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

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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 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 their 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 a good stability inside the active site with an estimated docking score equal to −8.054 kcal·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 to 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

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1. Introduction

Cancer treatment made a huge forward step by employing what is called targeted therapy. This latter is based on the conception of therapeutic agents meant to inhibit specific enzymes, proteins, or receptors that are involved in tumors growth and spread [1].

Anaplastic Lymphoma Kinase or 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 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]. That is what made their synthesis 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]. That 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}H-NMR (400 MHz, DMSO-d_6): δ = 1.07 (s, 6H, $2CH_3$), 1.13–1.23 (m, 3H, CH_3), 1.53–1.59 (m, 2H, CH_2-CH_3), 2.48 (s, 2H, CH_2-C), 2.97 (s, 2H, CH_2-CO), 3.94–3.98 (m, 2H, CH_2-N), 5.54 (s, 1H, CH), 12.63 (s, 1H, OH); Anal. Calc. for $C_{14}H_{19}NO_3$ 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 [12].

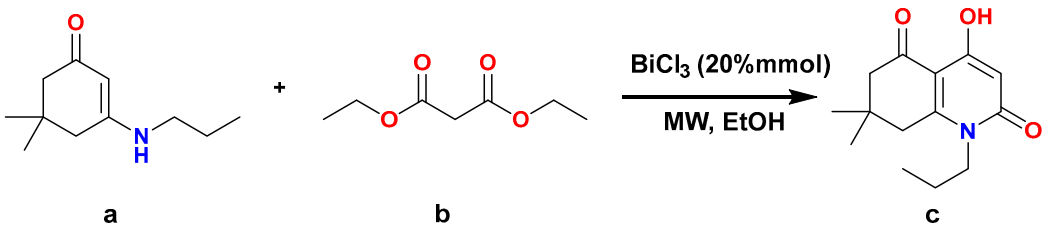
2.2.2. ADMET Prediction

The ADME parameters and druglikeness 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 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 to diethylmalonate under microwave irradiation and in presence of Bismuth Chloride as a catalyst.



Scheme 1. General procedure for the synthesis of 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). Precision of the docking protocol was ensured by re-docking of 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 shows that the two are in an almost 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 absence of water molecules.

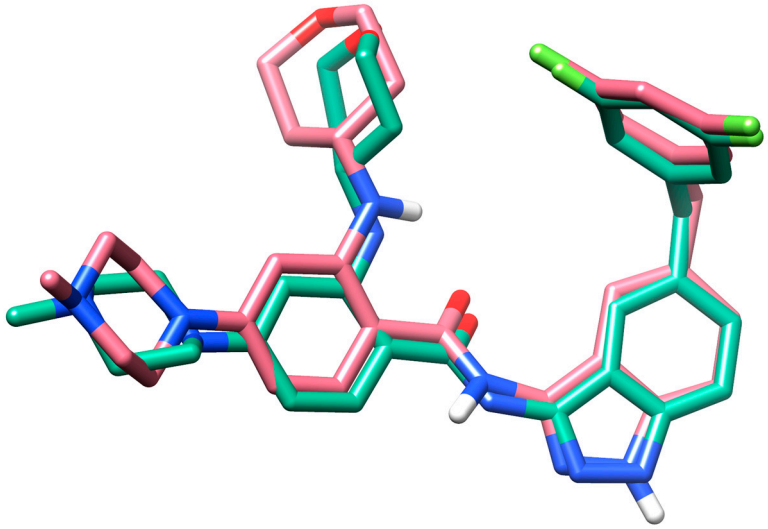
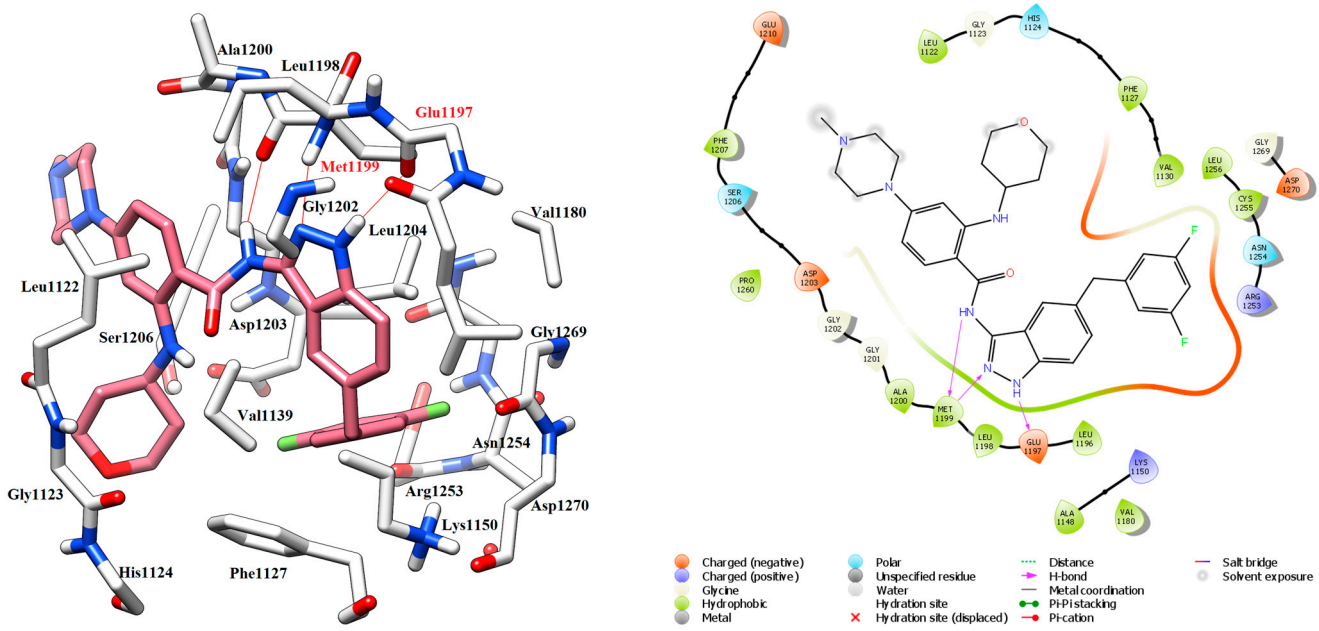


Figure 1. Superimposition of the docked reference ligand (pink) and the co-crystallized one (green).

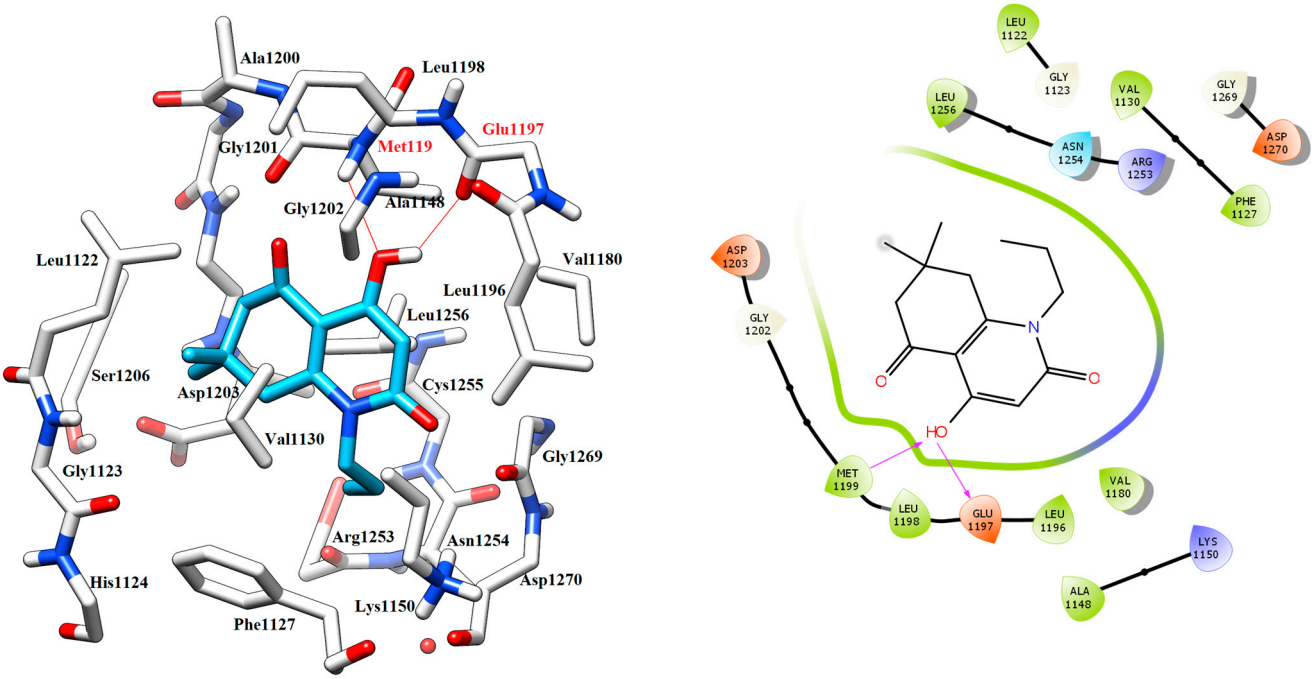
The studied compound showed a good stability inside the ALK active site with a docking score of −8.054 kcal·mol^{-1} and exhibited interesting interactions with the key residues of the ALK similar to those displayed by the co-crystallized ligand, namely Met1199 and Glu1197 (Table 1). The 3D and 2D views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

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}



Reference Ligand



Compound c

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

3.2.2. ADMET Prediction

In the purpose of studying the potentiality of the investigated analogue of 4-hydroxy-2-quinolone to become 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 an 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). Drug likeness score describes the possibility of a compound to be a drug-candidate by comparing its properties with known drugs, DLS graph (Figure 3) shows that the DLS of compound **c** (−0.28) is near to the drugs area (blue plot).

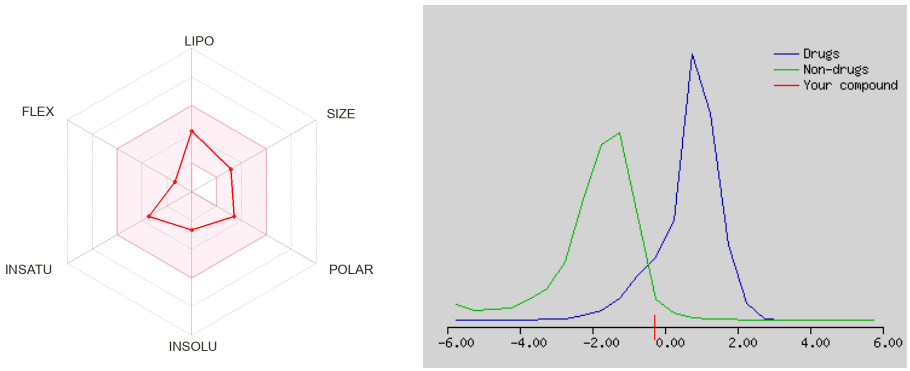


Figure 3. Bioavailability radar (**left**) and drug likeness estimation curve (**right**) of compound **c**.

4. Conclusions

A small heterocyclic compound analogous to 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 made interactions with residues that are responsible of the inhibitory activity. Results of ADMET prediction were promising as well since it appeared that the studied compound is drug-like according to the predicted pharmacokinetic properties.

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

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