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INSILICO SCREENING OF COUMARIN DERIVATIVES: AN ACETYLCHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE

***Sincy Mathew, Anjana K. B., Labeeba N. P. and Reeba K. R.**

Department of Pharmaceutical Chemistry, Grace College of Pharmacy, Palakkad, Kerala, 678006.

***Corresponding Author: Prof. Sincy Mathew**
Department of Pharmaceutical Chemistry, Grace College of Pharmacy, Palakkad, Kerala, 678006.

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ABSTRACT
Coumarin is a naturally occurring phytochemical with heterocyclic structures that display a wide range of biological activity against neurological diseases such as Alzheimer's disease. Acetylcholinesterase is a potential target in drug design against Alzheimer's disease. In silico research in medicine is thought to have the potential to speed the rate of discovery while reducing the need for expensive lab work and clinical trials. The present study was carried out to identify the coumarin derivatives against acetylcholinesterase and its mechanism of action was identified by molecular docking analysis. Docking was performed for 12 coumarin derivatives using PyRx and the binding energy of all of the docking structures was noted.

KEYWORDS: Acetylcholinesterase, Coumarin, Molecular docking, Protein validation, Ligand optimization.

INTRODUCTION
Insilico is an expression used to mean "performed on computer or via computer simulation".[1] In silico procedures become a prominent tool for drug design and discovery. It is helpful to identify and discover new potential drugs from sets of compounds. Molecular docking is an important technique in structural molecular biology and computer-assisted drug design. The main aim of molecular docking is to study the binding mode(s) of a ligand with a target protein and to produce binding energy and ligand-protein interaction. If greater the binding energy, then the greater will be the affinity between the molecule and target. PyRx is a Virtual Screening tool to study docking interaction between ligands as well as target proteins and to screen libraries of compounds against potential drug targets.[2]

Alzheimer's disease is the most common form of senile dementia, affecting 10% of individuals older than 65 and nearly 50% of those older than 85.[3] AD becomes increasingly common as the global population ages.[4] It occurs due to several factors including failure of cholinergic neurons in various parts of the brain, which gradually destroys thinking skills, memory, and, finally the capability to perform daily activities. According to the cholinergic hypothesis, AD is caused due to a decreased level of the neurotransmitter acetylcholine (ACh).[5] Choline esterase is a class of serine hydrolases that hydrolyze choline esters. The major function of this enzyme is the rapid hydrolysis of Ach at cholinergic synapses. AChE present in the cholinergic terminals accelerates this amyloid beta aggregation. The active site of AchE is located at the bottom of a narrow gorge and it consists of two subunits, a negatively charged anionic site and an esteratic site containing actual catalytic residue.[6] In this docking studies of coumarin and its 12 derivatives were performed using PyRx, which shows the binding energy and ligand-protein interaction.

MATERIALS AND METHOD
Ligand preparation
The ligands for the study were selected from the extensive literature search. The two- dimensional (2D) chemical structure of the ligand is sketched using chemsketch (Fig.1) and chemdraw. By using an online smiles translator, SMILE strings are converted into a three-dimensional structure and saved in PDB format.

Target protein preparation
The Protein Data Bank (PDB; http://www.rcsb.org/pdb/) is the single worldwide archive of structural data of biological macromolecules.[7] The crystal structure of the protein (Fig.2) 1ACJ with properties (Table 1) was collected from a protein data bank(PDB).

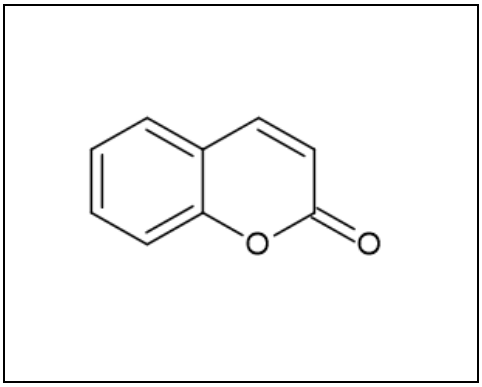

Fig 1: Structure of Coumarin.

Fig 2: Structure of target protein 1ACJ.

Table 1: Properties of the target protein.

Pdb id	Classification	Structure weight	Molecule	Length	Organism
1ACJ	Hydrolase	60.99kDa	Acetyl cholinesterase	537	Tetronarce californica

Ligand and protein validation

The prepared ligands were validated using web tools such as SWISS ADME, PROTOX 3, and ONLINE PASS PREDICTION. Computer-aided toxicity and pharmacokinetic prediction studies are alternative means to predict potential drug candidates. In-silico pharmacokinetic properties (ADME), drug-likeness, and toxicity profiles of the ligand were examined using Swiss ADME, and ProTox II web tools.[8] The Ramachandran plot has provided a potent validation check on protein structure models, showing the mapping of pairs of φ/ψ torsion angles of the polypeptide backbone on the backdrop of the allowed or expected values.[9]

Molecular docking

A computational ligand‑target docking approach was used to analyze structural complexes of the ACE (target) with coumarin (ligand) to understand the structural basis of this protein target specificity. Docking was carried out by PyRx.[10]

The binding mode and interaction of acetylcholinesterase with 12 ligands, was performed using PyRx software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. The protein was loaded in PyRx software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues All bonds of ligands were set to be rotatable. The docking site on the protein target was defined by establishing a grid box. The best conformation was chosen with the lowest docked energy after the docking search was completed and for each run, the best pose was saved.[11]

RESULTS AND DISCUSSION

Docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure-based drug design process. The Ligand-target docking was performed for the 1acj with all the 12 ligands. The best protein pose was selected for analysing the binding mode and the results were illustrated in Table 2.

The molecular docking of the ligands with the enzyme revealed that (Fig 3-14), it has exhibited the chemical interaction with the amino acids in the active pockets which are shown in Figure 15-26.

The docking result revealed that it is a very good inhibitor of acetylcholinesterase enzyme.

Table 2: Binding energy of ligands against 1acj.

Ligand	Binding energy(kcal/mole)
1MC	-8.5
2MC	-8.3
3MC	-8.2
4HC	-6.3
5HC	-7.8
6HC	-7.5
7CC	-6.3
8CC	-8
9CC	-7.8
10MOC	-7.9
11MOC	-7.6
12MOC	-7.6

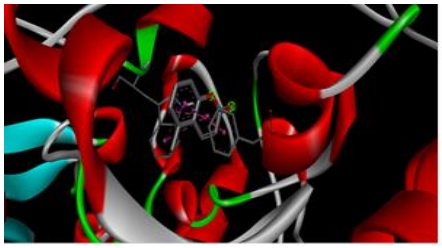

Fig 3:1MC

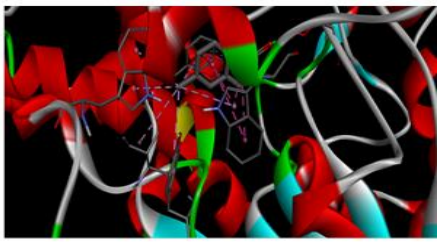

Fig 4: 2MC

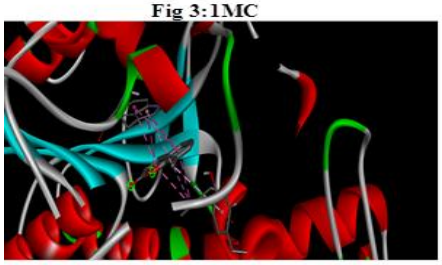

Fig 5: 3MC

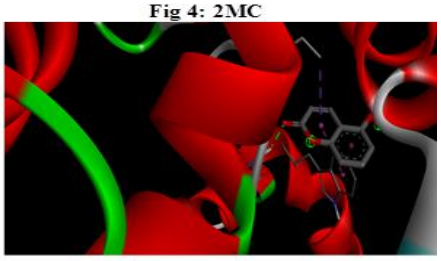

Fig 6: 4HC

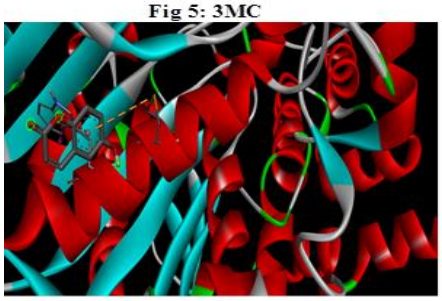

Fig 7: 5HC

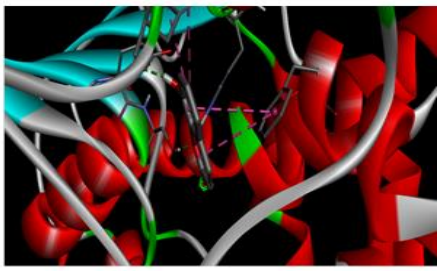

Fig 8: 6HC

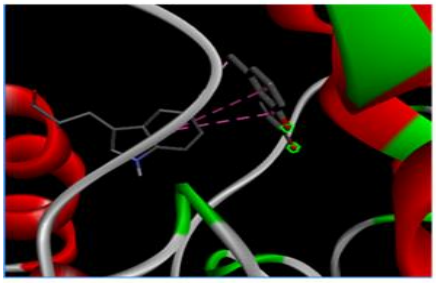

Fig 9:7CC

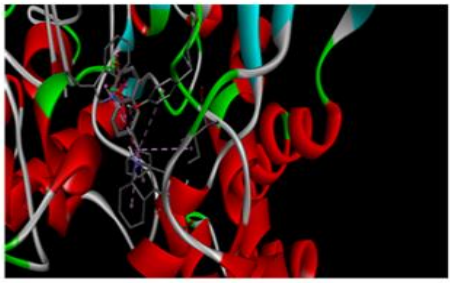

Fig 10: 8CC

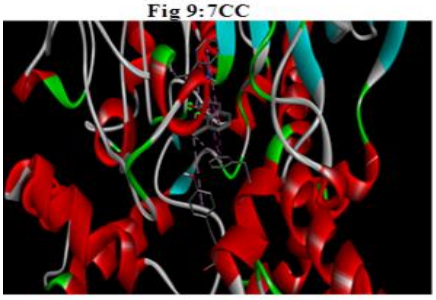

Fig 11: 9CC

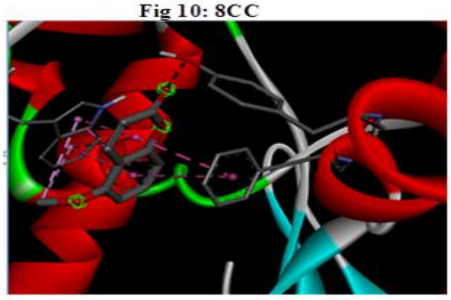

Fig 12:10MOC

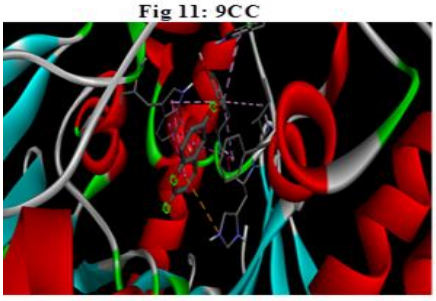

Fig 13: 11MOC

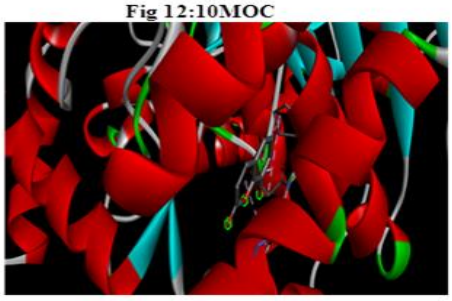

Fig 14: 12MOC

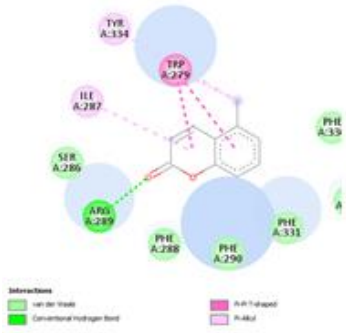

Fig 15: 1MC

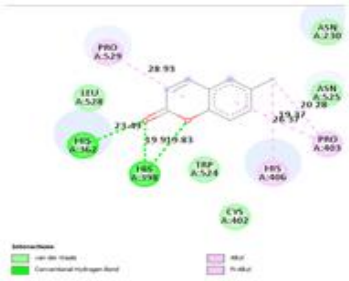

Fig 16: 2MC

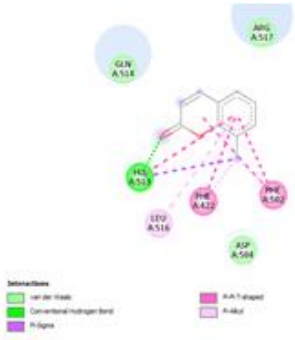

Fig 17: 3MC

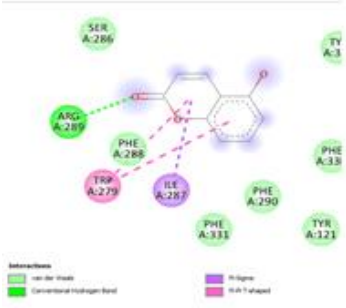

Fig 18: 4HC

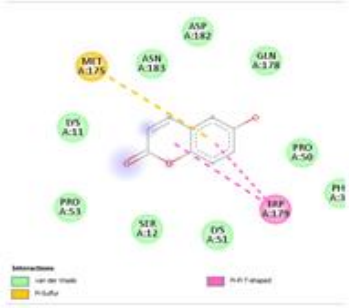

Fig 19: 5HC

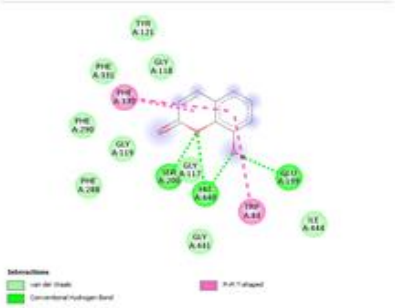

Fig 20: 6HC

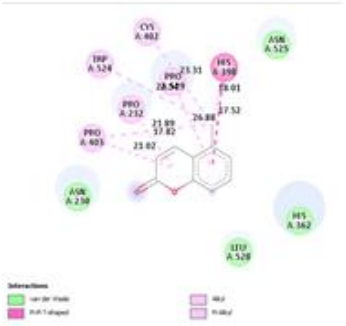

Fig 21: 7CC

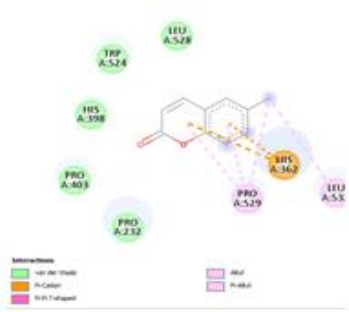

Fig 22: 8CC

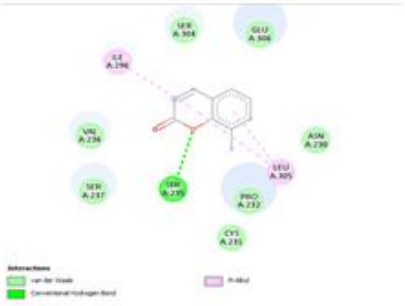

Fig 23: 9CC

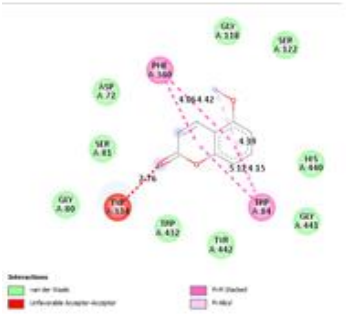

Fig 24: 10MOC

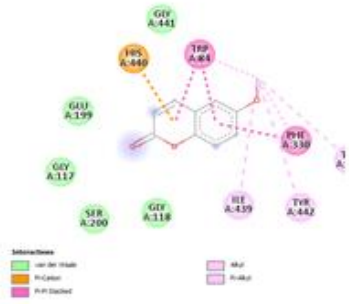

Fig 25: 11MOC

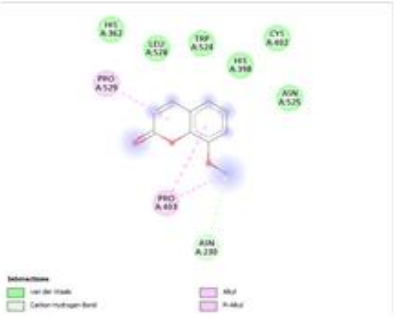

Fig 26: 12MOC

CONCLUSION

AChE inhibitors are the mainstay drugs for the clinical management of AD. Using a combination of various in silico techniques, we successfully identified potent novel AChE inhibitors. The docking result revealed that exhibited good binding interaction with the catalytic site of acetylcholinesterase. Therefore, 12 coumarin derivatives molecule plays an important role in inhibiting the acetylcholinesterase to treat Alzheimer's disease. The compound with the highest binding energy is 1MC, so it shows the greatest affinity to the enzyme.

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