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Predicting Probable Ligands to Inhibit HER2-EGFR in Gastric Cancer

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Abstract: *Cancer is a large group of diseases involving disordered cell growth. In this type of disease (cancer), cells will grow and divide very fast So that is uncontrollable and may be converted to malignant tumours.There are several types of cancer, including Gastric cancer. Unfortunately, Gastric cancer is a global health issue and also it is the second leading cause of cancer mortality in the world [3].*

Biology and chemical scientists across the world are trying to find the ways and more effective drugs to treatment for this disease. But it is very time consuming and expensive, for this reason Bioinformatics scientists try to do this process in much less time by using in silico methods and some software and tools and obtain a more favourable results.

For example, nowadays Bioinformaticians use some software and databases for discover or design any drugs and compounds with spend less of time and less cost .

Based on the previous studies, various molecular target agents have been investigated for Gastric cancer [4] and they have shown that over expression of human epidermal growth factor receptor (EGFR family is composed of known four receptors HER1, HER2, HER3 and HER4) or gene mutations in members of HER family are rare in Gastric cancer[6].

In this project we have choose two targets HER1 and HER2 of this family, because over expression of HER1 occurs in 24% of Gastric cancer and HER2 gene is amplified or over expressed in 10% to 22% of Stomach cancer[4],[14].

Also we have selected three drugs, Gefitinib, Erlotinib and Lapatinib and several similar compounds with them as inhibitors of HER1 and HER2, and We are trying to be the best ligand for these targets is selected.Lapatinib is a tyrosine kinase inhibitor (TKI) against HER2 and HER1 (EGFR), and it is an oral low-molecular weight [16]. It is used as a second – line or third –line therapy in patients with HER2- positive Gastric cancer (commonly used first-line therapy is chemotherapy). Lapatinib blocks receptor phosphorylation and activation [15].

Gefitinib and Erlotinib are EGFR inhibitors and they are small molecular weight compounds which inhibit tyrosine kinase. On the basis of this background we aimed of the present study to predict probably ligands to inhibit HER2 and EGFR in Gastric cancer.

I. Introduction

Gastric cancer, or Stomach cancer, connect to cancer arising from any part of the stomach. Despite a main decrease in occurrence and mortality over several decades, Gastric cancer is still the fourth most common cancer and the second most common cause of cancer death in the world [1]. Stomach cancer can often be cured if it is recognized and treated at an early stage. Unfortunately, Prognosis of this cancer is poor (5-year survival <5 to 15%) because most patients introduce with advanced disease [2].

Five types of standard treatment are used for treatment GC: Surgery, Chemotherapy, Radiation therapy, Chemo radiation, Targeted therapy. Today's more scientists are focused on Targeted therapy.

Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells [11].

Monoclonal antibody therapy and small molecules therapy are types of targeted therapy used in the treatment of gastric cancer [12].

In monoclonal antibody therapy, these antibodies can identify substances or drugs on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies are given by infusion. They may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells.

In small molecules therapy, using small molecules such as Gefitinib, Erlotinib to inhibit the tyrosine kinase activity, which is on the cytoplasmic side of the receptor.

The previous studies have shown, the **epidermal growth factor receptor** (EGFR) and one member of **human epidermal growth factor** (HER2), are observed in many kinds of human cancers, and have considered

some small molecule drug candidates (such as Gefitinib, Erlotinib, Lapatinib, etc) to inhibit their protein targets activities [14,16]. There is growing evidence that HER2 is an important biomarker and key driver of tumorigenesis in gastric cancer, with studies showing amplification or over expression in 7–34% of tumours [4]. The over expression of EGFR (Epidermal Growth Factor Receptor) occurs in 58-86% of gastric adenocarcinoma [4].**EGFR** can be targeted from the outside of the cell by intravenous monoclonal antibodies against the target protein (also known as a ligand) binding portion of the cell, or from the inside of the cell by oral small molecule inhibitors against the part of the receptor called the tyrosine kinase domain that activates the intracellular machinery [4,5]. Mutations affecting EGFR expression or activity could result in cancer. In addition EGFR drives the development of multiple solid tumor types, and EGFR provides a strong rationale for EGFR-TK as a targer molecule for the expansion of novel cancer therapies.

HER1/EGFR dimers are capable of activating multiple downstream signaling pathways [7].

Activation of HER1/EGFR mediated through ligand binding triggers a network of signaling processes that promote tumor cell proliferation, migration, adhesion, and angiogenesis, and decrease apoptosis. Therefore, inhibiting HER1/EGFR activity could effectively block downstream signaling events and, consequently, tumorigenesis [8].

Amplification or over expression of HER2 has an important role in several types of cancer (The ERBB2 gene is also called **HER2).**

One method is using small molecules as inhibitors to inhibit the EGFR tyrosine kinase, which is on the cytoplasmic side of the receptor. Because without kinase activity, EGFR and HER2 cannot activate themselves, which are prerequisite for binding of downstream adaptor proteins. Finally the proliferation and migration of tumor is diminished by stopping the activity of cells that rely on this pathway[8,16]. **Gefitinib**, **Erlotinib**, **Trastuzumab** and **Lapatinib** are examples of small molecule kinase inhibitors. It is noteworthy that we selected EGFR and HER2 as targets and considered "Gefitinim", "Erlotinib" and "lapatinib" as ligands.

Gefitinib (or **Iressa)** is a useful drug used for treatment of some type of cancers such as breast, lung and gastric cancer. Its chemical formula is $\mathbf{C_{22}H_{24}ClFN_4O_3}$. Gefitinib is in the form of a tablet and it is used orally. Gefitinib is used to inhibit the activity of epidermal growth factor receptor (EGFR) in target cells [13].

The EGFR pathway is involved in regulating growth and replication of a cell. In many cancer cells, this pathway is abnormal and provides continual growth stimulation of a cell. Gefitinib blocks part of the epidermal growth factor receptor pathway so that the cellular growth signals are inhibited.[17]

Actually Gefitinib is considered as the first selective inhibitor of epidermal growth factor receptor's tyrosine kinase domain. It inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK).

Gefitinib in the first step binds to the adenosine triphosphate (ATP)-binding site of the enzyme, after that inhibits EGFR tyrosine kinase. Thus the function of the EGFR tyrosine kinase is inhibited, and malignant cells are inhibited.

Erlotinib hydrochloride (Tarceva or OSI-774) is used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer. Its chemical formula is $C_{22}H_{23}N_3O_4$ .Erlotinib belongs to the quinazolinamines. These are heterocyclic aromatic compounds containing a quianazoline moiety substituted by one or more amine groups. We can use Erlotinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Also for use, in combination with gemcitabine, as the first-line treatment of patients with locally advanced, unrespectable or metastatic pancreatic cancer [18].

The target of Erlotinib (Similar to Gefitinib) is the epidermal growth factor receptor (EGFR) tyrosine kinase. It binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor.

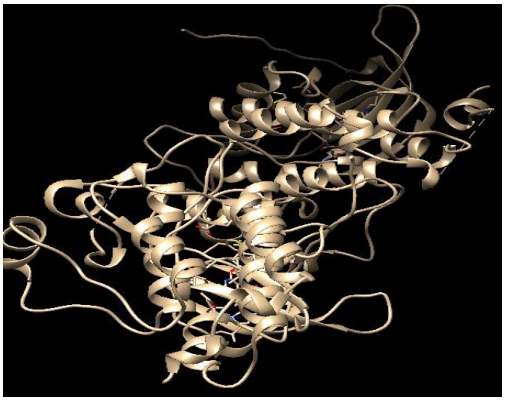
II. Softwares And Databases And Methodes

In the present study we have used **Blind Docking** method to predict the binding orientation of small molecule drug candidates (Gefitinib- Erlotinib-Lapatinib) to their protein targets (HER2- EGFR) in order to predict the affinity and activity of the small molecule when bound to each other to form a stable complex. For this aim we used some software and database such as, AutoDock Vina, Protein Data Bank, Pub Chem, Drug Bank and Discovery Studio visualize.

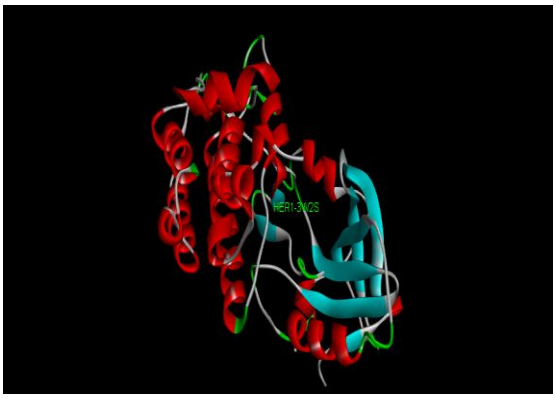
Receptor preparation:

In the first step we download the 3D crystal structures of HER1 and HER2 as target or receptor in pdb format from Protein Data Bank.

(PDB ID of HER1 is **3W2S** and PDB ID of HER2 is **3PP0**)



The structure of **HER2**



The structure of **HER1**

Ligand preparation:

In second step, download the structure of **Gefitinib** from PubChem compound, with CID-123631, and 14 other compound structures with 98% structure similarity from PubChem Structure Search, also for **Lapatinib** with CID- 208908, and 14 other compound structures with 97% structure similarity and for **Erlotinib** with CID- 176870, and 14 other compound structures with 95% structure similarity.

Make Grid box and Configuration file:

In Vina we must be determine a grid center and grid dimensions for AutoDock calculation. The grids increments of 1.00 Angstrom because to adjust the spacing to same range. By input the center of the grid we can determine adjust the grid size. The grid dimensions can change between 1 to 40 Angstroms.

Make the configuration file to prepare to run vina tool. In config file we can save the information, such as the grid box and the center of mass of target protein.

		HER1	**HER2**
1	Receptor =	3W2S.pdbqt	3PP0.pdbqt
2	Ligand =	CID-123631.pdbqt (e.g.)	CID-123631.pdbqt (e.g.)
3	Center_x =	5.479	8.308
4	Center_y =	9.145	19.41
5	Center_z =	28.793	5.965
6	Size_x =	60	60
7	Size_y=	60	40
8	Size_z=	60	40

Table1: Configuration files of HER1 and HER2

Run AutoDock:

To run AutoDock Vina, we have to go to the command prompt. In command prompt we write the address of our file .

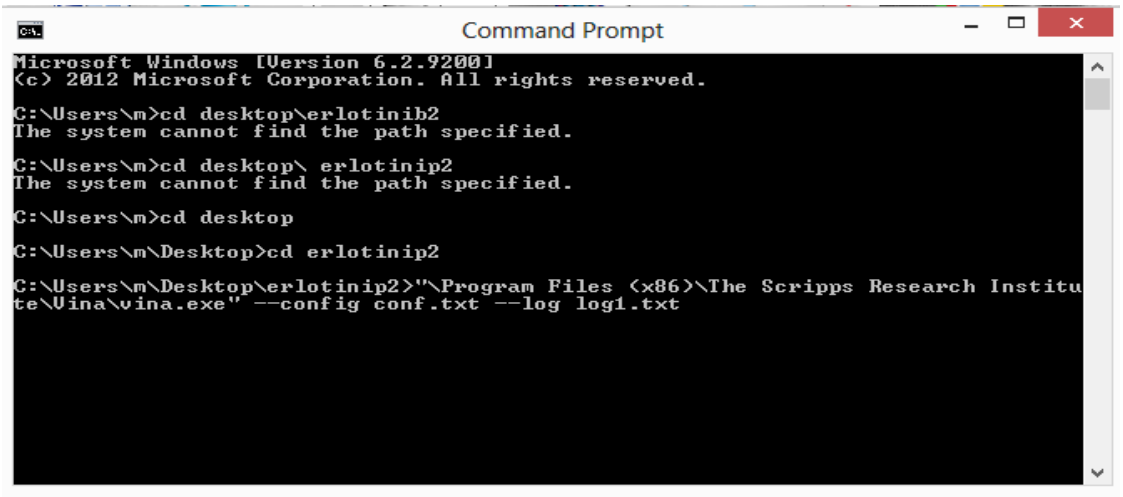


Figure 1: The command prompt page of Run AutoDock

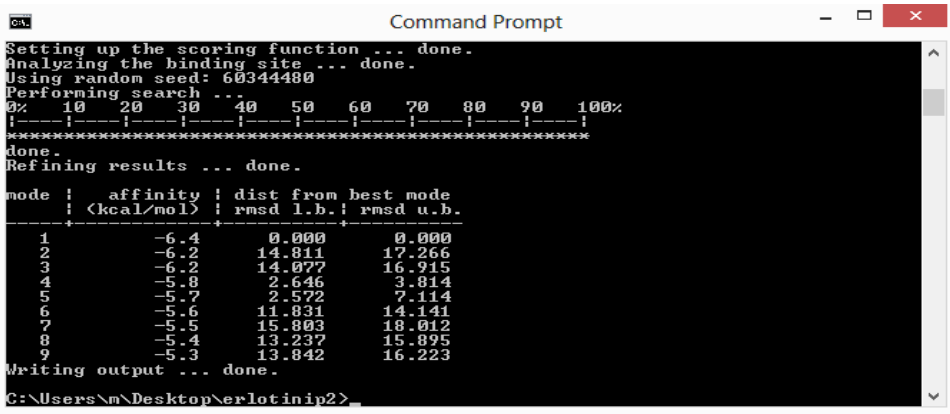


Figure 2: Output of AutoDock Vina

Output of Docking:
We have done docking for each of the selected ligands to HER1 and HER2 (as targets).

Table 2: The result of Docking of **Erlotinib** and 14 similar compounds with **HER1**

Ligand ID		Best Energy	Low/High Energy	H-bond residues
1	176870 (Main compound)	-6.5	-6.5 , -5.6	ARG 776 LYS 852
2	17813912	-6.4	-6.4 , -5.9	ARG 776 GLN 791 LYS 846 LYS 852
3	21336464	-6.7	-6.7 , -6.1	LYS 745
4	24825688	-6.8	-6.8 , -6.1	PRO 772 ARG 776 GLN 791 LYS 846 LYS 852
5	25124815	-6.7	-6.7 , -5.9	ARG 776 GLN 791 LYS 846 LYS 852
6	25125154	-6.8	-6.8 , -5.9	PRO 772 GLN 791 LYS 846 LYS 852
7	25125155	-6.9	-6.9 , -6.0	ARG 776 LYS 852
8	25125156	-7.0	-7.0 , -5.8	LYS 852
9	25125157	-6.4	-6.4 , -5.9	PRO 772 ARG 776 GLN 791 LYS 852
10	25125158	-6.7	-6.7 , -5.9	ARG 836 LYS 875
11	25125159	-6.7	-6.7 , -6.2	PRO 772 GLN 791 LYS 846 LYS 852
12	25125497	-6.7	-6.7 , -6.0	SER 768 ARG 776 GLN 791 LYS 852
13	25125498	-6.3	-6.3 , -5.9	GLY 724 LYS 745
14	25125499	-6.6	-6.6 , -6.2	ASP 837 VAL 876 LYS 879
15	25125500	-6.8	-6.8 , -6.2	PRO 772 ARG 776 GLN 791 LYS 846 LYS 852

Table 3: The result of Docking of **Erlotinib** and 14 similar compounds with **HER2**

Ligand ID		**Best Energy**	**Low/High Energy**	**H-bond residues**
1	176870 (Main compound)	-5.7	-5.7 , -4.9	PHE 731 PRO 922
2	17813912	-6.2	-6.2 , -5.4	ARG 756 ASN 758 GLU 770 LYS 883
3	21336464	-6.0	-6.0 , -5.5	GLU 770 GLY 882 LYS 883
4	24825688	-6.5	-6.5 , -5.6	ARG 756 GLU 770 LYS 883
5	25124815	-6.3	-6.3 , -5.7	GLU 770 GLY 882
6	25125154	-6.4	-6.4 , -5.2	ARG 756 ASN 758
7	25125155	-6.1	-6.1 , -5.2	LYS 762
8	25125156	-6.6	-6.6 , -5.6	ARG 756 ASN 758 GLU 770
9	25125157	-6.1	-6.1 , -5.4	No H-bond
10	25125158	-6.4	-6.4 , -5.3	ARG 756 GLU 770
11	25125159	-6.6	-6.6 , -5.5	ARG 756 GLU 770
12	25125497	-6.0	-6.0 , -5.4	PRO 761
13	25125498	-6.3	-6.3 , -5.2	ARG 756 GLU 770
14	25125499	-6.3	-6.3 , -5.4	ARG 756 GLU 770 LYS 883
15	25125500	-6.5	-6.5 , -5.5	GLU 770 GLY 882 LYS 883

Table 4: The result of Docking of **Gefitinib** and 14 similar compounds with **HER1**

Ligand ID		**Best Energy**	**Low/High Energy**	H-bond residues
1	123631 (Main compound)	-6.8	-6.8 , -6.0	ARG 776 LYS 852
2	10159951	-6.3	-6.3 , -5.6	No H- bond
3	11604752	-7.5	-7.5 , -6.4	ALA 722 LYS 754 ASP 837 ARG 841 LYS 875 VAL 876
4	11719266	-6.5	-6.5 , -5.7	LEU 718 GLY 724

				ASP 855
5	44129654	-6.1	-6.1 , -5.6	CYS 797 ASN 842
6	16091478	-7.2	-7.2 , -6.3	LYS 745 LYS 875
7	19077507	-6.8	-6.8 , -5.4	ARG 776 GLN 791 LYS 852
8	44158623	-5.8	-7.0 , -6.1	LYS 745
9	44158624	-7.5	-7.5 , -6.4	VAL 774 LYS 852 LEU 1017
10	44158625	-6.7	-6.7 , -6.3	ARG776 LYS 852
11	44158626	-7.3	-7.3 , -6.2	ALA 767 ASP 770 LYS 852 LEU1017
12	44416407	-6.2	-6.2 , -5.4	ARG 776 LYA 852
13	44416610	-7.4	-7.4 , -6.3	ARG 748 GLU 749 ALA 859 LEU 862
14	46243752	-6.4	-6.4 , -5.3	ARG 776 LYS 852
15	46243753	-7.0	-7.0 , -6.1	LYS 745 ASP 855 LYS 875

Table 5: The result of Docking of **Gefitinib** and 14 similar compounds with **HER2**

Ligand ID		Best Energy	Low/High Energy	H-bond residues
1	123631 (Main compound)	-6.4	-6.4 , -5.3	GLN 795
2	10159951	-6.6	-6.6 , -5.3	No H- bond
3	11604752	-6.2	-6.2 , -5.2	GLU 757 THR 759
4	11719266	-6.2	-6.2 , -5.5	No H- bond
5	44129654	-6.9	-6.9 , -5.6	ARG 756 GLU 757
6	16091478	-5.8	-5.8 , -5.2	No H- bond
7	19077507	-7.0	-7.0 , -5.7	No H- bond
8	44158623	-5.8	-5.8 , -5.3	ASN 764
9	44158624	-7.2	-7.2 , -5.9	LEU 869
10	44158625	-6.7	-6.7 , -5.7	ARG 756 GLU 757
11	44158626	-7.0	-7.0 , -5.6	LEU 869
12	44416407	-5.5	-5.5 , -4.7	No H- bond
13	44416610	-6.9	-6.9 , -5.3	AEG 756 ASN 758
14	46243752	-7.0	-7.0 , -5.6	LEU869
15	46243753	-5.8	-5.8 , -5.0	ARG756

Table 6: The result of Docking of **Lapatinib** and 12 similar compounds with **HER1**

Ligand ID		Best Energy	Low/High Energy	H-bond residues
1	208908 (Main compound)	-8.1	-8.1 , -7.3	CYS 797 ASP 800 PRO 877
2	10438224	-8.8	-8.8 , -7.9	LYS 745 CYS 797 ASP 800 ASP 855

				LYS 875
3	24743759	-8.1	-8.1 , -7.4	PHE 723 GLY 724 CYS 797 ASP 800
4	44199879	-8.3	-8.3 , -7.4	GLY 719 ASP 855
5	44199880	-8.1	8.1 , 7.1	LYS 745 CYS 797 ARG 841 ASP 855
6	44199881	-8.0	8.0 , 7.0	LYS 745 ASP 855
7	44199992	-8.9	-8.9 , -7.8	LYS 745 GLY 796 CYS 797 ASP 800 ASP 855
8	44199993	-7.6	-7.6 , -6.8	ARG 841
9	44199994	-7.8	-7.8 , -7.3	ASP 855 ARG 841
10	44200111	-8.1	-8.1 , -7.0	PHE 723
11	44200112	-8.3	-8.3 , -7.6	LYS 745 ASP 800 ASP 855 PRO 877
12	44201169	-7.5	-7.5 , -7.0	No H-bond
13	49849309	-8.5	-8.5 , -7.5	ASP 855

Table 7: The result of Docking of **Lapatinib** and 12 similar compounds with **HER2**

Ligand ID		Best Energy	Low/High Energy	H-bond residues
1	208908 (Main compound)	-8.4	-8.4 , -7.1	No H-bond
2	10438224	-8.3	-8.3 , -7.1	LEU 814 ILE 821 ASP 896 ILE 965 SER 969
3	24743759	-7.7	-7.7 , -6.8	ILE 821 GLY 901 CYS 950
4	44199879	-8.2	-8.2 , -6.9	No H-bond
5	44199880	-8.0	-8.0 , -6.8	No H-bond
6	44199881	-8.0	-8.0 , -6.5	No H-bond
7	44199992	-7.7	-7.7 , -6.7	ASP 896 ILE 965 SER 969
8	44199993	-8.3	-8.3 , -7.1	LEU 814 CYS 818 ILE 821 VAL 897 GLY 901 CYS 950
9	44199994	-8.8	-8.8 , -7.0	No H-bond
10	44200111	-8.3	-8.3 , -6.7	No H-bond
11	44200112	-7.5	-7.5 , -6.7	ILE 814 ILE 821 ASP 896 CYS 950
12	44201169	-8.0	-8.0 , -6.9	No H-bond
13	49849309	-7.9	-7.9 , -7.0	No H-bond

III. Conclusion

Based on the value of bonding energy, the best compound with high stability has minimum value of energy.

In conclusion and according of our analysis, we can consider that:

1. For **HER1** receptor and **Erlotinib** similarity compounds, the first ligand that we can choose is the substance with CID- 25125154, because it has minimum energy between these 15 compounds and it also has maximum H-bond (4 H- bonds) as the best.

The second best ligand is the substance with CID-25125156, because it has lowest energy.

Ligand ID		Best Energy	H-bond residues	Picture HER1+Ligand
1	176870 (Main compound)	-6.5	ARG 776 LYS 852	Figure A1
2	25125154	-6.8	PRO 772 GLN 791 LYS 846 LYS 852	Figure F1
3	25125156	-7.0	LYS 852	Figure H1

Table 8: Choose the best ligand of Erlotinib compounds for HER1 receptor

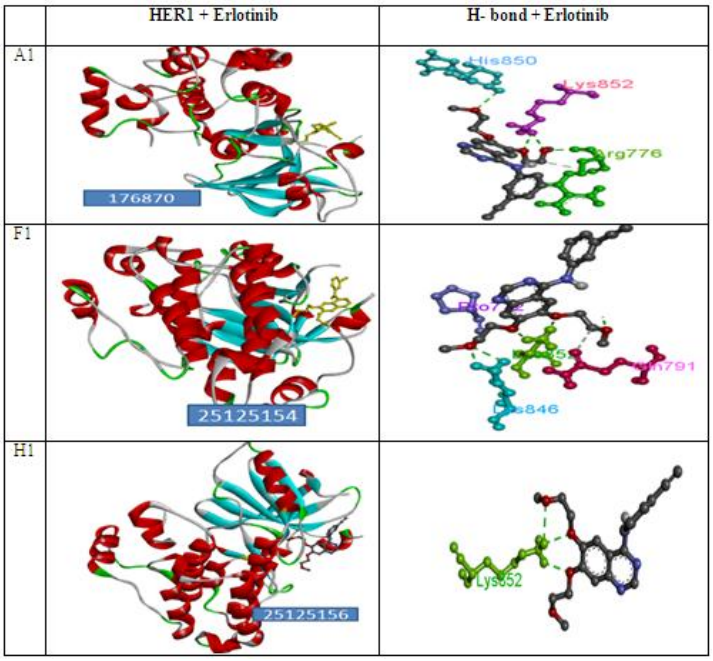


Figure 1: Docking structures of Erlotinib compounds and HER1 receptor

2. For **HER2** receptor and **Erlotinib** similarity compounds, the first ligand that we can select is the substance with CID- 25125156, because it has lowest energy between these 15 compounds and it also has maximum H-bond (3 H- bonds) as the best.

The second best ligand is the substance with CID-25125159, because it also has minimum value of energy and 2 H-bonds.

Ligand ID	Best Energy	H-bond residues	Picture HER2+Ligand
176870 (Main compound)	-6.4	GLN 795	Figure A2
25125156	-6.6	ARG 756 ASN 758 GLU 770	Figure H2
25125159	-6.6	ARG 756 GLU 770	Figure K2

Table 9: Choose the best ligand of Erlotinib compounds for HER2 receptor

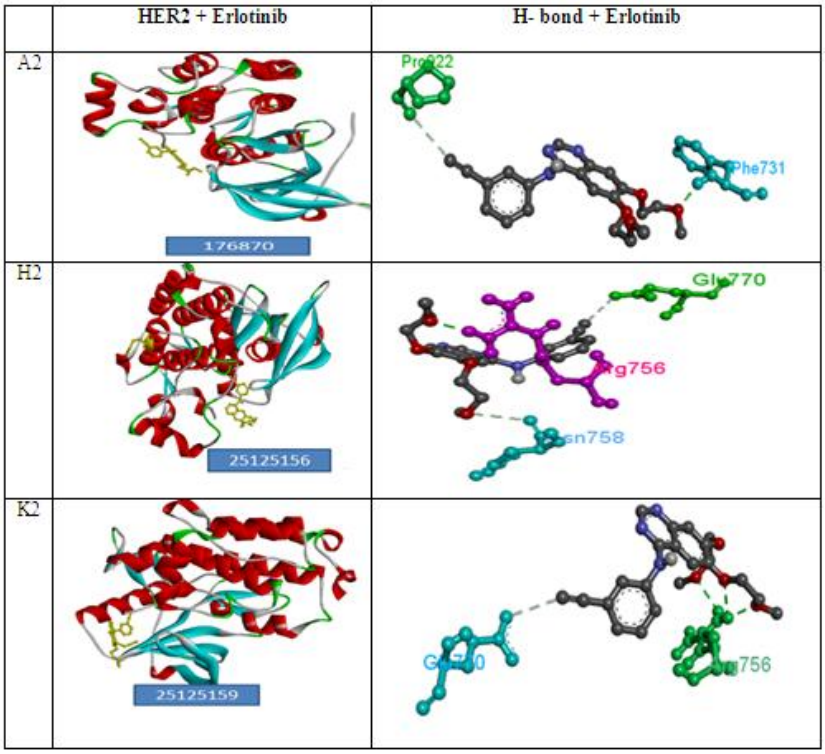


Figure 2: Docking structures of Erlotinib compounds and HER2 receptor

3. For **HER1** receptor and **Gefitinib** similarity compounds, the first ligand that we can choose is the substance with CID- 11604752, because it has minimum energy between these 15 compounds and it also has maximum H-bond (6 H- bonds) as the best.
The second best ligand is the substance with CID-44158624, because it also has lowest energy and 3 H- bonds.

Ligand ID	**Best Energy**	**H-bond residues**	**Picture HER1+Ligand**
123631 (Main compound)	-6.8	ARG 776 LYS 852	Figure A1
11604752	-7.5	ALA 722 LYS 754 ASP 837 ARG 841 LYS 875 VAL 876	Figure C1
44158624	-7.5	VAL 774 LYS 852 LEU 1017	Figure I1

Table 10: Choose the best ligand of Gefitinib compounds for HER1 receptor

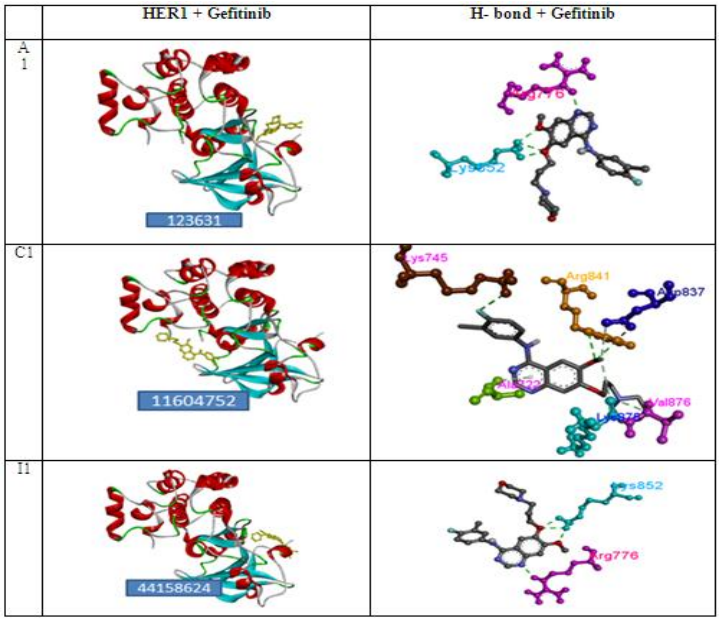


Figure 3: Docking structures of Gefitinib compounds and HER1 receptor

4. For **HER2** receptor and **Gefitinib** similarity compounds, the first ligand that we can select is the substance with CID- 44158624, because it has lowest energy between these 15 compounds as the best. Another best ligands are the substances with CID- 44158626 and CID- 46243752 , because they also have minimum value of energy.

Ligand ID	Best Energy	H-bond residues	Picture HER2+Ligand
123631 (Main compound)	-6.4	GLN 795	Figure A2
44158624	-7.2	LEU 869	Figure I2
44158626	-7.0	LEU 869	Figure K2
46243752	-7.0	LEU869	Figure N2

Table 11: Choose the best ligand of Gefitinib compounds for HER2 receptor

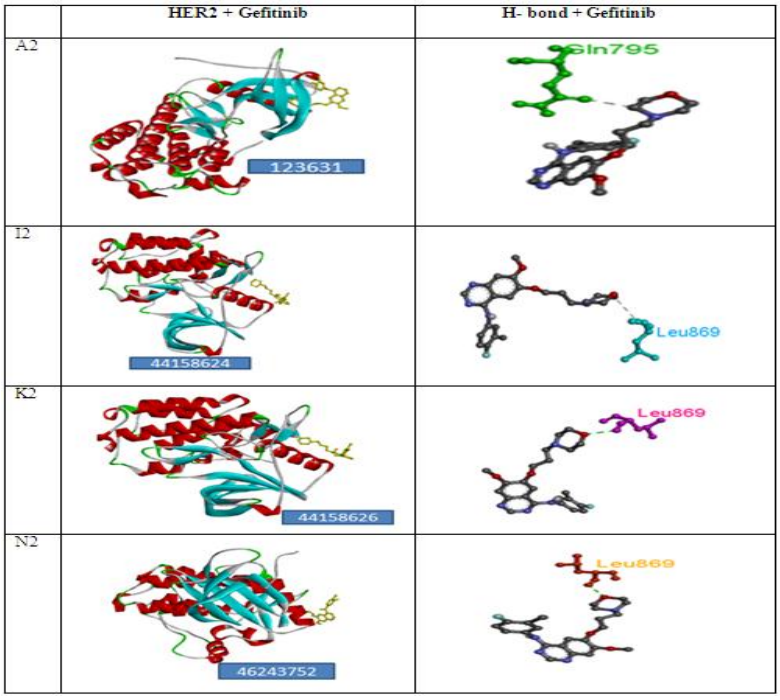


Figure 4: Docking structures of Gefitinib compounds and HER2 receptor

5. For **HER1** receptor and **Lapatinib** similarity compounds, the first ligand that we can choose is the substance with CID-44199992, because it has minimum energy and maximum numbers of H- bonds (5 H-bonds) between these 13 compounds, as the best.The second best ligand is the substance with CID- 10438224, because it also has lowest energy and 5 H- bonds.

Ligand ID	Best Energy	H-bond residues	Picture HER1+Ligand
208908 (Main compound)	-8.1	CYS 797 ASP 800 PRO 877	Figure A1
44199992	-8.9	LYS 745 GLY 796 CYS 797 ASP 800 ASP 855	Figure G1
10438224	-8.8	LYS 745 CYS 797 ASP 800 ASP 855 LYS 875	Figure B1

Table 12: Choose the best ligand of Lapatinib compounds for HER1 receptor

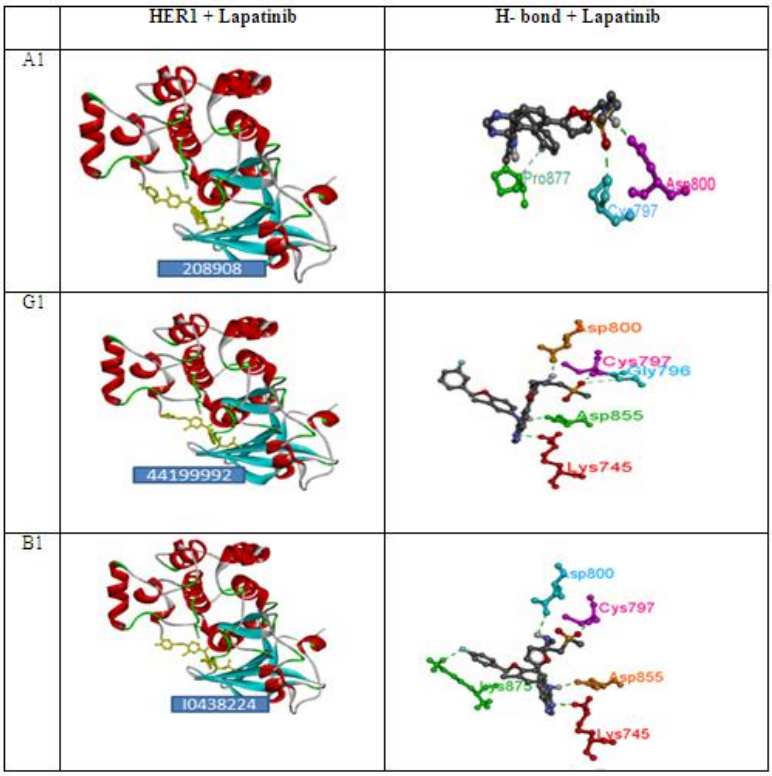


Figure 5: Docking structures of Lapatinib compounds and HER1 receptor

6. For **HER2** receptor and **Lapatinib** similarity compounds, the first ligand that we can select is the substance with CID- 44199993, as the best because it has lowest energy and highest number of H- bonds (6 H-bonds) between these 13 compounds . Another best ligand is the substances with CID- 10438224, because it also has minimum value of energy and 5 H-bonds.

Ligand ID	Best Energy	H-bond residues	Picture HER2+Ligand
208908 (Main compound)	-8.4	No H-bond	Figure A2
44199993	-8.3	LEU 814 CYS 818 ILE 821 VAL 897 GLY 901 CYS 950	Figure H2
10438224	-8.3	LEU 814 ILE 821 ASP 896 ILE 965 SER 969	Figure B2

Table 13: Choose the best ligand of Lapatinib compounds for HER2 receptor

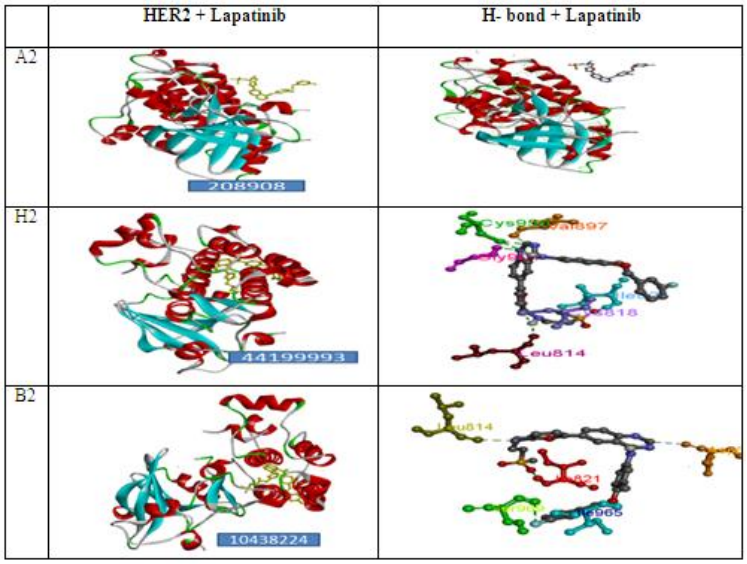


Figure 6: Docking structures of Lapatinib compounds and HER2 receptor

Refrences

[1]. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK: "Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial."(Aug 2010)

[2]. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. ActaPatholMicrobiolScand .

[3]. Ahmedin Jemal, Melissa M. Center, Carol DeSantis and Elizabeth M. Ward : "Global Patterns of Cancer Incidence and Mortality Rates and Trends." (2010).

[4]. Yasuhide Yamada: "Molecular therapy for gastric cancer" , (2013).

[5]. Dr west , published march2, (2009).

[6]. John Mendelsohna and Jose Baselgab: "Epidermal Growth FactorReceptor Targeting in Cancer" , (2006)

[7]. Zwick E, Bange J, Ullrich A : "Receptor tyrosine kinase signalling as a target for cancer intervention strategies". *Endocr. Relat. Cancer* (September 2001).

[8]. Targeting PI3K/AKT/Mtor Pathway And Mutant EGFR To Overcome Resistance To Tyrosine Kinase Inhibitors In Mutant EGFR-Mediated Lung Cancer1Department of Pathology and Yale Cancer Center, Yale University School of Medicine, New Haven CT, USA 06510, November 15th, 2013.

[9]. Greulich H, Chen TH, Feng W, Janne PA, Alvarez JV, Zappaterra M, Bulmer SE, Frank DA, Hahn WC, Sellers WR, et al.: "Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants." ,(2005).

[10]. Yun CH, Boggon TJ, Li Y, Woo MS, Greulich H, Meyerson M, Eck MJ: "Structures of lung cancerderived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity.",(2007)

[11]. Praetorius,NatalieP: "Mandal,TarunK: "Engineered Nanoparticles in Cancer Therapy" (2007)

[12]. John P. Lynch and David C: "Targeted Therapies for Hepatocellular Carcinoma", (2010)

[13]. Becker JC, Müller-Tidow C, Stolte M, Fujimori T, Tidow N, Ilea AM, Brandts C, Tickenbrock L, Serve H, Berdel WE, Domschke W, Pohle T: Acetylsalicylic acid enhances antiproliferative effects of the EGFR inhibitor gefitinib in the absence of activating mutations in gastric cancer. 2006 sep

[14]. Ann Oncol: "HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target", (2008).
[15]. Jin Won Kim, Hwang-Phill Kim, Seock-Ah Im, Soyeong Kang, Hyung Seok Hur, Young-KwanYoon, Do-Youn Oh, Jee Hyun Kim, Dong Soon Lee , Tae-You Kim, Yung-Jue Bang: " The growth inhibitory effect of lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase, in gastric cancer cell lines" ,(2008).
[16]. Hasinoff BB: "The dual-targeted HER1/HER2 tyrosine kinase inhibitor lapatinib strongly potentiates the cardiac myocyte-damaging effects of doxorubicin" , (2012).
[17]. Cancer Connect.com (http://news.cancerconnect.com/gefitinib/).
[18]. Cancer Metastasis Rev. Author manuscript; available in PMC, (2012).
[19]. Li Z, Xu M, Xing S, Ho W, Ishii T, Li Q, Fu X, Zhao Z : "Erlotinib Effectively Inhibits JAK2V617F Activity and Polycythemia Vera Cell Growth", (2007).
[20]. Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. New England Journal of Medicine. 2005;353(2):133–144.
[21]. Corso S, Ghiso E, Cepero V, Sierra JR, Migliore C, Bertotti A, Trusolino L, Comoglio PM, Giordano S "Activation of HER family members in gastric carcinoma cells mediates resistance to MET inhibition."- (2010 May)
[22]. Natasja Brooijmans : DOCKING METHODS, LIGAND DESIGN, AND VALIDATING DATA SETS IN THE STRUCTURAL GENOMICS ERA, 2009.
[23]. Oliviero Carugo and Sándor Pongor : A normalized root-mean-spuare distance for comparing protein three-dimensional structures
[24]. Law, V; Knox C, Djoumbou Y, Jewison T, Guo AC, Liu Y, Maciejewski A, Arndt D, Wilson M, Neveu V, Tang A, Gabriel G, Ly C, Adamjee S, Dame ZT, Han B, Zhou Y, Wishart DS. (Jan 2014). "DrugBank 4.0: shedding new light on drug metabolism".