

# Molecular Docking Study: Application to the Epidermal Growth Factor Receptor <sup>†</sup>

Faiza Asli \* and Imane Bensahbane

Group of Computational and Medicinal Chemistry LMCE Laboratory, University Mohamed Khider, Biskra 07000, Algeria; imane.bensahbane@univ-biskra.dz

\* Correspondence: faiza.asli@univ-biskra.dz

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**Abstract:** With the development of computer tools over the past 20 years, molecular modeling and more precisely molecular docking (molecular docking) has very quickly entered the field of pharmaceutical research. Our work consists of studying the inhibition of the enzyme EGFR (1M17) involved in cancer disease with deferent inhibitors derived from quinazoline and quinoline by molecular docking. The values of ligands L\_1 and L\_2 are the best ligands for inhibit the activity of 1M17 since it forms a stable complex with this enzyme by better binding to the active site. The results obtained show that the ligands L1 and L2 give weak interactions with the active site residues EGFR (1M17) which stabilize the complexes formed of this ligands, which gives a better binding at the level of the active site, and an RMSD of L\_1 [1.9563 Å] and of L\_2 [1.2483 Å]. [1.9563, 1.2483] Å. All the newly designed compounds passed the pharmacokinetic analysis (ADME–TOX) (ad-sorption, distribution, metabolism, excretion, and other physicochemical test) passed the drug-likeness test, and they also adhered to the Lipinski rule of five All the newly designed compounds passed the pharmacokinetic analysis (adsorption, distribution, metabolism, excretion, and other physicochemical test) passed the drug-likeness test, and they also adhered to the Lipinski rule of five.

**Keywords:** molecular docking; EGFR; quinazoline and quinoliène derivatives; ADME-T; interactions; MOE

## 1. Introduction

Due to the progress and development of the world and the spread of unhealthy foods, as well as the use of chemicals, in addition to the spread of alcohol and smoking, which led to the spread of several deadly diseases on a large scale, the most famous of which is cancer, which ranked first in the list of diseases that kill human lives, and humanity has known cancer since ancient times, as cancer is not a modern disease but a malignant disease [1] that affects cells and results in the abnormal and uncontrolled growth of normal cells and then the formation of a cancerous tumor.

Cancer is one of many diseases characterized by the proliferation of atypical cells that exhibit unregulated division and possess the capacity to infiltrate and deteriorate healthy bodily tissue. It often possesses a capacity to disseminate across the entire organism. Cancer is the primary global cause of death. However, the rates of survival are increasing for many different kinds of cancer. This is due to advancements in cancer detection, treatment, and prevention. The most common types of cancer include breast cancer [2].

Skin cancer is the 17th most common cancer worldwide. It is the 14th most common cancer in men and the 14th most common cancer in women [3]. Skin cancer is one of the most active types of cancer in the present decade [4]. As the skin is the body's largest organ, the point of considering skin cancer as the most common type of cancer among humans is understandable [5]. It is generally classified into two major categories:

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melanoma and non-melanoma skin cancer [6]. More than 1.5 million new cases are estimated in 2022. In 2022, an estimated 330,000 new cases of melanoma were diagnosed worldwide and nearly 60,000 people died from the disease. There are significant geographical variations in melanoma incidence rates across countries and regions of the world. In most regions of the world, melanoma occurs more often in men than in women [7]. The focus of our work has been on the epidermal growth factor receptor (EGFR), which is involved in the proliferation of cells. This shows how important it is to study this type of receptor in greater depth to better understand the mechanism of action and to contribute to the development of new inhibitors using new approaches to molecular modeling.

Molecular docking is the prediction and reproduction of protein-ligand and protein-ligand interactions [8–10]. The present work aims to perform a molecular docking study to select targeted pharmacological agents derived from quinazoline and quinoline as inhibitors capable of inhibiting the EGFR receptor (ID: 1M17), which is involved in cell proliferation [11]. In this context, we are interested in determining how the inhibitor interacts with the enzyme during the formation of the [EGFR-inhibitor] complex; the compound with the highest affinity is the one with the best activity and therefore inhibition. These results are likely to be of value in the development of an effective therapeutic tool against cancer.

Finally, to reduce the failure rate of drug candidates, the implementation of ADME (Absorption Distribution Metabolism and Elimination)-Tox (Toxicity) filters for chemotherapies in any screening process gave good pharmacokinetic performance and bioavailability, as well as excellent results.

## 2. Materials and Methods

Series of 213 derivative compounds of quinazoline and quinoline with reported biological activities  $IC_{50}$  in  $\mu M$  were prepared using Marvin Sketch (<https://www.chemaxon.com>) [12], and converted to 3D and optimized and other software programs were used to find optimal high-affinity compounds, were studied by molecular docking and ADME-T, and their EGFR inhibitory activities were tested with, MOE [13].

## 3. Results and Discussion

### 3.1. Interaction Energies of the Inhibitors

The results of the molecular docking of quinazoline and quinoline derivatives, obtained when only ten inhibitors were selected, show that the complexes formed by the ligands L148, L177, L198, L140, L143, L138, L161, L150, L164 and L136 have the lowest possible energy (degree) compared to the other ligands, even compared to the complex formed by the reference ligand in 1M17 (Table 1).

The results show that the ten ligands L148, L177, L198, L140, L143, L138, L161, L150, L164 and L136 form a complex with the receptor ID: 1M17. The ligands with the lowest score energies compared to the reference molecule show that these complexes are more stable.

On the other hand, the co-crystals (reference ligands) can be classified in the following order  $L148 < L177 < L198 < L140 < L143 < L138 < L161 < L150 < L164 < L136 < Erlotinib$ .

From the results, we conclude that interactions between active site residues and ligands L148, L177, L198, L140, L143, L138, L161, L150, L164 and L136 can form stable complexes.

However, the  $IC_{50}$  of the ligands: L148 ( $IC_{50} = 0.016 \mu M$ ), L177 ( $IC_{50} = 0.011 \mu M$ ), L198 ( $IC_{50} = 0.015 \mu M$ ) are lower than the  $IC_{50}$  value for erlotinib ( $IC_{50} = 0.020 \mu M$ ) and closer to the  $IC_{50}$  values of: L140 ( $IC_{50} = 0.030 \mu M$ ), L143 ( $IC_{50} = 0.031 \mu M$ ), L138 ( $IC_{50} = 0.020 \mu M$ ), L161 ( $IC_{50} = 0.024 \mu M$ ), L150 ( $IC_{50} = 0.026 \mu M$ ), L164 ( $IC_{50} = 0.007 \mu M$ ) and L136 ( $IC_{50} = 0.034 \mu M$ ). Note that the scores are very close to the scores of the reference ligands.

The complex formed by the ligand L148 has a low score energy (9.0419626 Kcal/mol) and forms three interactions with the active site residues: the first is a strong H-donor interaction (between atom N10 and residue ASP 831) with a distance of 2.98 Å, The second of weak H-acceptor type (between atom S18 and residue GLY 833) with a distance of distance 3.83 Å and the third of weak H-acceptor type (between atom N25 and residue LYS 721) with a distance of 3.71 Å. This ligand has an average IC50 value of 0.016 µM, suggesting that it can strongly inhibit the 1M17 enzyme (Table 1).

We also observe that the complex formed by the ligand L177 has a low Score energy (9.0158892 Kcal/mol) and forms three interactions with the active site residues, the first of average donor type (between atom C169 and residue ASP 831) with a distance of 3.33 Å, the second a strong H-donor (between atom C170 and residue GLN 767) with a distance of 3.05Å and the third a weak H-acceptor (between atom C170 and residue GLN 767) with a distance of 3.05Å. 3.05Å and the third is a weak H acceptor (between atom N43 and residue PRO 770 residue) with a distance of 3.63 Å, This ligand has a low value of IC50 = 0.011 µM, which is perhaps proposed as a second inhibitor of the enzyme.

The ligand L198 code (S5–68) has a low score energy (−9.0054464 Kcal/mol) and forms four interactions with the active site residues, the first of the H-acceptor type (between the N12 atom and residue LYS 704) at a distance of 3.19 Å, the second of the pi-H type (between the CD atom and residue LYS 721) at a distance of 3.90 Å, the third of the pi-H type (between the CD atom and residue LYS 721) with a distance of 4.33 Å and the fourth of the pi-H type (between the CD atom and residue LYS 721) with a distance of 4.33 Å. pi-H type (between the CD atom and residue LYS 721) with a distance of 4.33 Å and the fourth of the pi-H type (between the CA atom and residue GLY 772) with a distance of 3.54 Å.

The inhibitors L140 (−8.8247814 Kcal/mol), L143 (−8.7421417 Kcal/mol), L138 (−8.6277866 Kcal/mol), L161 (−8.3984995 Kcal/mol), L150 (−8.3727903 Kcal/mol), L164 (−8.1837978 Kcal/mol) and L136 (−8.1624002 Kcal/mol) have slightly low energy values, confirming that these ligands form complexes that are more complex than the previous ligands.

According to the energy value of the binding evaluation, compared to the ten compounds we can see that the values are optimal for all ten ligands. The values for L148 and L177 are the best ligands to inhibit the activity of 1M17, as they form a stable complex with this enzyme through better binding to the active site.

It is also evident that compound L148 has a low score energy (9.0419626 Kcal/mol) and forms three interactions with the active site residues: the first is a strong H-donor interaction (between atom N10 and residue ASP 831) with a distance of 2.98 Å. The second of weak H-acceptor type (between atom S18 and residue GLY 833) with a distance of distance 3.83 Å and the third of weak H-acceptor type (between atom N25 and residue LYS 721) with a distance of 3.71 Å. This ligand has an average IC50 value of 0.016 µM, suggesting that it can strongly inhibit the 1M17 enzyme.

We also observe that the complex formed by the ligand L177 has a low Score energy (9.0158892 Kcal/mol) and forms three interactions with the active site residues, the first of average donor type (between atom C169 and residue ASP 831) with a distance of 3.33 Å, the second a strong H-donor (between atom C170 and residue GLN 767) with a distance of 3.05 Å and the third a weak H-acceptor (between atom C170 and residue GLN 767) with a distance of 3.05 Å. 3.05 Å and the third is a weak H acceptor (between atom C170 and residue GLN 767) with a distance of 3.05 Å. and the third is a weak H acceptor (between atom N43 and residue PRO 770 residue) with a distance of 3.63 Å, this ligand has a low value of IC50 = 0.011 µM, which is perhaps proposed as a second inhibitor of the enzyme.

From the results obtained, we note that the values are considered to be perfect for the 10 ligands. The values for ligands L148 and L177 are the best ligands for inhibiting 1M17, Figure 1, illustrate the 2D interactions of these ligands since they form a stable complex with this enzyme by binding better to the active site.

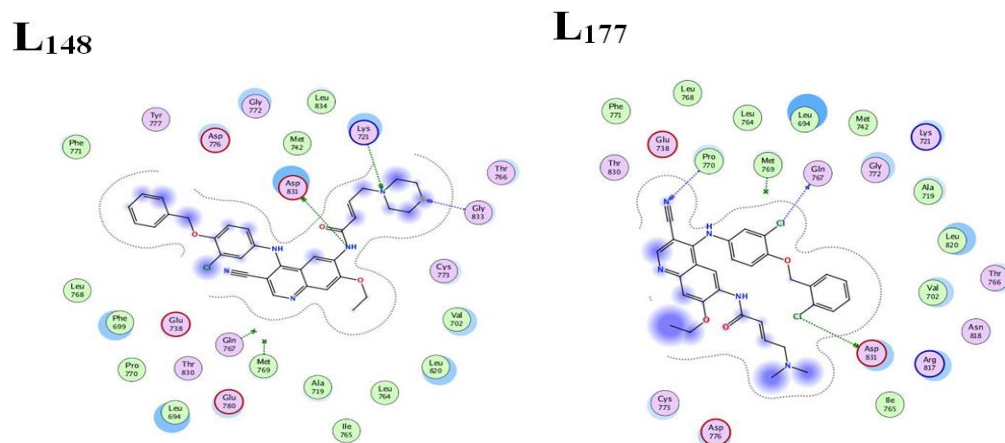


Figure 1. Interactions between L148, L177 and active site residue.

Table 1. Docking score and interactions between compounds and 1M17 active site.

N° of Ligands	IC <sub>50</sub> ( $\mu$ M)	S-Score (kcal mol)	RMSD ( $\text{Å}^\circ$ )	Bonds Between the Compounds Atoms and the Active Site Residues			
				Compound Atoms	Receptor Atoms	Interaction Type	Distance ( $\text{Å}^\circ$ )
L148	0.016	−9.0419	1.9563	N10	OD2	H-donor	2.98
				S18	CA	H-acceptor	3.83
				N25	NZ	H-acceptor	3.71
				CL69	OD2	H-donor	3.33
L177	0.011	−9.0158	1.2483	CL70	O	H-donor	3.05
				N43	CA	H-acceptor	3.63
				N12	NZ	H-acceptor	3.19
L198	0.015	−9.0054	1.6614	6-ring	CD	pi-H	3.90
				6-ring	CD	pi-H	4.33
				6-ring	CA	pi-H	3.54
L140	0.030	−8.8247	1.4567	CL67	OD1	H-donor	3.09
L143	0.031	−8.7421	1.5109	N12	OG1	H-acceptor	3.28
				6-ring	CG1	pi-H	3.82
				6-ring	CD	pi-H	3.94
				6-ring	N	pi-H	4.00
L138	0.020	−8.6277	2.0115	N10	OD1	H-donor	3.51
				O23	OD2	H-donor	3.16
				N47	N	H-acceptor	3.47
L161	0.024	−8.3984	1.9097	6-ring	CD1	pi-H	4.25
				CL55	O	H-donor	3.05
				N 24	N	H-acceptor	3.42
CL55	0.026	−8.3727	1.6572	6-ring	CB	pi-H	3.71
L164	0.007	−8.1837	1.7923	6-ring	CB	pi-H	3.74
				6-ring	CB	pi-H	4.65
				6-ring	CB	pi-H	4.05
L136	0.034	−8.1624	1.4415	6-ring	N	pi-H	4.05
Erlotinib	0.020	−8.0480	1.4130	N44	N	H-acceptor	3.13

### 3.2. ADMET Evaluation

The ADME proprieties of the best compounds were summarized in Table 2 to ensure compliance with the Lipinski, Veber and Egan rules, which describe various physicochemical properties of the calculated ligand molecules. All these molecules follow the rules of

Lipinski, Ghose, Veber and Egan. Finally, toxicity prediction results indicated that none of the compounds were toxic. We can confirm that these compounds do not cause oral bioavailability issues, have good properties compared to drugs for both targets (natural ligands), and have the potential to be selected as oral drugs against this disease.

**Table 2.** ADMET features of best selected compounds.

Properties	PubChem_CID	Lig-and_148	Ligand_177	Ligand_198	Ligand_140	Ligand_143	LRef	
	Formula	C33H32ClN5O3S	C31H29ClN5O3	C24H24BrN5O2	C22H17BrN4O3	C24H23ClFN5O2	C22H23N3O4	
	Molecular Weight (MW g/mol) <500	614.16	590.50	494.38	465.30	467.92	393.4	
<b>Physico-chemical properties</b>	Heavy atoms	43	41	32	30	33	29	
	Arom. heavy atoms	22	22	16	16	16	16	
	Rotatable bonds	12	12	9	7	9	10	
	H-bond acceptors < 10	6	6	5	5	6	6	
	H-bond donors < 5	2	2	2	2	2	1	
	TPSA 140 (Å <sup>2</sup> )	124.81	99.51	90.28	96.27	90.28	74.73	
	Lipinski violation	Yes	Yes	Yes	Yes	Yes	Yes	
<b>Drug-like-ness</b>	Veber violation	No	No	Yes	No	Yes	Yes	
	Ghose violation	No	No	No	Yes	Yes	Yes	
	Muegge Violations	No	No	Yes	No	Yes	Yes	
	Egan Violations	No	No	Yes	Yes	Yes	Yes	
	Bioavailability	0.55	0.55	0.55	0.55	0.55	0.55	
<b>Lipophilicity</b>	Consensus log Po/w < 5	5.26	5.48	3.86	3.40	4.10	3.20	
<b>Water solubility</b>	Log S (ESOL)	-7.22	-7.22	-5.52	-5.24	-5.37	-4.11	
	GI absorption	Low	Low	High	High	High	High	
	BBB permeant	No	No	No	No	No	Yes	
	P-gp substrate	Yes	Yes	No	No	No	No	
<b>Pharmacokinetics</b>	<b>CYP inhibitor</b>	1A2	No	No	No	Yes	No	Yes
		2C19	Yes	Yes	Yes	Yes	Yes	Yes
		2C9	Yes	No	Yes	Yes	Yes	Yes
		2D6	No	Yes	Yes	Yes	Yes	Yes
		3A4	No	No	Yes	Yes	Yes	Yes
<b>Medi. Chemistry</b>	Log Kp (cm/s)	-5.55	-5.27	-6.12	-6.23	-5.93	-6.35	
	Synthetic accessibility	4.33	4.10	3.52	3.47	3.44	3.19	
<b>Toxicity</b>	<b>Oral toxicity</b>	Oral rat acute toxicity LD50 (mol/kg)	2.426	3.033	2.531	2.386	2.641	2 368
		<b>Organ Toxicit</b>	Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive
	<b>Toxicity end-point</b>		Carcinogenicity	Inactive	Inactive	Inactive	Inactive	Inactive
		Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	active
		Mutagenicity	Active	Inactive	Inactive	Inactive	Inactive	active
		Immunotoxicity	Inactive	Inactive	active	active	active	active
		Ames toxicity	No	No	No	No	No	No
	<b>Others</b>	Skin sensitization	No	No	No	No	No	No
		hERG I inhibition	No	No	No	No	No	No
		hERG II inhibition	Yes	Yes	Yes	Yes	Yes	Yes

#### 4. Conclusions

In the present work, we have focused on the molecular interactions between the epidermal growth factor receptor abbreviated “EGFR” and quinazoline and quinoline derivatives quinazoline and quinoline derivatives as future inhibitors, using molecular docking to better understand the mechanism of inhibition of these enzymes. First, we designed and prepared 213 quinazoline and quinoline derivatives, then applied molecular docking to these inhibitors with the EGFR enzyme (ID: 1M17), the results obtained enabling us to determine the best stable complexes formed. Our studies are based on the calculation of interaction energies, RMSD and interaction distances between inhibitors and receptors. Depending on the results obtained, we can select the best inhibitor that has a high affinity for binding to the enzyme. The results show that the ten ligands L148, L177, L198, L140, L143, L138, L161, L150, L164 and L136 forming a complex with the receptor ID:1M17 have the lowest Score energies compared with the reference molecule, indicating that these complexes are more stable. They can be classified in the following order: L148 < L177 < L198 < L140 < L143 < L138 < L161 < L150 < L164 < L136. We conclude that the values obtained are considered to be perfect for all 10 ligands, and above all the L148 and L177 ligands are the best ligands to inhibit 1M17 activity, since they form a stable complex with this enzyme through better binding to the active site.

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#### References

1. Available online: [https://www.researchgate.net/publication/350471345\\_nzrt\\_aly\\_alsrtan\\_wtrq\\_lajh](https://www.researchgate.net/publication/350471345_nzrt_aly_alsrtan_wtrq_lajh) (accessed on).
2. Available online: <https://www.mayoclinic.org/ar/diseases-conditions/cancer/symptoms-causes/syc-20370588> (accessed on).
3. Available online: <https://www.wcrf.org/cancer-trends/skin-cancer-statistics/> (accessed on).
4. Ashraf, R.; Afzal, S.; Rehman, A.U.; Gul, S.; Baber, J.; Bakhtyar, M.; Mehmood, I.; Song, O.Y.; Maqsood, M. Region-of-Interest Based Transfer Learning Assisted Framework for Skin Cancer Detection. *IEEE Access* **2020**, *8*, 147858–147871. <https://doi.org/10.1109/ACCESS.2020.3014701>.
5. Byrd, A.L.; Belkaid, Y.; Segre, J.A. The Human Skin Microbiome. *Nat. Rev. Microbiol.* **2018**, *16*, 143–155. <https://doi.org/10.1038/nrmicro.2017.157>.
6. Elgamel, M. Automatic Skin Cancer Images Classification. *Int. J. Adv. Comput. Sci. Appl.* **2013**, *4*, 287–294. <https://doi.org/10.14569/IJACSA.2013.040342>.
7. Available online: <https://www.iarc.who.int/cancer-type/skin-cancer/> (accessed on).
8. Okines, A.; Cunningham, D.; Chau, I. Targeting the human EGFR family in esophagogastric cancer. *Nat. Rev. Clin. Oncol.* **2011**, *8*, 492.
9. Roskoski, R., Jr. The ErbB/HER receptor protein-tyrosine kinases and cancer. *Biochem. Biophys. Res. Commun.* **2004**, *319*, 1–11.
10. Hynes, N.E.; MacDonald, G. ErbB receptors and signaling pathways in cancer. *Curr. Opin. Cell Biol.* **2009**, *21*, 177–184.
11. Rukazenzov, Y.; Speake, G.; Marshall, G.; Anderton, J.; Davies, B.R.; Wilkinson, R.W.; Mark Hickinson, D.; Swaisland, A. Epidermal growth factor receptor tyrosine kinase inhibitors: Similar but different. *Anti-Cancer Drugs* **2009**, *20*, 856–866.
12. Calculator Plugins, Marvin 17.25, 0 2017. ChemAxon. Available online: <http://www.chemaxon.com> (accessed on).
13. *Molecular Operating Environment (MOE)*, 2015.10; Chemical Computing Group Inc.: Montreal, QC, Canada, 2015.

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