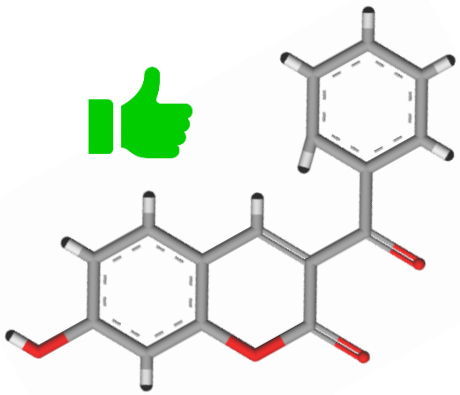
Quinazolinone-Schiff's bases available for biochemical and computational screening of hDPP III inhibitors

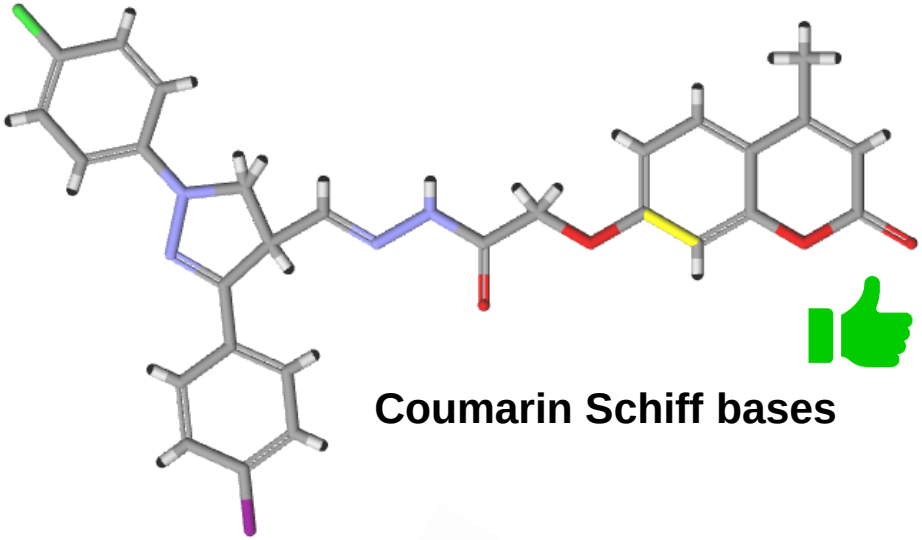
Dejan Agić

HrZZ Croatian Science Foundation

DPP III Minisymposium, Zagreb September 23rd 2022

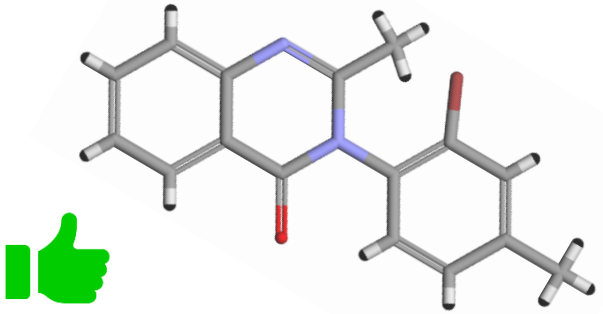


Coumarin derivatives



Coumarin Schiff bases

Quinazolinone Schiff bases

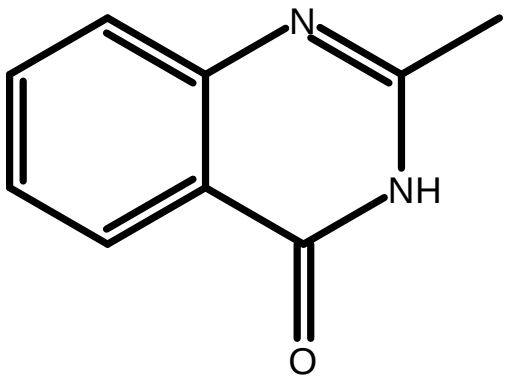


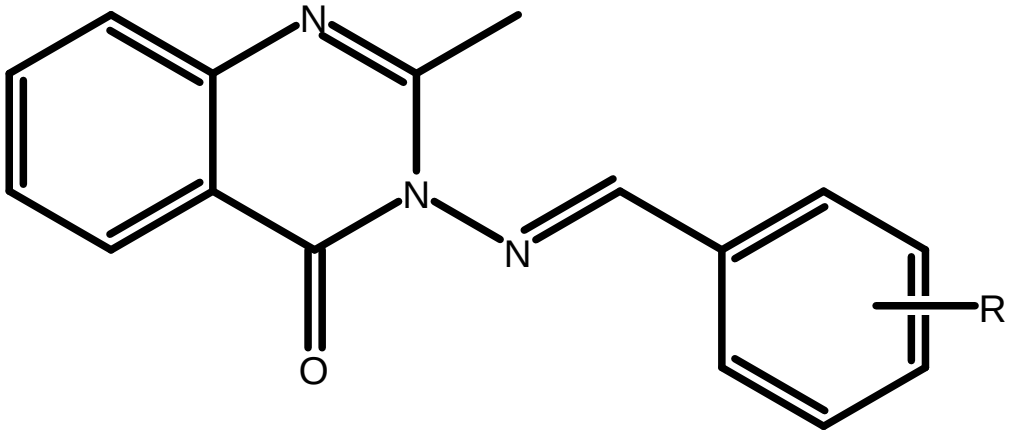
Quinazolinone derivatives

Experimental

precursor

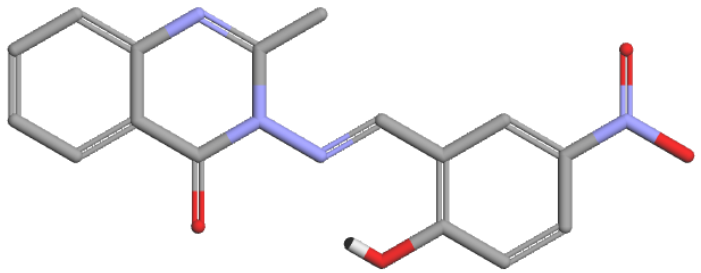
6 % inh





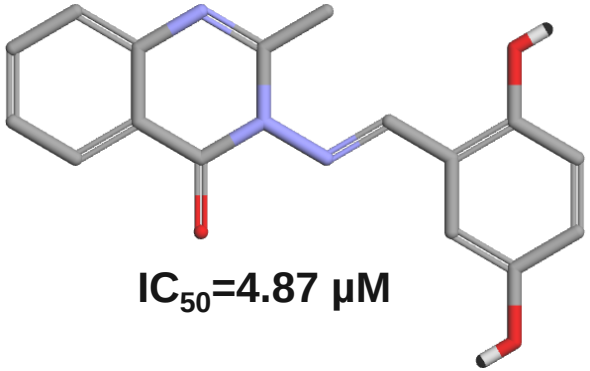
Compound	R	Inh (%)
1	2,4-$(OH)_2$	91
2	2-OH-3-OC_2H_5	61
3	2-OH	90
4	2-Cl	64
5	2-OH-5-Br	53
6	2,5-$(OCH_3)_2$	84
7	3,4,5-$(OCH_3)_3$	NA
8	2,3-$(OH)_2$	90
9	3-Cl	31
10	4-OCH_3	38
11	3-Br	30
12	styryl	32
13	4-N,N-$(CH_3)_2$	48
14	3,4-$(OH)_2$	82
15	2-OH-4-benzyloxy	2
16	3-OH	70
17	4-OH	66
18	3-OH-4-OCH_3	24
19	3,5-$(OH)_2$	74
20	2-OCH_3	85
21	H	39
22	2-OH-5-Cl	57
23	2-OH-5-NO_2	97
24	2-OH-3,5-$(Br)_2$	76
25	2,5-$(OH)_2$	91
26	4-Br	54
27	3-OCH_3-4-OH	42

23



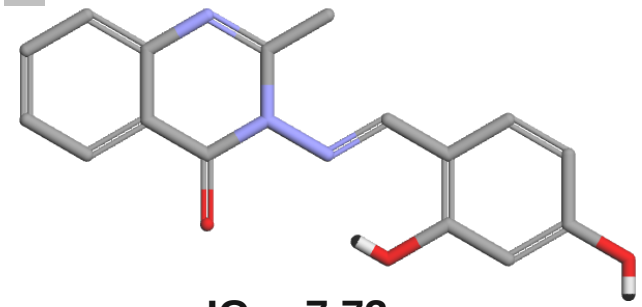
IC_{50}=0.90 μM

25



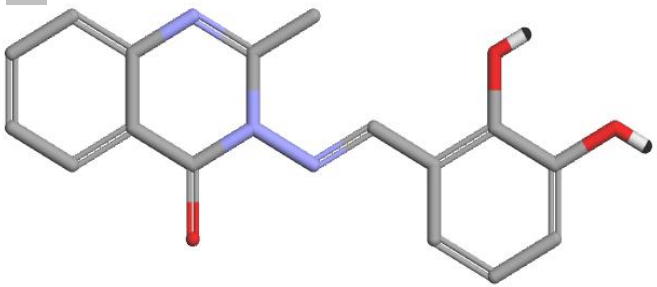
IC_{50}=4.87 μM

1



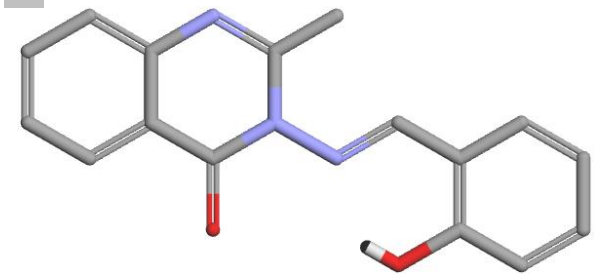
IC_{50}=7.73

8



IC_{50}=7.95

3



IC_{50}=8.70

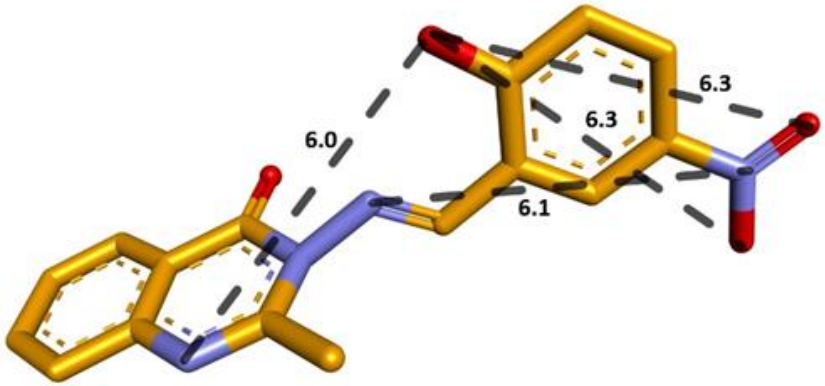
QSAR

- **log % hDPP III inh. = - 5.31 + 1.61 *IC1* + 0.79 *GATS6m* - 1.46 *EEig15d***

diversity of neighboring atom pairs

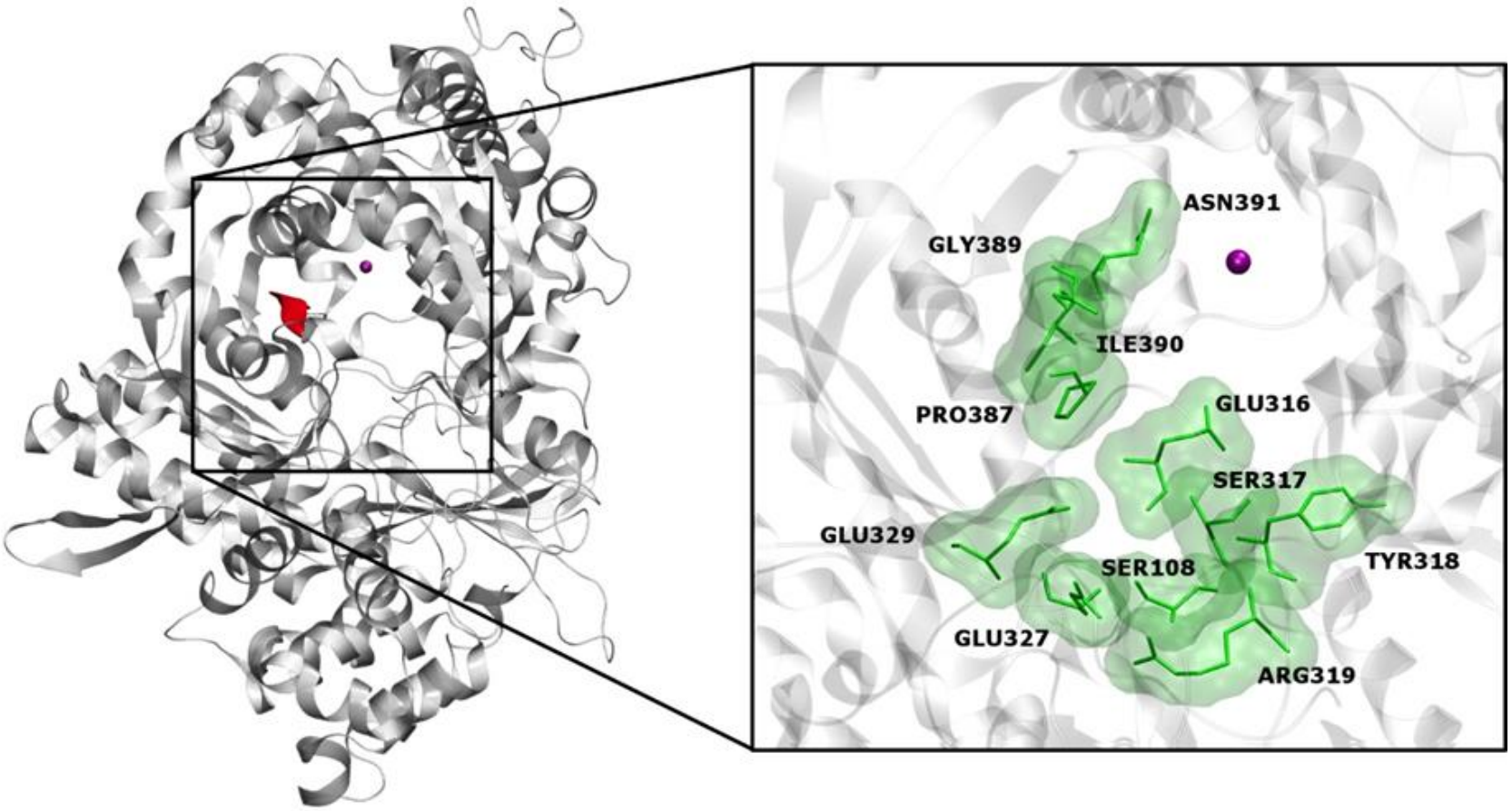
dependence of one atom on value of mass of other atoms at the 6 Å

presence of atoms higher polarity

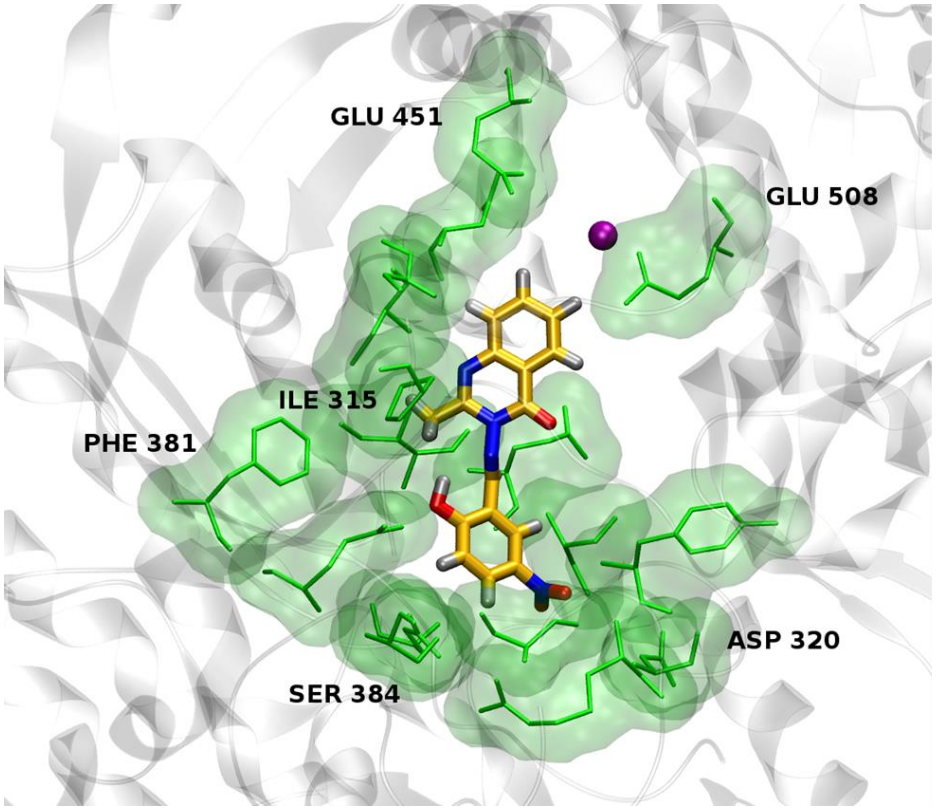


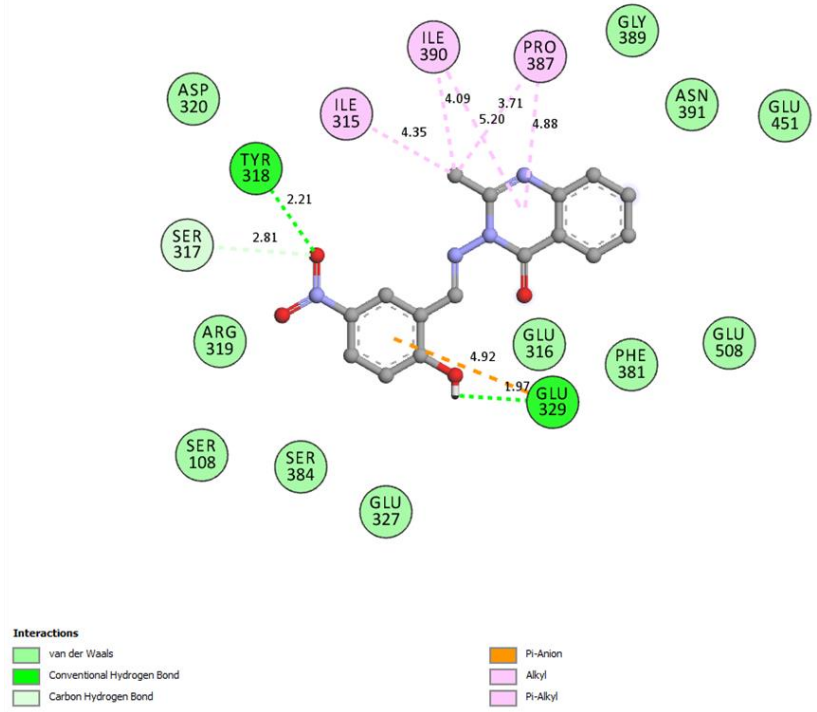
- **model satisfied all validation criteria, R^2 = 0.88**

Docking

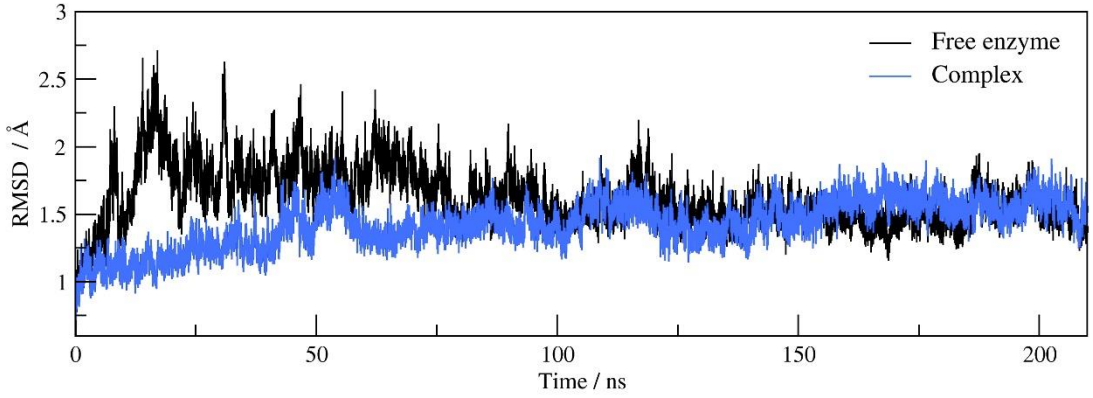

ASN391
GLY389
ILE390
PRO387
GLU316
SER317
GLU329
SER108
TYR318
GLU327
ARG319

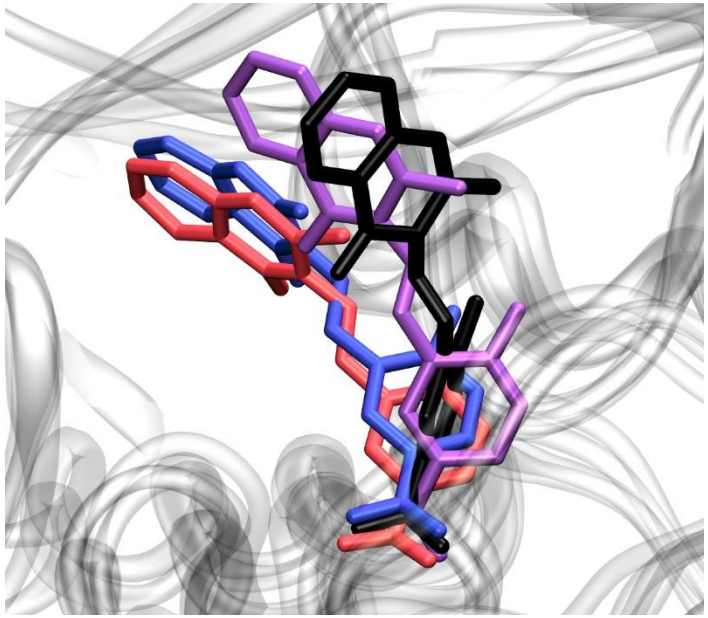
Residues	Subsites				
	S2	S1	S1'	S2'	S3'
PHE109	-	-	-	**25**	-
GLU316	**1, 3, 8, 23, 25**	-	-	-	-
TYR318	-	**1, 3, 8, 23, 25**	-	**1, 3, 8, 23, 25**	-
GLU329	-	**1, 3, 8, 23, 25**	-	-	-
PHE381	-	**1, 3, 8, 23**	-	-	-
PRO387	-	**1, 3, 8, 23, 25**	**1, 3, 8, 23, 25**	**1, 3, 8, 23, 25**	**1, 3, 8, 23, 25**
GLY389	-	**1, 3, 8, 23, 25**	**1, 3, 8, 23, 25**	-	-
ILE390	**1, 3, 8, 23, 25**	**1, 3, 8, 23, 25**	-	-	-
ASN391	**1, 3, 8, 23, 25**	-	-	-	-
GLU508	**1, 8, 23**	**1, 8, 23**	-	-	-
HIS568	**25**	**25**	**25**	-	-

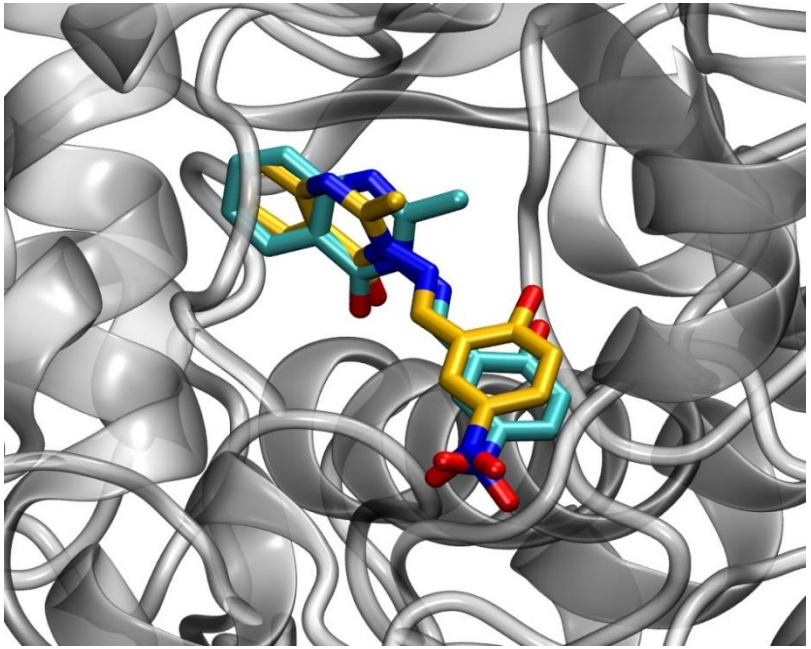

GLU 451
GLU 508
ILE 315
PHE 381
ASP 320
SER 384


ILE 390
PRO 387
GLY 389
ASP 320
ILE 315
ASN 391
GLU 451
4.09
3.71
5.20
4.88
4.35
TYR 318
2.21
SER 317
2.81
ARG 319
GLU 316
PHE 381
GLU 508
4.92
1.97
GLU 329
SER 108
SER 384
GLU 327
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Alkyl
Pi-Alkyl

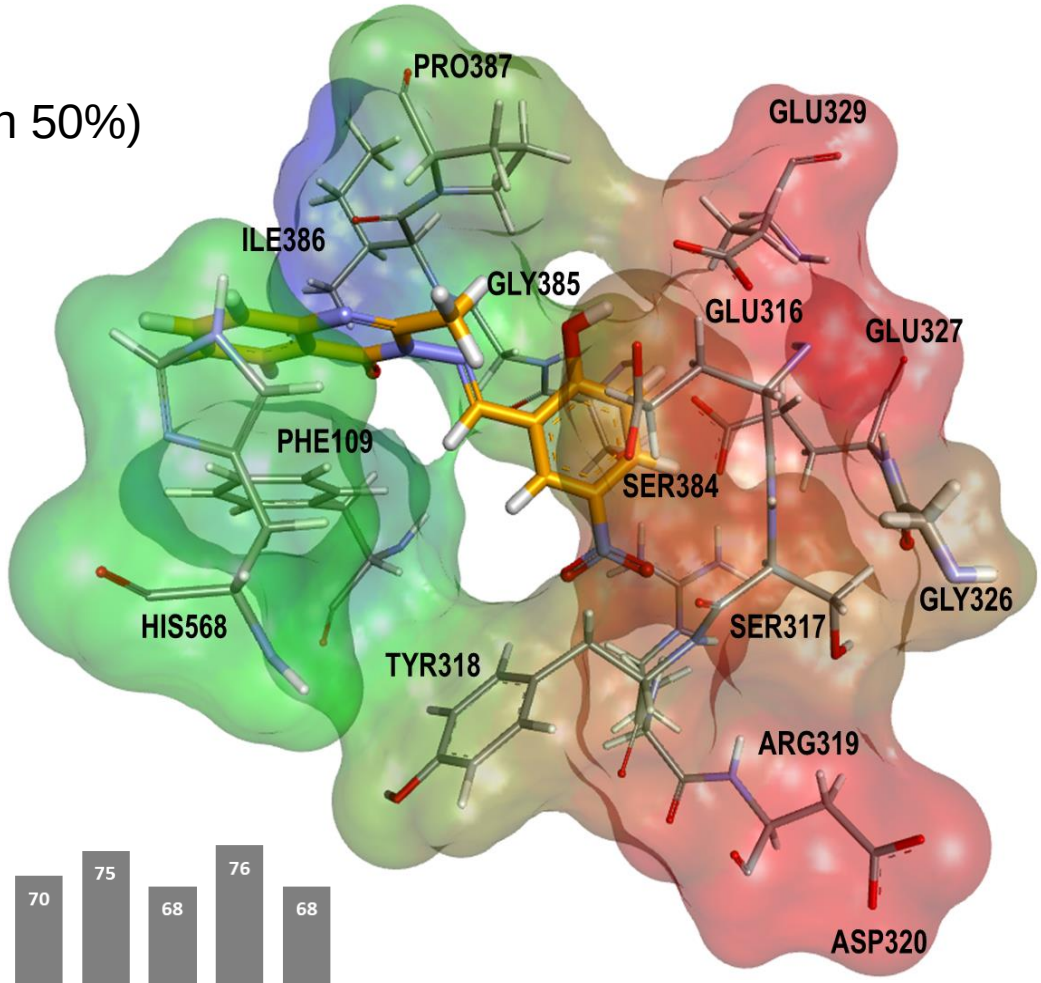
MD simulations

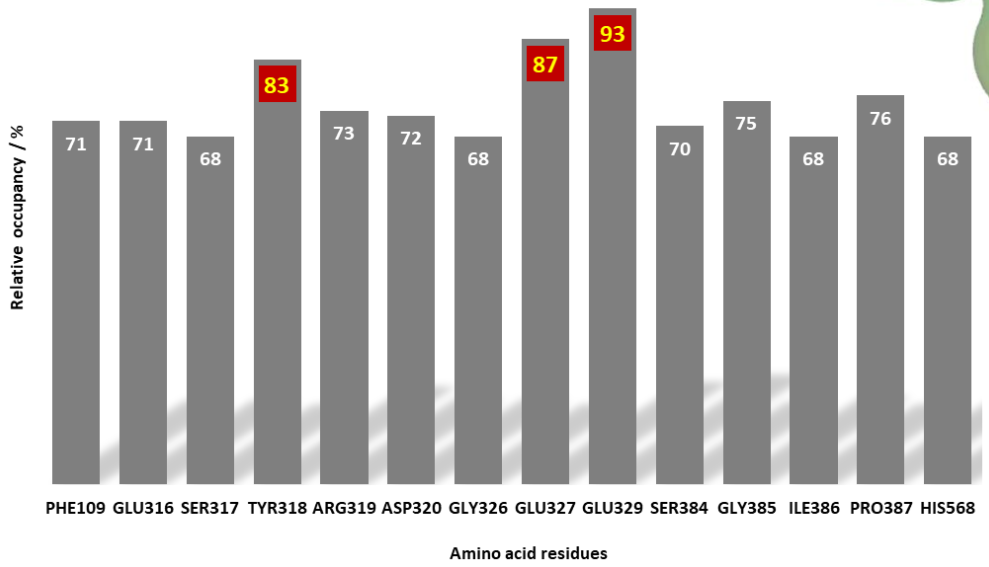


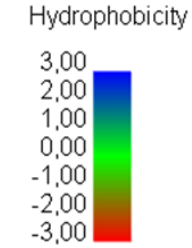




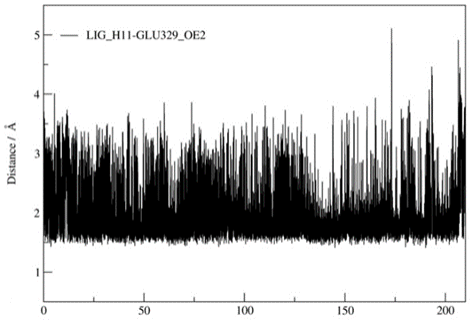
Relative occupancy (more than 50%) of native contacts

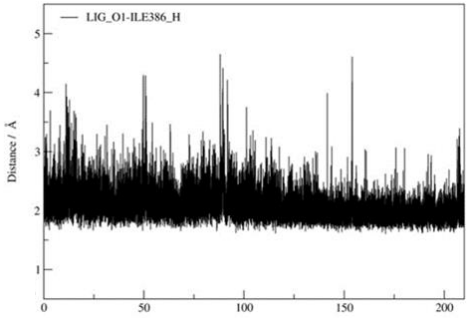


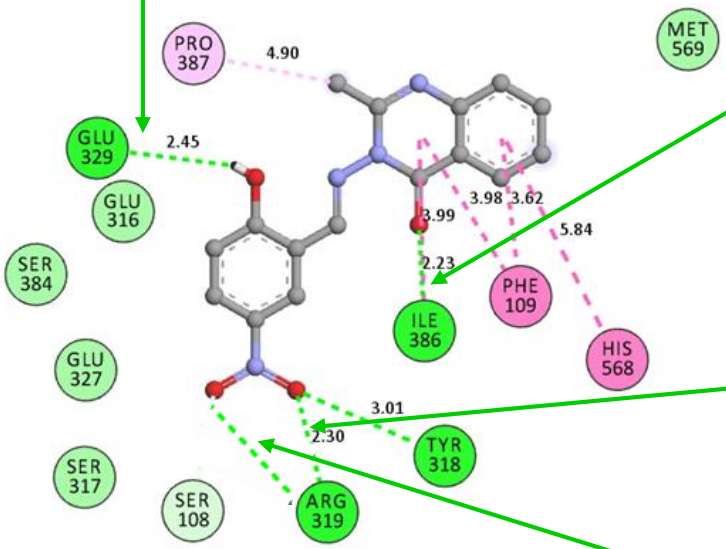




H- bonds


LIG_H11-GLU329_OE2
Distance / Å


LIG_O1-ILE386_H
Distance / Å


PRO 387
4.90
MET 569
GLU 329
2.45
GLU 316
3.98
3.62
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5.84
SER 384
2.23
PHE 109
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GLU 327
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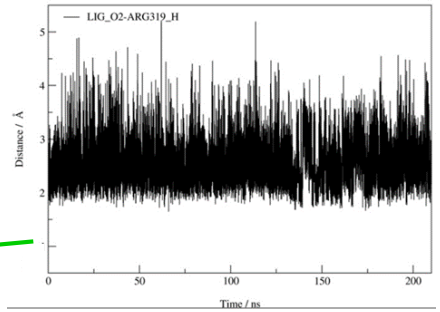
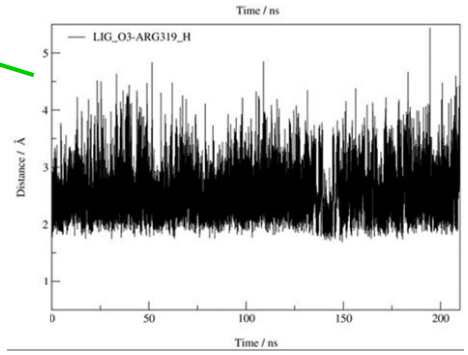
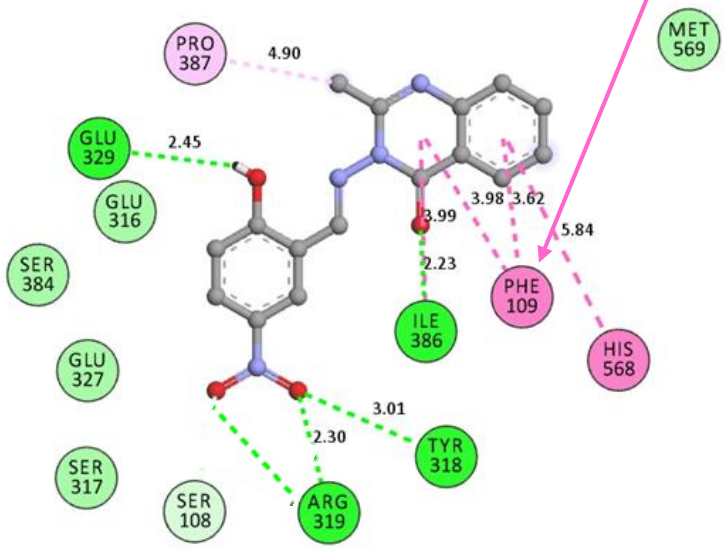
TYR 318
SER 317
SER 108
ARG 319


LIG_O2-ARG319_H
Distance / Å
Time / ns


Time / ns
LIG_O3-ARG319_H
Distance / Å
Time / ns


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Amide-Pi Stacked
Alkyl

π-π stacking


PRO 387
4.90
MET 569
GLU 329
2.45
GLU 316
3.98
3.62
3.99
5.84
SER 384
2.23
PHE 109
ILE 386
HIS 568
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3.01
2.30
TYR 318
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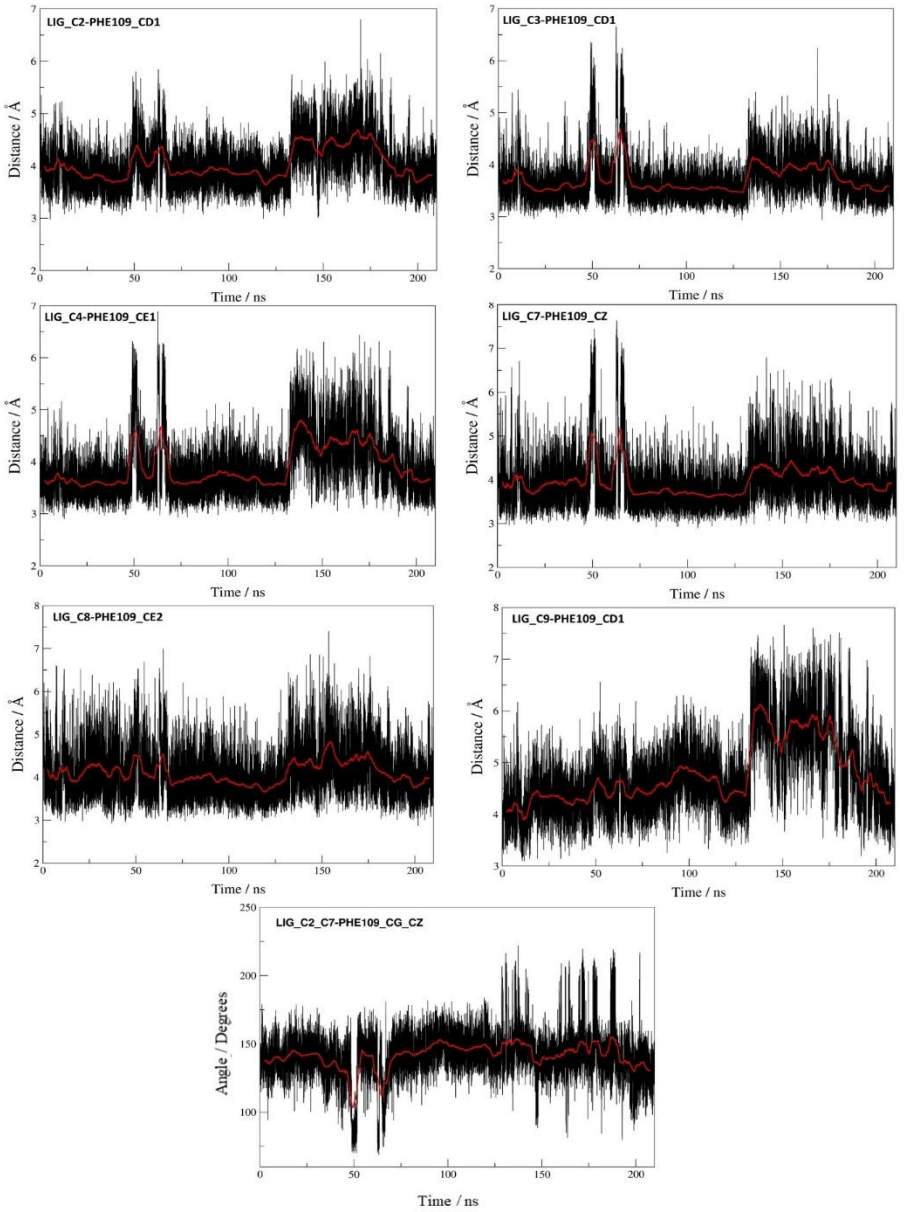
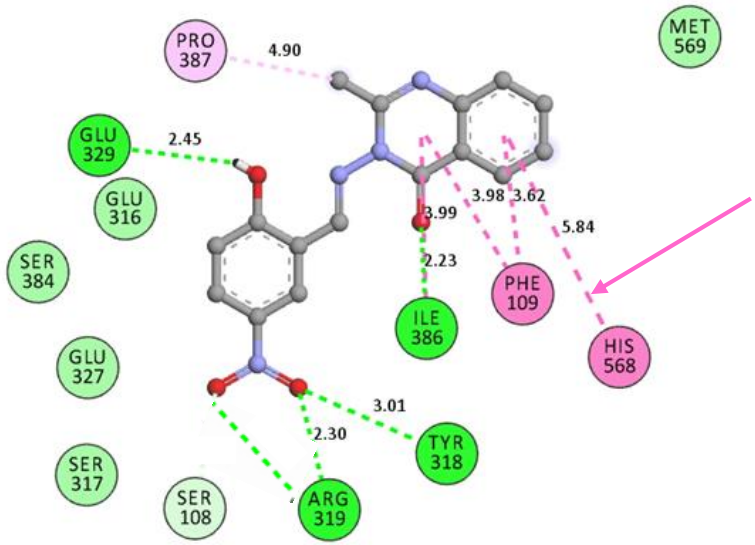
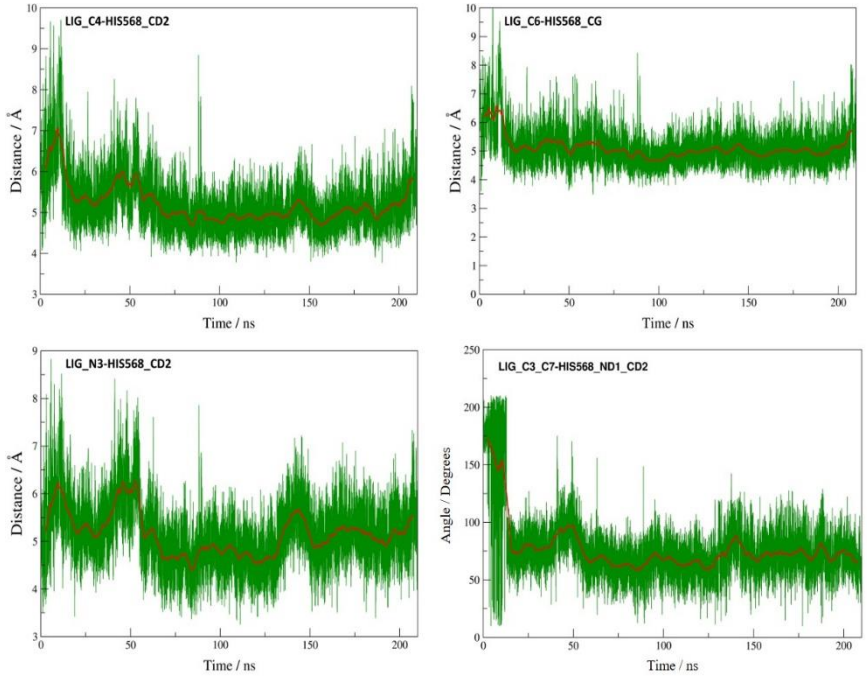

LIG_C2-PHE109_CD1
LIG_C3-PHE109_CD1
LIG_C4-PHE109_CE1
LIG_C7-PHE109_CZ
LIG_C8-PHE109_CE2
LIG_C9-PHE109_CD1
LIG_C2_C7-PHE109_CG_CZ
Distance / Å
Angle / Degrees
Time / ns

π-π T -shape





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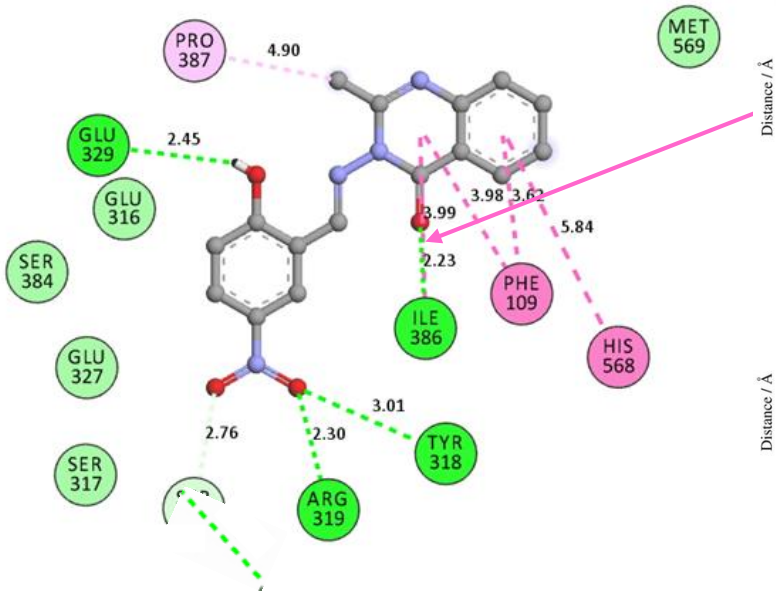
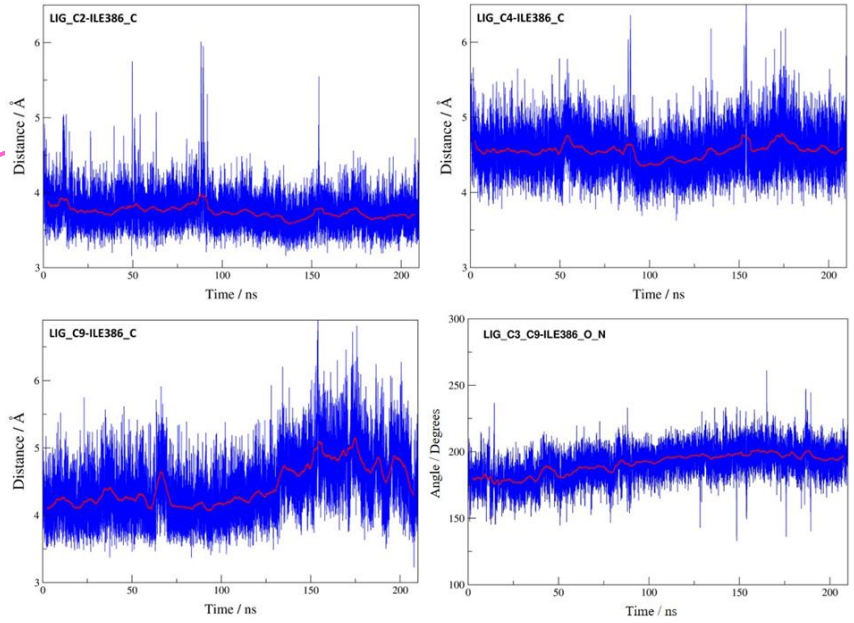
- Pi-Pi T-shaped
- Amide-Pi Stacked
- Alkyl

amide-π stacking





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Experimental and computational evaluation of dipeptidyl peptidase III inhibitors based on quinazolinone-Schiff's bases

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Thank you for your attention