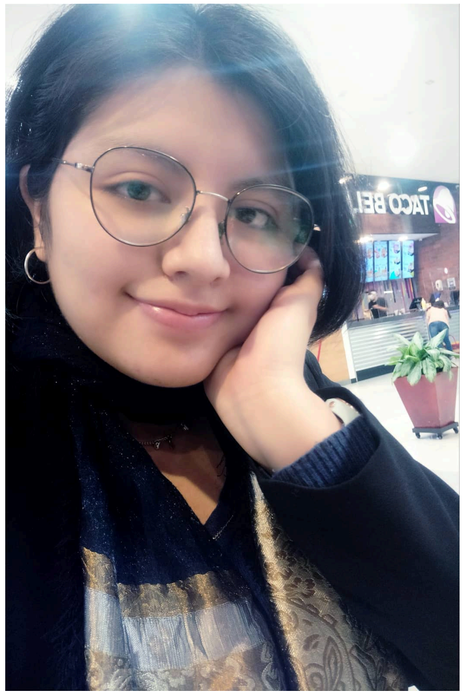
IN SILICO DESIGN OF QUERCETIN DERIVATIVES WITH POTENTIAL DUAL INHIBITORY ACTIVITY AGAINST GSK3β AND CDK5/p25 FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

Latorre Alessandra , Nájera Giulliano, Tamayo Jaime, Ore Kevin, Zavaleta Juan



Alessandra Latorre

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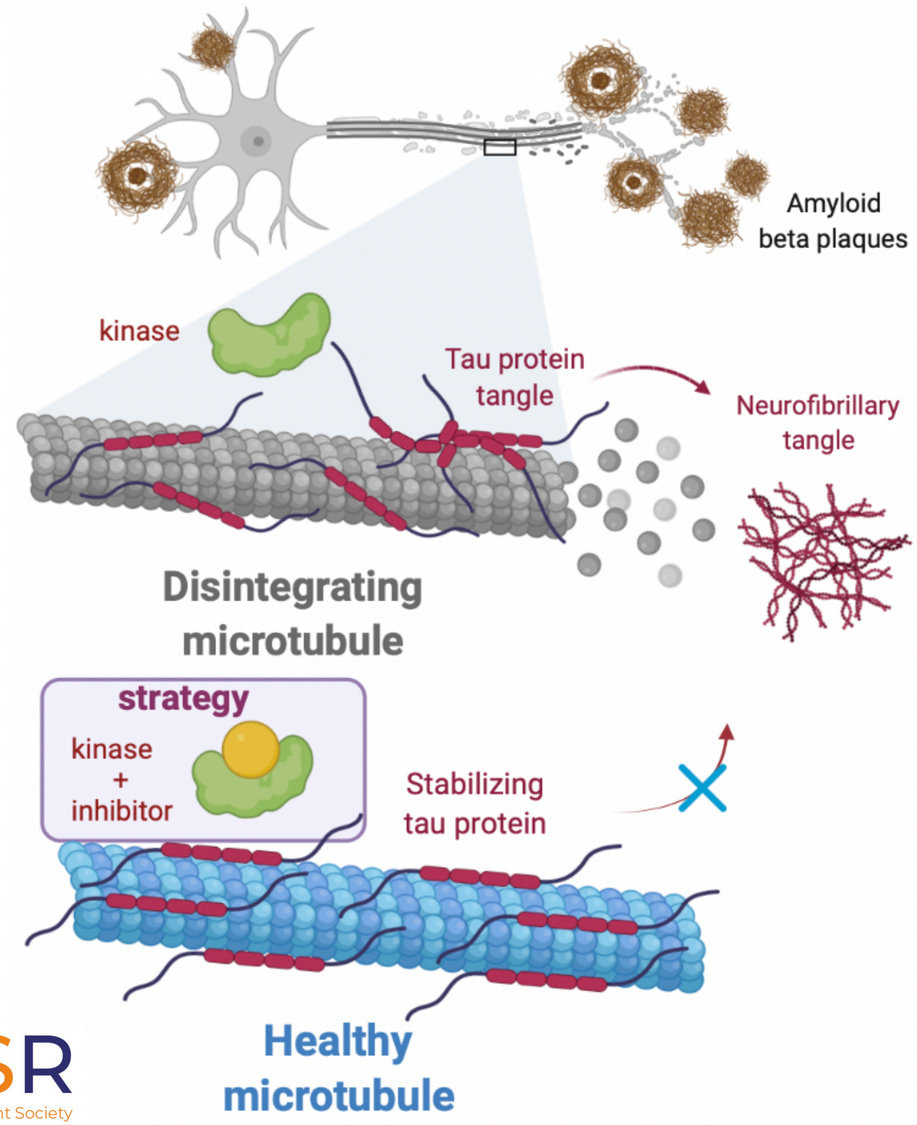
XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery

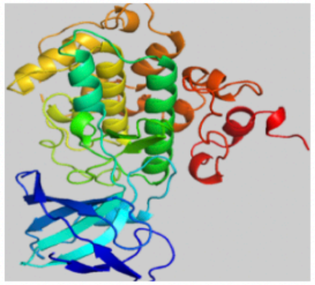
Moscow, Russia, may 25, 2022

hyperphosphorylation as a histopathological hallmark of Alzheimer's disease (AD)



GSK3β

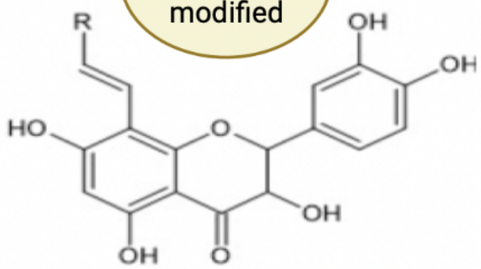
increase Aβ prduction



CDK5/p25

Aβ generation when hyperactive

Favonoids C8 modified



Quercetin

To **design in silico C8-substituted quercetin** derivatives **as dual inhibitors of GSK3β and CDK5/p25** using an integrative approach of physicochemical and toxicological properties together with **structural bioinformatics.**

OBJECTIVE

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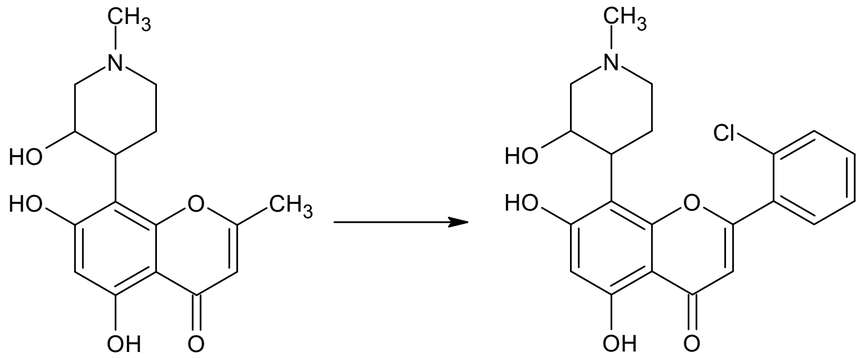
Despite scarce studies with substitutions of flavonoids at the 8 Carbon position, have shown to be great inhibitors of AD targets

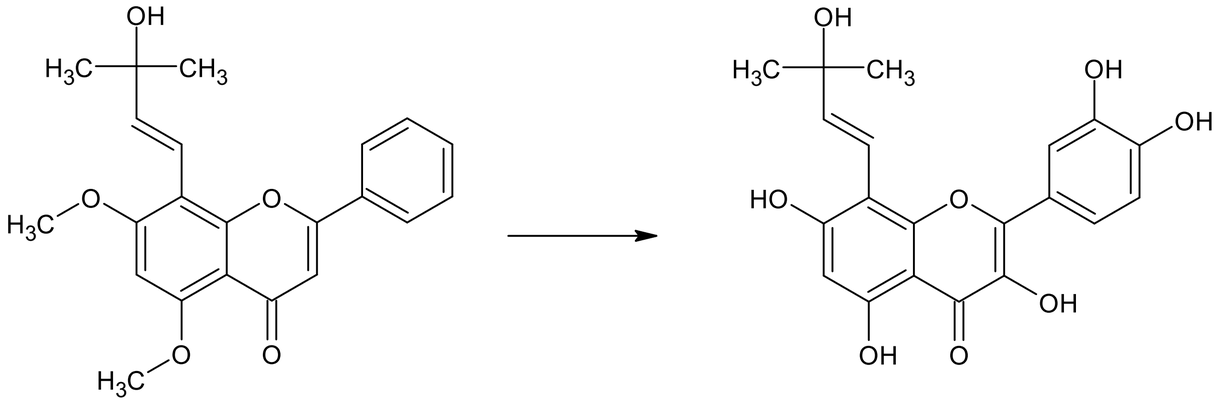
Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials.
Adrian M. Senderowicz
Investigational New Drugs 17: 313–320, 1999.



Rohitukina

Flavopiridol

Molecular interaction of human acetylcholinesterase with trans-tephrostachin and derivatives for Alzheimer's disease.
Arjun Pitchai
Heliyon 6 (2020)



trans-tephrostachin

New derivates

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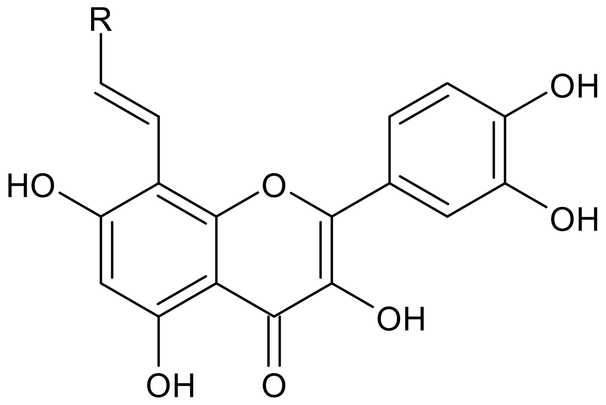
Online platforms and freely available software were used for screening.



BASE STRUCTURE (Quercetin)

DESIGN

613 bioisosteres were designed using the platform SwissBioisostere and MarvinSketch

SCREENING

Was performed based on kinase activity criteria. toxicity, Lipinski-Veber rules and pharmacokinetics

OPTIMIZATION

the 22 best bioisosteres were optimized

PRE-DOCKING

Preparation of GSK3ß and and CDK5/p25

DOCKING

3 times per ligand

ANALYSIS

The best structures and their interactions

2 BIOISOSTERES

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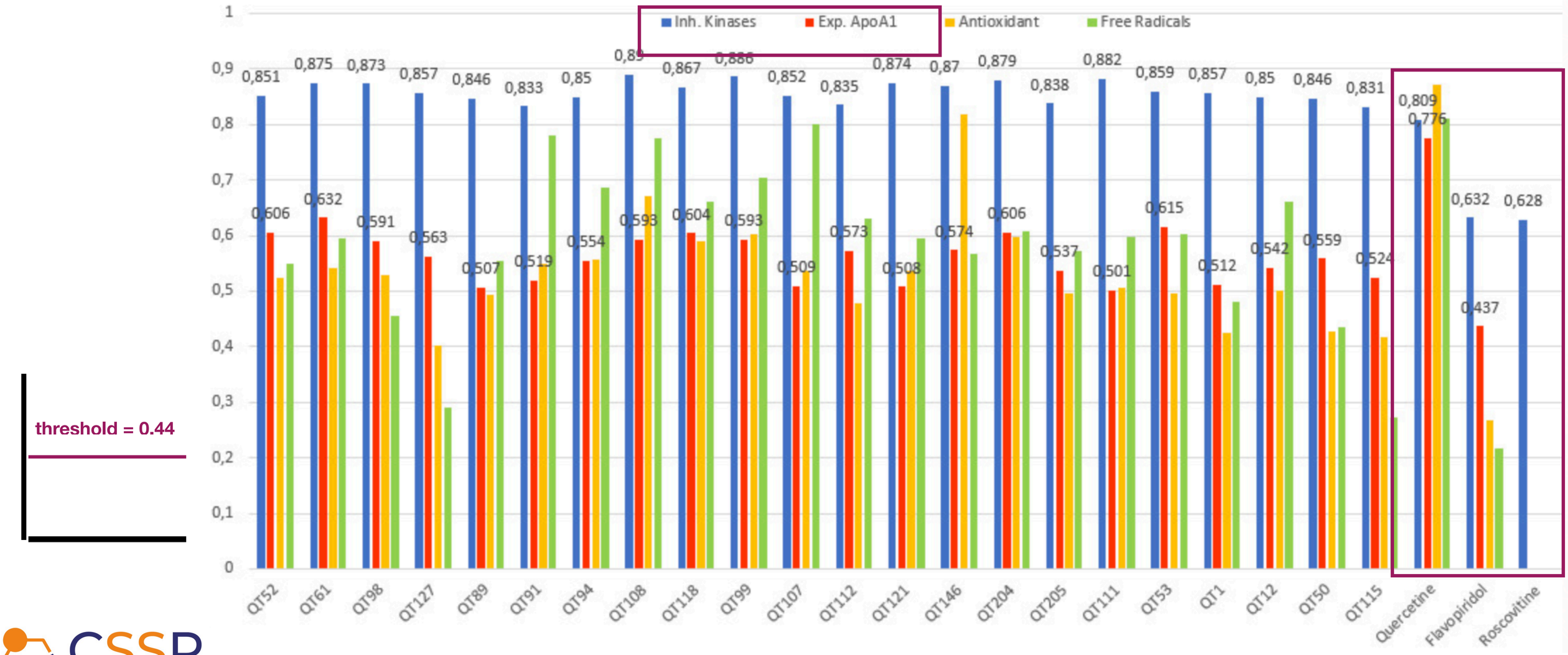
All 22 compounds overcome the probability of inhibition of Quercetin kinases as well as ApoA1 expression of Flavopiridol.



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None of the 22 molecules show any toxicity effects nor break more than 2 Lipinski's Rules..

	Toxicity			
Compound	Mutagenic	Tumorigenic	Reproductive effect	Irritant
QT52	none	none	none	none
QT61	none	none	none	none
QT98	none	none	none	none
QT127	none	none	none	none
QT89	none	none	none	none
QT91	none	none	none	none
QT94	none	none	none	none
QT108	none	none	none	none
QT118	none	none	none	none
QT99	none	none	none	none
QT107	none	none	none	none
QT112	none	none	none	none
QT121	none	none	none	none
QT146	none	none	none	none
QT204	none	none	none	none
QT205	none	none	none	none
QT111	none	none	none	none
QT53	none	none	none	none
QT1	none	none	none	none
QT12	none	none	none	none
QT50	none	none	none	none
QT115	none	none	none	none

	Lipinski - Veber					
Compound	MW	CLogP	H-A	H-D	RB	TPSA
QT52	471.461	1.5878	10	7	5	171.15
QT61	470.429	2.0945	10	7	4	184.98
QT98	410.341	1.3788	11	5	3	171.05
QT127	487.484	2.0503	10	5	3	173.21
QT89	440.363	1.6107	11	6	4	186.6
QT91	469.401	1.4601	11	7	5	193.94
QT94	484.499	3.0807	9	7	5	167.91
QT108	446.454	4.8451	7	5	4	127.45
QT118	444.435	2.7058	9	7	5	167.91
QT99	524.524	4.7593	8	6	6	147.68
QT107	453.402	2.4013	10	6	4	173.71
QT112	429.424	1.8060	9	7	6	159.71
QT121	389.334	1.3900	8	6	4	153.47
QT146	404.345	2.1684	8	6	4	147.68
QT204	546.477	4.5065	8	6	5	147.68
QT205	498.482	2.8049	10	7	6	184.98
QT111	454.39	1.9486	11	6	4	186.6
QT53	484.456	2.5224	10	6	5	173.98
QT1	431.396	0.7183	10	7	6	168.94
QT12	450.402	1.7633	10	6	4	173.46
QT50	488.512	2.6571	9	5	4	169.97
QT115	478.460	3.1822	11	6	4	181.91

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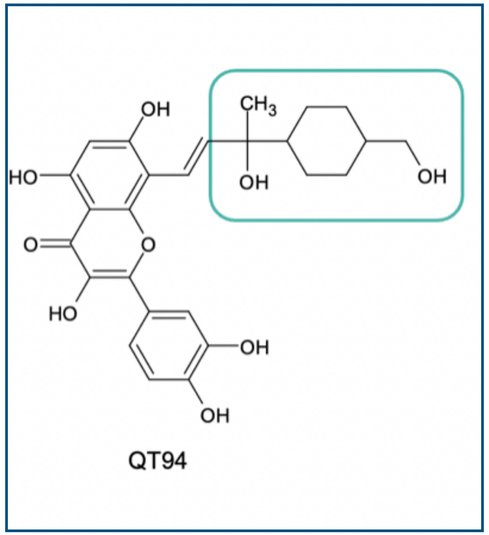
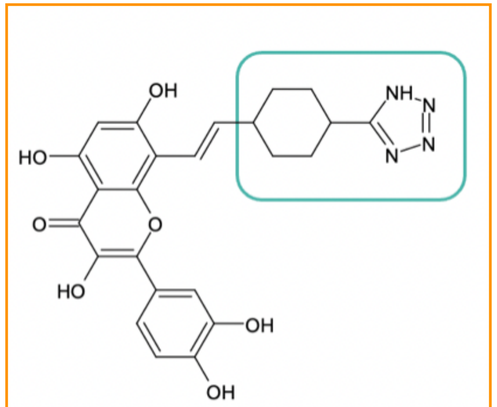
The 22 compounds have better affinity energy than the reference compounds for both proteins.

Ligand	GSK3β Energy (kcal/mol)	CDK5/p25 Energy (kcal/mol)
Quercetina	-9.77	-10.61
Roscovitina	-8.50	-9.04
Flavopiridol	-8.89	-10.96
QT1	-10.35	-11.72
QT12	-11.96	-12.84
QT50	-12.91	-12.91
QT52	-11.52	-12.86
QT53	-11.38	-13.42
QT61	-12.09	-12.21
QT89	-11.27	-12.47
QT91	-10.91	-12.66
QT94	-12.41	-13.94

Ligand	GSK3β Energy (kcal/mol)	CDK5/p25 Energy (kcal/mol)
QT98	-10.37	-9.58
QT99	-12.03	-13.26
QT107	-11.33	-13.14
QT108	-11.63	-12.31
QT111	-12.93	-13.04
QT112	-12.00	-13.33
QT115	-12.76	-13.79
QT118	-10.87	-12.35
QT121	-10.44	-13.40
QT127	-11.81	-12.13
QT146	-10.10	-11.06
QT204	-11.82	-12.93
QT205	-11.60	-13.03



QT94



QT115

	RMSD
Protein	AutoDock 4
GSK3B	0,775
CDK5/p25	1,796

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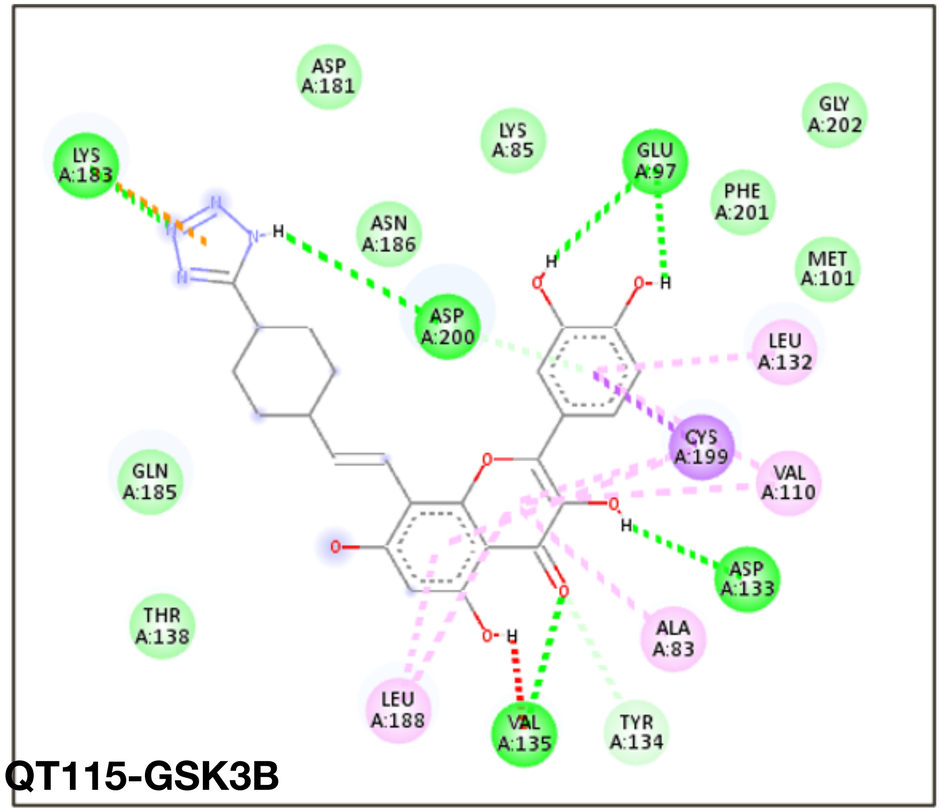
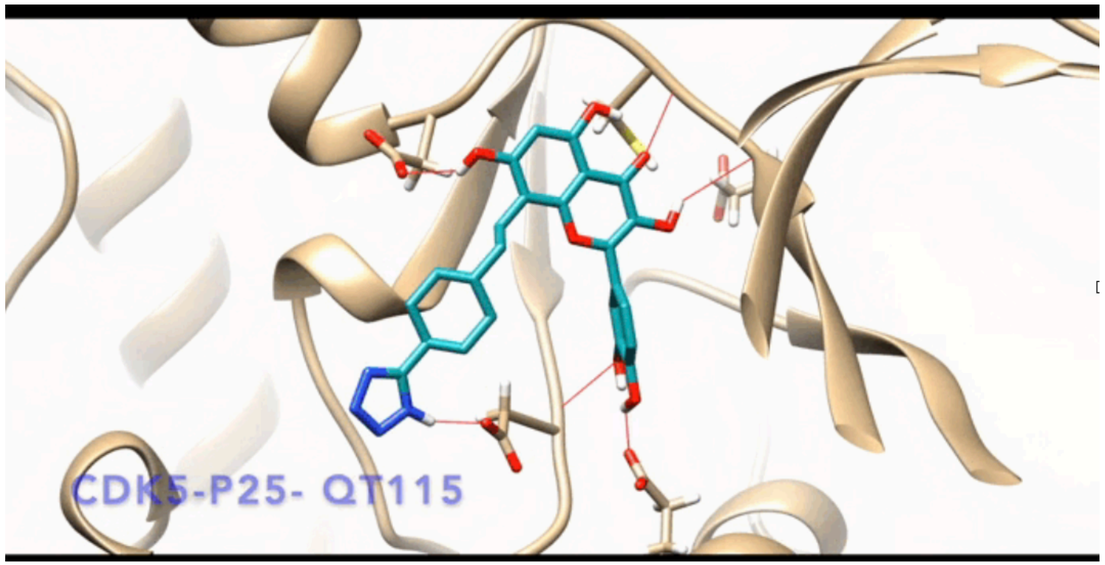
QT115 interacts with important residues of GSK3β (Val 135, Asp 133)



QT115-GSK3B



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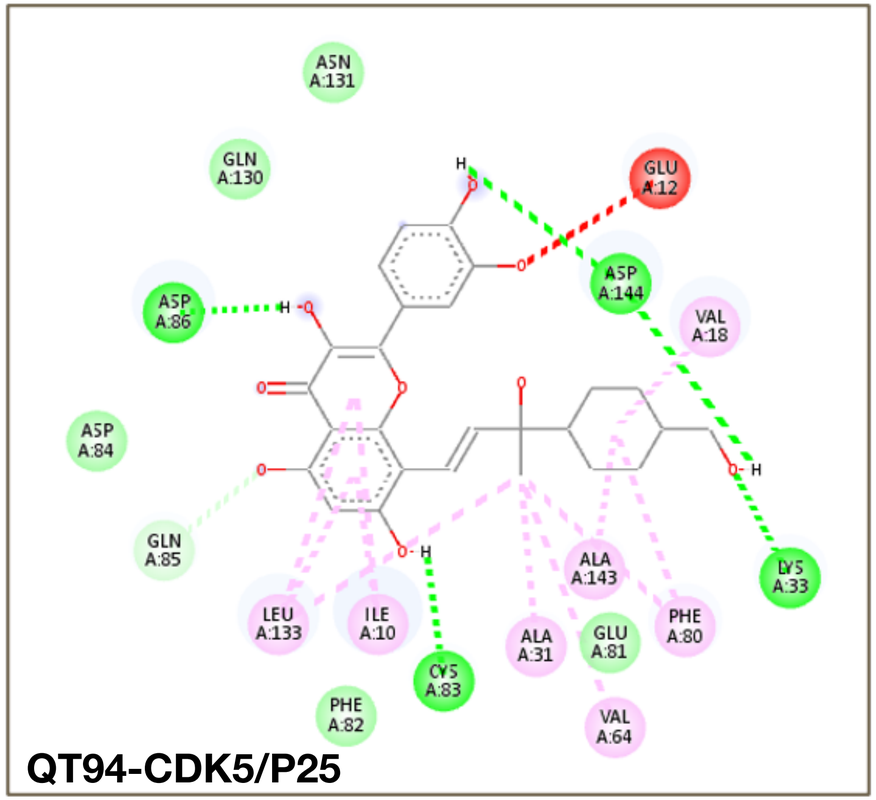

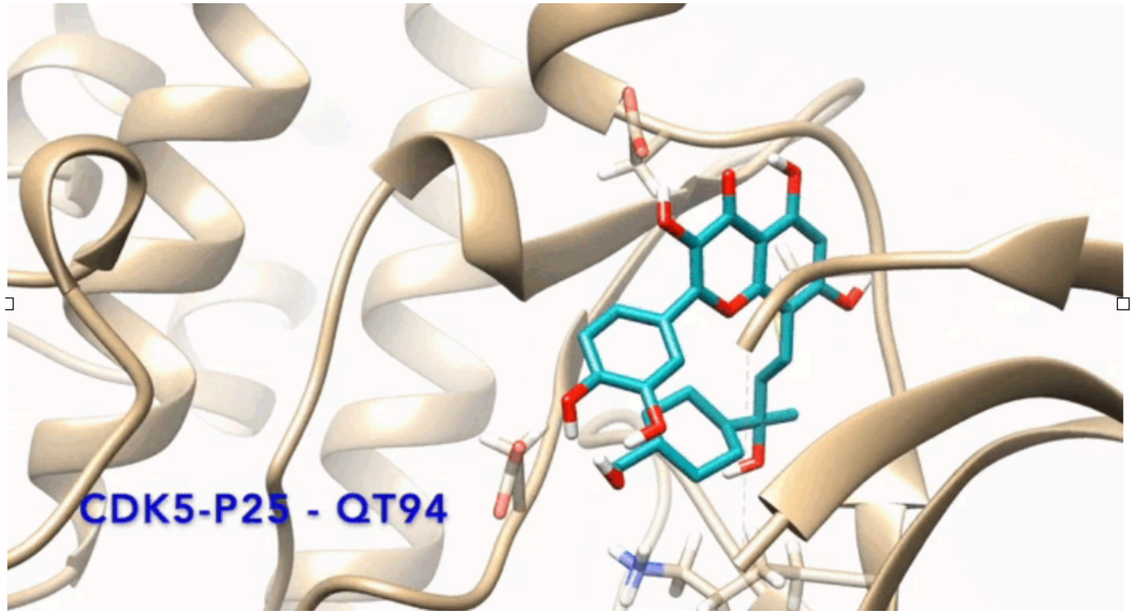

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Further studies are needed to confirm our work

The 22 C8-substituted quercetin derivatives produced by screening were shown to be likely dual inhibitors of GSK3β and CDK5/p25 for the treatment of Alzheimer's disease

Compounds QT94 and QT115 showed the best affinity energies towards GSK3β (-12.41Kcal/mol, -12.76Kcal/mol) and CDK5/p25 (-13.94Kcal/mol, -13.79Kcal/mol), respectively, as compared to quercetin, roscovitine and flavopiridol.

- Making a QSAR model

- Molecular dynamics studies

- Synthesis, encapsulation and in vitro biological assays (multidisciplinary)

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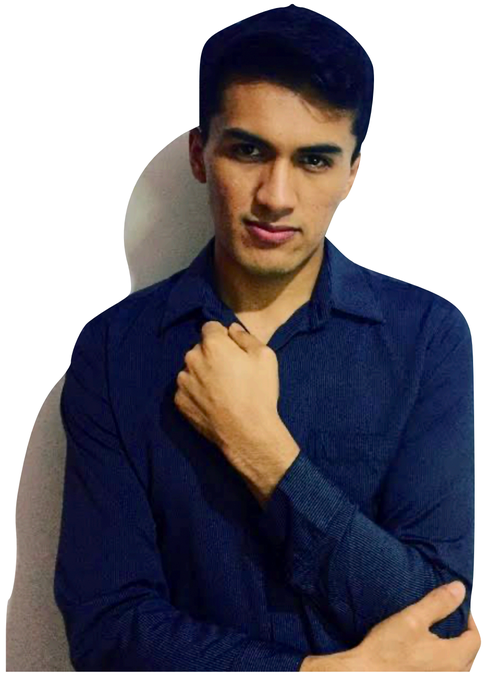
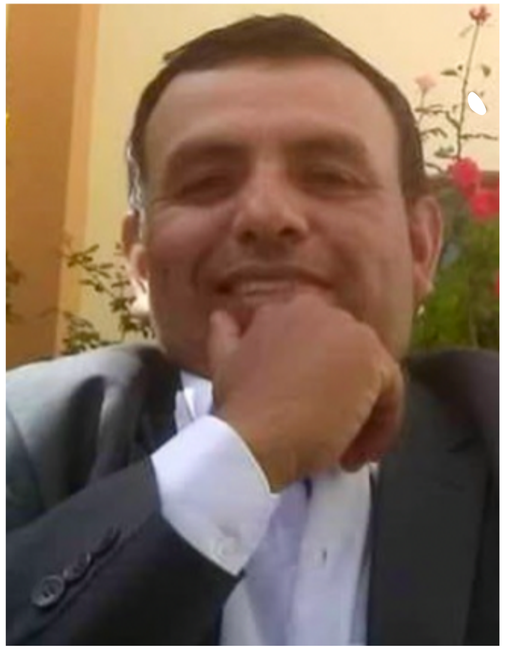
Special Thanks to the team and the organizing committee

Giulliano Nájera



Jaime Tamayo

Kevin Ore



Juan Zavaleta

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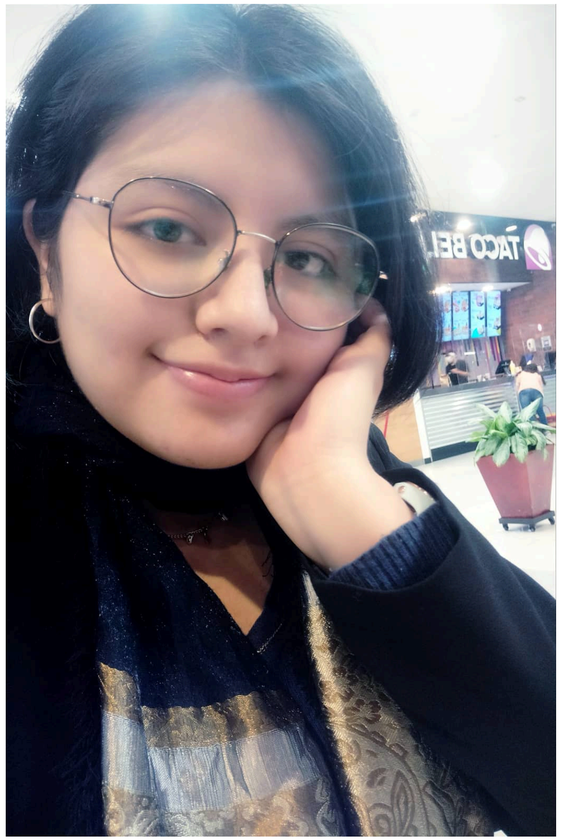

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