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Synthesis of quinolone derivatives and their molecular docking for antiepileptic activity

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ABSTRACT

Compounds having quinolone moiety are associated with wonderful biological activities. In the present study, Schiff bases of 1-amino-7-hydroxy-4-methylquinoline-2(1H)-one and 1-amino-7-hydroxy-2-methylquinoline-4(1H)-one with substituted aromatic carbonyl compounds were synthesized. The final test compounds were purified and characterized by IR, 1HNMR and Mass Spectral studies. M.P. of these compounds was confirmed by open capillary method instrument chemline cl 725. Docking study of quinolone derivatives was performed on the three high resolution crystal structures of hCA enzyme using Biopredicta module of VLife MDS 3.5 software to study the binding modes of quality and quantum interactions between synthesized compounds with the target enzymes (PDB pdb 3F8E). Synthesized compounds 14, 15, 31, 25 and 9 showed strong antiepileptic activity among all synthesized compound.

Capsule Summary: Schiff bases of 1-amino-7-hydroxy-4-methylquinoline-2(1H)-one as well 1-amino-7-hydroxy-2-methylquinoline-4(1H)-one by refluxing with substituted aromatic carbonyl compound was prepared and molecular docking was performed for antiepileptic activity evaluation.

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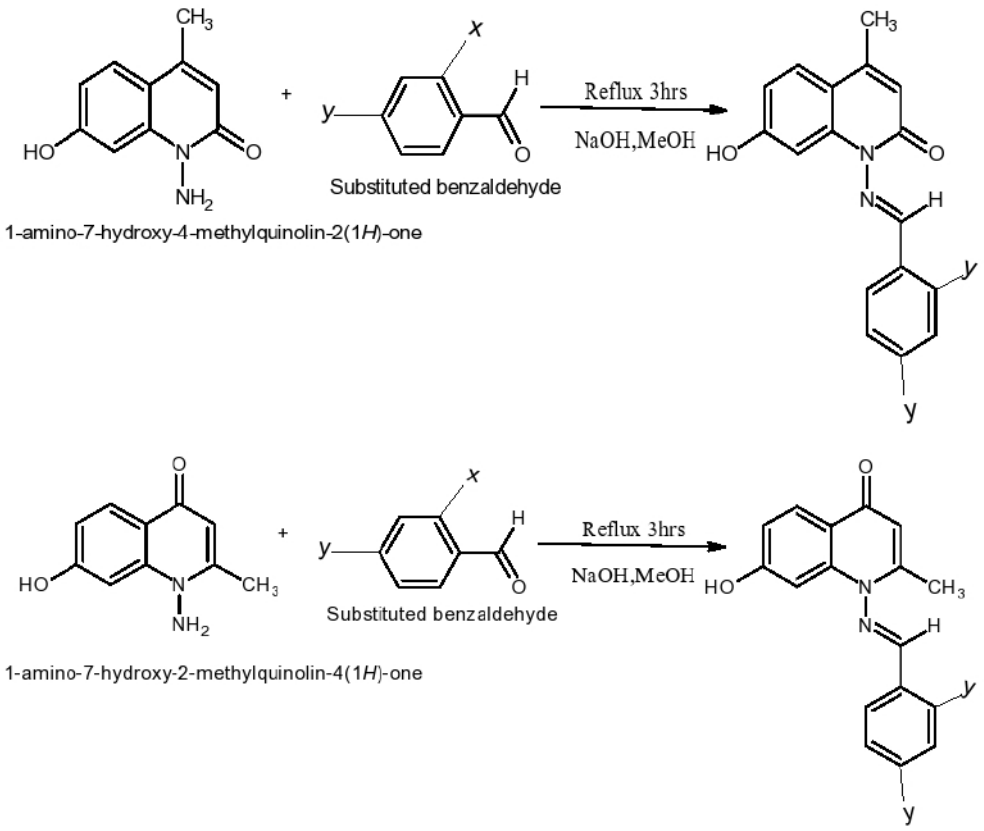
INTRODUCTION

The first clinically useful quinolone was naldixic acid, discovered by Lesher and co-workers (1962), which was generated from chloroquine, an antimalarial agent (Appelbaum and Hunter, 2000). A big revolution was made in 1980s when an analog of naldixic acid, enoxacin was derived with significantly increased spectrum of activity against Gram negative or Gram positive bacteria (Patrick, 2003). Today various molecules of quinolone were synthesized which shows multiple activities against various disease and microbial infection (Narule et al., 2003). Today computational such as docking used that aims to predict the best binding orientation between a pair of biomolecules starting from their "unbound" structures. Molecular docking is a frequently used tool in computer-aided structure-based rational drug design. It evaluates how small molecules called ligands (substrates, inhibitors, drugs or drug candidates) and the target macromolecule (receptor, enzyme or nucleic acid) fit together and to predict how small molecules bind to a target protein of known 3D-structure. Besides generating binding energies in the docking studies, the position of the ligands in the host's binding site can be visualized. It can be useful for developing better drug candidates and also for the understanding the nature of the binding (Ahamed et al., 2020; Das et al., 2020; Larik et al., 2020; Manjusha et al., 2020; Martin et al., 2020; Naveen et al., 2020; Rahuman et al., 2020; Selvaraj et al., 2020; Therasa Alphonsa, 2020; Wahid et al., 2020).



Scheme 1: Synthesis route

Molecular interactions play a key role in all biological reactions. Drugs are either mimicking or mitigating the effect of natural ligands binding to the receptor by exerting the pharmacological reactions. Computational methods are used to understand this mode of binding of ligands to their receptors which is called as Molecular Docking. It is an attempt to find out the "best" binding between different a set of molecules: a receptor and a ligand (Gupta et al., 2020; Inbal et al., 2003; Koca et al., 2020; Rizwana B et al., 2020; Shubhangi and Paul, 2020)). Subsequently two basic scoring functions, systematic method and probabilistic approach were used for docking analysis. Here, Schiff bases of 1-amino-7-hydroxy-4-methylquinoline-2(1H)-one and 1-amino-7-hydroxy-2-methylquinoline-4(1H)-one with substituted aromatic carbonyl compounds were synthesized. The final test compounds were purified and characterized by IR, 1HNMR and mass spectral studies, which were careened for antiepileptic activity.

MATERIAL AND METHODS

Synthesis approach

Compounds were synthesized as precisely reported elsewhere (Pradhan and Vishwakarma, 2018ab).

Docking study

It is reported that the anticonvulsant, antepileptic and antiseizure drugs may account for hCA inhibition (Supuran, 2008; Karataş et al., 2016). The choice of consistent hCA enzyme was based on reported literature (D'Ambrosio et al., 2015; Abuelizz et al., 2017). Hence, X-ray coordinates of the hCA II isomer was taken from the RCSB data bank (PDB file with code 3F8E). Water molecules and HET ATOM-like bound ligand data were removed from the PDB files of proteins during docking study. The crystal structures were refined using VLife MDS 3.5 software. The refinement of the receptors was done by completing the incomplete residues. The co-crystallized ligands lying within the receptors were modified by assigning missing bond order and hybridization states. The side chain hydrogens were then added to the crystal structures and their positions were optimized up to the RMS gradient 1 by aggregating the other part of the receptor. Conformers of optimized ligands were then generated by Monte Carlo method using default settings.

Identification of cavities

The cavities in the receptor were mapped to assign an appropriate active site, the basic feature used to map the

cavities were the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics. Hence all the cavities that are present in falcipain-2 receptor are identified and ranked based on their size and hydrophobic surface area as depicted in Figure 1. Considering the dimensions and hydrophobic surface area, Cavity-1 was found to be the best void as an active site.

The docking simulation was done using GRID batch docking. The grid based docking is a rigid and exhaustive docking method. In this method, after unique conformers of the ligand are generated, the receptor cavity of interest is chosen by the user and a grid is generated around the cavity (default grid interval size 1 Å). Cavity points are found and the center of mass of the ligand is moved to each cavity point. All rotations of ligand are scanned at each cavity point where ligand is placed. For each rotation a pose of the ligand is generated and the corresponding bumps are checked for each pose of ligand. The dock score (Wang et al., 2002) is calculated for each valid pose and the pose of the ligand with the best score is given as output to user.

Table 1: Best 30 PLP Score of different conformations of synthesized compounds

S. No	ligand	PLP Score
1	14_opt_P10	-35.2251
2	15_opt_P5	-34.3011
3	31_opt_P29	-34.0919
4	15_opt_P25	-33.6782
5	25_opt_P21	-33.5459
6	9_opt_P28	-33.0809
7	13_opt_P4	-32.9602
8	28_opt_P26	-32.1248
9	18_opt_P20	-31.9646
10	31_opt_P2	-31.6899
11	30_opt_P30	-31.5962
12	17_opt_P7	-31.5849
13	1_opt_P17	-31.3642
14	9_opt_P11	-31.1997
15	1_opt_P9	-30.9614
16	2_opt_P12	-30.8546
17	10_opt_P15	-30.844
18	29_opt_P22	-30.6811
19	26_opt_P1	-30.4479
20	18_opt_P27	-30.4034
21	18_opt_P14	-30.3815
22	16_opt_P18	-30.3406
23	25_opt_P19	-30.2321
24	31_opt_P3	-30.2083
25	1_opt_P8	-30.165
26	10_opt_P23	-30.0412
27	21_opt_P16	-29.981
28	15_opt_P24	-29.9639
29	7_opt_P6	-29.9573
30	16_opt_P13	-29.8683

Minimum Score: Molecule Name = 14_opt_P10 score = -35.225114

All the conformers were virtually docked at the defined cavity of the receptor. The parameters fixed for docking simulation was like this-number of bump allowed: 4, rotation angle of: 100°, exhaustive method, scoring function: dock score. By rotation angle, ligand would be rotated inside the receptor cavity to generate different ligand poses inside the receptor cavity. The ligand forming most stable drug receptor complex is the one which is having minimum dock score. After docking simulation, the best docked conformer of each ligand and receptor were merged and their complex was then energetically optimized by defining radius of 10 Å measured from the docked ligand. Stepwise energy optimization was done by first hydrogen; second side chains and finally, the backbone of receptor. The optimized complexes were then checked for various interaction of ligand with receptor like hydrogen bonding, hydrophobic bonding and van der Waal's interaction. The binding affinity was evaluated by binding free energy (kcal/mol), hydrogen bonding interaction, hydrophobic interaction and RMSD values.

RESULTS AND DISCUSSION

Docking study was performed on the three high resolution crystal structures of hCA enzyme using Biopredicta module of VLife MDS 3.5 software to study the binding modes of quality and quantum interactions between synthesized compounds with the target enzymes (PDB pdb 3F8E), results of which are depicted in Tables 1 and 2.

The reliability of the docking results were first checked by comparing the best docking poses obtained for the co-crystallized inhibitors with its bound conformations. This was done by removing each co-crystallized ligands from their active site and subjecting again to docking into the binding pocket in the conformations found in the crystal structures. As a result, RMSD of 0.8 was found suggesting that the docking procedures could be relied onto predict the binding modes of these compounds. To investigate the detailed intermolecular interaction between ligand and the targeted enzyme, VLife MDS 3.5 was used to perform docking study for understanding the binding mode of the synthesized compounds on hCA II (pdb 3F8E) and to obtain information for further structure optimization. The binding mode of the best docked compound 14 is shown in Fig. 2. The interactions underscore the importance of nitrogen atoms for binding and subsequent inhibitory capacity. The minimum PLP score of -35.23 kcal/mol for compound 14 indicates high binding affinity of the ligand towards hCA II.

Table 2: Hydrobhobic interaction between ligands and receptors

Residue Atom	Ligand Atom	Distance Interaction Type
1 GLN92A	1375N 15C 3.611	VDW_INTERACTION
2 GLN92A	1383H 20C 3.022	VDW_INTERACTION
3 HIS94A	1412C 19C 3.708	VDW_INTERACTION
4 HIS94A	1419H 19C 3.191	VDW_INTERACTION
5 HIS94A	1419H 21C 3.306	VDW_INTERACTION
6 HIS94A	1420H 22F 3.081	VDW_INTERACTION
7 VAL121A	1830C 20C 3.640	VDW_INTERACTION
8 VAL121A	1830C 21C 3.678	VDW_INTERACTION
9 VAL121A	1834H 21C 3.011	VDW_INTERACTION
10 PHE131A	1977C 9C 3.666	VDW_INTERACTION
11 PHE131A	1979C 9C 3.430	VDW_INTERACTION
12 PHE131A	1979C 16C 3.635	VDW_INTERACTION
13 PHE131A	1981C 14C 3.551	VDW_INTERACTION
14 PHE131A	1988H 9C 3.150	VDW_INTERACTION
15 PHE131A	1989H 16C 3.341	VDW_INTERACTION
16 PHE131A	1990H 14C 2.980	VDW_INTERACTION
17 LEU198A	3003C 19C 3.406	VDW_INTERACTION
18 LEU198A	3006H 18C 3.190	VDW_INTERACTION
19 LEU198A	3006H 19C 3.089	VDW_INTERACTION
20 LEU198A	3012H 20C 3.364	VDW_INTERACTION
21 LEU198A	3012H 21C 3.303	VDW_INTERACTION
22 LEU198A	3013H 15C 3.093	VDW_INTERACTION
23 LEU198A	3013H 17C 3.247	VDW_INTERACTION
24 LEU198A	3013H 18C 2.995	VDW_INTERACTION
25 LEU198A	3014H 20C 3.108	VDW_INTERACTION
26 THR199A	3022H 22F 2.749	VDW_INTERACTION
27 THR199A	3025H 22F 2.881	VDW_INTERACTION
28 THR200A	3033C 18C 3.722	VDW_INTERACTION
29 THR200A	3034O 17C 3.415	VDW_INTERACTION
30 THR200A	3034O 19C 3.356	VDW_INTERACTION
31 THR200A	3034O 22F 3.417	VDW_INTERACTION
32 THR200A	3039H 17C 3.307	VDW_INTERACTION
33 ILE91A	1354C 16C 4.911	HYDROPHOBIC_INTERACTION
34 GLN92A	1372C 16C 4.336	HYDROPHOBIC_INTERACTION
35 VAL121A	1829C 16C 4.472	HYDROPHOBIC_INTERACTION

The best docked molecule (compound 14) shows hydrophobic interactions with ILE91A, VAL121A, and Van der Waals interactions with GLN92A, HIS94A, VAL121A, PHE131A, LEU198A, THR199A. The superimposition of best fitted legend 14_opt_P10 with co-crystallized ligand of receptor is shown in Fig. 3. The least active compound of series Compound 16 shows poor affinity towards hCA II, as denoted by PLP score of -29.87 kcal/mol. Molecular docking helps the study of ligand–receptor interaction to identify active binding sites of receptor proteins, which helps to obtain the best geometry of ligand–receptor complex so that the energy of interaction between ligand and receptor is minimum. The minimum energy of interaction is represented by different scoring functions.

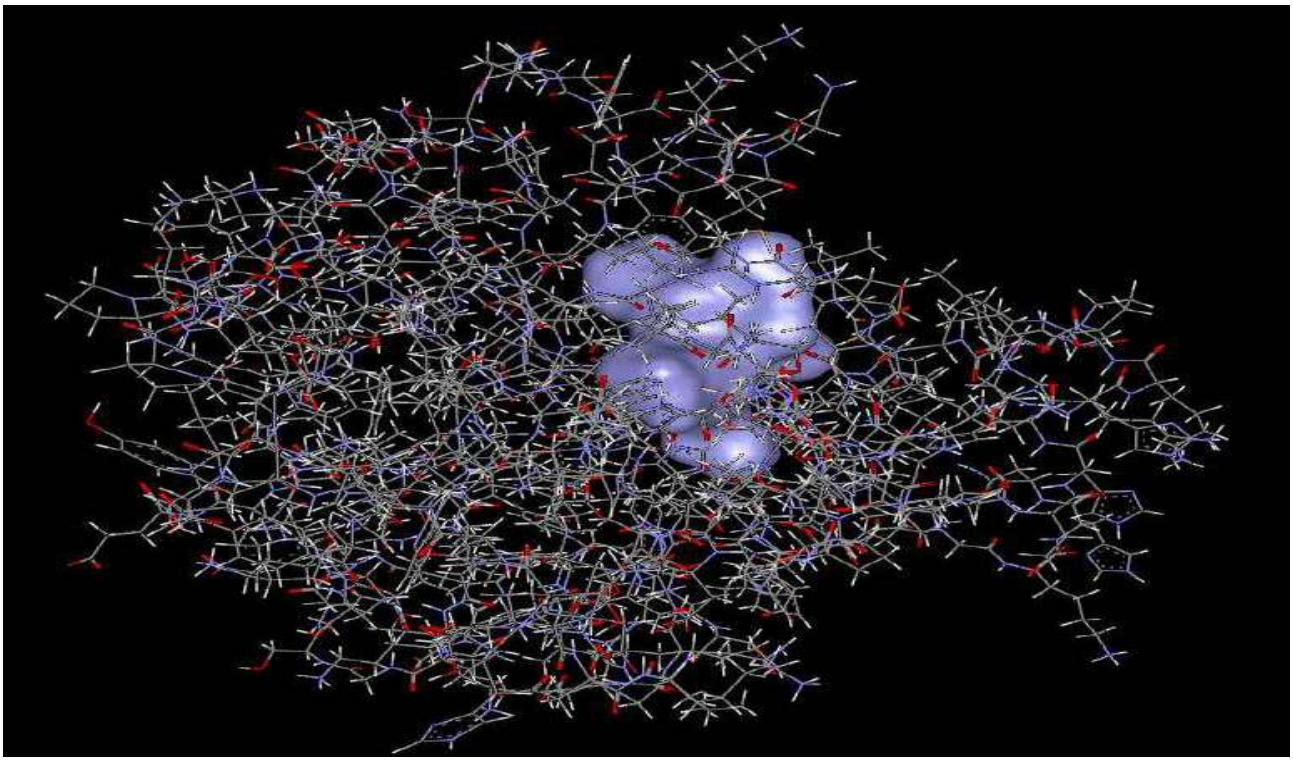


Fig. 1: Cavity 1 in receptor of hCA enzyme

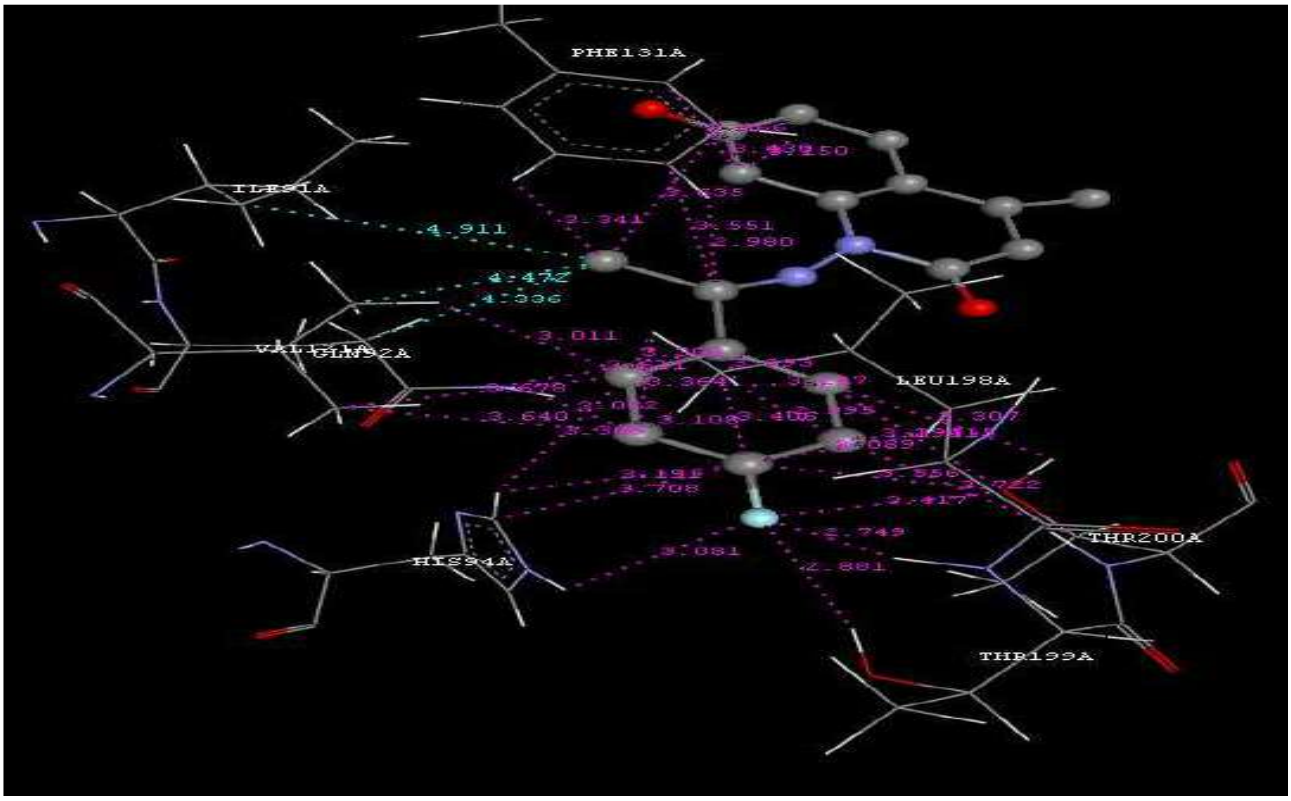


Fig. 2: Complete interactions of best docked molecule 14 with active site of hCA II

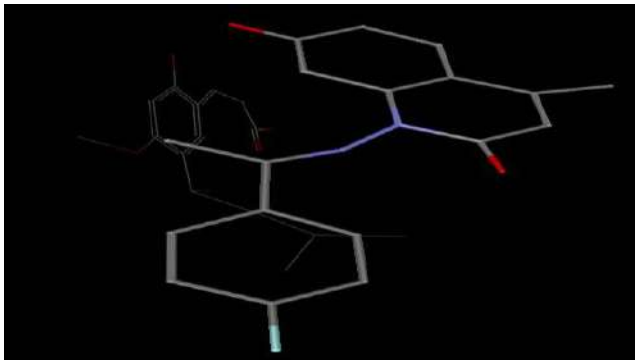


Fig. 3: Superimposition of best fitted compound with co-crystalized ligand of receptor

This utility allows screening of a set of compounds for lead optimization. The affinity of ligands to a receptor can be predicted with reasonable accuracy, yielding a relative rank ordering of the docked compounds with respect to affinity. Prediction of affinity is referred to as scoring.

For each ligand, the best docked structure was chosen, and this receptor-based alignment was used for further studies. The docking of best molecule into the hcf II receptor confirmed that ILE91A, VAL121A, GLN92A, HIS94A, VAL121A, PHE131A, LEU198A, THR199A interacted with the receptor. The present study illustrates a new hypothesis about the binding interaction of these synthesized compounds inside the receptor, encouraging future investigations on new residues that might be fundamental for the ligand-receptor interactions, because, hCA enzyme are an interesting therapeutic target for antiepileptic activity. On the basis of results of docking studies, the synthesized compounds 14, 15, 31, 25 and 9 were initially screened for biological activity, which was promising and antiepileptic activity studies will be reported in detail using *in vitro* and *in vivo* assays. The molecular interactions play a key role in biological reactions and docking (Akinpelu et al., 2020; Ambrosetti et al., 2020; Anwar et al., 2020; Shafi et al., 2020; Shahabadi and Zendehcheshm, 2020) is very helpful in order to study the antiepileptic activity of quinolone derivatives (De Sarro et al., 1999; Skyrianou et al., 2009; Skyrianou et al., 2011a; Skyrianou et al., 2010; Skyrianou et al., 2011b).

CONCLUSIONS

Schiff bases of 1-amino-7-hydroxy-4-methylquinoline-2(1H)-one and 1-amino-7-hydroxy-2-methylquinoline-4(1H)-one by refluxing were prepared. The compounds were purified and characterized by IR, 1HNMR and mass spectral studies. M.P. of these compounds was confirmed by open capillary method instrument chemline cl 725. Docking study was performed to study the binding modes of quality and quantum interactions between synthesized compounds with the target enzymes (PDB pdb 3F8E). Synthesized compounds 14, 15, 31, 25 and 9 were shown strong antiepileptic activity among all synthesized compound and have a practical importance.

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