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In silico screening of alkaloids as potential inhibitors of epidermal growth factor receptor

Bui Thanh Tung[1*], Pham Thi Kim Dung[2], Nguyen Nhu Son[1], Nguyen Bao Kim[1], Nguyen Hai Ha[1], Nguyen Thanh Tra[3]

[1]University of Medicine and Pharmacy, Vietnam National University-Hanoi, 144 Xuan Thuy Street, Dich Vong Hau Ward, Cau Giay District, Hanoi, Vietnam
[2]Hanoi Obstetrics and Gynecology Hospital, 929 La Thanh Street, Ngoc Khanh Ward, Ba Dinh District, Hanoi, Vietnam
[3]Research and Development Department, Phap Viet Xnk and Investment Joint Stock Company (PHAVIMEX), Lane 63, Phu Do Ward, Nam Tu Liem District, Hanoi, Vietnam

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Abstract:

The epidermal growth factor receptor (EGFR) belongs to the HER/erbB receptor tyrosine kinase (RTK) family, serving as a crucial target for cancer treatment. Anti-EGFR drugs, used as a primary treatment for patients with advanced EGFR gene mutations such as T790M, C797S, and L858R, have shown greater efficacy and safety compared to standard chemotherapy. This study aimed to screen alkaloid compounds with anticancer activity, extracted from the Selleckchem database that inhibit EGFR enzyme activity. The structure of the EGFR receptor was retrieved from the Protein Data Bank, whilst compounds were gathered from the alkaloids library within the Selleckchem database, with their structures downloaded from the PubChem database. Molecular docking was performed using Autodock Vina software. Lipinski's rule of five was employed to distinguish between compounds with drug-like and non-drug-like properties. The pharmacokinetic parameters of potential compounds were evaluated using the pkCSM tool. Our research indicates that amongst the screened alkaloids, four compounds - peiminine, sanguinarine chloride, dauricine, and irinotecan - are the most promising inhibitors of the EGFR receptor for the treatment of lung cancer. These compounds exhibit high binding affinity for the active sites of EGFR, thus inhibiting its activity. All aforementioned compounds adhere to Lipinski's rule and possess pharmacokinetic properties (absorption, distribution, metabolism, excretion, and toxicity - ADMET) that render them suitable for development into drugs.

Keywords: **alkaloid, cancer, epidermal growth factor receptor (EGFR), Lipinski's rule, molecular docking.**

Classification number: **3.3**

1. Introduction

The EGFR gene, located on the short arm of chromosome 7 (7p11.2), encodes a 170-kDa type I transmembrane growth factor receptor with tyrosine kinase (TK) activity [1]. EGFR forms part of the HER/erbB family of RTKs, encompassing HER1 (EGFR/erbB1), HER2 (neu, erbB2), HER3 (erbB3), and HER4 (erbB4). EGFR is comprised of an extracellular ligand-binding domain and an intercellular TK domain. As a cell surface protein, EGFR interacts with endogenous epidermal growth factor (EGF), instigating the EGFR receptor homo- or heterodimerisation process, followed by autophosphorylation and activation of several downstream pathways (STAT, MAPK, PI3K, AKT, PKC). This triggers cell proliferation, growth, and differentiation [2, 3]. Given EGFR's pivotal role in cell signalling and pathway involvement, it constitutes a significant target for cancer treatment [4]. Anti-EGFR drugs, used as first-line therapy in patients with advanced EGFR gene mutations such as T790M, C797S, and L858R, have exhibited superior efficacy and safety compared to conventional chemotherapy [5]. To date, numerous tyrosine kinase inhibitors (TKIs) have been employed to inhibit EGFR kinase overexpression, particularly erlotinib and gefitinib, which are highly selective for treating non-small cell lung cancer (NSCLC) and pancreatic cancer, while lapatinib is a dual inhibitor of EGFR and HER2 kinase, useful in metastatic breast cancer [6, 7]. However, these drugs can also induce adverse side effects, including vomiting, nausea, bleeding, diarrhoea, dry skin, skin rashes, and lung disease [8, 9].

Alkaloids, a highly diverse group of compounds, encompass approximately 3000 distinct entities derived from plants, fungi, and animals [10]. Alkaloids are low molecular weight organic nitrogen-containing compounds often classified chemically as pyrrolidines, pyridines, tropanes, pyrrolizidines, isoquinolines, indoles, quinolines and terpenoids and steroids. They have been shown to inhibit the topoisomerase

*Corresponding author: Email: tungbt.ump@vnu.edu.vn

enzyme, thereby blocking DNA replication and inducing cell death [11]. Thus, alkaloids have formed the basis for various drugs for diverse diseases, such as the asthma-relieving action of ephedrine, the analgesic action of morphine, and the anticancer effects of vinblastine [12]. Among phytochemicals, alkaloids demonstrate potential as anticancer agents.

Molecular docking is a highly applicable modelling technique in the research and development of novel drugs. This method aids in determining enzyme and ligand topology, offering an evaluation of the drug's pharmacological potential. The lower the binding energy (Gibbs free energy) of a protein-ligand complex (substance), the greater the pharmacological potential. This *in silico* method provides substantial cost and time savings for compound screening compared to experimental methods [13]. Our study was undertaken with the goal of screening alkaloids with anticancer potential to identify potential inhibitors of HER2 receptors via the molecular docking method.

2. Methodology

2.1. Molecular docking

Preparation of the protein structure: The crystal structures of the EGFR receptor (ID: 1M17) were collected from the RCSB protein data bank (http://www.rcsb.org/) [14]. Water molecules and co-ligand erlotinib (4-anilinoquinazoline inhibitor) were removed from the protein structure with the help of Discovery Studio Visualizer 4.0 software, while hydrogen atoms were added afterward using Autodock Vina. The binding site of the TK enzyme EGFR was re-established by MGL Autodock tools 1.5.7 within a 24 x 24 x 24 Å-sized gridbox, spacing of 1 Å, and (x,y,z) centre coordinates at (20.663, 4.206, 56.920). Finally, the protein structure files were saved in .pdbqt format for the docking process.

Preparation of the ligand structure: Data from 204 highly potential anticancer alkaloid compounds were collected and sorted from the Alkaloid Compound Library and Anti-cancer Compound Libraries I and II (http://www.selleckchem.com/). Their 3D structures were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). All compounds were optimised by Avogadro software using Conjugate Gradients and converted to .pdbqt format using Autodock tools.

Performance of molecular docking: Docking and screening of the 204 bioactive alkaloids against the EGFR receptor were performed using AutoDock Vina software. Molecular interactions of protein-ligand complexes showing promising binding free energies and molecular targets were visualized using Discovery Studio Visualizer 2020.

Validation of docking: To validate the docking protocol, the co-ligand of the co-crystal structure was docked in the target active site. The docking process was considered valid if the root mean square deviation (RMSD) value was less than or equal to 1.5 [15]. The binding capacity of the ligands was determined by their interactions with amino acids in the binding pocket as well as the binding energies calculated by the Autodock Vina scoring function.

2.2. Lipinski's rule of five

Lipinski's rule of five aids in the comparison of drug-like and non-drug-like molecules [16]. We evaluated Lipinski's rule of five with an online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) [17]. The chemical structures were downloaded from the PubChem database and adjusted to pH 7.0.

2.3. Prediction of ADMET

The ADMET profile includes five parameters: absorption, distribution, metabolism, excretion, and toxicity, which play a critical role in demonstrating the likelihood of success of a compound to become a drug. In this study, PkCSM tools (http://biosig.unimelb.edu.au/pkcsm/prediction) were used to predict the ADMET profile [18].

3. Results and discussion

3.1. Molecular docking

Docking protocol validation: To validate the docking protocol, a separated co-ligand is re-docked back into target protein's binding site to calculate the RMSD value between the redocked conformation and protein-bound ligand conformation. The results showed that the docking process was valid for EGFR with RMSD values of 1.40108 Å<1.5 Å. Therefore, the docking procedure can be performed (Fig. 1).

Fig. 1. Superposition of the re-docking pose and the original complexed ligand.

Screening of potential EGFR inhibitor: Molecular docking between 204 alkaloid ligands with anticancer potential against EGFR receptor was performed. The results were shown in Table 1.

Table 1. The docking results of 204 alkaloid compounds into EGFR receptor.

No	Compound	Binding energy (kcal/mol)
1	(-)-Huperzine A (HupA)	-7.0
2	(-)-Norepinephrine	-6.0
3	(-)-Sparteine sulfate	-6.5
4	(+)-Bicuculline	-10
5	(+)-Isocorynoline	-8.2
6	(+)-Matrine	-7.8
7	(S)-10- Hydroxycamptothecin	-9.3
8	2'-Deoxyguanosine monohydrate	-7.5
9	2'-Deoxyinosine	-7.6
10	3,3'-Diindolylmethane	-8.6
11	4-Aminoantipyrine	-6.9
12	4-Hydroxyquinazoline	-6.3
13	5'-Adenylic acid	-7.4
14	6-Biopterin	-7.1
15	7-Ethylcamptothecin	-9.9
16	9-Methoxycanthin-6-one	-8.4
17	Abiraterone acetate	-9.3
18	Acarbose	-7.9
19	Acetylcysteine	-4.6
20	Acetylcholine chloride	-4.3
21	Adenosine	-7.2
22	ADP	-7.5
23	Ajmaline	-8.6
24	Albendazole	-6.7
25	Allantoin	-5.9
26	Aloperine	-7.0
27	Aminocaproic acid	-4.8
28	Ampiroxicam	-9.4
29	Anamorelin	-8.5
30	Anisomycin	-6.9
31	Aristolochic acid A	-8.6
32	Atropine sulfatemonohydrate	-7.5
33	Benzamide	-5.7
34	Berbamine (dihydrochloride)	-8.3
35	Berberine chloride	-9.2
36	Berberrubine	-9.2
37	Bestatin	-7.2
38	Beta-alanine	-3.6
39	Betaine	-3.7
40	Boldine	-8.2
41	Brevianamide F	-8.4
42	Butylscopolamine Bromide	-7.5
43	Camptothecin	-10
44	Canertinib (CI-1033)	-8.0
45	Capecitabine	-7.0
46	Capsaicin (Vanilloid)	-6.8
47	Catharanthine	-7.6
48	Cephalotaxine	-8.3
49	Cepharanthine	-9.6
50	Cinchonine(LA40221)	-7.8
51	Colchicine	-7.7
52	Coptisine chloride	-9.8
53	Cordycepin	-7.4
54	Corynoline	-9.8
55	Corynoxine	-7.5
56	Crebanine	-8.9
57	Cyclocytidine HCl	-7.1
58	Cytidine	-7.1
59	Cytisine	-6.8
60	Chelidonine	-9.5
61	Chlorhexidine HCl	-8.6
62	Danofloxacin mesylate	-8.8
63	Dasatinib monohydrate	-8.6
64	Dauricine	-10.1
65	Daurisoline	-9.9
66	Decitabine	-6.6
67	Dehydrocorydalin	-8.1
68	Demethyleneberberine	-8.6
69	Dihydrocapsaicin	-6.5
70	DL-Norvaline	-4.7
71	Dopamine HCl	-5.6
72	Efavirenz	-8.1
73	Ellipticine hydrochloride	-8.7
74	Epigoitrin	-4.2
75	Ethionamide	-5.2
76	Evodiamine	-9.1
77	Fangchinoline	-9.4
78	Fenspiride HCl	-7.7
79	Fingolimod	-6.1
80	Folic acid	-8.4
81	Galanthamine HBr	-7.8
82	Gefitinib (ZD1839)	-8.5
83	Gelsemine	-7.9
84	Glutathione	-5.6
85	Gramine	-6.0
86	Guanosine	-7.4
87	Halofuginone	-8.0
88	Harmaline	-6.8
89	Harmine hydrochloride	-6.9
90	Harringtonine	-8.1
91	Higenamine hydrochloride	-8.0
92	Histamine	-4.6
93	Homatropine bromide	-7.5
94	Homoharringtonine	-8.3
95	Hydroquinidine	-7.8
96	Hydroxycamptothecin	-10
97	Hyoscyamine	-7.5
98	Indigo	-8.4
99	Indirubin	-9.0
100	Indole-3-acetic acid	-6.3
101	Indole-3-carbinol	-5.9
102	Irinotecan	-10.1
103	Isatin	-6.1
104	Isoguanosine	-7.5
105	isoleucine	-5.0
106	Isoliensinine	-10
107	Jatrorrhizine	-8.5
108	Jervine	-9.9
109	Kynurenic acid	-7.0
110	L-5-Hydroxytryptophan	-7.0
111	Lappaconite HBr	-9.1
112	Lappaconitine	-9.2
113	L-Arginine HCl (L-Arg)	-5.4
114	L-carnitine	-4.5
115	L-Cycloserine	-4.5
116	Leonurine	-6.6
117	Levoleucovorin calcium	-8.7
118	Liensinine	-9.8
119	L-Kynurenine	-6.5
120	Lobeline hydrochloride	-8.7
121	L-Ornithine hydrochloride	-5.2
122	L-serine	-4.0
123	L-Tryptophan	-6.6
124	Lycorine hydrochloride	-8.2
125	Melatonin	-7.0
126	Metronidazole	-5.4
127	Monocrotaline	-7.7
128	N-(5-Aminopentyl)acetamide	-4.9
129	N-Benzoyl-(2R,3S)-3-phenylisoserine	-7.7
130	Neferine	-9.6
131	Nicergoline	-8.2
132	Nicotinamide (VitaminB3)	-5.4
133	Nicotinamide N-oxide	-5.7
134	Nifuratel	-5.4
135	Nitidine chloride	-9.4
136	Nonivamide	-6.3
137	Nuciferine	-8.8
138	Nudifloric acid	-6.2
139	Orotic acid (6Carboxyuracil)	-5.9
140	Oxcarbazepine	-8.0
141	Oxindole	-5.7
142	Oxymatrine	-8.3
143	Palmatine chloride	-8.2
144	Palonosetron HCl	-8.7
145	Peiminine	-10.6
146	Penicillamine	-4.5
147	Pilocarpine HCl	-6.3
148	Pioglitazone	-8.0
149	Piperine	-7.9
150	Piperlongumine	-7.2
151	Primaquine diphosphate	-7.1
152	Procaine HCl	-6.1
153	Protopine	-8.4
154	Proxyphylline	-7.0
155	Puromycin 2HCl	-8.1
156	Quinine HCl dihydrate	-7.4
157	Raceanisodamine	-7.6
158	Reserpine	-9.1
159	Roquinimex	-7.8
160	Rutaecarpine	-9.3
161	Ruxolitinib phosphate	-8.4
162	S-(-)-Cotinine	-5.9
163	S-allyl-L-cysteine	-4.4
164	Santacruzamate A (CAY10683)	-6.7
165	Sanguinarine chloride	-10.3
166	Sarcosine	-3.7
167	Scopine	-5.6
168	Scopolamine HBr	-7.4
169	Scopolamine N-Oxide HydrobroMide Monohydrate	-7.8
170	Securinine	-7.4
171	Silodosin	-7.9
172	Sinapine thiocyanate	-6.4
173	Sinomenine hydrochloride	-6.8
174	S-Methyl-L-cysteine	-4.3
175	Songorine	-8.4
176	Sophocarpine	-7.6
177	Sophoridine	-8.4
178	Sorafenib	-8.9
179	Stachydrine hydrochloride	-5.0
180	Synephrine	-6.3
181	Taurine	-3.9
182	Tetrahydroberberine	-8.9
183	Tetrahydropapaverine HCl	-7.8
184	Tetramethylpyrazine	-4.9
185	Tetrandrine	-9.1
186	Tigecycline	-8.5
187	Tioconazole	-7.4
188	Topotecan HCl	-9.6
189	Tubercidin	-7.3
190	Tyramine	-5.5
191	Thymine	-5.3
192	Tranexamic Acid	-5.5
193	Trigonelline hydrochloride	-5.5
194	Tropisetron	-7.8
195	Tryptamine	-6.3
196	Tryptanthrin	-8.9
197	Uracil	-4.8
198	Uridine	-7.3
199	Veratramine	-9.6
200	Vidarabine	-6.9
201	Vincamine	-8.7
202	Vindoline	-7.4
203	Vinpocetine	-8.7
204	Vortioxetine	-7.5
205	Lapatinib (Positive control)	-9.2

The docking results from Table 1 show that 13/204 alkaloids had binding energies (kcal/mol) lower than the reference compound Lapatinib: (+)-Bicuculline; camptothecin, 7-Ethylcamptothecin, Coptisine chloride, Dauricine, Daurisoline, Hydroxycamptothecin, Irinotecan, Peiminine, Isoliensinine, Jervine, Liensinine and Sanguinarine chloride with binding energies (kcal/mol) of -10,0 (kcal/mol); -9,9 (kcal/mol); -10,0 (kcal/mol); -9,8 (kcal/mol); -10,1 (kcal/mol); -9,9 (kcal/mol); -10,0 (kcal/mol); -10,1 (kcal/mol); -10,0 (kcal/mol), -9,9 (kcal/mol), -9,8 (kcal/mol), -10,6 (kcal/mol) and -10,3 (kcal/mol), respectively. Lapatinib, the first dual inhibitor of EGFR and human epidermal growth factor receptor 2 (HER2) TKs, was approved by the US Food and Drug Administration (FDA) in 2007 [19]. The interactions of thirteen compounds with amino acids in the 1M17 receptor are shown in Table 2.

Table 2. Interactions of amino acids in the binding pocket with the 13 compounds.

Compound	Receptor	Hydrogen bonds	p-anion bonds	Other interactions
(+)-Bicuculline	1M17	MET769, PRO770		THR830, LEU800, LEU694, LEU820, VAL702
7 Ethylcamptothecin		THR766, ASP831		LEU820, VAL702, LEU694, CYS773
Camptothecin		THR766, ASP831		LEU820, VAL702, LEU694
Coptisine chloride		GLU738, ASP776		LEU820, LEU694, CYS773, VAL702, ALA719, LYS721
Dauricine		LYS721, ASP831	CYS773	LEU820, VAL702, ALA719, PHE699, ARG817
Daurisoline		LYS721, THR766	ASP831	LEU820, VAL702, ALA719, PHE699, ARG817, CYS773, MET742, GLY772, LEU 768
Hydroxy camptothecine		CYS751, ASP831		LEU820, VAL702, LEU694
Irinotecan		MET769, PRO770, ASP831		LEU820, LEU694, CYS773, VAL702, ALA719, LYS721
Isoliensinine		GLY697, GLY695, ASP831	ASP831	VAL702, ALA719, LYS721, PHE699, LEU694, MET742, THR766
Jervine		GLU738, ASP776		LEU820, VAL702, ALA719, LYS721
Liensinine		GLY695, ASP831	ASP831	LEU820, VAL702, ALA719, LEU694, PHE699, THR766
Peiminine		MET769		ASP831, PHE699, LEU694, VAL702
Sanguinarine chloride		CYS751, ASP831		LEU820, VAL702, ALA719, LYS721, PHE699, THR766

3.2. Lipinski's rule of five

Lipinski's rule of five aids in distinguishing between drug-like and non-drug-like molecules for the development of oral drugs. It predicts high probabilities of drug-like effectiveness or failure for molecules complying with two or more of the following rules: a molecular mass (MW) below 500 Dalton; high lipophilicity (expressed as LogP below 5); less than 5 hydrogen bond donors (HBD); less than 10 hydrogen bond acceptors (HBA1); and a molar refractivity (MR) between 40-130. The result of Lipinski's rule of five showed that all compounds satisfied more than two criteria. Thus, we focus on analysing the pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity, of these drugs.

3.3. Prediction of ADMET profile

The prediction of absorption, distribution, metabolism, excretion, and toxicity profile of four selected compounds are shown in Table 3.

Table 3. The results of ADMET profile of four selected compounds.

Properties	Dauricine	Irinotecan	Peiminine	Sanguinarine chloride
Absorption				
Water solubility (log mol/l)	-3.952	-3.57	-3.881	-4.848
Caco2 permeability (log P_{app} in 10^{-6} cm/s)	0.386	0.648	1.341	1.05
Intestinal absorption (human) (%)	88.177	99.879	91.574	70.472
Distribution				
VDss (human) (log l/kg)	-0.525	-2.741	0.1	0.142
BBB permeability (log BBB)	-1.054	-1.303	-0.009	0.41
Metabolism				
CYP2D6 substrate	Yes	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	Yes
Excretion				
Total clearance (log ml/min/kg)	0.987	0.939	-0.064	1.406
Toxicity				
AMES toxicity	No	No	No	Yes
Hepatotoxicity	No	Yes	Yes	No

In the absorption process, the human intestinal absorption (HIA) and human colon adenocarcinoma-2 cell line (Caco2) are two important parameters determining the absorption of a drug. A substance is considered poorly absorbed if the percentage absorbed in the human intestine is less than 30% [20]. The (human) intestinal absorption percentage of the four selected compounds was comparatively high/medium, especially irinotecan with a maximum absorption percentage of 99.879%. The Caco-2 cell line consists of human colon adenocarcinoma cells. A compound has high Caco-2 permeability if it has a Papp>8x10^{-6} cm/s, i.e., logPapp>0.9 [20]. The results show two compounds with a Caco-2 permeability greater than 0.9, namely peiminine and sanguinarine chloride.

The distribution of a substance is expressed through several parameters including lipid-solubility, concentration, as well as the binding capability to plasma proteins and transfer proteins. The steady-state volume of distribution (VDss) is the theoretical volume to which the total dose of a drug should be uniformly distributed to obtain the same plasma concentrations [20]. The higher the VDss, the more a drug will be distributed in tissue rather than plasma. Compounds are said to be well distributed to tissues if logVDss>0.45 and poorly distributed if logVDss<-0.15 [20]. All four compounds, dauricine, irinotecan, peiminine, and sanguinarine chloride, distributed poorly to tissues with logVDss values of -0.525, -2.741, 0.1, and 0.142, respectively. No compounds were well distributed. The ability of a drug to cross the blood-brain barrier is a factor to consider to help reduce toxicities and side effects or to improve the effectiveness of drugs whose pharmacological activity is within the brain [20]. There are two compounds (dauricine and irinotecan) which have poor blood-brain barrier ability because their logBBB values were all less than -1. This limits the effectiveness of the compound in treating conditions that affect the brain, because the compound is unable to reach its target site in the brain.

The cytochrome P450 enzymes play an important role in the metabolism of many drugs. The results show that all compounds are substrates of CYP3A4, thus indicating that these compounds are potentially metabolized by P450.

Regarding elimination, we predicted total clearance, which is shown in Table 3. The results demonstrate that the total clearance of dauricine, irinotecan, and sanguinarine chloride are the highest compared with peiminine.

In terms of toxicity, dauricine has no toxicity, while all remaining compounds have at least one toxicity.

In this study, we screened 204 alkaloids, which have anticancer abilities, from the alkaloid compound library and anti-cancer compound libraries I and II in order to evaluate their potential as EGFR inhibitors. Docking results show that 13 compounds had the lowest binding energies. Among these, dauricine, irinotecan, peiminine, and sanguinarine chloride were chosen as potential compounds for development into drugs. Although dauricine has not been studied as a potential treatment for lung cancer, there have been some studies showing that dauricine has the ability to suppresses the growth of pancreatic cancer *in vivo* [21, 22]. For many years, irinotecan, which has been used to treat a variety of cancers, is a flexible chemotherapeutic agent that works effectively in combination with a wide range of anticancer medicines. More clinical trials are needed to demonstrate the efficacy of this medication for lung cancer. Peiminine is an alkaloid derived from the bulb of *Fritillaria thunbergii* Miq and possesses anticancer and anti-inflammatory properties. Peiminine inhibits the progression of colorectal cancer through up-regulating miR-760 and inducing apoptosis and autophagy [23, 24]. Sanguinarine chloride, a benzophenanthridine alkaloid produced from the root of *Sanguinaria Canadensis*, can exhibit a clear-cut anticancer potential by inducing apoptosis and/or antiproliferative effects on tumour cells. This alkaloid's anti-tumour activity is the consequence of a combination effect on tumour cell proliferation and invasiveness, as well as modulation of the complicated phenomenon of tumour angiogenesis [25]. Sanguinarine, in particular, is a promising option for the development of novel lung anticancer medicines, either alone or in conjunction with existing chemotherapy regimens, due to its pro-apoptotic capability.

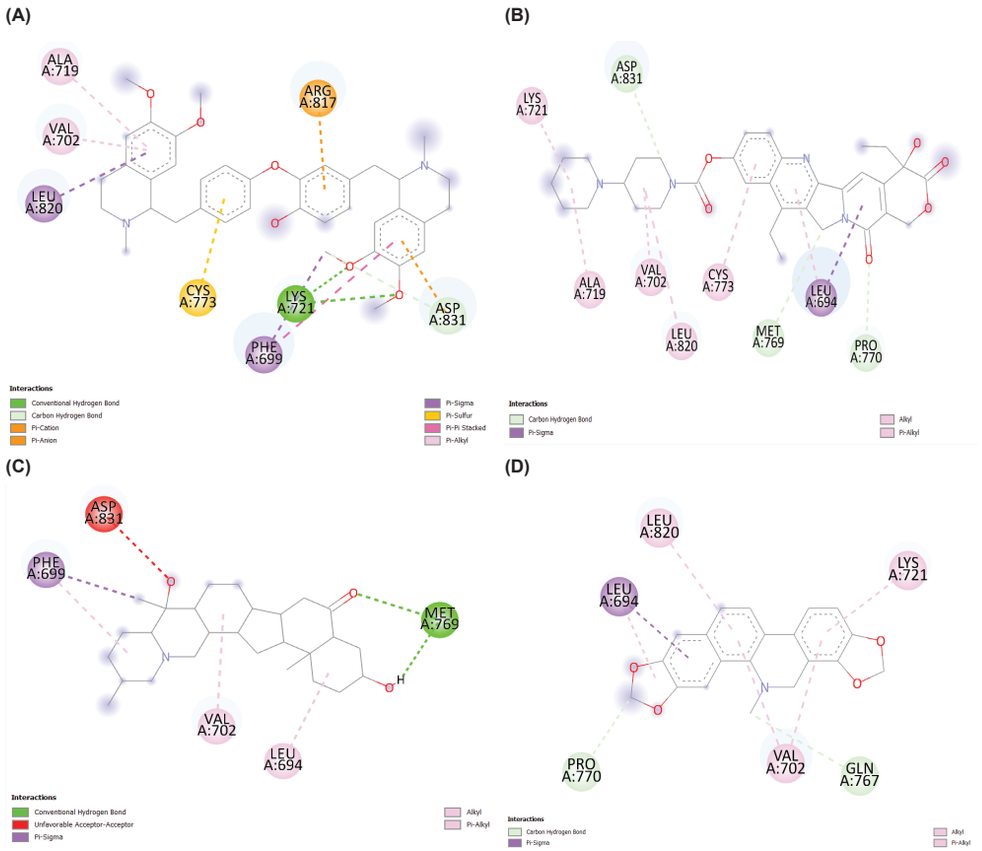

Fig. 2. Interactions between four potential compounds and the EGFR receptor. (A) Dauricine; **(B)** Irinotecan; **(C)** Peiminine; **(D)** Sanguinarine chloride.

In this study, we also evaluated the interactions between the four compounds with EGFR using Discovery Studio Visualizer 4.0 software, as shown in Fig. 2. The lapatinib positive control, with a binding energy of -9.2 kcal/mol, has hydrogen bonds and π interactions with amino acids MET769, ASP831, LEU820, VAL702, ALA719, and LYS721. All four compounds showed good binding ability at the active site of the enzyme through many important amino acids such as LEU820, VAL702, ALA719, LYS721, and ASP831 [26-29].

4. Conclusions

Our study elucidated that four alkaloid compounds (dauricine, irinotecan, peiminine, and sanguinarine chloride) are potential inhibitors of the EGFR enzyme for the treatment of lung cancer. These compounds exhibit strong binding affinity for the active sites of EGFR, thus inhibiting the activity of this enzyme. All the aforementioned compounds comply with Lipinski's rule and possess pharmacokinetic properties suitable for drug development. Hence, we propose to conduct further *in vitro* and *in vivo* studies of these four compounds with the aim of treating cancer.

CRediT author statement

Bui Thanh Tung: Conceptualization, Methodology, Supervision; Pham Thi Kim Dung and Nguyen Thanh Tra: Data curation, Writing - Original draft preparation; Nguyen Nhu Son, Nguyen Bao Kim, Nguyen Hai Ha: Software, Visualisation, Investigation, Writing - Reviewing and Editing.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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