Erythrinin C, from the Root of Pueraria peduncularis, is a potential antagonist against DHODH, a therapeutic target in Acute Myeloid Leukemia: An in silico study

ABSTRACT

Acute myeloid leukaemia (AML) is the second most common form of leukaemia with an annual incidence of 3.6 per 100,000 adults in the United States. A 5-year survival rate of a person with AML is less than 50%. Myeloid leukemogenesis has been reported to arise by a differentiation arrest at early progenitor stage of hematopoietic maturation of the bone marrow; this has led researchers to identify the human dihydroorotate dehydrogenase (DHODH) to be a therapeutic target in the differentiation therapy for AML. Several inhibitors of DHODH have been developed; however only a few have reached clinical trials of which include Brequinar, a strong DHODH inhibitor. Brequinar has reached a phase 2 clinical trials, however, several complication and toxicities have been reported in phase 1 clinical trials in patients with solid tumours. This ranges from myelosupression, thrombocytopenia, nausea, vomiting, skin rashes, mucositis, and this limit its use in AML. In view of this, research is focused on identifying potent DHODH inhibitors with little or no toxic effect that can be used in the differentiation therapy of AML.

Pueraria peduncularis belongs to the Leguminosae family and it is widely distributed in some parts of China, India, Pakistan, Nepal and Burma. A recent study has accessed and reported that flavonoids from root of Pueraria peduncularis have anti-tumour effects against cancer cell lines.

The aim of this study was to analyse flavonoids from (plant source) root of Pueraria peduncularis for their DHODH inhibitory potential via computational docking studies. For this, four (4) flavonoids (phytochemicals), as well as the DHODH co-crystallized inhibitor, BAY 2402234 which serve as the standard in the present study, were retrieved from the literature and screened for their inhibitory effects on DHODH. Erythrinin C was the lead compound with a binding energy of -11.395kcal/mol. Computational docking and scoring analysis were performed using Lead Finder tool implemented in Flare software of Cresset Inc. (2019, Litlington, UK). The target was validated to ensure that the right target was used for this analysis.

Keywords: DHODH, Pueraria peduncularis, Erythrinin C, docking

INTRODUCTION:

Acute Myeloid Leukaemia is a form of malignancy formed as a result of abnormal differentiation and proliferation of hematopoietic stem cells of the bone marrow. AML is characterised by a differentiation arrest at early progenitor stage of hematopoietic maturation. [1]. AML is the second most common form of leukaemia with an annual incidence of 3.6 per 100,000 adults and older in the United States [2]. A five-year survival rate of people with AML is less than 50% [3]. Since myeloid leukemogenesis is known to be a block in myeloid differentiation [4]; the aim of various researches is focused on the development of therapeutic agents that can overcome this differentiation block [5-6]. However, recent research has shown that inhibition of the Human Dihydroorotate Dehydrogenase DHODH overcomes differentiation blockade in AML, thereby revealing DHODH as a potential target in the differentiation therapy for AML [5].

DHODH is the enzyme that catalyses the oxidation of dihydroorotate to orotate in the mitochondria for the 4^{th} step of the de novo pyrimidine biosynthesis [7]. Several studies have suggested that rapidly growing malignant cells require a high amount of Pyrimidine to sustain their growth [8]. Uridine monophosphate (UMP) plays an important role as the first building block in the production of pyrimidine ribonucleoside and deoxyribonucleosides for the synthesis of RNA and DNA respectively. DHODH inhibitors deprive cells of UMP, UDP, and UTP by blocking this step [9]. David b. Sykes (2018) proposed that leukemic cells, and possibly malignant cells along many other lineages, have a lower tolerance for pyrimidine starvation when compared to their non-malignant counterparts.

Leukemic cells lines can be deprived of pyrimidine by CRISPR/Cas gene editing of DHODH [9]. Wu and wong et al, in their paper titled “Pharmacological inhibition of dihydroorotate dehydrogenase induces apoptosis and differentiation of acute myeloid leukemia cells,” reported that CRISPR/Cas-9 mediated gene knockout of DHODH induced apoptosis and normal differentiation of AML cell lines [6]. In their study on the differentiation therapy for AML, Skyes et al induced cell lines with myeloid differentiation arrest by fusing an estrogen receptor to Hox A9 (ER-HoxA9) and they performed a phenotypic screen of 330,000 compounds that could overcome this arrest, 11 out of the 12 hits compounds that best induce normal differentiation were inhibitors of DHODH [5].

Several inhibitors of DHODH have been developed and just a few have reached clinical trials. These include; leflunomide, teriflunomide, Brequinar sodium, BAY 2402234, AG-636 and ASLAN003 [9, 10, 11]. Only three of these DHODH inhibitors; Leflunomide, teriflunomide and Brequinar sodium, are FDA approved drugs. Leflunomide and teriflunomide are used in the treatment of rheumatoid arthritis and multiple sclerosis respectively. leflunomide and teriflunomide have been reported to be weak DHODH inhibitors of which limit their use in AML and other malignancies associated with DHODH [10]. Brequinar sodium is a strong inhibitor of DHODH and has been reported to have strong anti-tumour potential. A study of Brequinar anti-tumour properties showed that Brequinar inhibited the growth of a broad spectrum of human solid tumours implanted in nude mice [12]. Brequinar sodium is currently in phase 2 clinical trials, however, several complications and toxicities of Brequinar sodium have been reported in Phase 1 clinical trials in patients with solid tumours mainly; myelosupression, thrombocytopenia, nausea, vomiting, skin rashes and mucositis [13]. These side effects are disappointing and this limits its potential use in AML [11]. Therefore a better druggable compound is needed with better efficacy in the treatment of AML with little or no side effects, which is the aim of the present study to identify a novel phytochemical with a better inhibitory effect against DHODH with little or no side effects.

Flavonoids have long been known to exhibit broad-spectrum pharmacological activities including anticancer, anti-inflammatory, antioxidant, antifungal, anti-allergic and anti-viral [14]. Of most

important of these pharmacological activities, is their cytotoxicity against cancer cells. In this study, four (4) flavonoids from the root of Pueraria peduncularis (Grah. ex Benth.) were analysed for their inhibitory potential via computational studies.

Pueraria peduncularis (Grah. ex Benth.) Benth belongs to the Leguminosae family and it is widely distributed in some parts of China, India, Pakistan, Nepal and Burma. Methanol extracts from Pueraria peduncularis, are of medicinal and agricultural importance [15]. In a recent study to investigate the effect of active phytochemicals of P.penduncularis root extracts on Cancer cell lines, it was shown that 4 flavonoids from P.penduncularis root extract considered in this study; 8-O-methylretusin and Wighteone had an inhibitory effect on lung adenocarcinoma line by 31.10% and 32.12% respectively. Erythrinin C on the other hand had strong cytotoxicity against lung adenocarcinoma (42.07%) and breast cancer cell lines (47.86%). Genistein showed a weak inhibitory effect on breast cancer cell lines (12.80%) [16]. In view of the health benefits P.penduncularis and the antitumor effect of flavonoids from the root of P.penduncularis, this study aimed at revealing the inhibitory effect of Erythrinin C on DHODH with little or no side effects. This is achieved by a computational approach that yielded high-quality interactions between the Ligand (Erythrinin C) and the receptor (DHODH). Erythrinin C was then channelled to Lipinski rule of five on ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity), and was found to satisfy the rule of five on ADMET properties.

METHODOLOGY

Protein Preparation and Optimization:

The 3 dimensional crystal structure of Human Dihydroorotate dehydrogenase was retrieved from the protein data bank (PDB ID: 6QU7, Resolution: 1.52Å) in complex with ligand, (~{N}-(2-chloranyl-6-fluoranyl-phenyl)-4-[4-ethyl-3-(hydroxymethyl)-5-oxidanylidene-1,2,4-triazol-1-yl]-5-fluoranyl-2 [(2~{S})-1,1,1-tris(fluoranyl)propan-2-yl]oxy-benzamide) from RCSB PDB (http://www.rcsb.org/pdb/home/home.do) [17]. Protein preparation was done in Flare software version 3.0 Cresset Inc. (2019, Litlington, UK). Residues 'FMN' and 'JJE' were automatically extracted as Ligands by the Build Model tool implemented in Flare, which caps truncated protein with NME and ACE residues, allow the side chains to move a small amount to relieve steric clashes in the input coordinate, removes atoms from residues with incomplete backbone and assigns optimal ionization states of protein residues [18]. Ionization of the protein was set at pH 7.0 (default value). Water chains and hetero atoms were removed, only the protein 'A chains' was minimized. The size of the active site after extracting the ligands was 6Å. Protein Energy minimization was calculated in Flare software using default parameters (Gradient cutoff: 0.200kcal/mol/Å, Maximum iterations: 2000)

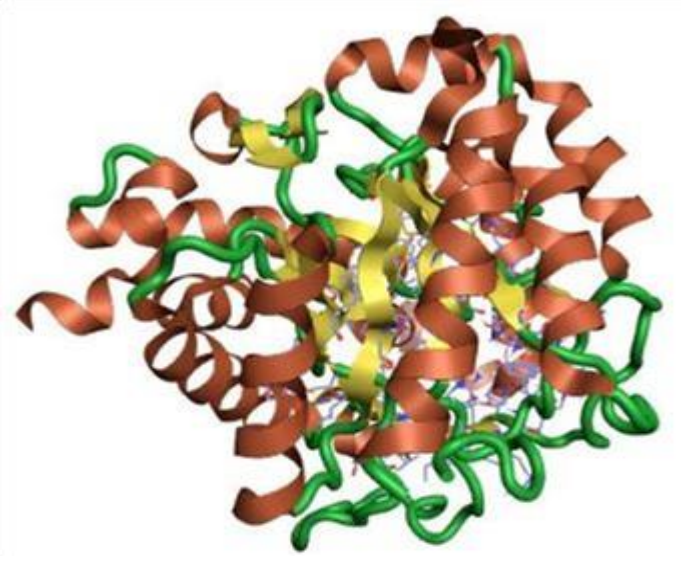

Figure 1: 3D structure of the prepared Human Dihydroorotate Dehydrogenase for docking

Ligand selection and preparation:

The chemical structures of four (4) phytochemicals (8-O-methylretusin, Wighteone, Genistein and Erythrinin C) were downloaded from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov). Ligands were prepared in Flare software; 2D-structures of ligands were converted to 3D-coordinates, hydrogen atoms were added to correct places. The co-crystallized inhibitor (PDB ID: JJE) used in the present study was extracted from the protein binding pocket to be docked. Whereas the other native ligand 'FMN' was extracted from the protein active site as the template ligand by default in Flare Software to seed the docking run. The template ligand was minimized within the protein active site using default calculation parameters in Flare (Gradient cutoff: 0.200kcal/mol/Å, Maximum iterations: 2000).

Docking and Scoring with Lead Finder

Docking and Scoring of the Ligands to the binding pocket of human dihydroorotate dehydrogenase were carried out using the Lead Finder docking algorithm implemented in Flare software. Template docking was performed to align all molecules to be docked by substructure to the orientation of the template ligand in the protein binding pocket and this conformation was used to seed the docking run using Lead Finder. Lead Finder was used to calculating the energy grid maps. The grid box size for ligand docking was set to span 6 Å (default value) in each direction from the template ligand. The box was positioned at (46.130; -13.18; -2.25) XYZ coordinates Figure 2. Ligands were minimized before docking using Lead Finder which samples and minimizes in torsional space. The docking run was carried out using the default Lead Finder genetic algorithm parameters; Pool Size: 1.0 and Population size: 1.00. Three scoring functions provided by Lead Finder were used to score the docked ligand poses which are; dG-score: estimates protein-ligand binding energy, VS-score: the correct rank ordering of active and inactive compounds in virtual-screening experiments and Rank Score: correct energy ranking of docked ligand poses.

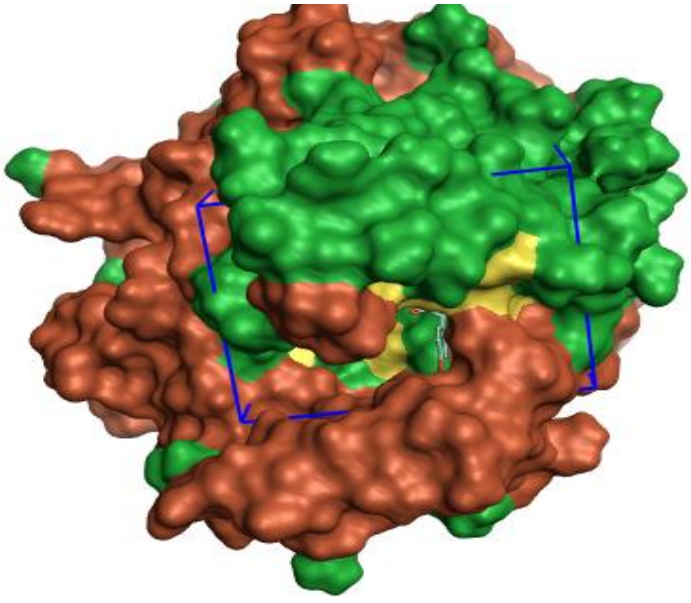

Figure 2: Grid box within which the Ligand bind (46.130; -13.18; -2.25) XYZ coordinates.

Results & Discussion:

The Human dihydroorotate dehydrogenase (DHODH) is the enzyme involved in the fourth step of de novo pyrimidine biosynthesis and whose inhibition overcomes the differentiation blockade in acute myeloid leukaemia [5]. It is, therefore, reasonable to think that inhibiting DHODH represents a sound pharmacological approach.

In this study, docking and scoring of four (4) phytocompounds from the root of P.penducularis against the human dihydroorotate dehydrogenase (DHODH) binding pocket was carried out to reveal their DHODH inhibitory potential. In the virtual screening experiment, the Lead Finder Vs-Score was used to rank order phytocompounds in other to discriminate between active and inactive compounds. The phytocompound, Erythrinin C was found to be the most active compound having been ranked top on the list of the Vs-score (Table 3). Based on the Lead Finder estimated binding energy (dG score), Erythrinin C was discovered as the lead compound with the binding energy of -11.395kcal/mol while that of wighteone, genistein and 8-o-methylretusin are -11.178, -8.909 and -7.895kcal/mol respectively (Table 3). Erythrinin C, the lead compound has a binding energy of -11.395kcal/mol, while the co-crystallized inhibitor (PDB Ligand ID: JJE) which serves as the standard has a binding energy of -9.206kcal/mol. The attained results show that Erythrinin C, the lead compound binds better to the receptor of DHODH than the co-crystallised inhibitor.

The highest binding energy (-11.395kcal/mol) attributed to the lead compound, Erythrinin C is believed to be as a result of its chemical interactions at the receptor's active site (Table 1; figure 6&7), which includes: Seventeen (17) Hydrogen bonds involving ARG136, GLN47, SER305, VAL143, ALA96, and PRO52 residues; Twenty-two (22) Hydrophobic interactions involving TYR356, PRO52, ARG136, VAL143, VAL134, PRO52 and ALA55 residues. While that of the co-crystalized inhibitor (PDB Ligand ID: JJE) which serves as the standard presents with the following chemical interactions at the binding pocket (Table 2; figure 6&7). Twenty-four (24) Hydrogen bonds involving PRO52, HIS56, VAL143, SER305, ASN145, LYS255 and ALA96 residues; Nineteen (19) Hydrophobic interactions involving VAL143, HIS56, TYR356, PRO52, VAL134, ARG136 and ALA96.

Hydrophobic interactions play a major role in the binding affinity of drugs to receptors [19]. It is obvious from the attained result, that the highest binding affinity of Erythrinin C to the receptor of DHODH, when compared to that of the co-crystallized inhibitor, is attributed to the number of hydrophobic interactions present in Erythrinin C (twenty-two Hydrophobic interactions) as compared to the standard (Nineteen Hydrophobic interactions).

The Lead compound, Erythrinin C was further evaluated for its pharmacokinetics profiling and presence of any toxic effect by subjecting it to the Lipinski's rule of five on ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity) properties; afterwards, the Lead compound fulfilled the Lipinski's rule of five on ADMET properties. Out of the four phytocompounds shortlisted in the virtual screening experiment, the lead compound Erythrinin C shows potent inhibition against the human dihydroorotate dehydrogenase with good pharmacokinetic properties without any adverse effect.

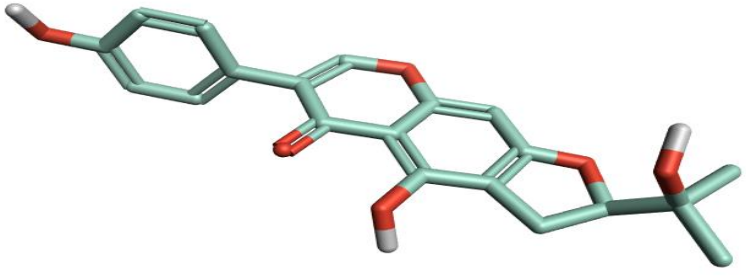

Figure 3: 3D Structure of Erythrinin C

Docking method validation

The accuracy of the docking protocol in this study was validated by re-docking the Co-crystallized inhibitor (PDB Ligand ID: JJE) back into the binding pocket of the Human Dihydroorotate Dehydrogenase DHODH (PDB: 6QU7). As stated, the re-docked pose overlapped almost totally with the experimental orientation, indicating that Lead Finder implemented in Flare re-docked the Co-crystallized inhibitor, with very high accuracy, back into the binding pocket of DHODH, this reveals that the docking methodology in this study was reliable and the docking scores obtained are correct (figure 4)

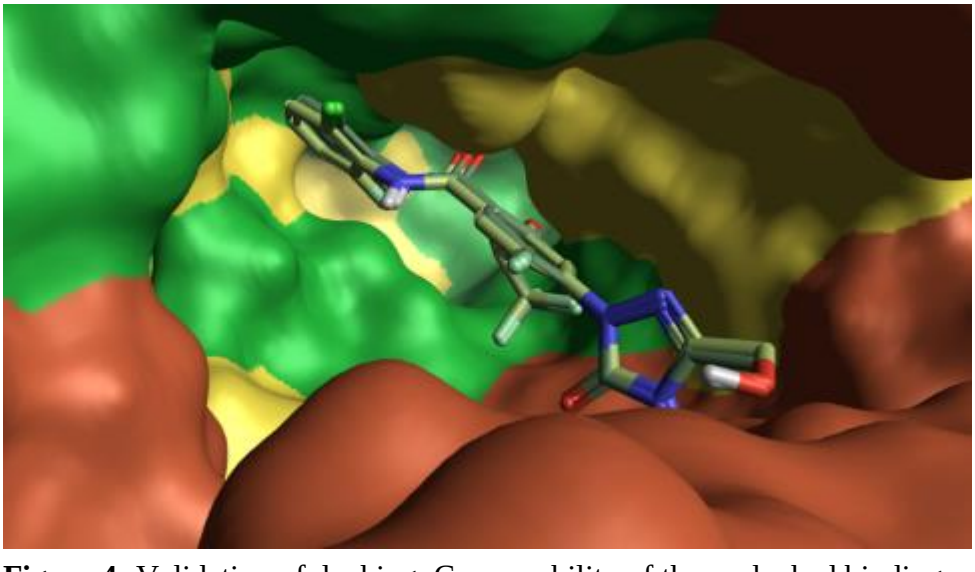

Figure 4: Validation of docking: Comparability of the re-docked binding mode

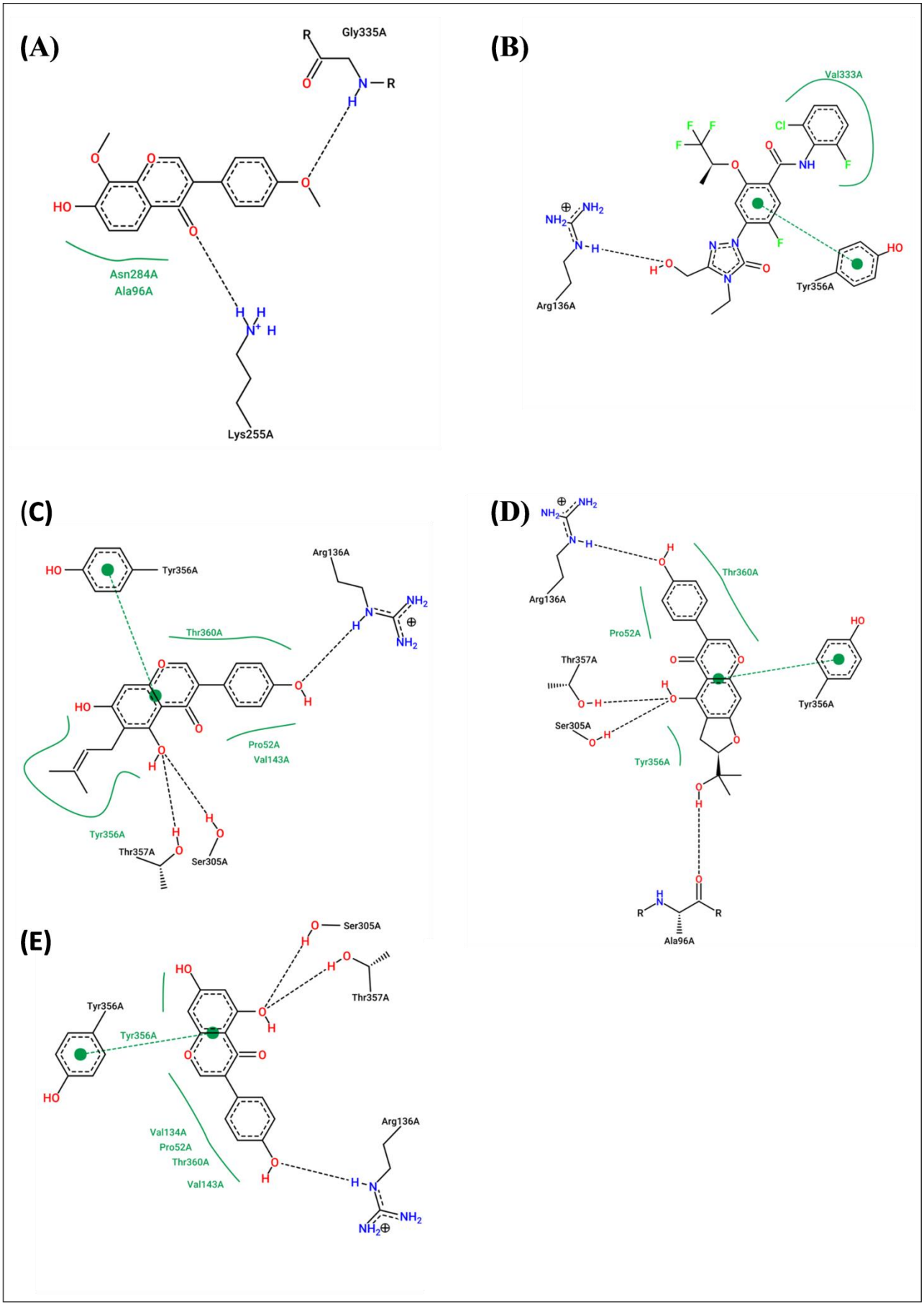

Figure 5: Pose view (a) 8-O-Methylrutesin (b) JJE (Co-crystallized inhibitor) (c) Weighteone (d) Erythrinin C (e) Genistein

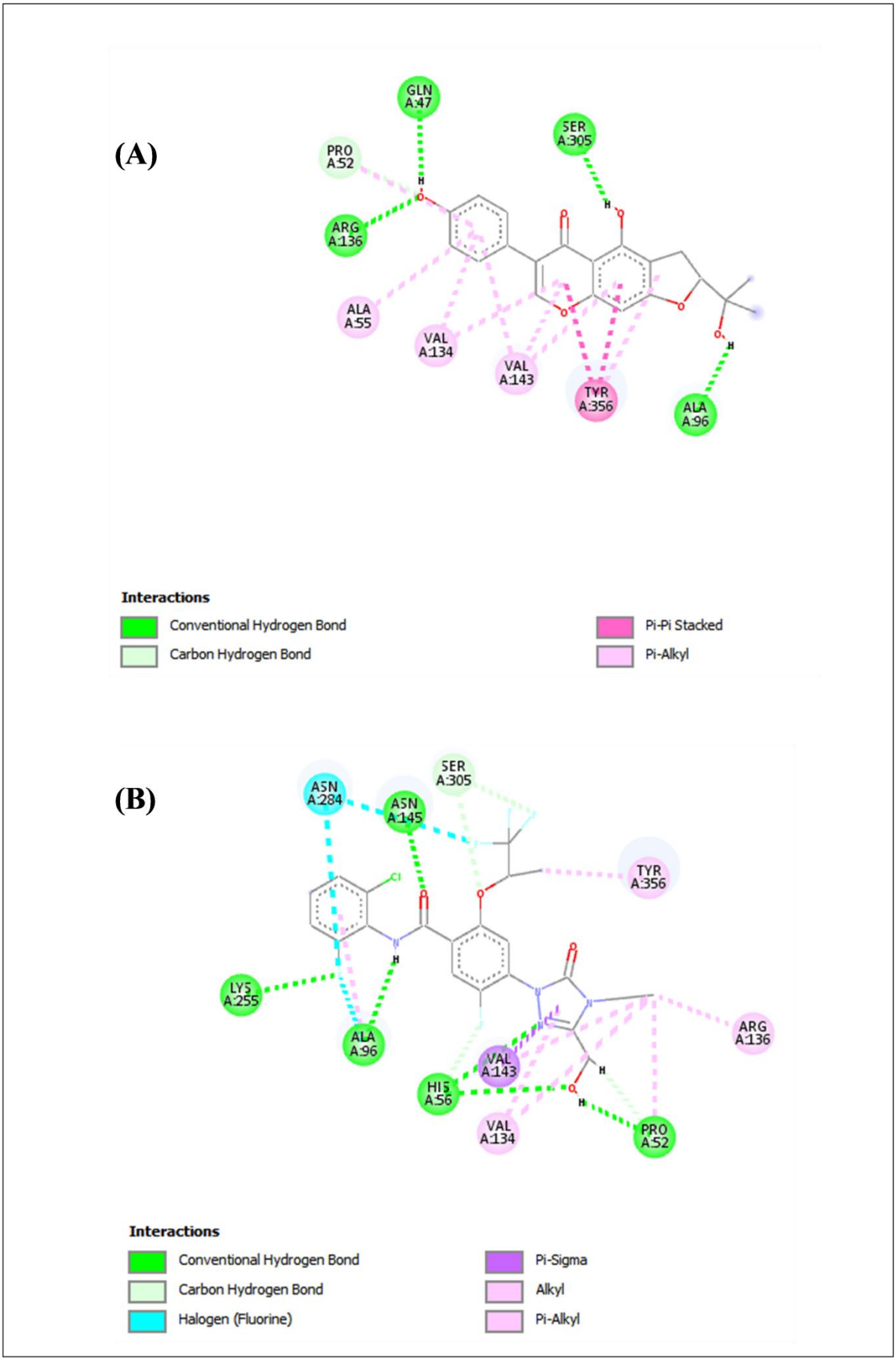

Figure 6: 2D interactions of ligands within the binding pocket (a) Erythrinin C (b) JJE

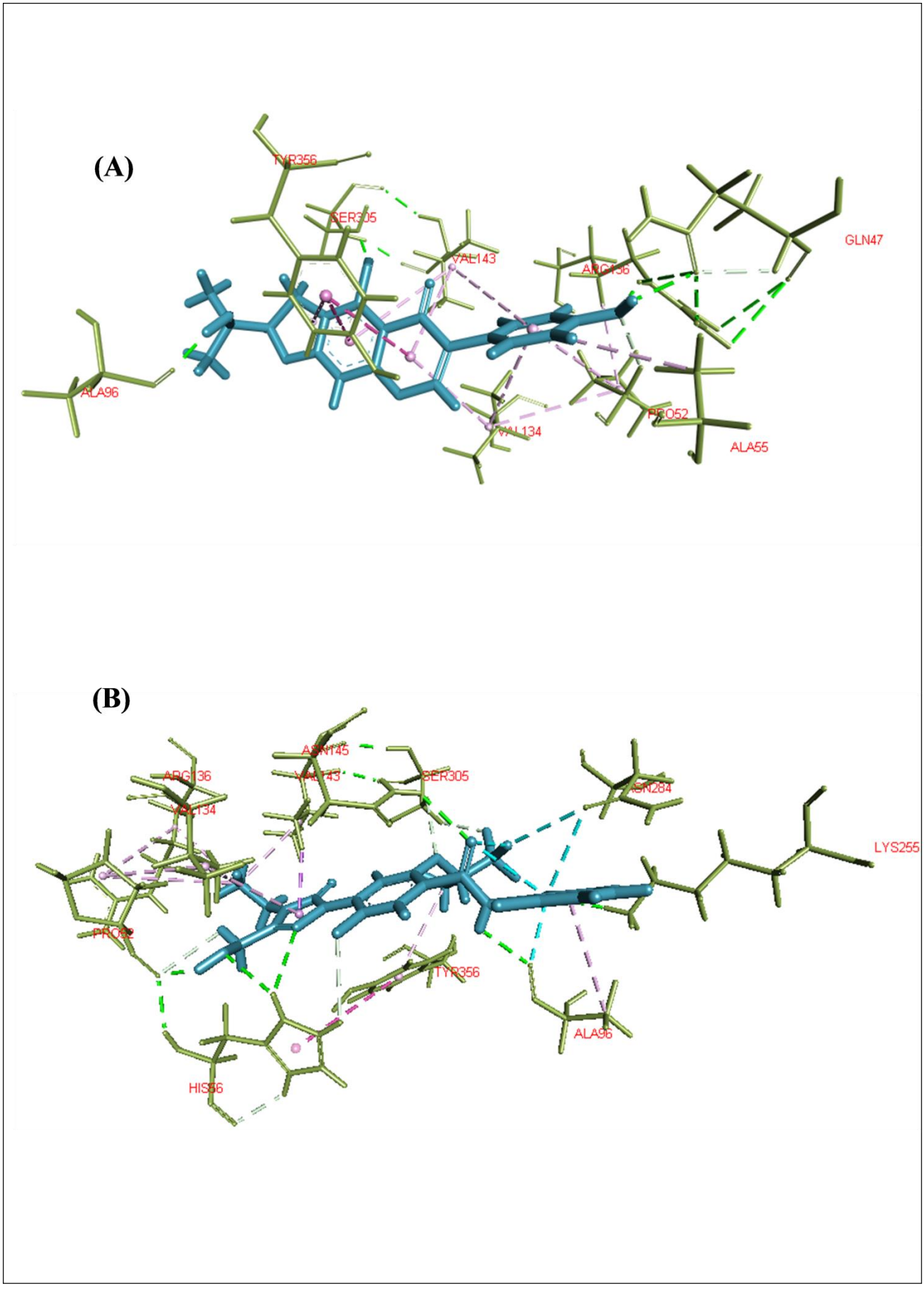

Figure 7: 3D interactions of ligands within the binding pocket (A) Erythrinin C (B) JJE

Table 1: Interaction table showing the various chemical interactions of Erythrinin C within the binding pocket

NAME	CATEGORY	TYPE
A:ARG136:HH21 - A:GLN47:OE1	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG136:HE - A:GLN47:OE1	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG136:HE - ERYTHRININ C:O5	Hydrogen Bond	Conventional Hydrogen Bond
A: ARG136:HH12 - A: GLN47: O	Hydrogen Bond	Conventional Hydrogen Bond
A: ARG136:HH22 - A: GLN47: O	Hydrogen Bond	Conventional Hydrogen Bond
A: VAL143: H - A: SER305: O	Hydrogen Bond	Conventional Hydrogen Bond
A: SER305: H - A: VAL143: O	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C: H1 - A: ALA96: O	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C:H2 - A:SER305:OG	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C:H3 - A:GLN47:OE1	Hydrogen Bond	Conventional Hydrogen Bond
A:GLN47:HA - A:GLN47:OE1	Hydrogen Bond	Carbon Hydrogen Bond
A:PRO52:HA - ERYTHRININ C:O5	Hydrogen Bond	Carbon Hydrogen Bond
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Pi Stacked
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Pi Stacked
A:PRO52 - A:VAL134	Hydrophobic	Alkyl
A:ARG136 - A:PRO52	Hydrophobic	Alkyl
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL134	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:PRO52	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:ALA55	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL134	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl
A:ARG136:HE - ERYTHRININ C:O5	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C:H1 - A:ALA96:O	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C:H2 - A:SER305:OG	Hydrogen Bond	Conventional Hydrogen Bond
ERYTHRININ C:H3 - A:GLN47:OE1	Hydrogen Bond	Conventional Hydrogen Bond
A:PRO52:HA - ERYTHRININ C:O5	Hydrogen Bond	Carbon Hydrogen Bond
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Pi Stacked
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Pi Stacked
A:TYR356 - ERYTHRININ C	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL134	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:PRO52	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:ALA55	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL134	Hydrophobic	Pi-Alkyl
ERYTHRININ C - A:VAL143	Hydrophobic	Pi-Alkyl

Table 2: Interaction table showing the various chemical interactions of the co-crystallized within the binding pocket

NAME	TYPES	CATEGORY
A: HIS56: H - A: PRO52: O	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS56:HD1 - A:JJE403:N2	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS56:HD1 - A:JJE403:O3	Hydrogen Bond	Conventional Hydrogen Bond
A: VAL143: H - A: SER305: O	Hydrogen Bond	Conventional Hydrogen Bond
A: ASN145:HD22 - A: JJE403: O	Hydrogen Bond	Conventional Hydrogen Bond
A:LYS255:HZ3 - A:JJE403:F	Hydrogen Bond	Conventional Hydrogen Bond
A: SER305: H - A: VAL143: O	Hydrogen Bond	Conventional Hydrogen Bond
A: JJE403:H5 - A: ALA96: O	Hydrogen Bond	Conventional Hydrogen Bond
A: JJE403:H17 - A: PRO52: O	Hydrogen Bond	Conventional Hydrogen Bond
A: HIS56:HD2 - A: HIS56: O	Hydrogen Bond	Carbon Hydrogen Bond
A:HIS56:HE1 - A:JJE403:F4	Hydrogen Bond	Carbon Hydrogen Bond
A:SER305:HB2 - A:JJE403:F3	Hydrogen Bond	Carbon Hydrogen Bond
A:SER305:HB3 - A:JJE403:O1	Hydrogen Bond	Carbon Hydrogen Bond
A: JJE403:H16 - A: PRO52: O	Hydrogen Bond	Carbon Hydrogen Bond
A:VAL143:HG13 - A:JJE403	Hydrophobic	Pi-Sigma
A:HIS56 - A:TYR356	Hydrophobic	Pi-Pi T-shaped
A:PRO52 - A:VAL134	Hydrophobic	Alkyl
A:ARG136 - A:PRO52	Hydrophobic	Alkyl
A:JJE403:C18 - A:PRO52	Hydrophobic	Alkyl
A:JJE403:C18 - A:VAL134	Hydrophobic	Alkyl
A:JJE403:C18 - A:ARG136	Hydrophobic	Alkyl
A:JJE403:C18 - A:VAL143	Hydrophobic	Alkyl
A:TYR356 - A:JJE403:C12	Hydrophobic	Pi-Alkyl
A:JJE403 - A:ALA96	Hydrophobic	Pi-Alkyl
A:JJE403 - A:VAL134	Hydrophobic	Pi-Alkyl
A:HIS56:HD1 - A:JJE403:N2	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS56:HD1 - A:JJE403:O3	Hydrogen Bond	Conventional Hydrogen Bond
A: ASN145:HD22 - A: JJE403: O	Hydrogen Bond	Conventional Hydrogen Bond
A:LYS255:HZ3 - A:JJE403:F	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen(Fluorine)
A: JJE403:H5 - A: ALA96: O	Hydrogen Bond	Conventional Hydrogen Bond
A: JJE403:H17 - A: PRO52: O	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS56:HE1 - A:JJE403:F4	Hydrogen Bond	Carbon Hydrogen Bond
A:SER305:HB2 - A:JJE403:F3	Hydrogen Bond	Carbon Hydrogen Bond
A:SER305:HB3 - A:JJE403:O1	Hydrogen Bond	Carbon Hydrogen Bond
A: JJE403:H16 - A: PRO52: O	Hydrogen Bond	Carbon Hydrogen Bond
A:ALA96:O - A:JJE403:F	Halogen	Halogen (Fluorine)
A:ASN284:OD1 - A:JJE403:F	Halogen	Halogen (Fluorine)
A:ASN284:OD1 - A:JJE403:F1	Halogen	Halogen (Fluorine)
A:JJE403:O - A:JJE403:F	Halogen	Halogen (Fluorine)
A:JJE403:O - A:JJE403:F1	Halogen	Halogen (Fluorine)
A:VAL143:HG13 - A:JJE403	Hydrophobic	Pi-Sigma
A:JJE403:C18 - A:PRO52	Hydrophobic	Alkyl
A:JJE403:C18 - A:VAL134	Hydrophobic	Alkyl
A:JJE403:C18 - A:ARG136	Hydrophobic	Alkyl
A:JJE403:C18 - A:VAL143	Hydrophobic	Alkyl
A:TYR356 - A:JJE403:C12	Hydrophobic	Pi-Alkyl
A:JJE403 - A:ALA96	Hydrophobic	Pi-Alkyl
A:JJE403 - A:VAL134	Hydrophobic	Pi-Alkyl

Table 3: Lead Finder estimated binding energy (dG), virtual screening score (Vs -Score) and rank score

S/N	Complex	dG, kcal/mol	Vs-Score	Rank Score
1	Erythrinin C	-11.395	-12.346	-16.346
2	Wighteone	-11.178	-11.736	-14.784
3	JJE	-9.206	-11.185	-10.789
4	Genistein	-8.909	-10.156	-13.485
5	8-o-Methylretusin	-7.895	-9.715	-12.972

Table 4: Lipinski's drug-like properties of Erythrinin C: The rule describes drug candidate's pharmacokinetics in the human body which also including their absorption, distribution, metabolism and excretion ("ADME") using an online server (http://admet.scbdd.com/)

Molecular Properties	Lipinski's rule of Five	Erythrinin C drug-like properties
Molecular weight	<500	354.358
Hydrogen bond Acceptor	<10	6
Hydrogen bond Donor	<5	3
LogP	<5	2.946

Conclusion:

Docking studies and ADMET (Absorption, Distribution, Metabolism, Excretion/Toxicity) evaluation of Erythrinin C with DHODH showed that this ligand is a drug-gable molecule, which docks well with DHODH. Therefore, Erythrinin C molecule plays an important role in inhibiting DHODH and thus should be implicated as a potential agent for the treatment of acute myeloid leukaemia.

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