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SYNTHESIS AND BIOLOGICAL DETERMINATION OF A NEW ANTHRACENE-9,10-DIONE DERIVATIVE AS A HUMAN CK2 INHIBITOR

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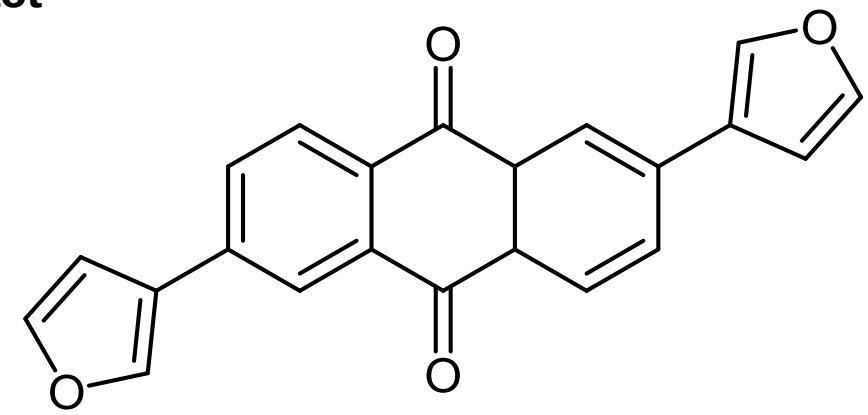
Graphical Abstract



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The chemical structure of compound 3

Abstract: Casein kinase 2 (CK2) is ubiquitous kinase protein emerging as a target for several human diseases including cancer. Several active CK2 inhibitors have been developed in the last few years; most of them have ATP-competitive type of inhibition, and only one inhibitor is in clinical trial as anticancer drug. Here we report on the synthesis of two derivatives of 2,6-diaryl-anthracene-9,10-dione, one of them, 2,6-di(furan-3-yl)anthracene-9,10-dione compound **3**, turned out to be active towards CK2, and ATP competitive with an IC_{50} value of 2.35 µM and a K_i value of 1.26 µM. Molecular modeling studies indicated that unlike emodin, compound **3** was not able to perform a hydrogen bond with Lys68, although the compound fits well in the active site of human CK2α, which explains the difference in the measured affinity between those two compounds.

Keywords: Protein kinase, CK2, Inhibitors, Synthesis, Cancer, Anthracene-9,10-dione.

Introduction

•Casein Kinase 2 (CK2) is an ubiquitous eukaryotic serine/threonine protein kinase. The human protein kinase CK2 was discovered in 1954 by Burnett and Kennedy.

•CK2 has important roles in different cellular functions, such as signal transduction, DNA repair and gene expression.

•CK2 enhances cancer phenotype by blocking apoptosis and stimulating cell growth.

•Thus, inhibition of CK2 can induce the physiological process of apoptosis leading to tumor cell death.

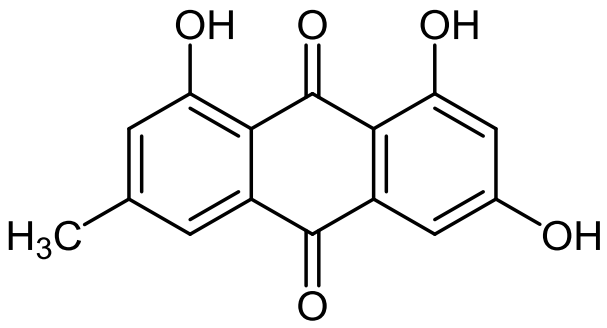
•CK2 is considered nowadays as dependable therapeutic target for the treatment of different types of cancer.

•The first known protein kinase inhibitor was described in the early 80's.

•Since then, a large number of compounds has been developed as kinase inhibitors including CK2 inhibitors.

•Most of the CK2 inhibitors contain a planar heterocyclic backbone which fits into the active site of the CK2α and competes with the ATP.

•Among the published inhibitors is emodin, which was described as an active CK2 inhibitor with a K_i value of 1.5 µM.



The chemical structure of emodin

The aim

•Modification of the structure of emodin by introducing two heterocycles in the emodin backbone with the aim to increase the inhibitory activity.

•The main idea was to explore if the furan oxygen (or pyrimidine nitrogen) can form hydrogen bonds with the amino acid residue and might have better orientation than emodin.

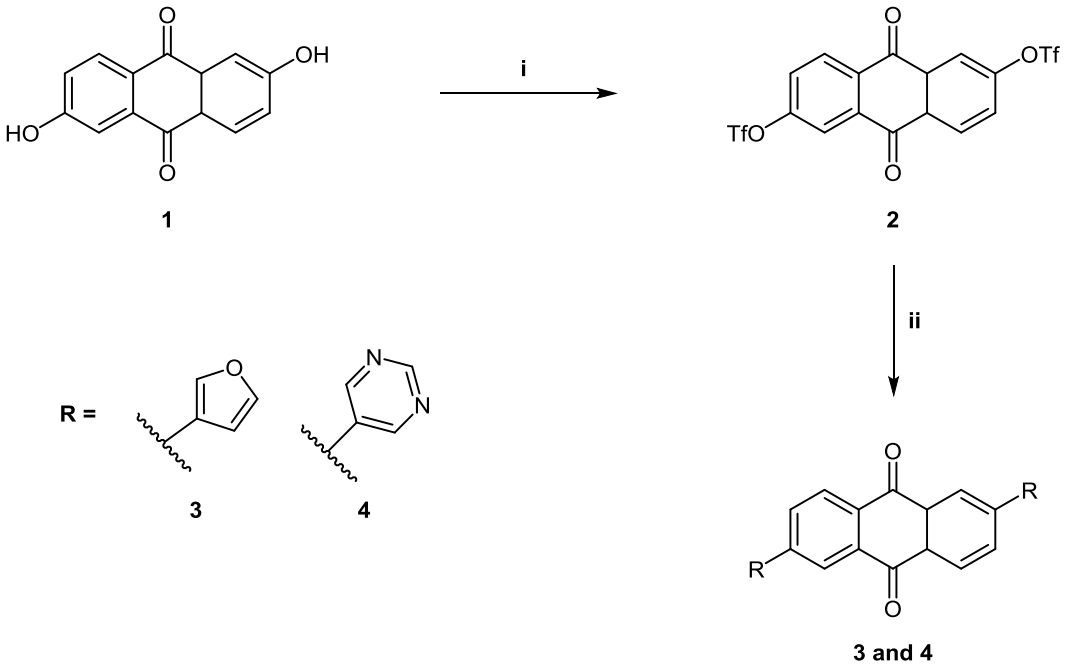
•To investigate if the aromatic furan or pyrimidine ring can form π-π interaction instead of the aromatic ring A of emodin.

Results and discussion

Two compounds were synthesized based on the 9,10-anthraquinone backbone bearing two furan or two pyrimidine rings in the 2nd and 6th positions and tested for inhibition using recombinant human protein kinase CK2.

Synthesis

The Suzuki coupling was applied for the synthesis of 2,6-diaryl-9,10-anthraquinones by transferring the 2,6-dihydroxy-9,10-anthraquinone into its bistriflate. The bistriflate was then reacted with arylboronic acids. Furan-3-boronic acid and 5-pyrimidinboronic acid were used to gain two new compounds namely 2,6-di(furan-3-yl)anthracene-9,10-dione (**3**) and 2,6-di(pyrimidine-5-yl)anthracene-9,10-dione (**4**),



i: Trifluoromethanesulfonic anhydride, Py., HCl ,
ii: arylboronic acid, Pd(PPh3)4, THF, Na_2CO_3.

Haidar et al. Pharmazie, 2015.

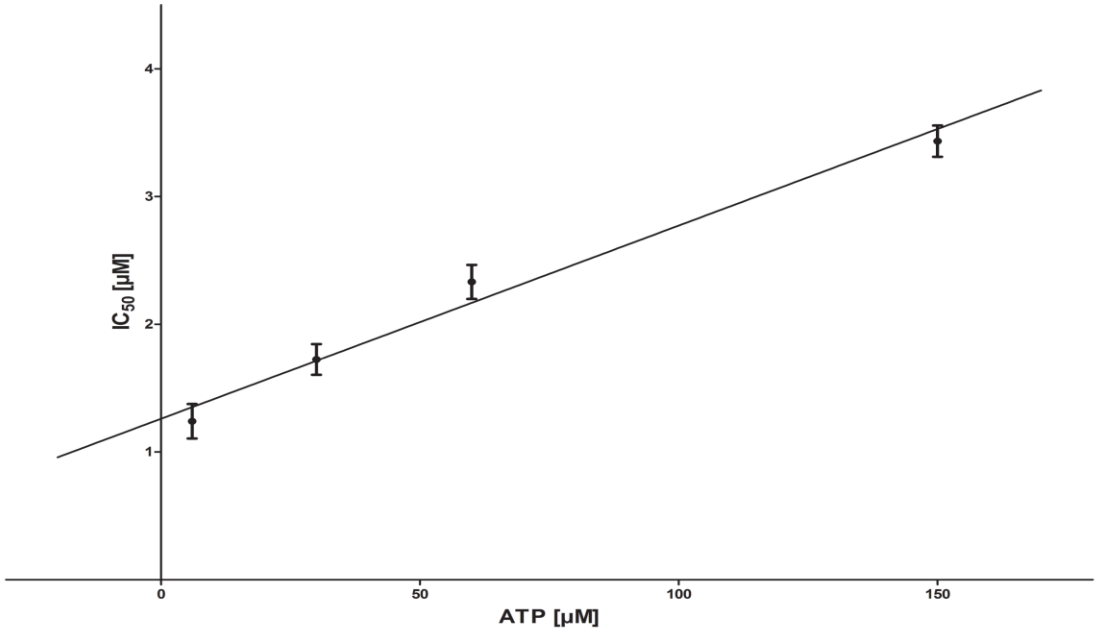
Biological Activity

The new synthesized compound 2,6 diaryl-9,10-anthraquinone (**3**) was tested for its inhibitory activity towards the human CK2 holoenzyme following the procedure described earlier by the Jose group (Gratz et al. Electrophoresis, 2010).

The IC_{50} of compound **3** turned out to be **2.35 µM.**
for comparison the IC_{50} value of emodin measured as a control was 0.58 µM.

Haidar et al. Pharmazie, 2015.

Kinetic Study: In order to validate the assumed ATP competitive mode of action for compound **3**. IC_{50} values were observed to increase linearly with the ATP concentration. This kinetic study demonstrated that compound **3** is indeed ATP competitive.



ATP-competitive inhibition of human CK2 by compound **3**. IC_{50} values were determined using nine different concentration of the inhibitor ranging from 0.001 to 50 µM and plotted against the respective ATP concentrations. The K_i value is defined as the Y-intercept and was calculated to be 1.26 µM (R^2 = 0.9299).

Haidar et al. Pharmazie, 2015.

Molecular Docking

•The crystal structure of human CK2alpha in complex with emodin (PDB code: 3C13), was used for performing the docking study using MOE.

•The original ligand of the structure was omitted and the docking simulation was performed.

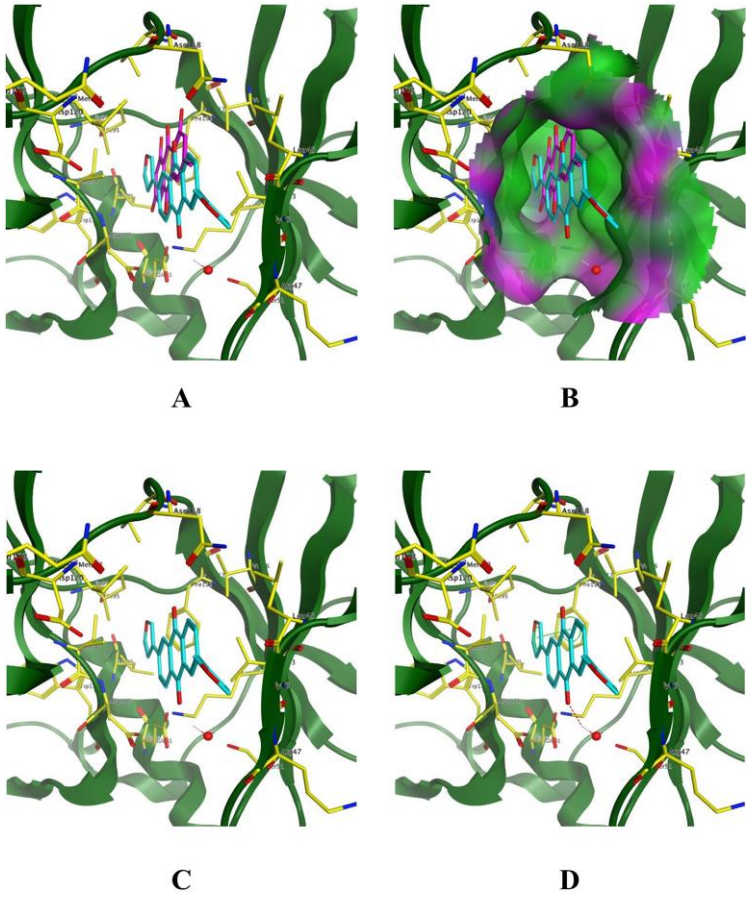
•The ligand to be docked, compound **3**, was provided in a conformational database created by the Conformations Import function in MOE.

•Triangle Matcher was chosen as the placement method and Rescoring 1 was set to London dG. Refinement was achieved by Forcefield and Rescoring 2 was set to London dG. All other parameters were kept at their default values.

Haidar et al. Pharmazie, 2015.

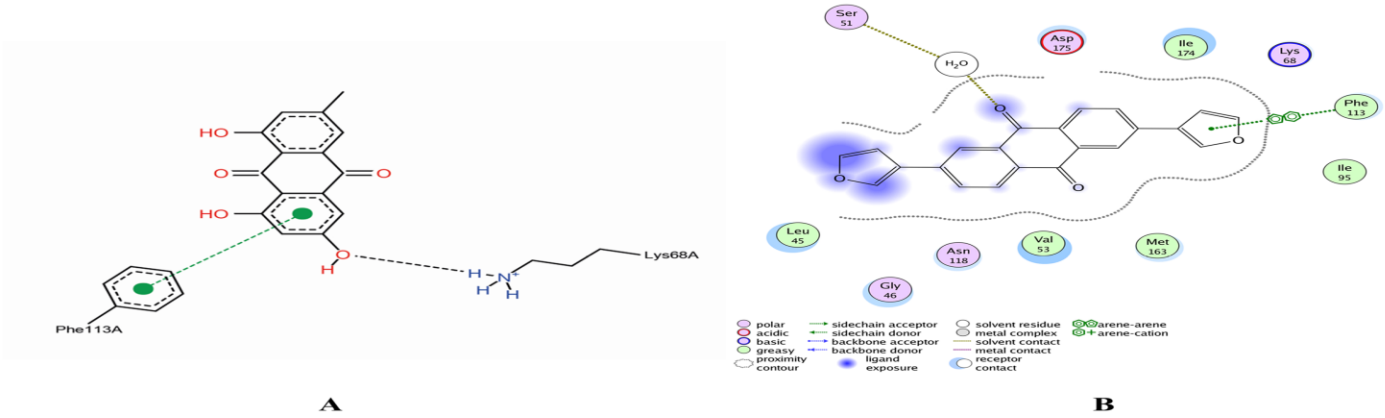
•Compound **3** fits well inside the ATP-binding pocket of human CK2, and forms π-π interactions with Phe113, as well as an indirect interaction via water molecule with Ser51 residue which may contribute to the affinity of the compound.

•Unlike emodin, compound **3** does not undergo direct hydrogen bonding with Lys68, which could be a reason for the reduced binding affinity.



A) Superimposition of the co-crystallized inhibitor emodin and the docked inhibitor **3**.
B) Illustration of the ATP-binding pocket with the two inhibitors.
C) Predicted binding mode of **3** in the ATP-binding site of human CK2 catalytic subunit.
D) Predicted interactions between **3** and the ATP binding site.

2D comparison of the interactions of emodin and compound **3** in the ATP-binding pocket of the CK2α.



A) 2D Interactions of emodin with the amino acid residues of the ATP-binding site of the human CK2α as shown in PDB.
B) Docking of compound **3** with the active site pocket of human CKα.

Haidar et al. Pharmazie, 2015.

Conclusion

• Novel compounds were synthesized and biologicaly evaluated as well as a kinetic study and modeling study were performed.

•Although compound **3** is less active than emodin depending on IC_{50}s results, it can help to further elucidate the topography of the active site of the enzyme.

• This work can be the basis for further studies to optimize the activity by preparing other derivatives.

Acknowledgments

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