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Docking Study of EGFR inhibitor as Anticancer Agents

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Research Article

Docking Study of EGFR inhibitor as Anticancer Agents

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Abstract

The Clinical Selective Anti-epidermal Growth Factor Receptor Therapy (EGFR) inhibitor GS-1101 (Idelalisib) is most widely used for the treatment of many tumour forms and has prevented life throughout the world. GS-1101 has been used both in the treatment and prevention of lymphoma and other tumours. Several GS-1101 derivatives with quinazoline moiety containing derivatives have been developed in silico studies based on these for the current study. The analysis already chosen against EGFR used PDB 4XEO for the present work. Designed molecule showed docking interaction with active site amino acid by hydrogen bond as well as Van der Waals interaction. The information obtained from this analysis, such as total energy and amino acid synergy, indicated the necessary binding interaction to maximize the lead molecule. Such results can be used to develop new anti-cancer agents that have common side effects and limited toxic effects.

Key words: Anti-cancer agents, EGFR inhibitor, In Silico study, Quinazoline derivatives

Introduction

Cancer spared by invasion to the surrounding tissues and by metastasis to distant sites [1]. Many of the newly approved cancer treatments target either the cell surface receptors or intermediate phosphor proteins and kinases at the head of the signaling pathway. Knowing the activation status of key phosphor protein signaling molecules in tumour cells can give critical information on the origin, type and status of these cells [2]. To date, few patients have been treated by an Epidermal Growth Factor Receptor Tyosine Kinase Inhibitor (EGFR TKI) alone and ultimately develop resistance and relapse in virtually all patients [3]. Anti-epidermal growth factor receptor therapy (EGFR) has recently been introduced to treat various types of cancer. At the time they were introduced into clinical practice, little understanding of the molecular basis of tumour sensitivity and tolerance to these novel targeted compounds remained. In the present research work, quinazoline with some heterocyclic moieties for development of the new molecule was used.

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Chemistry of Quinazoline

Quinazoline derivatives, which belong to the N containing hetrocyclic compounds, have caused their specific and distinct biopharmaceutical activities to be uniformly concerned. Work has already identified significant therapeutic activities for derivatives of quinazoline, including anti-cancer [4], anti-inflammatory [5], anti-bacterial [6], analgesic [7], anti-oxidant [8], anti-malarial [9], anti-HIV [10], anti-mutagenic [11], anti-leukemic [12], anticonvulsant [13], etc.

Quinazolinones are classified into the following five categories, based on ring substitution patterns [14]

- 2-Substituted-4(3H)-quinazolinones
- 3-Substituted-4(3H)-quinazolinones
- 4-Substituted-quinazolinones
- 2,3-Substituted-4(3H)-quinazolinones
- 2,4-Substituted-4(3H)-quinazolinones

Depending on the type of keto or oxo group, these compounds can be classified into three types. [15].

Of the three types of quinazolinone in many of the suggested biosynthetic pathways, 4(3H)-quinazolinones are more common as intermediates

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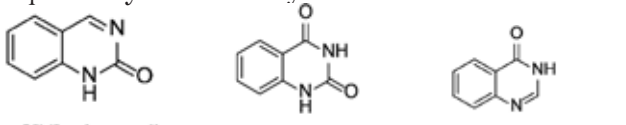
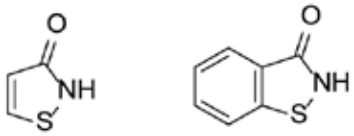
or as natural products. This effect is due in part to anthranilate-derived structure (anthranilic acid or various esters, anhydride isotope, anthranilamide, and anthranilonitrile), whereas 2(1H) quinazolinone is primarily a commodity [16].



Chemistry of Isothiazolinone and Benzo[d] isothiazol-3(2H)-on



Isothiazolinone is a hetrocyclic chemical compound related to isothiazole. Compared to many other simple heterocycles its discovery is relatively recent, with reports first appearing in the 1960s [13]. Benzisothiazolinone (BIT) is a widely used biocide and belongs to the group of isothiazolinones.

EGFR inhibitor

The Epidermal Growth Factor Receptor (EGFR, ErbB1, HER1) is a host cell in the ErbB receptor family. It is one of the four tyrosine kinases, such as HER2/c-neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4), which moves from the inactive monomer to the active homodimer after binding the ligand. It may also form a heterodimer with another member of the ErbB receptor family. Dimerization of EGFR involves the central function of the protein tyrosine kinase which causes auto phosphorylate of the residues of C-terminal tyrosine. Auto phosphorylated are downstream signaling cascades such as AKT, MAPK and JNK, which ultimately lead to synthesis of DNA, progression of the cell cycle, apoptosis and proliferation [17, 18, 19, 20].

In the research of silico, there is nothing but studies performed using computer software, when we design a new molecule is most significant. Molecular docking is one of the approaches used in finding and refining lead in silicon. Docking has often been used to predict the affinity and actions of small molecules to predict the binding orientation of small molecular drug candidates towards their protein targets. Docking thus plays a key role in the rational design of drugs [21]. Molecular docking provides a number of valuable tools for drug design and analysis; takes into account the exact position of the molecule at the target active site [22, 23]. Digital screening based on a structure designed to identify new active compounds generated for a specific target protein, providing a large number of successful molecules [27]. Docking reports help to locate the active compound with its receptor selectivity. The identification of molecular and structural features responsible for the specific biological behaviour or the prediction of modifications of compounds lead to an improvement in potency [23].

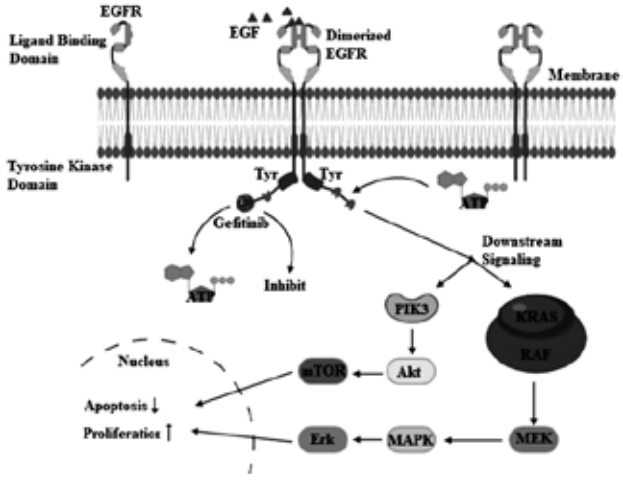


Figure 1: Mechanism of EGFR inhibitor

Types of Docking [21]

There are two types of docking:

- Rigid docking
- Flexible docking

1. **Rigid Docking**

   If we consider the molecules to be stable, we look at a 3D space transformation of one of the molecules at that moment which will make them optimally suited to the other molecules in terms of a scoring function. Confirmation of ligand may occur in the absence of a receiver or in the presence of a binding receptor.

2. **Flexible Docking**

   Aside from transformation, we regard molecular versatility as our goal of finding receptor and ligand molecules confirmations. There are three main approaches for an analysis of molecular

docking, based on ligand and receptor stability and stiffness [22, 23].

Rigid Ligand and Rigid Receptor Docking:
Both ligand and receptor are rigid bodies and provide minimal docking space, with only three transitional degrees of freedom within the ligand receptor complex within three rotations.

Flexible Ligand and Rigid Receptor Docking:
This is the mostly used docking process the ligand must connect with a more conformation-shifting rigid receptor.

Flexible Ligand and Flexible Receptor:
In the area of docking, versatile receptors pose a major challenge.

Molecular Docking Models [21]

The Lock and Key Theory: Back in 1890, as shown in Figure 2, Emil Fischer introduced a model called the "lock-and-key model" that explained how biological systems work. A substratum slides into the active site of a macromolecule as a key fit within a lock.

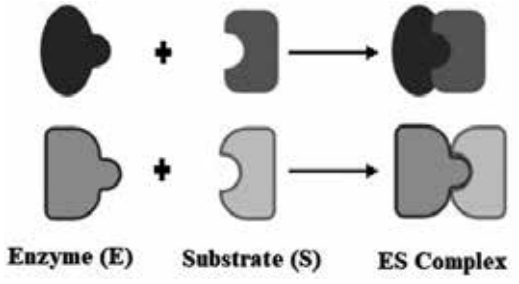


Figure 2: Lock and Key Model

The Induced-Fit Theory: In 1958, Daniel Koshland developed the induced match hypothesis. The basic idea is that both the ligand and thetarget can respond to each other through minor conformation shifts, as shown in Figure 3, until an optimum fit in the recognition cycle is reached.

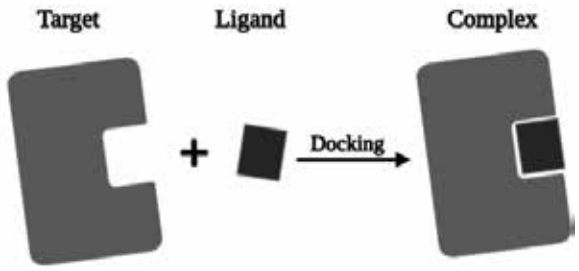


Figure 3: Induced-Fit Theory

The Conformation Ensemble Model: The Induced-Fit Theory: Daniel Koshland developed the "Induced Fit theory" in 1958. The basic idea is that, as shown in Figure 3, both the ligand and the target will slowly adjust to each other through minor conformation changes until an optimum fit is reached in the identification process [25].

Basic Requirements for Molecular Docking

The ligand docking approach requires components of a target protein structure, interesting molecules or a database containing existing components of a target protein structure, computer docking compound molecules, and a computational mechanism that helps to apply the necessary docking and scoring procedures. Most docking algorithms presume the protein is rigid; typically, ligand is called flexible. The binding of protein-binding pockets must be taken into account, in relation to the conformational degree of freedom. Docking can be achieved by compact molecules or fragments into protein active sites using various approaches such as clique-searching, geometric hashing, and clustering posing.

Ligand Representation [21]

Usually, when adding or removing hydrogens, the form most probable to be dominant is further modified given the pKa values are estimated. Ensuring precise printing of the atom is important.

Receptor Representation [21]

The quality of the receptor structure used plays a central role in the calculation of the docking success. In general, the higher the applied crystal structure resolution, the better the results of the docking will be observed.

Mechanism of Docking

The first prerequisite is a protein structure fit for docking testing. A biophysical approach such as x-ray crystallography, or less generally, Nuclear Magnetic Resonance (NMR) spectroscopy, has usually solved the structure. An arrangement of proteins is used to link up the system. A docking method is achieved using two parts, such as the search algorithm and scoring function. Existing computer tools that identify all possible transformations of each molecule and all possible ligand rotational and

translation orientations relative to the protein could not be used to scan the quest region exhaustively.

Receptor Preparation

- Depending on the docking system used
- Structure selection
- Site selection
- Sometimes hydrogen filtering has to be applied, some systems are more sensitive to placement than others
- Remove/include liquids, cofactors, metals
- Pre-docking remembers to consider missing residues or atoms.

Ligand preparation

- Where chiral centers produce isomers
- Calculate charges – estimate pKa's for each atom theoretically charged – produce a structure for each combination of charges for a given pH range.
- Minimize structures – Typically using the forcefield of molecular mechanics [26].

Table 1: List of Proposed Molecule with standard Molecule

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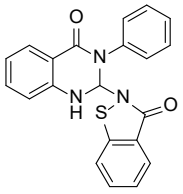
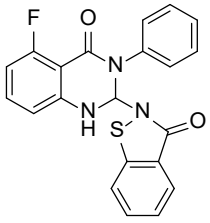
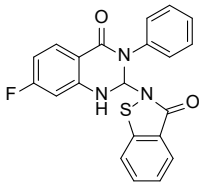
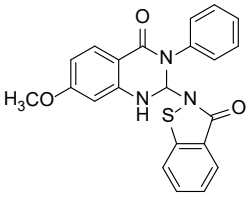
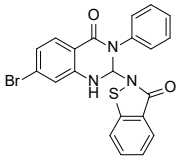
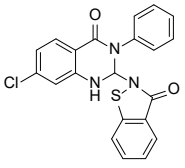
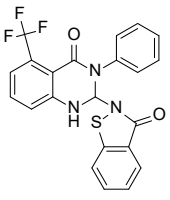
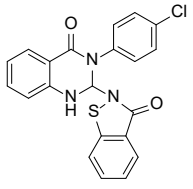
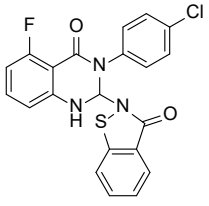
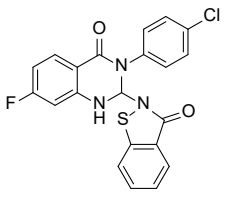
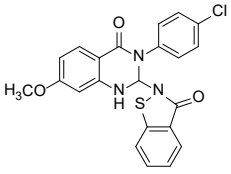
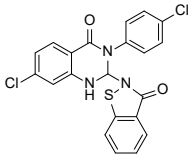
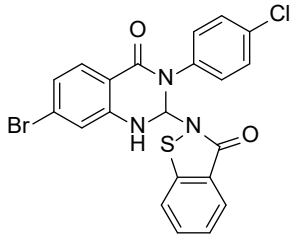
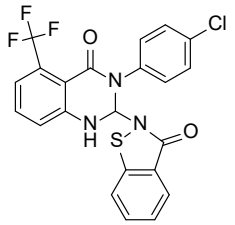
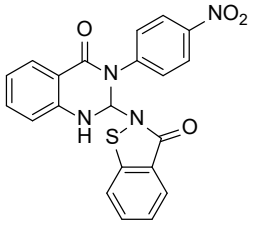
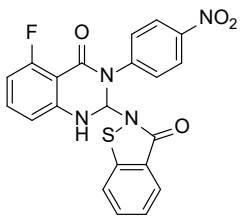
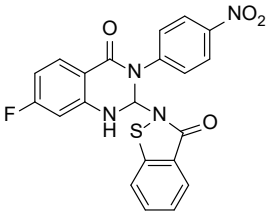
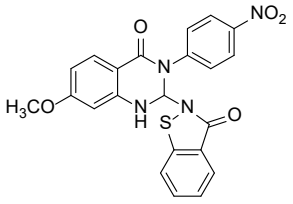
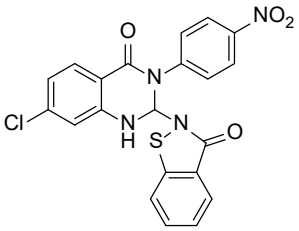
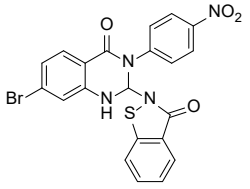
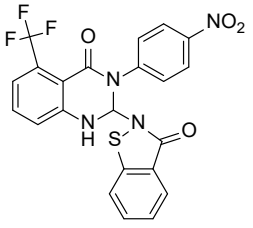
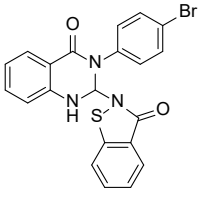
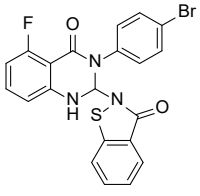
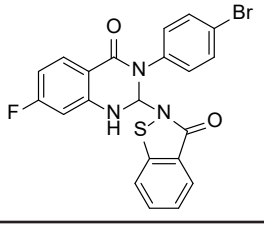
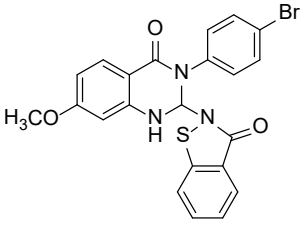
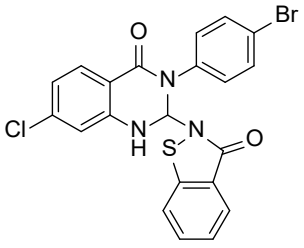
PPM1		PPM2	
PPM3		PPM4	
PPM5		PPM6	
PPM7		PPM8	
PPM9		PPM10	
PPM11		PPM12	

Araf MH, *et al*: Docking Study of EGFR inhibitor as Anticancer Agents

Sr No	Molecule structure	Sr No	Molecule structure
PPM13		PPM14	
PPM15		PPM16	
PPM17		PPM18	
PPM19		PPM20	
PPM21		PPM22	
PPM23		PPM24	
PPM25		PPM26	

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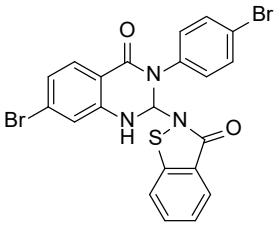
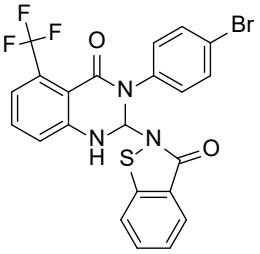
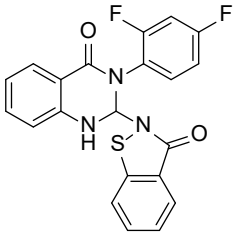
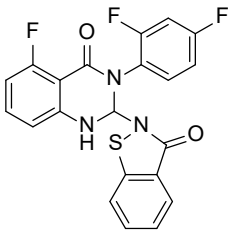
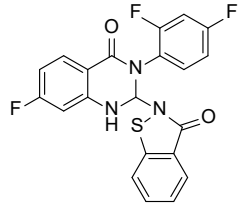
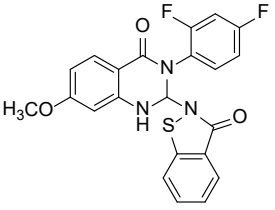
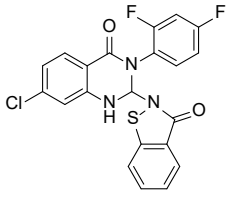
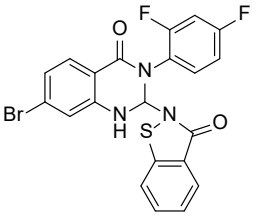
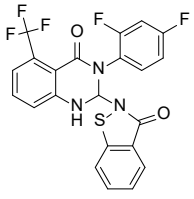
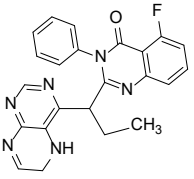
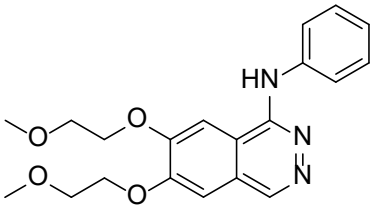
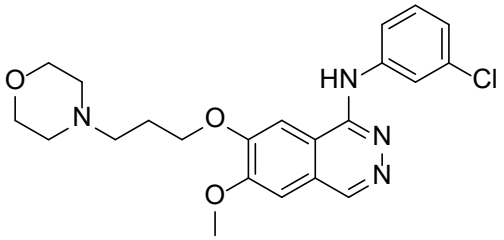
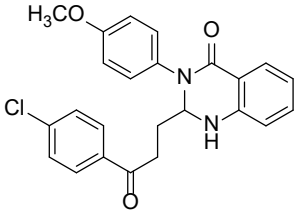
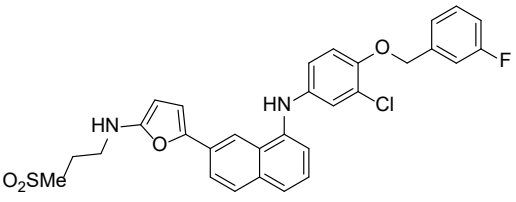
Sr No	Molecule structure	Sr No	Molecule structure
PPM27		PPM28	
PPM29		PPM30	
PPM31		PPM32	
PPM33		PPM34	
PPM35		GS1101	
Erlotinib		Gefitinib	
A. Ozair		Lepatinib	

Available Softwares for Docking

- Dock (1982, 2001)
- Flex (1996)
- Hammerhead (1996)
- Surflex (2003)
- SLIDE (2002)
- AutoDock (1990,1998)
- ICM (1994)
- MCDock (1999)
- GOLD (1997)
- GemDock (2004)
- Glide (2004)

We used the gem dock molecular docking program to test the new molecule in Silico.

Materials and Methods

Data set for Molecular Docking

Based on the knowledge of numerous GS1101 analogs acting as an anticancer agent, some of the molecules were developed and labeled PM-1 to PM-35 as shown in Table 1. The data set used for molecular docking to build such molecules includes 45 molecules in which 35 potential molecules (PPM), 05 normal literature molecules (STD-1 to STD-5) and 5 FDA approved marketable drugs. The chemical structure of the molecules and their name are listed in Table 1.

LIPINSKI'S Test for Oral Availability

One of the best ways to find orally available drug is following a Lipinski's "rule of five" (Ro5). The main aim to follow Ro5: it evaluates drug-likeness or determine if a chemical compound will have desired pharmacokinetic profile or not. We performed these studies on SWISS software to ensure the feasibility of molecules [24]. This methodology helps to reduce the conventional wastage and reduce the time of laboratory experiment trial and error and also to ensure oral bioavailability of the molecules.

Results and Discussion

LIPINSKI'S Rule of Five

For the calculation of drug-likeness property, the SWISS program was used. The result shows no violation of molecules, which leads to the identification of molecular weight and mlog P values, can affect enzyme activity. These molecules indicate orally safety profile (Table 2).

Table 2: Calculated Physicochemical Parameters (Pfizer's rule)

Sr no	Compound Name	MW	Log p	H-donor	H-acceptor	Violation
1	PPM1	373.43	3.44	1	2	0
2	PPM2	391.42	3.71	1	3	0
3	PPM3	391.42	3.75	1	3	0
4	PPM 4	403.45	3.43	1	3	0
5	PPM 5	452.32	4.17	1	2	1
6	PPM 6	407.87	3.97	1	2	0
7	PPM 7	429.41	4.40	1	5	1
8	PPM 8	407.87	3.93	1	2	0
9	PPM 9	425.86	4.20	1	3	1
10	PPM 10	425.86	4.21	1	3	1
11	PPM 11	437.90	3.90	1	3	0
12	PPM 12	442.32	4.46	1	2	1
13	PPM 13	486.77	4.54	1	2	1
14	PPM 14	463.86	5.01	1	5	1
15	PPM 15	418.43	2.66	1	4	0
16	PPM 16	436.42	2.94	1	5	0
17	PPM 17	436.42	2.98	1	5	0

Sr no	Compound Name	MW	Log p	H-donor	H-acceptor	Violation
18	PPM 18	448.45	2.67	1	5	0
19	PPM 19	452.87	3.20	1	4	0
20	PPM 20	497.32	3.28	1	4	0
21	PPM 21	474.41	3.75	1	7	0
22	PPM 22	452.32	4.01	1	2	0
23	PPM 23	470.31	4.29	1	3	0
24	PPM 24	470.31	4.32	1	3	1
25	PPM 25	482.35	4.01	1	3	0
26	PPM 26	486.77	454	1	2	1
27	PPM 27	531.22	4.63	1	2	2
28	PPM 28	508.31	5.09	1	5	2
29	PPM 29	409.41	3.98	1	4	0
30	PPM 30	427.40	4.27	1	5	1
31	PPM 31	427.40	4.30	1	4	1
32	PPM 32	439.43	3.95	1	5	0
33	PPM 33	443.85	4.53	1	4	1
34	PPM 34	488.30	4.61	1	4	1
35	PPM 35	465.40	5.08	1	7	1
36	GS1101	414.43	3.41	1	6	0
37	Erlotinib	369.41	2.84	1	6	0
38	Gafitinib	428.91	3.44	1	6	0
39	Ozair	420.89	4.26	1	3	1
40	Lepatinib	565.05	4.55	2	5	2

Molecular Docking Protocol

Preparation of Ligands

- The Chem Draw Ultra 8.0 program tested the ligands for their binding activities to 3MZ4 receptors (Chemical Structure Drawing Standard; Cambridge Soft Corporation, USA [2003]).
- These structures were converted into 3D structures using Chem3D Ultra 8.0 software and energy minimization of constructed 3D structures was energetically minimized using Allinger's energy minimization technique.
- Molecular Mechanics Strength Fields (MM2) followed by geometry optimization using semi-empirical AM-1 Quantum Mechanics (Austin Model-1).

Docking of Ligand and Receptor

- An export receptor prepared in the last move of docking applications iGemdock version 2.1.
- Click the Binding Page to register.
- Set population size 200 to 20 years, with two solutions.
- Now pick ligand from where saved in mol scripts, and click submit and dock so that the docking process begins.
- Maximum binding energy comes as a result of the docking.
- Save the profile of relationship research and contact and export in excel.

Ramachandran Plot Analysis

- The plot of Ramachandran is used to imagine the amino acid residue backbone.
- Used for structural analysis and for calculation of potential Phi and Psi angles representing amino acid residues.
- Manufactured using different applications, such as Discovery Studio Visualiser (BIOVIA) plot Ramachandran [30, 31].
- Counting: 180 → +180 (vertical and horizontal axis)

- Allowed/Low Energy Region: the highest point density region on the map.

Ramachandran Plot Result of PDB ID 4XEO (Crystal structure of GS1101 EGFR Protein)

To see the correctness of optimized protein. Generate a Ramachandran plot for human histone deacetylase inhibitor 8, a protein that contains both β-sheet and α-helix (PDB ID 4XEO) [27]. The blue and pink regions seen in Figure 4 represent the favoured and allowed regions as defined by Discovery studio software.

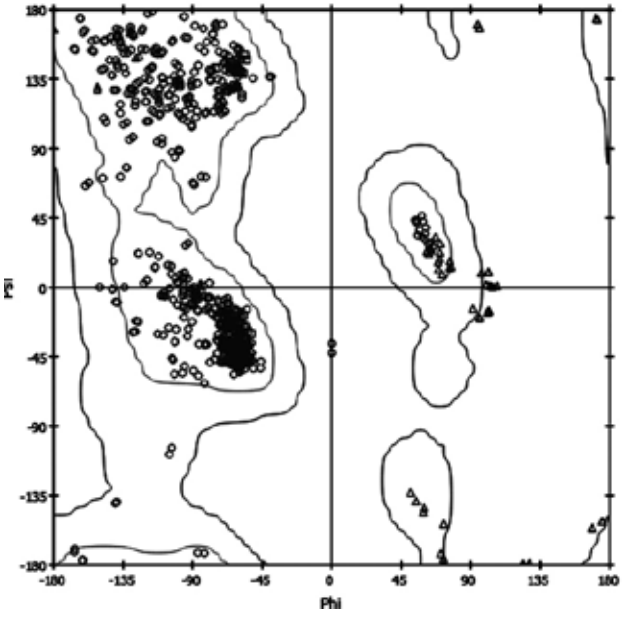


Figure 4: Ramchandran Plot of Estrogen Receptor Alpha Protein PDB ID 4XEO

Interaction Profile

The docking score obtained for all molecules was represented in Table 3. It contains total energy, Vander Waal interaction energy, hydrogen bond-binding energy, and electrostatic energy scores.

PyMol and iGEM dock version 2.1 Software

In this figure, one can easily understand the amino acid binding of the specific site of the molecule. Table 4 describes the interaction profile of amino acid by hydrogen bond and Van der Waals bond with a particular energy which is easily predictable and is used for the determination of highest energy score with amino acid-binding.

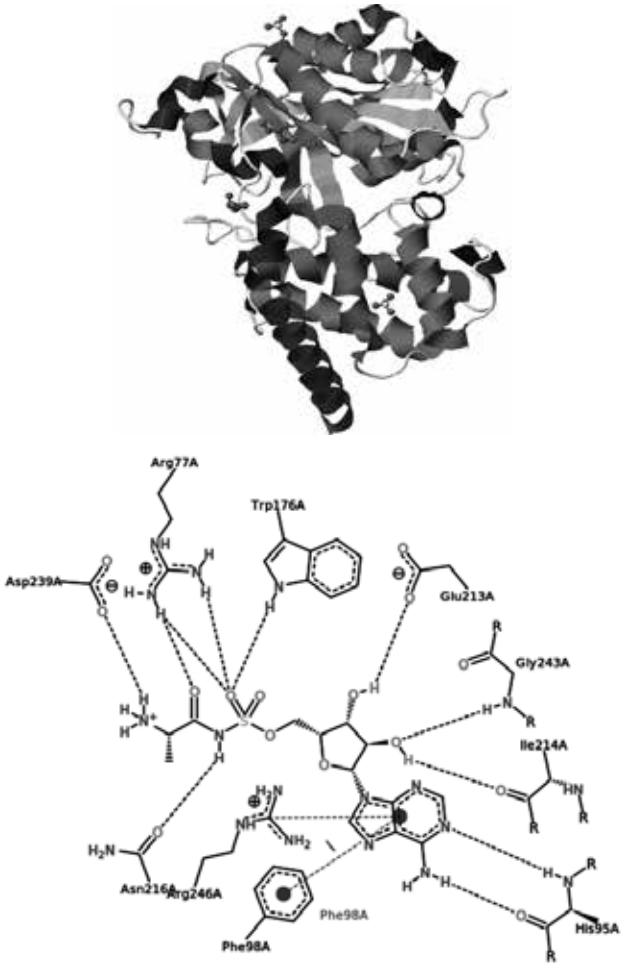
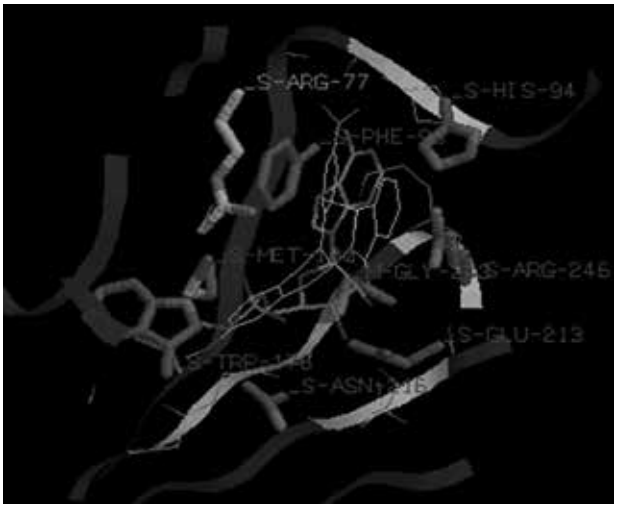


Figure 5: Interaction Profile of the GS1101 Present in to the 4XEO PDB ID [27]

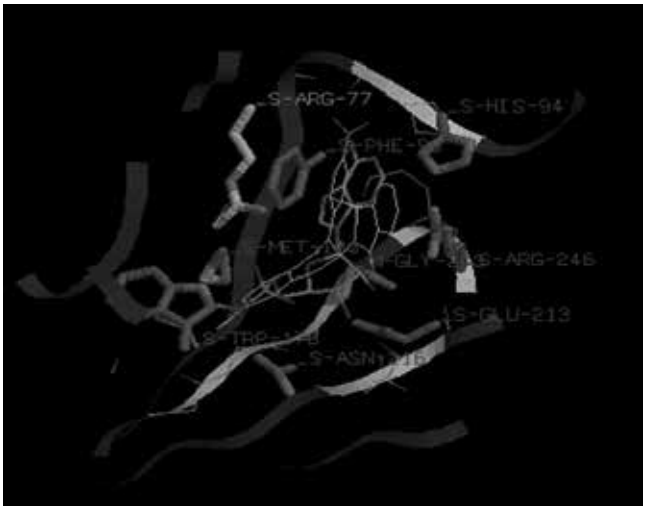
Table 3: Docking Score (kcal/mol) of GS1101 derivatives

Sr no	Compound	Energy	Van der Waals bond	H - Bond	Electrostatic score
1	1	-118.72	-114.634	-4.08642	0
2	2	-107.234	-102.265	-4.96892	0
3	3	-119.051	-112.39	-6.66131	0
4	4	-110.58	-91.1494	-19.4306	0
5	5	-120.217	-116.717	-3.5	0
6	6	-110.725	-107.225	-3.5	0
7	7	-108.286	-103.981	-4.30525	0
8	8	-124.695	-117.939	-6.75583	0
9	9	-98.9106	-95.4823	-3.4283	0

Sr no	Compound	Energy	Van der Waals bond	H - Bond	Electrostatic score
10	10	-100.413	-96.3395	-4.07348	0
11	11	**-128.317**	-120.516	-7.80101	0
12	12	-109.404	-105.904	-3.5	0
13	13	-115.566	-99.1562	-16.4093	0
14	14	-96.9274	-92.2162	-4.7112	0
15	15	-120.842	-110.385	-10.5338	0.0766402
16	16	-64.0492	-56.5492	-7.5	0
17	17	-124.401	-118.007	-6.39441	0
18	18	**-141.343**	-132.468	-10.0583	1.18369
19	19	**-131.087**	-123.505	-8.79947	1.2175
20	20	**-127.465**	-104.518	-23.4399	0.49314
21	21	-89.1073	-77.3068	-11.8005	0
22	22	-104.363	-94.6369	-9.72572	0
23	23	-98.4053	-94.9053	-3.5	0
24	24	-118.834	-112.392	-6.44179	0
25	25	-116.327	-112.766	-3.5609	0
26	26	-113.208	-109.708	-3.5	0
27	27	-123.053	-118.825	-4.22831	0
28	28	-103.983	-94.4918	-9.4916	0
29	29	-100.254	-94.9613	-5.29255	0
30	30	-116.019	-105.312	-10.7068	0
31	31	-103.608	-94.3881	-9.2204	0
32	32	-104.896	-95.8586	-9.03775	0
33	33	-105.44	-96.5778	-8.86222	0
34	34	-102.425	-98.9253	-3.5	0
35	35	-103.066	-100.504	-2.56232	0
36	Ozair	-126.425	-112.427	-13.9985	0
37	Erlotinib	-135.786	-122.118	-13.6679	0
38	Gafitinib	-143.994	-134.416	-9.57823	0
39	GS1101	**-130.837**	-123.735	-7.10152	0
40	Lepatinib	-147.462	-140.275	-7.18739	0

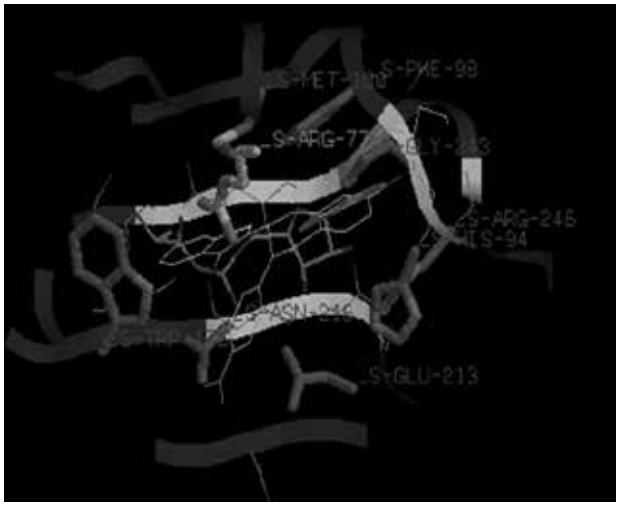


PPM 18

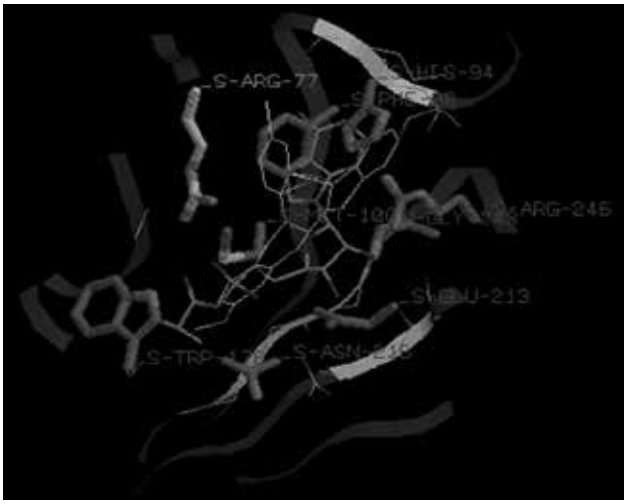


PPM 19

Araf MH, *et al*: Docking Study of EGFR inhibitor as Anticancer Agents



PPM 20



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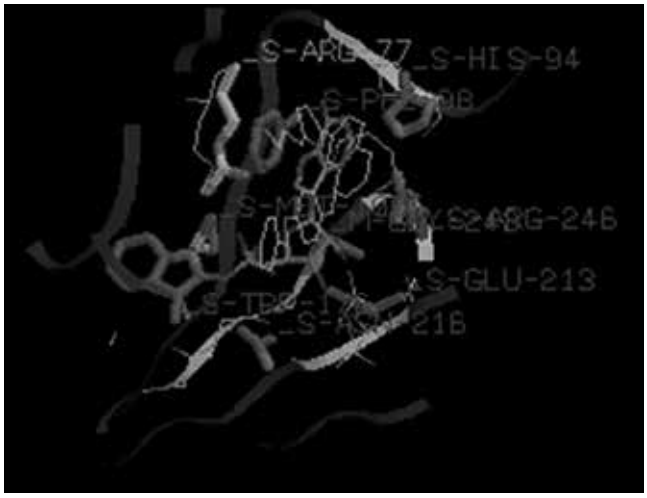

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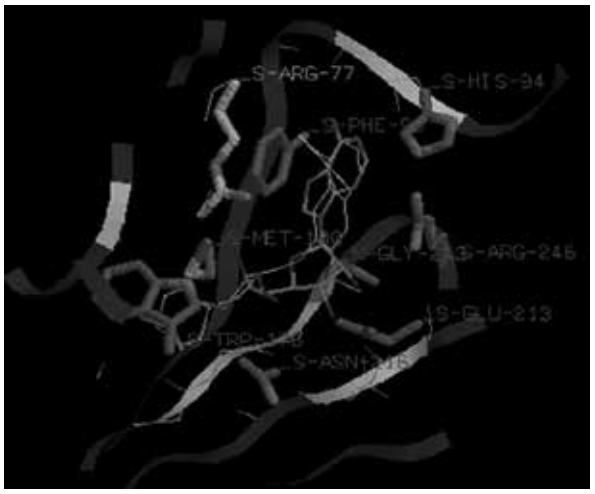

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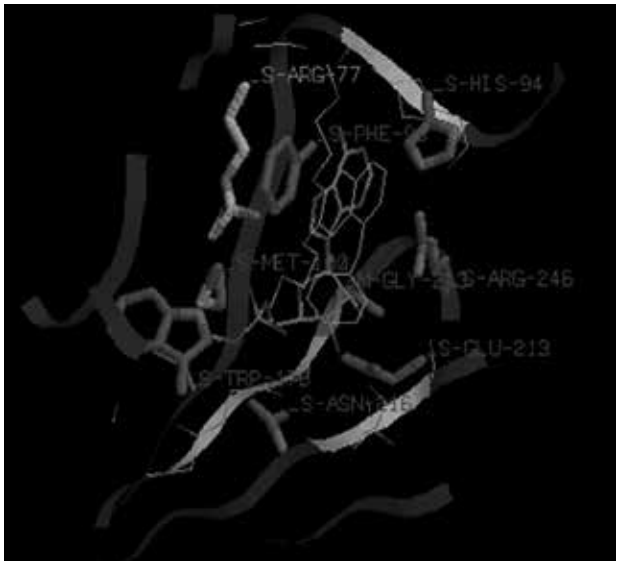

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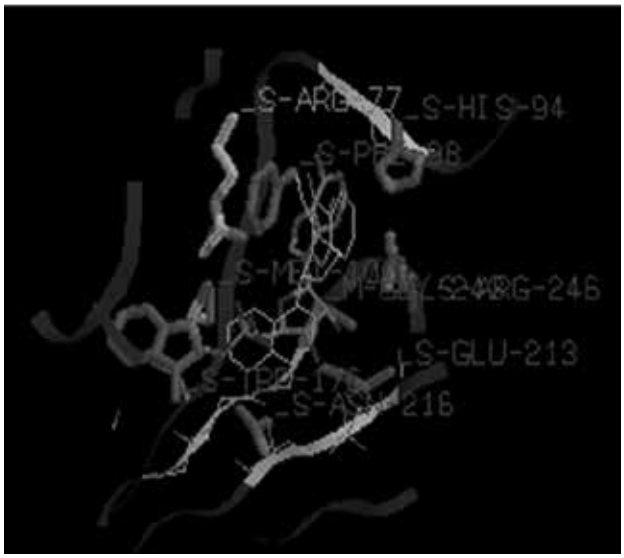

GS1101

Figure 6: Proposed Molecule-1 Interaction Profile by PyMol and iGEM dock version 2.1 Software

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Table 4: Molecular interaction of Amino acid by Hydrogen Bond and Van der Waals bonding

Sr no	Compound	Energy	H-bonding	Van der Waals **bonding**
1	1	-118.72	E, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
2	2	-107.234	E	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
3	3	-119.051	E, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
4	4	-110.58	E, J, O	S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
5	5	-120.217	M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
6	6	-110.725	E	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
7	7	-108.286	E	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
8	8	-124.695	E, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
9	9	-98.9106	G, M, N	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
10	10	-100.413	E, M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
11	11	-128.317	E, L, N	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
12	12	-109.404	M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
13	13	-115.566	E	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
14	14	-96.9274	M, N	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
15	15	-120.842	E, J, L, M	P, Q, S, T, U, V, W, X, Y, Z, AB, AF
16	16	-64.0492	G, O	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
17	17	-124.401	E, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
18	18	-141.343	E, H, L, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
19	19	-131.087	E, H, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
20	20	-127.465	E, J, O	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
21	21	-89.1073	E, J	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
22	22	-104.363	E, H	P, Q, R, S, T, U, V, W, X, Z, AA, AB, AC, AD, AE, AF
23	23	-98.4053	M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
24	24	-118.834	E, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
25	25	-116.327	E, N	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
26	26	-113.208	M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
27	27	-123.053	E, N	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
28	28	-103.983	E	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
29	29	-100.254	N	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
30	30	-116.019	E, H	P, Q, R, S, T, U, V, W, X, Z, AD, AE, AF
31	31	-103.608	E	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
32	32	-104.896	E, G, N	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
33	33	-105.44	G, N	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
34	34	-102.425	M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
35	35	-103.066	E, H	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
36	Ozair	-126.425	E, J, M	P, Q, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
37	Erlotinib	-135.786	E, F	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
38	Gefitinib	-143.994	H, J, K, M	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
39	GS1101	-130.837	L	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF
40	Lepatinib	-147.462	E, I	P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF

Where,

Amino Acid (H-BONDING): **E**-ARG 77, **F**-TYR 93, **G**-HIS 94, **H**-HIS 95, **I**-ASP 173, **J**-TRP 176, **K**-ASP 239, **L**-GLY 241, **M**-GLY 243, **N**-ARG 246, **O**-MG 506

Amino Acid (Van der Waals **bonding**) **P**-ARG 77, **Q**-HIS 82, **R**-ASN 83, **S**-s-HIS 94, **T**-m-HIS 94, **U**- s-HIS 95, **V**- m-HIS 95, **W**-PHE 98, **X**-MET 100, **Y**-TRP-176, **Z**-GLU 213, **AA**-s-ASN 216, **AB**-m-ASN 216, **AC**-GLY-241, **AD**-MET 242, **AE**-GLY 243, **AF**-AG 24 6

EGFR-like Properties of Compound:

To access the EGFR activities of the compounds, the authors used 40 molecules and 3XEO (Protein Data Bank [PDB] id) for docking studies. To determine if the novel compounds were Epidermal Growth Factor Receptors, they were docked with AlaRS Protein. Among 40 molecules, five molecules (PPM-8, PPM-11, PPM-18, PPM-19, PPM-20,) displayed EGFR action same as standard molecules; in which PPM-18 showed higher binding energy than the conventional molecules. Standard drugs such as GS1101 showed hydrogen bond interaction with Gly241 as per PDB id 4XEO. Our molecule showed hydrogen bond interaction with ARG 77, HIS 95, GLY 241, GLY 243 and other than like, ARG 77, F-TYR 93, HIS 94, HIS 95, ASP 173, TRP 176, ASP 239, GLY 241, GLY 243, ARG 246, MG 506 according to ligand present into the ligand. PDB id 4XEO (interaction of AlaRS with GS1101) showed Van der Waals interaction with amino acid, such as ARG 77, HIS 82, ASN 83, HIS 94, HIS 94, HIS 95, HIS 95, PHE 98, MET 100, TRP-176, GLU 213, ASN 216, ASN 216, GLY-241, MET 242, GLY 243, AG 246. Our molecule showed more Van der Waals interaction than standard molecule present in PDB.

Conclusion

In the present work, molecular docking studies have been conducted to explore possible binding modes of GS1101 derivatives as anticancer agents into PDB ID 4XEO. The iGemdock version 2.1 software was used to dock GS1101 derivatives as anticancer agents. Our docking results showed that ARG 77, HIS 95, GLY 241, GLY 243 made an essential contribution in hydrogen bond formation and ARG 77, HIS 82, ASN 83, HIS 94, HIS 94, HIS 95, HIS 95, PHE 98, MET 100, TRP-176, GLU 213, ASN 216, ASN 216, GLY-241, MET 242, GLY 243, and AG 246 made an essential contribution in Van der Waals interaction. Our docking result suggests the possible confirmation of binding site of GS1101 derivatives as anticancer molecules to 4XEO. Further, identified favoured binding modes of 4XEO to GS1101 derivatives leading for the development of new anticancer molecules and also provided valuable insights interaction of molecules with the different amino acid.

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