9.09	45.27
4	Cpd 4	0.00	40.05	0.00	-9.45	45.62
5	Cpd 5	2.82	40.37	0.00	-7.13	52.82

Table-4. Ligand Interactions Data of Docking results with IM78 Green colors are representing Hydrogen bonds

S.No	Compound Name	Interacting amino acids	Interacting atoms	H-distance
1	Cpd 1	Lys57,Thr58 Gly114,Arg56 Glu116,Ser78 Tyr110,Thr58 Lys57,Ileu117 Arg79, Ala115	Lys57:NZ------O13: Thr58:N-----O18 Gly114:N----- O18 Thr58:OG1----H31	2.836 2.736 2.868 2.763
2	Cpd 2	Lys57,Thr58 Gly114,Arg56 Glu116,Ser78 Tyr110,Thr58 Lys57,Ileu117 Arg79, Ala115	Ileu117:N-----O13 Gly114:N------O13 Arg56:NH1-------13 Lys57:NZ--------O18 Thr58:N--------O19	3.384 3.543 3.283 2.854 2.517
3	Cpd 3	Lys57,Thr58 Gly114,Arg56 Glu116,Ser78 Tyr110,Thr58 Lys57,Ileu117 Arg79, Ala115	Arg56:N---------O18 Thr58:N--------O17 Arg79:N------O16 Lys57:NZ--------O13	3.244 3.309 3.517 3.212
4	Cpd 4	Lys57,Thr58 Gly114,Arg56 Glu116,Ser78 Tyr110,Thr58 Lys57,Ileu117 Arg79, Ala115	Gly114:N------O17 Thr58:N-------- 17 Thr58:OG1------O17 Thr58:OG1------O17 Lys57:NZ--------O13 Arg56:N--------- O17	2.861 2.816 2.313 3.430 56 2.129
5	Cpd 5	Lys57,Thr58 Gly114,Arg56 Glu116,Ser78 Tyr110,Thr58 Lys57,Ileu117 Arg79, Ala115	Arg56:N---------O20: Lys57:NZ------O13 Thr58:N--------O16	3.211 3.002 3.386

Compound with distance 1.363 is observed. The active site of the 3G75protein is stabilized by Ile86, Ileu175, through hydrophobic interactions (Fig. 2b).

COMPOUND 3 was showing reasonably good activity with protein 3G75active site. It showed docking score of 39.27. Arg84, Asp81of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Asp81:OD1---HN12: of the Compound with distsnce1.864 is observed. The active site of the 3G75protein is stabilized by Ile86, Ileu175, through hydrophobic interaction (Fig. 2c).

COMPOUND 4 was showing reasonably good activity with protein 3G75active site. It showed docking score of 32.56. Arg84, Asp81, Ileu175 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Asp81:OD1---HN12: of the Compound with distsnce1.141 is observed. The active site of the 3G75protein is stabilized by Ile86, Ileu175, through hydrophobic interactions (Fig. 2d).

COMPOUND 5 was showing reasonably good activity with protein 3G75active site. It showed docking score of 32.56. Arg84, Asp81 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Asp81:OD1---HN12: of the Compound with distsnce2.120 is observed. The active site of the

Figure-3. Binding orientations of the binding modes of the compounds 1 to 5 in the active site of Candida albicans DHFR (PDB id IM78.

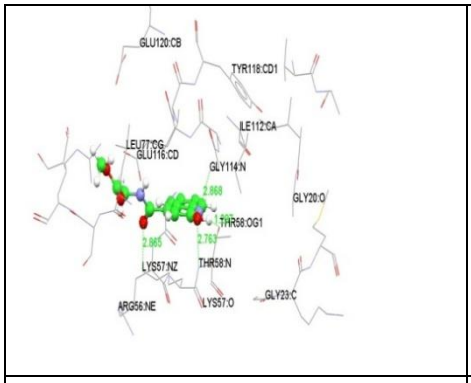


Fig. 3a Compound 1
Docking score 41.72

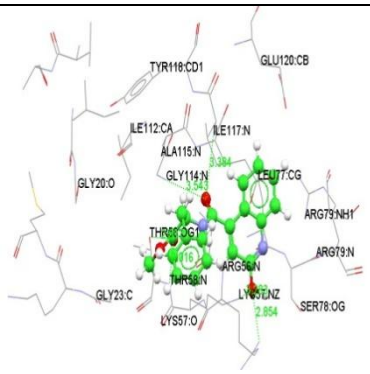


Fig. 3b Compound 2
Docking score 45.34

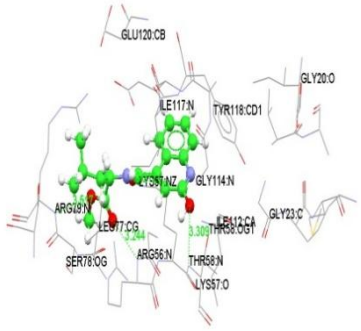


Fig. 3c Compound 3
Docking score 45.27

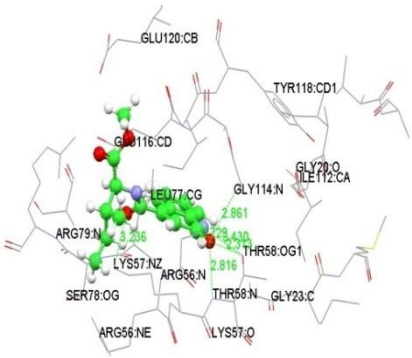


Fig. 3d Compound 4
Docking score 45.62

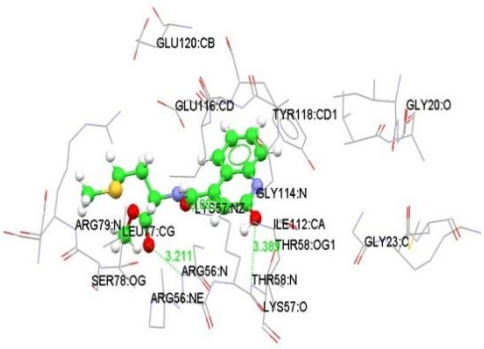


Fig. 3e Compound 5
Docking score 52.82

3G75protein is stabilized by Ile86, Ileu175, through hydrophobic interactions (Fig. 2e)

Docking Study of Peptide Derivatives (Compound 1 to Compound 5) With DHFR of Candida Albicans (IM78) Protein.

In the present study 2- Hydroxy Quinoline -4- Carboxylic Acid peptide derivatives were synthesised and molecular docking study of all Optimized compounds was performed against DHFR of Candida Albicans. Subsequently, the antimicrobial activities were evaluated to ensure the maximum potent antimicrobial agents among 2- Hydroxy Quinoline -4- Carboxylic Acid peptide derivatives.

COMPOUND 1 was showing reasonably good activity with protein IM78active site. It showed docking score of 41.72. Lys57, Thr58, Gly114, of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Thr58: N--------O18 of the Compound with distance 2.736 is observed. The active site of the IM78 protein is stabilized through Gly114, Ileu117, Ala115 hydrophobic interactions (Fig. 3a).

COMPOUND 2 was showing reasonably good activity with protein IM78active site. It showed good docking score of 45.34. Ileu117, Gly114, Arg56, Lys57, Thr58 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Thr 58: N-O19: of the compound with distance 2.517 is observed. The active site of the IM78protein is stabilized by Gly114, Ileu117, Ala115, through hydrophobic interactions. (Fig. 3b)

COMPOUND 3 was showing reasonably good activity with protein IM78active site. It showed docking score of 45.27. Arg56, Thr58, Arg79, Lys57of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Lys57:NZ--------O13: of the Compound with distance 3.212 A0 is observed. The active site of the IM78protein is stabilized by Gly114, Ileu117, Ala115, through hydrophobic interactions (Fig. 3c).

COMPOUND 4 was showing reasonably good activity with protein IM78active site. It showed docking score 45.62. Gly114, Thr58, Lys57, Arg56 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Arg56: N--------- O17 of the

Compound with distance 2.313A0 is observed. The active site of the IM78protein is stabilized by Gly114, Ileu117, Ala115, through hydrophobic interactions (Fig. 3d).
COMPOUND 5 was showing reasonably good activity with protein IM78active site. It showed good docking score of 52.82. Arg56, Lys57, and Thr58 of the protein showed hydrogen bonding interactions with the compound and the strong hydrogen bond between Lys57: NZ------O13: of the Compound with distance 3.002A0 is observed. The active site of the IM78protein is stabilized by Gly114, Ileu 117 Ala115, through hydrophobic interactions (Fig. 3e).

Conclusions

All the quinoline peptide conjugates showed increasing antibacterial activity against the tested cultures15,16. A good activity shown by 2 to 5 against Staphylococcus aureus(23mm) and gram-negative bacteria such as Klebsiella pneumonia (22mm and 23mm), whereas, an activity of 18 to 24 mm was observed was for other derivatives. The antifungal activity of synthesized compounds was tested against C. albicans. Of all the compounds 2 and 5 showed good activity of 24 mm against the tested fungal strain when compared to others.

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Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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