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RESEARCH ARTICLE OPEN ACCESS

IN SILICO STUDY OF SOYBEAN (*Glycine max* L.) ISOFLAVONES FOR ANTI-BREAST CANCER THROUGH HER2 TARGETING

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ABSTRACT

Breast cancer is one of the leading causes of death worldwide, including in Indonesia. Elevated HER2 expression significantly contributes to breast cancer progression by stimulating cell proliferation. Targeted therapies like trastuzumab have limitations due to potential side effects, such as cardiotoxicity. This study aims to identify the possible role of soybean (*Glycine max* L.) isoflavone compounds in inhibiting HER2 using an in silico approach prediction of physicochemical properties, pharmacokinetics, and bioactivity through SwissADME and PASS Online. The Hex 8.0.0 docking tool and Biovia Discovery Studio 2019 looked into how molecules interact with each other in complicated ways. Our study revealed that physicochemically the compounds acetylgenistin, acetylglycitin, and acetyldaidzin met Lipinski's Rule of Five criteria (BM (< 500), Log P (< 5), HBD (< 5), HBA (< 10), and MR (40-130)), pharmacokinetically the compound acetylgenistin met the ADME parameters and bioactively all six compounds had anticancer activity (Pa > 0.2). The results indicated that all isoflavone compounds interacted with HER2, with malonylgenistin, acetylgenistin, and acetyldaidzin exhibiting the lowest binding energy values of -286.6, -283.4, and -277.7 kcal/mol, respectively. These findings suggest that soybean (*Glycine max* L.) isoflavone compounds have potential as anticancer drug candidates in inhibiting HER2.

Key words: Breast cancer, HER2, Isoflavones, in silico

INTRODUCTION

One of the most common chronic diseases and one of the leading causes of death globally is cancer. According to the 2022 Global Burden of Cancer Study (GLOBOCAN), there were around 9.7 million cancer-related deaths and 19.9 million new cancer diagnoses worldwide (Bray et al., 2024). Among the various types of cancer, breast cancer significantly contributes to global mortality rates. It was the second most common cancer diagnosed in women in 2022, with 2.3 million new cases and 666,000 fatalities

(Bray et al., 2024). In 2022, it was the second most prevalent cancer found in women, with 2.3 million new cases and 666,000 deaths (Rizka et al., 2022).

In Indonesia, breast cancer rates are pretty high, with 65,858 new cases in 2020 and 22,430 deaths from breast cancer (Khaerunnisa et al., 2023). Human Epidermal Receptor-2 (HER2), found in about 10-30% of breast cancer cases, plays a vital role in cancer progression. HER2 controls the cell cycle and can turn on pathways that help cells grow and survive malignant cells (Suhandi, 2021). Overexpression of the HER2 gene can trigger signaling pathways that accelerate cancer progression (Zhu et al., 2024). Therefore, HER2 is a potential target in developing breast cancer therapy (Ton Tai et al., 2023). Various breast cancer therapies have been developed, one of which is targeted therapy that focuses on inhibiting specific molecules that support cancer cell growth. To treat breast cancer, the FDA has authorized trastuzumab, a monoclonal antibody specifically designed to bind the extracellular region of HER2 (Maadi et al., 2021). Despite its effectiveness, prolonged administration of trastuzumab may lead to adverse effects, including cardiotoxicity and heart failure (Mutiah et al., 2021).

The development of natural material-based therapies, such as isoflavone compounds in soybean seeds, is growing. Isoflavones are secondary metabolite compounds found in soybean plants (*Glycine max* L.) and show potential as anticancer agents. Isoflavones have been shown to promote the growth of hormone-sensitive breast cancer cell lines and mouse tumor development (Pejčić et al., 2023). Based on estimated mass (m/z) values, the UPLC-ESI-Q-TOF-MS/MS analysis of soybean seed methanol extract shows that there are six main isoflavone compounds: malonylglycitin, malonylgenistin, malonyldaidzin, acetylglycitin, acetylgenistin, and acetyldaidzin. (Lee et al., 2018). In previous research in vitro, soybean seed extract isoflavones (*Glycine max* L.) showed the ability to prevent the development of breast cancer. They can disrupt signaling pathways involved in cell regulation, such as NF-κB, PI3K/Akt, and MAPK/ERK, particularly in mice exposed to DMBA induction (Maulana et al., 2024). In silico research shows that acetyldaidzin has a strong binding affinity by forming three hydrogen bonds in its macromolecular interaction of -7.09 kcal/mol and the lowest activity in malonyldaidzin compounds with a binding energy of -5.91 Kcal/mol to estrogen receptor alpha (Abdulkadir et al., 2024). This study aims to identify the physicochemical profile, pharmacokinetic properties (ADME), and bioactivity of isoflavone compounds in soybean plants and analyze the interaction of isoflavone compounds with HER2 receptors in breast cancer In Silico.

MATERIALS AND METHODS

Data mining

This study utilizes HER2 (Human Epidermal Growth Factor Receptor 2) as the target receptor. The three-dimensional structure of HER2 (PDB ID: 3PP0) was acquired from the RCSB PDB (https://www.rcsb.org/) in PDB format (Ton Tai et al., 2023). The NCBI PubChem database (https://www.ncbi.nlm.nih.gov/) was utilized to acquire the ligand structures of malonylglycitin (CID: 23724657), malonylgenistin (CID: 15934091), malonyldaidzin (CID: 9913968), acetylglycitin (CID: 10228095), acetylgenistin (CID:

5315831), acetyldaidzin (CID: 53398699), as well as the 3D structure of trastuzumab (CID: 146160902) in SDF format (Tribudi et al., 2022).

Physicochemistry, pharmacokinetics, and bioactivity prediction

This study used the SwissADME web server (http://www.SwissADME.ch) to look at the physicochemical and pharmacokinetic properties of isoflavone compounds (malonylglycitin, malonylgenistin, malonyldaidzin, acetylglycitin, acetylgenistin, and acetyldaidzin) to see if they may be used as breast cancer drugs (Tribudi et al., 2022). Physicochemical parameters to be identified are H bond acceptor, H bond donor, molecular weight, log P, and molar refractivity) (Abdulkadir et al., 2024). Furthermore, pharmacokinetic parameters investigated were GI absorption, P-gp substrate, BBB permeant (Blood Brain Barrier Permeability), inhibition potential against cytochrome P450 enzymes (specifically CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), Log Kp (skin permeation), and Water solubility (Log S).

Bioactivity predictions were investigated for potential identification as breast anticancer using the PASSOnline (Way2Drug) webserver to determine biological activity (Kartika, 2024).

Molecular docking and visualization

The ligands trastuzumab, acetylglycitin, acetylgenistin, acetyldaidzin, malonylglycitin, malonylgenistin, and the HER2 receptor were molecularly docked using Hex 8.0 software in Shape+Electro+DARS mode. The molecular complexes generated from molecular docking were saved in pdb format (Tribudi et al., 2022). Visualization of ligand-receptor complexes was carried out using Discovery Studio 2019 Client.

Data analysis technique

Ligand and receptor complexes successfully docked are then analyzed for amino acid residues, type, and binding energy of receptor-ligand interactions identified using Discovery Studio software (Agustin et al., 2022). The prediction data results were analyzed using Microsoft Excel 2019 software.

RESULT AND DISCUSSION

Analysis of Physicochemical, Pharmacokinetic, and Bioactivity Predictions

Physicochemical, pharmacokinetic, and bioactivity properties illustrate the feasibility of a compound as a drug candidate. Physicochemistry is one of the critical parameters that can affect drug absorption and permeability. The physicochemical properties test uses Lipinski's Rule of Five parameters. Lipinski's Rule of Five states that a compound that satisfies the following requirements is likely to exhibit favorable oral bioavailability: a molecular weight of less than 500 Daltons, a LogP value of less than 5, a maximum of five hydrogen bond donors, a maximum of ten hydrogen bond acceptors, and a molar refractivity between 40-130 (Astuty & Komari, 2022).

Physicochemical prediction results showed that acetyldaidzin, acetylglycitin, and acetylgenistin met molecular weight requirement < 500, which favors oral absorption. All isoflavone compounds had log P values < 5, indicating amphiphilic properties that allow

water solubility and the ability to penetrate lipophilic membranes, thus supporting effective systemic absorption and distribution. The molar refractions of all compounds were within the appropriate range (40-130), signaling good potential for biological interaction. Additionally, absorption is impacted by the quantity of hydrogen bond donors and acceptors. Acetyldaidzin fulfills the requirements of the number of HBA < 10 and HBD < 5. At the same time, acetylglycitin and acetylgenistin have HBA > 10 due to the glycoside groups high in oxygen, making them more hydrophilic and inhibiting cell membrane penetration. All three compounds fulfill Lipinski's Rule of Five, with acetyldaidzin having no violations, while the other two have only one violation. Thus, acetyldaidzin is predicted to have better permeability and absorption than the other two compounds, which may require deglycosylation or dosage form modification to improve bioavailability.

The pharmacokinetic properties of six isoflavone compounds were predicted using the SwissADME web server, focusing on key ADME parameters, including absorption, distribution, metabolism, and excretion. The analysis showed that all compounds have low gastrointestinal absorption and are P-gp substrates, which may inhibit oral absorption. However, all compounds' water solubility (Log S) values, especially malonylgenistin (-2.64), showed good solubility compared to trastuzumab, supporting the potential for systemic distribution. Regarding distribution, all compounds could not cross the blood-brain barrier (BBB permeant: No), indicating safety to the central nervous system and preference for distribution to peripheral tissues. Metabolic predictions showed that all six compounds did not inhibit major CYP450 enzymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and most of CYP3A4, indicating good metabolic potential without significant risk of drug interactions.

Compounds with a log Kp value greater than -2.5 exhibit relatively low skin permeability (Novianty, 2023). The excretion value seen from skin permeability (Log Kp) shows that all compounds have a value < -2.5 cm/s, indicating the compound has good permeability. Two compounds, malonylglycitin and malonyldaidzin, had lower log Kp values than trastuzumab, namely -9.3 and -9.09. Prediction of drug-likeness based on Lipinski's Rule shows that acetylglycitin, acetylgenistin, acetyldaidzin, and trastuzumab fall into the category of potential drug candidates. Although its absorption value was still low, Acetylgenistin showed the most optimal ADME profile. Therefore, dosage form modifications are needed to improve its bioavailability through oral and parenteral routes.

The bioactivity test using the Prediction of Activity Spectra for Substances (PASS) showed that all isoflavone compounds have the potential to be breast-anticancer agents, with a Pa value > 0.2 indicating more vigorous potential biological activity. The higher the Pa value, the more likely the compound is to exhibit pharmacological effects against the target.

Molecular Docking Analysis

Molecular docking is also carried out in developing drugs based on natural materials in addition to physicochemical, pharmacokinetic, and bioactivity tests. This

study illustrates how acetylglycitin, acetylgenistin, acetyldaidzin, malonylglycitin, and malonylgenistin interact molecularly with the HER2 receptor (3PP0).

Based on the visualization results, all compounds have binding energy values and can interact with the target receptor. The docking results indicated five amino acid residues participating in the malonylglycitin-HER2 complex: ASP924 (Aspartic Acid 924), ARG811 (Arginine 811), LYS921 (Lysine 921), GLY919 (Glycine 919), PRO942 (Proline 942), and ALA920 (Alanine 920). Hydrogen and hydrophobic bonds stabilize this interaction. The malonylgenistin complex forms five amino acid residue bonds LYS921 (Lysin 921), ARG814 (Arginine 814), THR917 (Threonine 917) PRO942 (Proline 942) and ALA920 (Alanine 920). Hydrogen and hydrophobic bonds stabilize the malonylgenistin-HER2 complex interaction. The malonyldaidzin-HER2 complex forms three amino acid residues, namely GLU837 (Glutamic acid 837), THR875 (Threonine 875), and GLU964 (Glutamic acid 964). Electrostatic, hydrogen, and hydrophobic bonds stabilize the contact. Acetylglycitin binds to residues ARG970 (Arginine 970), GLU837 (Glutamic acid 837), ARG968 (Arginine 968), and ARG970 (Arginine 970), ARG968 (Arginine 968) and ARG970 (Arginine 970). Hydrogen, hydrophobic, and electrostatic bonds stabilize these interactions.

The acetylgenistin-HER2 complex forms six amino acid residue bonds, namely VAL988 (Valine 988), PRO707 (Proline 707), and ILE989 (Isoleucine 989). These bonds are stabilized by hydrogen and hydrophobic bonds. The acetyldaidzin complex forms three amino acid residue bonds, namely ARG898 (Arginine 898), HIS901 (Histidine 901), and GLU837 (Glutamic acid 837). Residues ARG898 (Arginine 898) and HIS901 (Histidine 901) GLU837 (Glutamic acid 837) have interactions with ligands, namely Conventional Hydrogen Bonds, which are stabilized by Hydrogen bonds that strengthen ligand affinity. Residue HIS901 (Histidine 901) is a Hydrogen Carbon bond. Hydrogen bonds, which improve the ligand's binding affinity to the protein and add to the residue complex's overall stability, further stabilize the association. Trastuzumab forms seven amino acid residue bonds, namely SER834 (Serine 834), ARG981 (Arginine 981), PRO780 (Proline 780), and LYS831 (Lysin 831), SER977 (Serine 977). Hydrogen bonding and hydrophobic interactions are key indicators of a drug's biological activity, as they influence its physicochemical properties and molecular stability (Pratama et al., 2024).

Interestingly, this result aligns with another study that reported that lutein compounds also bind to ARG811 residues (Cahyani et al., 2021). The interaction of methyl gallate compounds with HER2 has the same amino acid residue as the malonyldaidzin compounds, which bind the amino acid residue GLU837. In contrast, acetylglycitin and acetyldaidzin bind ARG970 and GLU837 (Komari et al., 2022). Isoflavone compounds interact with residues 703-1029, which are essential in inhibiting enzymatic activity in phosphorylation cascades (Aertgeerts et al., 2011). All isoflavone compounds (malonylglycitin, malonylgenistin, malonyldaidzin, acetylglycitin, acetylgenistin, and acetyldaidzin) can interact and create amino acid residue bonds with the HER2 receptor, according to the findings of this study's chemical bonding investigation. The existence of many hydrogen and non-covalent bonds between the

receptor and ligand significantly influences the strength and stability of the interaction. The more bonds formed, the stronger the binding force that binds the ligand molecule to the receptor.

In addition to chemical interactions, binding energy is a critical factor in determining the stability of a molecular complex. It reflects the strength of the interaction between molecules, where more negative binding energy values indicate stronger and more stable binding affinity. The results showed that all isoflavone compounds were able to interact with HER2, with the three compounds malonylgenistin, acetylgenistin, and acetyldaidzin having the lowest binding energy, -286.6, -283.4, and -277.7kcal/mol, respectively. These bond energy values are relatively low and approach the bond energy value of trastuzumab, which is -368.2 kcal/mol. This indicates a high affinity for the receptor, influenced by the number and type of interactions and the presence of amino acid residues involved in the bond.

CONCLUSION

Based on the study's results, isoflavone compounds from *Glycine max* L. show potential as breast anticancer drug candidates. Physicochemically, acetyldaidzin met all Lipinski's Rule of Five criteria, while acetylglycitin and acetylgenistin met four criteria. Pharmacokinetic analysis showed acetylgenistin had a good ADME profile, including solubility, distribution, metabolism, and excretion. Bioactivity tests indicated that all compounds had Pa > 0.2 as an anticancer. In addition, all compounds were able to interact with the HER2 receptor through hydrogen bonding and non-covalent interactions, with the three compounds malonylgenistin, acetylgenistin, and acetyldaidzin showing the lowest binding energy (≤ -277.7 kcal/mol), close to the value of trastuzumab (-368.2 kcal/mol), thus strengthening the potential of isoflavone compounds as HER2-targeted therapeutic agents.

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TABLE

Table 1. Predicted Physicochemical, Pharmacokinetic, Bioactivity of Soybean (*Glycine max* L.) Isoflavone Compounds

Physicochemical	Malonylglycitin	Malonylgenistin	Malonyldaidzin	Acetylglycitin	Acetylgenistin	Acetyldaidzin	Trastuzumab (positive control)
Moleculer weight	532.45	518.42	502.42	488.44	474.41	458.41	493.48
Log Po/w	1.48	1.41	1.87	2.46	2.31	2.24	2.86
H-bond donor	5	6	5	4	5	4	3
H-bond acceptor	13	13	12	11	11	10	8
MR	126.9	122.43	120.4	120.32	115.85	113.83	126.64
Pharmacokinetic							
GI Absorption	Low	Low	Low	Low	Low	Low	High
BBB permeant	No	No	No	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP1A2	No	No	No	No	No	No	No
CYP2C19	No	No	No	No	No	No	No
CYP2C9	No	No	No	No	No	No	Yes
CYP2D6	No	No	No	No	No	No	No
CYP3A4	No	No	No	Yes	No	Yes	No
Log Kp (cm/s)	-9.3	-9.05	-9.09	-8.81	-8.57	-8.61	-9.07
Log S	-3.33	-2.64	-3.24	-3.99	-3.3	-3.89	-6.79
Lipinski	No	No	No	Yes	Yes	Yes	Yes
Bioactivity							
Pa (*probability to be active*)	0.311	0.294	0.249	0.450	0.444	0.40	0.383

Table 2. Interaction between malonylglycitin, malonylgenistin, malonyldaidzin, acetylglycitin, acetylgenistin, acetyldaidzin with HER2

Interactions	Point Interaction	Chemistry Bond	Type	Energy Binding (kcal/mol)
Malonylglycitin - HER2	B:ASP924:HN - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	-262.3
	:LIG1:H - B:ARG811:O	Hydrogen Bond	Conventional Hydrogen Bond	
	B:ALA920:CA - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - B:LYS921:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - B:GLY919:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1 - B:ALA920	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:ALA920	Hydrophobic	Pi-Alkyl	
Malonylgenistin - HER2	B:ARG814:HH11 - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	-286.6
	B:ARG814:HH12 - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	
	B:LYS921:HN - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	
	B:THR917:CB - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1 - B:PRO942	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:ALA920	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:PRO942	Hydrophobic	Pi-Alkyl	
Malonyldaidzin - HER2	:LIG1:H - B:GLU837:O	Hydrogen Bond	Carbon Hydrogen Bond	-275.9
	:LIG1:H - B:GLU837:OE1	Hydrogen Bond	Carbon Hydrogen Bond	
	B:GLU964:OE2 - :LIG1	Electrostatic	Pi-Anion	
	B:THR875:CG2 - :LIG1	Hydrophobic	Pi-Sigma	
Acetylglycitin - HER2	B:ARG970:CD - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	-272
	:LIG1:H - B:GLU837:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1:H - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	B:ARG968:NH2 - :LIG1	Electrostatic	Pi-Cation	
	B:ARG970:NH2 - :LIG1	Electrostatic	Pi-Cation	
	:LIG1 - B:ARG968	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:ARG970	Hydrophobic	Pi-Alkyl	
Acetylgenistin - HER2	B:ILE989:HN - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	-283.4
	:LIG1:H - B:VAL987:O	Hydrogen Bond	Carbon Hydrogen Bond	
	:LIG1 - B:VAL988	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:ILE989	Hydrophobic	Pi-Alkyl	
	:LIG1 - A:PRO707	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:VAL988	Hydrophobic	Pi-Alkyl	
Acetyldaidzin - HER2	B:ARG898:HH21 - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	-277.7
	:LIG1:H - B:HIS901:NE2	Hydrogen Bond	Conventional Hydrogen Bond	
	:LIG1:H - B:GLU837:OE1	Hydrogen Bond	Carbon Hydrogen Bond	

Table 3. Interaction of Trastuzumab (positive control) with HER2

Interactions	Point Interaction	Chemistry Bond	Type	Energy Binding (kcal/mol)
Trastuzumab (positive control) - HER2	B:SER834:HG - :LIG1:O	Hydrogen Bond	Conventional Hydrogen Bond	-368.2
	B:ARG981:HH21 - :LIG1:F	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen (Fluorine)	
	B:PRO780:CD - :LIG1:O	Hydrogen Bond	Carbon Hydrogen Bond	
	B:LYS831:CE - :LIG1:N	Hydrogen Bond	Carbon Hydrogen Bond	
	B:SER977:HG - :LIG1	Hydrogen Bond	Pi-Donor Hydrogen Bond	
	B:LYS831 - :LIG1	Hydrophobic	Alkyl	
	B:VAL973 - :LIG1	Hydrophobic	Alkyl	
	:LIG1 - B:VAL973	Hydrophobic	Alkyl	
	:LIG1 - B:LYS831	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:VAL973	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:LYS831	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:VAL973	Hydrophobic	Pi-Alkyl	
	:LIG1 - B:VAL973	Hydrophobic	Pi-Alkyl	

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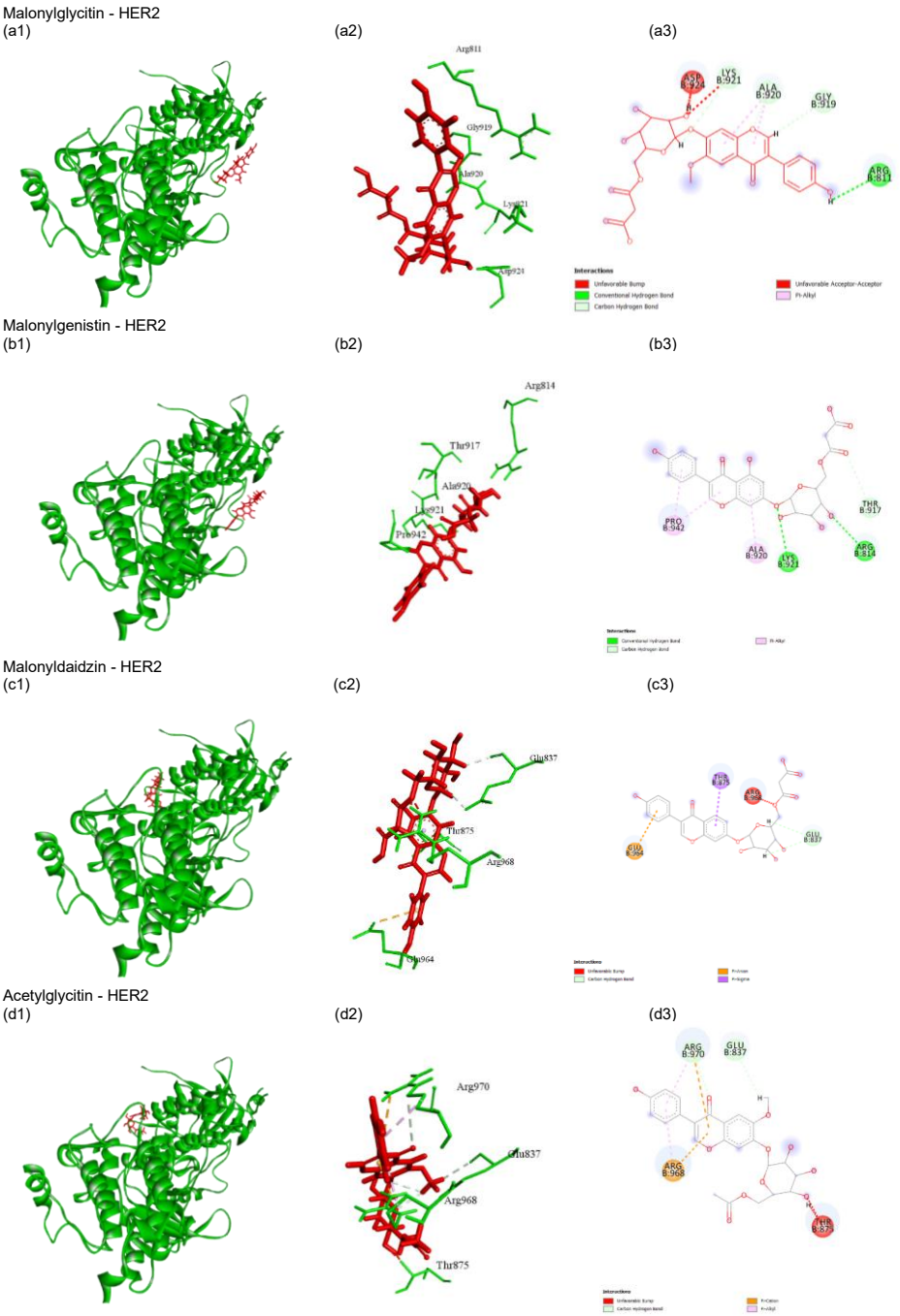

Figure 1. Molecular docking results of the interaction between malonylglycitin (a), malonylgenistin (b), malonyldaidzin (c), acetylglycitin (d), acetylgenistin (e), acetyldaidzin (f), and trastuzumab (g) complexes with HER2. Number 1 shows the visualization of

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ligand-receptor molecular complexes. Receptor and ligand interaction with 3D structure in number 2 and 2D in number 3

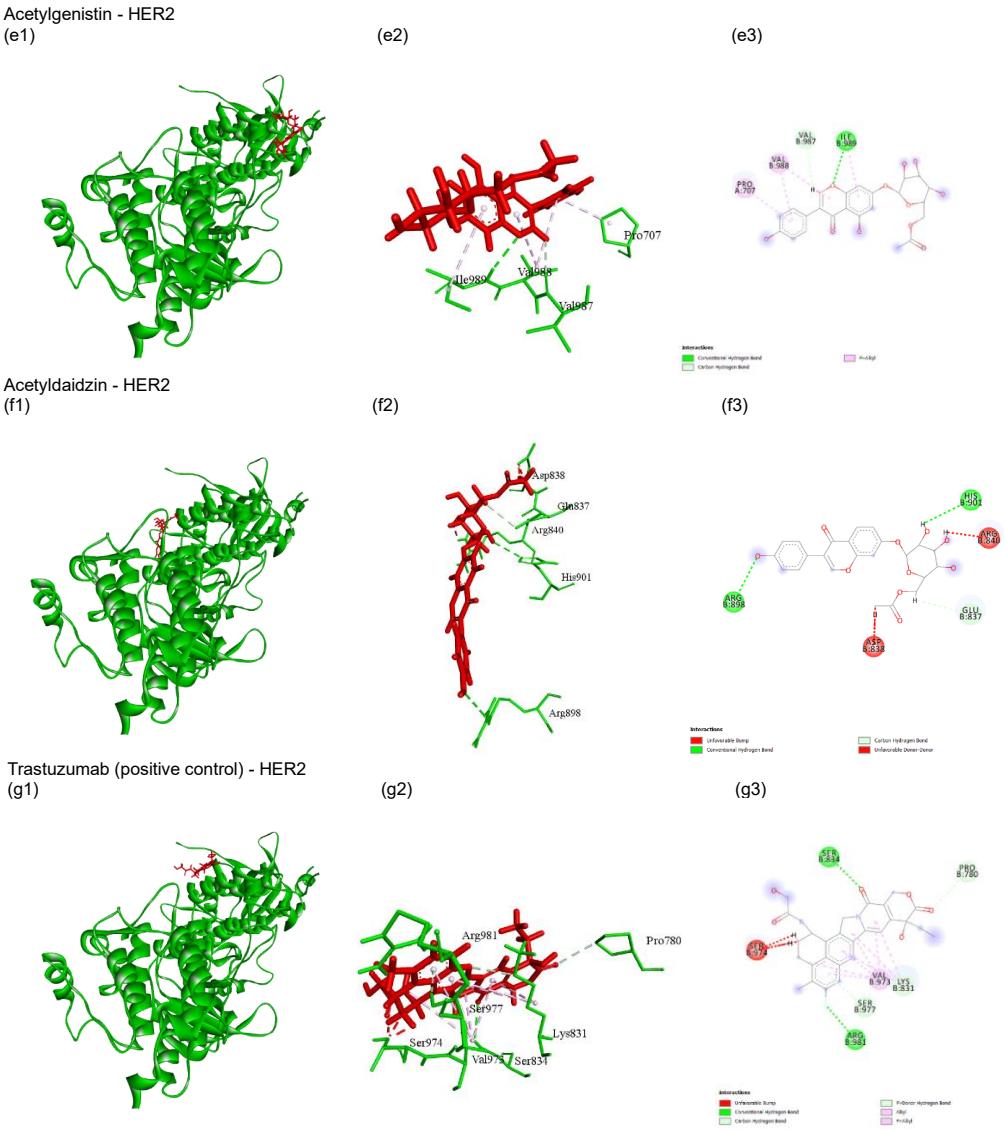

Figure 1. Molecular docking results of the interaction between malonylglycitin (a), malonylgenistin (b), malonyldaidzin (c), acetylglycitin (d), acetylgenistin (e), acetyldaidzin (f), and trastuzumab (g) complexes with HER2. Number 1 shows the visualization of ligand-receptor molecular complexes. Receptor and ligand interaction with 3D structure in number 2 and 2D in number 3 (Continued)