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Development of Pharmacophore Model for Indeno[1,2-*b*]indoles as Human Protein Kinase CK2 Inhibitors and Database Mining

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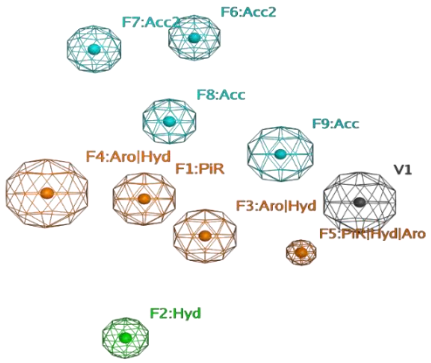
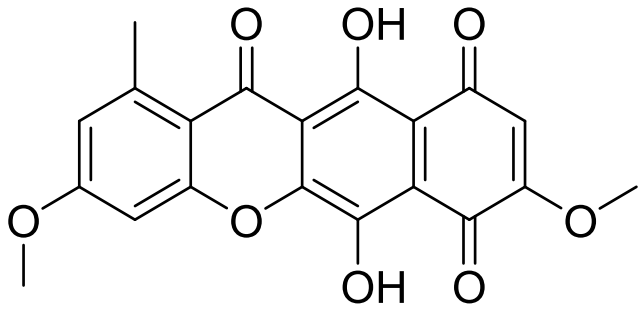
Graphical Abstract



Common feature pharmacophore model of indenoindole CK2 inhibitors



Bikaverin, IC_{50} = 1.24 µM

Abstract:

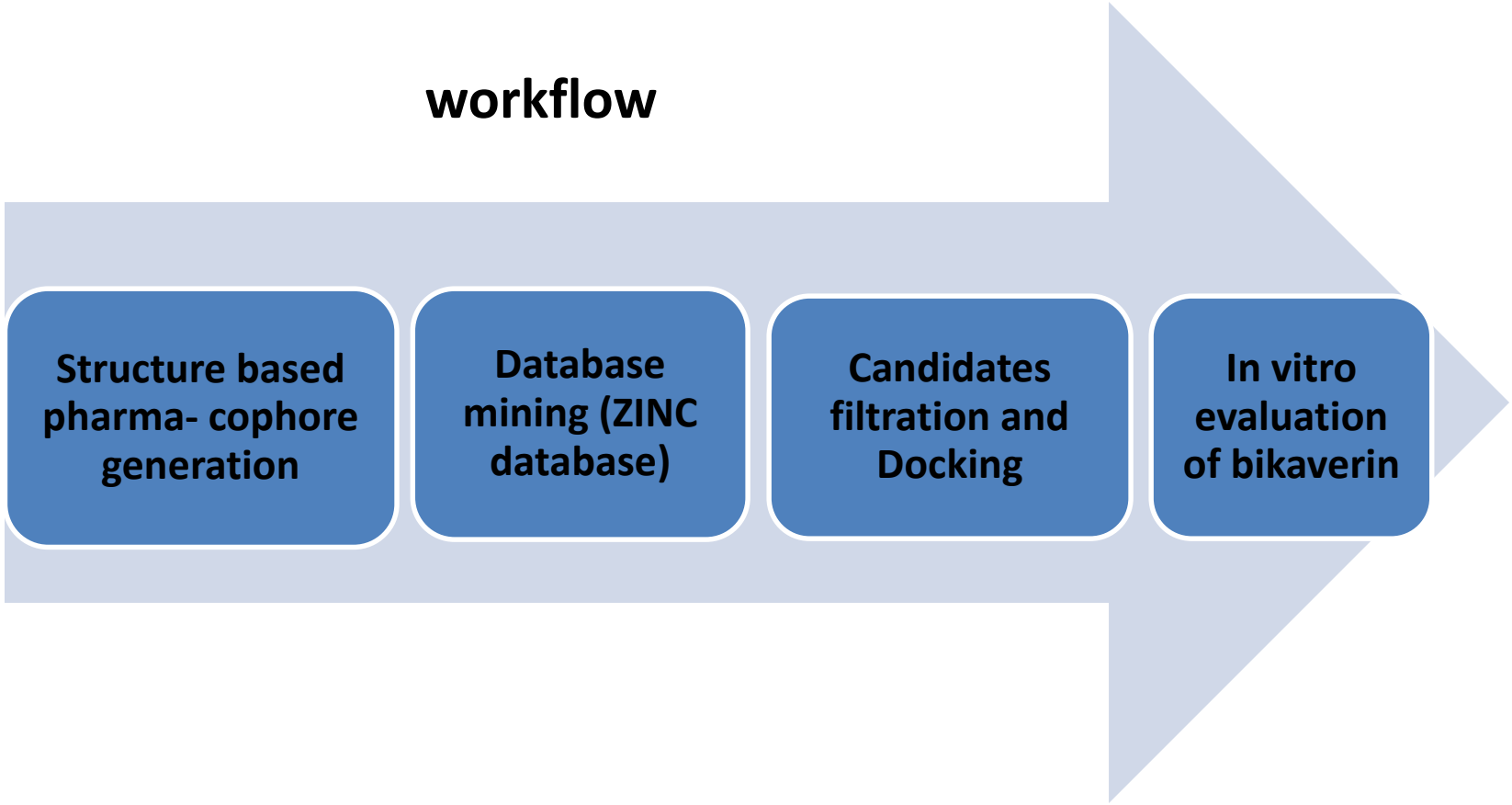
Casein kinase 2 is a ubiquitous kinase protein emerging as a target for the treatment of cancer. Several active CK2 inhibitors have been developed in the last few years; most of them have ATP-competitive type of inhibition. Indeno[1,2-*b*]indoles present a class of natural and synthetic compounds; many of them have different bioactivity. Here we report on the development of a ligand-based pharmacophore on the basis of different active Indeno[1,2-*b*]indoles (training set), the pharmacophore model was challenged against small library of Indeno[1,2-*b*]indoles (test set), the study was performed using MOE software. Our model demonstrates good performance in the test set, 85% of the medium or high inhibitory activity compounds were identified, while only 17% of the low or no inhibitory activity compounds were misclassified. Several structures were suggested as possible active CK2 inhibitors by using this model as a base for search in the ZINC database among them was bikaverin which was then further studied.

Keywords: CK2, pharmacophore, ZINC database, bikaverin.

Introduction

- CK2 is heterotetrameric holoenzyme and it is ubiquitously expressed in mammalian cells.
- CK2 enhances cancer phenotype by blocking apoptosis and stimulating cell growth.
- Inhibition of this enzyme can induce the physiological process of apoptosis leading to tumor cell death.
- Different Backbones were used as skeleton for CK2 inhibitors, among them Indeno[1,2-*b*]indoles.
- Molecular modeling is widely used nowadays for drug design and screening.
- Virtual screening of data base is considered as important tool in drug discovery to obtain large amount of data.
- One important concept in computer-aided drug design (CADD) is pharmacophore, since this method can reduced the complexity of molecular interactions between compound and target to a set of few features. Several pharmacophore screening software are available, among them is MOE which was proofed as an effective tool.
- In this study a pharmacophore model was created and used to discover new leads by searching the ZINC database, since virtual screening based on hypothetical pharmacophore model is usually rapid and helpful method to extract leads with divers chemical structures.

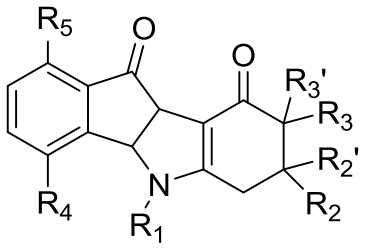
Results and discussion



Results and discussion

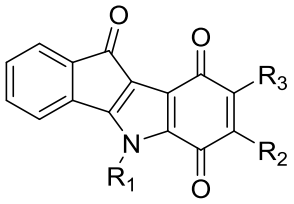
- In this work the structures of the 50 tested Indeno[1,2-*b*]indoles and their IC_{50} values are presented in the following tables.
- The pharmacophore model was based on the five most active compounds which were aligned.
- The pharmacophore was able to identify 85% of the active compounds and only four compounds from the non active compounds were also selected as false positive (17%).
- The features of this model were used to search the ZINC database. 55 compounds were selected by matching most features of the pharmacophore and can be considered as hit compounds.
- Docking study was performed to select the best candidates, and the 3D X-ray crystallography structure of CK2 from PDB ID (3C13) was used.
- The top three ranking conformations with minimum S score were selected after visual 2D control.
- One selected candidate was **bikaverin** which is a reddish pigment produced by different fungal species. It has diverse biological activities, such as antibiotic, antifungal and anticancer properties.

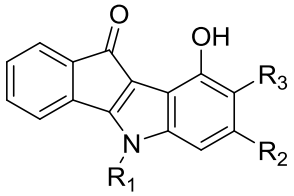
Training and test sets



Code	R_1	R_2	$R_{2'}$	R_3	$R_{3'}$	R_4	R_5	IC_{50} (μM)
1	$CH(CH_3)_2$	H	H	H	H	O-CH_2CH= C$(CH_3)_2$	H	0.025
2	$CH(CH_3)_2$	CH_3	H	H	H	H	H	0.17
3	$CH(CH_3)_2$	H	H	H	H	H	H	0.36
5	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	H	H	H	0.61
8	CH_2CH_2(ortho-OMe)Ph	H	H	H	H	H	H	1.40
9		H	H	H	H	H	H	1.44
14	$CH_2CH_2C_6H_5$	CH_3	H	H	H	H	H	2.50
18	CH_2CH_2 (para- OMe)Ph	H	H	H	H	H	H	4.10
22	CH_2CH_2 (meta- OMe)Ph	H	H	H	H	H	H	5.10
23	CH_2CH_2 $CH_2C_6H_5$	H	H	H	H	H	H	6.00
24	$CH_2CH_2C_6H_5$	H	H	H	H	H	H	7.00
26	$CH(CH_3)_2$	H	H	CH_3	H	H	H	9.20
28	$CH(CH_3)_2$	H	H	$(CH_2Ph)_2$	CH_2Ph	H	H	>10
29	CH_2(para- OMe)Ph	H	H	H	H	H	H	>10
32	$CH(CH_3)_2$	H	H	H	H	H	O-CH_2CH=C$(CH_3)_2$	>10
37	$CH(CH_3)_2$	(para-F)Ph	H	H	H	H	H	>10
39	$CH(CH_3)_2$	furan-2-yl	H	H	H	H	H	>10
40	CH_2Ph	H	H	H	H	H	H	>10
41	CH_2CH_2Ph	Ph	H	H	H	H	H	>10
43	H	CH_3	H	$COOCH_3$	H	H	H	>10
44	H	H	H	H	H	H	H	>10
45	CH_2Ph	CH_3	H	$COOCH_3$	H	H	H	>10
46	$CH(CH_3)_2$	H	H	$CH(CH_3)_2$	H	H	H	>10
47	CH_2Ph	CH_3	CH_3	H	H	H	H	>10
48	CH_2Ph	CH_3	H	H	H	H	H	>10
49	$CH(CH_3)_2$	Ph	H	H	H	H	H	>10
50	CH_2Ph	Ph	H	H	H	H	H	>10

Training and test sets

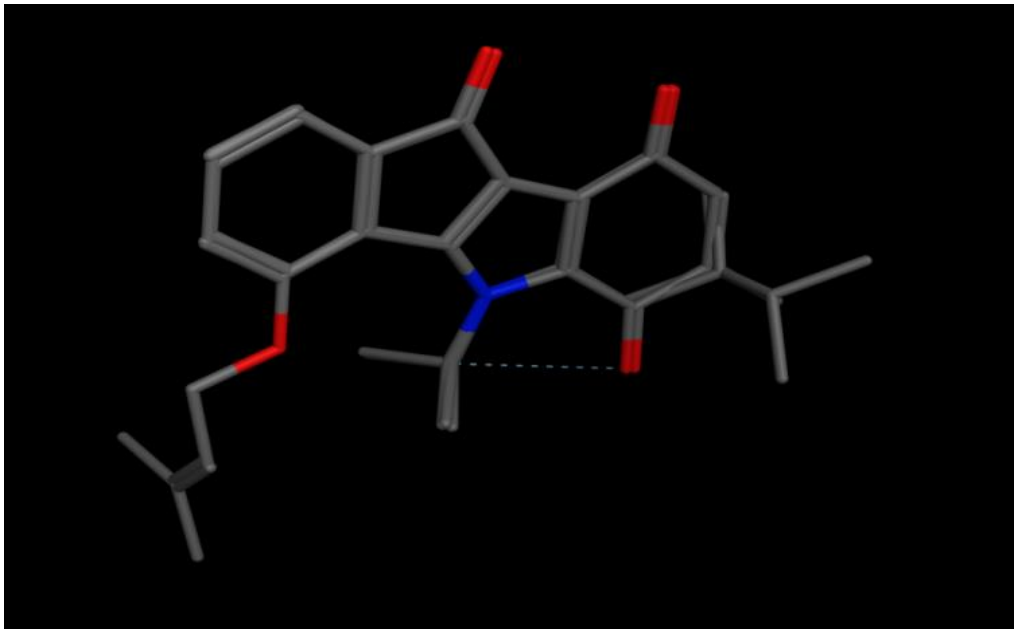




Code	R_1	R_2	R_3	IC_{50} (μM)
4	$CH(CH_3)_2$	CH_3	H	0.43
11	$CH(CH_3)_2$	furan-2-yl	H	1.65
13	$CH_2C_6H_5$	H	H	2.20
17	$CH_2CH_2C_6H_5$	CH_3,	H	4.10
19	$CH(CH_3)_2$	$CH(CH_3)_2$	H	4.76
20	$CH(CH_3)_2$	H	CH_3	4.90
21	$CH(CH_3)_2$	H	H	5.50
31	$CH(CH_3)_2$	H	$CH(CH_3)_2$	>10
34	$CH(CH_3)_2$	(para-F)Ph	H	>10
35	$CH(CH_3)_2$	Ph	H	>10
36	CH_2CH_2Ph	H	H	>10

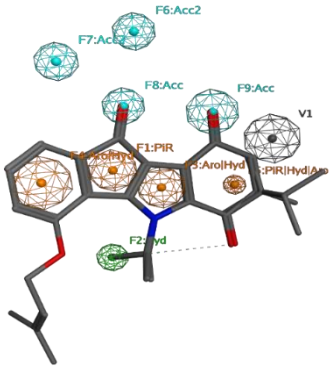
Code	R_1	R_2	R_3	IC_{50} (μM)
6	$CH(CH_3)_2$	CH_3	H	1.27
7	CH_2CH_2(ortho-OMe)Ph	H	H	1.30
10	$CH(CH_3)_2$	$CH(CH_3)_2$	H	1.65
12	$CH(CH_3)_2$	H	H	2.00
15	$CH(CH_3)_2$	(para-F)Ph	H	2.77
16	$CH(CH_3)_2$	furan-2-yl	H	3.63
25	$CH_2CH_2C_6H_5$	H	H	7.50
27	CH_2Ph	Ph	H	>10
30	$CH_2CH_2C_6H_5$	CH_3	H	>10
33	$CH(CH_3)_2$	H	CH_3	>10
38	$CH(CH_3)_2$	H	$CH(CH_3)_2$	>10
42	CH_2Ph	H	H	>10

Results and discussion

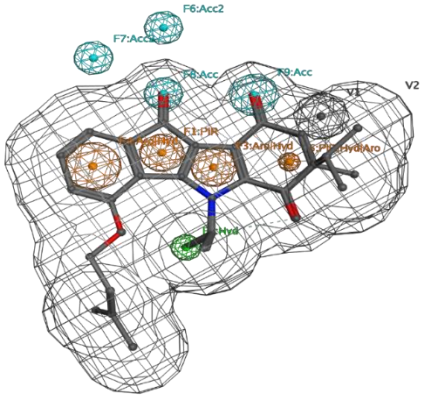


Alignment of the training set of CK2 inhibitors

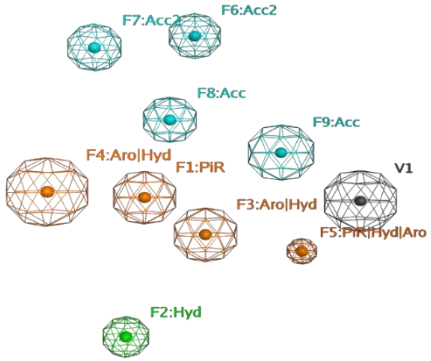
Results and discussion



(a)



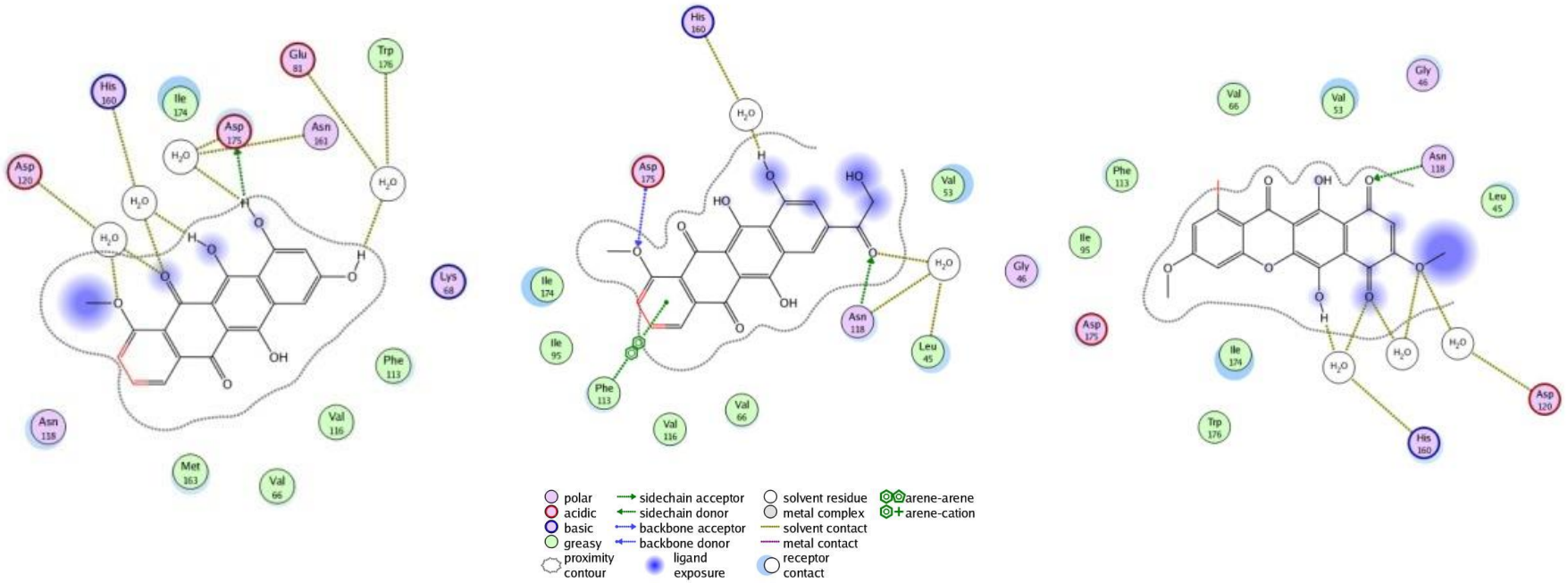
(b)



(c)

The pharmacophore model (a) Alignment of common feature pharmacophore model with training set (b) Alignment of common feature pharmacophore model with training set with occupied volume (c) Common feature pharmacophore model of indenoindole CK2 inhibitors

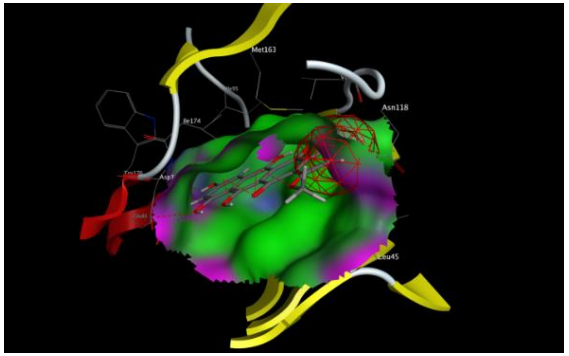
Results and discussion



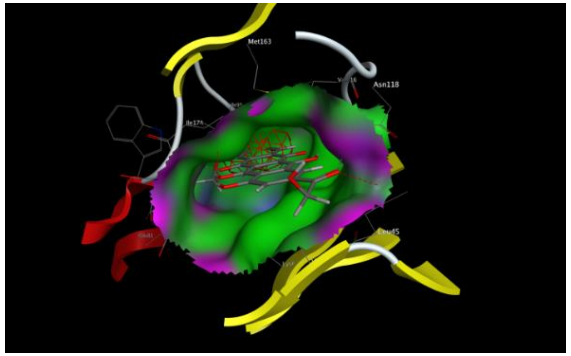
(a) **(b)** **(c)**

2-D interactions between the three best selected compounds and the receptor. (a): (ZINC35643753), (b): (ZINC44136135), (c): (ZINC05765165).

Results and discussion



(a)



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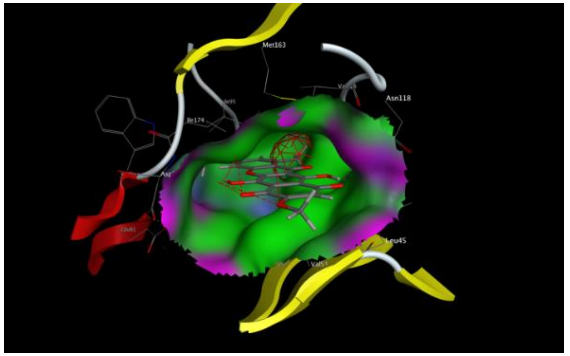


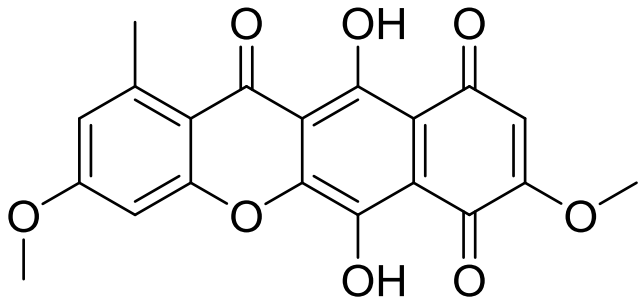
(c)

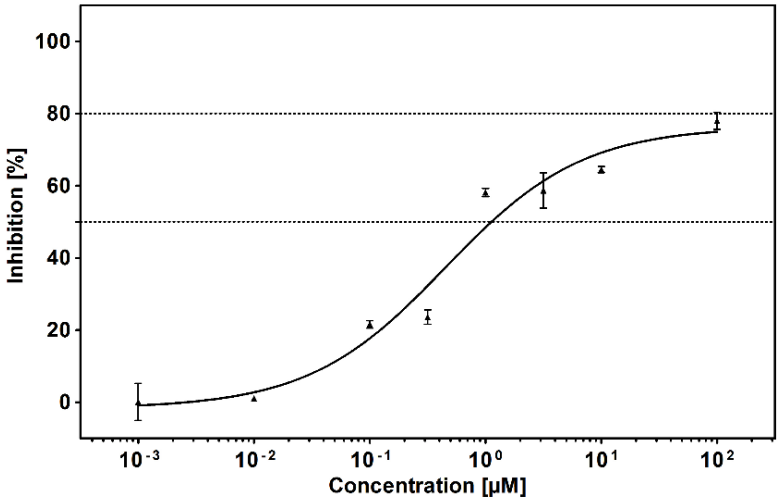
Binding mode of the selected ligands with the binding site of CK2 (a): (ZINC35643753), (b): (ZINC44136135), (c): (ZINC05765165).

Results and discussion

- Bikaverin was active toward CK2 enzyme with IC_{50} value of 1.24 μM.
- The cell variability was tested using MTT assay, and cell proliferation was determined using EdU-click assay using breast cancer cells (MCF-7).
- Cell viability was reduced by 50 % after treatment with 1 μM bikaverin for 24 h. Incubation of MCF-7 cells with 5 μM bikaverin for 48h caused complete inhibition of cell proliferation.

Results and discussion

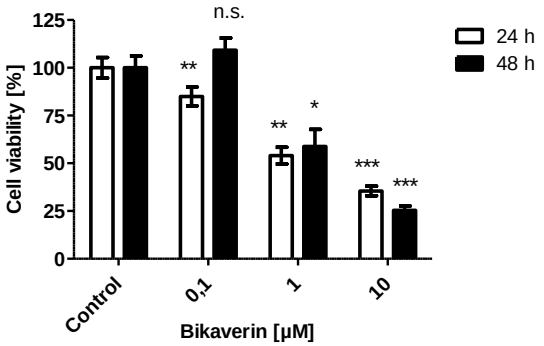




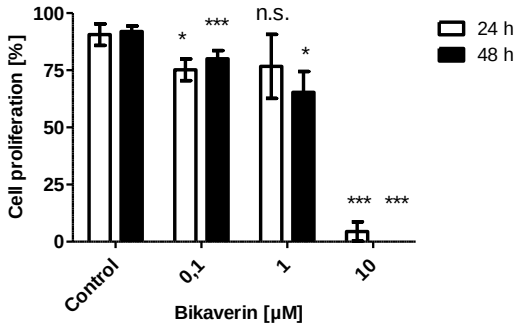
The chemical structure of bikaverin (6,11-dihydroxy-3 ,8- dimethoxy- 1-methylbenzo[b]xanthene-7,10,12-trione), first isolated from the culture of *Fusarium vasinfectum*

Determination of the IC_{50} value towards recombinant human CK2 of bikaverin.

Results and discussion



(a)



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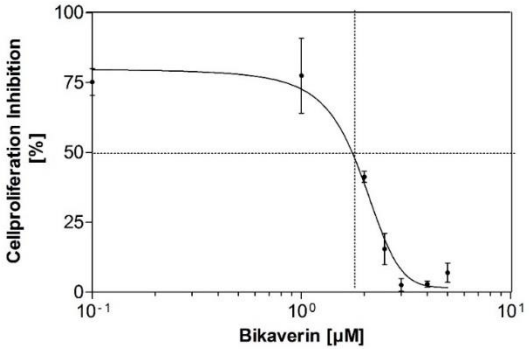

(c)

Evaluation of Bikaverin in MCF-7 cells (a) cell vaibility effect (b) cell proliferation EdU (c) cell proliferation

Conclusions

In this study we were able to invest the accumulated results from indenoindoles to participate in finding hypothetically the necessary ligand binding requirement for ATP binding CK2 inhibitors.

It is possible to use this model to further identify new inhibitors for this enzyme from other databases, as well as for rational design of new lead inhibitors.

Also the three selected compounds from the database can be considered as lead compounds especially bikaverin.