

Proceeding Paper

In Silico Investigation of a New 4-Hydroxyquinolone Analogue as an Anaplastic Lymphoma Kinase (ALK) Inhibitor: Molecular Docking and ADMET Prediction [†]

Yousra Ouafa Bouone *, Abdeslem Bouzina and Nour-Eddine Aouf

Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Department of Chemistry, Sciences Faculty, Badji-Mokhtar-Annaba University, Box 12, Annaba 23000, Algeria; abdeslem.bouzina@univ-annaba.dz (A.B.); aoufnouredine18@gmail.com (N.-E.A.)

* Correspondence: yousra-ouafa.bouone@univ-annaba.org

[†] Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: <https://ecsoc-27.sciforum.net/>.

Abstract: In the search for new potential drug candidates acting as anticancer agents, we were interested in a small molecule derived from 4-hydroxy-2-quinolone, which is newly synthesized from the condensation of a β -enaminone and diethylmalonate under microwave irradiation. This compound was subjected to an in silico study in order to investigate its potentiality to act against lung cancer through inhibiting a tyrosine kinase: Anaplastic Lymphoma Kinase (ALK). A docking simulation was performed in the active pocket of the human ALK complexed with a commercialized anticancer agent—Entrectinib (Pdb: 5FTO)—using Schrodinger suite. The studied derivative showed good stability inside the active site with an estimated docking score equal to $-8.054 \text{ kcal}\cdot\text{mol}^{-1}$. In addition, significant interactions, similar to those formed by the co-crystallized ligand, were present in the studied compound, counting hydrogen bonds with Met1199 and Glu1197 as well as hydrophobic contacts with residues in the cavity of the ALK. Keeping in mind that the pharmacokinetic properties and the toxicity of a drug candidate are very important factors in conceiving a safe admissible therapeutic substance, we carried out an ADMET prediction for the studied molecules using SwissADME, MolSoft, and ProTox-II, which gave promising results.

Keywords: Anaplastic Lymphoma Kinase; tyrosine kinase; cancer therapy; 4-hydroxy-2-quinolone; β -enaminone



Citation: Bouone, Y.O.; Bouzina, A.; Aouf, N.-E. In Silico Investigation of a New 4-Hydroxyquinolone Analogue as an Anaplastic Lymphoma Kinase (ALK) Inhibitor: Molecular Docking and ADMET Prediction. *Chem. Proc.* **2023**, *14*, 83. <https://doi.org/10.3390/ecsoc-27-16139>

Academic Editor: Julio A. Seijas

Published: 15 November 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

A huge forward step in cancer treatment has been achieved by employing what is called targeted therapy. This therapy is based on the conception of therapeutic agents meant to inhibit specific enzymes, proteins, or receptors that are involved in tumor growth and spread [1].

Anaplastic Lymphoma Kinase, also known as ALK, is one of the tyrosine kinases considered as drug targets for lung cancer healing [2]. This receptor tyrosine kinase figures within the insulin receptor superfamily and plays a key role in several physiological functions by catalyzing the phosphorylation reaction of tyrosine residues [3]. ALK structural fusions have been revealed as oncogenic in different types of cancer including non-small cell lung cancer (NSCLC) [4]. Various ALK inhibitors were designed and developed as anti-lung cancer agents such as crizotinib, alectinib, and entrectinib [5].

4-hydroxy-2-quinolone derivatives constitute a large class of nitrogen-based heterocycles presenting different benefits in the medical area by exhibiting several biological activities [6]. This is why their synthesis has been widely reported in the literature [7].

The use of computer-aided drug design based on the structure comprising molecular docking simulation and pharmacokinetics and toxicity predictive tools showed a rising

interest in conceiving new drug candidates [8]. This is why we directed our work into synthesizing a new molecule analogous to 4-hydroxy-2-quinolone. Further, we performed a computational study covering a docking simulation with the ALK and a prediction of the ADMET properties.

2. Materials and Methods

2.1. Synthesis

2.1.1. General Procedure for the Synthesis of Compound a

The synthesis of the β -enaminone derivative was completed according to the method described by Redjemia et al. [9]

2.1.2. General Procedure for the Synthesis of Compound c

The synthesis of the studied compound was performed according to the method previously described by our group [10] involving the use of microwave irradiation and BiCl_3 as a catalyst.

4-hydroxy-7,7-dimethyl-1-propyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (Entry c). Crystal; 52% Yield; IR (KBr, cm^{-1}): 3436.45, 2970.53, 1738.49, 1658.73, 1531.01, 1454.94; $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 1.07 (s, 6H, 2 CH_3), 1.13–1.23 (m, 3H, CH_3), 1.53–1.59 (m, 2H, $\text{CH}_2\text{-CH}_3$), 2.48 (s, 2H, $\text{CH}_2\text{-C}$), 2.97 (s, 2H, $\text{CH}_2\text{-CO}$), 3.94–3.98 (m, 2H, $\text{CH}_2\text{-N}$), 5.54 (s, 1H, CH), 12.63 (s, 1H, OH); Anal. Calc. for $\text{C}_{14}\text{H}_{19}\text{NO}_3$ C, 67.45; H, 7.68; N, 5.62; Found: C, 67.40; H, 7.70; N, 5.68.

2.2. In Silico Study

2.2.1. Molecular Docking

Molecular docking study was carried out using Schrodinger suite (glide) [11] and 3D visualization using Chimera software (version 1.11.2) [12].

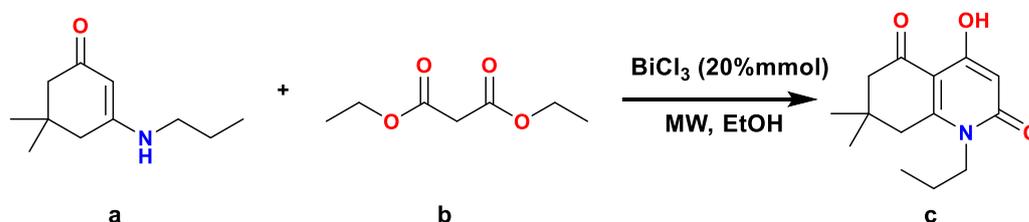
2.2.2. ADMET Prediction

The ADME parameters and drug likeness of the synthesized compound were concluded using SwissADME [13] and MolSoft [14] online servers. Moreover, a general prediction of the studied compound's toxicity was completed employing the ProTox-II online server [15].

3. Results and Discussion

3.1. Synthesis

A new modified analogue of 4-hydroxyquinolone was synthesized using the green procedure previously reported by our group [10]. The synthetic route leading to the desired compound is outlined in Scheme 1. The β -enaminone was reacted with diethylmalonate under microwave irradiation and in the presence of bismuth chloride as a catalyst.



Scheme 1. General procedure for the synthesis of a 4-hydroxy-2-quinolone analogue.

3.2. In Silico Study

3.2.1. Molecular Docking

In order to explore the binding mode of the investigated compound with the active site of ALK, we performed a docking simulation (PDB: 5FTO). The precision of the docking protocol was ensured by re-docking the reference ligand (Entrectinib) inside the cavity

of the ALK. The superimposition of the docked reference ligand and the co-crystallized one pictured in Figure 1 show that the two are in almost the same position with an RMSD equal to 0.748 Å, which validated the docking protocol using SP (standard precision) for the Glide docking calculation and prepared protein in the absence of water molecules.

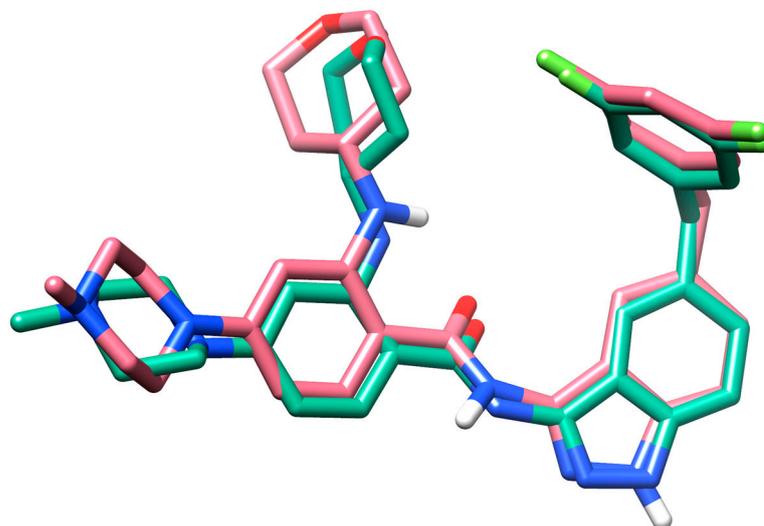
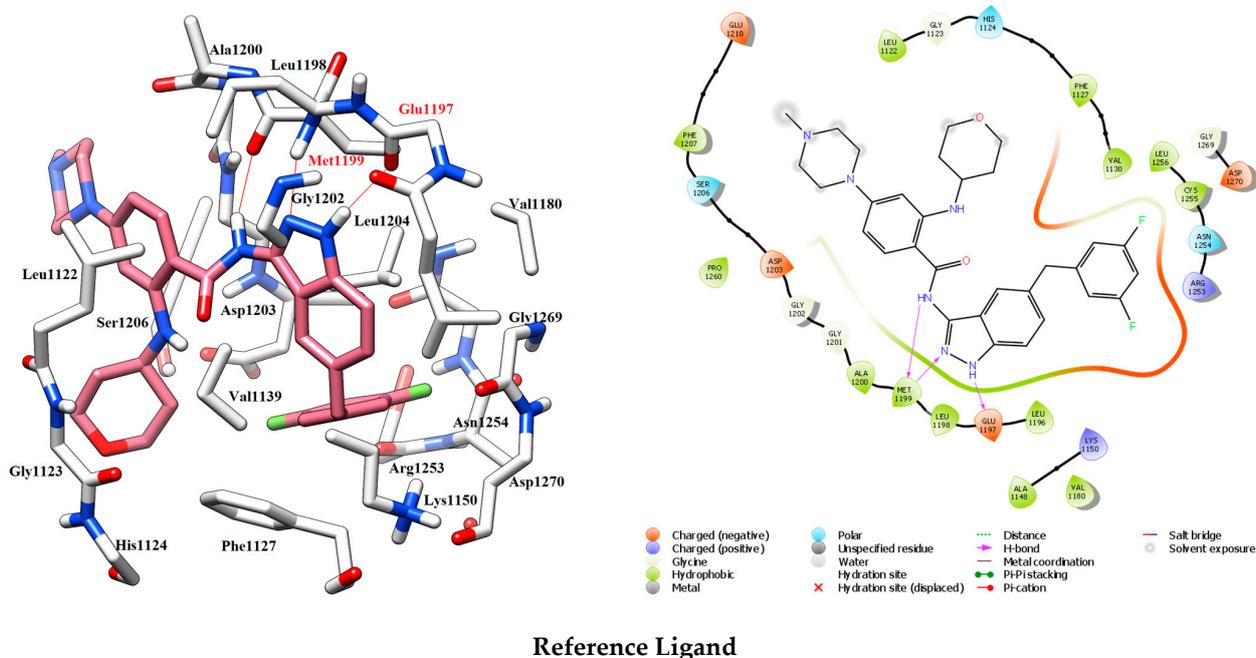


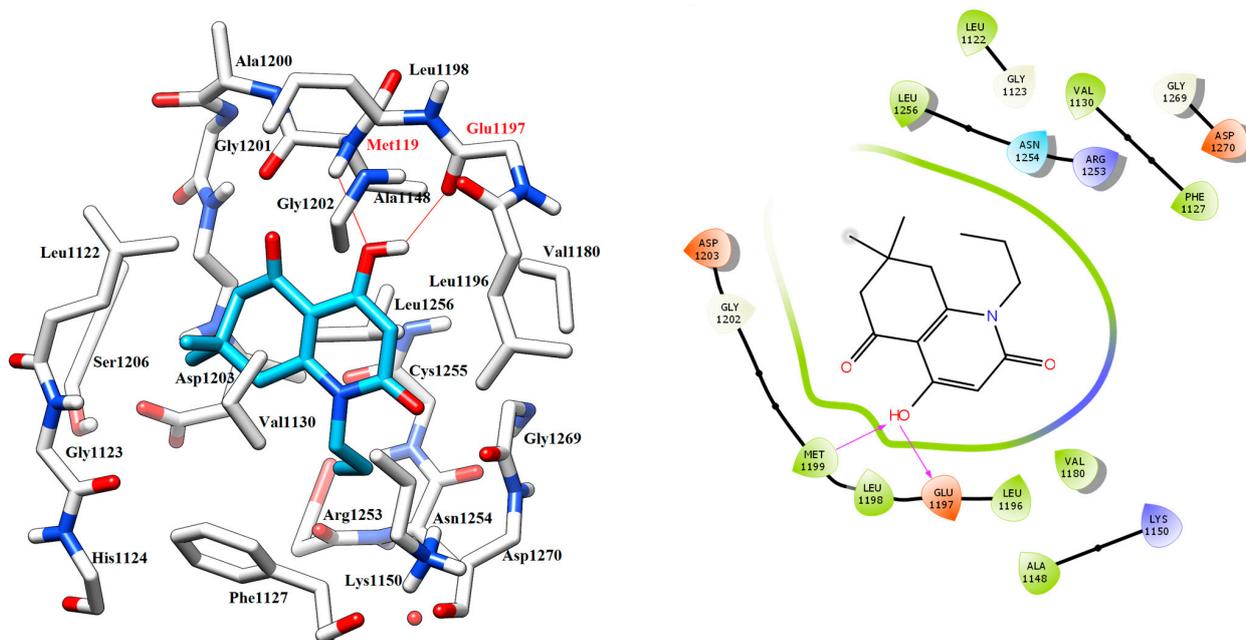
Figure 1. Superimposition of the docked reference ligand (pink) and the co-crystallized one (green).

The studied compound showed good stability inside the ALK active site with a docking score of $-8.054 \text{ kcal} \cdot \text{mol}^{-1}$ and exhibited interesting interactions with the key residues of the ALK similar to those displayed by the co-crystallized ligand, namely Met1199 and Glu1197 (Table 1). The 3D and 2D views of the co-crystallized and the synthesized ligands are shown in Figure 2.



Reference Ligand

Figure 2. Cont.



Compound c

Figure 2. 3D (left) and 2D (right) views of the ligands interactions inside the cavity of ALK.

Table 1. H-bonds and interactions of the studied compound and the reference ligand.

Compound	H-Bonds	Hydrophobic Interactions	Docking Score
c	Met1199, Glu1197.	Leu1122, Leu1256, Val1130, Phe1127, Met1199, Leu1198, Leu1196, Val1180, Ala1148.	-8.054 kcal·mol ⁻¹
Reference ligand	Met1199 (2), Glu1197.	Leu1122, Phe1127, Val1130, Leu1256, Cys1255, Phe1207, Pro1260, Ala1200, Met1199, Leu1198, Leu1196, Ala1148, Val1180.	-11.966 kcal·mol ⁻¹

3.2.2. ADMET Prediction

For the purpose of studying the potentiality of the investigated analogue of 4-hydroxy-2-quinolone in becoming a drug candidate, we performed an in silico prediction of the pharmacokinetic parameters and the toxicity ADMET using online accurate predictive tools, specifically SwissADME, MolSoft, and Protox-II.

The predicted pharmacokinetics properties are depicted in Table 2.

Table 2. Predicted pharmacokinetics properties, DLS score, and toxicity of compound c.

Properties	Compound c
Molecular weight (g per mole)	249.31
Rotatable bonds	2
H-bond donor	1
H-bond acceptor	3
Violations	0
Log $P_{o/w}$ iLOGP	2.62
Log S ESOL	-2.67
GI	High
BBB	Yes
Log Kp (cm/s)	-6.50
Bioavailability score	0.55
TPSA (Å ²)	59.30
DLS score	-0.28
Predicted LD50 (mg/kg)	1370

According to the parameters in Table 2, the studied compound respects the Lipinski's rule of five [16] with a molecular weight under 500, 3 H-bond acceptor, 1 H-bond donor, 2 rotatable bonds, and a LogP equal to 2.62. The bioavailability radar gives additional information about whether the compound is drug-like or not according to levels of polarity, solubility, saturation, lipophilicity, flexibility, and size. The bioavailability radar of the explored molecule represented in Figure 3 shows that the above-mentioned properties are within the norms (pink area). The drug likeness score describes the possibility of a compound being a drug candidate by comparing its properties with known drugs; the DLS graph (Figure 3) shows that the DLS of compound c (-0.28) is near to the drugs area (blue plot).

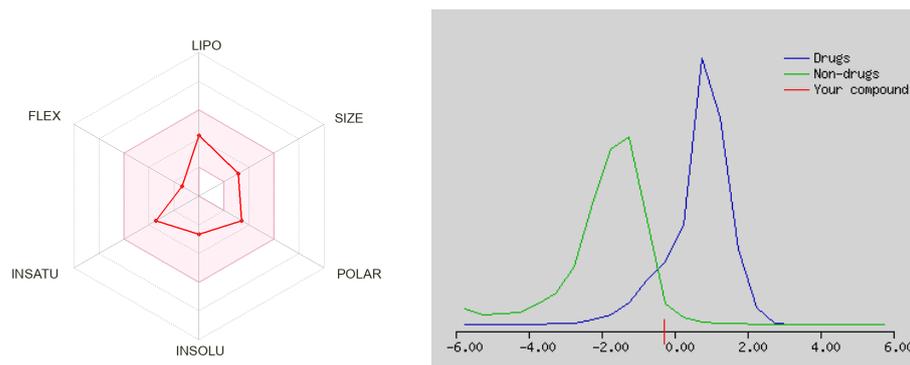


Figure 3. Bioavailability radar (left) and drug likeness estimation curve (right) of compound c.

4. Conclusions

A small heterocyclic compound, analogous to a 4-hydroxy-2-quinolone scaffold, was synthesized and was subjected to an in silico study in order to predict its aptitude to become a drug candidate for the treatment of lung cancer through inhibiting Anaplastic Lymphoma Kinase. The studied ligand showed an interesting stability inside the active site of ALK and interacted with residues that are responsible for the inhibitory activity. The results of ADMET prediction were promising as well since it appeared that the studied compound is drug-like according to the predicted pharmacokinetic properties.

Author Contributions: Conceptualization, A.B.; methodology, Y.O.B. and A.B.; software, Y.O.B. and A.B.; investigation, Y.O.B. and A.B.; writing—original draft preparation, Y.O.B. and A.B.; writing—review and editing, Y.O.B., A.B. and N.-E.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported financially by The General Directorate for Scientific Research and Technological Development (DG-RSDT), Algerian Ministry of Scientific Research, Applied Organic Chemistry Laboratory (FNR 2000).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available in this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Lee, Y.T.; Tan, Y.J. Molecular targeted therapy: Treating cancer with specificity. *Eur. J. Pharmacol.* **2018**, *834*, 188–196. [[CrossRef](#)] [[PubMed](#)]
- Shaw, A.T.; Solomon, B. Targeting anaplastic lymphoma kinase in lung cancer. *Clin. Cancer Res.* **2011**, *17*, 2081–2086. [[CrossRef](#)] [[PubMed](#)]
- Della Corte, C.M.; Viscardi, G.; Di Liello, R.; Fasano, M.; Martinelli, E.; Troiani, T.; Ciardiello, F.; Morgillo, F. Role and targeting of anaplastic lymphoma kinase in cancer. *Mol. Cancer* **2018**, *17*, 30. [[CrossRef](#)] [[PubMed](#)]

4. Shiota, M.; Fujimoto, J.; Semba, T.; Satoh, H.; Yamamoto, T. Hyperphosphorylation of a novel 80 kDa protein-tyrosine kinase similar to Ltk in a human Ki-1 lymphoma cell line, AMS3. *Oncogene* **1994**, *9*, 1567–1574. [[PubMed](#)]
5. Khan, M.; Lin, J.; Liao, G.; Tian, Y.; Liang, Y.; Li, R.; Liu, M.; Yuan, Y. ALK Inhibitors in the Treatment of ALK Positive NSCLC. *Front. Oncol.* **2019**, *8*, 557. [[CrossRef](#)] [[PubMed](#)]
6. Proisl, K.S.; Kafka, S.; Kosmrlj, J. Chemistry and Applications of 4-Hydroxyquinolin-2-one and Quinoline-2,4-dione-based Compounds. *Curr. Org. Chem.* **2017**, *21*, 1949–1975. [[CrossRef](#)]
7. Abdou, M.M. Chemistry of 4-Hydroxy-2(1H)-quinolone. Part 1: Synthesis and reactions. *Arab. J. Chem.* **2014**, *10*, S3324. [[CrossRef](#)]
8. Tabeshpour, J.; Sahebkar, A.; Zirak, M.R.; Zeinali, M.; Hashemzaei, M.; Rakhshani, S.; Rakhshani, S. Computer-aided Drug Design and Drug Pharmacokinetic Prediction: A Mini-review. *Curr. Pharm. Des.* **2018**, *24*, 3014–3019. [[CrossRef](#)] [[PubMed](#)]
9. Redjemia, R.; Bouzina, A.; Bouone, Y.O.; Mansouri, A.; Bahadi, R.; Berredjem, M. Copper (I) bromide (CuBr): A highly efficient catalyst for the synthesis of β -enaminone derivatives using ultrasound irradiation under solvent-free conditions. *Res. Chem. Intermed.* **2022**, *48*, 4947–4962. [[CrossRef](#)]
10. Bouone, Y.O.; Bouzina, A.; Sayad, R.; Djemel, A.; Benaceur, F.; Zoukel, A.; Ibrahim-Ouali, M.; Aouf, N.-E.; Bouchareb, F. BiCl₃-catalyzed green synthesis of 4-hydroxy-2-quinolone analogues under microwave irradiation. *RSC Adv.* **2023**, *13*, 28030–28041. [[CrossRef](#)] [[PubMed](#)]
11. Friesner, R.A.; Banks, J.L.; Murphy, R.B.; Halgren, T.A.; Klicic, J.J.; Mainz, D.T.; Repasky, M.P.; Knoll, E.H.; Shelley, M.; Perry, J.K.; et al. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **2004**, *47*, 1739–1749. [[CrossRef](#)] [[PubMed](#)]
12. Pettersen, E.F.; Goddard, T.D.; Huang, C.C.; Couch, G.S.; Greenblatt, D.M.; Meng, E.C.; Ferrin, T.E. UCSF Chimera—a visualization system for exploratory research and analysis. *J. Comput. Chem.* **2004**, *25*, 1605–1612. [[CrossRef](#)] [[PubMed](#)]
13. Available online: <https://www.swissadme.ch/> (accessed on 12 September 2023).
14. Available online: <https://www.molsoft.com/> (accessed on 12 September 2023).
15. Available online: https://tox-new.charite.de/prottox_II/ (accessed on 12 September 2023).
16. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.