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Computational Design of New Analogues from Lyngbyastatin-2 against Epidermal Growth Factor Receptor (EGFR) through Molecular Docking

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Authors' contributions

This work was carried out in collaboration among all authors. Authors RV and MM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FA and MSAA managed the analyses of the study. Author MS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Cyanobacteria are considered as a rich source of secondary metabolites with potential applications in oncology to find out new therapeutic agents to suppress cancer. Lyngbyastatin-2 is a secondary metabolite from marine cyanobacteria and has antimicrobial and anticancer properties. It acts as an inhibitor molecule against cancer cells. In the present study, Lyngbyastatin-2 a bioactive compound from *Lyngbya majuscula* was selected as a ligand and four types of analogues were prepared using ChemDraw software. These analogues docked with Epidermal Growth Factor Receptor (EGFR), which is key molecule play a major role in ovarian cancer using Hex 8.0.0 molecular docking method. Among 4 analogues tested, Lyngbyastatin-2 analogue-1 (L2A1) showed high energy bonding (-618.27 KJ/mol) with EFGR molecule and considered as an effective inhibitor

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molecule to treat ovarian cancer based on e-values. A strong chemical interaction observed between EGFR protein and L2A1 ligand molecules and it may be leads to improve the efficiency of inhibitor. This study is the first attempt to analyze the analogues of lyngbyastatin-2 with EGFR and further *in vitro*, *in vivo* studies are required to prove its anticancer potential against ovarian cancer based on the predictions of *in-silico* studies.

Keywords: Lyngbyastatin-2; analogues; ChemDraw; ovarian cancer; molecular docking; EGFR.

1. INTRODUCTION

Epithelial ovarian cancer, defined as cancers arising either from the mesothelial lining of the ovaries (either from the epithelial surface lining or cortical ovarian cysts formed by invaginations of the surface epithelium) or from the fallopian tube epithelium [1,2]. It accounts for 90% of ovarian malignancies [3]. Aberrant epidermal growth factor receptor (EGFR) expression detected in up to 60% of ovarian cancers and commonly occurs in all histologic subtypes of ovarian cancer [4,5]. Moreover, over expression of the aberrant EGFR protein has been reported in 9% to 62% of human ovarian cancers. Increased EGFR expression has been strongly associated with high tumor grade, cell proliferation index, aberrant P53 expression and poor patient outcome [6,7]. Even though, several strategies have been attempted to block EGFR activity, only two types of inhibitors such as monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors are currently used in the clinical practice [8]. Small molecule inhibitors directed against EGFR generally prevent homo- and heterodimerization between it and other EGFR family members [9].

However, the clinical significance of these different mechanisms of inhibition is not yet well known. Considering this, there is an immediate need of future studies using EGFR antagonists in ovarian cancer should focus on determining reliable predictors for patient responsiveness to anti-EGFR therapy. Moreover, the drug development requires extensive *in vitro*, *in vivo* clinical testing and time-consuming process. Now a days, *in silico* virtual screening has become a reliable, cost effective and time-saving technique that is complementary to *in vitro* screening for the discovery and optimization of potent lead and hit compounds. These approaches have paved the way to solve many biological issues, which have led to the identification of novel inhibitors against numerous diseases [10-12].

Structure based drug design helps to provide potent and significant compounds more productively in the drug discovery process. In this context, the natural products derived from medicinal plants have gained significance in the treatment of cancer. In the last two decades, a large screening of marine compounds has been conducted, and marine cyanobacteria have yielded many novel and bioactive secondary metabolites, including anti-cancer compounds [13]. The genus *Lyngbya* appears to be an emerging source of bioactive peptides. Lyngbyastatin-2 is effective bioactive compound that is isolated from *Lyngbya majuscula*. It is possible that the ability to produce a wide range of defensive secondary metabolites has contributed to the high degree biological adaptation observed for cyanobacteria [14,15]. A report from Sanchez et al. isolated and identified a series of almiramides A–C from *Lyngbya majuscula* which showed a strong in vitro anti-parasitic activity against Leishmania. Various authors synthesized types of lyngbyastatins 4 to 10 and reported that they were strong cancer inhibitors [16-18]. Recently, Sangeetha et al. reported that lyngbyastatin-2 has a good binding affinity among 315 bioactive compounds from Cyanobacteria[19]. Presently, study of lyngbyastatin-2 are attracted many researchers worldwide to find natural medicines from the marine source, however studies related ovarian cancer is very limited [19,20].

Hence, based on the above facts and information, the present work was to isolate lyngbyastatin-2 from *L. majuscula* and design their analogs, finally lynbyastatin-2 analogs were molecular docked against EGFR in ovarian cancer using *in silico* methods.

2. MATERIALS AND METHODS

2.1 Retrieval of Target Protein

The ovarian cancer causing EGFR enzyme structure (PDB file number 1IVO) was considered as target protein and retrieved from protein data bank [21]. There are four chains form the structure of EGFR, first two chains A and B contain 622 amino acids and second two chains C and D contain 53 amino acids.

2.2 Preparation of Receptors

The cyanobacterial bioactive compounds of *L. majuscula* were retrieved from Chemspider database [22], which was later converted into 3-D structures using Swiss Pdb viewer [23]. Lyngbyastatin-2 was taken for preparation of different analogues using ChemDraw [24].

2.3 Identification of Molecular Docking Protocols

The molecular docking between receptor and ligand was carried out by Hex8.0.0 docking program [25]. It was performed by adjusting appropriate parameters such as twist range-360, receptor range-180,ligand range-180, FFT mode-3D fast lite, grid dimension-0.6 and distance range-40. The obtained scores of binding energy was tabulated and analyzed.

2.4 Virtual Screening and Interaction Analysis

The identified drug and receptor interaction studied by Schrodinger suite program [26].

3. RESULTS

Lyngbyastatin-2 drug molecule selected as receptor against EGFR. The molecular formula of lyngbyastatin-2 is $C_{56}H_{94}N_6O_{13}$. The average mass is 1059.378 Da. Monoisotopic mass is 1058.687866 Da. (Fig.1A). A total of four types of lyngbyastatin-2 analogues were prepared using ChemDraw software. ChemDraw can be inserted in MS office documents using the object function under the insert pull-down menu, such structures can be edited through OLE. Synthesis of analogues briefly described below.

3.1 Lyngbyastatin-2 analogue-1 (L2A1)

Esterified cyameluric acid with 4' -cyanobiphenyl-4-carboxylic acid is linked at 28th position Hydroxyl group is introduced at the 23rd position. (3s)-tetrahydro-2-methyl-2H-pyran-3-ol is attached at the 5th position (Fig. 1B).

3.2 Lyngbyastatin-2 analogue-2 (L2A2)

One of the OH group in cyameluric acid is esterified with 4' - cyanobiphenyl-4-carboxylic acid and the other OH group is esterified with 2-hydroxy- 4'-cyanobiphenyl-4-carboxylicacid is linked at 28th position. Hydroxyl group is introduced at the 23rd position. (3s)-tetrahydro-2-methyl-2H-pyran-3-ol is attached at the 5th position (Fig. 1C).

3.3 Lyngbyastatin-2 analogue-3 (L2A3)

One of the OH group in cyameluric acid is esterified with 4' - cyanobiphenyl-4-carboxylic acid and the other OH group is esterified with 2,4'-dicyanobiphenyl-4-carboxylic acid is linked at 28th position.Hydroxyl group is introduced at the 23rd position. (3s)-tetrahydro-2-methyl-2H-pyran-3-ol is attached at the 5th position (Fig. 1D).

3.4 Lyngbyastatin-2 analogue-4 (L2A4)

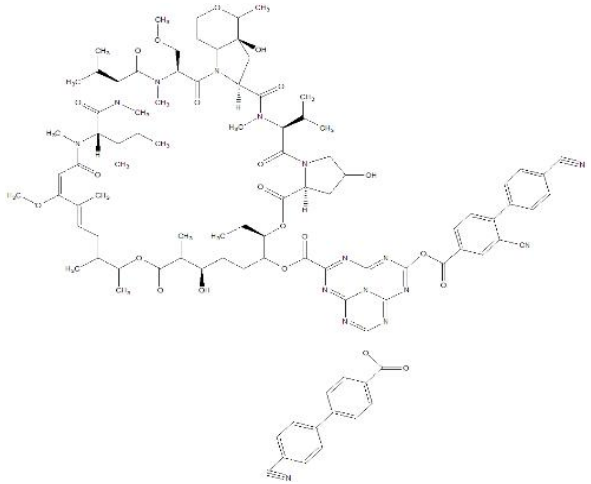
Esterified cyameluric acid with 2,4' dicyanobiphenyl-4-carboxylic acid is linked at 28th position. Hydroxyl group is introduced at the 23rd position and (3s)-tetrahydro-2-methyl-2H-pyran-3-ol is attached at the 5th position (Fig. 1E).

3.5 Structure of EGFR Molecule and Its Active Binding Site

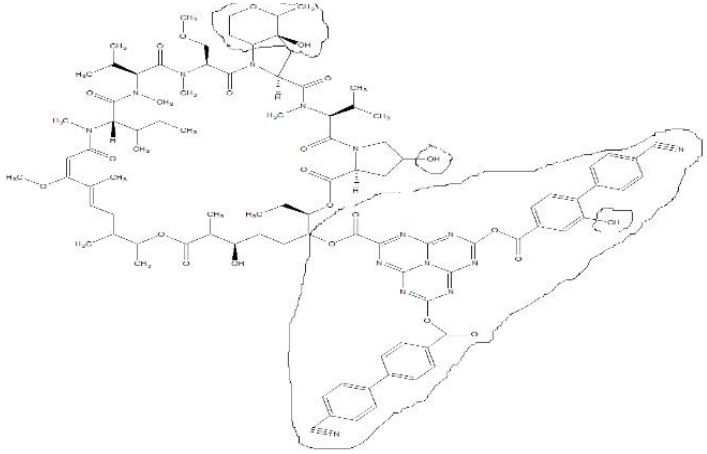
EGFR molecule was containing two polypeptide chains formed by 622 amino acids each with 1433 helices as a whole. The molecule also showed 1530 sheets with 657-hydrogen bonding. This EGFR was also an effective antigenic molecule due to its exomembrane topology. EGFR receptor contains ten possible ligand-binding sites and all were located on the surface of the receptor protein. The area of the binding sites was ranging from 16.2 to 400.7 Å2 and the volume of the cavities from 12.8 to 800.8 Å3. Based on the virulence of protein we targeted one major active binding site (Fig. 1F).

3.6 Molecular Docking

Molecular docking analysis done between target molecule EGFR and ligand molecules of lyngbyastatin-2 and its analogues using Hex 8.0.0 software. Based on the docking score values, the lowest e-value observed in docking of L2A4 with EGFR and the score was -602.43KJ/mol. A highest e values observed in L2A1-EGFR and score was -618.27 KJ/mol (Table 1; Fig. 1G). An effective chemical interaction takes place between EGFR protein and L2A1 ligand molecule through the Van der Waals forces, electrostatic and hydrogen bonding (Fig. 1H).



A



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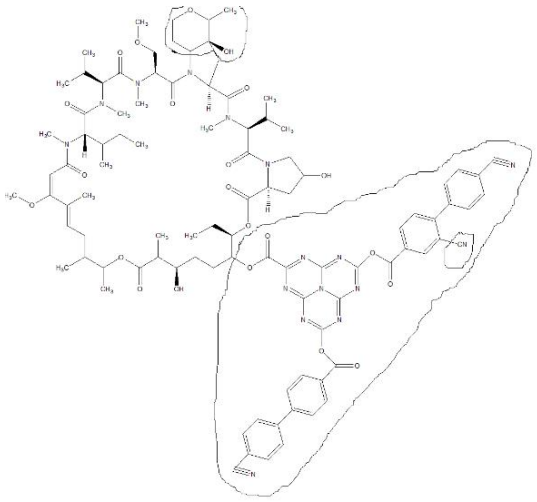

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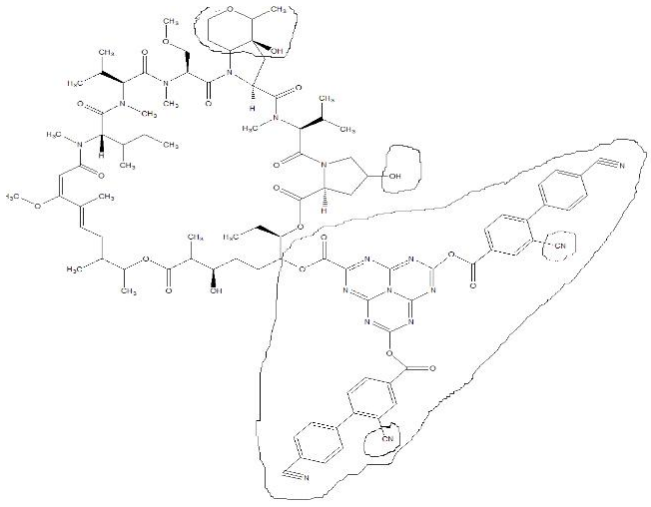

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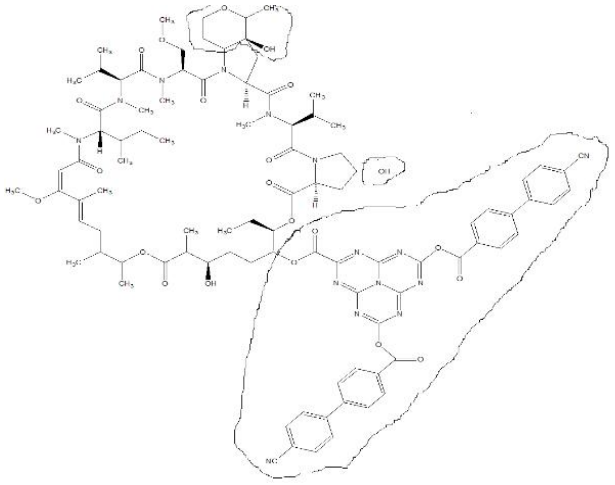

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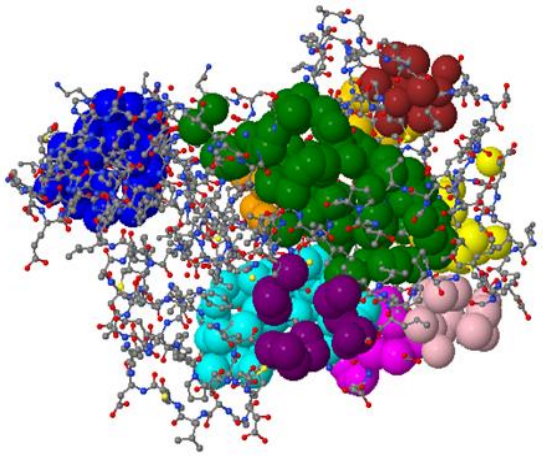
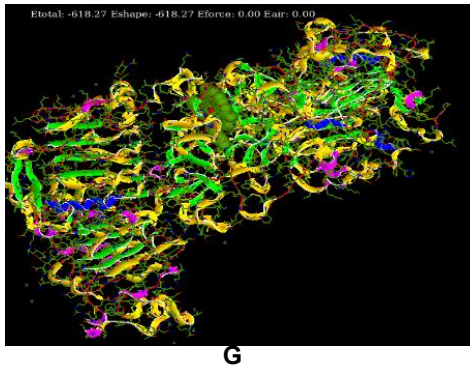
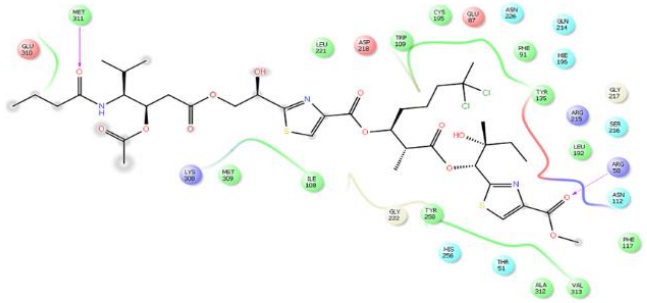


F



G



H

Fig. 1. Molecular structure of Lyngbyastatin-2 (A), Lyngbyastatin-2 analogue-1 (B), Lyngbyastatin-2 analogue-2 (C), Lyngbyastatin-2 analogue-3 (D), Lyngbyastatin-2 analogue-4 (E), Active ligand binding sites of EGFR shown in different colors green color indicates major active site (F), Molecular docking of lyngbyastatin-2 analogue-1 with EGFR (Parallel sheet, Anti parallel sheet, helix and loop structures were indicated in green, yellow, blue and red color respectively) (G), Molecular interactions of Lyngbyastatin-2 analogue-1 with major active sites of EGFR (H)

Table 1. Molecular docking results of lyngbyastatin-2 and analogues with EGFR

Name of the ligands docked with EGFR	Binding free energy (KJ/mol)	Number of H bonds	Amino acids residues involved in ligand-EGFR interactions	EGFR residues making only non-polar interactions
Lyngbyastatin-2	-541.40	0	GLY, TYR, HIS, THR, ALA, VAL, PHE, ASN, ARG, LEU, SER, ARG, GLY, TYR, HIS, PHE, GLN, ASN	GLY,ALA,VAL,PHE, LEU,GLY,PHE
Lyngbyastatin-2 analogue-1	-618.27	2	MET, GLU,LYS,MET,ILE, GLY, TYR, HIS, THR, ALA, VAL, PHE, ASN, ARG, LEU, SER, ARG, GLY, TYR, HIS, PHE, GLN, ASN, GLU, CYS, TRP, ASP, LEU	MET,ILE,GLY,ALA, VAL, PHE,CYS,LEU
Lyngbyastatin-2 analogue-2	-617.16	1	MET, GLU,LYS,MET,ILE, GLY, TYR, HIS, THR, ALA,VAL,PHE,ASN,ARG,LEU,SER,ARG,GLY,TYR,HIS, PHE,GLN,ASN,GLU	MET,MET, ILE, GLY,ALA,VAL,PHE, LEU,GLY,PHE
Lyngbyastatin-2 analogue-3	-615.14	1	MET, GLU,LYS,MET,ILE, GLY, TYR, HIS, THR, ALA,VAL,PHE,ASN,ARG,LEU,SER,ARG,GLY,TYR,HIS, PHE,GLN,ASN	MET, MET, ILE, VAL, PHE, LEU, GLY,PHE
Lyngbyastatin-2 analogue-4	-602.43	1	MET,ILE, GLY, TYR, HIS, THR,ALA,VAL,PHE,ASN,ARG,LEU,SER,ARG,GLY,TYR, HIS,PHE,GLN,ASN,GLU,CYS,TRP,ASP,LEU	MET, ILE, GLY, ALA,VAL,PHE,LEU, GLY,PHE,CYS,LEU

4. DISCUSSION

Ovarian cancer is the highest mortality rate of the cancers distinctive to women. In recent literature, various authors reported that computational methods are playing increasingly larger and more important role in drug discovery in cancer biology [27-30].

Lyngbyastatins is secondary metabolites of marine cyanobacterium *L. majuscula* and it has tremendous anticancer activities [18,16,31]. Bai et al. [32] described that the synthetic lyngbyastatin 1-Ibu-epilyngbyastatin 1 mixture had significant activities against cancer cells and in stimulating actin polymerization. Taori and his co-workers extracted identified lyngbyastatins 4 to 6 from the marine cyanobacterium and reported that it has a wide range of defensive secondary metabolites has contributed to drug development [18]. However, very limited study reports available using lyngbyastatin 2 and their analogues [19]. Thus, in this study, lyngbyastatin 2 structure derived from protein data bank and their analogues were prepared using ChemDraw software. These molecules consider at ligand molecules and attempted to find suitable drug molecule by molecular docking analysis against suitable receptor molecule causing ovarian cancer.

In computer-aided drug designing method, selection of receptor molecule is very important for increasing efficiency of drug. The term receptor is a protein molecule that responds to the specific ligand molecules. Usually, a receptor enzyme molecule has 10 possible ligand binding sites out of which only one functions as active site, it fits with one specific type of ligand molecule (drug). A tighter fit between an active site and the ligand molecule increases the efficiency of the reaction. The active site is the small portion of the enzyme lined with amino acid residues and undergoes a chemical reaction. The active site is usually found in a 3-D groove or pocket of the enzyme, these residues are involved in recognition of the ligands [33]. By considering this, in the present study EFGR was

selected as receptor against ovarian cancer cells and analyzed further molecular docking. It contains 10 possible ligand-binding sites and site-1 results showed as major active site with high binding efficiency causes high virulent effects in ovarian cancer, this leads to poor outcome.

In the present study, lyngbyastatin-2 was taken into consideration to produce different analogues. While preparing the analogues, in the lyngbyastatin-2 structure some molecules added Esterified cyameluric acid with 4' -cyanobiphenyl-4-carboxylic acid, Hydroxyl group and (3s)-tetrahydro-2-methyl-2H-pyran-3-ol in different positions. In literature, lyngbyastatin act as an inhibitor molecule with chymotrypsins showing an IC50 value of 0.3μM [34]. Lyngbyastatins 4-10, a group of compounds were all described as elastase inhibitors [16,18,35] with an IC50 range from 0.03 (lyngbyastatin 4) to 210 μM (lyngbyastatin 9). Lyngbyastatins are also strong chymotrypsin inhibitors, but with less potency than elastase, IC50 = 0.3 μM [34,36]. Moreover, there have been no reports available so far anticancer activities by *in silico* methods. Hence, we failed to compare with similar kind of studies. However, analogues of synthetic drug molecules have been synthesized and studied against various cell lines by in-vitro laboratory methods [37,38].

Analogues of synthetic chemicals have been attempted by many researchers to improve the efficiency of the drugs. Alex Mathew and Nixon Raj, [39] reported that raloxifene and toremifene drugs were effective against breast cancer cells after the modifications in the chemical structure using *in silico* methods. They prepared analogues structure using Chemsketch software and energy values calculated by Hex 8.0.0 program. Another study by Rath et al., developed a new class of synthetic curcumin analogs called diarylidenyl-piperidones, which have higher anti-ovarian cancer activity and enhanced bio-absorption than curcumin. Very recently, Pal and his co-workers synthesized truncated carbocyclic nucleoside analogues and found that 1b and d analogues showed better cytotoxic activities against breast and ovarian cancer cell lines [40]. The present *in silico* study reports showed that L2A1 have very good bonding with target molecule than other 3 analogues tested.

Moving to the bonding analysis between receptor and ligand molecules, the interaction of hydrophobic amino acids of ligand with the hydrophobic zones on the binding site of the receptor surface is an important event in docking interaction [41]. The non-covalent bonds held together with the ligand-receptor association. These bonds are weak by nature and must therefore work together to have a significant effect. In addition, the combined bond strength is greater than the sum of the individual bonds. In the present study, major active binding site of EGFR was efficiently suppressed by L2A1. The active binding site of the receptor, EGFR molecule is lined with 22 amino acids from which 20 of them are hydrophobic, 2 polar and with three hydrogen bonds. In this case, effective chemical interaction takes place between protein and ligand molecule through the Van der Waals forces, electrostatic and hydrogen bonding. These reactions were found whenever the side chains of non-polar (hydrophobic) amino acids of antigen-antibody come together. Hydrogen bonds of EGFR-L2A1 complex stabilize the ligand-receptor interaction and other weak interactions such as Van der Waals forces, hydrophobic interactions and electrostatic forces improve the binding specificity between ligand and receptor. These interactions occur over large area of the molecules, improving the binding affinity. This multiple bonding between the ligand and the receptor ensure that the ligand could be bound tightly to the receptor [42].

5. CONCLUSION

Marine cyanobacterial bioactive compound, lyngbyastatin-2 and their analogues were synthesized using ChemDraw software and analyzed molecular docking with EGFR. Lyngbyastatin-2analog-1 has showed high-energy value with EGFR molecule and showed effective ligand-receptor interactions of hydrogen bonding and Vander Walls forces. In conclusion, L2A1 and EGFR showing very good bonding interactions with high score of energy values and Lyngbyastatin-2 analog-1 can consider potential drug candidate treating ovarian cancer. To the best of our knowledge, the present study is the first report of lybyastatin-2 analogues testing molecular interaction with EGFR. However, further *in vitro* and *in vivo* studies are needed to establish its anticancer potential against ovarian cancer based on the predictions of *in silico* studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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