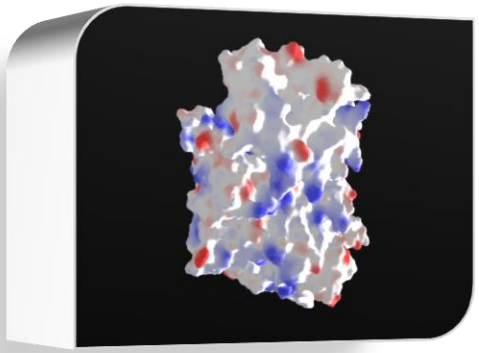
Human Protein Kinase CK2 Inhibitors: discovering new scaffolds

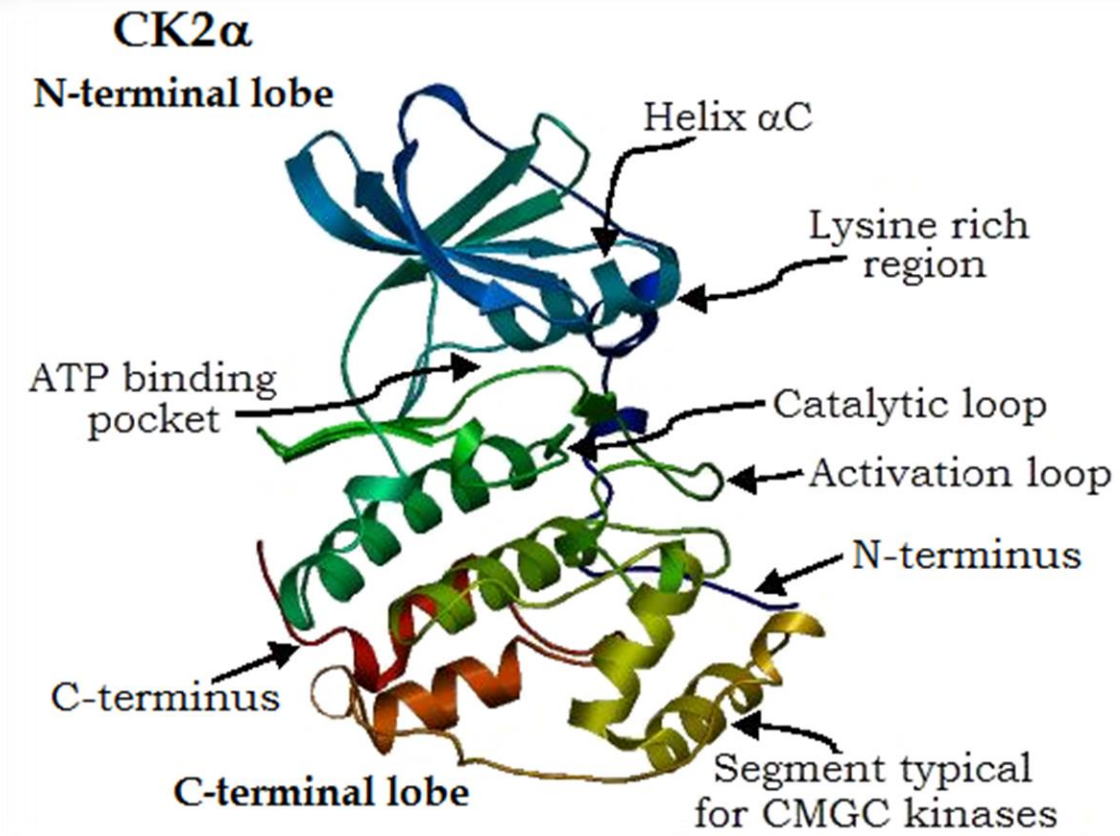
trinity of drug discovery: targets, compounds, and chemical spaces

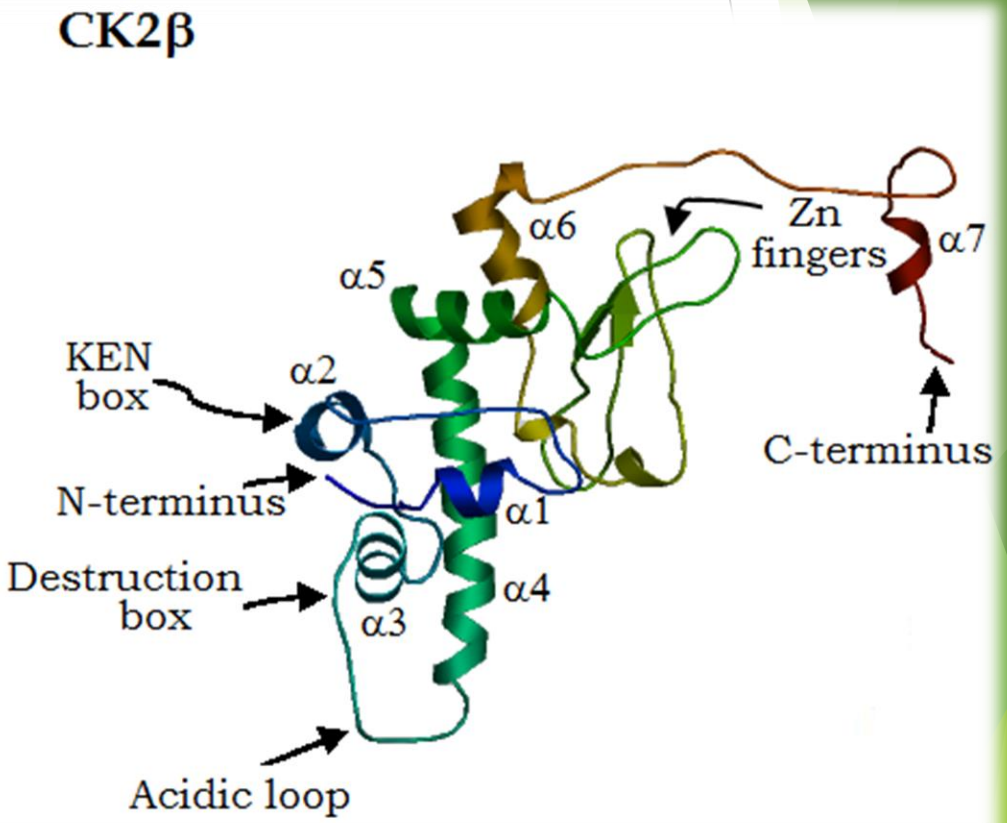
OTAVA chemicals



DEVELOPMENT OF CK2 INHIBITORS

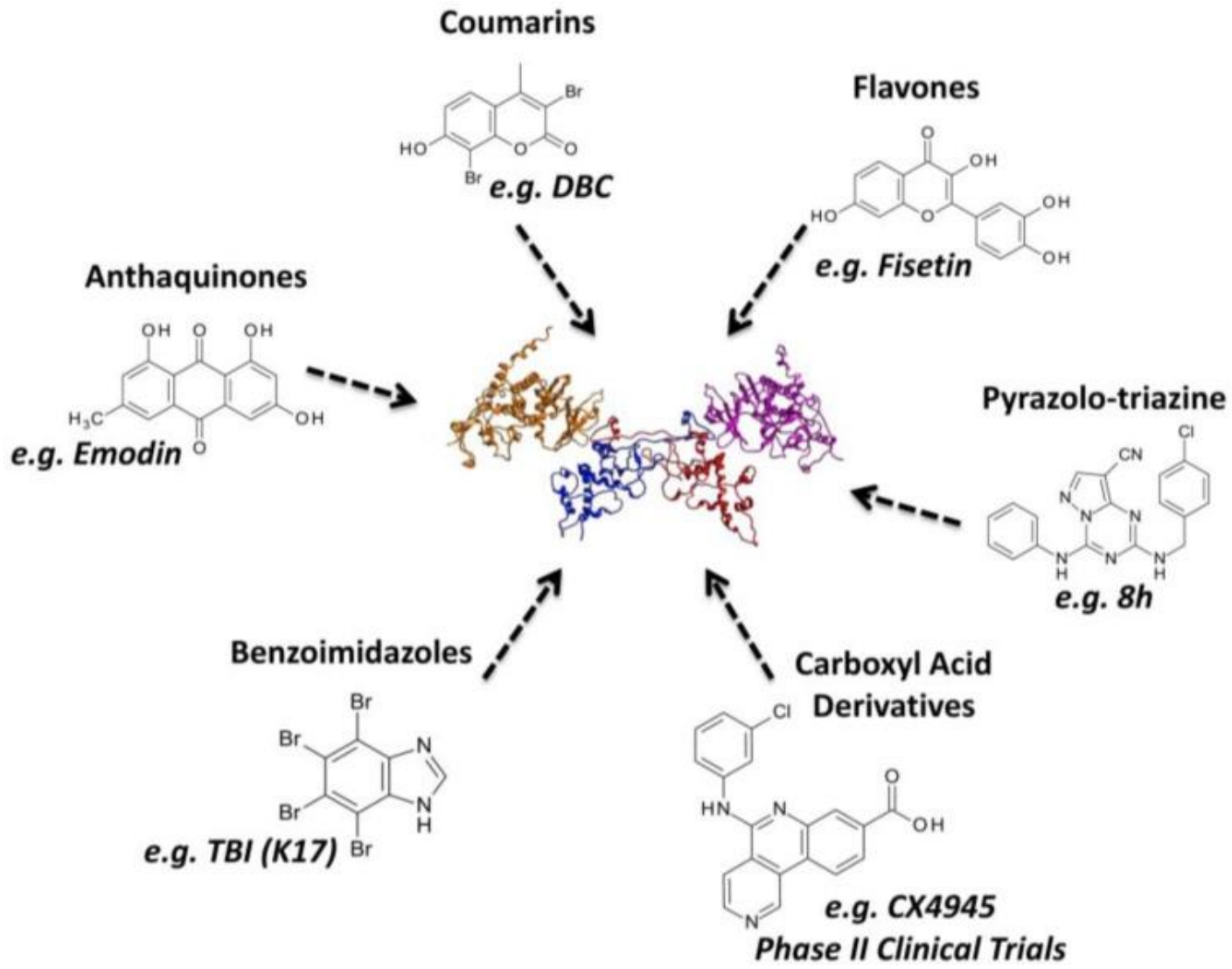
TARGET: Human Protein Kinase CK2





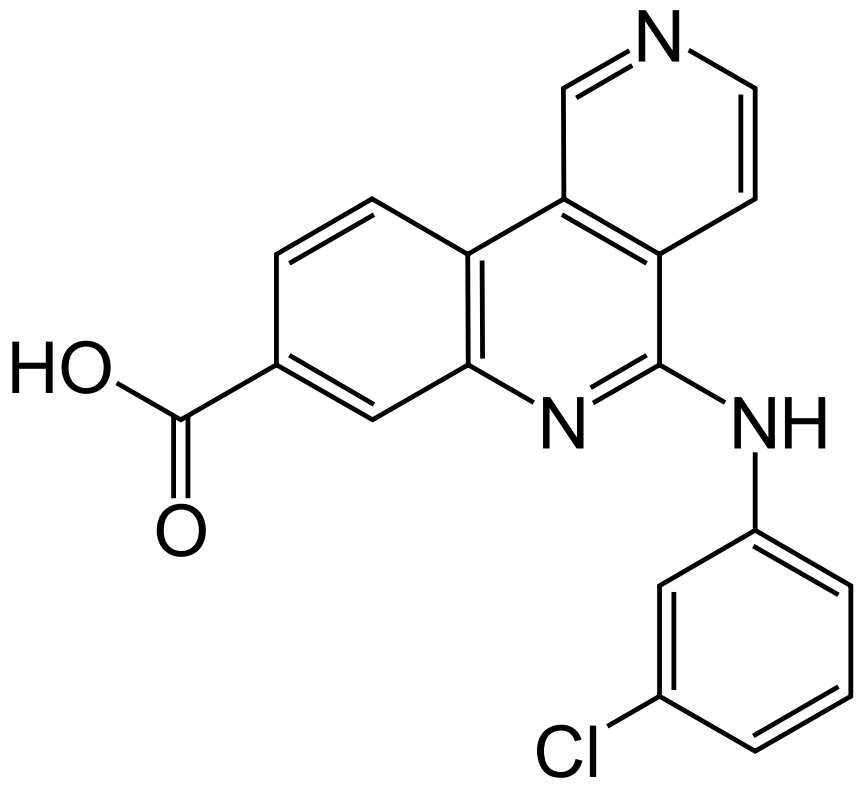
OTAVA chemicals

REPRESENTATIVE FAMILIES OF CK2 INHIBITORS



OTAVA chemicals

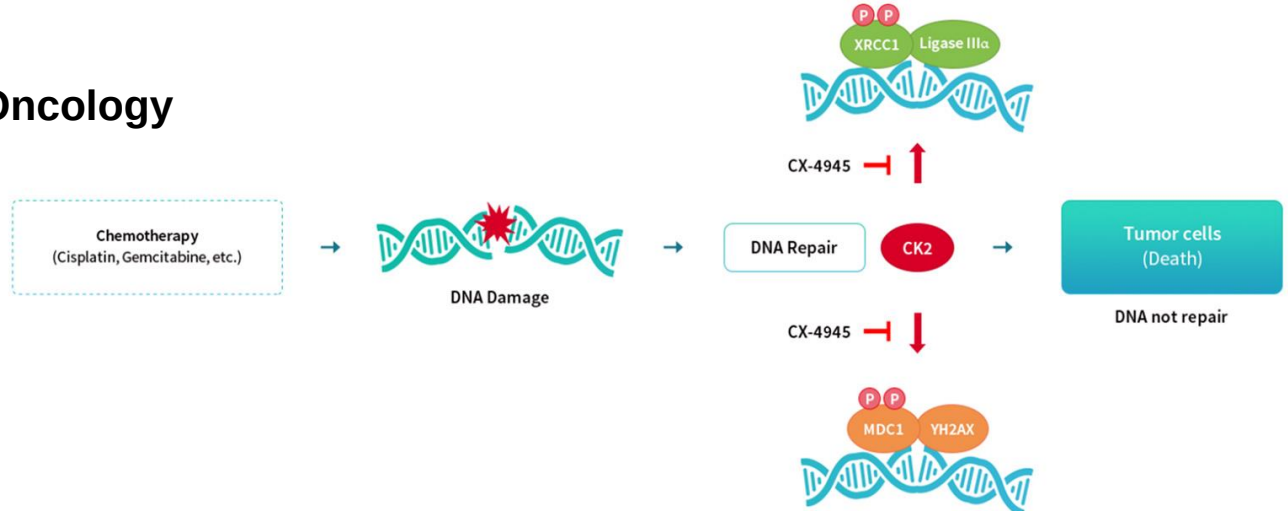
SILMITASERTIB



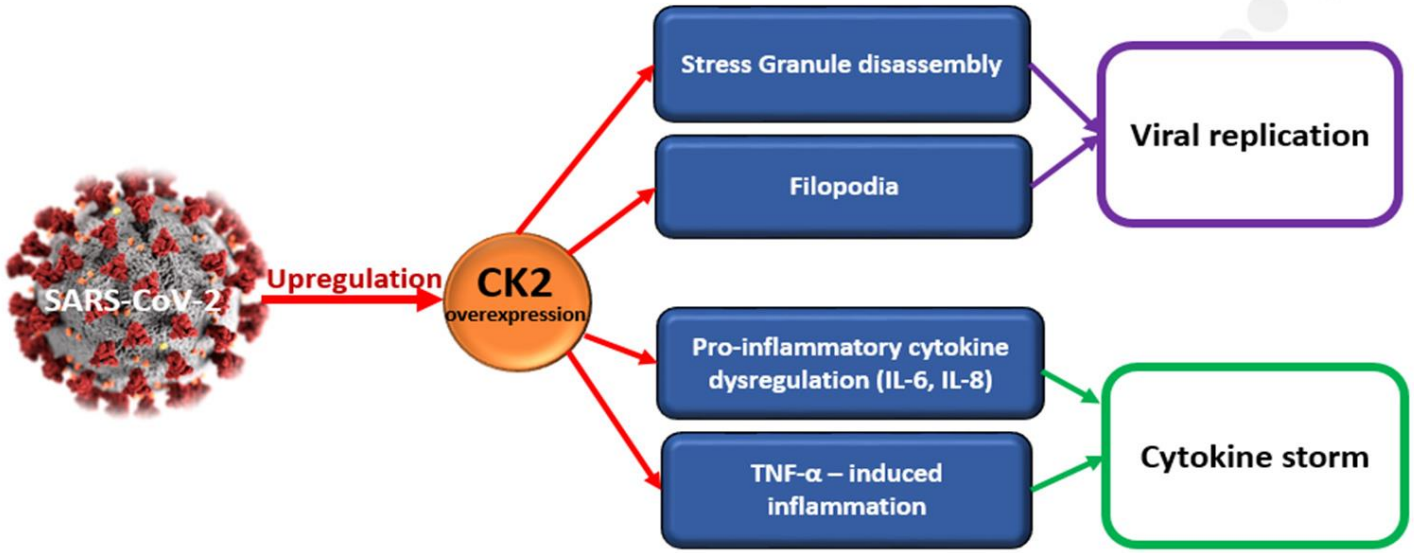
CX-4945, is a small-molecule inhibitor of protein kinase CK2

OTAVA chemicals

Oncology



Infectious Disease



Developed by Senhwa Biosciences of Taiwan
https://www.senhwabio.com/en/products/CK2

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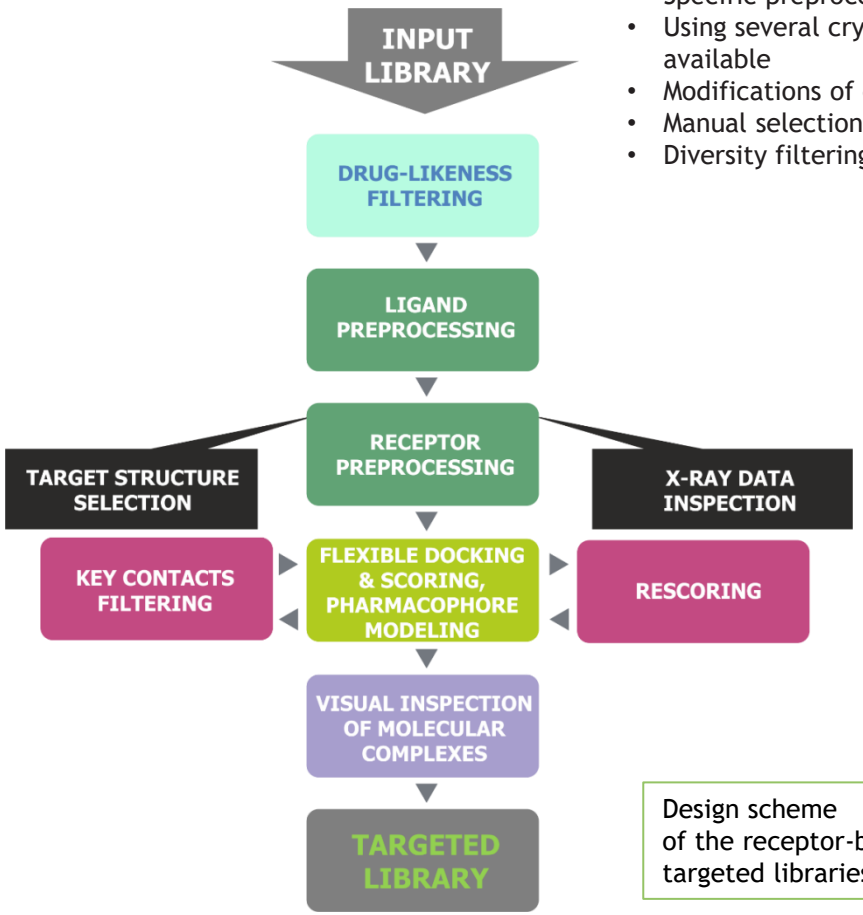
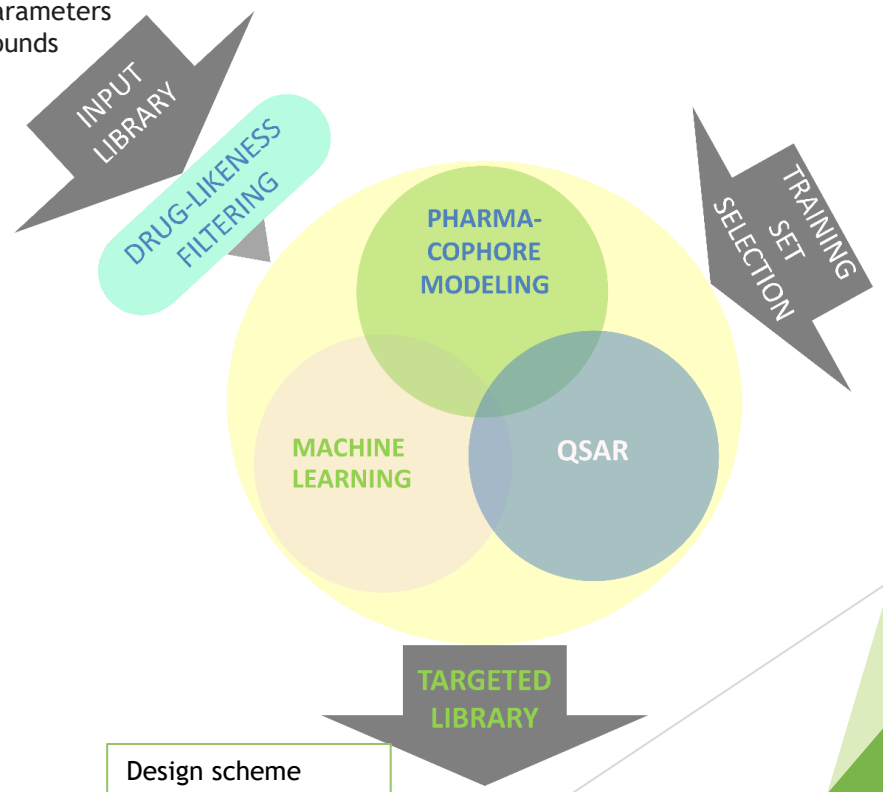
Approaches for Targeted Libraries Design

- We use a wide range of ligand- and receptor-based approaches for targeted libraries design.
- If the input data is enough, we use several methods at the same time, combining them.



- Specific preprocessing
- Using several crystal structures or models if available
- Modifications of calculation parameters
- Manual selection of the compounds
- Diversity filtering

Design scheme of the receptor-based targeted libraries



Design scheme of the ligand-based targeted libraries

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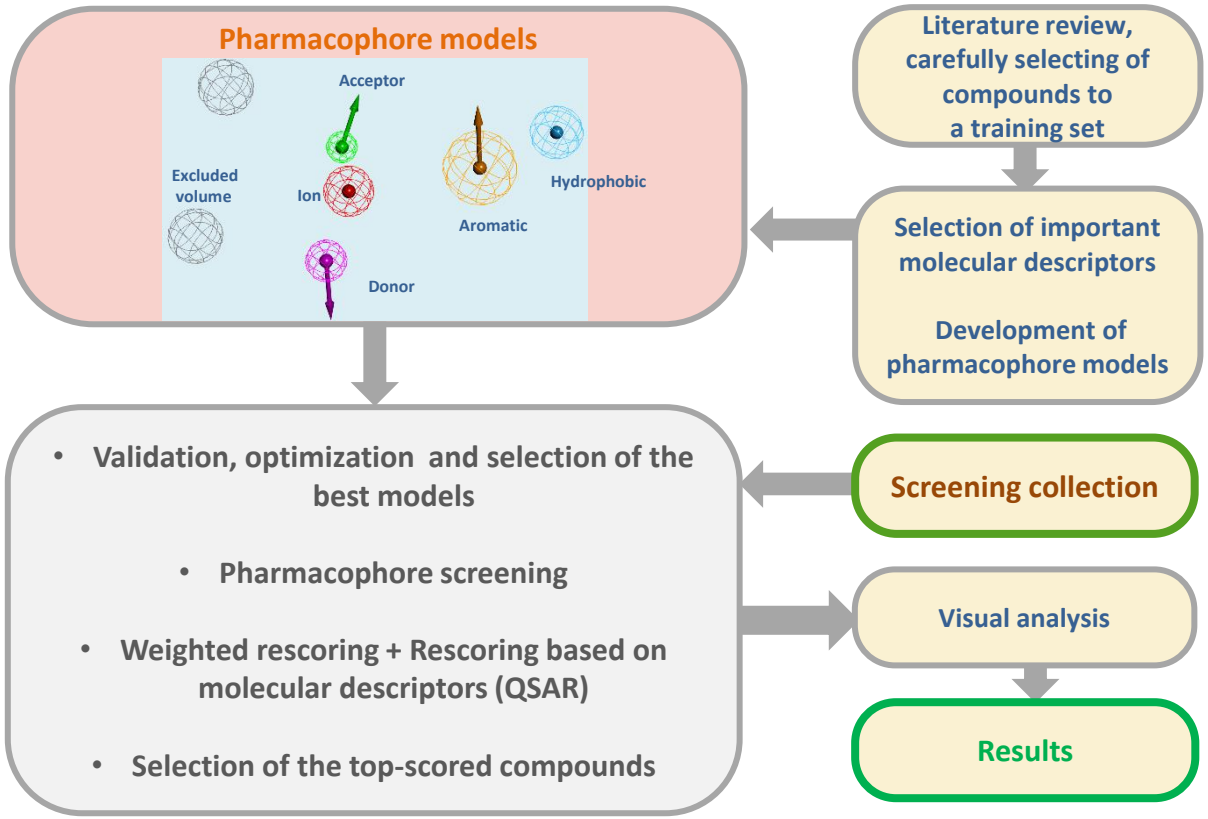
Ligand-based Approaches

Ligand-based pharmacophore modeling



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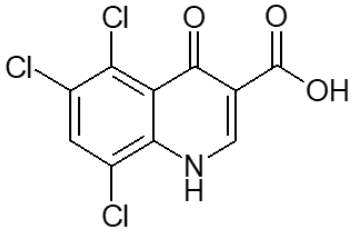
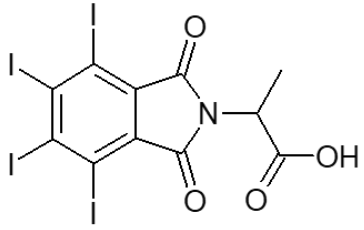
Examples of CK2 inhibitors developed by OTAVA

Ouinolone 7



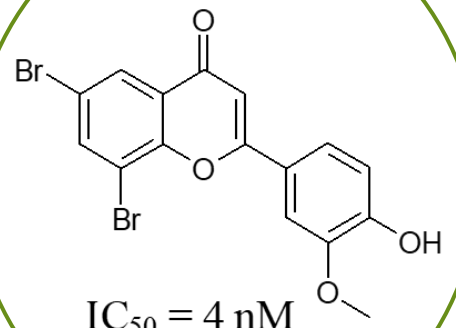
IC_{50} = 300 nM
K_i = 60 nM

TID46



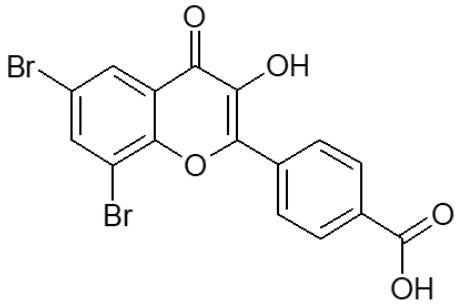
IC_{50} = 150 nM
K_i = 100 nM

FNH79



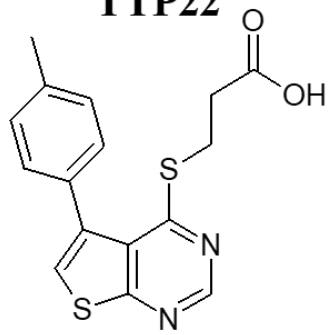
IC_{50} = 4 nM
K_i = 1.8 nM

FLC25



IC_{50} = 9 nM
K_i = 2.5 nM

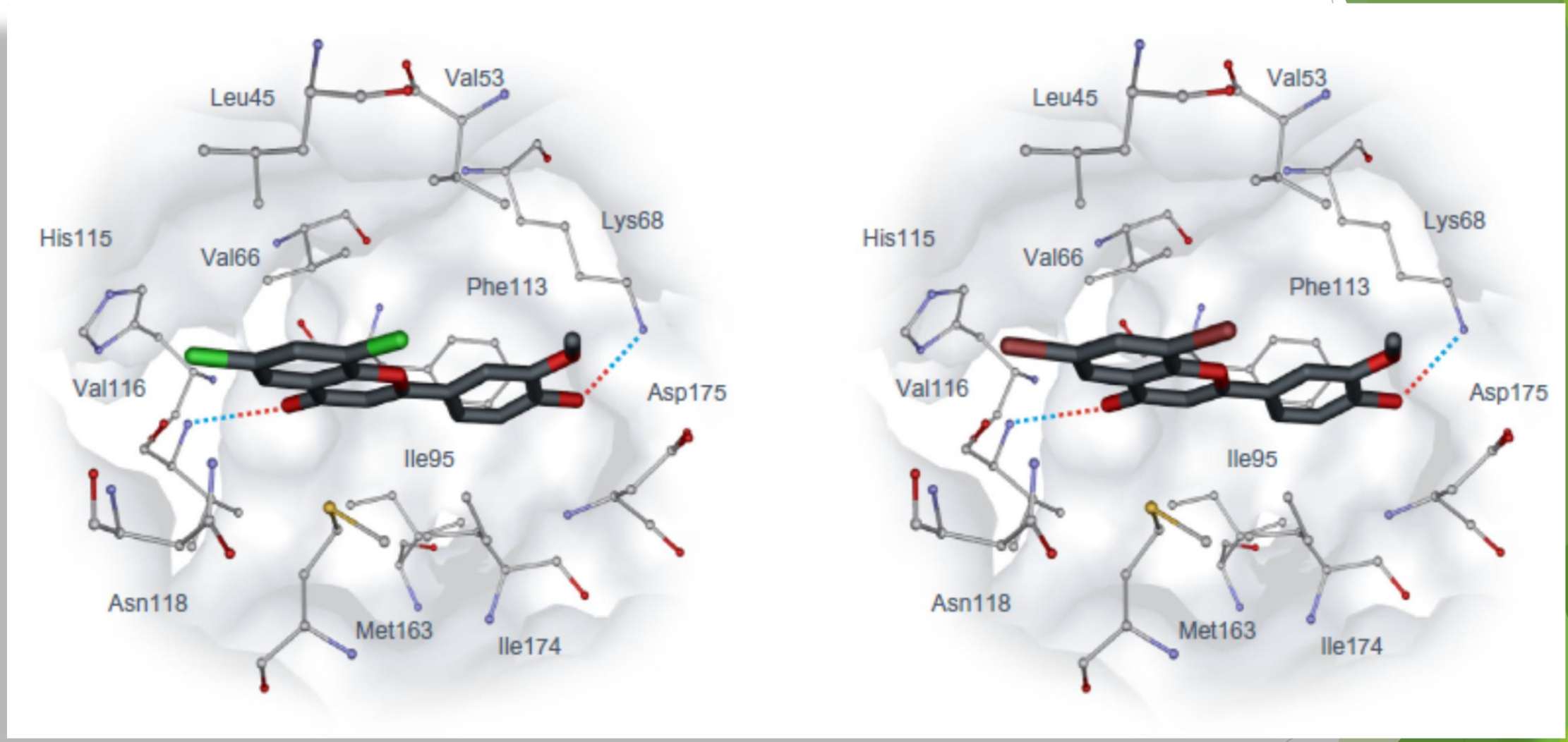
TTP22



IC_{50} = 90 nM
K_i = 40 nM

Protein Kinase	FNH79
CK2	0.8
JNK3	103
ROCK1I	89
Tie2	85
Aurora A	55
Met	87
FGFR1	74
ASK1	126

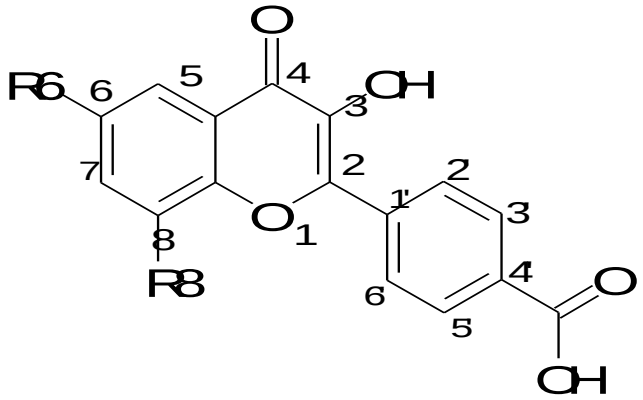
OTAVA chemicals

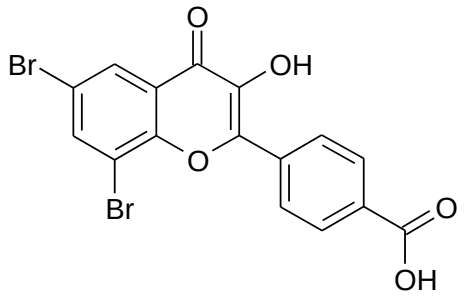


OTAVA chemicals

CK2 INHIBITORS: CASE STUDY

3-hydroxy-4’-carboxyflavones – novel inhibitors of protein kinase CK2

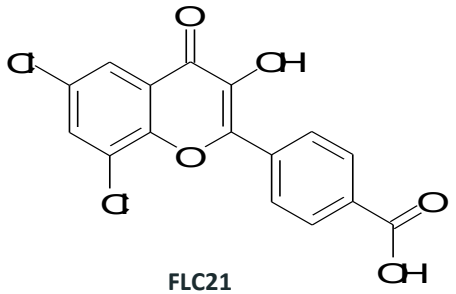




FLC26

IC_{50}=9 nM

Ki = 2.5 nM



FLC21

IC_{50}=40 nM

Ki = 13 nM

Mol Cell Biochem 2011, 356, 107

CK2 INHIBITORS: CASE STUDY

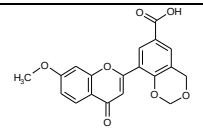
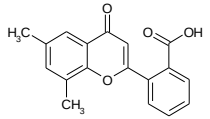
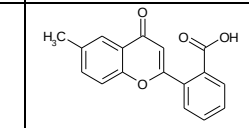
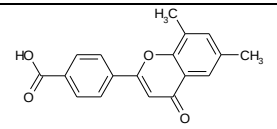
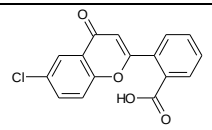
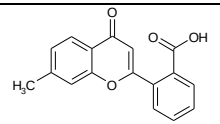
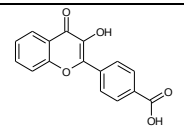
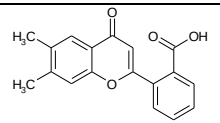
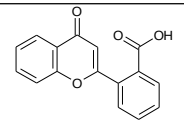
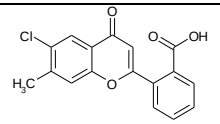
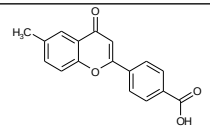
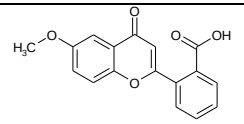
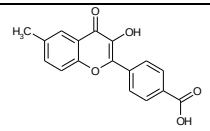
150,000 compounds

↓ Docking

2,500 compounds

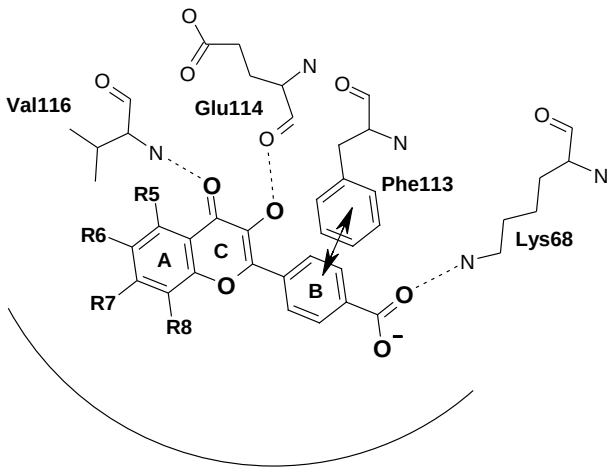
↓ Visual selection

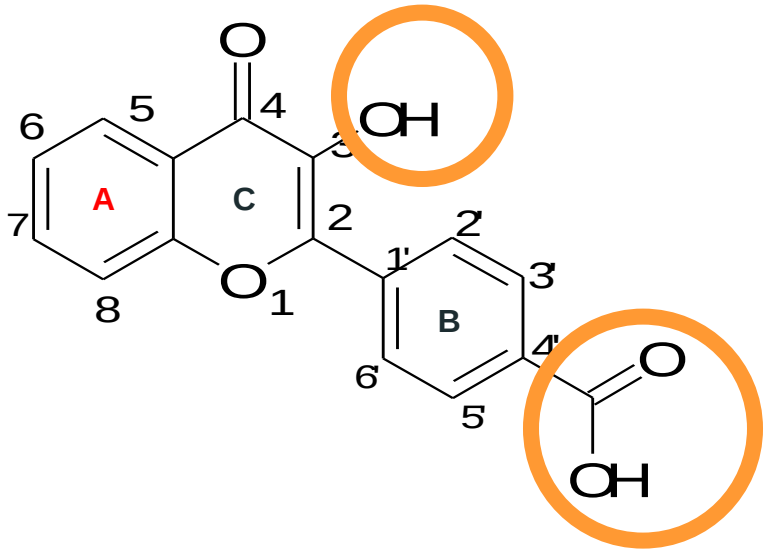
500 compounds
(including 13 carboxyflavonols)

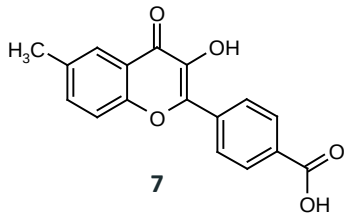
Compound ID	Structure	IC_{50}, μM	Compound ID	Structure	IC_{50}, μM
1		8	**8**		>40
2		>40	**9**		5
3		>40	**10**		>40
4		1,3	**11**		35,0
5		>40	**12**		>40
6		8	**13**		>40
7		0,6			

OTAVA chemicals

CK2 INHIBITORS: CASE STUDY



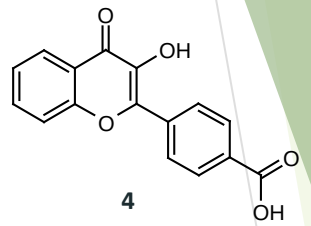




7

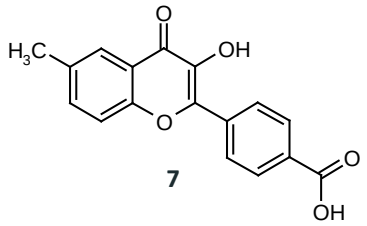
IC_{50} = 0.6 µM

<



4

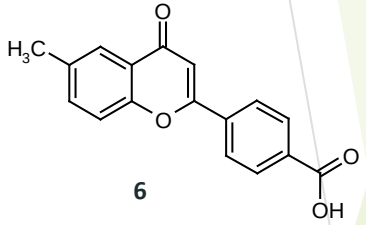
IC_{50} = 1.3 µM



7

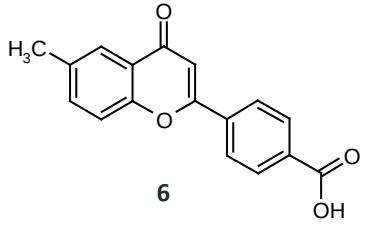
IC_{50} = 0.6 µM

<



6

IC_{50} = 8 µM



6

IC_{50} = 8 µM

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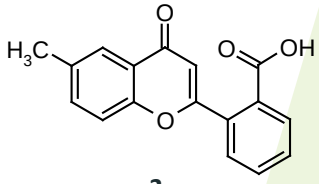
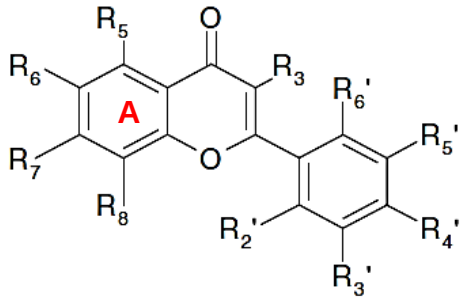


2

IC_{50} > 40 µM

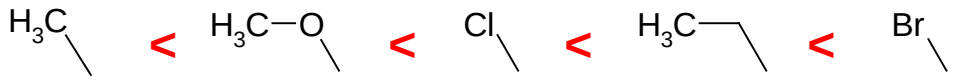
CK2 INHIBITORS: CASE STUDY



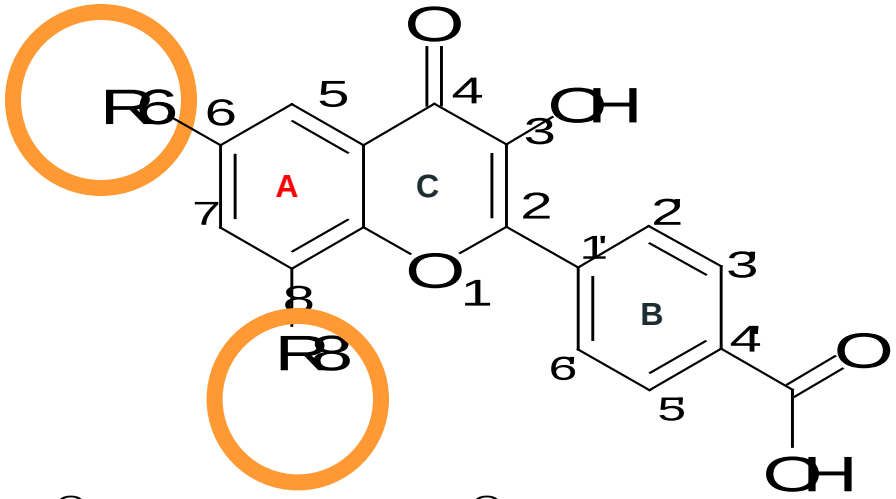
Compound	R_2'	R_3'	R_4'	R_5'	R_6'	R_3	R_5	R_6	R_7	R_8	IC_{50} (μM)
14	H	H	CO_2H	H	H	OH	H	Me	Me	H	0.3
15	H	H	CO_2H	H	H	OH	H	OMe	H	H	0.25
16	H	H	CO_2H	H	H	OH	H	NHAc	H	H	0.72
17	H	H	CO_2H	H	H	OH	H	Cl	Me	H	0.17
18	H	H	CO_2H	H	H	OH	H	Cl	H	H	0.18
19	H	H	CO_2H	H	H	OH	H	Me	H	Me	0.07
20	H	H	CO_2H	H	H	OH	H	Et	H	H	0.16
21 (FLC21)	H	H	CO_2H	H	H	OH	H	Cl	H	Cl	0.04
22	H	H	CO_2H	H	H	OH	H	H	Me	H	0.7
23	H	H	CO_2H	H	H	OH	H	Br	H	H	0.08
24	H	H	CO_2H	H	H	OH	H	H	OMe	H	0.29
25	H	H	CO_2H	H	H	OH	H	Cl	H	Me	0.05
26 (FLC26)	H	H	CO_2H	H	H	OH	H	Br	H	Br	0.009

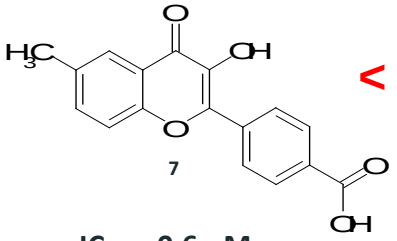
OTAVA chemicals

CK2 INHIBITORS: CASE STUDY

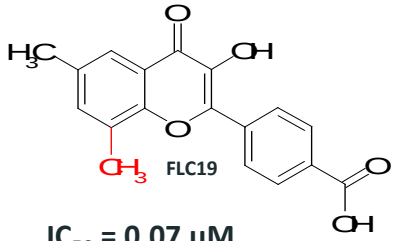
R6 = 

IC_{50} = 0.6 µM IC_{50} = 0.25 µM IC_{50} = 0.18 µM IC_{50} = 0.16 µM IC_{50} = 0.08 µM

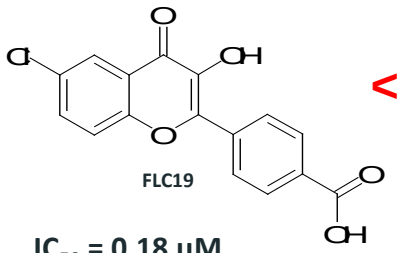



7

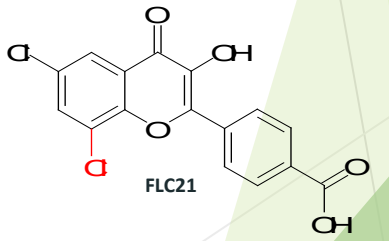
IC_{50} = 0.6 µM


FLC19

IC_{50} = 0.07 µM


FLC19

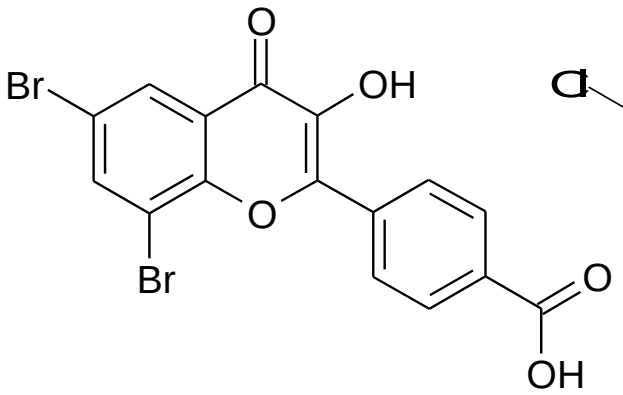
IC_{50} = 0.18 µM


FLC21

IC_{50} = 0.04 µM

CK2 INHIBITORS: CASE STUDY

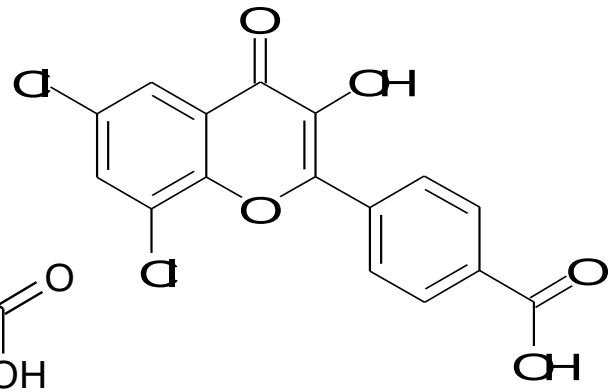
3-hydroxy-4’-carboxyflavones –
novel inhibitors of protein kinase CK2



FLC26

IC_{50}=9 nM

Ki = 2.5 nM



FLC21

IC_{50}=40 nM

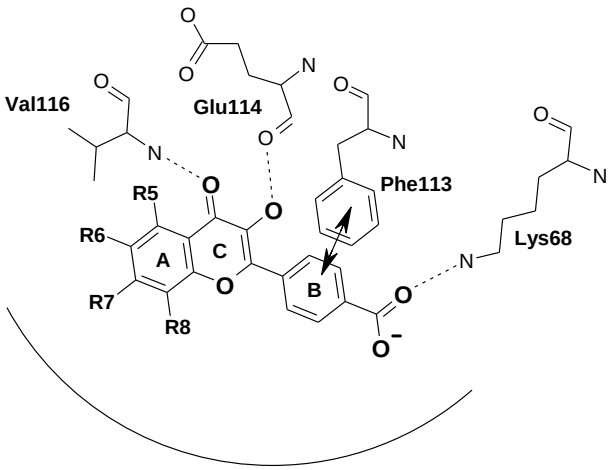
Ki = 13 nM

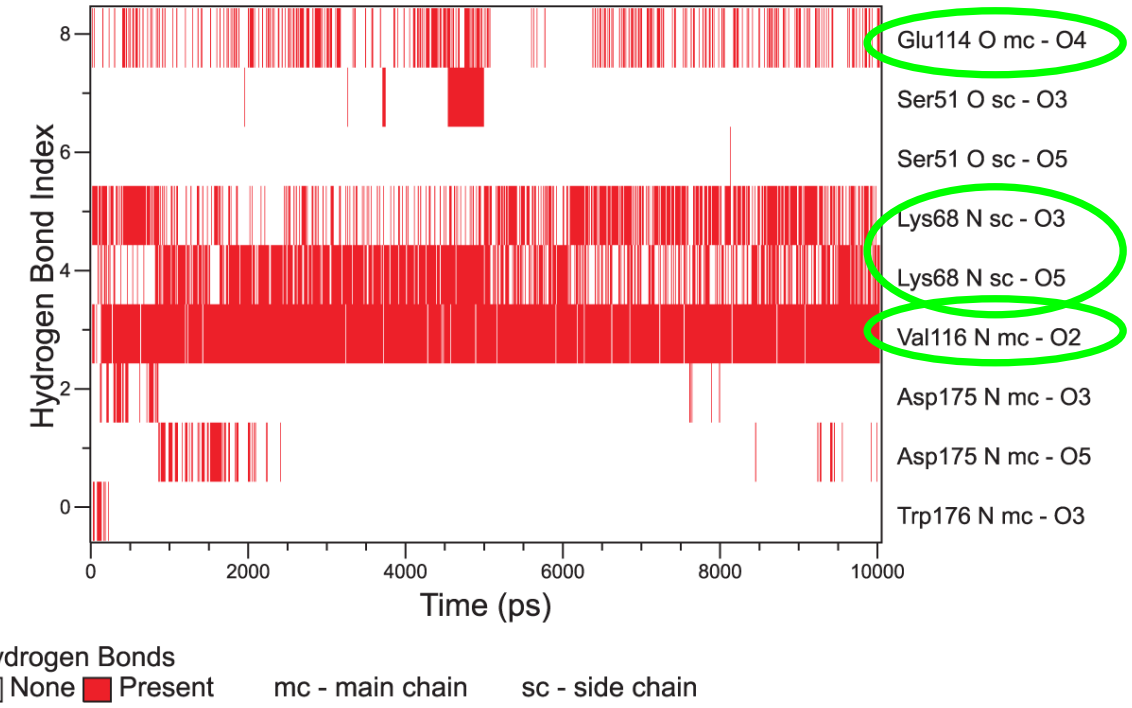
Kinase	FLC21	FLC26
CK2	2.3	1.1
Jnk3	102	101
Rock1	106	91
Tie2	90	103
Ask1	119	73
Aurora A	41	13
Met	30	16
FGFR1	70	34

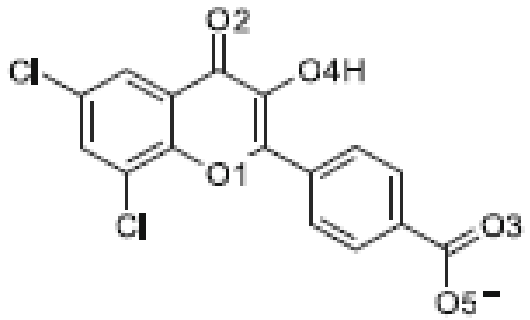
Selectivity profile of FLC21 and FLC26

OTAVA chemicals

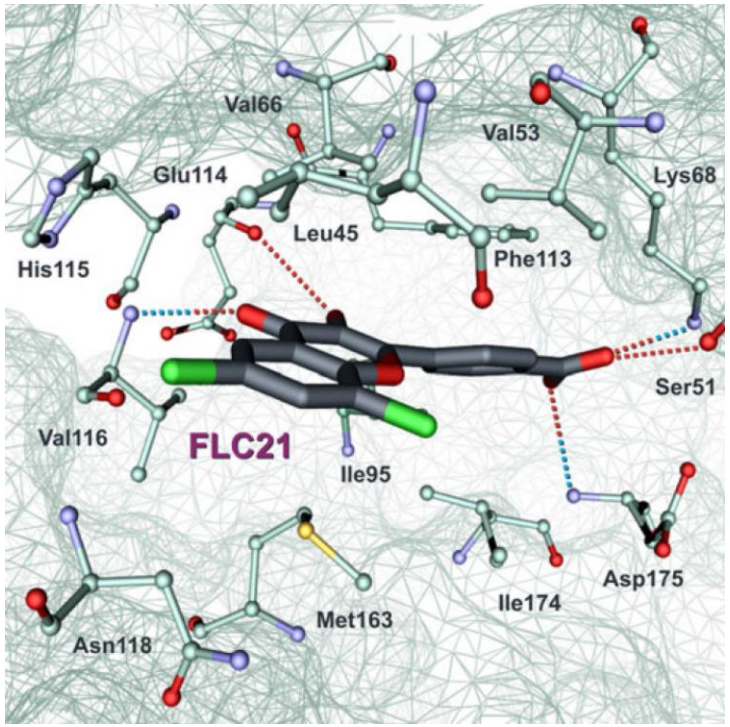
CK2 INHIBITORS: CASE STUDY



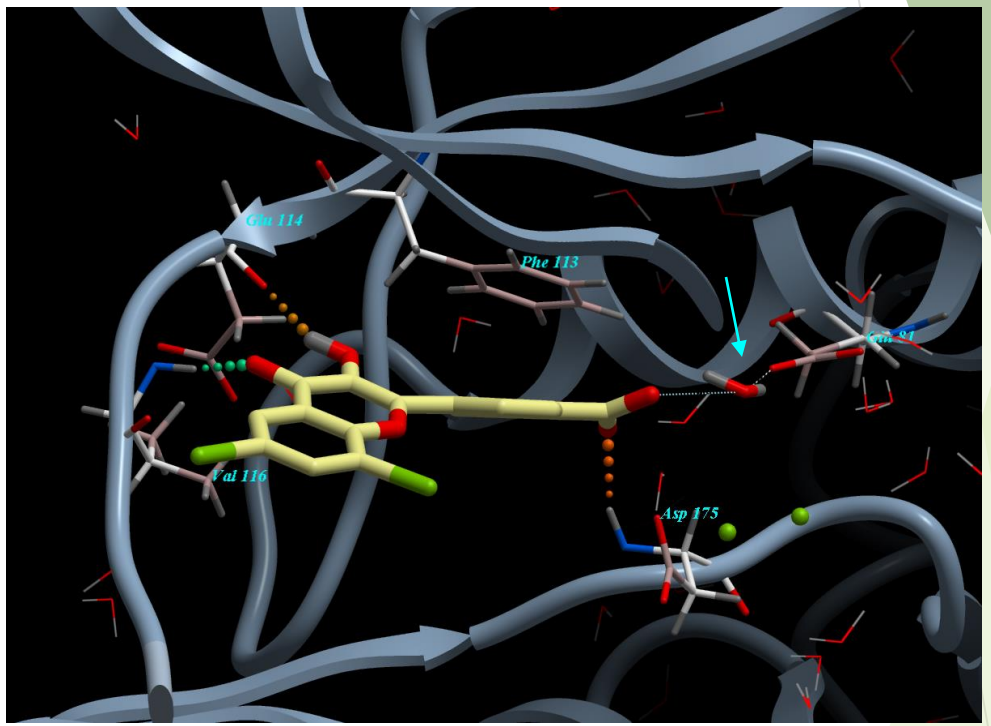




CK2 INHIBITORS: CASE STUDY



Complex of **CK2–FLC21** obtained using molecular modeling



Complex of **CK2–FLC21** obtained by X-RAY analysis

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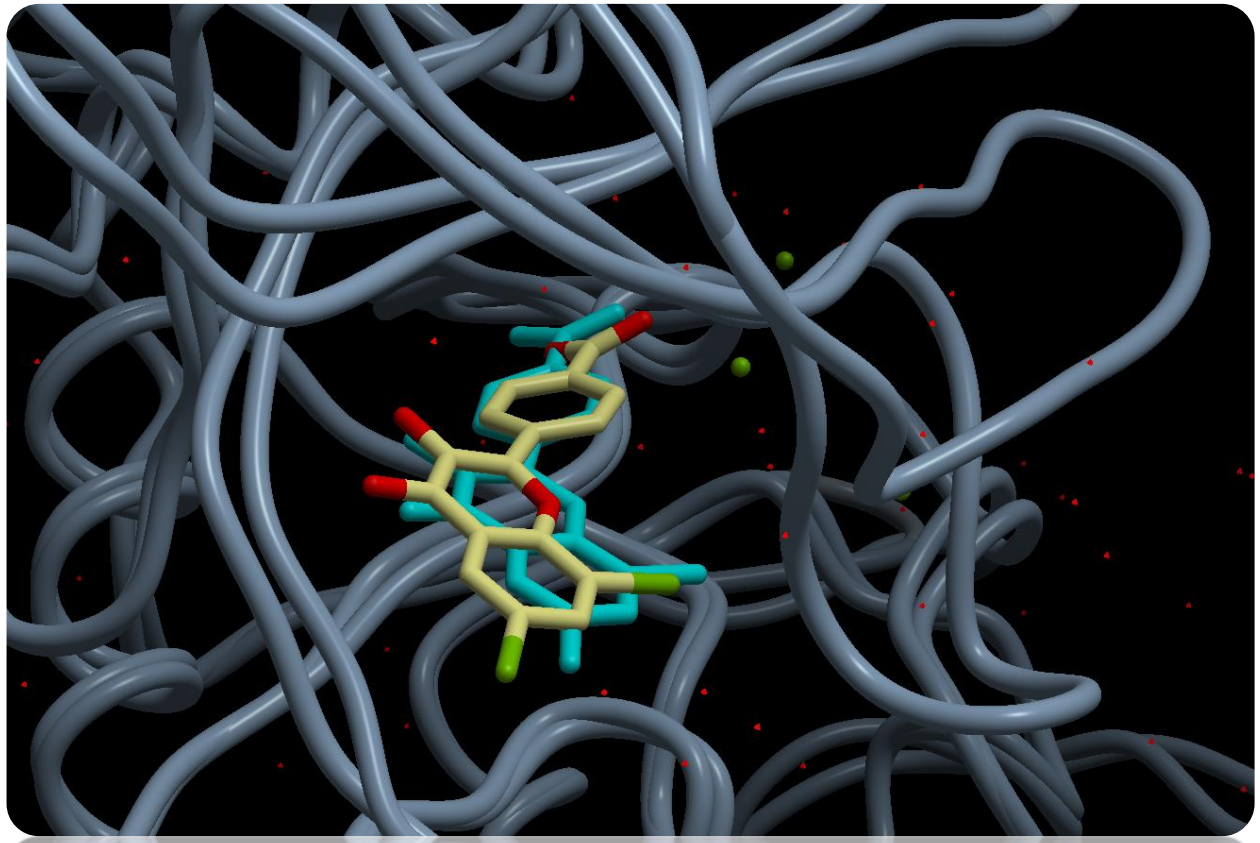
CK2 INHIBITORS: CASE STUDY



Superposition of **CK2–FLC21** complexes obtained with molecular modeling (blue) and X-Ray analysis (atom coloured)

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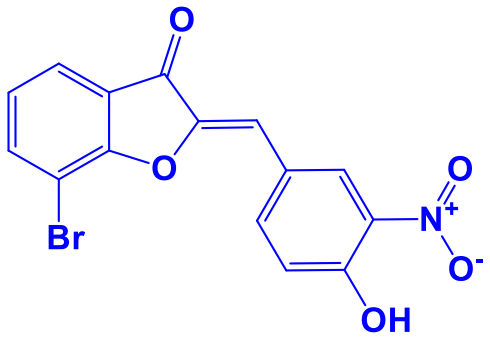
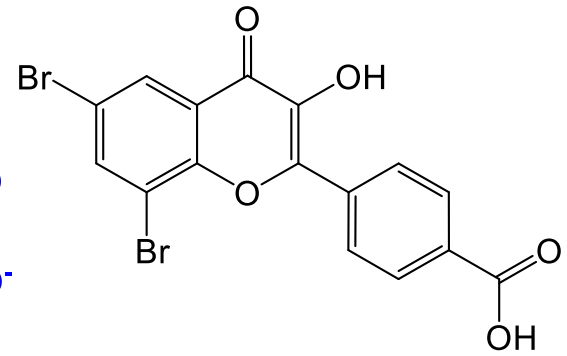
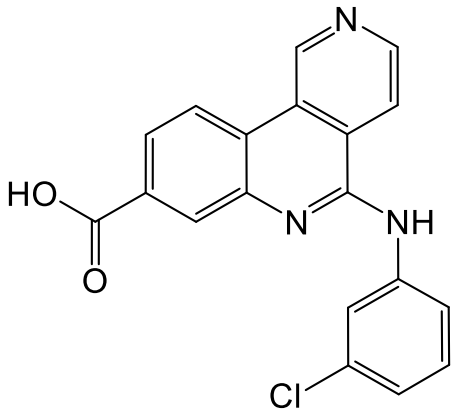
Flavone inspired discovery of benzylidenebenzofuran-3(2*H*)-ones (aurones) as potent inhibitors of human protein kinase CK2



12m (BFO13)
IC_{50} = 3.6 nM
CLogP = 3.5
CLipE = 4.94



FLC26
IC_{50} = 9 nM
CLogP = 3.7
CLipE = 4.7



CX-4945
IC_{50} = 1 nM
CLogP = 4.16
CLipE = 4.84

Bioorganic Chemistry 2020, 102, 104062

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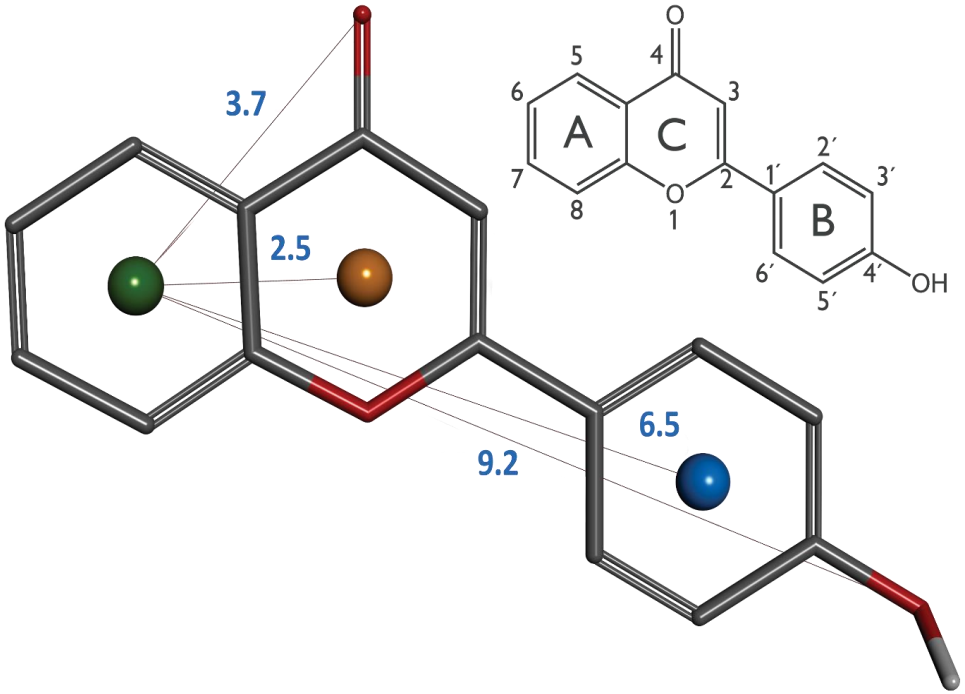
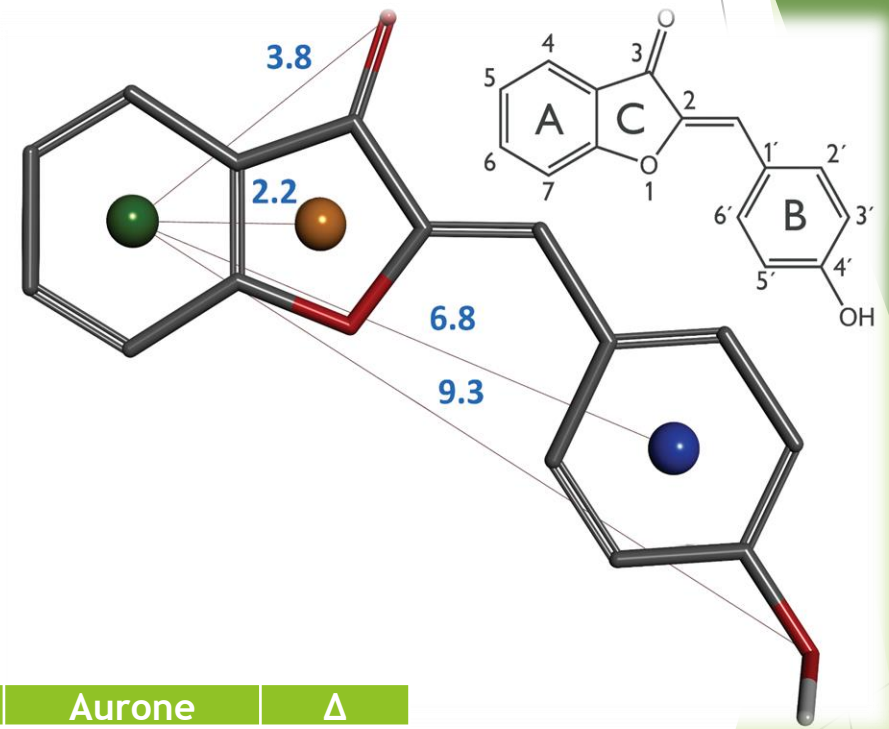
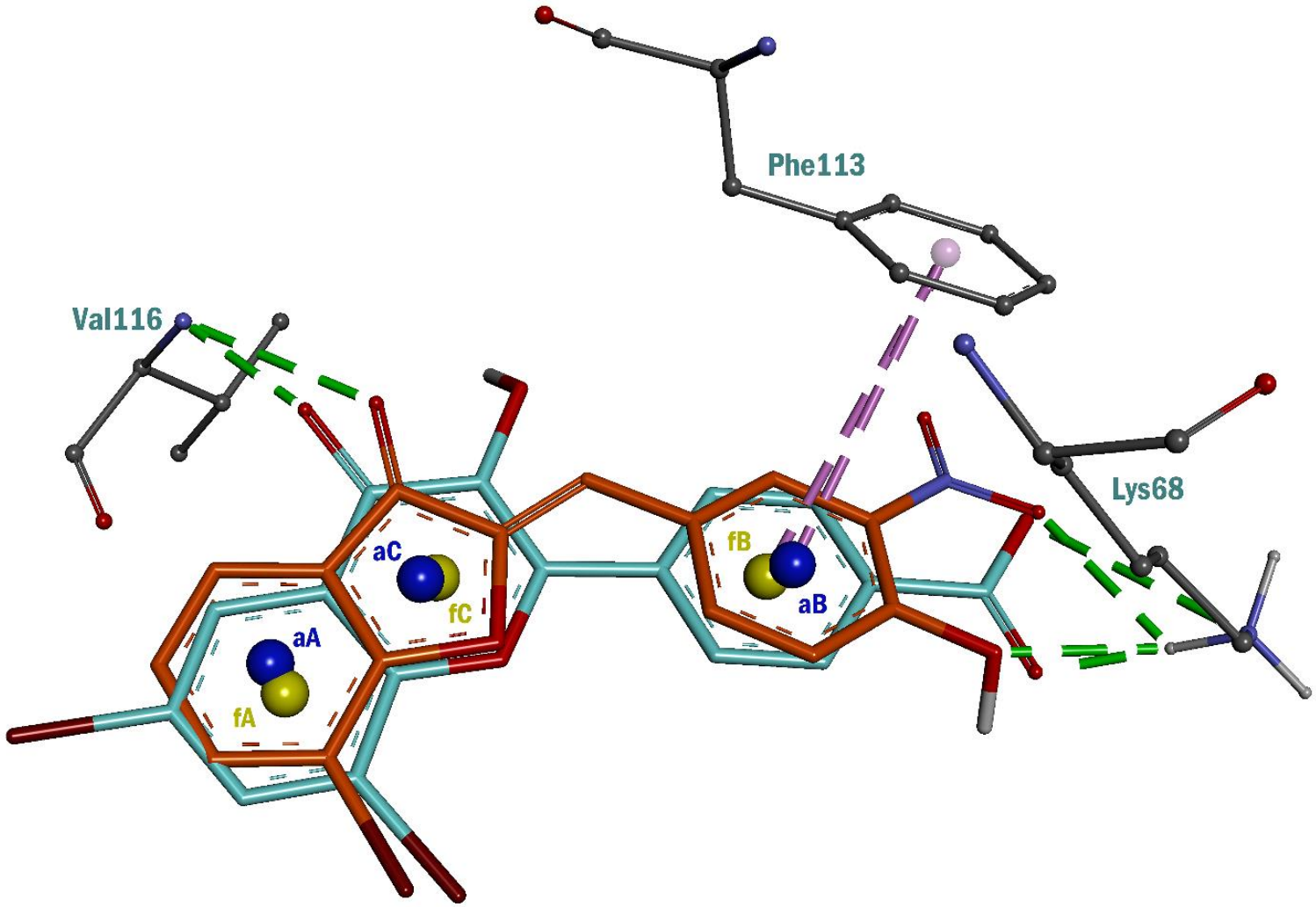
Comparison of distances between key interaction points of flavone with same points of aurone derivatives





Distance	Flavone	Aurone	Δ
A-C	2.5 Å	2.2 Å	0.3 Å
A-B	6.5 Å	6.8 Å	0.3 Å
A-carbonyl group (3-position in ring C)	3.7 Å	3.8 Å	0.1 Å
A-carboxyl group (4’-position in ring B)	9.2 Å	9.3 Å	0.1 Å



Comparison of binding modes of FLC26 (blue), obtained with crystallographic analysis (PDB ID: 4UBA) and inhibitor 12m (orange), obtained with molecular docking

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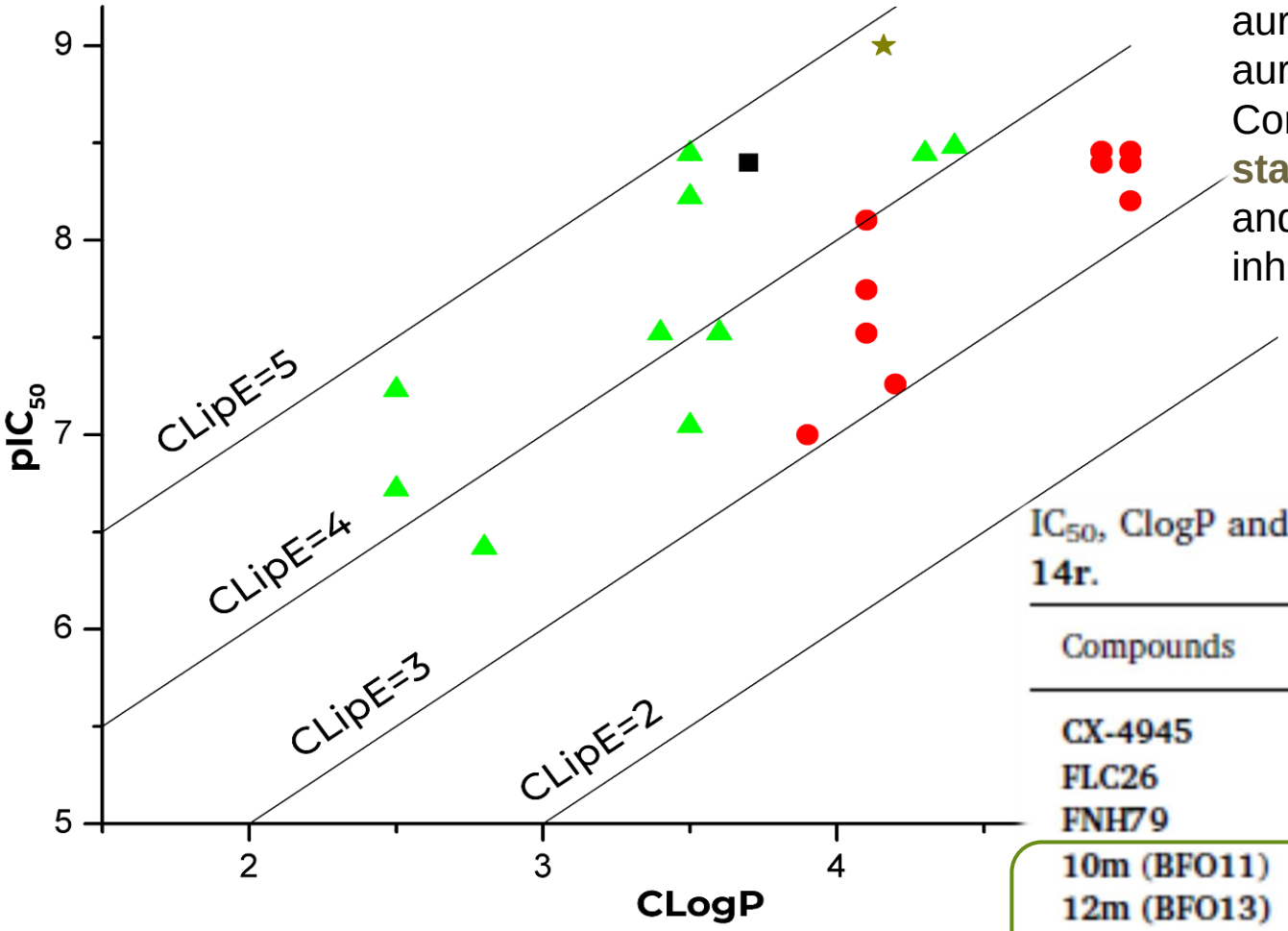

A plot of CLogP versus pIC_{50}. The **green triangles** indicate aurone derivatives after optimization, the **red circles** – aurone derivatives before optimization.
Compounds **FLC26** (**black square**) and **CX-4945** (**green star**) included as reference inhibitors of protein kinase CK2 and belongs to flavones and naphthyridines families of CK2 inhibitors, respectively

IC_{50}, ClogP and CLipE values of CX-4945, FLC26, FNH79, **10m**, **12m**, **12l** and **14r**.

Compounds	IC_{50}, μM	ClogP	CLipE
CX-4945	0.001	4.16	4.84
FLC26	0.009	3.92	3,85
FNH79	0.004	4.2	4.48
10m (BFO11)	0.006	3.5	4.72
12m (BFO13)	0.0036	3.5	4.94
12l (BFO12)	0.0033	4.4	4.08
14r (BFO15)	0.059	2.5	4.73

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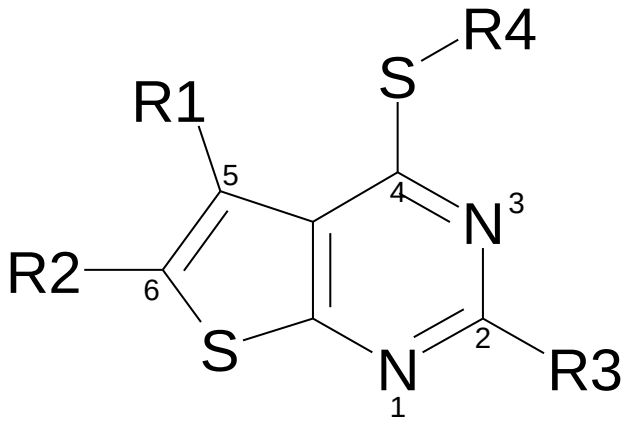
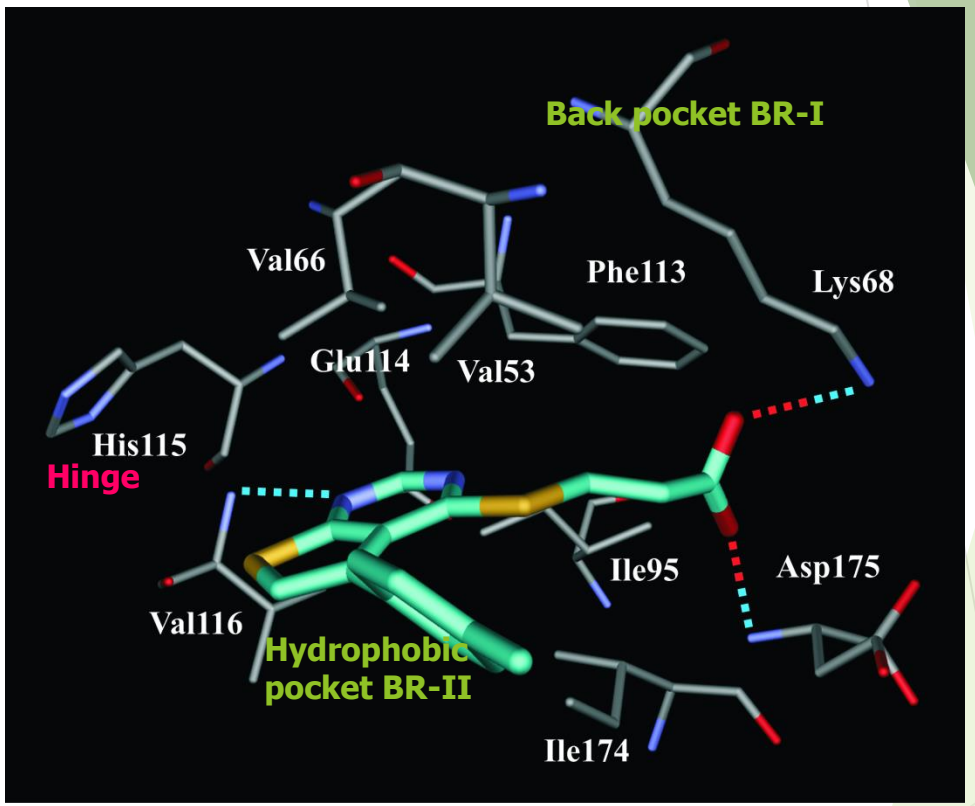
Substituted thieno[2,3-*d*] pyrimidin-4-ylthio)carboxylic acids as inhibitors of human protein kinase CK2





R1 4-FC_6H_4 < 3,4-$CH_3C_6H_3$ = 4-ClC_6H_4 < 4-$C_2H_5OC_6H_4$ < 4-$CH_3C_6H_4$

R4 CH_2CH_2COOH > CH_2COOH > $CH(CH_3)COOH$ > $CH_2CH_2CH_2COOH$ = $CH(C_2H_5)COOH$

European Journal of Medicinal Chemistry 46 (2011) 870

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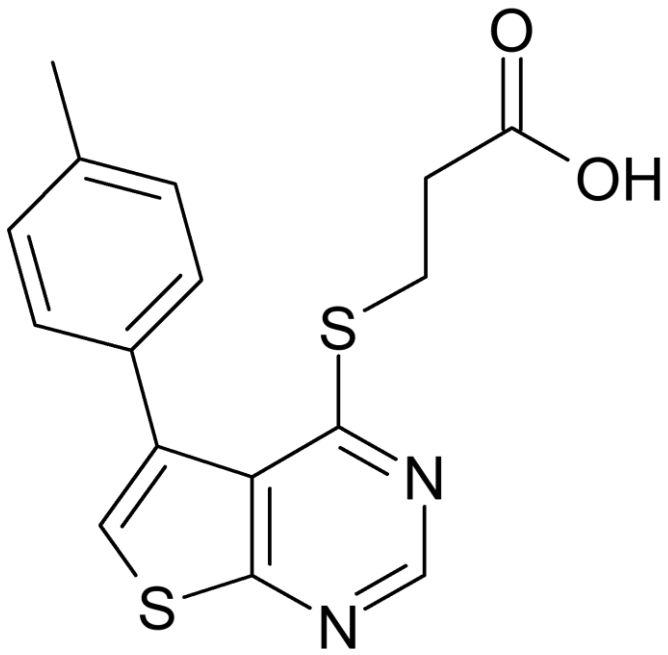

TTP22

IC_{50}=100 nM

K_i = 40 nM

Protein Kinase	Kinase residual activity in presence of TTP22, %	Kinase residual activity in presence of TTP25, %
CK2	0.72	0.86
Jnk3	104	94
Rock1	126	115
Tie2	70	76
Ask	92	100
Aurora A	23	48
c-Met	114	115
FGFR	92	99

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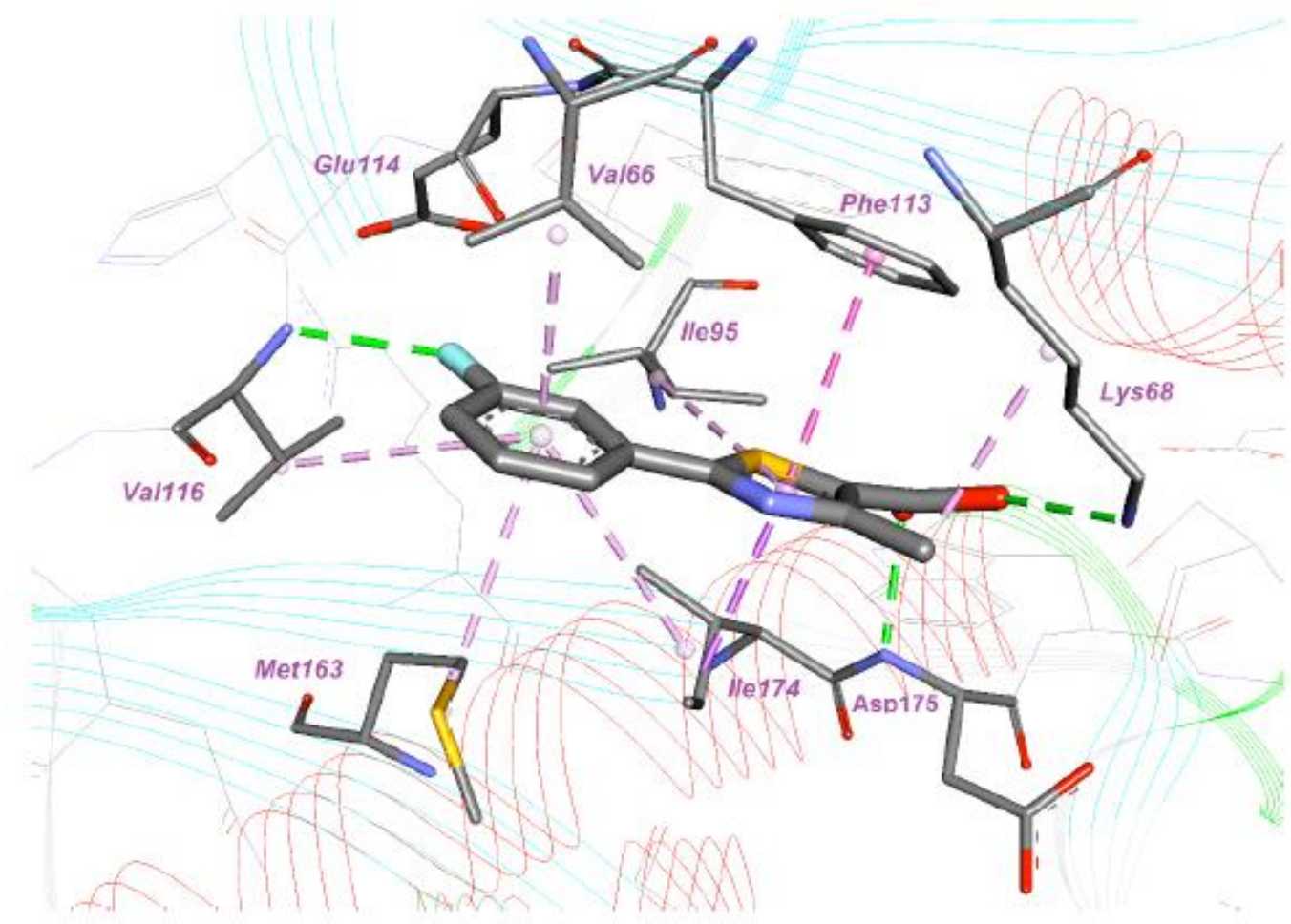
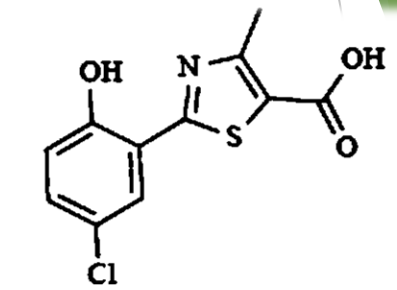
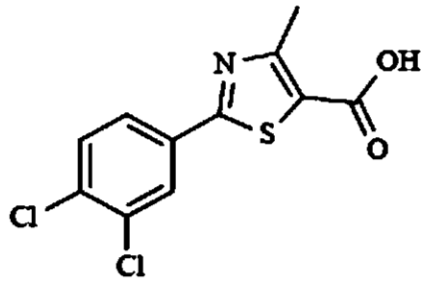
Identification of 1,3-thiazole-5-carboxylic Acid Derivatives as Inhibitors of Protein Kinase CK2





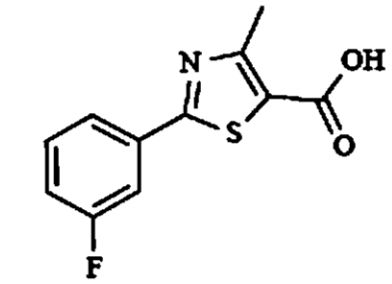
Compound 1

LogP = 2.8
LogS = -3.6
MW = 270
IC_{50} = 0.8 µM
LE = 0.5
LELP = 5.6



Compound 3

LogP = 2.6
LogS = -3.6
MW = 237
IC_{50} = 0.4 µM
LE = 0.56
LELP = 4.64



Compound 2

LogP = 3.7
LogS = -5
MW = 288
IC_{50} = 3.5 µM
LE = 0.45
LELP = 8.2

Current Enzyme Inhibition, 2018, *14,* 1-8

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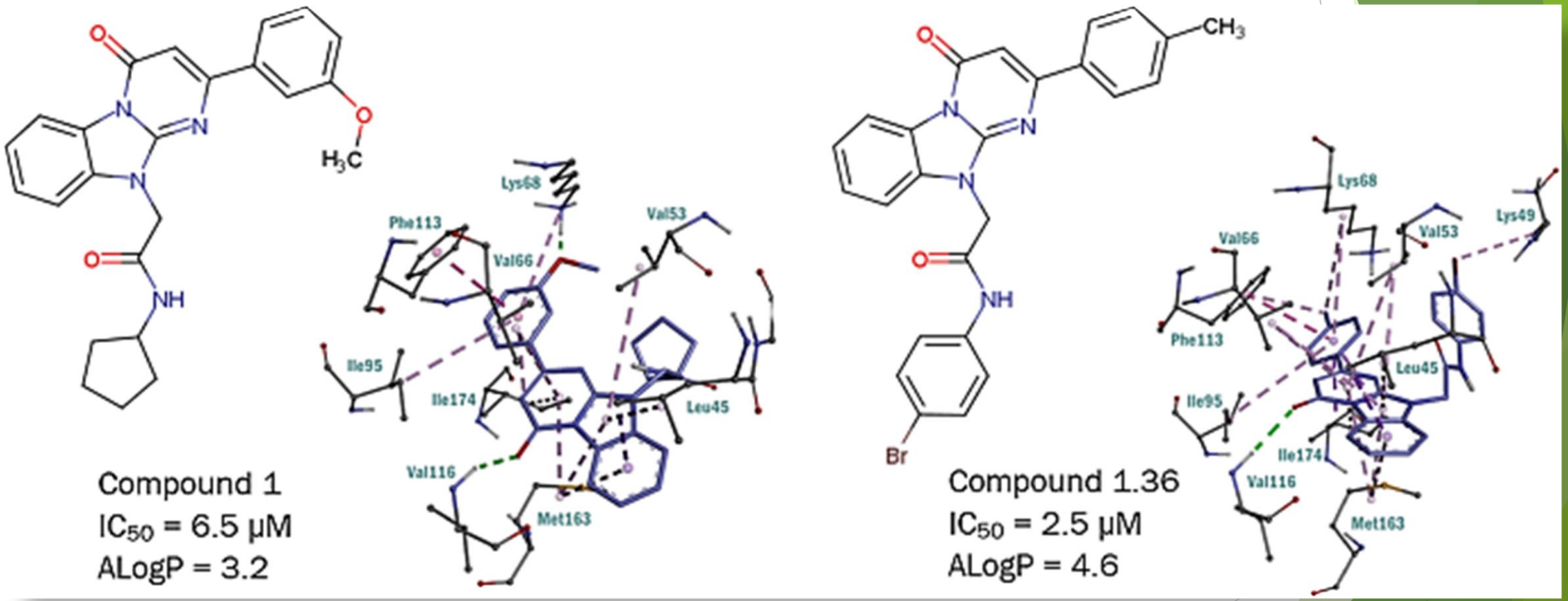
Dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-4-ones as a new class of CK2 inhibitors



Molecular Diversity 2018, 22, 991

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Virtual screening of a small organic compounds library was performed by

- molecular docking and
- pharmacophore screening

298 compounds were selected for biochemical testing according to the results of virtual screening. The compound activity was determined by *in vitro* biochemical tests using γ-P32 ATP.

In vitro experiments showed that **18 compounds** have inhibitory activity against CK2 with IC_{50} in the range of 1.4 to 20 μM

The active compounds belonged to **15 chemical classes**

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“When the chemistry is right, all the experiments work”

Gregory Benford, *Shipstar*

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"*CHEMriya*" — alluding to *Mriya*, the Ukrainian word for "*dream*" — is a chemical space comprising 11 billion tangible screening compounds that are not present in any other commercial chemical catalog

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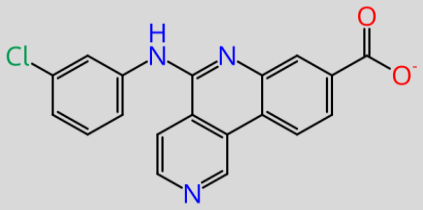
Query



Matching

Results

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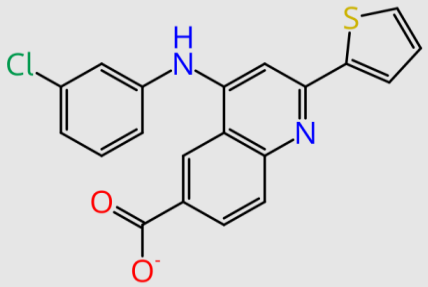
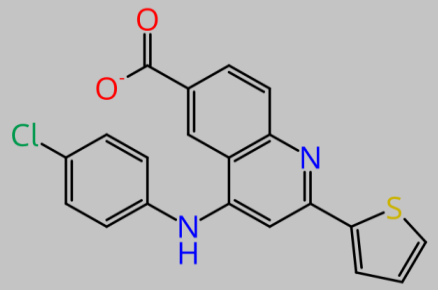
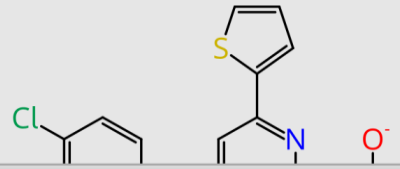
☑	1		0.980	11bn-CHEMriya_2021-04	YAS_R004__...OTV1000234
☑	2		0.980	11bn-CHEMriya_2021-04	YAS_R004__..._OTV998833
☑	3		0.980	11bn-CHEMriya_2021-04	YAS_R004__..._OTV998833

Query: Silmitasertib.mol

Search in: 11bn-CHEMriya_2021-04

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ACKNOWLEDGEMENTS:

MOLECULAR DESIGN GROUP

ORGANIC CHEMISTRY GROUP

BIOLOGICAL GROUP

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