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Research Article

Synthesis and Molecular Docking studies of Heterocyclic Chalcone Derivatives as BRCA1 inhibitors

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Abstract

According to Claisen-Schmidt condensation a series of novel substituted Indolyl Chalcone derivatives were synthesized and evaluated Docking study. The synthesized compounds have been characterized by TLC, elemental analysis, IR and ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Claisen-Schmidt condensation, Chalcone and Docking

1. Introduction

Chalcone can be prepared in a number of ways the simplest being aldolic condensation between benzaldehydes and acetophenones[1]. This method allows for the rapid synthesis of several chalcones using common inexpensive reagents and was used to prepare a library of 154 synthetic chalcones with different substitutions that were subsequently screened for activity against bacterial and fungal strain. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[2], anti-inflammatory[3], analgesic[4], antiulcerative[5], antimalarial[6], antidiabactics[7], antidepressant[8], anticonvulsant[9], anticancer[10] and antioxidant[11] activities. Antibacterial and antifungal activity of chalcones has been investigated by a number of researchers[12].

Molecular docking[13] is a very popular method introduced to investigate molecular association and is particularly useful in the drug discovery field to study the binding of small molecules (ligands) to macromolecules (receptor). Docking is frequently used to predict the binding orientation of small drugs candidates to their protein targets in order to in turn predict the affinity and activity of a small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been direct docking.

2. Materials and Methods

The melting point of the compounds was determined in open capillaries, using Eligo digital melting point apparatus and expressed in degree Celsius and the values were uncorrected. IR spectra of the compounds were recorded on Shimadzu 8201 spectrophotometer using KBr and the values are expressed in 4000-400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 MHz Spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. All the solvents used were analytical grade. The purity of the compound was checked by TLC using silica gel plates.

2.1 General Method of Preparation of Chalcone

2,3-dimethoxy acetophenone and Thiophene –2– carboldehyde were commercially purchased (Aldrich) and used as received. HPLC–grade organic solvents were used for the TLC. Equimolar quantity of 2,3-dimethoxy-acetophenone (0.01 mol) and Thiophene–2–caboldehyde (0.01 mol) were dissolved in 20 ml of ethanol was cooled to 5-10^{0}C in an ice bath. The reaction mixture was magnetically stirred for 3h. In the cold solution, 10 ml of 10% Sodium hydroxide solution was added drop wise. A flocculants precipitate was formed. The precipitate was filtered

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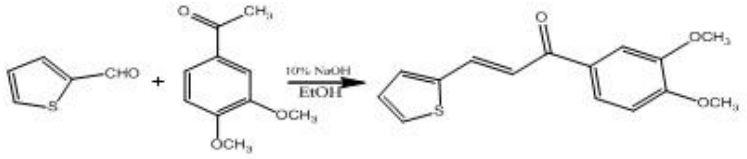
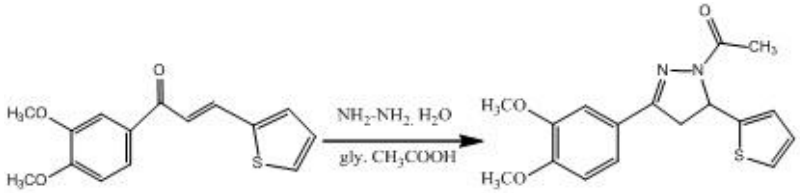
and washed with cold water and recrystallise from ethanol. The reaction mixture was purified by TLC on a silica gel column (n-hexane: acetone, 7:3).



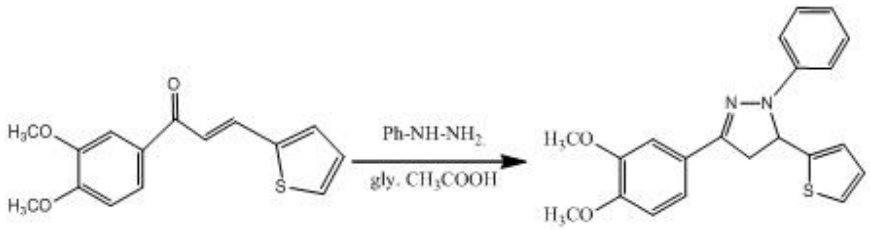
2.1.1 Preparation of 1-(5-(3,4-Dimethoxyphenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-ethanone

A mixture of chalcone (0.001 mol) and hydrazine hydrate (0.001 mol) in 20 mL acetic acid was refluxed for 8h. The reaction mixture was cooled and poured into 50 mL of ice cold water. The precipitate was collected by filtration and purified by recrystallization from ethanol. The progress of the reaction was monitored by TLC (3:9, methanol: n-hexane) the obtained solid was crystallized from EtOH. Colour-Yellow.



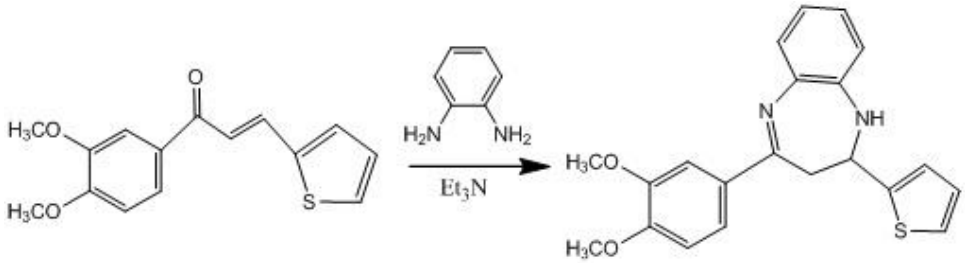
2.1.2 Preparation of 5-(3,4-Dimethoxy-phenyl)-1-phenyl-3-thiophen-2-yl-4,5-dihydro-1H-pyrazole

The solution of appropriate chalcone (0.001 mol) was refluxed with phenyl hydrazine (0.001mol) in dry EtOH (30 ml) and catalytic amount of glacial acetic acid for at 80^0C for 8h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue obtained was purified by TLC (2:8, diethyl ether:petroleum ether) the obtained solid was crystallized from EtOH. Colour-Yellow.



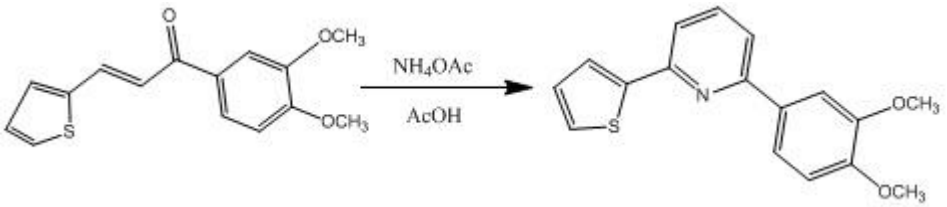
2.1.3 Preparation of 2-(3,4-dimethoxy-phenyl)-4-(thiophen-2-yl)-2,3-dihydro-1H-benzo[b] [1,4] diazepine

In the absence of sunlight, a solution of chalcone (0.001mol) and 1, 2-diaminobenzene (0.001mole) in absolute ethanol (15 mL) was refluxed in the presence of triethyl amine (3 mL) for 15h. The progress of the reaction was monitored by TLC (2:8, ethylacetate:Chloroform). The reaction mixture was cooled to 0°C and left overnight. The precipitate formed was filtered off and recrystallized from ethanol affording light yellow crystals. Yield: 74%.



2.1.4 Preparation of 2-(3,4-dimethoxyphenyl)-6-(thiophene-2-yl)pyridine

A mixture of chalcone (0.001 mol) and ammonium acetate (0.001mol) in glacial acetic acid (10 mL) was refluxed for 6 h. The reaction mixture was cooled and poured into ice-cold water (50mL). The precipitate was collected by filtration and recrystallized in ethanol to get white powder. Yield: 56%.



2.2 Molecular Docking Study

2.2.1 Preparation of Protein

Crystal structure of BRCA1 was extracted from protein data bank (PDB ID: 1T15) and after retrieving protein structure were further carried into prepare the protein using protein preparation wizard, water molecules were removed hydrogen atoms, protein structure energy was minimized until the average root mean square was reached 0.30Å. Then, prepared protein further executed for molecular docking studies. The protein molecule BRCA1 for which active site is going to be predicted was chosen from Protein data bank and saved in sequence format. After that, the downloaded structure was submitted to CASTp on line server to visualize and recognize the active site residues. Upon inspection, active site or binding site residues includes ASN 1678, ILE 1680, SEP 8, LEU 1701. Chem draw assistance has been taken to sketch the synthesized nine molecules. The sketched was then prepared by Ligprep, where 2D structure gets organized into 3D structure and different tautomers were also the result of Ligprep. Ligands were ionized at a pH range about 7.0± 2.0 to preserve the qualities for molecualr docking.Glide is employed for the rapid docking of five molecules into the active site of the target receptor. The grid based docking was carried out with box measuring up to 20 Å preferable ranges. The Glide algorithm is operates with a systematic search of positions, orientations, and conformations of the ligand in the receptor binding site using funnel type approach and follows a unique scoring method. Glide score and glide energy was analyzed using XP visualize. The glide score and glide energy were reported in table 1.

2.2.2 Binding mode analysis Heterocyclic Chalcone Derivatives

Docking simulation of 2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile into BRCA1 resulted in the formation of single hydrogen bond interaction with bond distance of (2.13Å) and it was observed that backbone hydrogen atom of residue of ILE 1680 act as hydrogen bond donor to interact with oxygen atom of the 2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile . The Glide Score and Glide Energy value for 2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile were observed -3.1Kcal/mol and -34.54Kcal/mol. Furthermore LEU 1679, 6 VAL 1654, PHE 1662, TRP 1782 a number of hydrophobic interaction were found between 2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile into BRCA1. Docking simulation of 5 within the active site of the BRCA1 has been analyzed. The Glide Score and Glide Energy value for compound 2 were -2.6Kcal/mol and –21.32Kcal/mol. Upon the examination of docking features between 5 into BRCA1 it was found only one hydrogen bond interaction with bond length(1.70 Å). The oxygen atom of trhew SEP 8 were nicely interacted with hydrogen atom of the 5. Furthermore LEU 1701, PRO 9, LEU 1679 a number of hydrophobic interaction were bound between 5 into BRCA1. Docking simulation of 1, 5-(3,4-dimethoxyphenyl)-1-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole within the active site of the BRCA1 has been analyzed. The Glide Score and Glide Energy value for com pound 2 were -2.6Kcal/mol and –21.91Kcal/mol. LEU 1701, PRO 9, LEU 1679 a number of hydrophobic interaction were bound between 1, 5-(3,4-dimethoxyphenyl)-1-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole into BRCA1. Docking simulation of 1-acetyl-5-(3,4-dimethoxyphenyl)-3-(2-thienyl)-4,5-dihydro-1H-pyrazole within the active site of the BRCA1 has been analyzed. The Glide Score and Glide Energy value for compound 2 were -2.4Kcal/mol and –24.64Kcal/mol. The LEU 1705, PRO 9, LEU 1679, TRP 1782 a number of hydrophobic interaction were bound between 1-acetyl-5-(3,4-dimethoxyphenyl)-3-(2-thienyl)-4,5-dihydro-1H-pyrazole into BRCA1. Docking simulation of 2-(3,4-dimethoxyphenyl)-6-(2-thienyl)pyridine within the active site of the BRCA1 has been analyzed.The Glide Score and Glide Energy value for 2-(3,4-dimethoxyphenyl)-6-(2-hienyl)pyridine were observed -4.4Kcal/mol and -43.31Kcal/mol. Upon the examination of docking features between 2-(3,4-dimethoxyphenyl)-6-(2-thienyl)pyridine and BRCA1. it was found only one hydrogen bond interactions. the side chain hydrogen atom of the ASN 1678 were well interacted with oxygen atom of the2-(3,4-dimethoxyphenyl)-6-(2-thienyl) with bond length (2.15Å), intestingly only one π-cation interaction were formed between compound and LYS 1702, Furthermore PRO 9, ILE 1680, VAL 1654 a number of hydrophobic interaction were bound between 2-(3,4-dimethoxyphenyl)-6-(2-thienyl)pyridine into BRCA1.

Figure 1: Binding mode analysis of Heterocyclic Chalcone Derivatives with Target protein BRCA1.

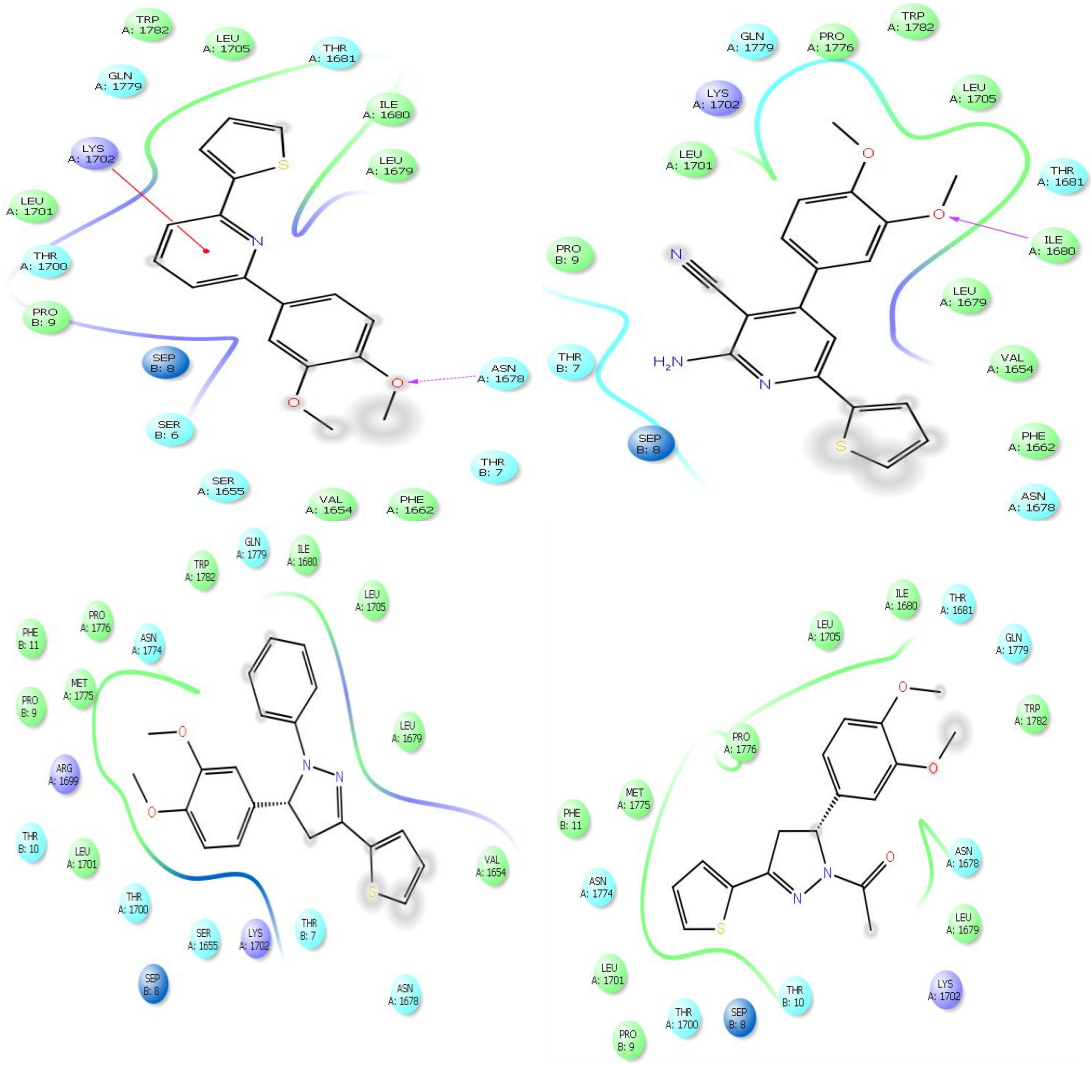


Figure 1: 2-(3,4-dimethoxyphenyl)-6-(2-thienyl)pyridine
2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile;
1,5-(3,4-dimethoxyphenyl)-1-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole;
1-acetyl-5-(3,4-dimethoxyphenyl)-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole.

Table 1: Glide extra-precision (XP) results for five molecules by use of Schrodinger 9.5.

Compound Name	Glide Score	Glide Energy	No. of Hydrogen bond interactions	Interacting Residues	Distance (Å)
2-(3,4-dimethoxyphenyl)-6-(2-thienyl)pyridine	-4.4	-43.31	1	ASN 1678	2.15
2-amino-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)nicotinonitrile	-3.1	-34.54	1	ILE 1680	2.13
1, 5-(3,4-dimethoxyphenyl)-1-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole	-2.6	-21.91	1	LEU 1701	2.37
1-acetyl-5-(3,4-dimethoxyphenyl)-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole	-2.4	-24.64	-	-	-

4. Conclusion

A series of Chalcone derivatives were successfully synthesized and characterized spectroscopically by IR, 1H and 13C-NMR. The study of docking it involves protein along with the BRCA1 in one hydrogen bond proves to be a most stable complex inhibiting the activity of integrase. In order to evaluate accuracy of docking, binding energy and numbers in cluster was used. The interaction shows that it binds to the protein and specifically interferes with its strand transfer activity.

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Author contributions

Conceived and designed the experiments, Performed the experiments, T. Analyzed the data, Contributed software facility, Wrote the paper, Assisted in writing the paper and referencing.

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