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Synthesis, characterization and in silico study of novel 4-hydroxyquinolone derivative

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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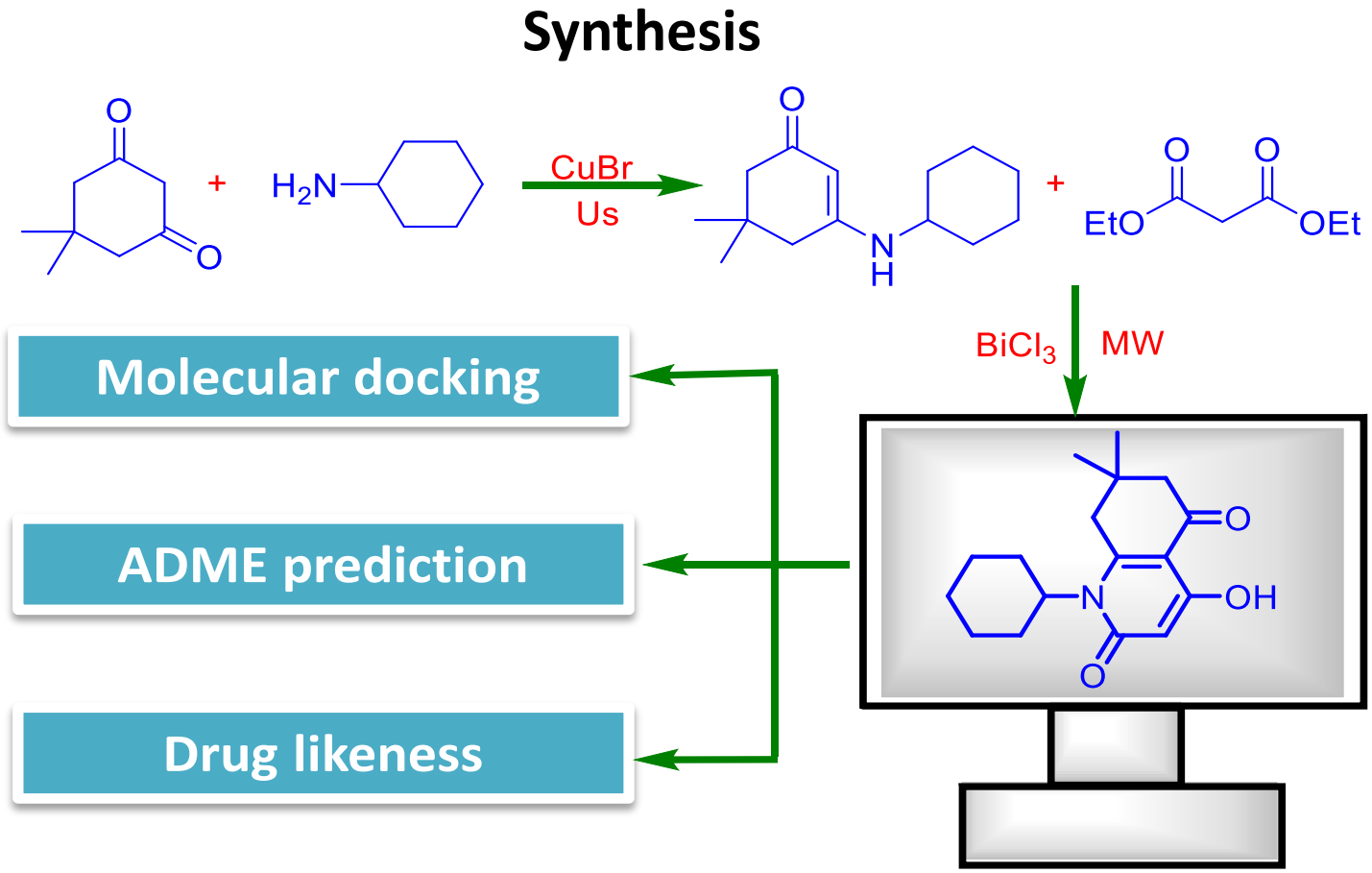
Graphical Abstract



Abstract:

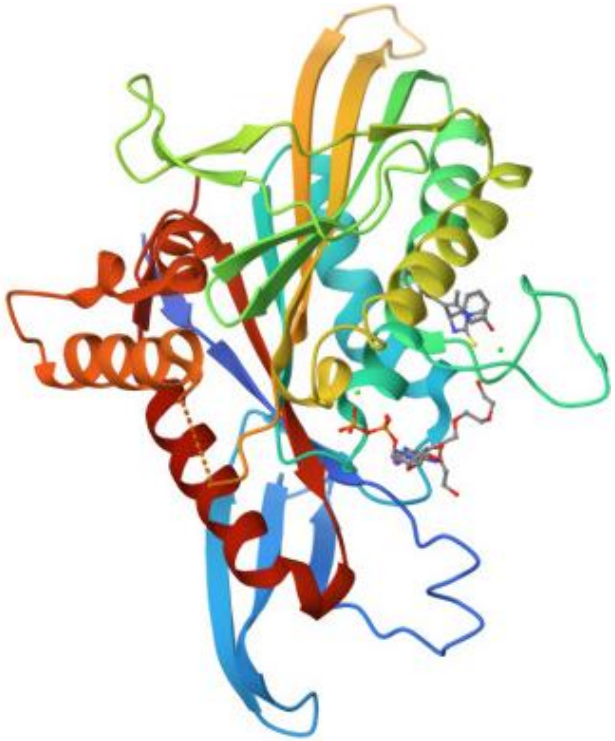
Heterocyclic chemistry plays a crucial role in drug design and the development of novel biologically active compounds. Many synthetic products with diverse pharmacological benefits feature heterocyclic structures, making them essential in the medicinal field.

One notable class of heterocycles is 4-hydroxyquinolin-2-one, which hold significant importance in medicinal chemistry. 4-hydroxyquinolin-2-ones find wide-ranging applications as therapeutic agents, exhibiting antibacterial, anticancer, antiproliferative, analgesic, antiallergenic, and antitubercular activities. They have also been identified as antagonists of the cannabinoid type 2 receptor and modulators of glycogen synthase kinase GSK-3.

To continue our research into the synthesis of new bioactive agents; we synthesized and characterized a derivative of 4-hydroxyquinolin-2-one. This synthesis involved a two-step process: initially, we produced an enaminone by condensing cyclohexylamine with dimedone, employing ultrasonic irradiation and CuBr as a catalyst. Subsequently, in the second step, we reacted the prepared enaminone with diethylmalonate, utilizing microwave irradiation. Moreover, a molecular docking study was performed to explore the binding mode of studied compound within the active site of Eg5 enzyme. The results showed a good stability of the 4-hydroxyquinoilone inside the cavity with an interesting docking score. Additionally, we conducted an in-silico investigation to predict the drug-likeness and ADME (Absorption, Distribution, Metabolism, and Excretion) properties of the compound, utilizing MolSoft and SwissADME as precise predictive tools.

Keywords: 4-hydroxyquinolone, docking study, green synthesis, ADME analysis.

Introduction

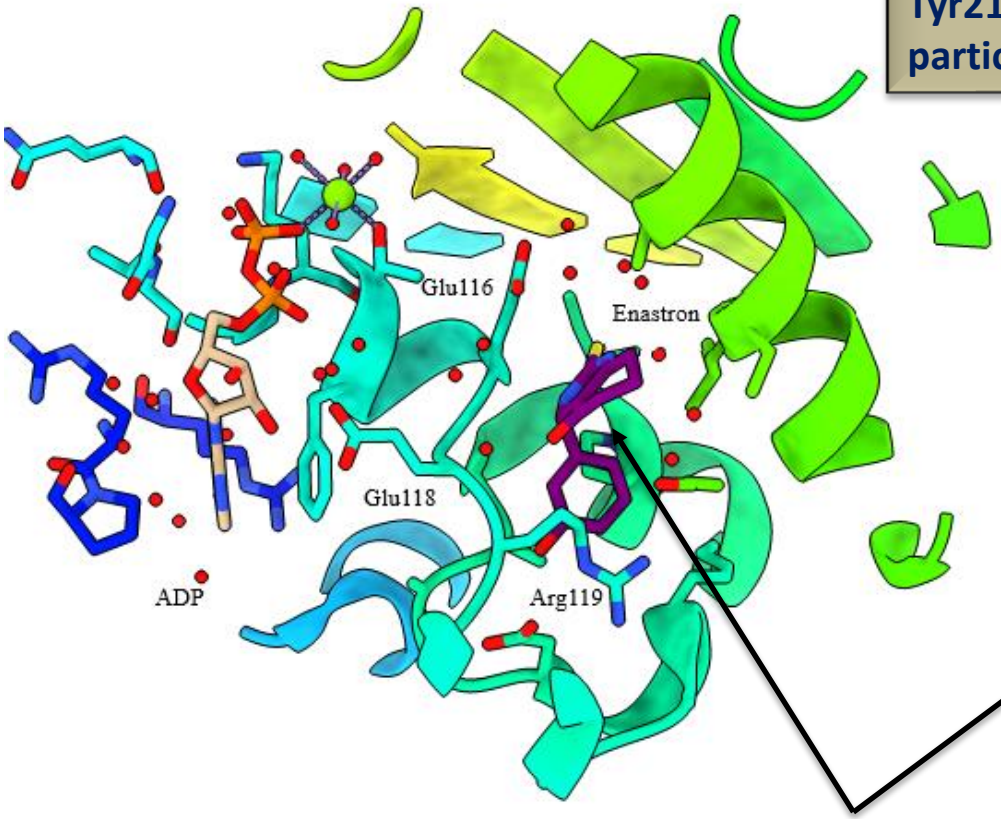


kinesin spindle protein KSP (Eg5)

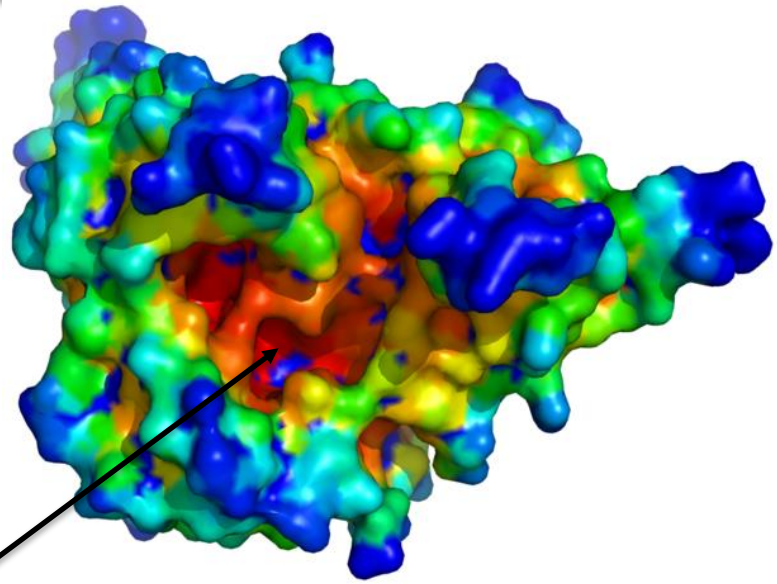
The kinesin spindle protein (KSP) also known as Eg5 enzyme, a member of the kinesin superfamily found in various tissues like testis, thymus, tonsils, and bone marrow, is one of the interesting targets for *cancer chemotherapy drug development*. Eg5 plays a key role during the mitotic phase of cell division by forming bipolar spindles. An overexpression of this enzyme is observed in solid tumors and leukemia. Eg5 inhibition can result in stopping mitosis and causing apoptosis of cancer cell lines.

Introduction

Key Interactions: Glu118 and Glu116 engage in hydrogen bonding, while Pro137, Leu214, Trp127, Tyr211, Ala118, Ile136, Ala133, and Leu132 participate in hydrophobic interactions



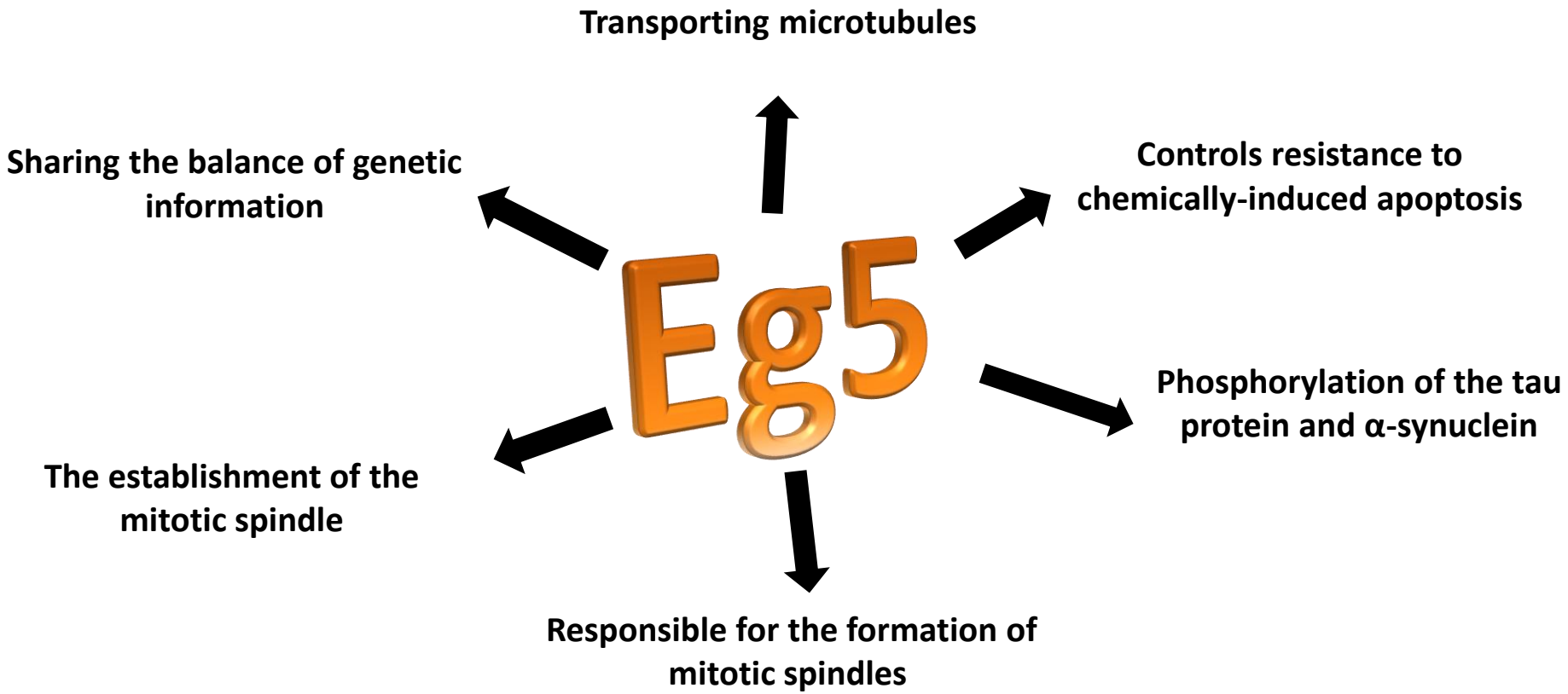
Active site of Eg5 enzyme



Electrostatic Eg5 enzyme

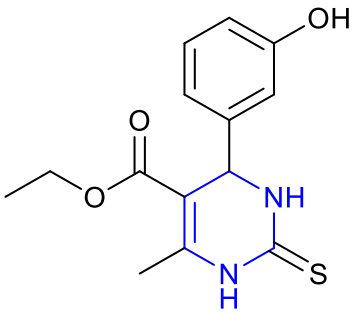
Introduction

Therapeutic target

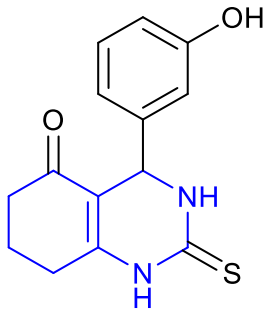


Introduction

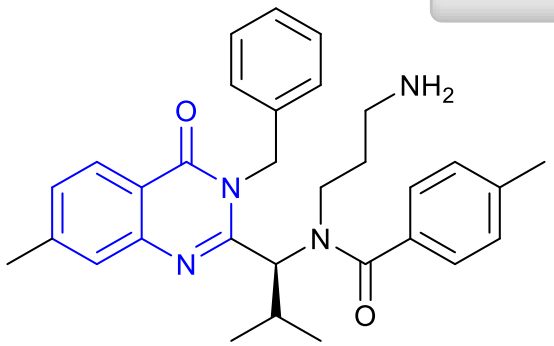
Monastrol



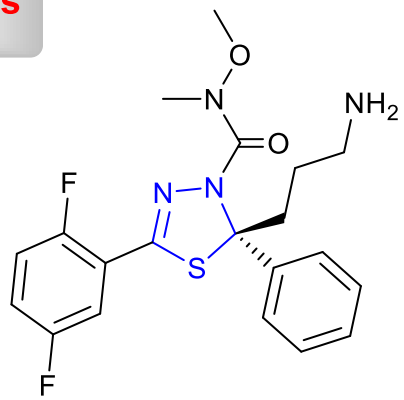
Enastron



Eg5 inhibitors



Ispenisib



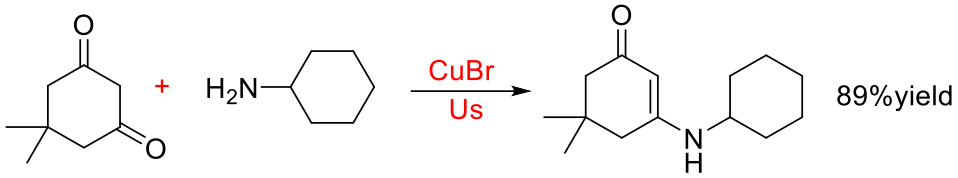
Filanesib

Results and discussion

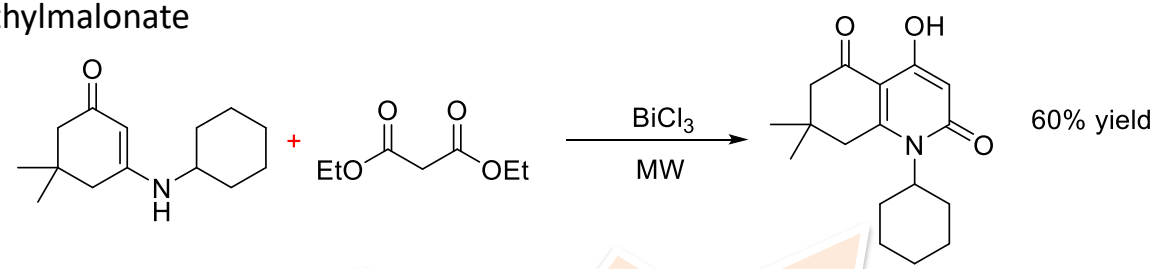
A Two Step Producere For The synthesis of 4-hydroxyquinolone derivative

The synthesis of a hydroxyquinolone derivative is accomplished in two distinct steps

The initial step involves the preparation of an enaminone



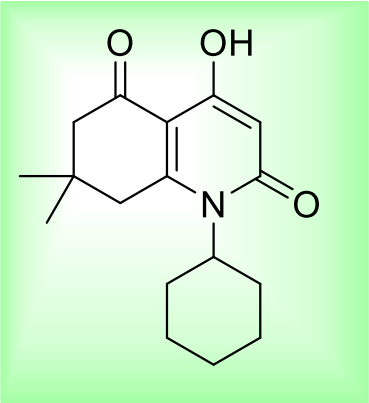
The subsequent step comprises the condensation of the prepared enaminone with diethylmalonate



A new, rapid, and environmentally friendly method for synthesizing hydroxyquinolone have being developed

Results and discussion

Structural characterization



The structures of the prepared 4-hydroxyquinolone was confirmed by spectroscopic methods (^{1}H, ^{13}C) NMR, IR, and EA.

In ^{1}H NMR spectrum, the formation of the enolic form was confirmed by a signal appearing as a singlet at 12.37 ppm. Additionally, the proton attached to the C(α) (Carbon adjacent to C(OH)) appeared as a singlet at 5.61 ppm.

^{13}C NMR spectrum exhibited signal at 95.58 ppm that indicates the C(α).
Carbonyl groups signals of ketone and amide functions appeared at 201.27 and 202.60 ppm.

The FT-IR spectrum showed the characteristic bands of the three functions, namely enolic OH function characterized by a stretching at 3230 cm^{-1}, ketone and amide functions confirmed by C=O stretching bands at 1647 and 1738 cm^{-1}, and C=C band absorbed at 1511 cm^{-1}.

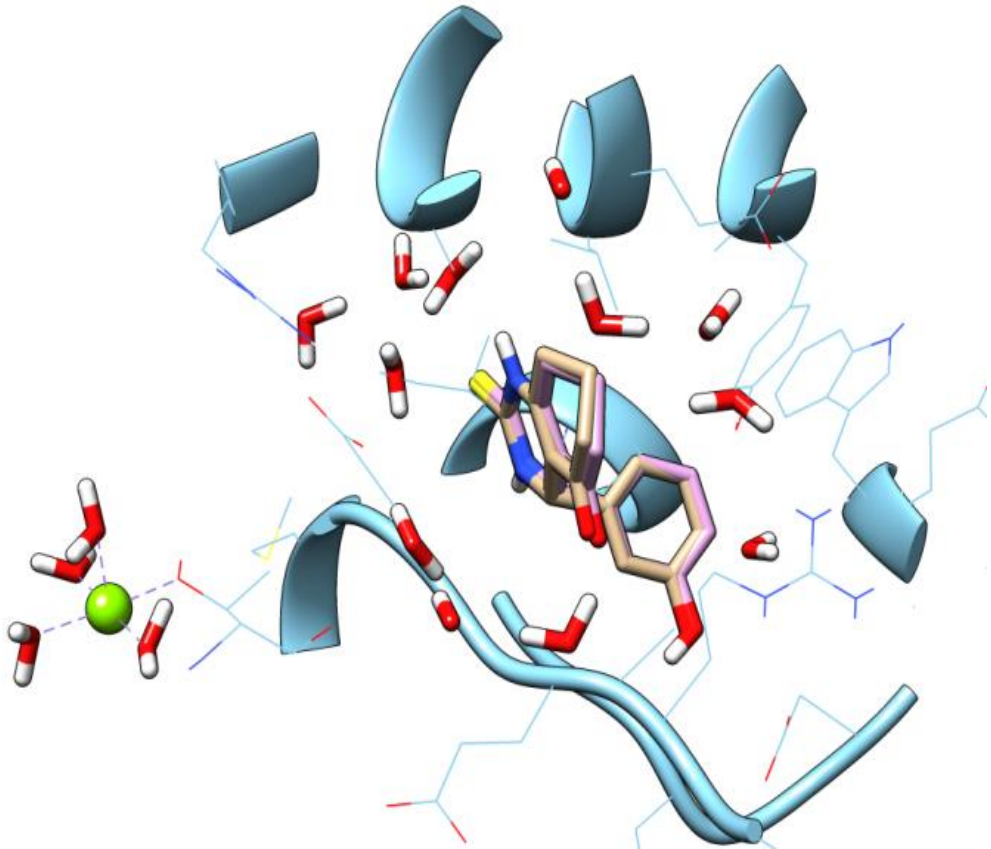
Results and discussion: *in silico* study

Molecular docking | **RSC pdb: 2X7C**

Accuracy of docking protocol was examined by re-docking of **Enastron** in the active site of kinesin spindle protein (**Eg5**).

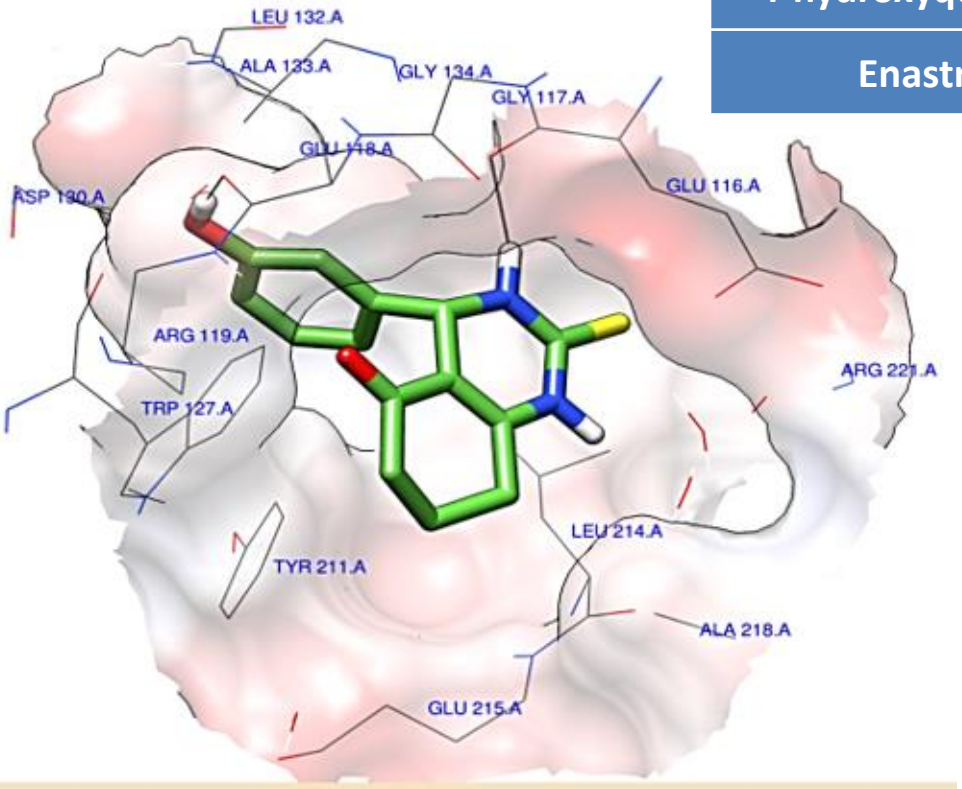
Molecular docking study was performed using *Schrodinger suite* (version 11.8) and *Chimera X* programs.

RMSD = 0.22 Å confirms validation of docking protocol using Extra Precision scoring function, in the presence of water molecules.



Results and discussion: molecular docking

	Docking score	Binding energy
4-hydroxyquinolone	-6.90	-29.69
Enastron	--9.44	-42.58

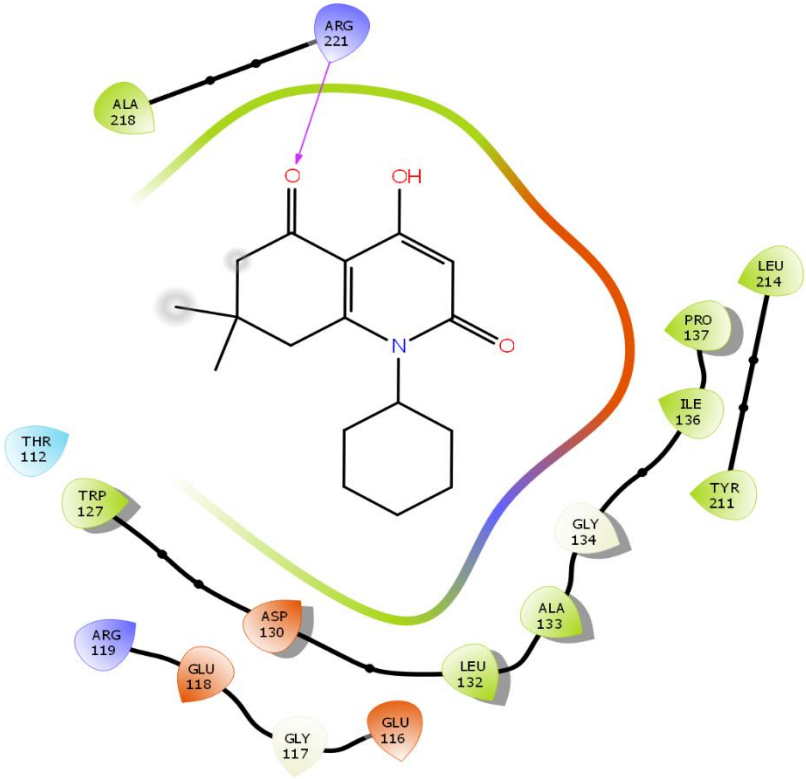


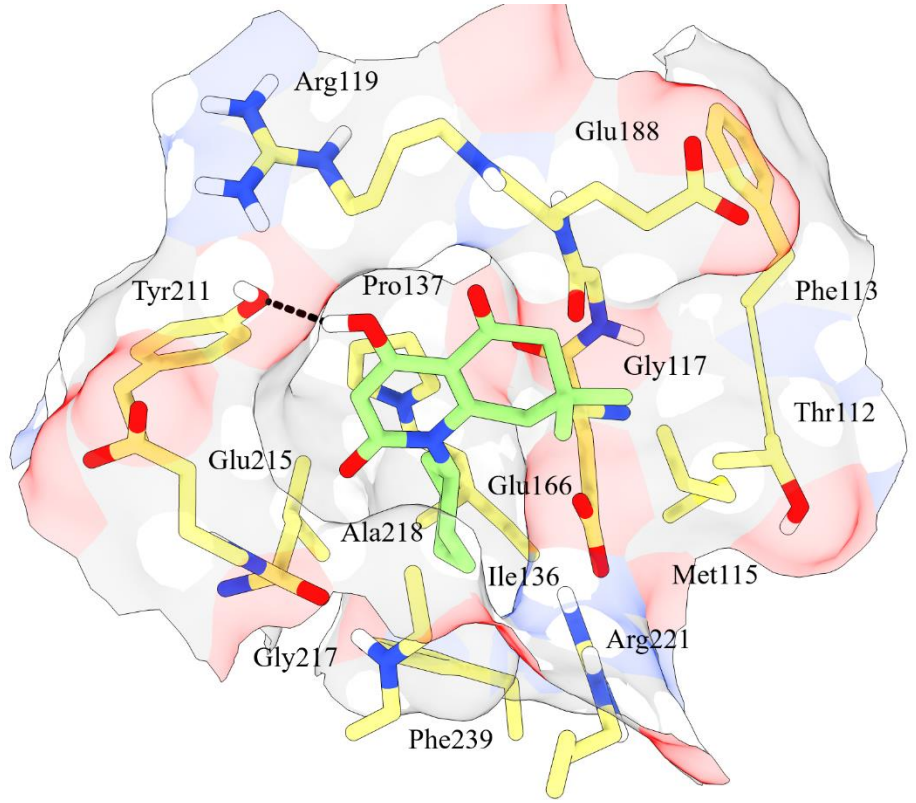
3D binding disposition of **Enastron** in the active site of Eg5. The amino acid residues were shown as wire model and H bonds were shown as black lines.

4-hydroxyquinolone was docked into the active site of Eg5, demonstrating good stability within the cavity, as evidenced by a glide score comparable to that of the co-crystallized ligand.

Two hydrogen bonds were formed between Enastron and the active site residues Glu116 and Glu118 of the Eg5 enzyme as well as hydrophobic interactions with the residueswhile Pro137, Leu214, Trp127, Tyr211, Ala118, Ile136, Ala133, and Leu132.

Results and discussion: molecular docking





Analysis of the molecular docking results showed that the interactions within the active site of Eg5 enzyme were attributed to hydrogen bond with **Tyr211** residue. Moreover, the compound developed an important hydrophobic interactions with Arg119, Pro137, phe239 and Arg221.

Results and discussion: ADME study

ADMET study

Pharmacokinetic properties and toxicity were predicted using *in silico* tool (SwissADME) and Molsoft.

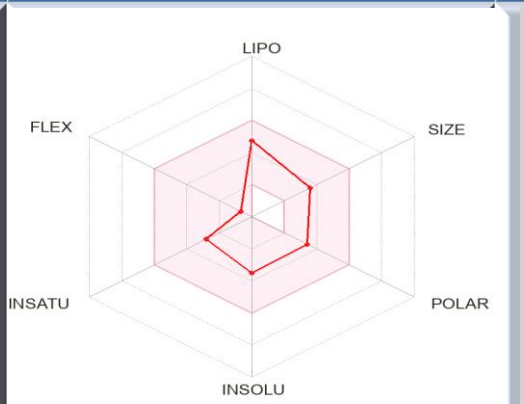
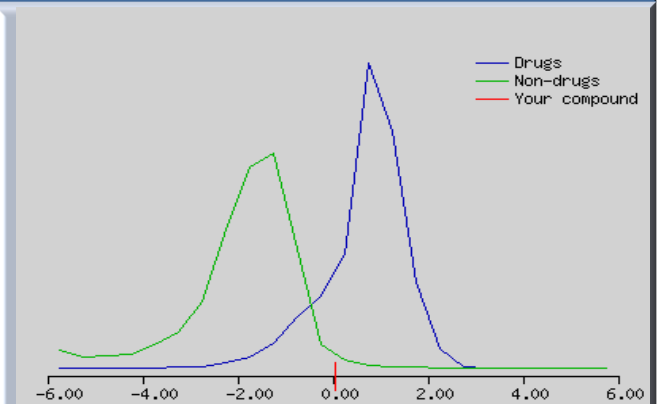
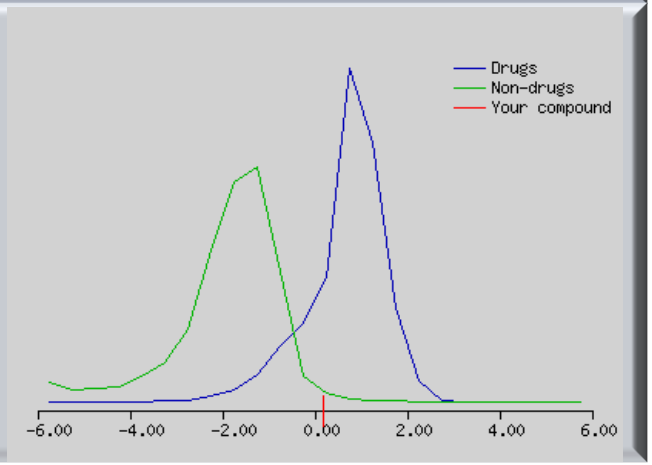
Property	4-hydroxyquinolone	Enastron
Molecular weight (g/mole)	289.37	302.39
Rotatable Bonds	1	1
H-bond donor	3	3
H-bond acceptor	1	2
Log Po/W iLogP	2.88	2.13
Log S ESOL	-3,52	-3,10
GI	High	High
BBB	No	No
Log Kp (cm/s)	-6.10	-6,75
Bioavailability Score	0.55	0.55
TPSA (Å²)	59.30	93.45
P-gp substrate	No	No

Results and discussion: ADME study

Swiss ADME and MolSoft

The Hydroxyquinolone was in the optimal range of flexibility, lipophilicity, solubility, polarity, and size.

The Hydroxyquinolone have physicochemical profiles that make it suitable for oral administration according to Lipinski, Ghose, Veber, and Egan.

	Bioavailability radar	Drug likeness
Hydroxy-quinolone		
Enastron		

Conclusion

In conclusion, we have outlined the synthesis of a novel derivative of hydroxyquinolone, which was successfully obtained in a high yield. The structure of the compound has been confirmed through spectroscopic techniques, including IR, NMR, and EA.

Furthermore, our molecular docking study revealed that hydroxyquinolone interacts with the Eg5 enzyme in satisfactory manner. The compound formed a hydrogen bond with the Tyr 211 residue.

Additionally, we conducted an evaluation of the absorption, distribution, metabolism, and excretion (ADME) properties of the synthesized compound. Our findings indicate that the compound possesses a favorable physicochemical profile, making it well-suited for oral administration according to the Lipinski, Ghose, Veber, and Egan criteria.

Acknowledgments

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