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RESEARCH ARTICLE

Molecular Docking of Benzoylurea Derivatives as Potential Anti-Breast Cancer Agent and Its Admet Profiles

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Abstract

Objective: At present therapy for breast cancer leads to target cell therapy. One of the compounds that can be developed as anti-breast cancer agents is benzoylurea. Benzoylurea has the same pharmacophore group with hydroxyurea as urea derivatives which have anticancer activity. This study aims to predict the anticancer activity and ADMET profile of seven benzoylurea-derived compounds as candidates cytotoxic agent for breast cancer. Method: Biological activity of benzoylurea derivatives is predicted through molecular modeling (in silico) using the Autodock program, ADME profiles and toxicity can be predicted using the pkCSM program and the Protox II online tool. In silico test was carried out by docking between benzoylurea derivatives and HER2 receptor targets, PDB ID. 3PP0. Result: All benzoylurea-derived compounds studied were compliant with Lipinski's 5 legal requirements. The 4-tertier butylbenzoylurea compound shows a better ADME profile and its toxicity is predicted to have mutagenic properties but not hepatotoxic properties. The smallest docking score of seven benzoylurea derivatives is 4-tertier butylbenzoylurea, therefore the compound has the best cytotoxic activity. Conclusion: the 4-tertier butylbenzoylurea compound is chosen as the compound to be synthesized and further developed.

Keywords: *Molecular docking; Benzoylurea; Anti-breast cancer; ADMET profiles.*

Introduction

Cancer that is frightening for women in the world is breast cancer which is the second most common cancer in the world. The prevalence of breast cancer with new cases in 2018 is 24.2% in women spread across 154 countries and breast cancer deaths by 15% [1]. Efforts to develop anticancer drugs are still being made to overcome drugs that are not selective against cancer cells and also to drugs that have experienced resistance.

Efforts to develop existing drugs can be made by designing drugs that aim to get new drugs with the desired biological effects and reduce the side effects that exist through structural modification. Structural modification is carried out by synthesizing several derivatives of the guiding compound, identifying the structure and testing its biological activity [2]. Before a compound is synthesized, a method is needed to predict the physicochemical properties of a drug molecule, its pharmacokinetic profile and toxicity and its interactions with the receptor. The method for predicting the molecular properties of drugs is called molecular modeling or in silico [3].

In silico technique is done through a simulation of drug-receptor interaction process or called docking with the help of computers [4]. Docking is an attempt to align the ligand as a small molecule into the target cell, which is a large protein molecule [5]. The development of anticancer drugs is currently aimed at targeting cancer cells. The class of anticancer drugs that have a mechanism of action on target cells is the

tyrosine-kinase inhibitor group. Tyrosine kinase receptors are a group of erbB receptors that play a key role in the signal transduction pathway by regulating cell division and differentiation.

Under certain conditions such as excessive receptor expression and mutations, these receptors can become hyperactive, causing uncontrolled cell proliferation [6,7,8]. Among the tyrosine kinase receptors that have been identified as important in breast cancer are the human epidermal growth factor receptor (HER-2 or erbB-2). Deregulation of growth signals due to hyperactivation of the HER-2 receptor is seen in breast cancer [9].

About 20% -30% of breast cancer patients is overexpressed with HER2, resulting in intracellular signaling irregularities that correlate with aggressive tumour growth and poor clinical prognosis [10]. Some benzoylurea-derived compounds show good cytotoxic activity compared to hydroxyurea using the Brine Shrimp Lethality Test (BST) method [11].

Cytotoxic activity tests were also carried out on compounds 1- (4-trifluoromethyl-benzoyl) - 3-benzoylurea using MCF7 cells and gave results that the compounds could be used as anticancer agents [12]. In this study, an in silico test was performed on seven benzoylurea-derived compounds using the Autodock Tools 4.2.6 program to predict its anticancer activity.

The in silico test is done through docking with the HER2 receptor using the PDB code: 3PP0, the original ligand is SYR127063 [13]. The docking results were compared with hydroxyurea as a drug compound containing urea and lapatinib as a drug used clinically. In silico test results in the form of bond energy values or docking scores.

The smaller the docking score indicates the more stable the drug-receptor binding so that can be improved the anticancer activity. After the in silico test, the prediction of pharmacokinetic profiles (ADME) and toxicity was performed using the pkCSM program and the Protox II online tool. Benzoylurea-derived compounds that have the greatest anticancer activity will be selected for further synthesis based on the docking score and ADMET profile.

Materials and Methods

Programs

Chem Bio Draw Version 15 (CambridgeSoft), a licensed software; Chem Bio 3D Version 15 (CambridgeSoft), a licensed software; Marvin Sketch and Avogadro software; Autodock Tools 4.2.6; SMILES Translator; pkCSM dan Protox II online tool is free online tool.

Receptor

The molecular structure of receptor HER2 can be downloaded via the protein data bank site. In this study, HER2 receptor with PDB ID: 3PP0 was selected as a target protein, because it contains a ligand 2-{2-[4-({5-chloro-6-[3 (trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5*H*pyrrolo [3,2-*d*]pyrimidin-5yl] ethoxy}-ethanol (SYR127063) [13].

Ligand

The structure of benzoylurea derivatives and comparison compounds, hydroxyurea (HU) and lapatinib, were drawn 2-D molecular structures using Marvin Sketch programme and then copied into Avogadro to make the structure 3-D. The structure of the ligand in the 3-D form is stored as *Mol2 file [2].

Molecular Docking

The ligands in the 3-D form are docking with HER2 receptors (3PP0) using Autodock Tools. The results obtained in the form of a docking score are the energy needed in the ligand-receptor interaction process. From the docking score, it can be predicted the anticancer activity of compounds through HER2 signaling inhibition [2].

Prediction of Admet of Compounds

Prediction of physicochemical properties such as molecular weight (BM), logarithm of octanol / water partition coefficient (log P), number of bonds between atoms that can rotate (Torsion); Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), Polar Surface Activity (PSA) and pharmacokinetic profiles (ADME) and the toxicity of benzoylurea-derived compounds were carried out using pkCSM and Protox II online tools [15]. Before docking, seven benzoylurea derivatives and comparison compounds (hydroxyurea and lapatinib) were drawn 2-D molecular structure with Chem-Bio Draw Ultra Version 15 program, then copied in the Chem-Bio 3D Ultra Version 15 program to make 3-D structures, then stored as *SD file or *PDB file.

Compounds in the 3-D structure are translated into the SMILES format using the Online SMILES Translator [14]. Furthermore, the compound in the form of SMILES format is processed using pkCSM online tool [15] to predict the ADME and the toxicity of the compounds. Prediction of oral toxicity (LD50) in rodents and the classification of compound toxicity based on the Globally Harmonized System (GHS) using the Protox II online tool [16, 17].

Results and Discussion

The chemical structure of benzoylurea derivatives and comparative compounds, hydroxyurea (HU) and lapatinib, can be seen in Figure 1 and Table 1.

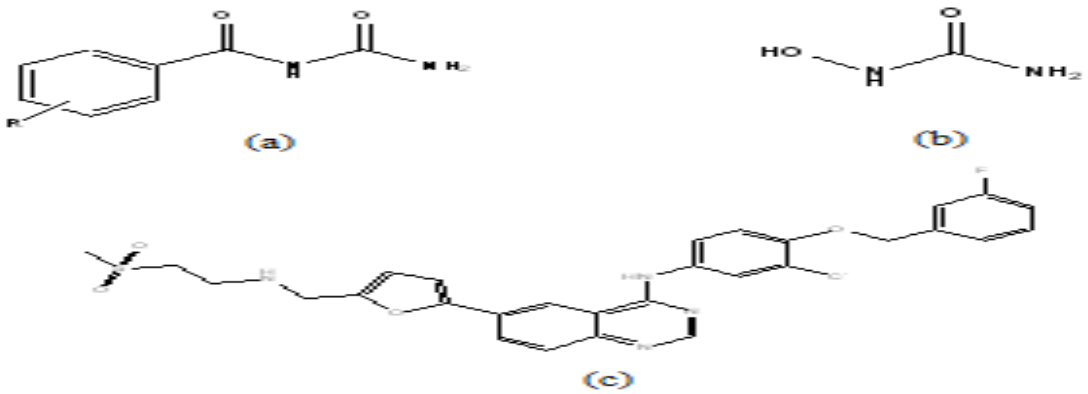


Fig. 1: **Benzoylurea derivatives (a), Hydroxyurea (b), and Lapatinib (c)**

Table 1: Chemical structure of benzoylurea-derived compounds

Compound Code	Position	R	Name of Compound
BU-1	4	H	benzoylurea
BU-2	4	OCH_3	4-methoxybenzoylurea
BU-3	4	$C(CH_3)_3$	4-tertier butylbenzoylurea
BU-4	4	CF_3	4-trifluoro methylbenzoylurea
BU-5	2	Cl	2-chloro benzoylurea
BU-6	4	Br	4-bromo benzoylurea
BU-7	4	NO_2	4-nitro benzoylurea
HU	Comparative compound		Hydroxyurea
Lapa	Comparative compound		Lapatinib

Prediction of Physicochemical Properties and ADMET Profile

Lipinski analyzed 2,245 drugs from World Drugs Index data and concluded that the compound would be difficult to absorb and the permeability would be low if it had: a molecular weight higher than 500, a log value of the octanol / water partition coefficient (log P) higher than +5; donor H-bonds (HBD) expressed by the number of O-H and N-H groups, greater than 5; and the H-acceptor (HBA) bond expressed by the number of O and N atoms is greater than 10. The analysis is known as the Lipinski law of five because all values are multiples of the number five [18]. In silico prediction of the physicochemical properties of the benzoylurea-derivatives can be seen in table 2, and the ADMET profile is shown in Table 3.

Table 2: Prediction of in silico values of physicochemical properties of benzoylurea derivatives and comparison compounds using pkCSM online tool.

Compound Code	BM	Log P	HBA	HBD	Torsion	PSA (A^2)	Legal Requirements 5 Lipinski
BU-1	164,164	0,4951	2	2	1	69,374	Yes
BU-2	194,19	0,5037	3	2	2	80,853	Yes
BU-3	220,272	1,7926	2	2	1	94,834	Yes
BU-4	232,161	1,5139	2	2	1	88,236	Yes
BU-5	198,609	1,1485	2	2	1	79,677	Yes
BU-6	243,06	1,2576	2	2	1	83,242	Yes

BU-7	209,161	0,4033	4	2	2	84,027	Yes
HU	76,056	-0,9561	2	3	0	28,539	Yes
Lapa	581,069	6,1391	8	2	11	235,650	Yes

BM = molecular weight; LogP = logarithm of octanol/water partition coefficient; Torsion = bond between rotating atoms (rotatable bond); HBA = hydrogen bond acceptors; HBD = hydrogen bond donors; PSA = polar surface activity

Based on table 2, it can be seen that the molecular weight of benzoylurea derivatives has a range of 164.164 to 243.06 (<500), log P values in the range 0.4033 - 1.7926 (<5), the number of HBD with a value of 2 (<5), and the number of HBAs in the range 2-4 (<10). These results indicate that all the benzoylurea derivatives studied were compliant with Lipinski's legal requirements [18].

Table 3: ADMET profile of benzoylurea derivatives using pkCSM and Protox online tools.

Compound Code	Absorption			Distribution			Metabolism		Excretion	Toxicity			
	Intestinal abs (%)	Skin Permeability (cm/h)	Caco-2 Permeability (cm/s)	VDss	BBB Permeability	CNS Permeability	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Total Clearance (ml/min/kg	Ames Toxicity	Hepatotoxicity	LD_{50} (mg/kg)	Class
BU-1	65,745	-3,155	0,016	-0,4	0,074	-2,927	No	No	0,378	No	No	818	4
BU-2	85,598	-3,224	0,382	-0,311	-0,243	-2,685	No	No	0,617	No	No	2000	4
BU-3	92,819	-2,852	0,895	0,019	0,014	-2,174	No	No	0,236	Yes	No	1950	4
BU-4	88,86	-3,314	0,062	-0,544	-0,395	-2,954	No	No	0,136	No	Yes	3000	5
BU-5	69,722	-3,247	0,023	-0,376	-0,108	-2,933	No	No	0,087	No	No	1950	4
BU-6	69,94	-3,254	0,029	-0,378	-0,152	-2,931	No	No	-0,207	No	No	1950	4
BU-7	73,573	-2,791	0,081	-0,563	-0,549	-2,701	No	No	0,67	Yes	No	570	4
HU	73,127	-4,319	0,494	-0,495	-0,545	-3,488	No	No	0,659	Yes	No	5760	6
Lapa	97,254	-2,735	-0,098	0,083	-1,076	-3,153	No	Yes	0,565	No	Yes	1500	4

The compound is said to have excellent absorption if the value of intestinal absorption is above 30% [19]. It can be seen in Table 3 that benzoylurea-derived compounds have proper intestinal absorption, and the highest intestinal absorption value is BU-3 compound. HU has lower intestinal absorption value than BU-3 while lapatinib has a slightly higher absorption value than BU-3. Skin permeability is an essential consideration for the development of transdermal drugs. To predict whether a compound can penetrate the skin, it can use a skin permeability constant that is log Kp (cm/h). If the log Kp> -2.5 means that the compound has a relatively low penetration in the skin [19].

Based on table 3, benzoylurea-derived compounds have log Kp in the range of -2.791 to -3.314 cm/h (<-2.5), therefore it can be said that benzoylurea-derived compounds have good penetration into the skin. Likewise, HU and lapatinib as comparison compounds have good penetration into the skin. Caco-2 is a cell line derived from human colorectal

adenocarcinoma epithelial cells. This cell is used extensively as an in vitro model of human intestinal mucosa to predict absorption of drugs given orally. The compound that is predicted to have a high Caco-2 permeability if it has a log Papp value> 0.90 cm / s [19]. From table 3, it is known that all benzoylurea-derived compounds and comparison compounds have low Caco-2 permeability.

Among the seven benzoylurea-derived compounds, compounds with BU-3 codes have log Papp of 0.895 (close to 0.9). Volume distribution (VDss) is the volume required for a drug dose to be homogeneously distributed at a balanced level in blood plasma. The higher the distribution volume, the more drugs are distributed in the tissue than in the plasma.

Based on the pkCSM prediction, that the distribution volume (VDss) is low if the log VDss <-0.15 and the distribution volume is high if the log VDss> 0.45 [19]. All of the benzoylurea-derived compounds, only compounds with BU-3 code (4-tertier butylbenzoylurea) can be distributed equally in blood plasma, as well as lapatinib as comparison compound.

The ability of drugs to penetrate the brain through the blood-brain barrier (BBB) is an important parameter to reduce side effects and toxicity or to improve the pharmacological activity of drugs in the brain. BBB permeability is measured in vivo in animal models as log BB. If the log BB> 0.3 is said to be the compound can penetrate the blood-brain barrier directly, but the compound with log BB <-1 means that it is poorly distributed into the brain [19].

In addition to BBB permeability, CNS (Central Nervous System) permeability is also essential, namely the ability of drugs to be able to penetrate the CNS. Log PS expresses CNS permeability if compounds with log PS> -2 are considered to be able to penetrate the CNS, whereas compounds with log PS <-3 are predicted not to be penetrated CNS [19].

It can be seen in Table 3 that all benzoylurea-derived compounds are predicted to penetrate moderately into BBB and CNS. HU as a comparative compound is predicted to be moderately penetrated into BBB but not penetrated into CNS, whereas lapatinib can not penetrate either into the BBB or CNS.

Cytochrome P450 is an enzyme that is responsible for the metabolism of many drugs. Inhibitors of these enzymes can change the pharmacokinetics of these drugs, so it is critical to evaluate whether a compound can affect cytochrome P450. There are two main isoforms responsible for metabolism, namely 2D6 (CYP2D6) and 3A4 (CYP3A4) [19].

From table 3, it can be seen that all benzoylurea-derived compounds do not affect or inhibit CYP2D6 and CYP3A4. HU also does not affect both the enzymes except lapatinib can affect the CYP3A4 enzyme. Drug clearance is measured by the proportionality constant CLtot and occurs primarily as a combination of hepatic clearance and renal clearance.

The higher the CLtot value of the compound, the faster the excretion process [19]. Based on table 3, the CLtot of benzoylurea-derived compounds is in the range of -0.207 to 0.67 ml/min/kg. The CLtot values state that the speed of excretion of benzoylurea-derived compounds can be predicted. To determine the toxicity of compounds, the Ames Toxicity test and hepatotoxicity test can be done. Ames Toxicity is a method used to assess the potential for mutagenic compounds using bacteria.

The test results stated positive means showing the compound is mutagenic and can be carcinogenic [19]. The compound that showed at least one pathological or physiological hepatic event was considered hepatotoxic and highly related to liver disruption [20]. From table 3 it can be seen that compounds with BU-3 and BU-7 codes, 4-tertier butylbenzoylurea and 4-nitro benzoylurea are positive in the Ames Toxicity test, whereas compounds with BU-4 code (3-trifluoro methylbenzoylurea) are predicted to be hepatotoxic.

HU is also positive in the Ames Toxicity test and lapatinib is positive in hepatotoxicity. The lethal dose (LD50) is the number of compounds administered which can cause the death of 50% of experimental animals. LD50 is a standard measurement of acute toxicity

that is used to assess the relative toxicity of a different compound.

To determine the prediction of the toxicity of benzoylurea derivatives, an acute oral toxicity test for rodent (LD50) and acute toxicity classification of compounds based on Globally Harmonized System (GSH) using the Protox II online tool.

Based on table 3, it can be seen that benzoylurea derivatives are predicted to have LD50 values ranging between 570 - 3000 mg/kg and are included in the toxicity class 4 and 5 based on GHS. There are six benzoylurea-derived compounds namely BU-1 to BU-3 and BU-5 to BU-7 which belong to the 4 GSH toxicity class (300 <LD50 ≤ 2000) with the indication "harmful if swallowed", this means that the compound is predicted to be of a slightly toxic. One benzoylurea-derived compound, BU-4 which belongs to class 5 GSH (2000 <LD50 ≤ 5000) with an indication "may be harmful if swallowed", this means that the compound is predicted to have relatively low acute toxicity. Lapatinib is included in the toxicity class 4 according to GSH, this means that lapatinib is a slightly toxic compound. HU is predicted as non toxic compound according GSH classification.

Molecular Docking

Molecular docking is done to determine the pharmacological activity of benzoylurea derivatives and to explain the interaction between ligands and receptors. The docking results of benzoylurea derivatives and comparative compounds with HER2 receptor targets (PDB code: 3PP0) and its interaction with amino acids target on HER2 receptor can be seen in Table 4 and 5.

Table 4: Docking score of benzoylurea derivates and comparative compounds by docking with Autodock Tools

Compound Code	Docking Score
BU-1	-5,88
BU-2	-5,88
BU-3	-7,01
BU-4	-6,02
BU-5	-6,42
BU-6	-6,55
BU-7	-6,42
HU	-3,02
Lapa	-10,80

From table 4, the compound that has the smallest docking score is a BU-3 compound. This shows that BU-3 compound is predicted to has the best anticancer activity among benzoylurea derivatives. The smaller the docking score indicates that the ligand-receptor bond is more stable.

Anticancer activity of benzoylurea-derived compounds is predicted to be still lower compared to lapatinib.

When the benzoylurea-derived compounds are compared with hydroxyurea, the anticancer activity of benzoylurea derivatives is predicted to be better.

Based on table 5, BU-3 compound has the most number of hydrogen bonds among the benzoylurea derivatives. The hydrogen bonds are strengthened by the steric interactions on Val 734, Lys 753 and Leu 796 which cause BU-3 compound to has the smallest docking score. HU has 5 hydrogen bonds and 1 steric interaction while lapatinib has 4 hydrogen bonds and is strengthened with many steric interactions which causes the predicted anticancer activity of lapatinib to be better than benzoylurea derivatives.

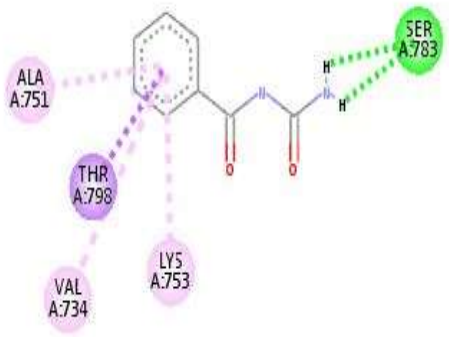
However,there are many cases found that lapatinib has resistance [21, 22] so it is necessary to develop new drugs that can overcome the deficiencies of lapatinib and are selective against cancer cells.

2D View of the interaction of the benzoylurea derivates and comparative compounds with HER2 receptor targets can be seen in Figures 2 and 3. Amino acids receptor targets HER2 involved in interactions with benzoylurea derivatives and comparative compounds can be seen in Table 5.

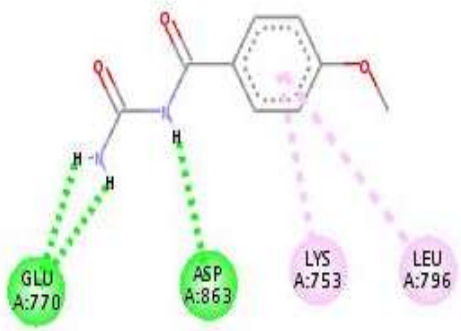
Table 5: Interaction of benzoylurea derivatives and comparative compounds with amino acids on HER2 receptor

Compound Code	Hydrogen Bond and Steric Interactions																				
	Ser783	**Ser728**	**Asp863**	**Asn850**	**Thr862**	**Arg849**	**Glu770**	**Gln799**	**Ala751**	**Val734**	**Lys753**	**Thr798**	**Leu796**	**Lys758**	**Leu785**	**Met801**	**Met774**	**Phe864**	**Leu852**	**Leu726**	**Cys805**
BU-1	2H	-	-	-		-		-	1S	1S	1S	1S									
BU-2			1H				2H				1S		1S								
BU-3	-	2H	1H	1H	1H	-		-		1S	2S		1S								
BU-4			1H				2H		2S	1S	1H2S		2S								
BU-5	2H		1S		1H				1S	2S	2S	1S									
BU-6			1H				2H		1S	1S	1H1S		1S								
BU-7			1H		1H		2H				1S										
HU	-	1H1S	1H	1H	-	2H		-	-	-	-	-	-	-	-		-				
Lapa	-	1H	-	-	1H	-		2H	2S	1S			2S	2S	1S	1S	1S	1S	1S	2S	1S

H:hydrogen bond; S:Steric Interactions (Van der Waals and Hydrophobic Bonds)



(a)



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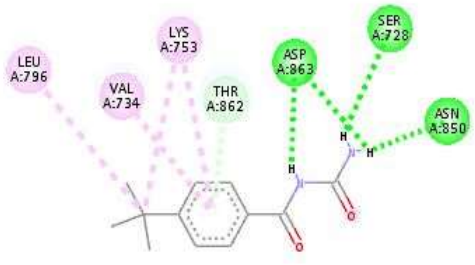

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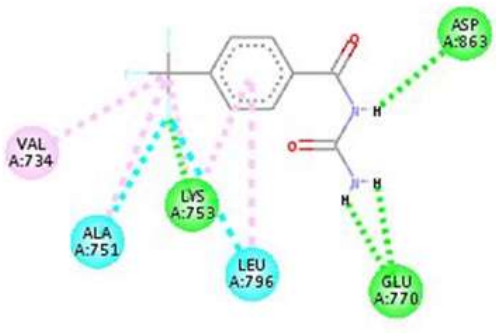
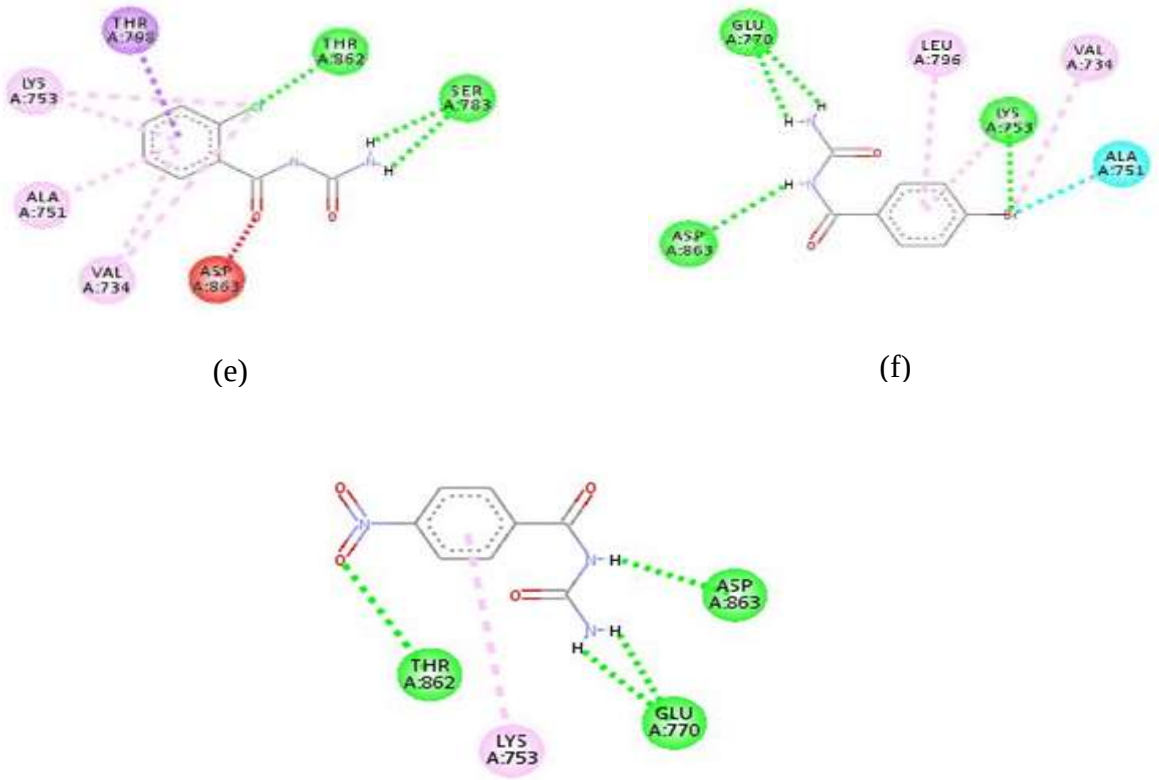


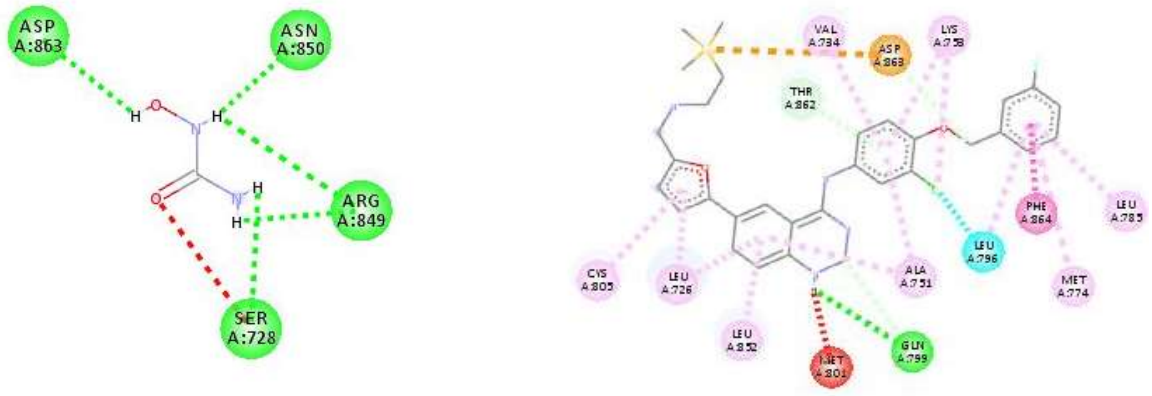
(d)



(e) (f)

(g)

Fig. 2: The binding mode 2D view of the benzoylurea derivates with HER2 receptor targets: BU-1(benzoylurea)(a); BU-2 (4-methoxybenzoylurea)(b); BU-3(4-tertier butylbenzoylurea) (c); BU-4(4-trifluoro methylbenzoylurea) (d); BU-5 (2-chloro benzoylurea) (e); BU-6 (4-bromo benzoylurea) (f); BU-7 (4-nitro benzoylurea) (g)



(a) **(b)**

Fig. 3: The binding mode 2D view of the comparative compounds with HER2 receptor targets: HU (Hydroxyurea) (a); Lapatinib(b)

Conclusion

From the results of research on molecular docking and ADMET profiles, it can be concluded that the BU-3 compound (4-tertier butylbenzoylurea) is the compound selected for further synthesis and in vitro testing of anticancer activity on breast cancer cells.

Acknowledgements

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