

MOLECULAR DOCKING STUDY OF Fe(III) COMPLEXES CONTAINING SALEN-TYPE SCHIFF BASES

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ABSTRACT

Our previous work reported the synthesis of Fe(III) complexes containing unsymmetrical salen-type Schiff bases from the reaction of 2-hydroxynaphthaldehyde with substituted salicylaldehyde. The cytotoxic activities of these compounds were then evaluated against KB and HepG2 cancer cell lines. The results indicated that Fe(III) complexes exhibited significant anticancer potential, with low IC₅₀ values ranging for both KB and HepG2. To further investigate the binding mode between the ligands and a biological target, molecular docking analysis was performed in this study. Epidermal growth factor receptor (EGFR) tyrosine kinase was chosen as a receptor model because of its relevance to anticancer drug development. The molecular docking results revealed that the stabilization of the Fe(III) complex-receptor was mainly influenced by the nature and position of substituents on the salicylidene moiety. Specifically, among six studied compounds, two high-potency complexes achieved a robust network of 16 interactions, including key salt bridges and attractive charge bonds with Asp831, which were absent in less active derivatives. These findings provide valuable insights into the potential inhibitory mechanisms of the synthesized Fe(III) complexes and support their potential development as novel anticancer agents targeting EGFR.

Keywords: Fe(III) complexes, unsymmetrical salen-type Schiff bases, cytotoxicity, HepG2, KB cell line, molecular docking.

1. INTRODUCTION

Cancer represents a significant health challenge that threatens global health and causes high mortality, following cardiovascular diseases [1, 2]. Since the sixteenth century, metal complexes have been used for the therapeutic treatment of cancer and leukemia [3, 4]. Iron-salen complexes have been well studied since 1931. They have a wide range of physicochemical and biological properties, including inhibitory activity against various cancer cell lines, such as MCF-7, HepG2. [5] via different mechanisms. Iron-salen derivatives may produce hydroxyl radicals in the presence of reducing agent of dithiothreitol and damage DNA [6]. The type of central metal and ligand are related to the anticancer activity of the metallic complexes. In our previous study, a series of Fe(III) complexes bearing unsymmetrical salen-type Schiff bases derived from 2-hydroxynaphthaldehyde and substituted salicylaldehydes were prepared [7]. Their cytotoxicity was evaluated on cancer cell lines including KB and HepG2. The results showed that the synthetic Fe(III) complexes have excellent cytotoxicity on human cancer cells, with IC₅₀ values ranging from 0.81 to 14.14 μ M for KB and from 1.87 to 63.31 μ M for HepG2. In this study, molecular docking was conducted to further examine the orientation, interaction, and conformation of the potential inhibitors in the active site of epidermal growth factor receptor (EGFR). EGFR, a transmembrane receptor tyrosine kinase, is involved in signaling processes related to cancer cell growth and survival [8-9]. Therefore, EGFR was selected as a representative kinase target for molecular docking to investigate its interaction with Fe(III) complexes.

2. MATERIALS AND RESEARCH METHODOLOGY

The crystal structure of EGFR tyrosine kinase with its co-ligand (PDB ID: 1M17) at a resolution of 2.6 Å was downloaded from the Protein Data Bank (www.rcsb.org). The preparation of the protein for docking studies follows these steps: first, water molecules, heteroatoms and co-ligands were removed from the protein. Second, missing residues were added, followed by polar hydrogens, and Kollman charges using AutoDockTools 1.5.7. For ligand preparation, two dimensional (2D) and three-dimensional (3D) structures of the ligands were generated by ChemDraw and Chem3D, respectively. The ligands were optimized using the MMFF94 molecular mechanical force field and 3D geometry optimization calculations using the Avogadro software. These optimized structures were used as inputs for the AutoDockTools. Prepared protein and ligand structures were saved in the PDBQT format for calculating the energy grids. The grid box was defined with a grid spacing of 0.375 Å and dimensions of $40 \times 40 \times 40$ grid points. The grid center was set at (22.014, 0.253, 52.794). The native ligand was redocked first and generated a root-mean-square deviation (RMSD) of 1.508 Å. The Fe(III) complexes were subsequently docked within the same grid box. For each ligand, poses with RMSD values below 2 Å were considered, and the conformation showing the most negative binding energy was selected as the most favorable docking pose. Molecular docking calculations were performed using AutoDock 4.2 through command-line execution. The calculation has been conducted using an Intel (R) Core (TM) i3-10400 CPU @ 2.90 GHz workstation. The ligand-receptor interactions were visualized by using Discovery Studio 2021. The physicochemical properties of the Fe(III) complexes were predicted using SwissADME.

3. RESULTS AND DISCUSSION

Six salen-type Schiff base complexes were well prepared [7] and Fig 1 presented their structures:

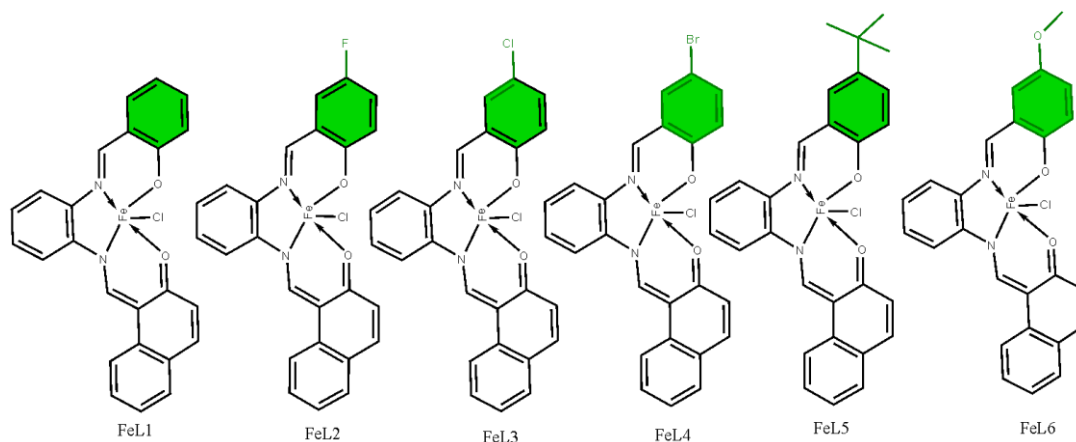


Fig. 1. The structure of six salen-type Schiff base complexes

The MTT dye reduction method was used to evaluate the cytotoxicity of these Fe(III) complexes against two human cancer cell lines KB and HepG2. Interestingly, based on the IC_{50} value [8], all studied compounds exhibited the cytotoxic activity in the following order: $FeL1 \sim FeL6 > FeL2 > FeL5 > FeL3 > FeL4$. To elucidate and support *in vitro* studies, molecular docking was performed. Based on the docking results (Table 1), the binding energy scores (ΔG_{dock}) are close to the experimental free energies (ΔG_{exp}) where ΔG_{exp} was calculated according to the following equation [10]:

$$\Delta G_{exp} = RT(\ln IC_{50} \times 10^{-6})/1000$$

Where:

- R is the gas constant of $1.987 \text{ cal mol}^{-1} \cdot \text{K}^{-1}$;
- T is the temperature, set at 298.15 K;
- IC_{50} values obtained from our previous report and expressed as μM .

Table 1. Calculated and experimental binding energy scores (kcal/mol) of studied compounds

Entry	Compounds	IC ₅₀ (μM) ^[8]		ΔG _{exp} (kcal/mol)		ΔG _{dock} (kcal/mol)
		KB	HepG2	KB	HepG2	
1	FeL1	0.81	3.18	-8.3	-7.5	-6.9
2	FeL2	3.53	25.45	-7.4	-6.3	-5.8
3	FeL3	10.97	63.31	-6.8	-5.7	-5.9
4	FeL4	14.14	56.53	-6.6	-5.8	-6.0
5	FeL5	8.31	28.31	-6.9	-6.2	-6.2
6	FeL6	2.61	1.87	-7.6	-7.8	-7.1

The plot of ΔG_{exp} against ΔG_{dock} was depicted on Fig. 2.

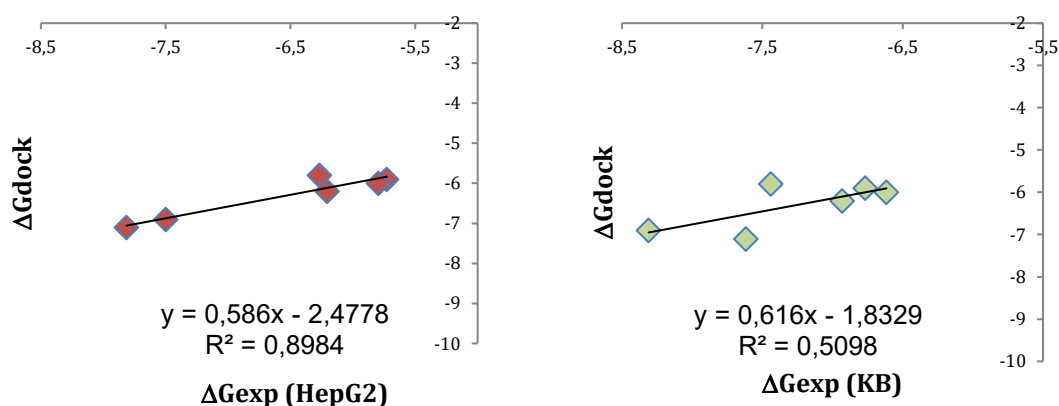


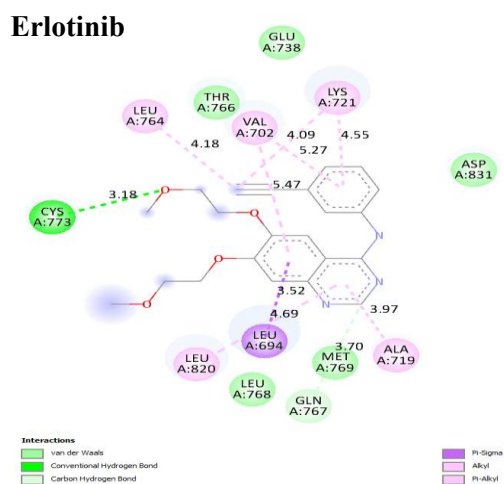
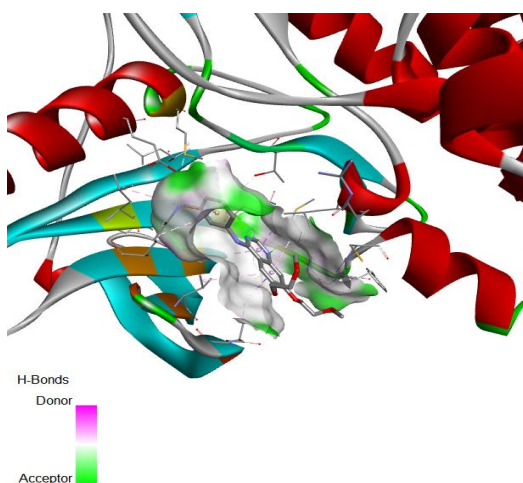
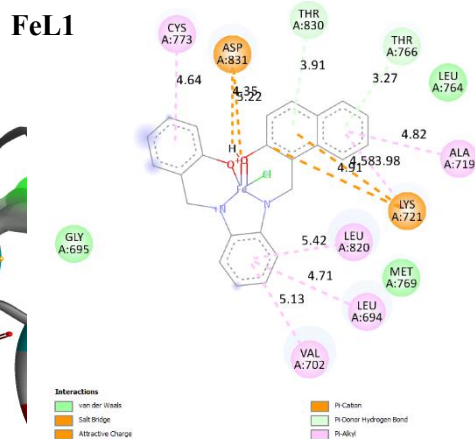
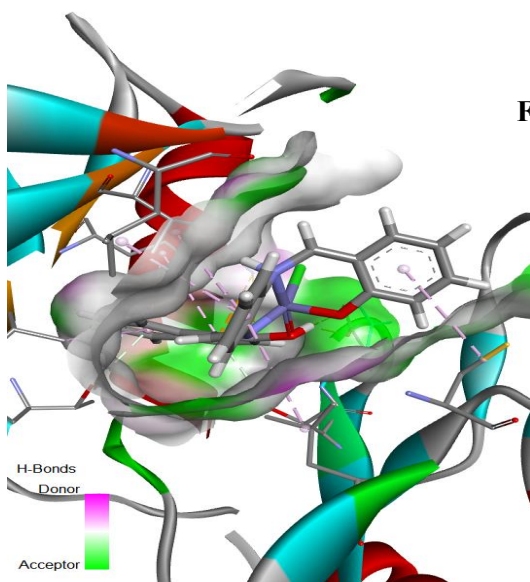
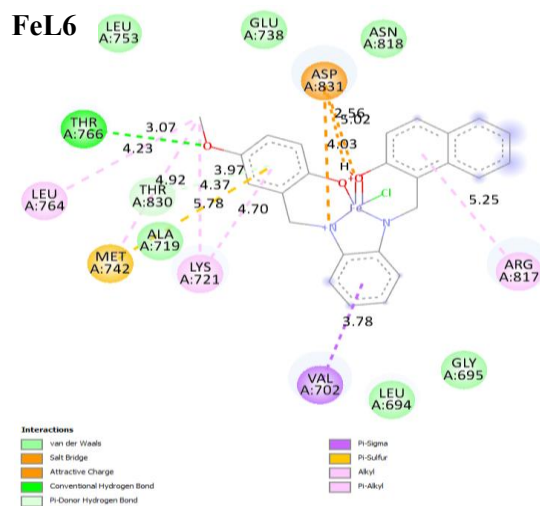
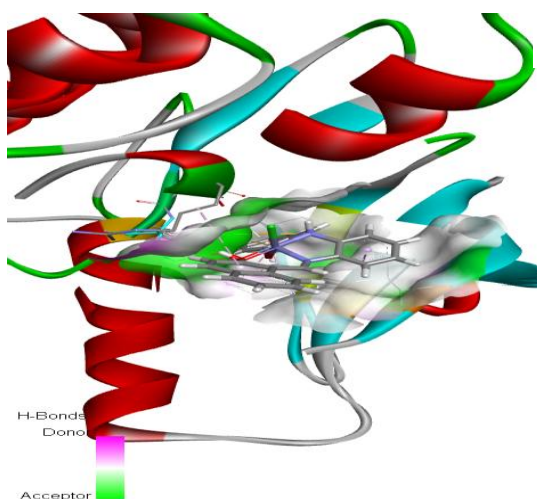
Fig. 2. Correlation between the binding free energy calculated from experimental inhibitory data ΔG_{exp} and docking scores (ΔG_{dock})

Among the studied complexes, FeL1 was the most active against KB cells (IC₅₀ = 0.81 μM) and good activity against HepG2 (IC₅₀ = 3.18 μM), whereas FeL6 was the most potent on HepG2 (IC₅₀ = 1.87 μM) and strong activity on KB (2.61 μM). These trends are consistent with the experimental binding free energies (ΔG_{exp}) and docking scores (ΔG_{dock}), where the most active compounds display the most negative ΔG_{exp} as well as ΔG_{dock} values. A reasonably linear correlation was obtained between ΔG_{exp} and the docking scores (ΔG_{dock}), particularly for HepG2 with a Pearson correlation of R = 0.95 and R² = 0.8984, indicating that the docking protocol reproduces the experimental data very well for this cell line. The moderate correlation observed for KB with R = 0.71 and R² = 0.5098 still supports the predictive value of the docking calculations to rationalize the observed cytotoxicity and to optimize the synthesis of new inhibitors from this series. The docking score of HepG2 cells exhibited a better correlation with the experimental binding free energy than that of KB cells. The EGFR tyrosine kinase has been reported to regulate proliferation and migration in hepatocellular carcinoma cells, including HepG2 cells which may account for the higher correlation [11]. In contrast, the more complex cellular response in KB cell line, including altered EGFR expression, multidrug resistance, and other cellular factors may resulted the weaker correlation of this cell [12]. Moreover, in vitro cytotoxicity of these complexes may also be influenced by several factors such as binding affinity, cellular uptake, membrane permeability, intracellular metabolism.

The relationship between structure and cytotoxic activity of the synthesized Fe(III) complexes were further investigated by molecular docking analysis. The binding orientations and interaction profiles of Fe(III) complexes within the active site of EGFR tyrosine kinase were recorded. The results are presented in Table 2 and Fig 3.

Table 2. Main interactions of the studied Fe(III) complexes and the native ligand (erlotinib) with the EGFR receptor

Entry	Hydrogen bond(s)	van der Waals / hydrophobic interactions	Electrostatic interactions	Remark/Total interactions
FeL1	π -donor H-bonds: Thr830 (3.91 Å), Thr766 (3.27 Å)	π -alkyl: Cys773 (4.64 Å), Ala719 (4.82 Å), Leu820 (5.42 Å), Leu694 (4.71 Å), Val702 (5.13 Å), Lys721 (3.98 Å); vdW: Glu738, Leu764, Met769, Gly695	Asp831: salt bridge (3.22 Å), attractive charge (4.35 Å); Lys721: π -cation (4.91 Å), attractive charge (4.58 Å)	FeL1 formed 16 interactions in total, including 2 H-bond interactions, 10 vdW/hydrophobic contacts, and 4 electrostatic interactions.
FeL2	C-H bond: His781 (3.22 Å)	π -alkyl: Leu694 (4.41 Å, 4.84 Å), Leu820 (5.19 Å); π - π T-shaped: Phe771 (5.46 Å); π -sigma: Gly772 (3.74 Å); vdW: Glu780, Tyr777, Met769, Lys704	-	FeL2 formed 10 interactions in total, including 1 carbon hydrogen-bond-related interaction and 9 vdW/hydrophobic contacts.
FeL3	Conventional H-bond: Leu694 (1.94 Å)	π -alkyl: His781 (4.95 Å), Tyr777 (4.98 Å), Val702 (5.00 Å, 4.53 Å); π -sigma: Leu694 (3.65 Å); π -sulfur: Cys773 (5.71 Å); vdW: Glu780, Asp776, Gly695, Lys704	-	FeL3 formed 12 interactions in total, including 1 conventional hydrogen bond and 11 vdW/hydrophobic contacts.
FeL4	Conventional H-bond: Leu694 (1.93 Å)	π -alkyl: Tyr777 (5.12 Å), His781 (5.03 Å), Val702 (4.93 Å, 4.56 Å); π -sigma: Gly772 (3.97 Å), Leu694 (4.19 Å); π -sulfur: Cys773 (5.64 Å); vdW: Glu780	-	FeL4 formed 11 interactions in total, including 1 conventional hydrogen bond and 10 vdW/hydrophobic contacts.
FeL5	-	π -alkyl: Val702 (5.20 Å, 5.08 Å); π -sigma: Leu694 (3.66 Å), Gly772 (3.40 Å); π -sulfur: Cys773 (3.71 Å); vdW: Lys721, Met769, Gly695, Asp776, Tyr777	-	FeL5 formed 10 interactions in total, including 10 vdW/hydrophobic contacts.
FeL6	Conventional H-bond: Thr766 (3.07 Å); π -donor H-bond: Thr830 (4.92 Å)	Alkyl: Leu764 (4.23 Å); π -alkyl: Lys721 (4.70 Å), Arg817 (5.25 Å); π -sigma: Val702 (3.78 Å); π -sulfur: Met742 (5.78 Å), Ala719 (3.97 Å); vdW: Leu753, Glu738, Asn818, Leu694, Gly695	Asp831: salt bridge (2.56 Å), attractive charge (5.02 Å, 4.03 Å); Met742: attractive charge/contact (4.37 Å)	FeL6 formed 16 interactions in total, including 2 H-bond-related interactions, 10 vdW/hydrophobic contacts, and 4 electrostatic interactions.
Erlotinib	Conventional H-bond: Cys773 (3.18 Å); C-H bond: Gln767 (3.70 Å)	Alkyl / π -alkyl: Leu764 (4.18 Å), Val702 (5.27 Å), Lys721 (4.09 Å, 4.55 Å), Leu820 (4.69 Å), Ala719 (3.97 Å); π -sigma: Leu694 (3.52 Å); vdW: Glu738, Thr766, Asp831, Met769, Leu768	-	Erlotinib formed 14 interactions in total, including 2 H-bond-related interactions and 12 vdW/hydrophobic contacts.



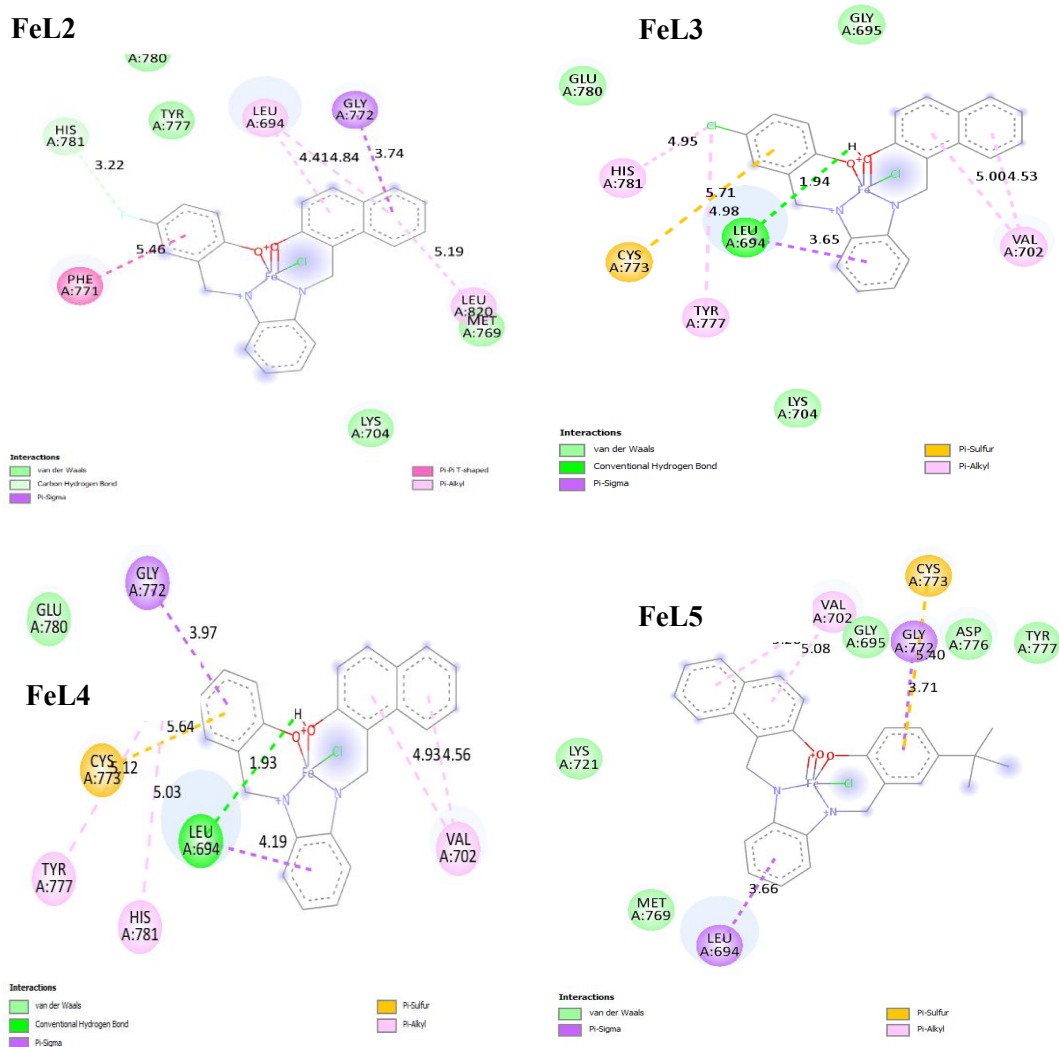


Fig 3. The 3D and 2D interactions of the studied Fe(III) complexes with the EGFR receptor

Based on the docking results, the studied Fe(III) complexes were divided into two groups. Group I included FeL1 and FeL6 showing higher cytotoxicity than the remaining complexes in Group II. In Group I, FeL1 and FeL6 showed the lowest docking scores, -6.9 and -7.1 kcal/mol, respectively. These complexes settle in the same orientation in the binding pocket (Fig 4). The strong bioactivity of FeL1 may be attributed to both the high number and the quality of its interactions with the receptor. Indeed, FeL1 interacted with the receptor through 16 interactions, including two π -donor hydrogen bonds, ten van der Waals/hydrophobic, and four electrostatic interactions. Notably, two important electrostatic contacts of FeL1 with Asp831 and Lys721 were observed. The interaction with Asp831, including a salt bridge and attractive charge interactions, contributed to the stabilization of FeL1 in the binding pocket and strengthened the FeL1-receptor interaction. In addition, the aromatic moiety of FeL1 was stabilized by the π -cation and attractive charge interactions with Lys721. The orientation of FeL1 inside the ATP-binding region of EGFR receptor was supported by the two π -donor hydrogen bonds with Thr830, and Thr788, along with several π -alkyl interactions involving Cys773, Ala710, Leu820, Leu694, Val702, and Lys721 residues. FeL6 also interacted with the receptor through 16 interactions, including two hydrogen bonds, ten van der Waals/hydrophobic, and four electrostatic interactions. Interestingly, FeL6 interacted with polar residues of EGFR through a conventional hydrogen bond with Thr766 and a π -donor hydrogen bond with Thr830. FeL6 formed strong electrostatic interactions with Asp831 through one salt bridge and two attractive charge interactions. In addition, the hydrophobic

interaction of FeL6 with several residues, namely Leu764, Lys721, Arg817, Val702, Met742, Ala719, Leu753, Glu738, Asn818, Leu694, and Gly695 contributed to the stabilization of this complex in the active site of EGFR receptor.

To validate docking protocol as well as to assess the docking results of the Fe(III) complexes, erlotinib was used as a control. Its docking score was -7.3 kcal/mol, and its interaction profile indicated its stabilization in the binding pocket through several important interactions with Leu764, Val702, Lys721, Leu820, Ala719, Leu694, Glu738, Thr766, Asp831, Met769, and Leu768. Therefore, FeL1 and FeL6 may be considered potential EGFR inhibitors, as they exhibited docking behavior similar to that of erlotinib.

Group II contains the FeL2–FeL5 complexes. Their structure showed different substituents on the salicylidene aromatic ring. FeL2–FeL4 contained halogen with increasing size from F to Cl and Br, which affected both the steric environment and electronic distribution of the aromatic ring. FeL5 containing a bulky tert-butyl group, which causes greater steric hindrance around salicylidene fragment. Therefore, these substituents significantly disturbed the favorable conformation of the studied ligands within the EGFR active pocket. Although several hydrophobic and van der Waals interactions are still present, the absence of a strong salt bridge and attractive charge interactions with Asp831 in this group may account for their weak cytotoxicity. This analysis indicated that the substituents on salicylic part of the studied complexes impacted ligand orientation, interaction types, and binding affinity.

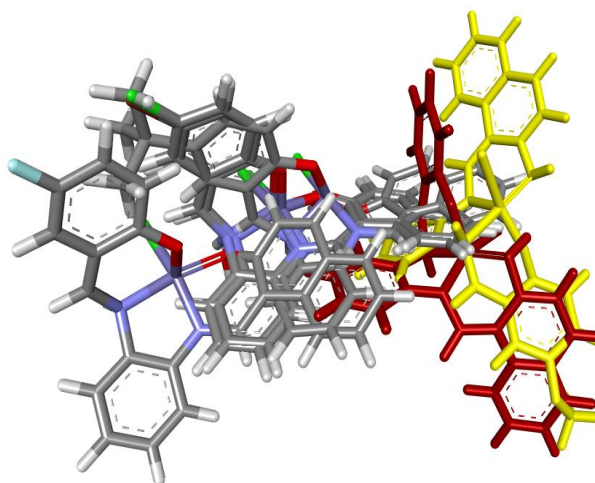


Fig 4. Binding orientation of FeL1 (red) and FeL6 (yellow) within the EGFR active site

In addition, to assess the drug-likeness and absorption potential, the physicochemical properties of FeL1 and FeL6 were further evaluated. The results are presented in Table 3 and showed a good agreement with the docking results and in vitro cytotoxicity. Both compounds satisfied the Lipinski, Veber, and Egan criteria. FeL6 violated one rule of both Ghose and Muegge filters, whereas FeL1 violated one Muegge rule. A favorable balance between solubility and membrane permeability of these complexes was reflected in the Log P values of 3.69 and 3.63 for FeL1 and FeL6, respectively.

Table 3. Physicochemical properties and drug-likeness of FeL1 and FeL6

Entry	MW	LogP	nHA	nHD	Lipinski	Ghose	Veber	Egan	Muegge
FeL1	457.71	3.69	2	0	Yes	Yes	Yes	Yes	1 violation
FeL6	487.74	3.63	3	0	Yes	1 violation	Yes	Yes	1 violation

4. CONCLUSION

In summary, the relationship between structure and cytotoxic activity of the synthesized Fe(III) complexes was investigated through molecular docking analysis. Among the studied compounds, FeL1 and FeL6 may be considered potential EGFR inhibitors based on their favorable in vitro

cytotoxicity and docking results. This suggestion was supported by their interaction profiles within the EGFR receptor, including a high number of contacts and key interactions with Asp831 residue, and low docking score. Molecular docking study also revealed that the substituents on the salicylidene moiety of the Fe(III) complexes strongly influenced ligand orientation, binding affinity, and interaction type which may directly affect the bioactivity of the studied compounds. These findings provide a basis for further structural modification of salicylidene substituents to improve EGFR-binding potential in this series.

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REFERENCES

- [1] W. Yang, Y. Hu, Y.-S. Yang, F. Zhang, Y.-B. Zhang, X.-L. Wang, J.-F. Tang, W.-Q. Zhong, and H.-L. Zhu, "Design, modification and 3D QSAR studies of novel naphthalin-containing pyrazoline derivatives with/without thiourea skeleton as anticancer agents," *Bioorganic & Medicinal Chemistry*, vol. 21, no. 5, pp. 1050–1063, 2013, doi: <https://doi.org/10.1016/j.bmc.2013.01.013>
- [2] X.-Q. Sun, L. Chen, Y.-Z. Li, W.-H. Li, G.-X. Liu, Y.-Q. Tu, and Y. Tang, "Structure-based ensemble-QSAR model: a novel approach to the study of the EGFR tyrosine kinase and its inhibitors," *Acta Pharmacologica Sinica*, vol. 35, no. 2, pp. 301–310, 2014, <https://doi.org/10.1038/aps.2013.148>
- [3] S. Agrawal, "Drug-metal complexes in research-A review," *International journal of science managemnet and engineering research IJSMER*, vol. 1, no. 1, pp. 10–11, 2016.
- [4] Z. Ghanbari, M. R. Housaindokht, M. Izadyar, M. R. Bozorgmehr, H. Eshtiagh-Hosseini, A. R. Bahrami, M. M. Matin, and M. J. Khoshkholgh, "Structure-Activity Relationship for Fe(III)-Salen-Like Complexes as Potent Anticancer Agents," *The Scientific World Journal*, pp. 1–10, 2014, doi: <https://doi.org/10.1155/2014/745649>
- [5] R. Herchel, Z. Sindelar, Z. Travnický, R. Zboril, and J. Vanco, "Novel 1D chain Fe(III)-salen-like complexes involving anionic heterocyclic N-donor ligands. Synthesis, X-ray structure, magnetic, ^{57}Fe Mössbauer, and biological activity studies," *Dalton Transactions*, no. 44, pp. 9870–9880, 2009, doi: <https://doi.org/10.1039/b912676g>
- [6] K. I. Ansari, J. D. Grant, G. A. Woldemariam, S. Kasiri, and S. S. Mandal, "Iron(III)-salen complexes with less DNA cleavage activity exhibit more efficient apoptosis in MCF7 cells," *Organic & Biomolecular Chemistry*, vol. 7, no. 5, pp. 926–932, 2009, doi: <https://doi.org/10.1039/b816858j>
- [7] Q. T. Nguyen, P. N. Pham Thi, and N. V. Tuyen, "Synthesis, spectral characterization, and in vitro cytotoxicity of some Fe(III) complexes bearing unsymmetrical salen-type ligands derived from 2-hydroxynaphthaldehyde and substituted salicylaldehydes," *Journal of Chemistry*, vol. 2021, no. 1, 2021, doi: <https://doi.org/10.1155/2021/8028064>
- [8] P. Wee and Z. Wang, "Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways," *Cancers*, vol. 9, no. 5, 2017, doi: <https://doi.org/10.3390/cancers9050052>
- [9] P. Maity, J. Chatterjee, K. T. Patil, S. Arora, M. K. Katiyar, M. Kumar, A. Samarbakhsh, G. Joshi, P. Bhutani, M. Chugh, N. S. Gavande, and R. Kumar, "Targeting the Epidermal Growth Factor Receptor with Molecular Degradable: State-of-the-Art and Future Opportunities," *Journal of Medicinal Chemistry*, vol. 66, no. 5, pp. 3135–3172, 2023, doi: <https://doi.org/10.1021/acs.jmedchem.2c01242>
- [10] S. Almahmoud, X. Wang, J. L. Vennerstrom and H. A. Zhong, "Conformational Studies of Glucose Transporter 1 (GLUT1) as an Anticancer Drug Target," *Molecules*, vol. 24, no. 11, 2019, doi: <https://doi.org/10.3390/molecules24112159>
- [11] P. Huang, X. Xu, L. Wang, B. Zhu, X. Wang, and J. Xia, "The role of EGF-EGFR signaling pathway in hepatocellular carcinoma inflammatory microenvironment," *Journal of Cellular and Molecular Medicine*, vol. 18, no. 2, pp. 218–230, 2014, doi: <http://doi.org/10.1111/jcmm.12153>

- [12] H. Takano, K. Kohno, N. Shiraishi, S.-I. Sato, K.-I. Asoh, M. Yakushinji, M. Ono, and M. Kuwano, "Altered expression of epidermal growth factor receptor gene in a classical multidrug-resistant variant of a human cancer cell line, KB," *Japanese Journal of Cancer Research*, vol. 80, no. 4, pp. 373-379, 1989, doi: <http://doi.org/10.1111/j.1349-7006.1989.tb02322.x>

Additional information

Author contributions

Dao Thi Nhung: Methodology, Writing - review & editing; Tuyet Anh Dang Thi: Conceptualization, Writing - review & editing, Project administration, Supervision, Resources, Funding acquisition; Nguyen Quang Trung: Investigation, Formal analysis and Phan Van Thoai: Investigation.

Conflict of interest

The authors declare that they have no conflict of interest and no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript. AI tool was used only for language polishing and stylistic refinement.

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