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Research Article

Insilico Screening Of Novel Pyrimidinones As Potential Her2 Inhibitors Targeting Breast Cancer

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ABSTRACT

The molecular docking and ADME screening of newer 4-[4-(dimethylamino)phenyl]-6-phenylpyrimidin-2(5H)-ones derivatives were carried out. One of the major subtypes of breast cancer has overexpression of HER2. So here, all the compounds are screened for HER2 inhibitor activity. The ADME studies are performed on the SWISSADME webserver. The docking studies are performed in Autodock Vina integrated PyRx. Results depict that all derivatives binding affinity is greater than standard trastuzumab at the active site of HER2 and have significant ADME properties.

INTRODUCTION

Breast cancer (BC) is a heterogenous disease and the most commonly diagnosed type of malignancy among women. It is the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases and 6,85,000 deaths globally [1]. The global burden of breast cancer is anticipated to cross 2 million by the year 2023 [2]. Breast cancer is described based on the hormone receptor expression pattern, human epidermal growth factor receptor(HER2) and human receptors(ER/PR) [3]. Human epidermal growth factor receptor 2 (HER2) having tyrosine kinase activity is overexpressed in 15-30% of invasive breast cancer. HER2 gene amplification is associated with reduced survival and a higher recurrence rate in breast cancer [4]. The treatment of BC comprises chemotherapy, radiation therapy, and surgery. The long-term challenge of current chemotherapeutic drugs is the commencement of drug resistance [5] and cytotoxic effects at sites other than target sites. This prompts the development of novel molecules with high specificity, greater potency, minimal off-target effects, and drug resistance [6]. Pyrimidines are nitrogen-containing compounds that have anti-cancer potential due to their significant role in nucleic acid synthesis [7]. The synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid

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(RNA) depends on several pyrimidine derivatives including adenine, guanine, cytosine, thymine, and uracil [8,9]. Here, 4-[4-(dimethylamino)phenyl]-6-phenylpyrimidin-2(5H)-ones derivatives were designed and docked for their anti-breast cancer HER2 inhibiting activities.

MATERIALS AND METHODS

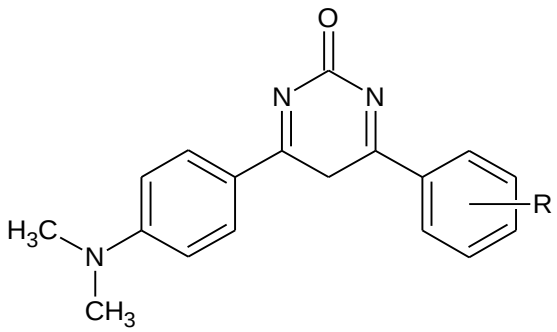

Figure 1 structure of designed compound

Table 1 different derivatives of designed compound

PR1 – 3-amino	PR14 – 2-hydroxy
PR2 – 4-fluoro	PR15 – 2-methoxy
PR3 – 4-methoxy	PR16 – 2-fluoro
PR4 – 3-hydroxy	PR17 – 2-chloro
PR5 – 4-nitro	PR18 – 4-carboxy
PR6 – 4-methyl	PR19 – 2-methyl
PR7 – 2-chloro, 3-hydroxy	PR20 – 4-ethyl
PR8 – 3-methyl	PR21 – 4-amino
PR9 – 3-nitro	PR22 – 2-amino
PR10 – 4-hydroxy	PR23 – 3-bromo
PR11 – 4-hydroxy, 3-methoxy	PR24 – 2-carboxy
PR12 – 4-chloro	PR25 – 4-bromo
PR13 – 3-chloro	TRZ - Trastuzumab

Receptor Protein preparation

The crystal structure of the kinase domain of human HER2 along with cocrystallized ligand (PDB ID: 3PP0, 2.25 Å) were downloaded from RCSB protein data bank in pdb format. It is viewed and water molecules, ligand, and Chain-B were removed using Biovia Discovery Studio 2024 software while retaining chain A for docking study [10].

Screening for compounds

SWISS-ADME web server was used for the screening of compounds. The compounds were filtered Lipinski's rule of five (RO5). Then drug-likeliness, pharmacokinetics, medicinal chemistry and physicochemical properties were analyzed for the prediction of absorption, distribution, metabolism and excretion (ADME) of compounds [11].

Ligand preparation

The two dimensional structures of pyrimidinone derivatives were drawn with the help of ChemSketch and then, converted to 3D structure using Chem3D pro 12.0 software. The ligands molecular geometry optimization was achieved with energy minimization applying molecular mechanics (MM2) force field and saved in PDB format [12].

Molecular docking using PyRx

AutoDock Vina integrated into PyRx was used for the molecular docking. The optimization was done with Open Babel and PyRx to prepare them for docking. The grid was arranged to cover only the

active site of the HER2 protein. Visualization of docking results was done using Biovia Discovery Studio 2024. Docking result analysis mostly focused on binding affinity and binding site on HER2 [13,14].

Protein validation

In the validation of docking protocols, the ligand such as positive control trastuzumab was docked against the active site of 3PP0. The amino acid residues Leu755, Arg756, Phe731, Ala763, Gly865 And Glu766 were found in common interaction for these selected control against the target [11].

RESULT AND DISCUSSION

Insilico ADME studies

The insilico ADME studies are carried out in SWISSADME web server There are five different types of rule-based filters, namely Lipinski filter, Ghose filter, Veber filter, Egan and Muegge filter. Lipinski filter includes Molecular weight 500, MLOGP (lipophilicity) 4.15, hydrogen bond acceptors 10, and hydrogen bond donors 5 [15]. Ghose's filter has a molecular weight of 480, a lipophilicity of 0.4 WLOGP (5.6), a molar refractivity of 40, and a number of atoms of 20 [16]. The number of rotatable bonds is 10 and the total polar surface area is 140 in Veber's filter [17].WLOGP (Lipophilicity) 5.88 and total polar surface area 131.6 are included in Egan's filter [18]. Muegge's filter contains the following parameters: 200 molecular weight 600, 2 XLOGP3 (lipophilicity) 5, total polar surface area 150, number of rings 7, number of carbon > 4, number of heteroatoms > 1, number of rotatable bonds 15, hydrogen bond acceptors 10, and hydrogen bond donors 5 [19]. All the compounds obey all these filter and show drug likeness. Different physicochemical properties are tabulated in table 2. These shows that all the compounds are promising drug candidates, having improved ADME properties than the standard drug.

Table 2 different physicochemical properties of drug

Derivatives	Molecular weight (g/mol)	Rotatable bonds	H- bond acceptors	H- bond donors	TSPA (Å^2)	Log P
PR1	306.36	3	3	1	71.05	2.65
PR2	309.34	3	4	0	45.03	3.50
PR3	321.37	4	4	0	54.26	3.21
PR4	307.35	3	4	1	65.26	2.79
PR5	336.34	4	5	0	90.85	2.58
PR6	305.37	3	3	0	45.03	3.54
PR7	341.79	3	4	1	65.26	3.36
PR8	305.37	3	3	0	45.03	3.54
PR9	336.34	4	5	0	90.85	2.64
PR10	307.35	3	4	1	65.26	2.78
PR11	337.37	4	5	1	74.49	2.81
PR12	325.79	3	3	0	45.03	3.73
PR13	325.79	3	3	0	45.03	3.74
PR14	307.35	3	4	1	65.26	2.81
PR15	321.37	4	4	0	54.26	3.15
PR16	309.34	3	4	0	45.03	3.53
PR17	325.79	3	3	0	45.03	3.73
PR18	335.36	4	5	1	82.33	2.74
PR19	305.37	3	3	0	45.03	3.52
PR20	319.40	4	3	0	45.03	3.83
PR21	306.36	3	3	1	71.05	2.65

PR22	306.36	3	3	1	71.05	2.63
PR23	370.24	3	3	0	45.03	3.82
PR24	335.36	4	5	1	82.33	2.76
PR25	370.24	3	3	0	45.03	3.82

Molecular docking results

All compounds has greater binding affinity than the standard trastuzumab. The different binding energy of derivatives are tabulated in table 3.

Table 3 binding energy of derivatives

Derivatives	Binding energy (Kcal/mol)
PR1	-8.2
PR2	-8.4
PR3	-8.1
PR4	-8.1
PR5	-8.3
PR6	-8.5
PR7	-8.0
PR8	-8.7
PR9	-8.8
PR10	-8.1
PR11	-8.1
PR12	-8.4
PR13	-8.3
PR14	-8.3
PR15	-8.3
PR16	-8.4
PR17	-8.5
PR18	-8.7
PR19	-8.8
PR20	-8.4
PR21	-8.2
PR22	-8.6
PR23	-8.6
PR24	-8.6
PR25	-8.3
TRZ	-6.9

The compounds PR9 and PR19 shows maximum binding affinity than the trastuzumab. PR9 interact with Ala867, Phe731, Ile767, Leu755, Arg756, Arg868 through hydrogen and hydrophobic bonds. PR19 interact with Phe731, Ile767, Ala867, Arg756 through hydrogen and hydrophobic bonds [20]. The 2d and 3d interaction at the active site of HER2 are shown in figure 2 and 3.

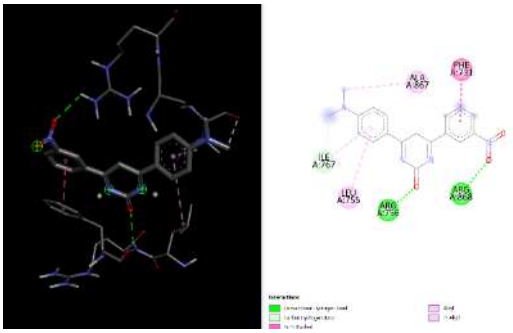

Figure 2 2d and 3d interaction of PR9 at the active site of HER2.

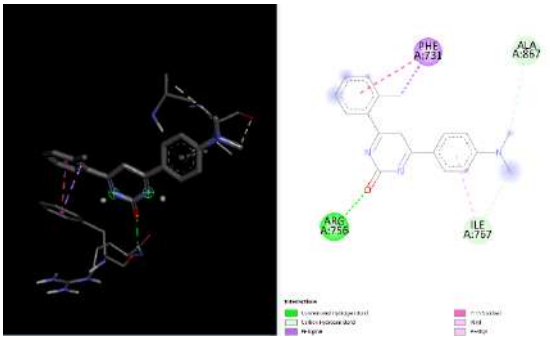

Figure 3 2d and 3d interaction of PR19 at the active site of HER2

CONCLUSION

Newer pyrimidionone derivatives were designed and docked. Results show that all the compounds have greater affinity than the standard compound. The compounds are screened for ADME properties. It also depicts the derivatives as promising candidates as HER2 inhibitors. Further investigation is needed for its anticancer activity. For that, the selected derivatives are synthesized using suitable methods, and their invitro anticancer activities are studied in the future.

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