International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 282-287. **ijppr.humanjournals.com** ISSN: 2349-7203

In Silico Study of Synthesized Chalcone Derivative Against Alzheimer and Cancer Target

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Received: 2024-08-10 Revised: 2024-08-17 Accepted: 2024-08-20

ABSTRACT

Chalcone is an organic compound contains α,β- unsaturated ketone. It is widely distributed in variety of fruits, vegetables, tea and other plants as flavonoids and isoflavanoid biosynthetic precursor. Chalcone is known for its versatile Pharmacological activities and it can also be easily synthesized in laboratories by reaction between two aromatic scaffolds. These characteristics of chalcone made a seed for researchers to investigate over its application and designing a simple synthetic routes. This study discuss about the Claisen Schmidt method of synthesis of a α,β-unsaturated ketone derivative by three different technique and docking study of synthesized chalcone. The structure of synthesized compound was characterized by using spectroscopical studies and preliminary QSAR studies have been done with various software. Cyclin dependent kinase-6 (CDK-6) and acetylcholinesterase are chosen as a target for molecular docking to study the binding affinity and to predict the pharmacological action of synthesized chalcone derivative against breast cancer and neurodegenerative disease (Alzheimer's).

Keywords: Chalcone, Claisen Schmidt reaction, Molecular docking, Cyclin dependent kinase-6 (CDK-6), acetylcholinesterase

INTRODUCTION

Chalcone, an α, β- unsaturated ketone $C_6H_5C(O)CH=CHC_6H_5$, is the building block of numerous significant biological substances.[1] A chalcone is a widely distributed simple chemical structure as flavonoids and isoflavonoids found in a variety of fruits, vegetables and other plants. Since most natural chalcones are brown in color, the word "chalcone" comes from the Greek word "chalcos," which means "bronze."[2]

Due to their wide range of pharmacological and therapeutic possibilities, chalcones and their derivatives continue to be extremely important in medicinal chemistry even in the twenty-first century. Chalcones having different substituents in different positions have been reported to possess different pharmacological activity. Several biological activity are displayed by the chalcones derivatives, includes antitubercular, antiviral, antiulcerative, anticancer, antibacterial, anticonvulsant, anti-HIV, antihyperglycemic, anti-inflammatory, antileishmanial, antimicrobial, antioxidant, and antiprotozoal properties. [3,4,5,6,7]

The general constitutions of chalcone are 1, 3-diphenyl propen-1-one in which two aromatic rings are joined together by unsaturtated ketonic compound. Wide range of chalcone derivative is synthesized by treating aromatic aldehydes with aryl ketones in the presence of an appropriate amount of condensing agents.

Various methods involved in the synthesis of chalcone derivatives includes Claisen Schmidt condensation, Friedel crafts acylation, ultra sound irradiation, microwave irradiation, Schiff's reaction and one-pot synthesis using various catalyst.[8,9,10]

In this study synthesize of chalcone was done by using Claisen -Schmidt condensation reaction, in presence of base catalyst which gives α, β- unsaturated ketone or aldehyde.

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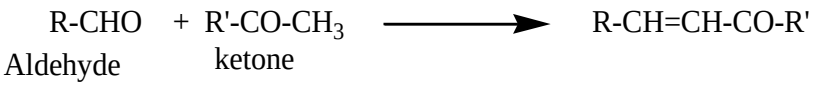


Figure 1: General reaction of chalcone synthesis

Synthesis have been done in three different methods and comparative study of yield is carried out. The structure of synthesised compound is studied by using IR and NMR spectroscopy. The purity of compound is determined by thin layer chromatography. Preliminary QSAR study of the synthesised compound was done by using the software.

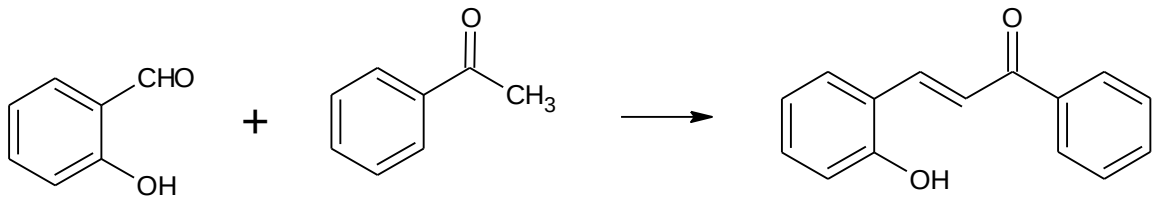
Molecular docking is carried out for synthesised chalcone to analyse their binding interaction with the target protein. Cyclin dependent kinase-6 and acetylcholinesterase were selected as a target to study anti-cancer (breast cancer) and anti-alzheimer activity respectively. The binding affinity and binding pose of synthesised chalcone against target protein was compared with the standard drugs.

MATERIALS AND METHODS

Salicylaldehyde, Acetophenone, Ethanol, Ammonium hydroxide, Benzene and Ethyl acetate are the chemicals used for the synthesis of chalcone. All the chemicals and reagents used were analytical grade.

Experimental work:

In this study, chalcone was synthesized from acetophenone and salicylaldehyde by using Claisen -Schmidt condensation reaction, in presence of ammonium hydroxide as base catalyst which gives 2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one.



Salicylaldehyde **Acetophenone** **(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one**

Figure 2: Synthesis of chalcone [(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one]

Method 1:

Combine salicylaldehyde and acetophenone in a 1:1 molar ratio in the reaction vessel. Add a catalytic amount of a base (Ammonium hydroxide) to the reaction mixture slowly. Place the reaction vessel in an ice bath to maintain a lower temperature. This helps control the reaction and reduce side reactions. Continuously stir the mixture for 2hrs with magnetic stirrer while allowing the Claisen-Schmidt condensation to occur. Purify the crude product and recrystallize using alcohol. The percentage yield for the synthesized compound was found to be 85%.

Method 2:

In the microwave reaction vessel, combine salicylaldehyde and acetophenone in a 1:1 molar ratio. Add a catalytic amount of base (Ammonium hydroxide) to the reaction mixture. Place the stir bar in the reaction vessel and stir the mixture. Subject the reaction mixture to microwave irradiation. Use the appropriate power and time settings, typically shorter reaction times are required compared to conventional heating methods. The crude product is purified and recrystallized from ethanol. The percentage yield for the synthesized compound was found to be 91%.

Method 3:

Combine salicylaldehyde and acetophenone in a 1:1 molar ratio in the reaction vessel. Add a catalytic amount of a base (Ammonium hydroxide) to the reaction mixture and reflux for about 2 hours. Completion of reaction is identified by using TLC using a suitable

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developing solvent (Benzene: Ethyl acetate 9:1) and visualize the spots under UV light. Purify the crude product using chromatography or recrystallization. The percentage yield for the synthesized compound was found to be 87%.

The purified chalcone product is analysed using spectroscopic methods (e.g., NMR, IR) to confirm its structure.

Colour reaction for chalcones:

- Synthesized product is dissolved in ethanol and add few drops ethanolic ferric chloride gives deep violet colour due to the formation of complex between ferric ion which shows the structure have phenolic hydroxyl group (chalcone).

- Synthesized product is dissolved in ethanol and add few drops of conc.H_2SO_4 which gives red colour due to the formation of carbonium ion. This shows the presence of chalcone.

PREDICTIVE QSAR

The molecular properties of the synthesised compound is studied by using molinspiration software and Boiled egg model.

Table 1: Molecular property of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one

Molecular properties	Molinspiration value
Log P	3.72
Molecular Weight	226.28
No. of atom	17
No. of hydrogen bond acceptors	2
No. of hydrogen bond donors	1
No. of rotatable bond	4

Table 2: Drug likeliness score of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one

Drug likeliness	Bioactivity score
GPCR Ligand	-0.17
Ion channel modulator	0.05
Kinase inhibitor	-0.48
Nuclear receptor ligand	-0.05
Protease inhibitor	-0.32
Enzyme inhibitor	0.15

The **B**rain **O**r **I**ntestina**L** **E**stimate**D** permeation method (BOILED-Egg) is proposed as an accurate predictive model that works by computing the lipophilicity and polarity of small molecules.

- Gastrointestinal absorption: The white of the BOILED-Egg shows the compound is predicted to be absorbed in GIT.

- BBB permeation: The yolk of the BOILED-Egg, shows the compound is predicted to enter the BBB.[12]

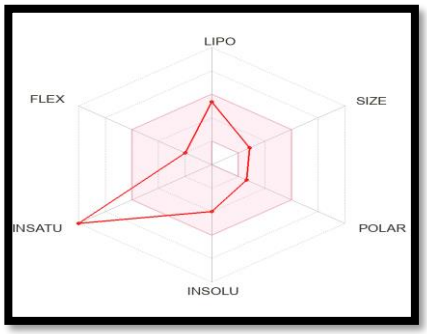

Figure 3: Bioavailability radar

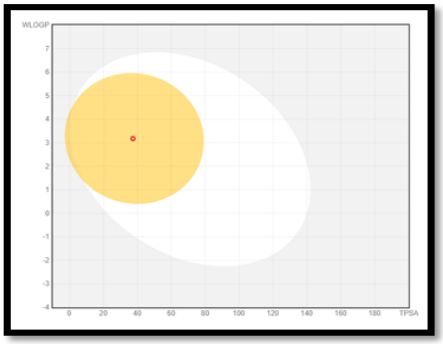

Figure 4: Boiled egg model

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MOLECULAR DOCKING STUDIES:

The 2D structure of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one was sketched using Marvin and it is converted to 3D structure, saved in PDB format in working folder. Target proteins are downloaded from RCSB Protein data bank.

Active site for desired proteins was identified from PDB sum using LIGPLOT diagram. The docking study of the synthesized compounds was carried out using AUTODOCK 4.2 version against targets like CDK-6 and acetylcholinesterase. The final docked image is studied using chimera (**Fig: 5, 6**). The docking interaction were then compared with standard drug.(**Table: 3, 4**)

RESULT AND DISCUSSION

Anti-cancer activity:

Liganded x-ray crystal structure of cyclin-dependent kinase-6 (CDK6) (PDB ID: 4AUA). The active site for this structure, determined through PDB sum, exhibits a resolution of 2.31Å. Within the A chain, specific amino acids contribute to the active site: Val101, Glu99.The active site selection was facilitated within a grid box of dimensions 60*60*60.

Palbociclib is an endocrine-based chemotherapeutic agent used in combination with other antineoplastic agents to treat HER2-negative and HR-positive advanced or metastatic breast cancer was chosen as standard drug for docking.

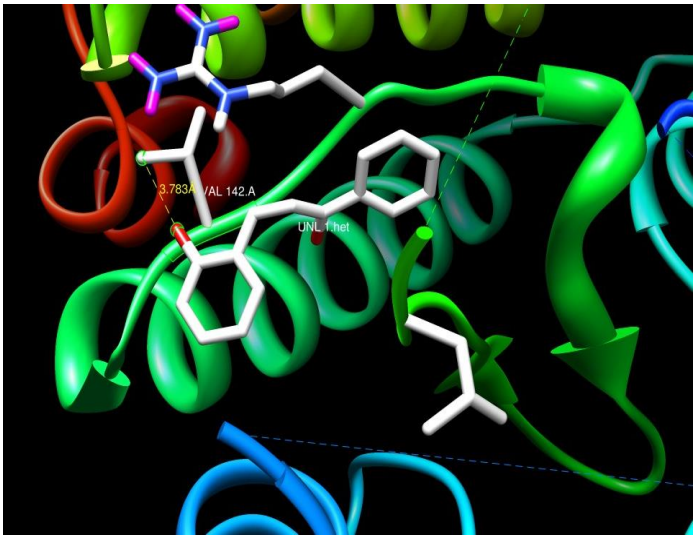

Figure 5: Docked image of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one against cyclin-dependent kinase-6 (CDK6)

Table 3: Docking results of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one and standard drug towards target protein CDK6

S.NO	COMPOUND	H-BOND INTERACTION	H-BOND DISTANCE (Å)	BINDING ENERGY kcal/mol
1.	(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one	PRO_3: A: VAL 142: HN PRO_3: A: GLY 165: HN	3.783	-6.86
2.	Palbociclib	PRO3: A: ASN 150: HD22 1 LIG-2: :UNL 1 : H	9.124	-7.89

Anti-cholinesterase activity:

Three dimensional structure of the anti-alzheimer drug, e2020 (aricept), complexed with its target acetylcholinesterase. (PDB ID: 1EVE). The active site for this structure, determined through PDB sum, exhibits a resolution of 2.50Å. The proteins are processed to remove the complexed heteroatoms and saved as PDB. Within the A chain, specific amino acids contribute to the active site: Asn416 (A).

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Donepezil is an acetylcholinesterase inhibitor used to treat the behavioral and cognitive effects of Alzheimer's disease and other types of dementia was chosen as standard drug for docking. Donepezil selectively and reversibly inhibits the acetylcholinesterase enzyme, which normally breaks down acetylcholine.

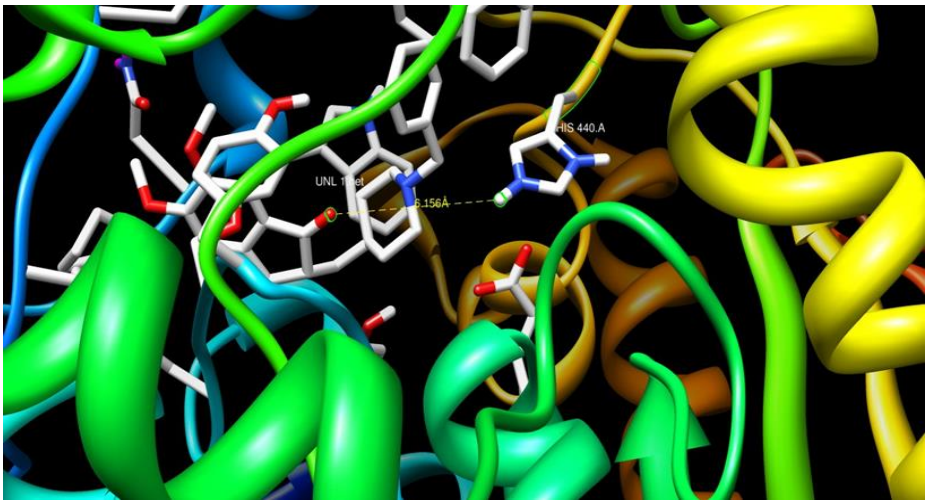

Figure 6: Docked image of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one against acetylcholinesterase (1EVE)

Table 4: Docking results of (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one and standard drug towards target protein 1EVE

S.NO	COMPOUND	H-BOND INTERACTION	H-BOND DISTANCE (Å)	BINDING ENERGY kcal/mol
1.	(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one	PRO: A: HIS 440 : HE 2	5.946	-7.73
2.	Donepezil	PRO_3: A: HIS 440 : HE 2	6.156	-10.27

CONCLUSION

In this study, chalcone was synthesized from the reaction between salicylaldehyde and acetophenone in the presence of ammonium hydroxide, the base catalyst (**Fig: 2).** The purity of the synthesized compounds was checked by using Thin Layer Chromatography using the solvent system chloroform: ethyl acetate (9:1).The chemical structure of the synthesized compounds was characterized by using UV ,FT-IR, ^{13}C and ^{1}H NMR Spectroscopy.

Molecular properties and bioactivity score of synthesized compounds were studied using molinspiration and Swiss ADME software. The parameters were according to the Lipinski rule of 5, this shows that the synthesised compound is likely to be a drug **(Table: 1, 2**). The **B**rain **O**r **I**ntestina**L** **E**stimate**D** permeation method (BOILED-Egg) has predicted that the synthesised compound has ability to cross Blood Brain Barrier **(Fig: 3, 4).**

The synthesized compound (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one produced maximum binding affinity (-6.86 kcal/mol) compared to the standard drug Palbociclib (-7.89 kcal/mol) against the targeted enzyme CDK-6. The synthesized compound (2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one produced maximum binding affinity (-7.73kcal/mol) compared to the standard drug Donepezil (-10.27kcal/mol) against the targeted enzyme acetylcholinesterase (1EVE).Docking studies indicates that the synthesized compound shows significant anticancer and anti- Alzheimer's activity.

ACKNOWLEDGEMENT

Authors are thankful to the management of Shri Venkateshwara college of pharmacy, Ariyur, Puducherry for carrying out the studies in Laboratory.

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How to cite this article:
Priyadharshini Selvam et al. Ijppr.Human, 2024; Vol. 30 (8): 282-287.

Conflict of Interest Statement: All authors have nothing else to disclose.