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Identification of Potential Allosteric Site Binders of Indoleamine 2,3-Dioxygenase 1 from Plants: A Virtual and Molecular Dynamics Investigation

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pharmaceuticals MDPI

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UFRJ

LMMBEC Laboratório de Modelagem Molecular e Biologia Estrutural Computacional

IPPN WALTER MORS UFRJ

Abstract: Ligand and structure-based computational screening tools were carried out to identify flavonoids with potential anticancer activity. Kushenol E, a flavonoid with proven anticancer activity and, at the same time, an inhibitor of the allosteric site of the enzyme indoleamine 2,3-dioxygenase-1 (IDO1), was used as the reference compound. Molecular docking and molecular dynamics simulations were performed for the screened flavonoids, which showed anticancer activity. Two of these flavonoids were identified as potential inhibitors of IDO1. Molecular dynamics simulations were also used to assess the conformational profile of IDO1.

Keywords: cancer, immunology, flavonoids, IDO1, virtual screening, molecular docking, molecular dynamics, free energy

Introduction

pharmaceuticals

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Article

Identification of Potential Allosteric Site Binders of Indoleamine 2,3-Dioxygenase 1 from Plants: A Virtual and Molecular Dynamics Investigation

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Laboratório de Modelagem Molecular e Biologia Estrutural Computacional, Instituto de Pesquisas de Produtos Naturais Walter Mors, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Av. Carlos Chagas Filho, 373, Bloco H, Cidade Universitária, Rio de Janeiro 21941-599, RJ, Brazil

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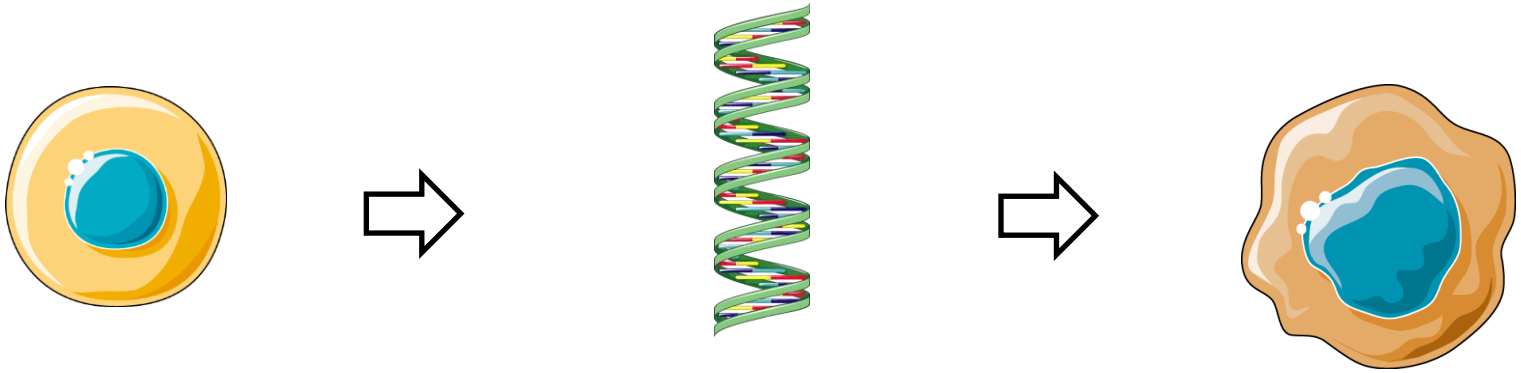
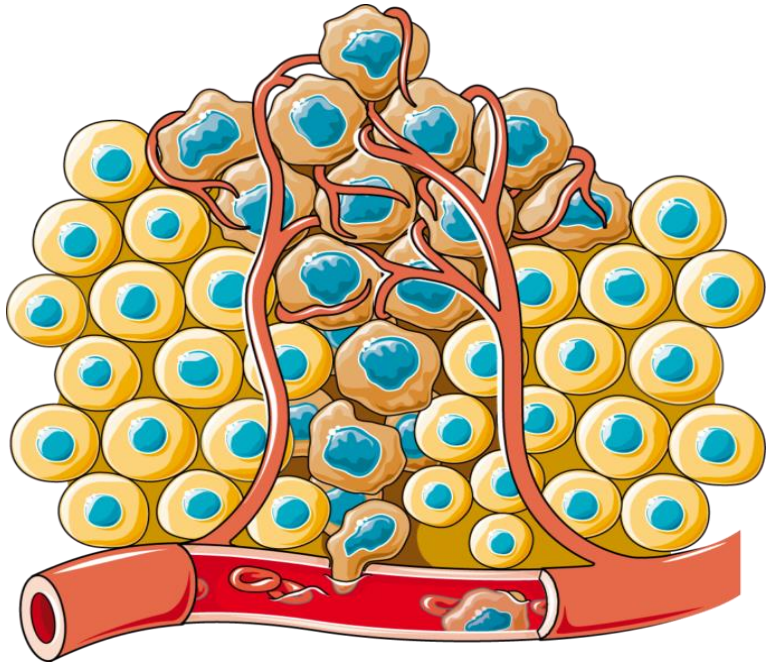
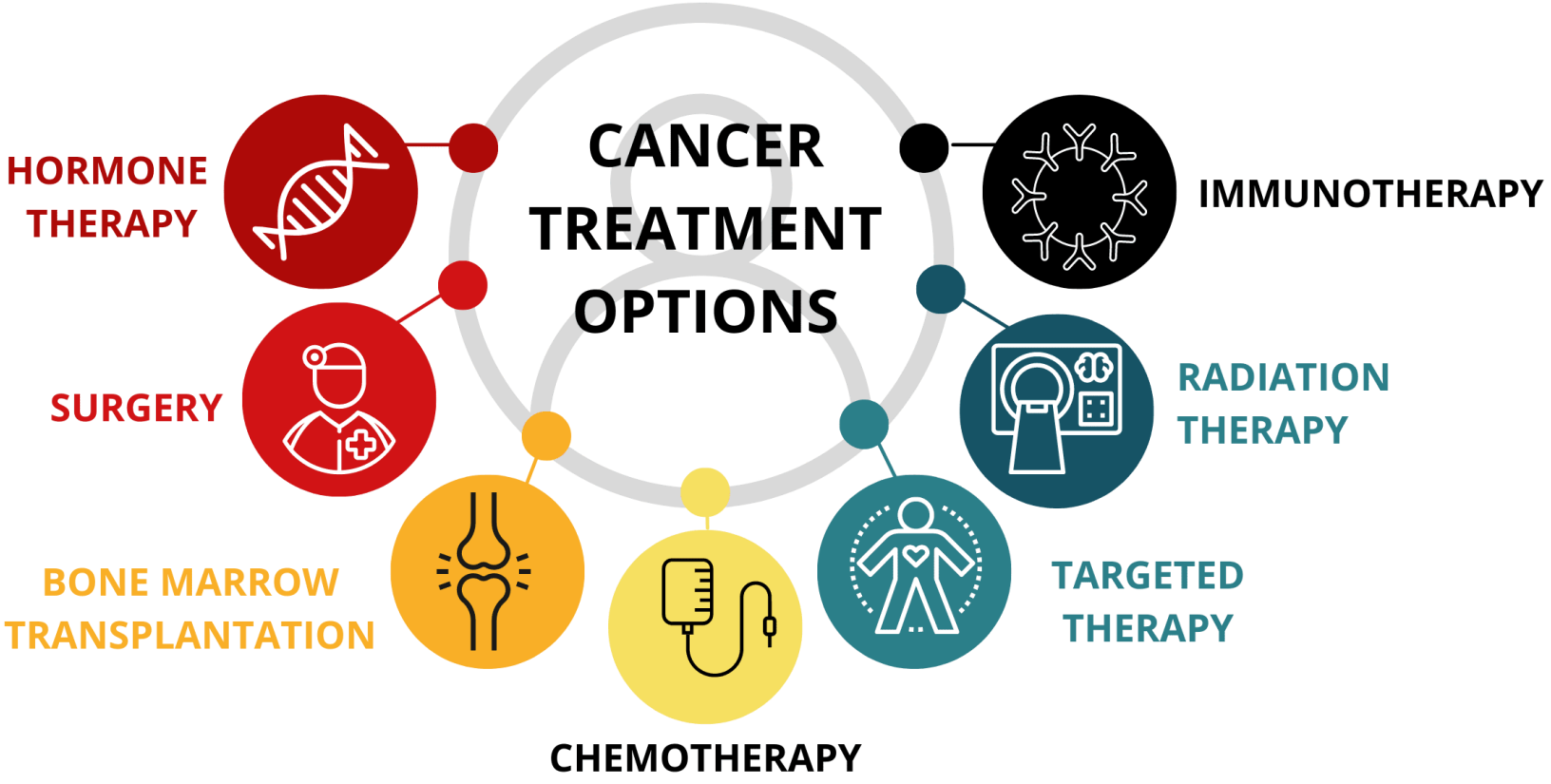
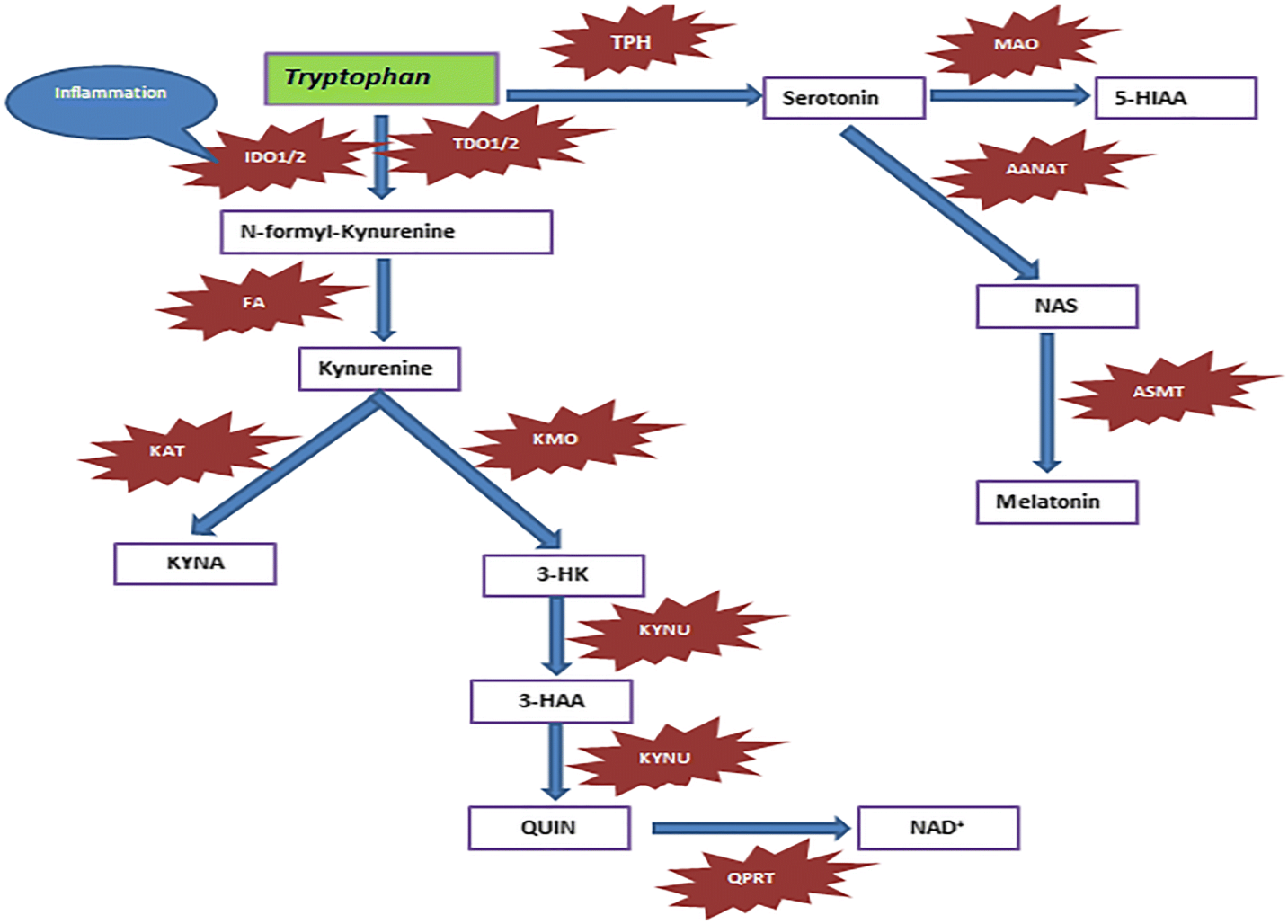




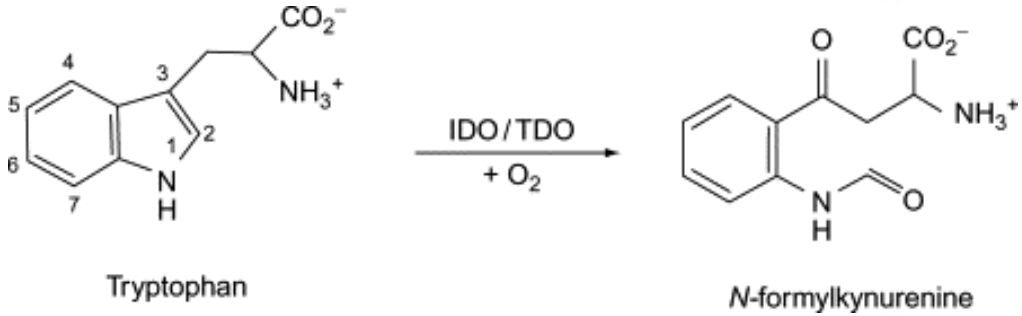


https://ebismedical.com/cancer-treatments/

Kyrurenine pathway

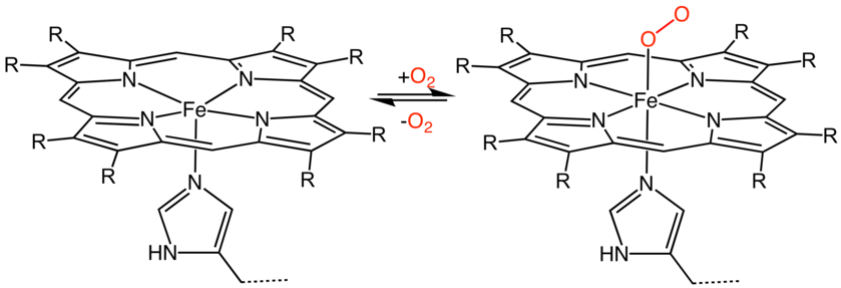


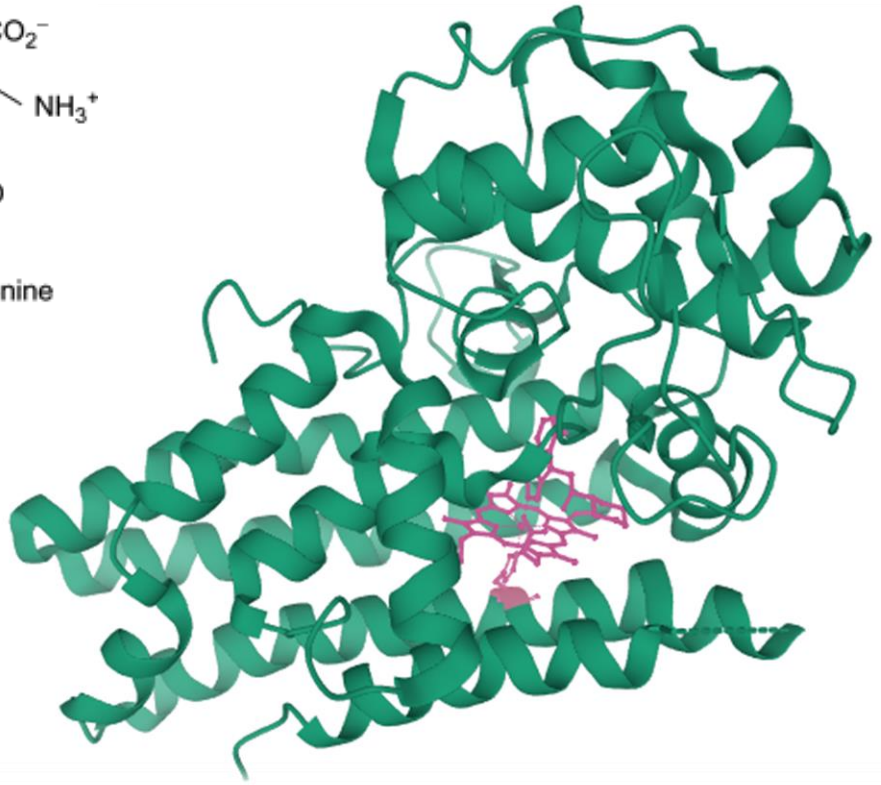
Indoleamine 2,3-dioxygenase-1

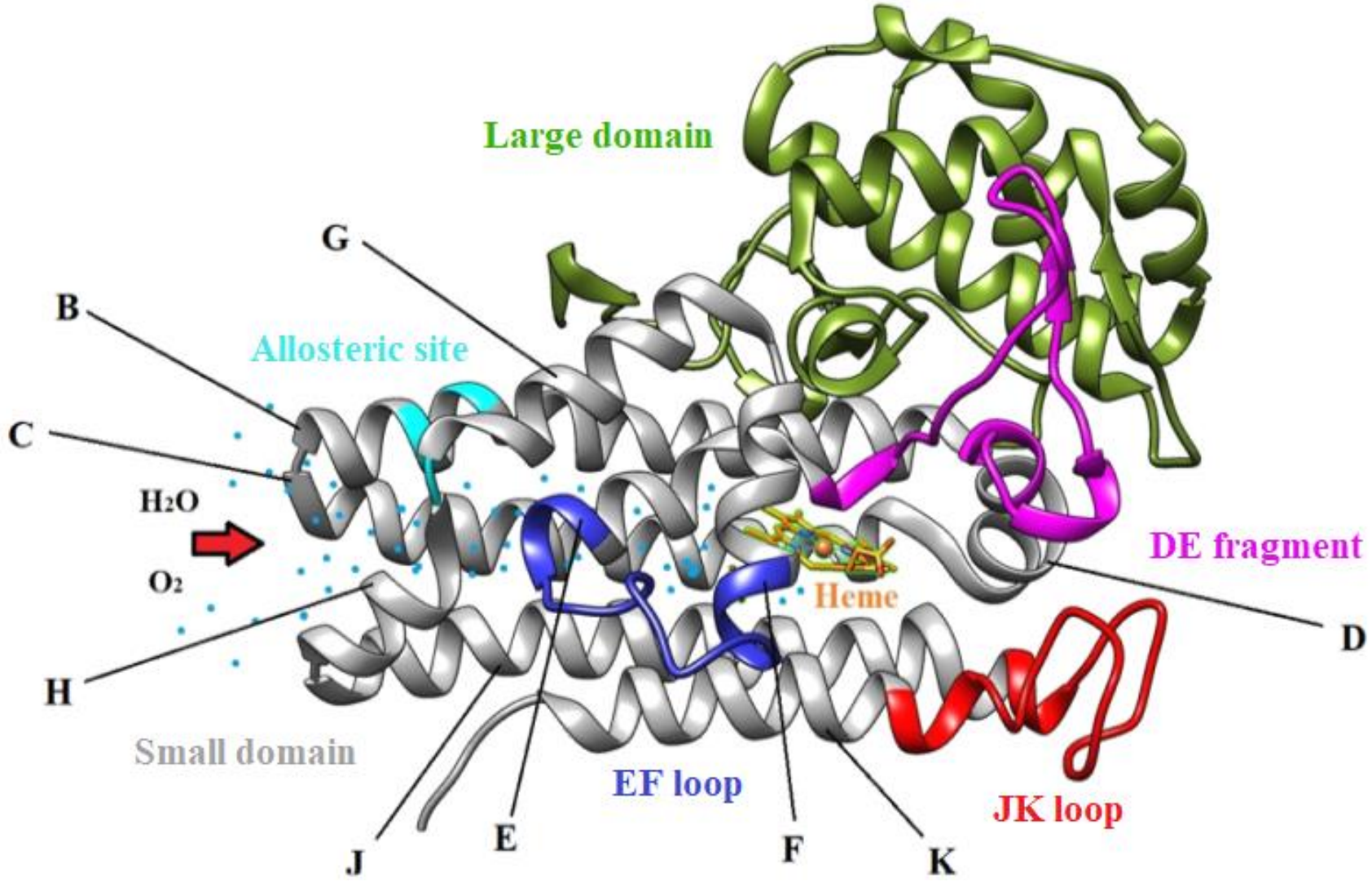


Tryptophan

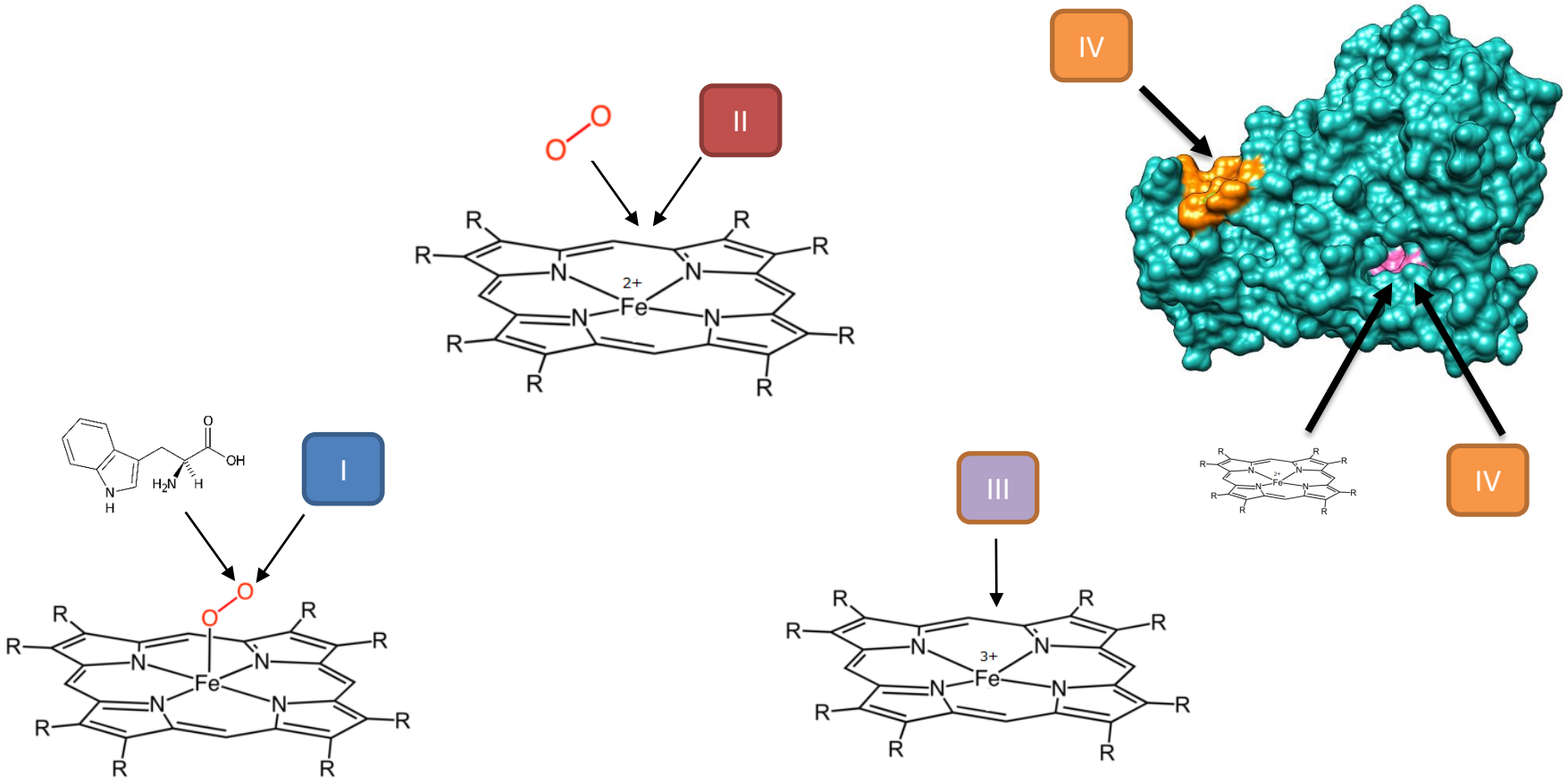
N-formylkynurenine







Inhibitors

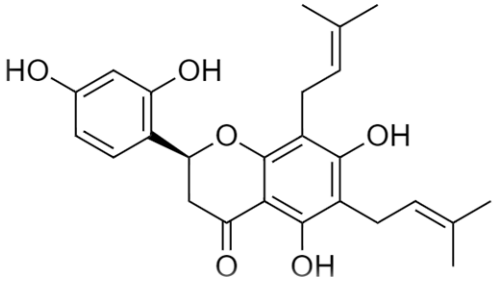


Röhrig, U. F., Reynaud, A., Majjigapu, S. R., Vogel, P., Pojer, F., et al. 2019, September 17. Inhibition Mechanisms of Indoleamine 2,3-Dioxygenase 1 (IDO1). Journal of Medicinal Chemistry. American Chemical Society (ACS).

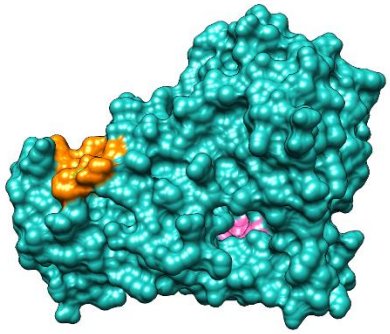
Inhibitory effects of flavonoids isolated from Sophora flavescens on indoleamine 2,3-dioxygenase 1 activity

Sophora flavescens K.

- Allosteric site elucidation by molecular docking and main residues (Pro182 e Phe185)
- Flavonoid from *Sophora flavescens* K.
- Kushenol E



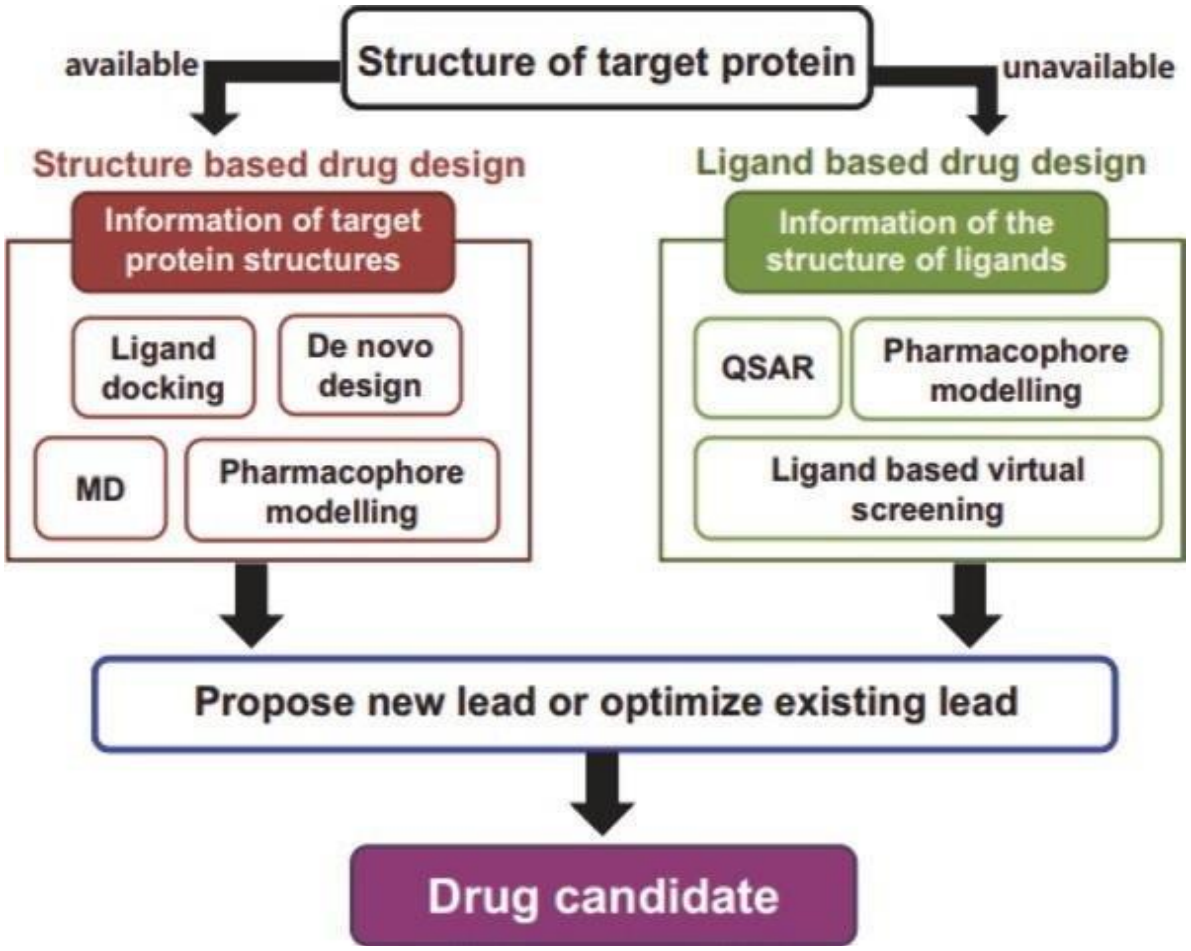
Kushenol E



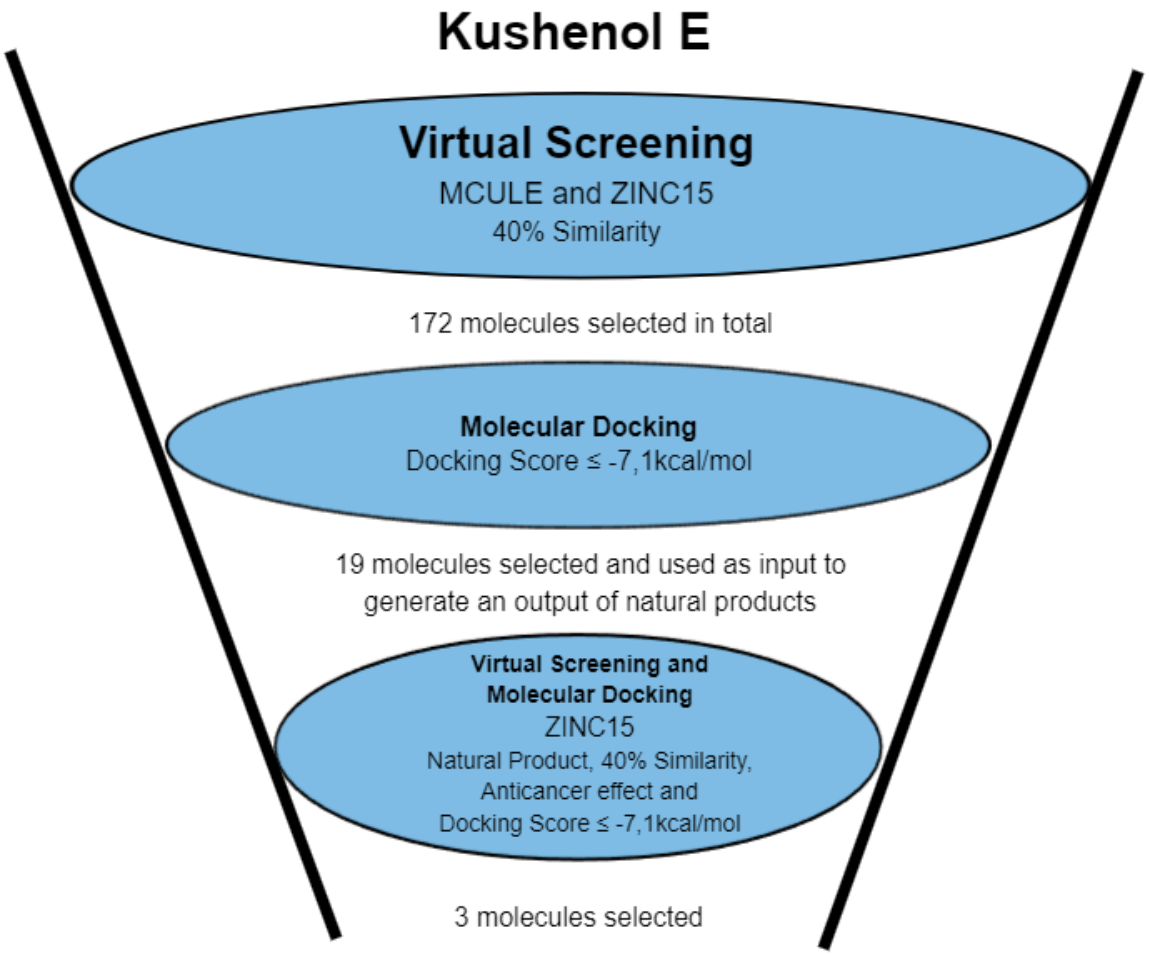
Allosteric site

Kwon M, Ko SK, Jang M, et al. Inhibitory effects of flavonoids isolated from *Sophora flavescens* on indoleamine 2,3-dioxygenase 1 activity. *J Enzyme Inhib Med Chem*. 2019;34(1):1481-1488. doi:10.1080/14756366.2019.1640218

Computer aided drug design

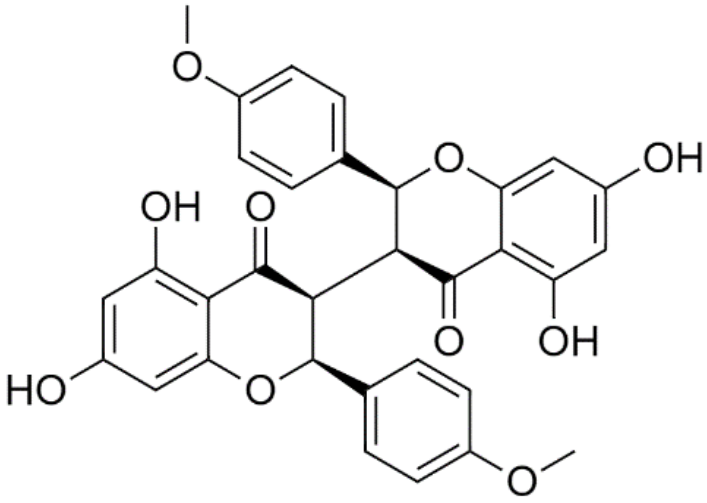


Results


Kushenol E
Virtual Screening
MCULE and ZINC15
40% Similarity
172 molecules selected in total
Molecular Docking
Docking Score ≤ -7,1kcal/mol
19 molecules selected and used as input to generate an output of natural products
Virtual Screening and Molecular Docking
ZINC15
Natural Product, 40% Similarity,
Anticancer effect and
Docking Score ≤ -7,1kcal/mol
3 molecules selected

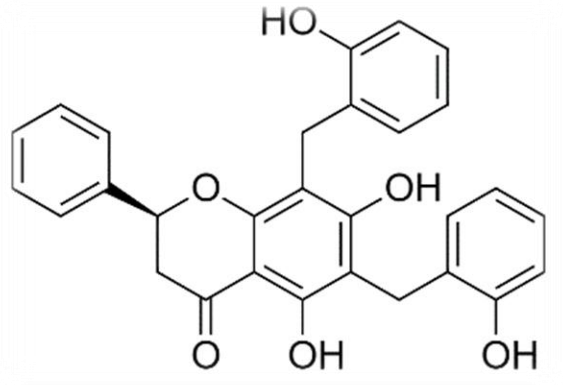
NPs	Affinity (kcal/mol)	NPs	Affinity (kcal/mol)
chamuvaritin	-7,9	Kushenol C	-6,5
chamaejasmin B	-7,9	butin	-6,5
dichamanetin	-7,8	strobopinin	-6,4
chamaejasmin	-7,7	rhamnocitrin	-6,4
neochamaejasmin A	-7,6	7-benzyloxycoumarin	-6,3
obovatin	-7,5	naringenin	-6,3
isochamanetin	-7,5	uvaretin	-6,2
B-naphthoflavone	-6,9	pinocembrin	-6,1
pinobanksin	-6,9	genkwanin	-6,1
techtochrysin	-6,8	glabranin	-6
sophoraflavanone B	-6,7	7-hydroxyflavanone	-6
strobopinin methylether	-6,7	apigenin diethylether	-6
diuvaretin	-6,6	2-hydroxyflavanone	-6
izalpinin	-6,6	asebogenin	-5,9
Kushenol E	-6,6		

Chamaejasmin B



Stellera chamaejasme L

Dichamanetin

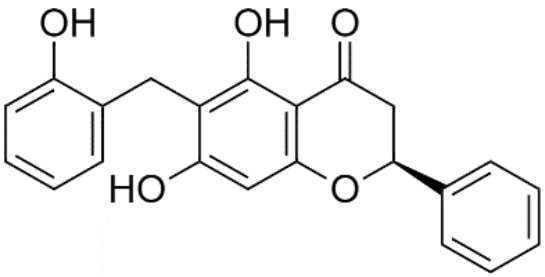


Piper sarmentosum Roxb.

Xylopia pierrei (Hance) Kuntze

Uvaria chamae P.Beauv.

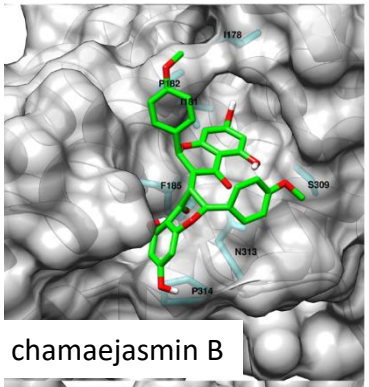
Isochamanetin



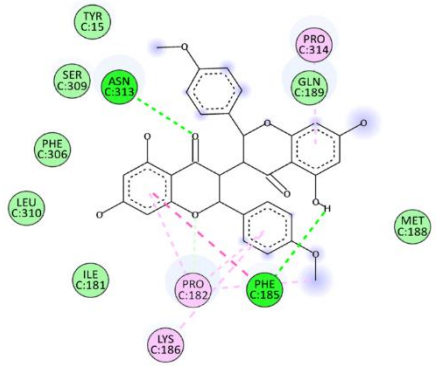
Uvaria chamae P.Beauv.

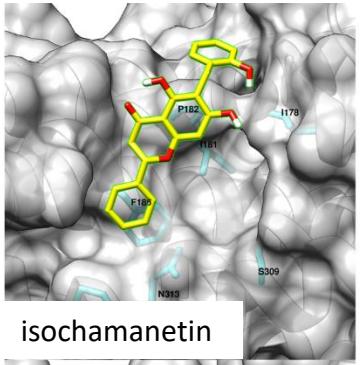
Xylopia pierrei (Hance) Kuntze

Sphaeranthus amaranthoides Burm.f

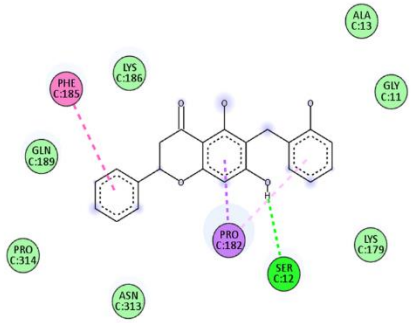


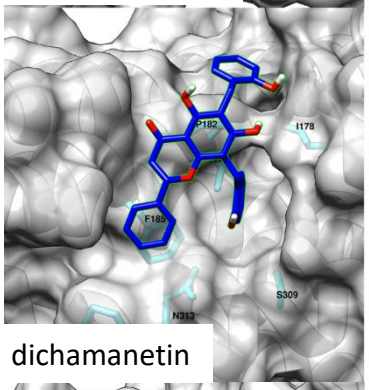
chamaejasmin B



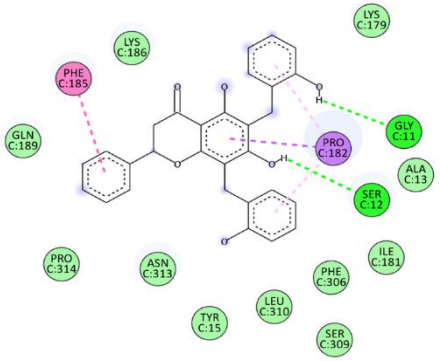


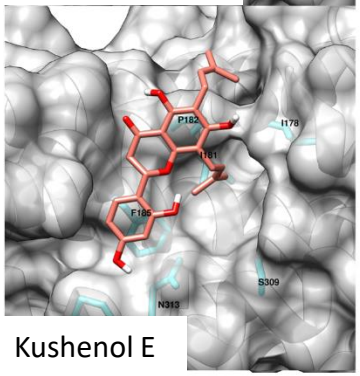
isochamanetin



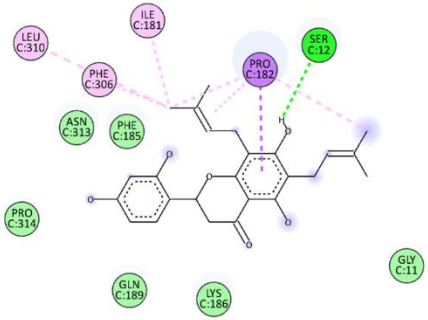


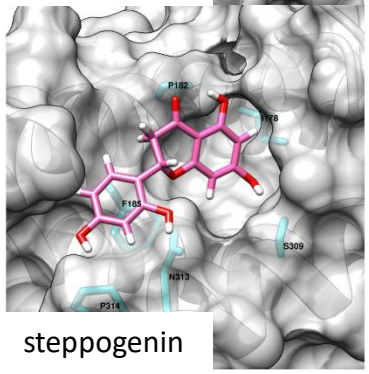
dichamanetin



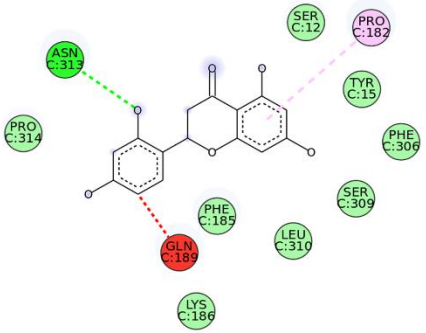


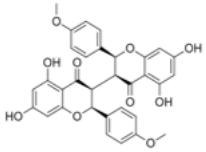
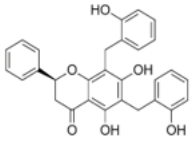
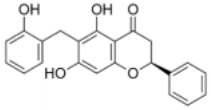
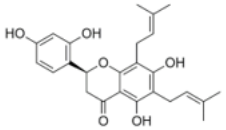
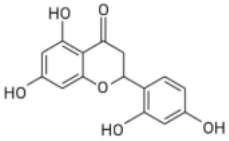
Kushenol E

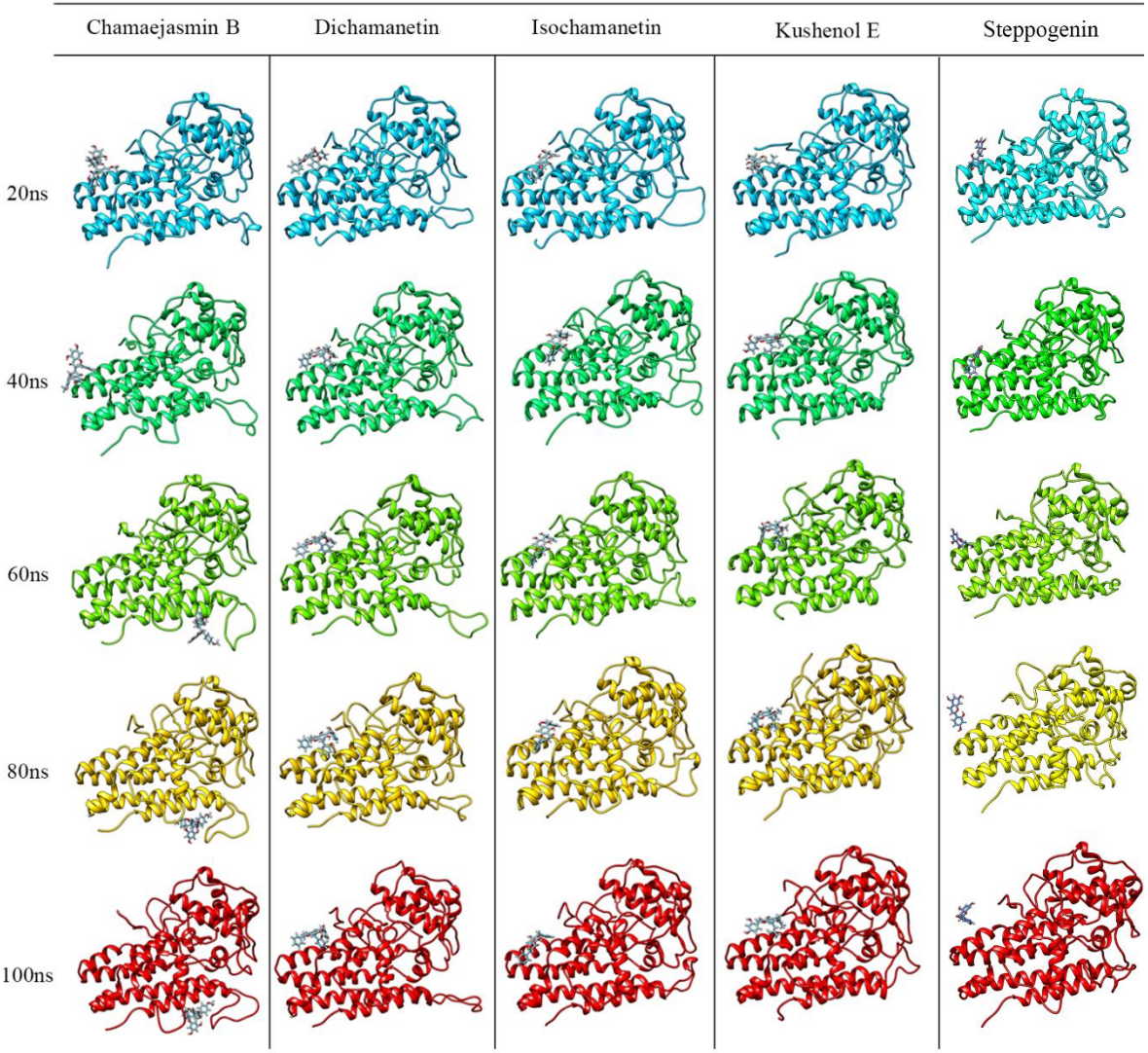




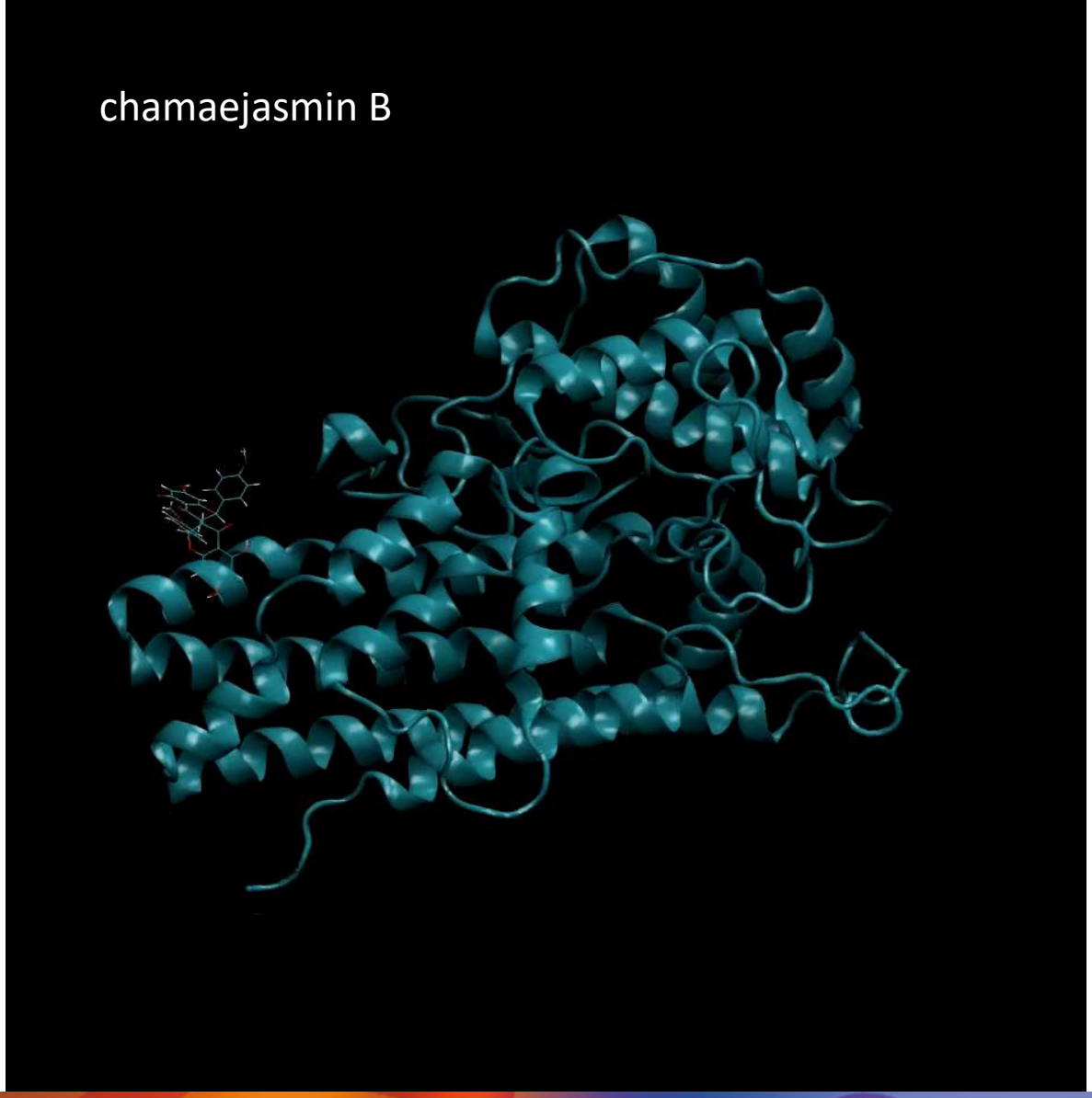
steppogenin



Compound	Molecular structure	H bond	van der Waals	pi-alquil	pi-sigma	pi-pi	alquil	Unfavorable
chamaejasmin B		Phe185, Asn313	Tyr15, Ile181, Gln189, Met188, Phe306, Ser309, Leu310	Pro182, Pro314	---	Phe185	Lys186, Pro182	---
dichamanetin		Ser12, Gly11	Ala13, Tyr15, Lys179, Ile181, Lys186, Gln189, Phe306, Ser309, Leu310, Asn313, Pro314	Pro182	Pro182	Phe185	---	---
isochamanetin		Ser12,	Gly11, Ala13, Lys179, Lys186, Gln189, Asn313, Pro314	Pro182	Pro182	Phe185	---	---
Kushenol E		Ser12	Gly11, Lys179, Phe185, Lys186, Gln189, Asn313, Pro314	Pro182	Pro182	---	Ile181, Pro182, Phe306, Leu310	---
steppogenin		Asn313	Ser12, Tyr15, Phe185, Lys186, Phe306, Ser309, Leu310, Pro314	Pro182	---	---	---	Gln189

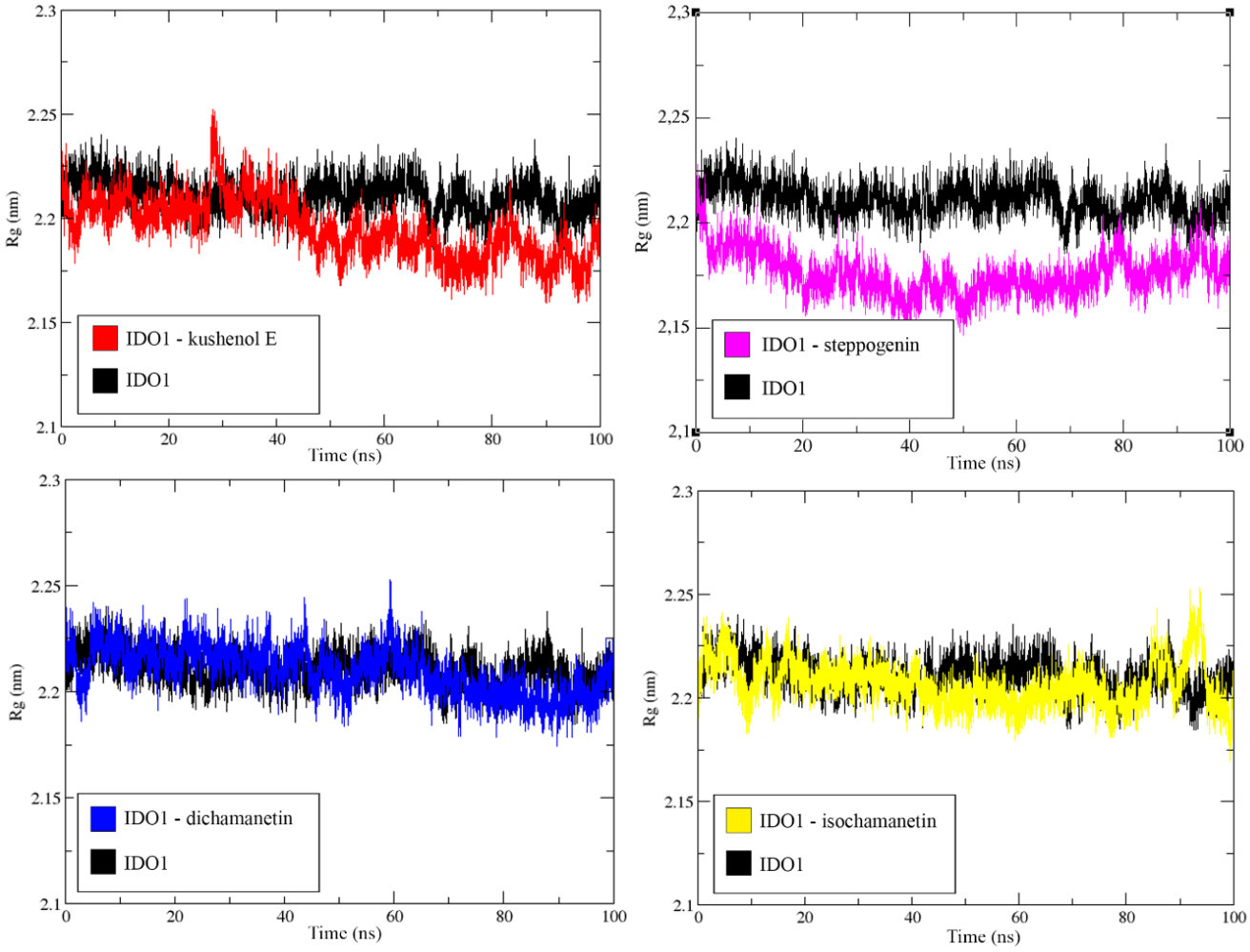


chamaejasmin B

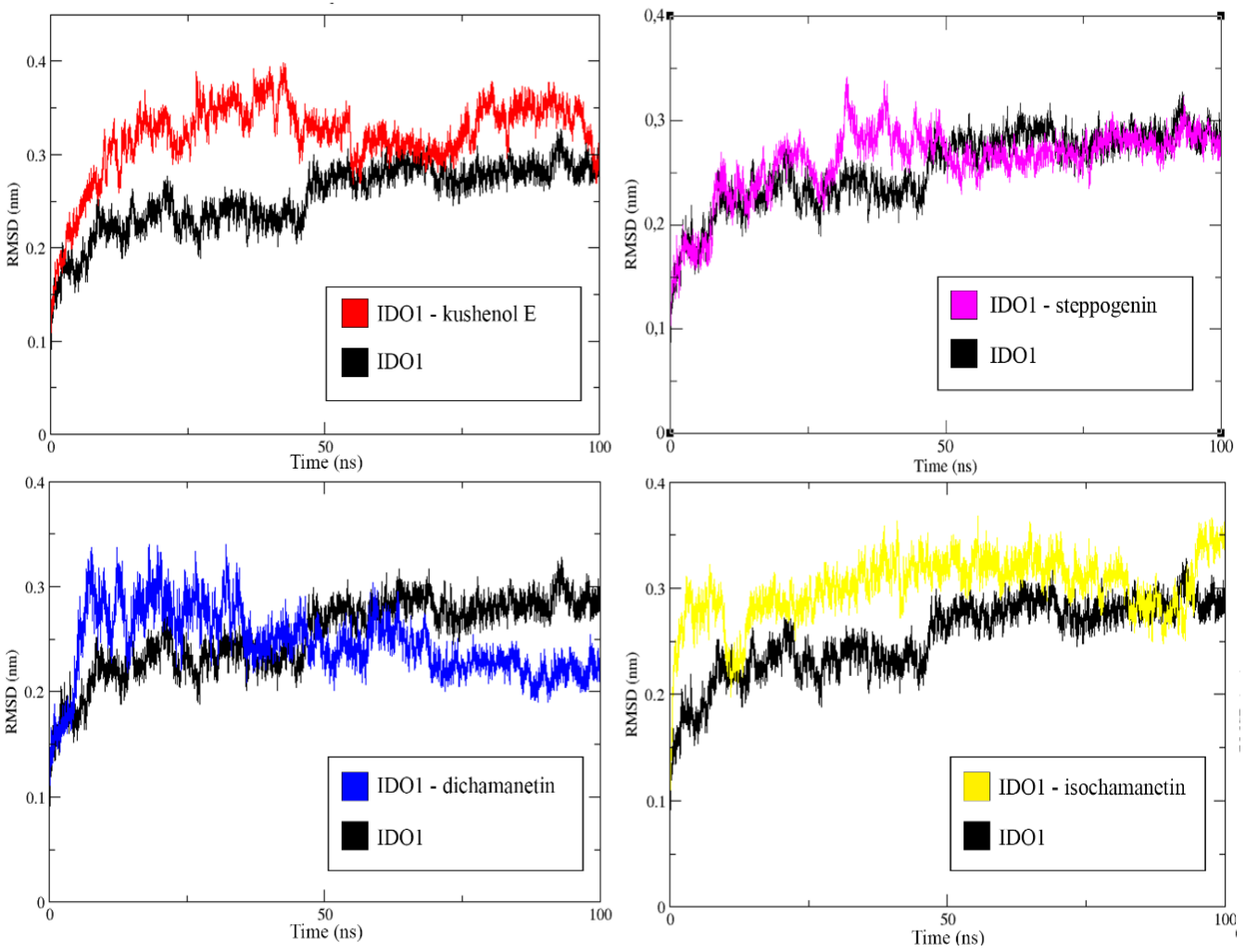


dichamanetin

Radii of gyration

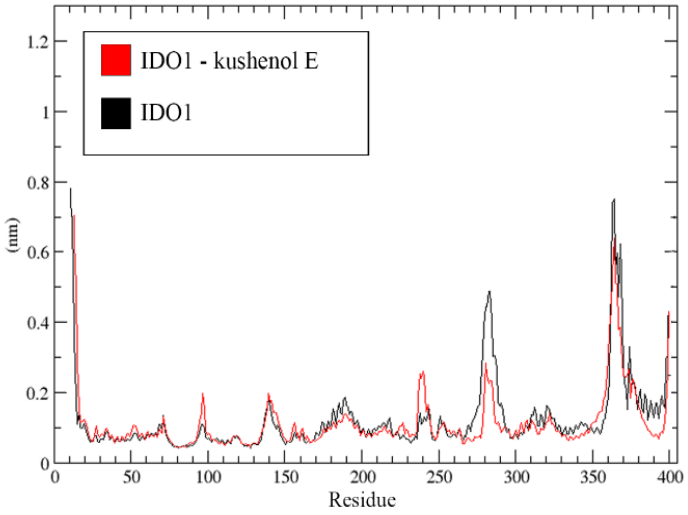


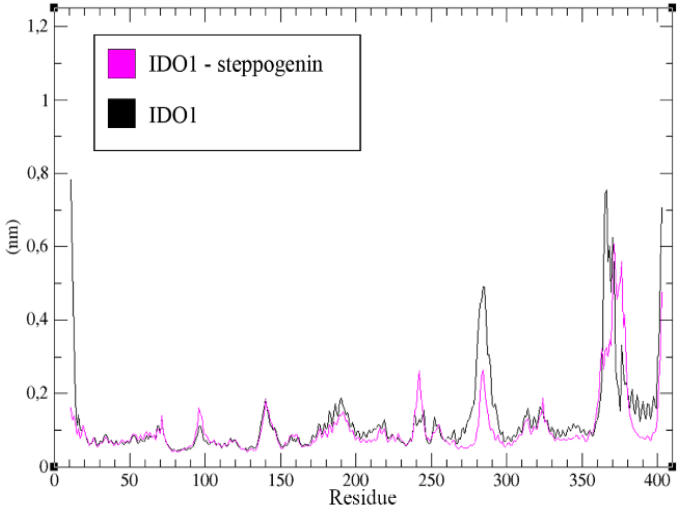
RMSD

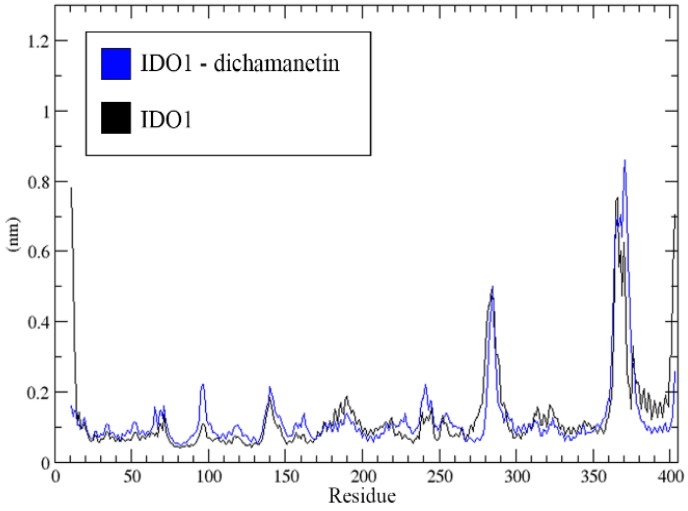

RMSD (nm)
Time (ns)
IDO1 - kushenol E
IDO1
IDO1 - steppogenin
IDO1
IDO1 - dichamanetin
IDO1
IDO1 - isochamanetin
IDO1

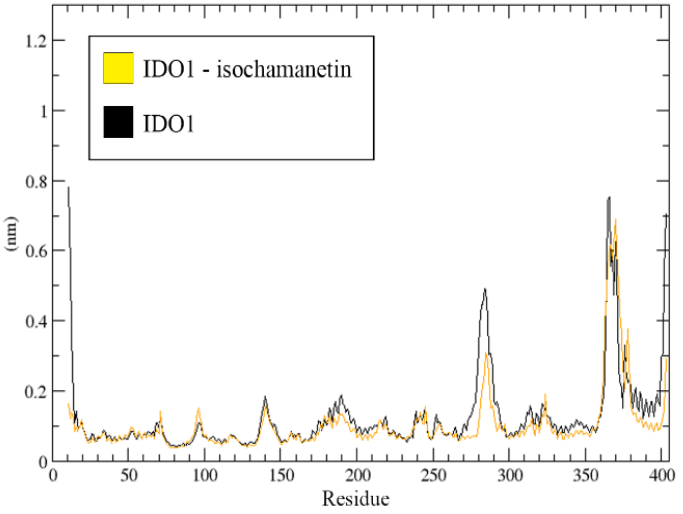
RMSF

- EF loop (Gly278 - His287)
- JK loop (Pro361 – Thr-378)

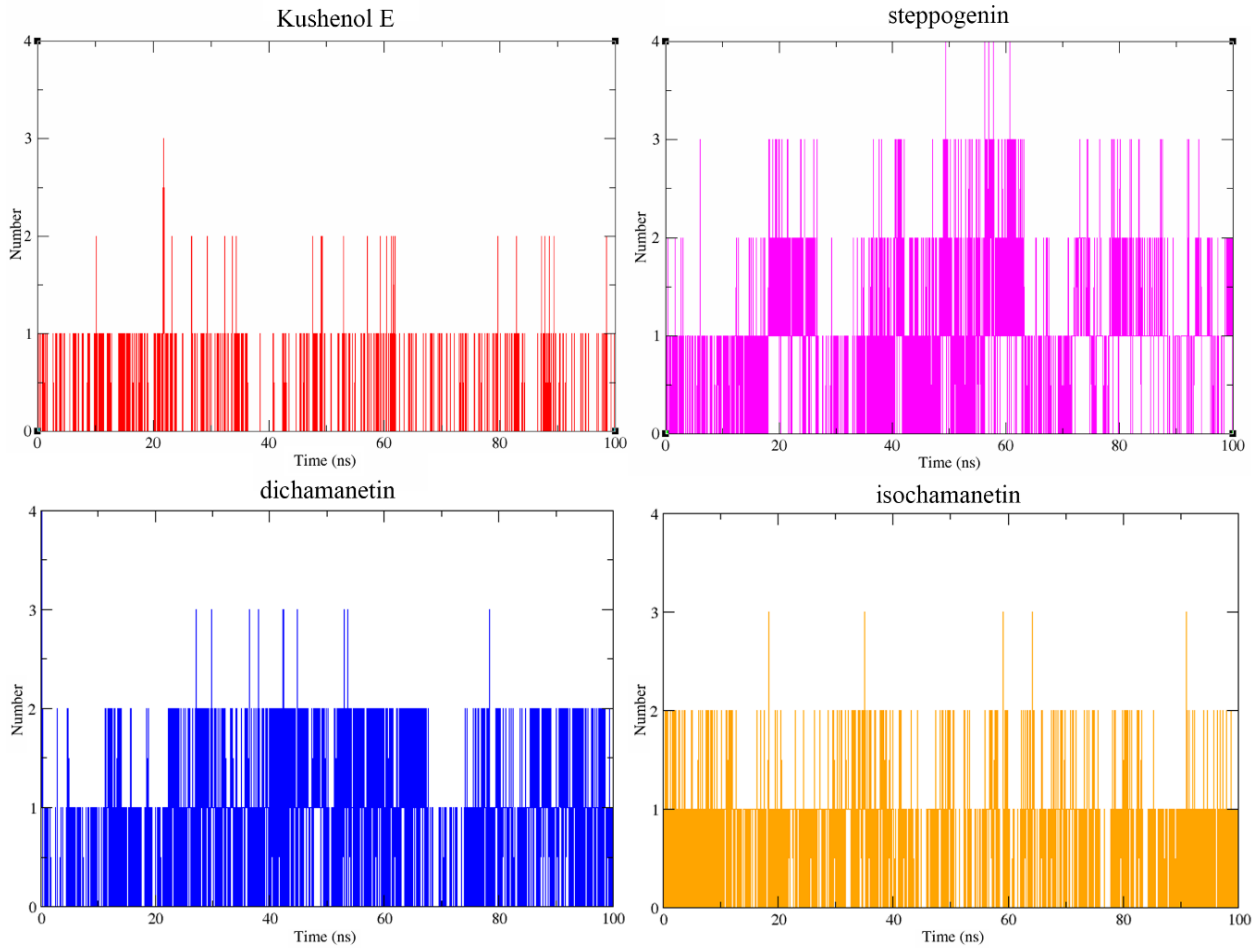




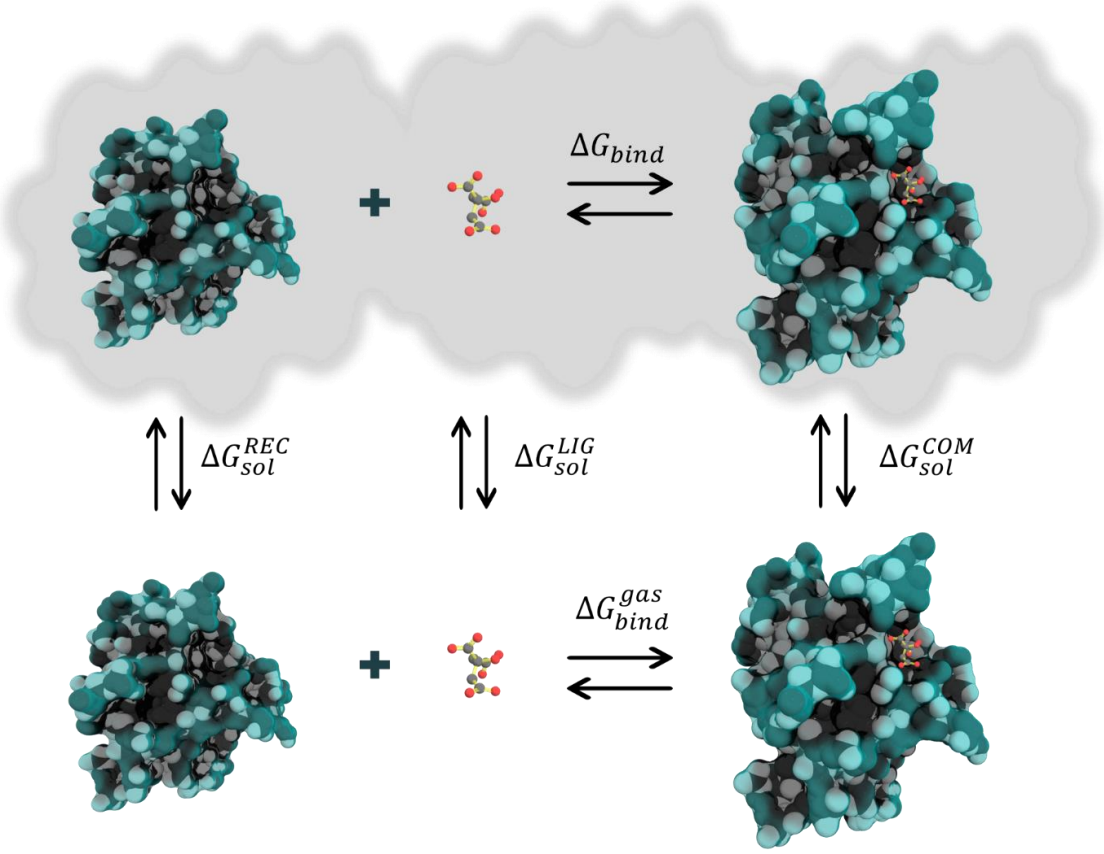




Hydrogen bonds



Free energy calculations MM-PBSA



$$\Delta G_{bind} = \langle G_{COM} \rangle - \langle G_{REC} \rangle - \langle G_{LIG} \rangle$$

Free energy calculations

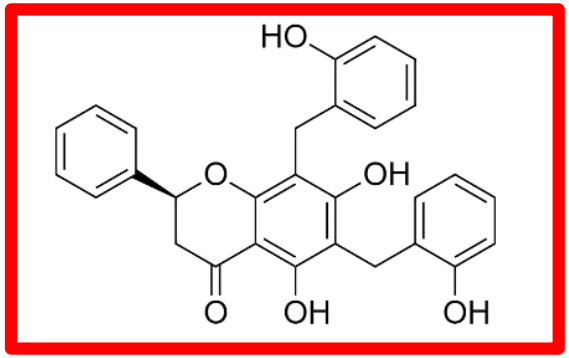
Energy Component	Kushenol E ΔG (kcal/mol)	Steppogenin ΔG (kcal/mol)	dichamanetin ΔG (kcal/mol)	isochamanetin ΔG (kcal/mol)
van der Waals	-33.4464 +/- 2.7222	-12.6589 +/- 5.4591	-38.7571 +/- 2.8011	-33.1692 +/- 2.6773
Electrostatic	-0.4995 +/- 2.3494	-9.5176 +/- 5.6553	-8.1238 +/- 3.5253	-2.7772 +/- 2.1816
Polar Solvation	16.2786 +/- 3.5898	18.1821 +/- 8.5497	25.4326 +/- 4.2624	17.7325 +/- 2.3312
SASA	-3.9866 +/- 0.2390	-1.7428 +/- 0.7148	-4.4861 +/- 0.2483	-3.8790 +/- 0.3585
Free energy of interaction	**-21.6563 +/- 3.1142**	**-5.7373 +/- 5.2005**	**-25.9345 +/- 3.1214**	**-22.0960 +/- 3.1859**

Energy contribution per residue

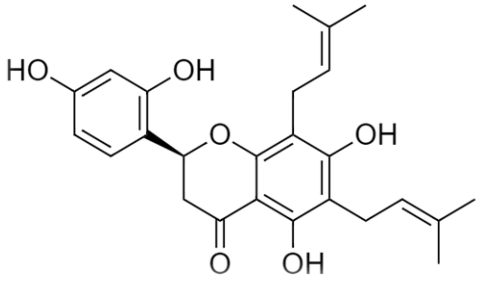
Allosteric site	Kushenol E ΔG (kcal/mol)	steppogenin ΔG (kcal/mol)	dichamanetin ΔG (kcal/mol)	isochamanetin ΔG (kcal/mol)
Lys 179	-5.6572 +/- 0.009	0.0522 +/- 0.0146	-10.2480 +/- 0.0138	-0.1242 +/- 0.0023
Ile181	-5.5043 +/- 0.003	-0.0478 +/- 0.0006	-7.1328 +/- 0.0045	-5.9646 +/- 0.0042
Pro182	-2.7174 +/- 0.009	-0.6856 +/- 0.0075	-2.9304 +/- 0.0094	-0.9383 +/- 0.0058
Phe185	-9.7036 +/- 0.0064	-0.1037 +/- 0.0017	-10.9729 +/- 0.0063	-2.6943 +/- 0.0152
Lys186	-0.0069 +/- 0.0271	-0.6023 +/- 0.0201	-12.8116 +/- 0.0194	-3.0506 +/- 0.0093
Met188	-0.1075 +/- 0.0007	-0.0451 +/- 0.0006	-0.1199 +/- 0.0006	-6.0922 +/- 0.0049
Gln189	-4.2292 +/- 0.0045	-0.0770 +/- 0.0020	-4.7260 +/- 0.0061	-7.7712 +/- 0.0108
Phe306	-13.3145 +/- 0.0084	-0.0055 +/- 0.0003	-14.2844 +/- 0.0076	-7.4103 +/- 0.0070
Ser309	0.0639 +/- 0.0090	0.0004 +/- 0.0012	0.1190 +/- 0.0077	2.6300 +/- 0.0092
Leu310	-6.0265 +/- 0.0047	-0.0027 +/- 0.0004	-6.1063 +/- 0.0043	-6.0442 +/- 0.0048
Asn313	3.2576 +/- 0.0086	-0.0099 +/- 0.0015	-0.0466 +/- 0.0065	-0.0041 +/- 0.0150
Pro314	-0.0440 +/- 0.0013	-0.0007 +/- 0.0007	-0.0231 +/- 0.0009	-5.5250 +/- 0.0143

Conclusion

- Identification of Natural Products that Interact with the allosteric Site
- Dichamanetin, isochamanetin and Kushenol E within the same flavonoid class
- Future work is needed to verify its biological diligence



Dichamanetin



Kushenol E

Acknowledgments