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UREA AND THIOUREA DERIVATIVES AS AN ENDOTHELIAL GROWTH FACTOR RECEPTOR AND HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 INHIBITORS MOLECULAR DOCKING STUDIES

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ABSTRACT

Using molecular docking we evaluate the binding mode, interaction and inhibition potential of urea and thiourea derivatives against EGFR and HER-2. The result of molecular docking shows that the urea derivatives (U_1-U_4)possess high binding energies against EGFR having -9.62 kcal/mol, -10.15 kcal/mol, -10.03 kcal/mol and -10.31 kcal/mol respectively. Similarly urea derivative (U_1-U_4) shows the binding energies value of -11.33 kcal/mol, -11.09 kcal/mol, -12.11 kcal/mol and -11.23 kcal/mol respectively against HER-2. Thiourea derivatives against EGFR shows the binding energies -9.90 kcal/mol, -10.17 kcal/mol, -11.07 kcal/mol and -10.13kcal/mol of compounds (T_1-T_4) respectively. Thiourea derivatives like (T_1-T_4) show the binding energies value of -10.37kcal/mol, -10.71 kcal/mol,-10.79 kcal/mol and -10.72kcal/mol respectively against HER-2. All compounds show high inhibitory properties against EGFR and HER-2 proteins which is comparable to the binding energies values of standard (Sorafenib and Regorafenib) These inhibitors compounds like urea and thiourea derivatives are shows good results and can be used for the treatment of breast cancer due to their capacity for the successfully modification of the activity of drugs used against breast cancer. There may be powerful EGFR, HER-2 inhibitor with high and improved efficiency and less side effects as a product for further research and evaluation of these drugs. The conclusion obtained from this study is that urea and thiourea derivatives show better inhibitory activity against selected proteins.

INTRODUCTION:

One of the most common and death causing cancer in women is breast cancer and increasing day to day in females.(An *et al.*, 2023)Worldwide mostly death occurs in women due to the breast cancer followed by lung cancer.(Cao *et al.*, 2021) WHO reported that in 2020 breast cancer found in women is 2.3 million, and 685000 deaths occurs from it.(Burstein *et al.*, 2021) While in 2021 fatality rate has increased in women from 685000 to 963000.(Eissa *et al.*, 2023)It means that in every 14 seconds worldwide breast cancer has been detecting.(Cao *et al.*, 2021) Breast cancer is more common in Asia as compared to the other continent especially in Pakistan.(Elseginy *et al.*, 2020) Report suggested that Pakistani women have diagnosis 11% with breast cancer.(Feng *et al.*, 2020) Latest study (2023) shows that the breast cancer has more chances in the middle class. That may be they were underestimating (61.4%) in which (25.9%) patients has belonging to swat Valley with breast cancer.(Almubayedh and Ahmad, 2020) Different factors responsible for breast cancer including Alcohol (Alcohol drinkers are 30% more risk of breast cancer).(Ghomashi *et al.*, 2023) Age less than 30 having low risk of breast cancer and then increasing gradually to the age of 80 years.(Cancer, 2019) In breast cancer the growth of tumour, epidermal growth factor (EGF) is the prime agent.(André *et al.*, 2021) A secreted protein called vascular endothelial growth factor (VEGF) is involved in angiogenesis associated with tumour and squarely energizes endothelial cell growth.(Khan *et al.*, 2023) Transportation in the cycle and continuity of cell signaling molecules and activation to exit from the pathways which causes tumors. Endothelial growth factor (EGF) play important role in signaling of growth factor receptor (EGFR) pathway. Breast cancer, intern, is divided into different subtypes based on the presence or absence of the estrogen receptor (ER) Progesterone receptor and HER-2 receptor. Which has been related to the clinical as well as experimental endocrine therapy resistance.(Lei *et al.*, 2021) New cure for breast cancer has been introduced to block the receptors of ER and growth factors. This treatment is highly recommended for breast cancer. (Mohanty *et al.*, 2022)

In breast cancer the tumor needed blood vessels formation (angiogenesis). The newly form blood vessels assist to the growing tumors by providing extra nourishment and also give a potential routes for tumor and metastasis.(Anderson and Simon, 2020) The prime factor in angiogenesis is VEGF.(Bakshi *et al.*, 2022) Literature study show that different VEGF group including VEGF-A, VEGF-B, VEGF-C, and VEGF-D perform as central role in breast cancer.(Abd El-Salam *et al.*, 2023)And their receptors such as VEGFR-1, VEGFR-2, VEGFR-3 are run in the starting of signaling among the cells.(Al Kawas *et al.*, 2022) It is prove that VEGF act as a vital angiogenic factor in breast cancer.(Zhang and Chu, 2019) according to literature it is necessary to block signaling produced by EGF/EGFR associated with HER2 for which a lot of therapies were used in which one is chemotherapy play a essential role by using small organic natural and synthetic molecules as a EGF/EGFR inhibitors.(Derakhshani *et al.*, 2020)

A number of natural products are used to inhibit the action of endothelial growth factors and its receptors i.e. Curcumin, Wogonin, Emodin, Sauchinone, Lycopene, Genipin, Denbinobin ursolic acid, Genistein, Dauricine, Caffeic acid phenethyl ester (CAPE), Bevacizumab, Sorafenib, and Regorafenib.(Hu *et al.*, 2020) Among the synthetic compounds urea and thiourea derivatives are highly biological active in nature having anti-bacterial, anti-viral, anti-inflammatory, and anticancer properties. These moieties play essential role in inhibition of EGF and EGFRs due to similar urea linkage with sorafenib.(Chandrasekhar *et al.*, 2020)

We learn that the bioactive and inhibition nature of urea and its analogues thiourea against EGF and EGFR, we are planned to design some urea and thiourea derivatives for the inhibition potential of EGFR and HER2. We are expecting that these compounds will be best potential against these receptors and will be lead for best future drugs.

Objectives:

To explore the binding mechanism of anti-breast cancer drugs,
To develop a novel class of urea and thiourea as a anti-breast cancer

Based on these studies, we will insight potent drugs that can target EGFR/HER2 and will lead economic drugs.

Methodology

Some important compounds including urea and thiourea derivatives are used for the current study to test the inhibitory properties of selected compounds against ore target proteins (EGFR and HER-2) along with urea derivatives (U1-U4), thiourea derivatives (T1-T4), two standard compounds Sorafenib (S) and Regorafenib (R) are also included in our study for testing against the selected proteins. (**Figure 1**)

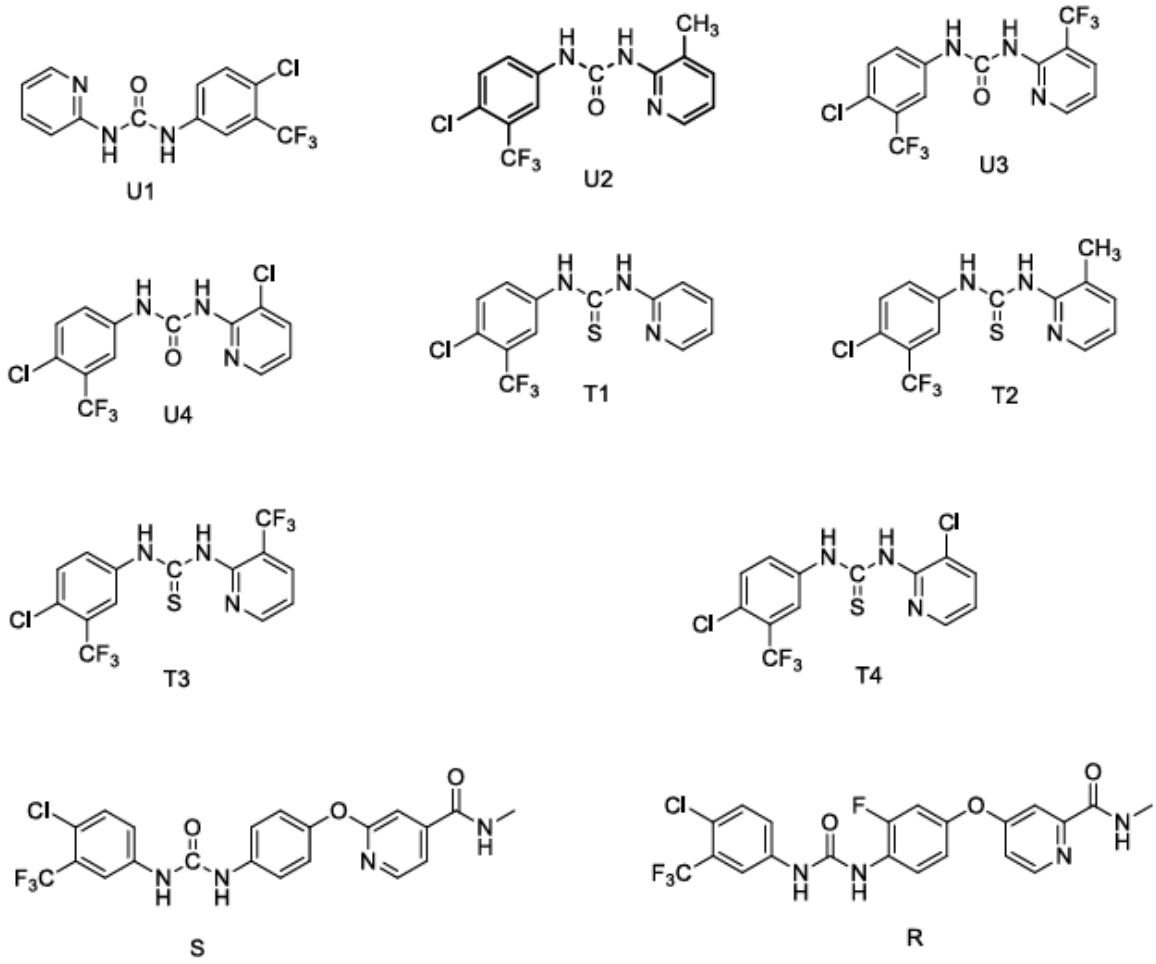

Figure 1. Structural formulae of urea and thiourea derivatives (U1-U4, T1-T4) and standard Sorafenib (S) and Regorafenib (R)

Software used for docking

The software we use in our docking study are Chem Draw, Chem3D, Open babel, AutoDock tools, PyMoL and Discovery studio. All these software's are used for making legends, preparing proteins and for the optimization along with docking of legends with selected proteins.

General methodology of molecular docking

The binding interaction mechanism of the synthesized urea and thiourea derivatives was tested for their inhibition against selected proteins like EGFR and HER-2 which play important and key role in breast cancer. The crystal structure of selected proteins was first obtained for protein data base then the protein are further

prepared theoretically with the help of AutoDock tools and then further optimized by the removing of all non-polar hydrogen, heteroatoms and water molecules in order to simplify their calculations. The beast docking confirmers of our compounds which shows the lowest value of binding energy will be selected for further investigations. The images in which protein ligands interactions were shown and the docking pose of selective urea and thiourea derivatives against the targeted proteins are visualized by PyMoL, AutoDockVina, Discovery studio etc.

Optimization of urea and thiourea derivatives

All of the selected compounds like urea derivatives as well thiourea derivatives are optimized by using different software like PyMoL, Discovery studio, Open babel GUI etc.

Preparation of target proteins

The structures of EGFR and HER-2 was obtained from protein data Base in PDB format which required many problems to be resolved after the removal of water molecules, heteroatoms, and non-polar hydrogen along with the repairing of missing atoms the target protein were prepared. And then modified by using AutoDockVina in order to add polar hydrogen followed by the addition of charges. (Butt *et al.*, 2020)

Molecular docking of compounds including urea derivatives (U1-U4),

thiourea derivatives (T1-T4) and standard (S and R) with EGFR and HER-2 Molecular docking is one of the most important tools for finding the interactions among inhibitors and the targeted proteins. The optimized compound (U1-U4), (T1 T4) and (S and R) was docked theoretically in the active pocket of proteins EGFR and HER-2 by using MGI tools, AutoDockVina for compounds (U1-U4, T1-T4, S and R) then different conformers were generated in which top ranked conformation which showing the lowest binding energy values of compounds (U1-U4, T1-T4,S and R) was got importance for further analysis in the inhibition of proteins interactions were visualized after the docking in PyMoL, AutoDock tools and discovery studio which helps in the visualization of receptors and ligand interaction like hydrogen bonding, π-π interactions, hydrophobic interactions, van dar waal interactions etc

RESULTS AND DISSCUSSIONS

In advanced research study breast cancer is still a great problem, which represents a prime medical priority. One of the most common cancer in women is breast cancer worldwide and also the most important death causing cancer. About 25% of all women having cancer are diagnosing with breast cancer each year in the word. Tumors in breast commonly initiate from the ductal hyper proliferation and then developed into metastatic carcinomas by a regular stimulation of different carcinogenic factors.In Asia the highest rate of breast cancer is found in Pakistan and latest demographic trends says that in coming years this rate should be increasing every year. Many factors are involved in breast cancer development in which the most commonly studies factors and their receptors are endothelial growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) which provide a signaling pathway to generate breast cancer. EGFR and HER-2 signaling is widely studied to a large extend during the occurrence of breast cancer and play a very important role in breast cancer development. Breast cancer is still a challenging problem for the discovery of new anti-breast cancer drugs. Urea and Thiourea linker is highly bioactive having a lot of biological applications as it is present in Sorafenib and Regorafenib as a standard drugs used for the treatment of breast cancer.

Molecular docking study of U1-U4 and T1-T4 within the EGFR and HER-2 binding pocket

The study of docking was performed for the indentation of binding interaction of compound U1 against the active site of EGFR in breast cancer. Our study on docking process of compound U1 against EGFR showing the binding energy value is -9.62 kcal/mol and the value of inhibition constant is 88.06 nanomolar Binding energies and inhibitions constants of all selected compounds against EGFR and HER-2 are given

in
Table 1. And their interacting residues of active site of targets with the nature of interactions and bond distances are given in **Table 2.**
Molecular docking investigation show that the compound U1 on treatment with EGFR show interaction with TYR-998, PRO-794 which is halogen interaction and also a Pi -cation interaction with LYS-728and ARG-999 (**Figure**.**2**) By the reaction of the compound U1 with HER-2 show the binding energy of -11.33 kcal/mol along with the inhibition constant of 4.95 nanomolar. The information collected by U1 with HER-2 is the compound U1 show interaction with amino acid SER-783, GLU-770 and LYS-753 and get stability by conventional hydrogen bond followed by Pi-Pi T-shaped interaction with PHE-864.U1 also show a halogen interaction with ASP-863 along with some Van der Waal interactions with ARG-784and ALA-771 (**Figure**.**3**) The compound U2 shows binding energy value of -10.15 kcal/mol against EGFR with the estimated inhibition constant of 36.56 nanomolar. This compound U2 shows inhibitory character against EGFR. Docking investigations give information that the U2 blocked the active sites of EGFR and show interaction with MET-1002 and stabilized by the Pi-Pi interaction between sulfur and nitrogen. (S…N, 3.5Å) selected compound also show some halogen interaction with TYR-998 followed by Van der Waal interaction with PHE-795 (**Figure**.**4**). The compound U2 also shows interaction with HER-2 giving the binding energy value of -11.09 kcal/mol along with 7.47 nanomolar value of estimated inhibition constant. The compound U2 having the ability to block the reactive sites of protein HER-2 we collect the information by docking that the compound U2 joined to the active site of HER-2 and make a strong interaction with ASP-863 and THR-862 and get stability with one hydrogen bonding and two Pi-Pi interactions like ASP-863 (O…HN, 2.0Å),(O…N, 3.0Å) and THR-862 (S…O, 2.8Å) this compound also get stability by the formation of conventional hydrogen bond with SER- 783,Pi-Pi-T shaped interaction with PHE-864 and Van der Waal interaction with GLY-729 (**Figure**.**5**) The selected compound U3 when used against EGFR give the binding energy value of -10.03 kcal/mol with the estimated inhibition constant of 44.60 nanomolar. The compound U3 with EGFR block the active sites of EGFR and shows a Pi-Pi interaction to the GLY-729 this interaction present between the oxygen of amino acid and nitrogen of ligand GLY-729 (O…N, 3.3Å) U3 with the followed protein also form Pi-cation interaction with LYS-728 and also involved in the formation of Van der Waal interaction with ARG-999 (**Figure. S1**) On molecular docking with HER-2 U3 show the binding energy -12.11 kcal/mol and the inhibition constant value is 1.33 nanomolar. The active site of HER-2 was blocked by U3 forming strong interaction with ASP-863 by making two hydrogen bonds and one Pi-Pi interaction with ASP-863 (O…HN, 2.0Å), (O…HN, 2.5Å) and (O…N, 3.3Å) followed by Pi-Pi T shaped interaction with PHE-864 along with Van der Waal interaction with the residue SER-728 (**Figure. S2**) (Hafez *et al.*, 2025) The mode of binding of candidate compound U4 showing the binding energy of -10.32 kcal/mol with the inhibition constant of 27.37 nanomolar The selected compound U4 was fitted well in the active pocket of EGFR making an interaction with MET-1002. Which make two Pi-Pi interactions (S…HN, 2.7Å), (S…N, 3.5Å) apart from these interactions U4 with EGFR shows some other interactions like Pi-cation interaction with ASP-1003 and halogen interaction with TYR-998 (**Figure**. **S3**) On treatment with HER-2 protein the compound U4 give the binding energy value of -11.23 kcal/mol and give the value of estimated inhibition constant is 5.89 nanomolar. The study of molecular docking of U4 with HER-2 protein show that there are strong interactions present with active sites of HER-2 like SER-783, THR-862, and ASP-863 residues which is stabilized by two hydrogen bonding and three Pi-Pi interactions like SER-783(O…HO, 2.5Å), THR-862 (S…O, 2.6Å), (N…O, 3.2Å) and ASP-863 (O…HN, 2.2Å),(O…N, 3.1Å) along with these interactions alkyl interaction with VAL-734 and halogen interaction with ASN-850 also present. (**Figure. S4**) (Chouhan *et al.*, 2024)
On the other side T1 with EGFR showing the binding energy of -9.90 kcal/mol along with the inhibition constant of 55.43 nanomolar. The result of molecular docking of compound T1 with EGFR show the

interactions like conventional hydrogen bonds with THR-854, LEU-773, ALA-743 and LEU-788 along with halogen interaction with CYS-775,ARG-776 and MET-766 this docking result also show Pi- sigma interaction with PHE-856 and halogen interactionwith ARG-776 (**Figure S5**) On treatment with HER-2 the selected compound T1 give the binding energy value of -10.37 kcal/mol with the inhibition constant of 25.04 nanomolar. T1 reacted with the THR-798 and LEU-785 residues of HER-2 and get stabilized by conventional hydrogen bonds followed by Pi-Pi T shaped interaction with PHE-864other then attractive charge present with the amino acid ASP-863 and halogen interaction present with ARG-784 (**Figure. S6**) T2 is another selected compound which is used against EGFR showing the binding energy of -10.17 kcal/mol along with inhibition constant value of 34.99 nanomolar. The compound T2 cover and blocked the reactive pocket of EGFR protein providing a strong interaction of hydrogen bonding to the amino acid THR-854 of protein EGFR.(O…HN, 1.9Å)there are some attractive charges found with ASP-855,Pi-donor hydrogen bonds are found with PHE-856 along with Pi-Pi-T shaped interaction with amino acid MET-776 (**Figure. S7**) (Hafez *et al.*, 2025) T2 also show binding energy value of -10.71 kcal/mol and inhibition constant of 14.13 nanomolar against HER-2 on molecular docking. The selected compound T2 react and blocked the active site of protein HER-2. This compound on treatment with HER-2 shows strong interactions like two hydrogen bonds along with Pi-Pi interaction with the residues ASP-863 and THR-862 of HER-2 protein. One hydrogen bond is form with amino acid ASP-863 and ligand T2 (O…HN, 2.1Å) another hydrogen bonds forms between amino acid THR-862 and T2 (O…HN, 2.3Å) along with these hydrogen bonding a Pi-Pi interaction also present between ASP-863 and T2 (O…N, 2.8 Å) halogens interaction with ASN- 850 and Van der Waal interaction with GLY-729 were also seen. (**Figure. S8**) T3 by the process of molecular docking with EGFR give the energy value of -11.07 kcal/mol on binding along with the inhibition constant 7.73 nanomolar. T3 react with EGFR and form a strong hydrogen bond with THR-854. This hydrogen bond form with oxygen of amino acid of protein EGFR and hydrogen attached to nitrogen of ligands like (O…HN, 2.0Å) there are some halogen interaction also present with the amino acids PHE-856 and ASP-855 along with Van der Waal interaction with LYS-745 (**Figure. S9**) (Bıçak and Gunduz, 2023) The compound T3 also react with HER-2 and releasing the energy amount of -10.79 kcal/mol on binding with HER-2 while the inhibition constant value showing hear is 12.37 nanomolar on molecular docking process. The selected compound T3 also shows the attraction with THR-862 and SER-783 residues of protein HER-2 and stabilized by the two hydrogen bonds with on Pi-Pi interaction both the hydrogen bonds is show in-between THR-862 and T3 (O…HN, 1.9Å),(O…HN, 2.4Å) while the Pi-Pi interaction present between SER-783 and T3 (O…N, 3.0Å) and some alkyl interactions with LEU-796 and VAL-734 followed by halogen interaction with ASP-863. (**Figure. S10**) Our next selected compound is T4 which react with EGFR and give the binding energy value of -10.13 kcal/mol and the inhibition constant value of 37.81 nanomolar. The compound T4 react with EGFR it blocked the active sits of the protein EGFR by the formation of conventional hydrogen bond with the residue THR-790, CYS-745 and LEU-777 along with halogen interaction with ARG-776, CYS-775 and MET-766.and some Van der Waal interactions with LEU-858amino acids (**Figure. S11**) T4 by docking process with HER-2 show the binding energy value of -10.72 kcal/mol with inhibition constant of 13.79 nanomolar. T4 when docked with HER-2 it show that the T4 react with ASP-863 amino acid and get stability by the formation of hydrogen bonding followed by Pi-Pi interaction.ASP-863 form hydrogen bond with T4 (O…HN, 2.2Å) and Pi-Pi interaction is present between ASP-863 and T4 (O…N, 3.2Å) some halogen interactions with GLY-729 and Pi-Pi T shaped interaction with PHE- 864 also found. (**Figure. S12**) (Li *et al.*, 2022)

Molecular docking study of Sorafenib and Regorafenib within the EGFR and HER-2 binding pocket

Sorafenib on the treatment with EGFR on molecular docking show the binding energy value of -13.32 kcal/mol followed by the inhibition constant value of 172.24 picomolar (Table.10) Sorafenib when reacted with EGFR it blocked the active pocket of EGFR and interact with PHE- 856 and CYS-775 parts

of protein EGFR and stabilized by a hydrogen bond and Pi-Pi interaction.(O…HN, 2.3Å) and (N…O, 3.4Å) some other interactions like Pi-sigma with MET766, Halogen interaction with LEU-718 and Pi-Alkyl interaction with LEU-858 also present. (**Figure. S13**) Sorafenib on molecular docking with HER-2 release the binding energy value of -14.22 kcal/mol with inhibition constant of 37.72 picomolar. Sorafenib form a hydrogen bond with ASP-863 amino acid of HER-2 protein and block the active site of HER-2 (O…HN, 2.3Å) the selected compound with HER-2 also involved in the formation of halogen interactions with the amino acids LEU-726 and GLY-804 and Van der Waal interaction with amino acids THR-862 and GLU-770. (**Figure. 14**) (Fan *et al.*, 2014) Regorafenib on molecular docking with EGFR the binding energy released is -13.81 kcal/mol and the inhibition constant value of 74.98 picomolar. The active site of EGFR was blocked by Regorafenib due to the attraction of Regorafenib with PHE-856 and CYS-775 residues of EGFR and get stability by forming a hydrogen bond CYS- 775 (O…HN, 2.3Å) as well as a Pi-Pi interaction with PHE-856 (O…N, 3.3Å) Regorafenib also form Pi-sigma interaction with MET-766, Halogen interaction with LEU-718 and Van der Waal interactions with amino acids GLY-719 and VAL-769.(**Figure. S15**) Regorafenib when react with HER-2 the binding energy is -13.82 kcal/mol and inhibition constant value of 74.70 picomolar. HER-2 and Regorafenib when treated the active site of HER-2 was blocked by Regorafenib by the reaction with MET-801 and THR-862and form two strong hydrogen bonds (O…HN, 2.3Å) and (O…HN, 2.1Å) Regorafenib on the reaction with HER-2 also form carbon-hydrogen bond with ASP-808, Halogen interactions with SER-783 and ARG-784 and Van der Waal interaction with amino acid ALA-751. (**Figure. S16**) (Al-Otaibi *et al.*, 2022)

Table 1. Binding energies in (kcal/mol) and inhibition constant selected compounds with EGFR and HER-2

Compounds	Binding Energy (kcal/mol)		Inhibition Constant	
	EGFR	***HER-2***	***EGFR***	***HER-2***
U1	-9.62	-11.33	86.06 nM	4.95 nM
U2	-10.15	-11.09	36.56 nM	7.47 nM
U3	-10.03	-12.11	44.60 nM	1.33 nM
U4	-10.32	-11.23	27.37 nM	5.89 nM
T1	-9.90	-10.37	55.43 nM	25.04 nM
T2	-10.17	-10.71	34.99 nM	14.71 nM
T3	-11.07	-10.79	7.73 nM	12.37 nM
T4	-10.13	-10.72	37.81 nM	13.74 nM
Sorafenib	-13.32	-14.22	172.24 pM	37.72 pM
Regorafenib	-13.81	-13.81	74.98 pM	74.98 pM

Table 2. Residues involved in interactions and their distances of selected compounds with EGFR and HER-2

Compounds	Enzymes	Interacting amino acids	Interactions	Types of interactions	Distances(Å)
U1	EGFR	TYR-998, PRO-794 LYS-728 ARG-999	S...F, N...F, O...S, O...N	π–π interaction	3.1, 3.4, 3.5
	HER-2	SER-783 GLU-770 LYS-753 PHE-864	S...HN, O...HN, O...S O...S	H-Bonding, π-π interaction	3.4, 3.5, 3.7
U2	EGFR	MET-1002	S...N	π-π interaction	3.5
	HER-2	THR-862 ASP-863	S...O O...HN, O...N	π-π interaction H-Bonds	2.8, 2.0, 3.0
U3	FGFR	GLY-729	O...N	π-π interaction	3.3
	HER-2	ASP-863	O...HN, O...N	H-Bonding, π-π interaction	2.0, 2.5, 3.3
U4	EGFR	MET-1002	S...HN, S...N	H-Bonding, π-π interaction	2.7, 3.5
	HER-2	SER-783 THR-862, ASP-863	O...HO, S...O, N...O O...HN, O...N	H-Bonding, π-π interaction	2.5, 2.6, 3.2, 2.2, 3.1
T1	EGFR	THR-854 LEU-773 ALA-743 LEU-788 CYS-775 ARG-776 MET-766	O...HN, O...HN, O...HN O...HN, S...Br, N...F, N...F	H-Bonding, π-π interaction	3.1, 3.4, 3.5, 3.3, 3.4
	HER-2	THR-798 LEU-785 PHE-864	O...HN, O...HN, O...N	H-Bonding, π-π interaction	2.9, 2.9, 3.7
T2	EGFR	THR-854	O...HN	H-Bonds	1.9
	HER-2	ASP-863, THR-862	O...HN, O...N, O...HN	H-Bonding, π-π interaction	2.1, 2.8, 2.3
T3	EGFR	THR-854	O...HN	H-Bonding,	2.0
	HER-2	THR-862, SER-783	O...HN, ...HN, O...N	H-Bonding, π-π interaction	1.9, 2.4, 3.0
T4	EGFR	THR-790, LYS-745, LEU-777, ARG-776 CYS-775 MET-766	O...HN S...HN O...HN, S...F, S...F S...F	H-Bonding, π-π interaction	2.9, 3.1, 2.8, 3.6, 3.6, 3.9
	HER-2	ASP-863	O...HN, O...N	H-Bonding, π-π interaction	2.2, 3.2
Sorafenib	EGFR	PHE-856, CYS-775	N...O, O...HN	π-π interaction, H-Bonding,	3.4, 2.3
	HER-2	ASP-863	O...HN	H-Bonding	2.3
Regorafenib	EGFR	PHE-856 CYS-775	N... O, O... HN	π-π interaction H-Bonding	3.3, 2.3
	HER-2	MET-801, THR-862	O...HN, O...HN	H-Bonding,	2.3, 2.1

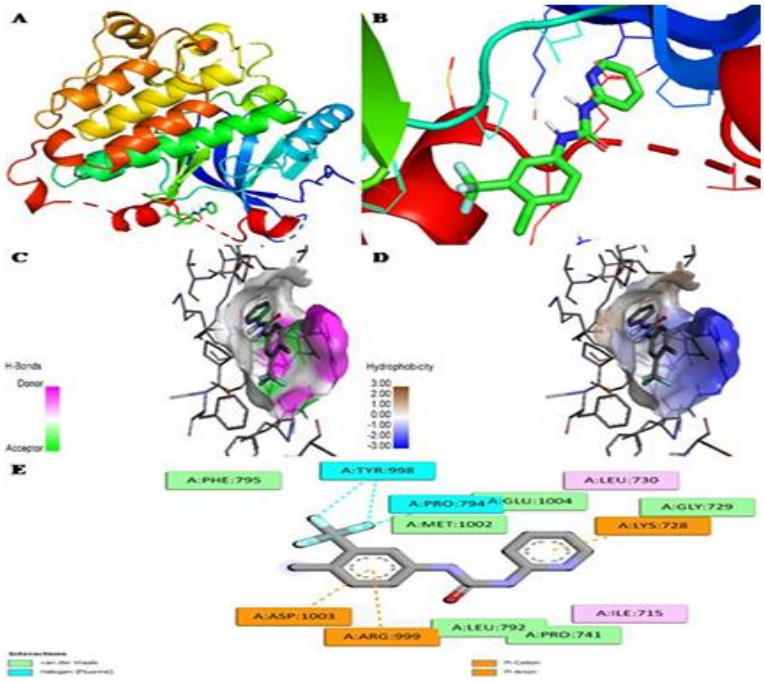

Figure2. Binding pose of U1 with EGFR, (A) complex, (B) 3D interactions, (C) hydrogen bonding, (D) hydrophobic interactions, and (E) 2D interactions

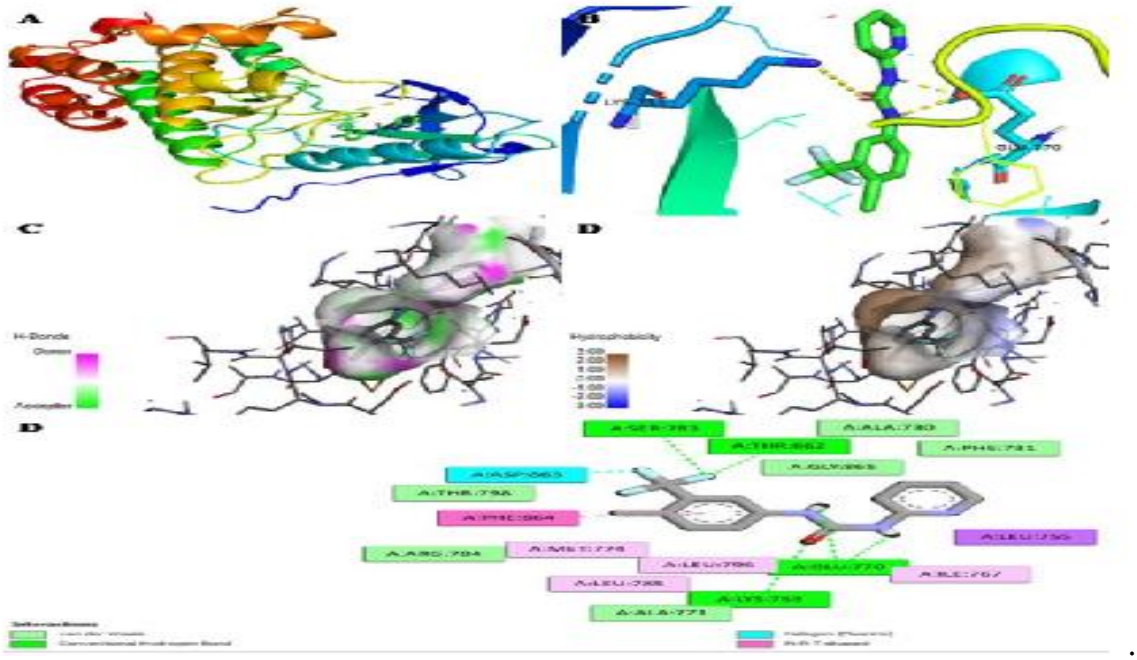

Figure3. Binding pose of U1 with HER-2, (A) complex, (B) 3D interactions, (C) hydrogen bonding, (D)

hydrophobic interactions, and (E) 2D interactions.

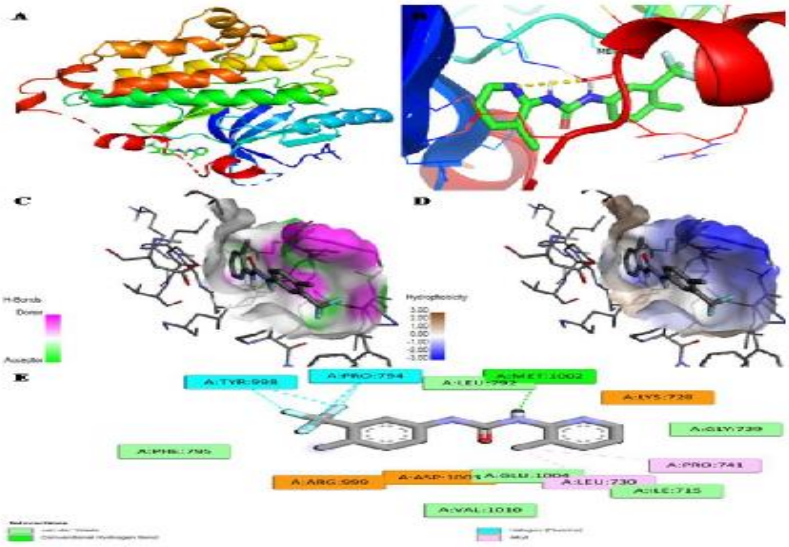

Figure4. Binding pose of U2 with EGFR, (A) complex, (B) 3D interactions, (C) hydrogen bonding, (D) hydrophobic interactions, and (E) 2D interactions.

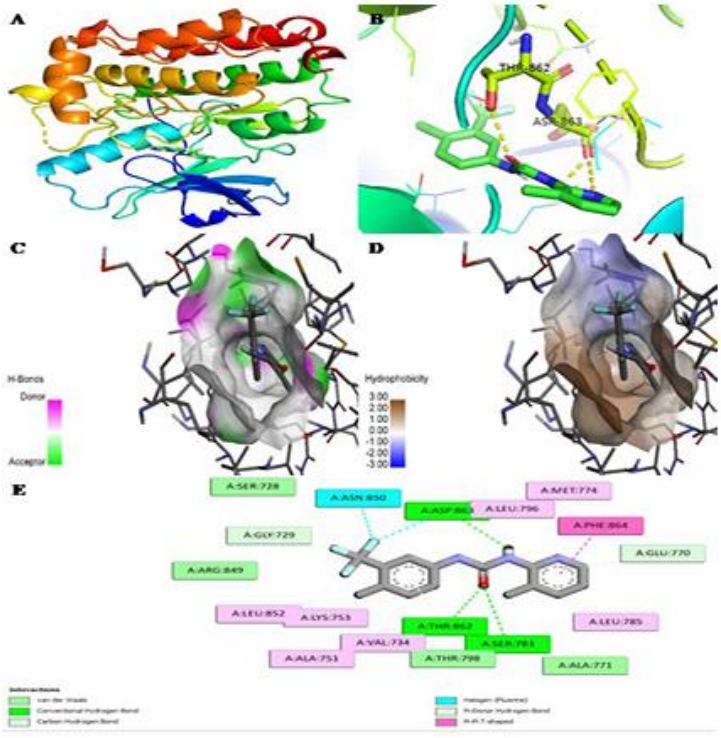

Figure5. Binding pose of U2 with HER-2, (A) complex, (B) 3D interactions, (C) hydrogen bonding, (D)

hydrophobic interactions, and (E) 2D interactions.

Conclusion

In this study, we investigated the inhibition potential of selected compounds urea derivatives (U_1-U_4), thiourea derivative (T_1-T_4) and standard compounds Sorafenib and regorafenib (S and R) against endothelial growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) with the help of molecular docking. Urea derivatives show binding energies -9.26 to -10.13 kcal/mole against EGFR and -11.09 to -12.11 kcal/mol gainst HER-2 showing that urea derivative are good inihibitors for HER-2 as compared to EGFR
And thiourea derivatives show binding energies -9.90 to -11.07 kcal/mole against EGFR and -10.37 to -10.79 kcal/mol gainst HER-2 showing that these derivative equalay inihibit thess targets. Consequently our compounds (U_1-U_4) and (T_1-T_4) having a great potential against EGFR and HER-2 and can be used for pharmacological investigations for the developing treatments against breast cancer

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Conflict of Interest
The authors declare no conflict of interest

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