Influence of the DPP III cancer mutations on the KEAP1-NRF2 signaling pathway

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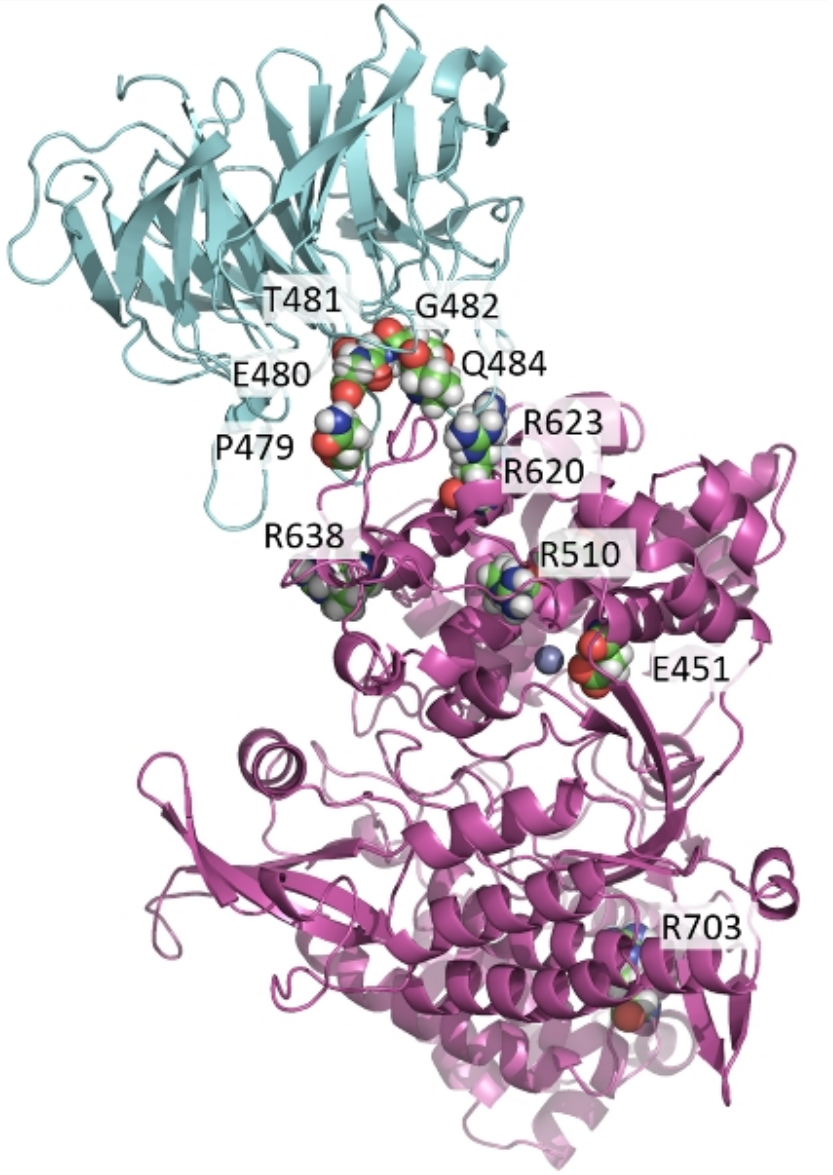
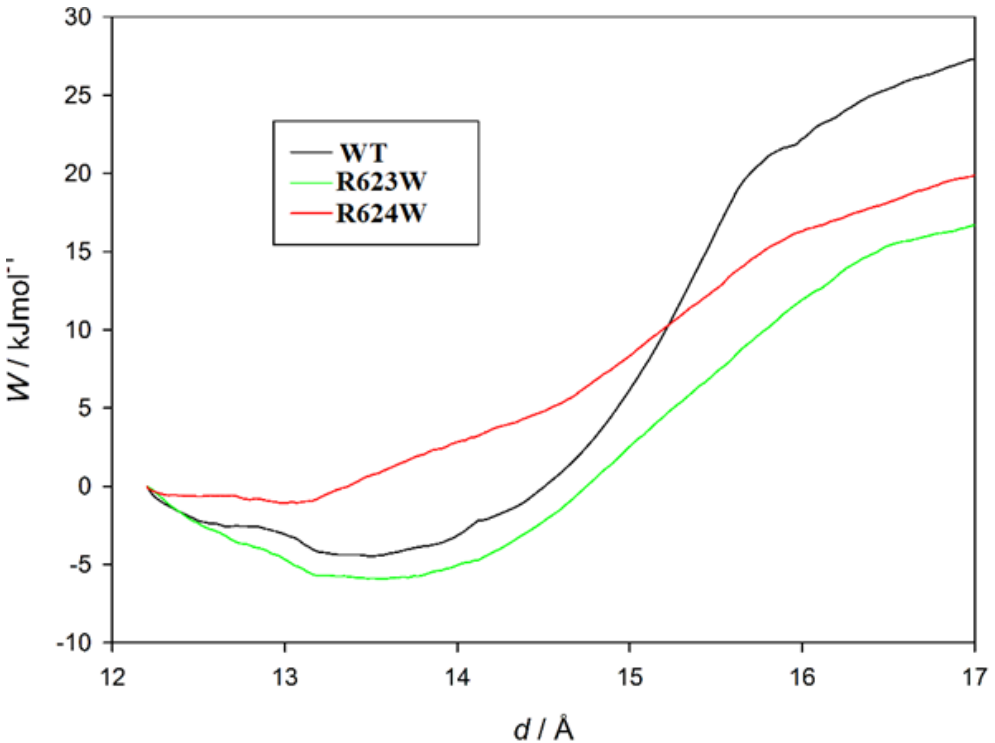
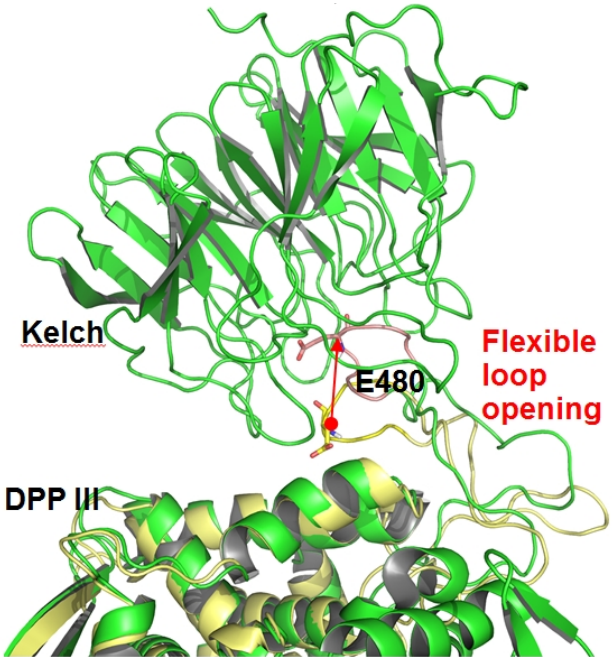
Working Meeting of the BioRe project, IRB, Zagreb, 14.02.2022.

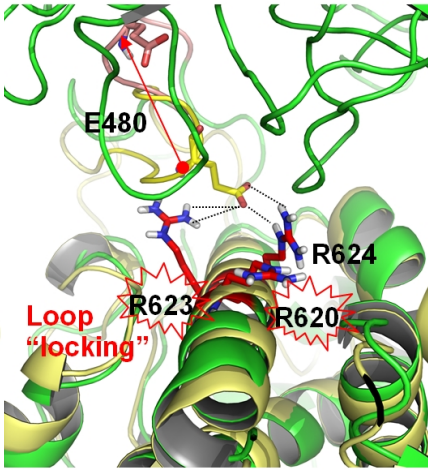
Mutacije DPP III



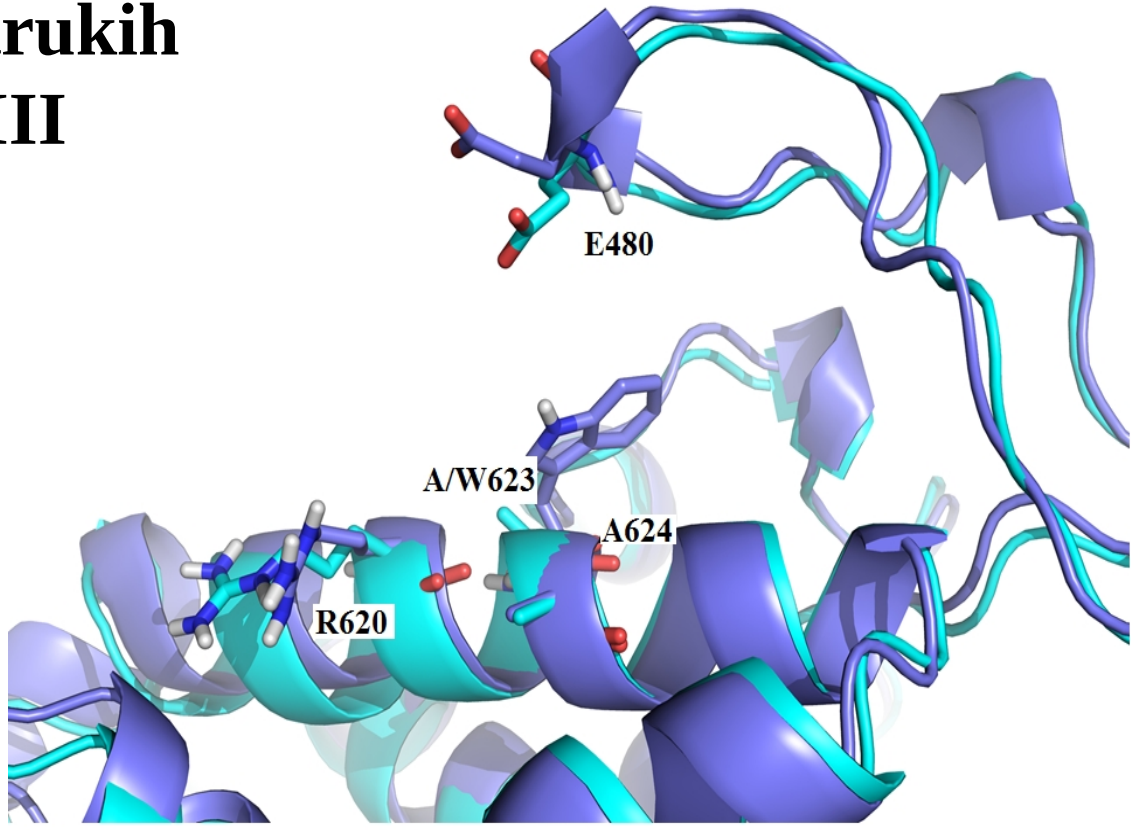
Otvaranje petlje ETGE DPP III







Spontano otvaranje petlje kod dvostrukih mutanata DPP III

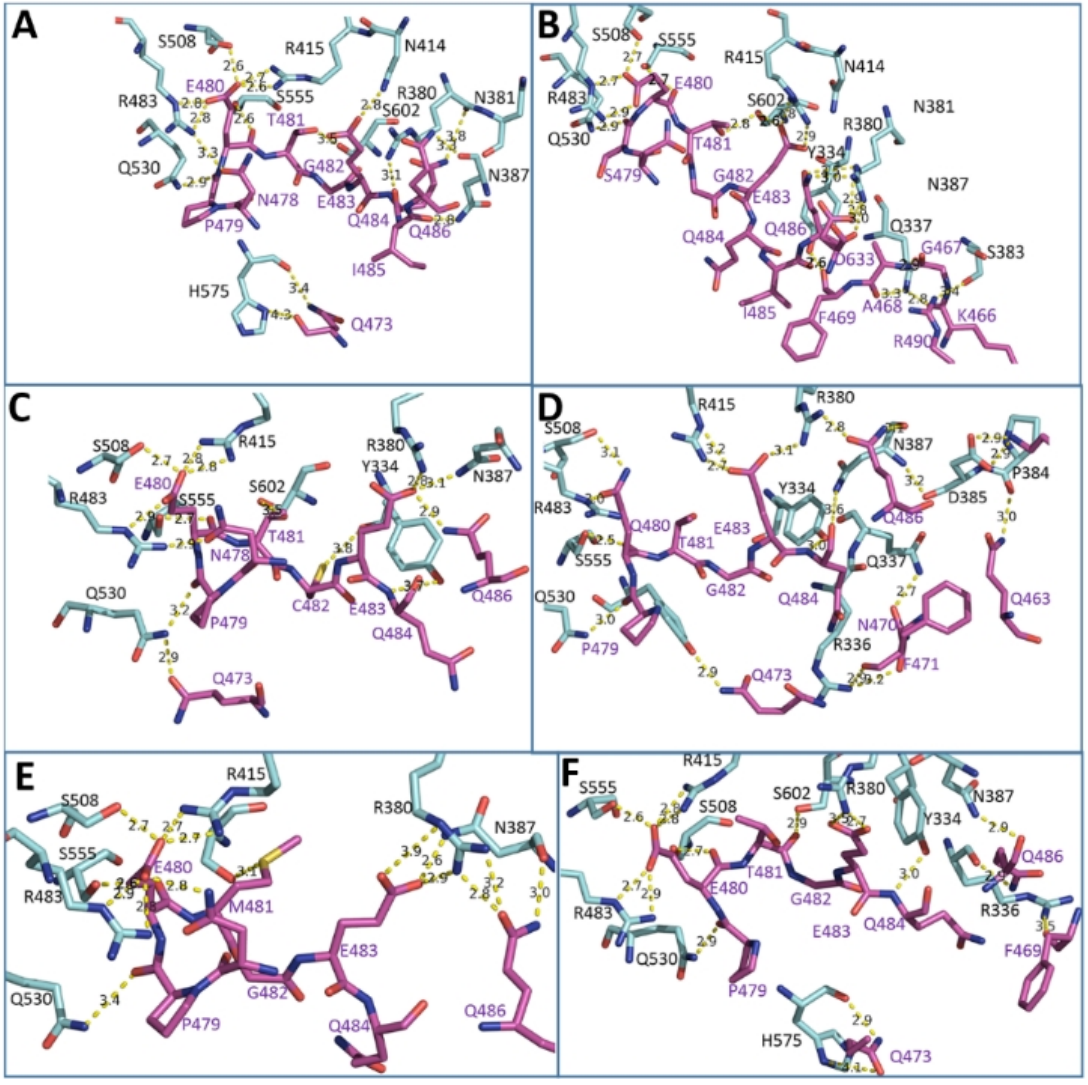


Računi MM-GBSA za simulacije varijanti DPP III u kompleksu s domenom Kelch

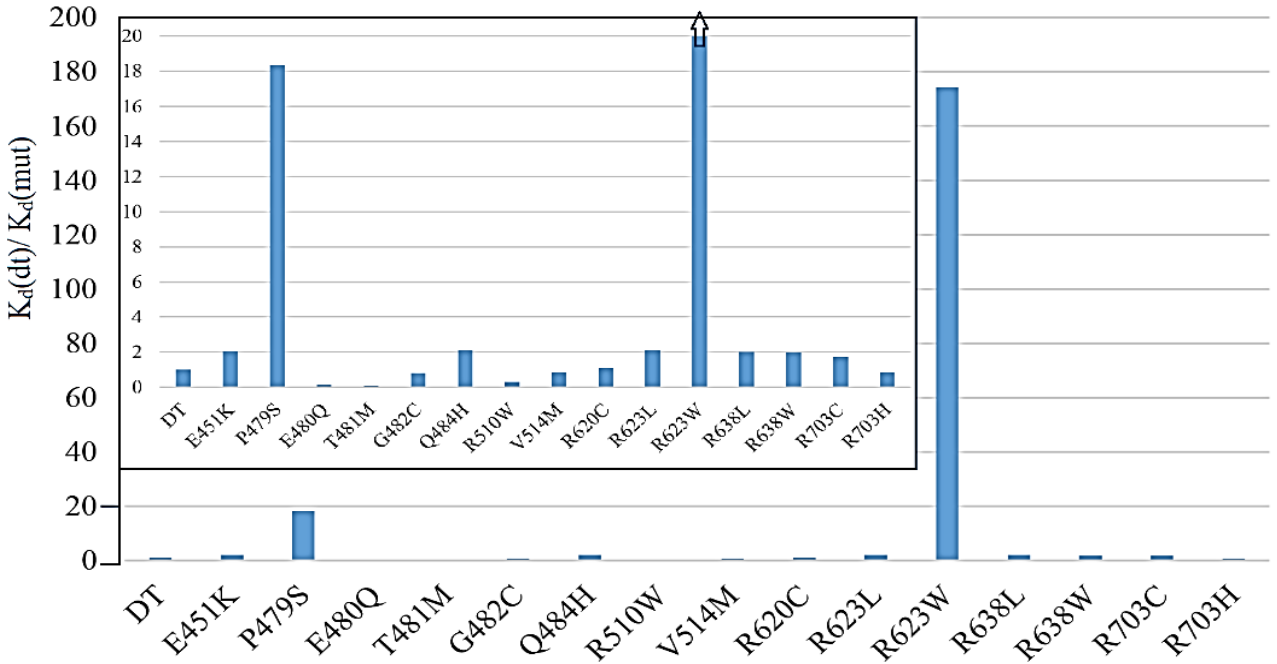
Varijanta DPP	**MM-GBSA-min (kcal/mol)**
WT	**-80**
P479S	-116
E480Q	-42
T481M	-63
G482C	-56
R510W	-69
R623W	-65

Međumolekulske interakcije varijanti DPP III s domenom Kelch

Varijanta DPP	Ukupno H-veze
WT	**14.7**
P479S	20.6
E480Q	8.8
T481M	13.1
G482C	10.4
R510W	13.6



Mjerenja interakcije varijanti DPP III s domenom Kelch MST-om



DPP III	K_d (WT)/ K_d(mut)
WT	**1.0**
E451K	2.1
P479S	**18.4**
E480Q	0.1
T481M	0.1
G482C	0.8
Q484H	2.1
R510W	0.3
R623W	**160.0**
R638L	2.0
R638W	2.0
R703C	1.7

Zaključak

Mutacija DPP III R623W omogućuje lakše otpuštanje ETGE petlje i smanjuje K_d

Supstitucija P479S neposredno ispred ETGE čini motiv sličnijim onom NRF2 (EETGE) i blago povećava afinitet vezanja

Supstitucija E480Q u DPP III narušava interakcije s KEAP1

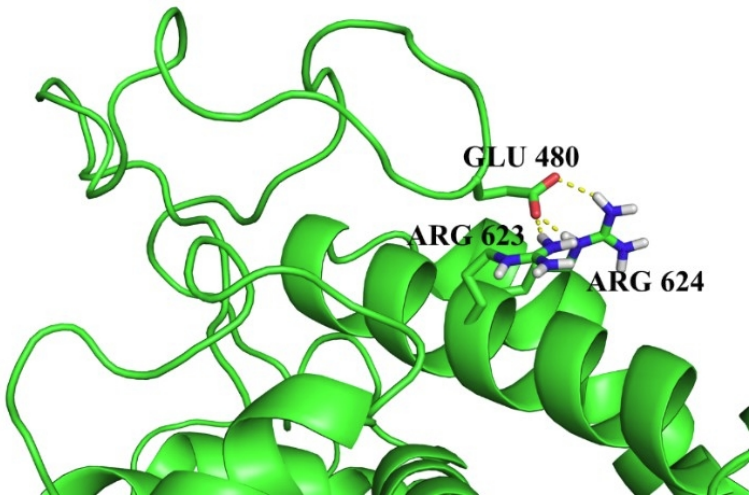
Objavljeni radovi

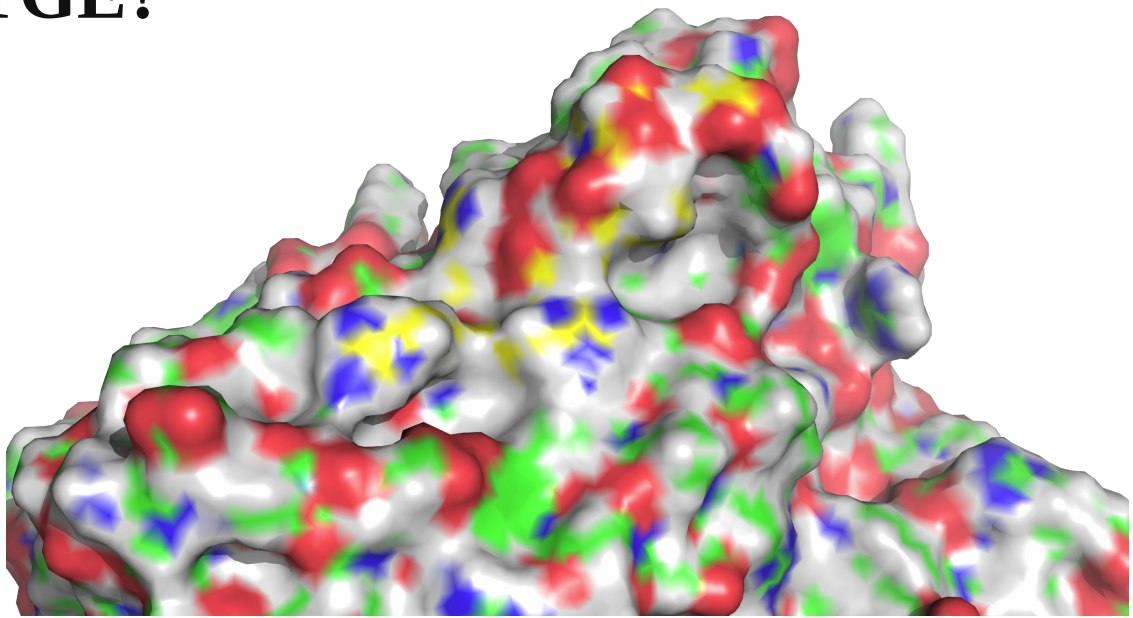
Matić, S.; Kekez, I.; Tomin, M.; Bogár, F.; Šupljika, F.; Kazazić, S.; Hanić, M.; Jha, S.; Brkić, H.; Bourgeois, B.; et al. *Binding of dipeptidyl peptidase III to the oxidative stress cell sensor Kelch-like ECH-associated protein 1 is a two-step process*. J. Biomol. Struct. Dyn. 2021,39, 6870–6881, doi:10.1080/07391102.2020.1804455

Matić, S.; Tomašić Paić, A.; Sobočanec, S.; Pinterić, M.; Pipalović, G.; Martinčić, M.; Matovina, M.; Tomić, S. *Interdisciplinary Study of the Effects of Dipeptidyl-Peptidase III Cancer Mutations on the KEAP1-NRF2 Signaling Pathway*. Int. J. Mol. Sci. 2022, 23, 1994. https://doi.org/10.3390/ijms23041994

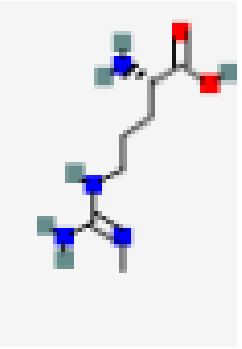
Inhibicija interakcije DPP III s domenom Kelch

Spriječiti otvaranje petlje ETGE?

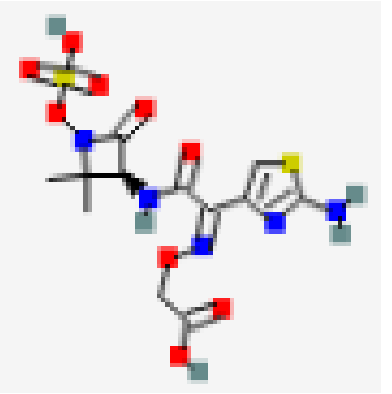




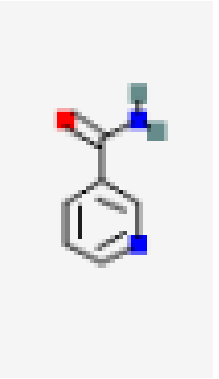
N-monomethyl-arginine



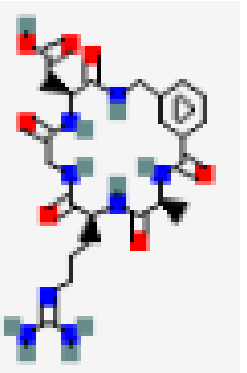
Tigemonam

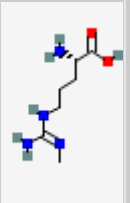
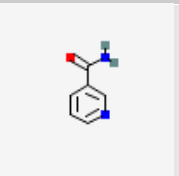
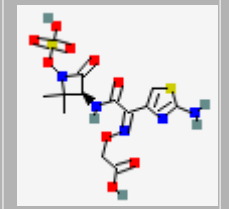
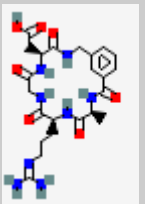


Nicotinamide

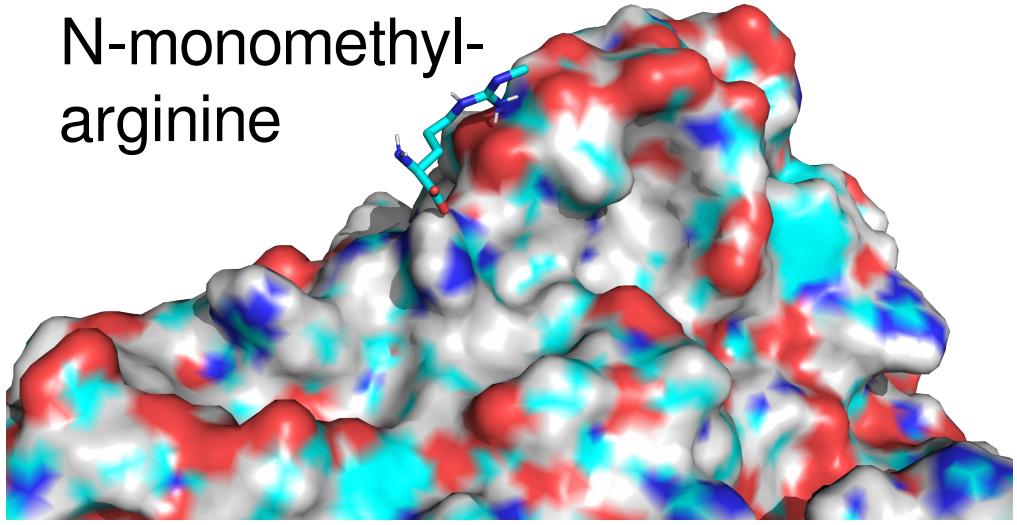


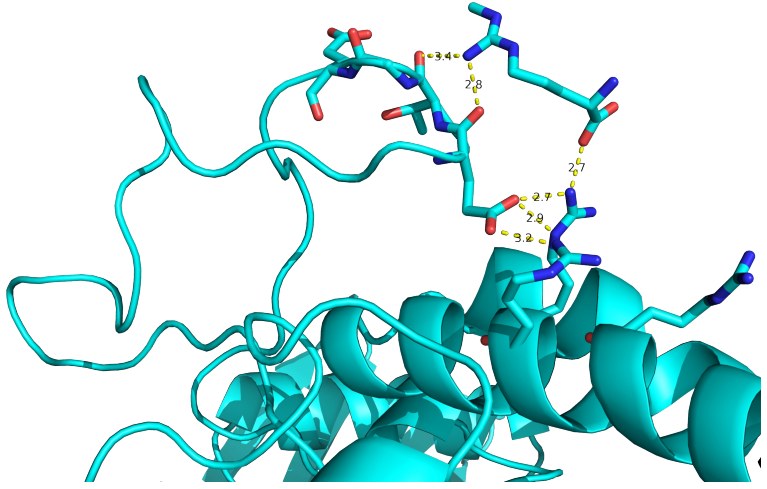
Cyclo(Ala-Arg-Gly-Asp-3-Aminomethylbenzoyl)



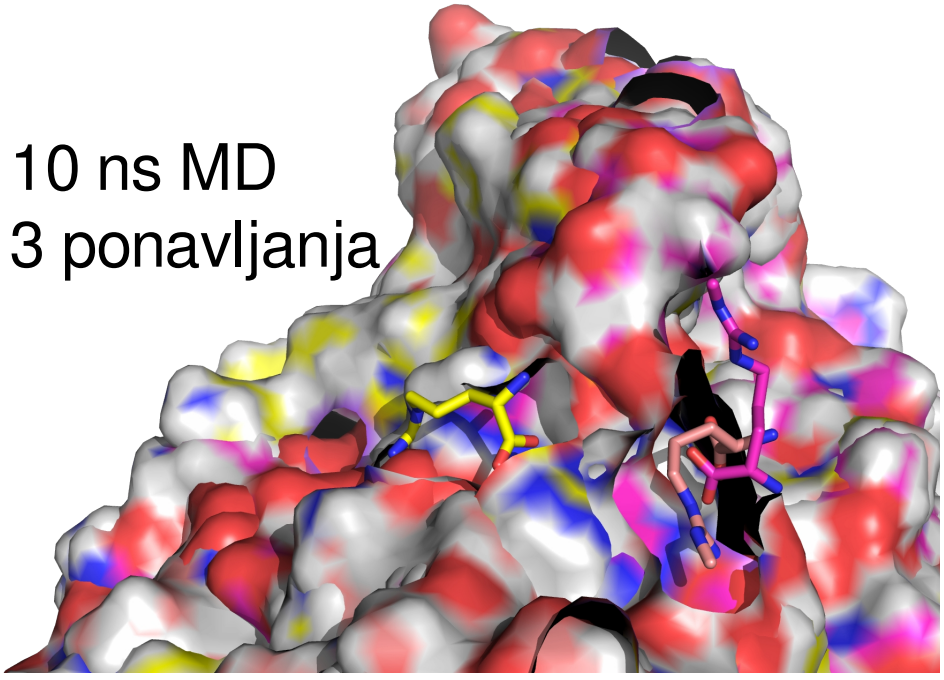
Ime	Struktura	Opis
N-monomethyl-arginine		Tilarginine is a pan-nitric oxide synthase (NOS) inhibitor, with potential immunomodulating and antineoplastic activities. Upon administration, tilarginine binds to and inhibits NOS, a free radical signaling molecule that promotes angiogenesis, metastasis, and immunosuppression in the tumor microenvironment (TME). Reduction in NOS activity may abrogate the immunosuppressive TME, enhance tumor antigen-specific immune response and inhibit tumor cell proliferation. Tilarginine has been investigated for the basic science, treatment, and diagnostic of Obesity, Type 2 Diabetes, Ocular Physiology, and Regional Blood Flow. N(omega)-methyl-L-arginine is a L-arginine derivative with a N(omega)-methyl substituent. It is a member of guanidines, a non-proteinogenic L-alpha-amino acid and a L-arginine derivative. It is a conjugate acid of a N(omega)-methyl-L-argininate. It is a tautomer of a N(omega)-methyl-L-arginine zwitterion.
Nicotinamide		Niacinamide or Nicotinamide (NAM) is a form of vitamin B3 found in food and used as a dietary supplement and medication. As a supplement, it is used by mouth to prevent and treat pellagra (niacin deficiency). While nicotinic acid (niacin) may be used for this purpose, niacinamide has the benefit of not causing skin flushing. As a cream, it is used to treat acne. It is a water-soluble vitamin. Niacinamide is the supplement name while Nicotinamide (NAM) is the scientific name. Side effects are minimal. At high doses liver problems may occur. Normal amounts are safe for use during pregnancy. Niacinamide is in the vitamin B family of medications, specifically the vitamin B3 complex. It is an amide of nicotinic acid. Foods that contain niacinamide include yeast, meat, milk, and green vegetables.
Tigemonam		Tigemonam is a monobactam antibiotic
Cyclo(Ala-Arg-Gy-Asp-3-Aminomethylbenzoyl)		cyclic RGD peptide (XJ735) specific to integrin alphavbeta3, indicating that this integrin was likely involved in L-isoaspartyl methyltransferase (PIMT) regulation

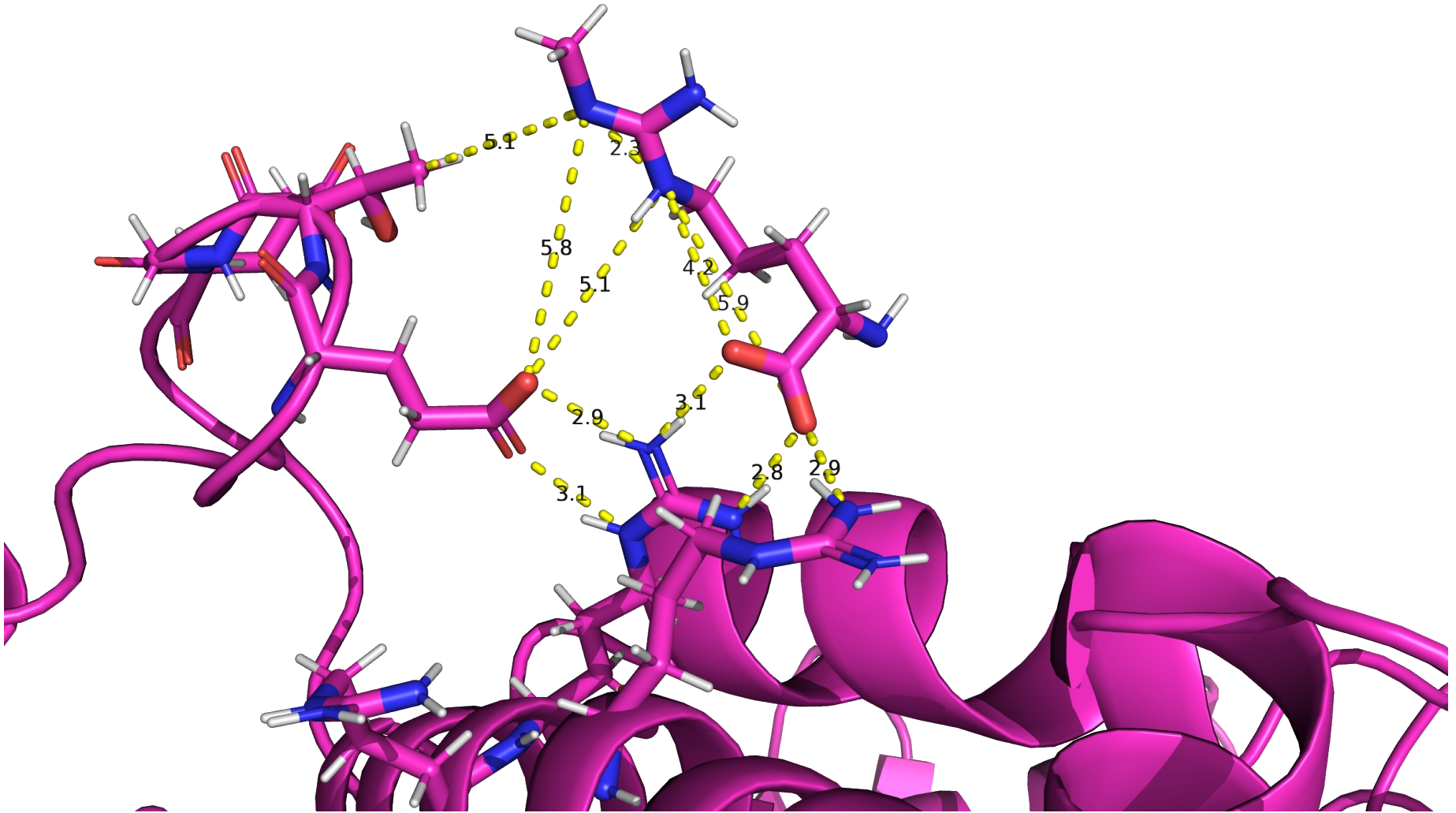
N-monomethyl-
arginine



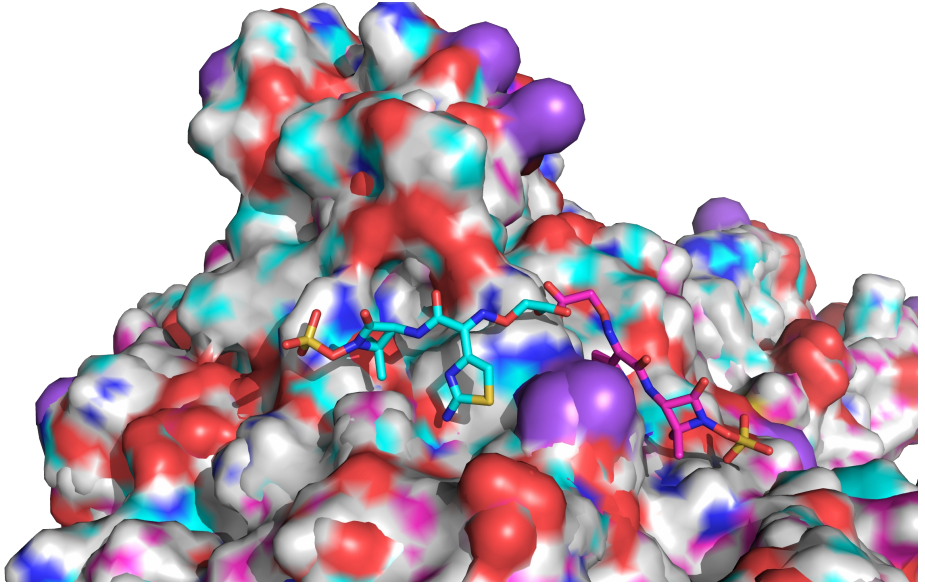


10 ns MD
3 ponavljanja




5.1
2.3
5.8
5.1
4.2
5.9
2.9
3.1
3.1
2.8
2.9

Tigemonam



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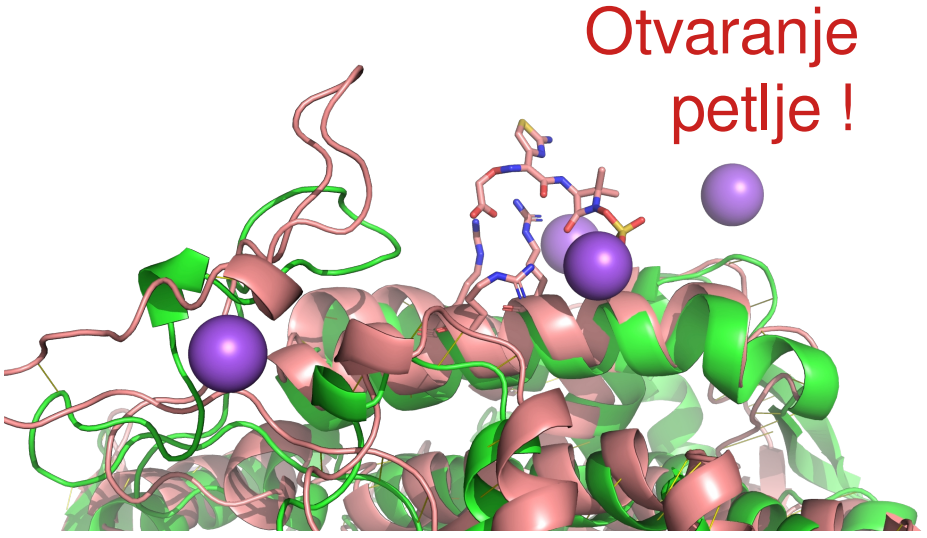

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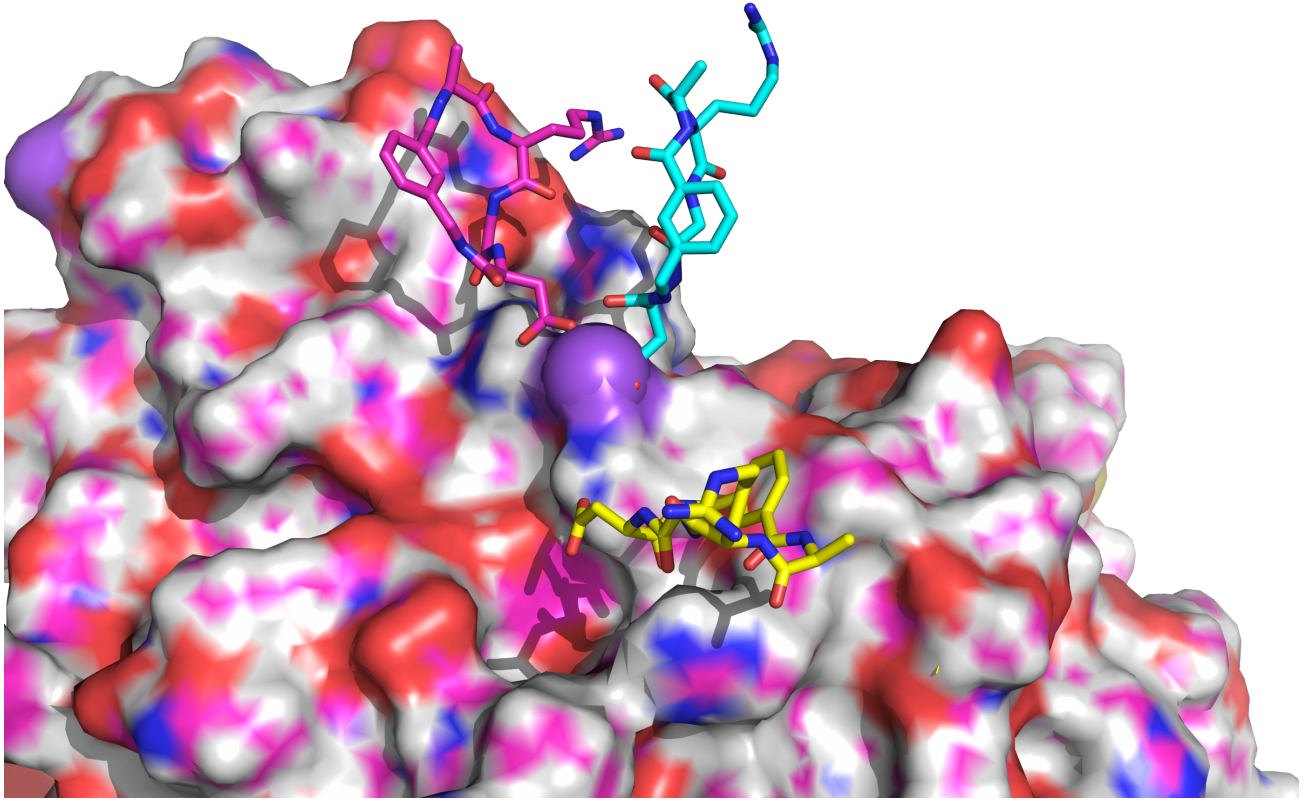

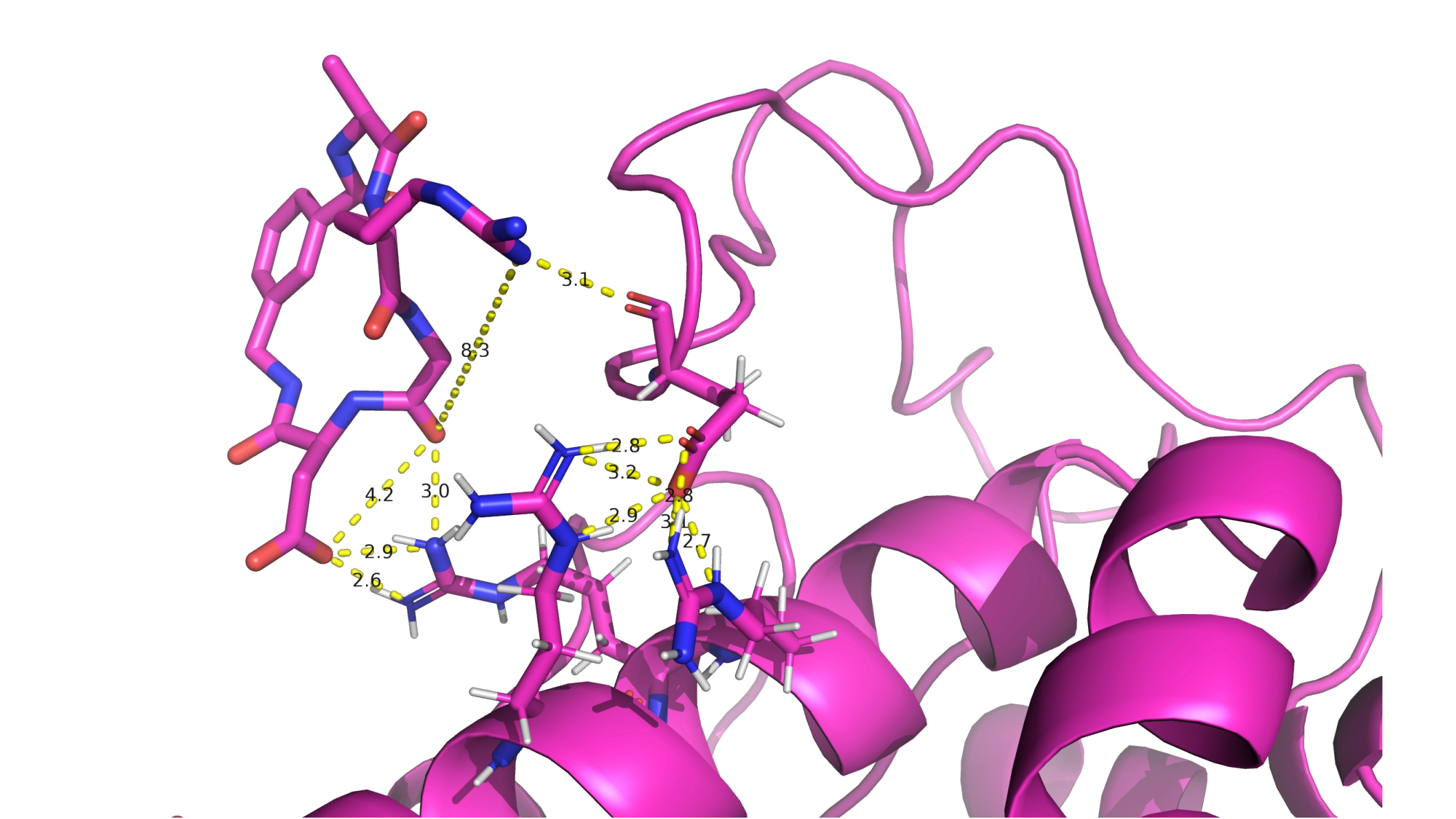
3.1
8.3
2.8
3.2
4.2
3.0
2.8
2.9
3.1
2.7
2.9
2.6

Pitanja

Koja je optimalna veličina i položaj polarnih skupina za stabilnu interakciju?

Mogu li male molekule inhibirati otvaranje petlje stabilnom interakcijom?

Za koje molekule bi se mogla eksperimentalno ispitati inhibicija interakcije DPP III – Kelch i kojom metodom?