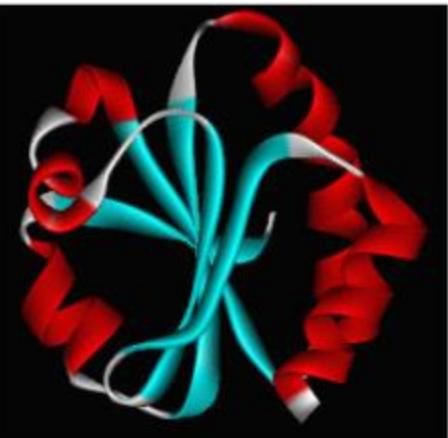




Drug Design & Discovery



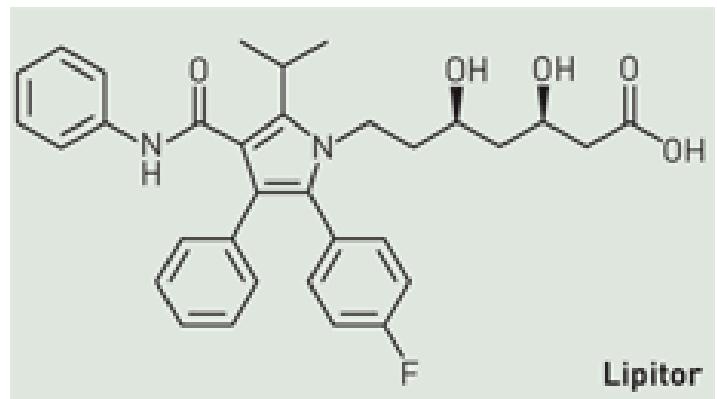
Drugs



Targets



Natural sources



Synthetic sources

Medicinal Chemistry

The science that deals with the discovery or design of new therapeutic agents and their development into useful medicines.

It involves:

- Synthesis
- Structure-Activity Relationships (SAR)
- Receptor interactions
- Absorption, distribution, metabolism, and excretion + Toxicology (ADME+T)



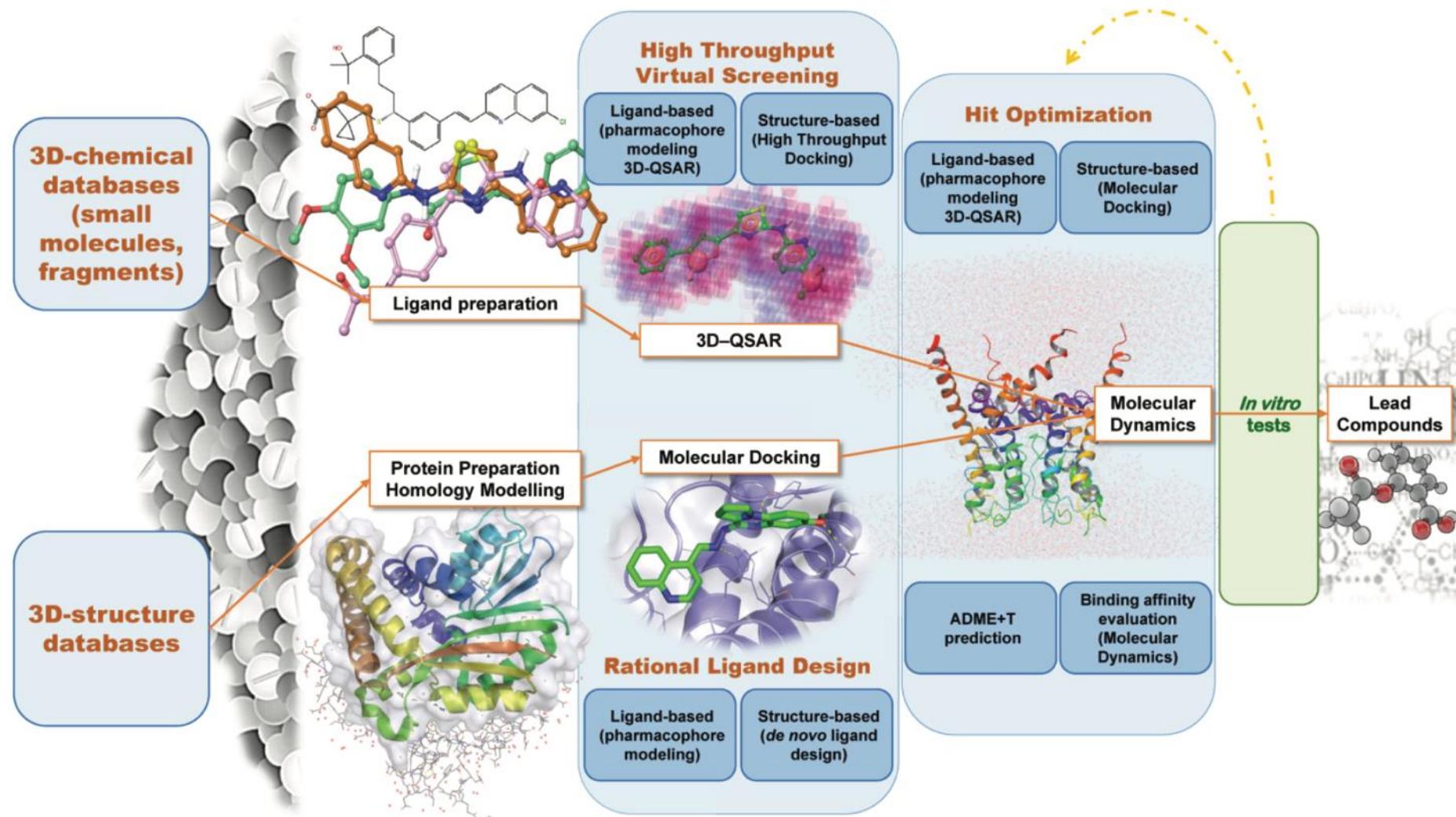
Lipinski Rule of Five (1997)

- ▶ Poor absorption and permeation are more likely to occur when there are more than 5 hydrogen-bond donors, more than 10 hydrogen-bond acceptors, the molecular mass is greater than 500, or the log P value is greater than 5.
- ▶ Further research studied a broader range of physicochemical and structural properties
- ▶ Related problems:
 - ▶ Compound toxicity
 - ▶ Compound mutagenicity
 - ▶ Blood-brain barrier penetration
 - ▶ Central nervous system activity

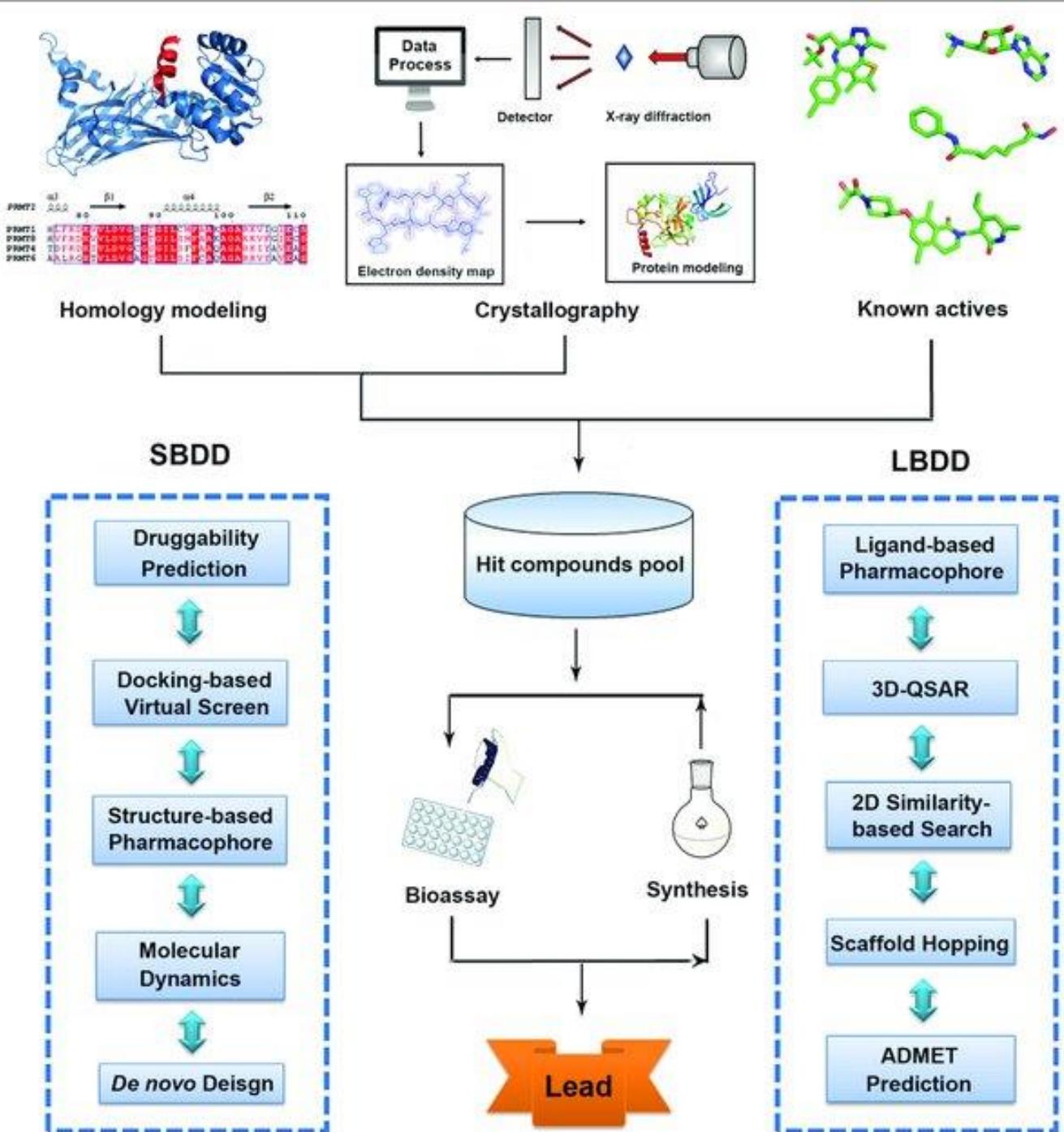
In Silico ADME Models

- ▶ Computational methods can predict compound properties important to ADME, e.g.
 - ▶ LogP, a liphophilicity measure
 - ▶ Solubility
 - ▶ Permeability
 - ▶ Cytochrome p450 metabolism
- ▶ Means estimates can be made for millions of compouds, helping reduce “attrition” – the failure rate of compounds in late stage

CADD = Computer Assisted Drug Design



The use of CADD was found to helpfully reduce the time, finances, and resources used to fight against the new diseases that can be caused by natural phenomena or human lifestyle

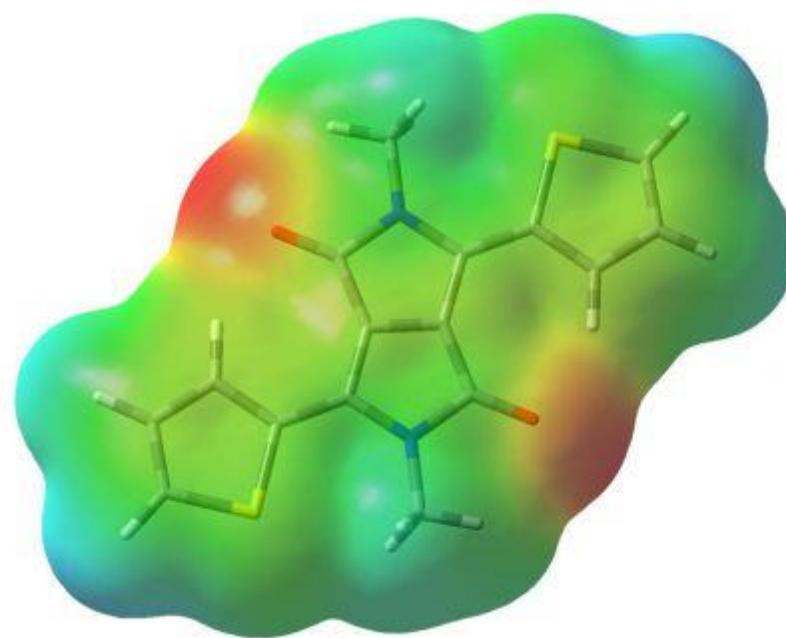


Structure Base Drug Design (SBDD)
Vs
Ligand Base Drug Design (LBDD)

interdisciplinary approach

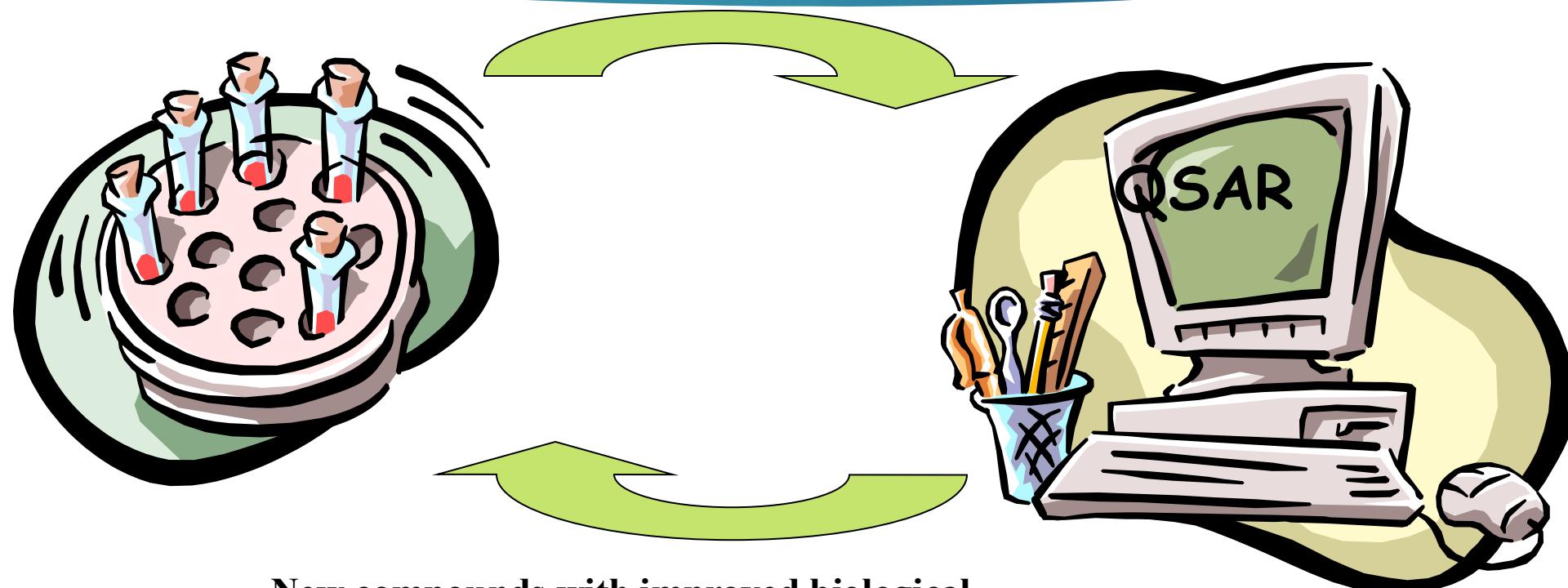
Q.S.A.R.

(Quantitative Structure and Activity Relationship)



QSAR (Quantitative Structure and Activity Relationship) and Drug Design

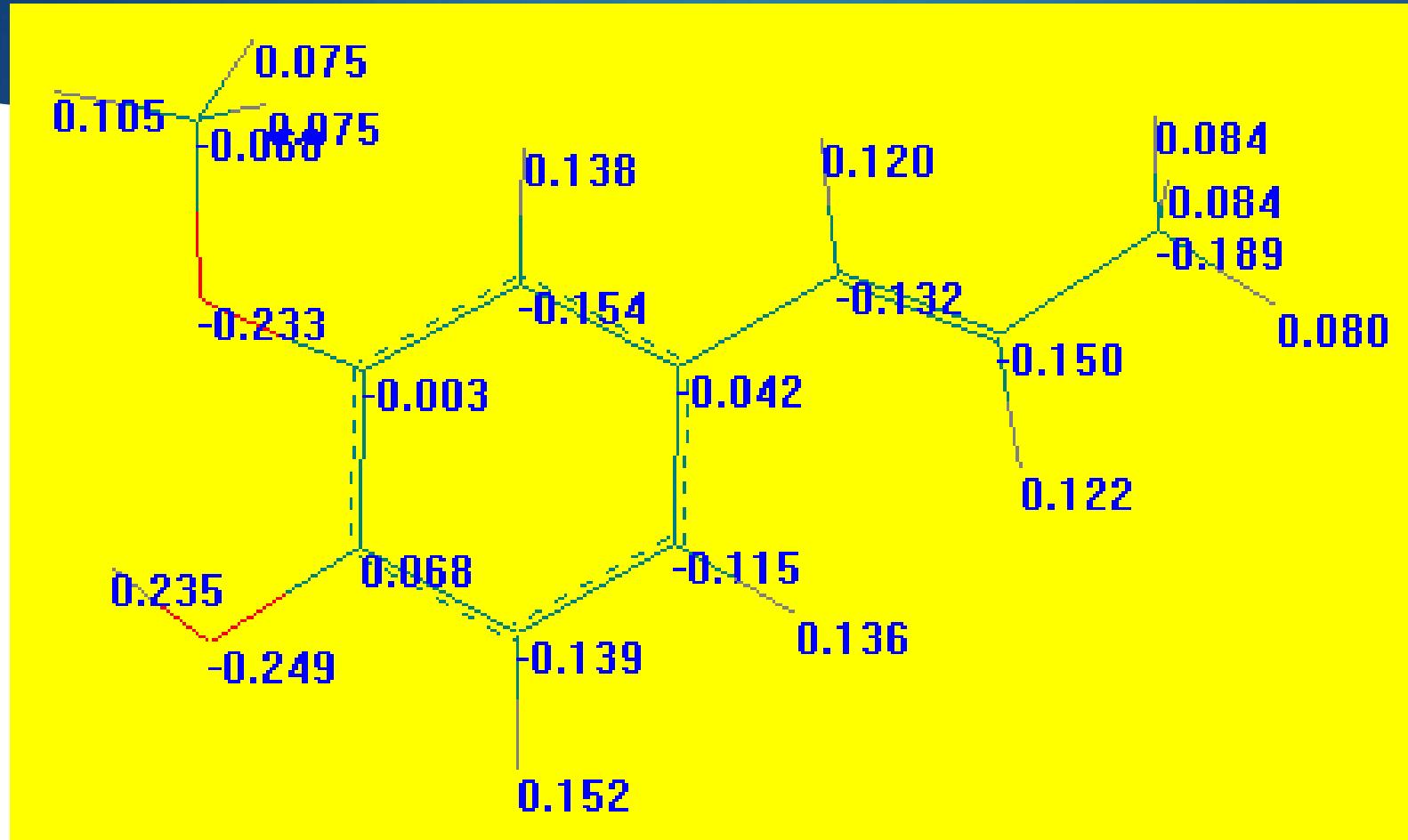
Compounds + biological activity



New compounds with improved biological
activity

$$\text{Biological activity} = C_0 + (C_1 * P_1) + \dots + (C_n * P_n)$$

Descriptor example:
Atomic Charge Neto



*Compare to the
electronegativity
concept*

Molecular Properties in QSAR

- ▶ Many other molecular properties have been incorporated into QSAR studies; some of these are measurable physical properties, such as:

- ▶ density
- ▶ ionization energy
- ▶ $H_{\text{vaporization}}$
- ▶ molecular weight
- ▶ $H_{\text{hydration}}$
- ▶ lipophilicity parameter $\pi = \log P_x - \log P_H$
- ▶ pK_a
- ▶ boiling point
- ▶ refractive index
- ▶ dipole moment (μ)
- ▶ reduction potential

Molecular Properties in QSAR

- ▶ Other molecular properties (descriptors) that have been incorporated into QSAR studies include calculated properties, such as:

- ▶ ovality
- ▶ HOMO energy
- ▶ polarizability
- ▶ molecular volume
- ▶ vdW surface area
- ▶ molar refractivity
- ▶ hydration energy
- surface area, molec. volume
- LUMO energy
- charges on individual atoms
- solvent accessible surface area
- maximum + and - charge
- hardness
- Taft's steric parameter

Requirements to use QSAR Method

Enough data to compile the QSAR equation (Data: Structure and activity)

DESIGN OF HYDROXY XANTHONES DERIVATIVES AS ANTICANCER USING QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR), EMMY YUANITA*, HARNO DWI PRANOWO, JUMINA, JUMINA, MUSTOFA MUSTOFA, Asian J Pharm Clin Res, Vol 9, Issue 2, 2016, 180-185

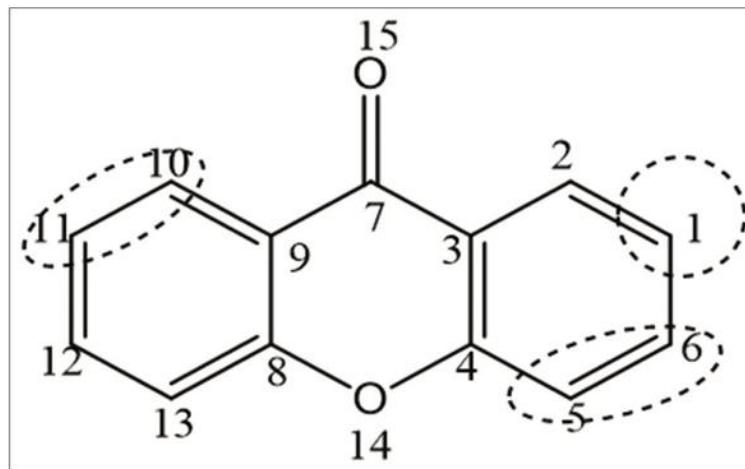


Fig. 3: Structure of xanthone

**QSAR, Molecular Docking,
synthesis, activity**

$$\text{Log IC}_{50} = -9.132 \text{ qC1} + 28.853 \text{ qC5} + 2.456 \text{ qC6} - 7.375 \text{ qC10} - 5.112 \text{ qC11} + 3.900$$

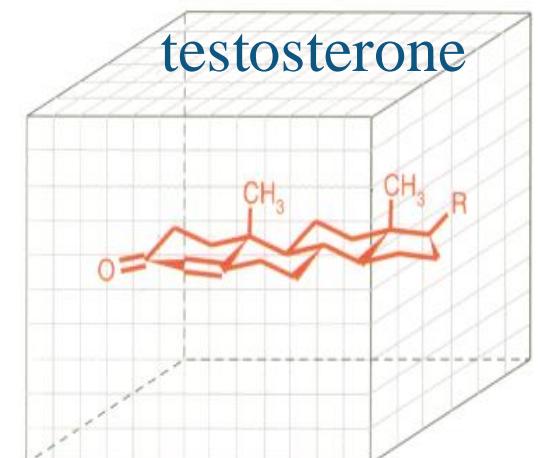
Some statistical parameters ($n=24$; PRESS=0.999; $r^2=0.782$; SEE=0. 235; R=0. 885; $F_{\text{Cal}}/F_{\text{tab}} = 4.68$).

Recommended Halogen substituted hydroxy xanthone derivatives

H-xanthen-9-one	0.068
I-xanthen-9-one	0.207
xanthen-9-one	0.019
H-xanthen-9-one	0.003
I-xanthen-9-one	0.005
xanthen-9-one	0.001
oxy-9H-xanthen-9-one	0.013
oxy-9H-xanthen-9-one	0.035
y-9H-xanthen-9-one	0.003
hydroxy-9H-xanthen-9-one	0.147
hydroxy-9H-xanthen-9-one	0.484
droxy-9H-xanthen-9-one	0.038
tahydroxy-9H-xanthen-9-one	0.029
tahydroxy-9H-xanthen-9-one	0.264
hydroxy-9H-xanthen-9-one	0.036

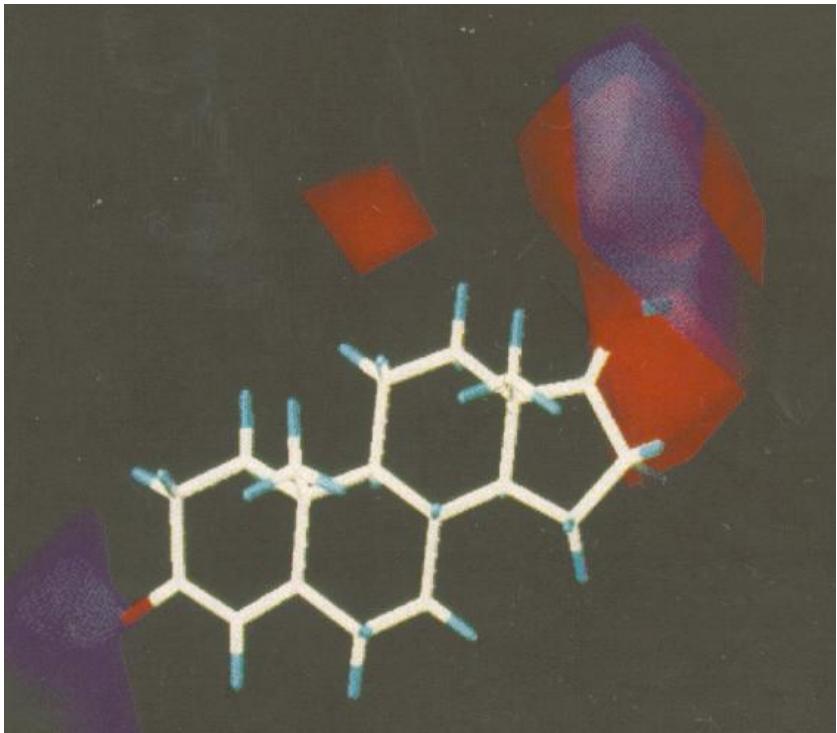
3 Dimensional QSAR Methods

- ▶ Important regions of bioactive molecules are “mapped” in 3D space, such that regions of hydrophobicity, hydrophilicity, H-bonding acceptor, H-bond donor, π -donor, etc. are rendered so that they overlap, and a general **3D pattern of the functionally significant regions** of a drug are determined.
- ▶ **CoMFA** (Comparative Molecular Field Analysis) is one such approach:

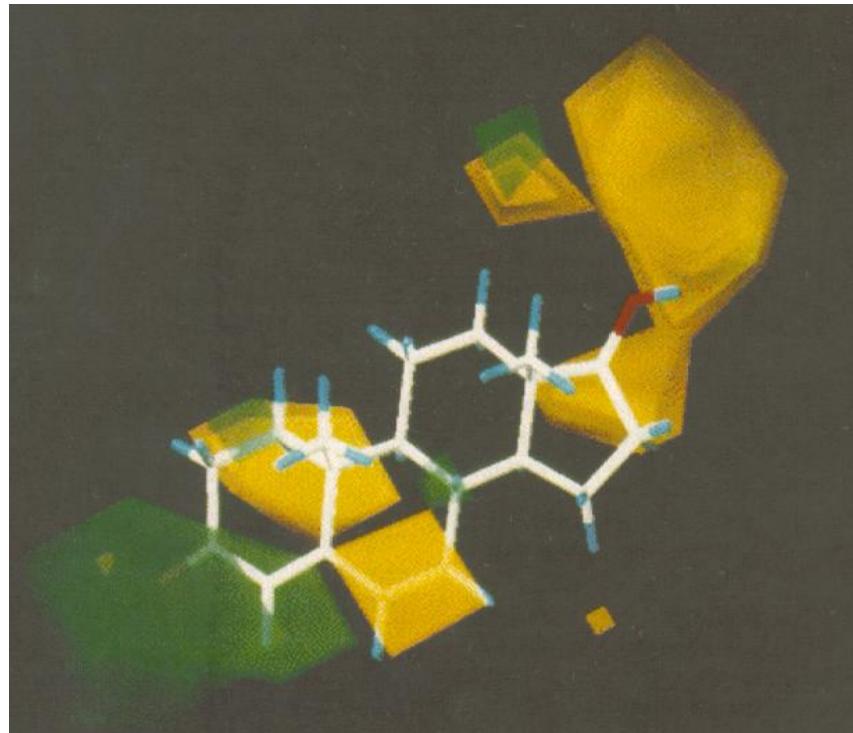


CoMFA of Testosterone

Blue means electronegative groups enhance, red means Electn' g. gr' ps reduce binding



Green means bulky groups enhance, yellow means they reduce binding



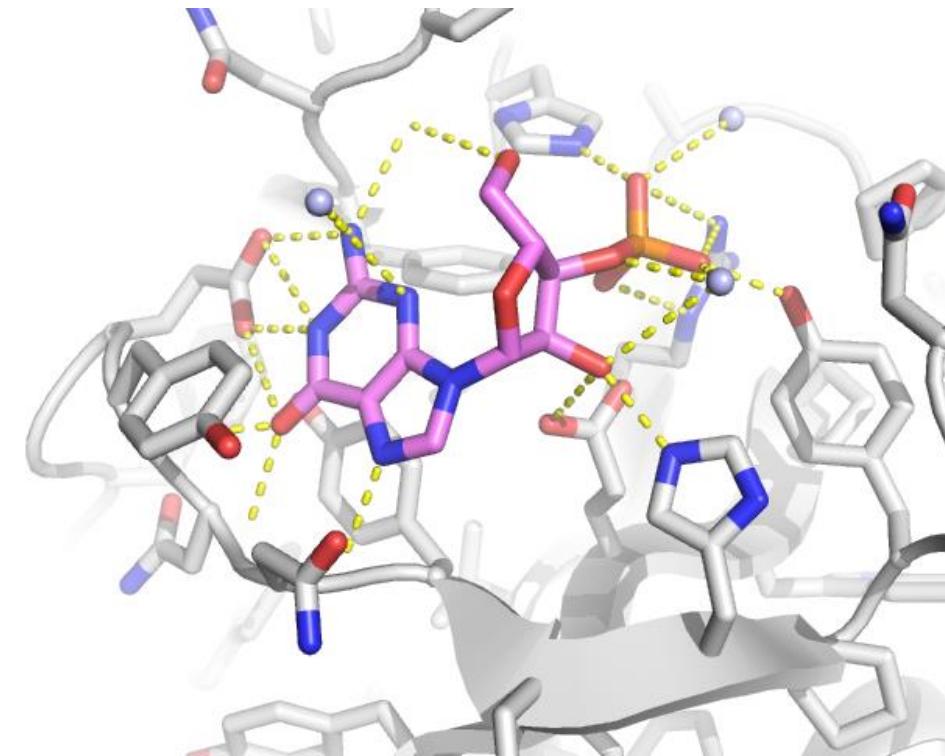
What is Protein-Ligand Docking?

Definition:

Computationally predict the structures of protein-ligand complexes from their conformations and orientations. The orientation that maximizes the interaction reveals the most accurate structure of the complex.

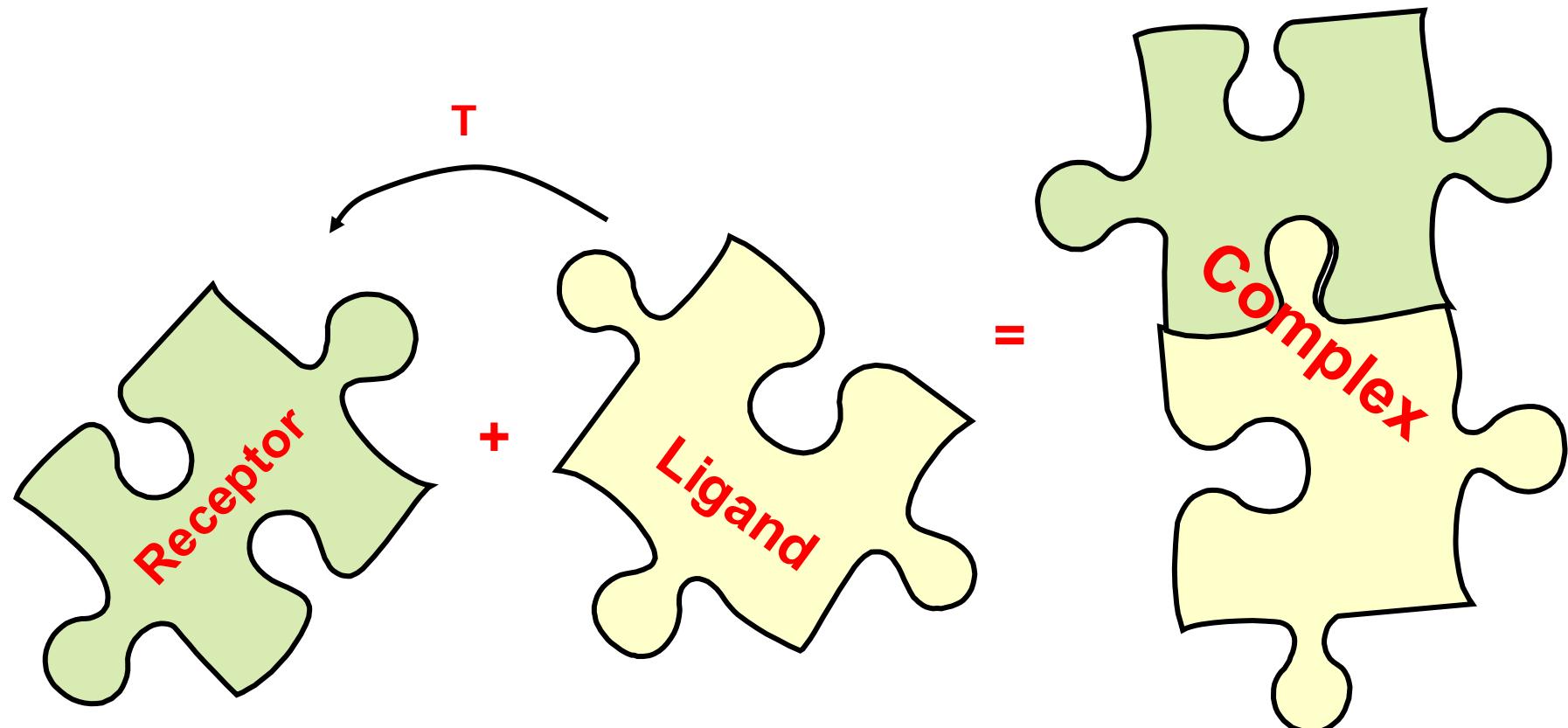
Importance of complexes

Structure _{vs} function _{vs} Supramolecular Chemistry

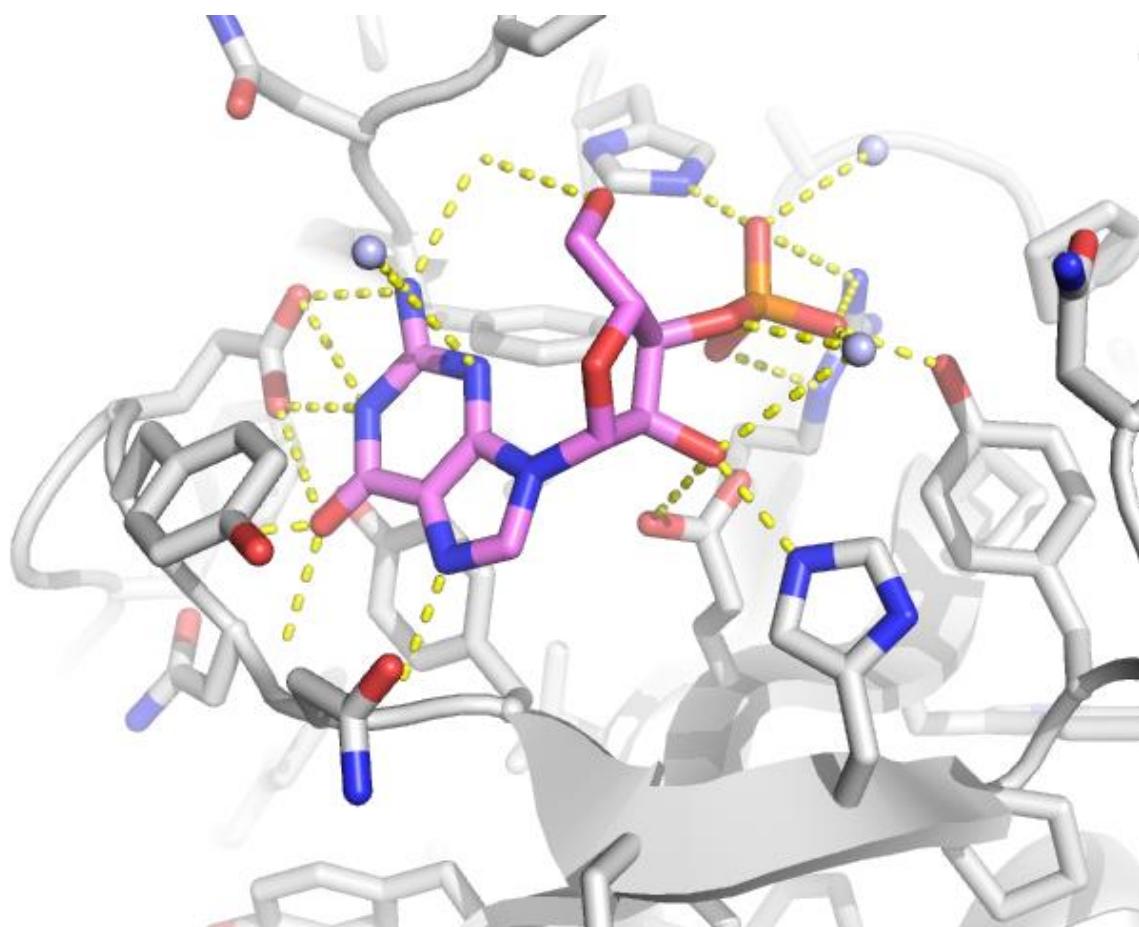


What is Docking?

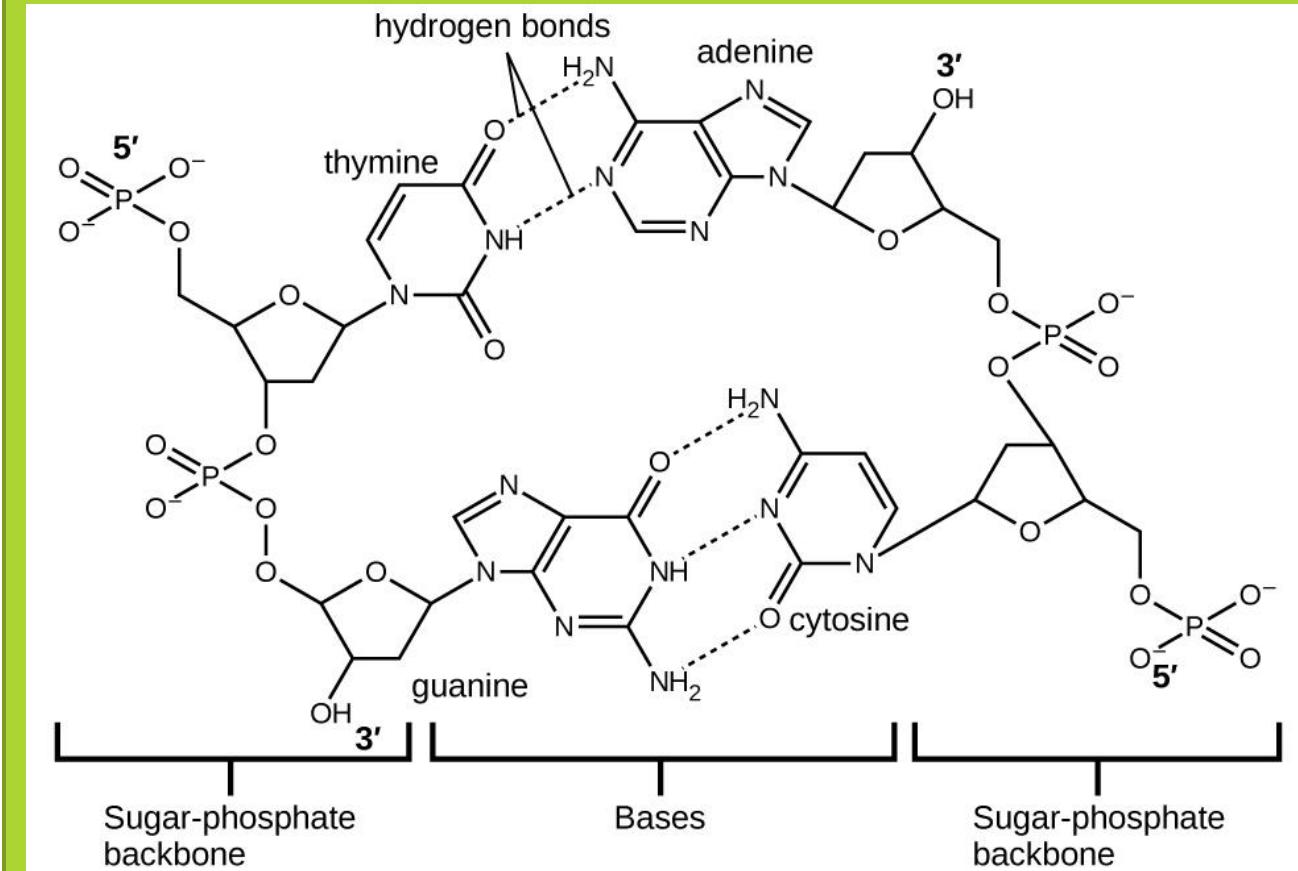
- Given two molecules find their correct association:



Bonding in Protein

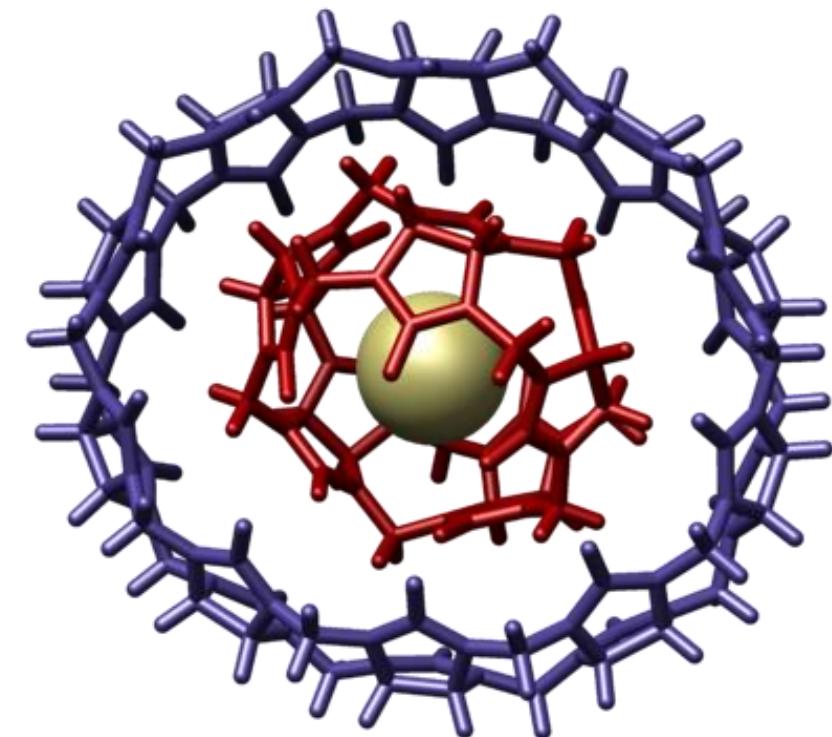


Bonding in Protein

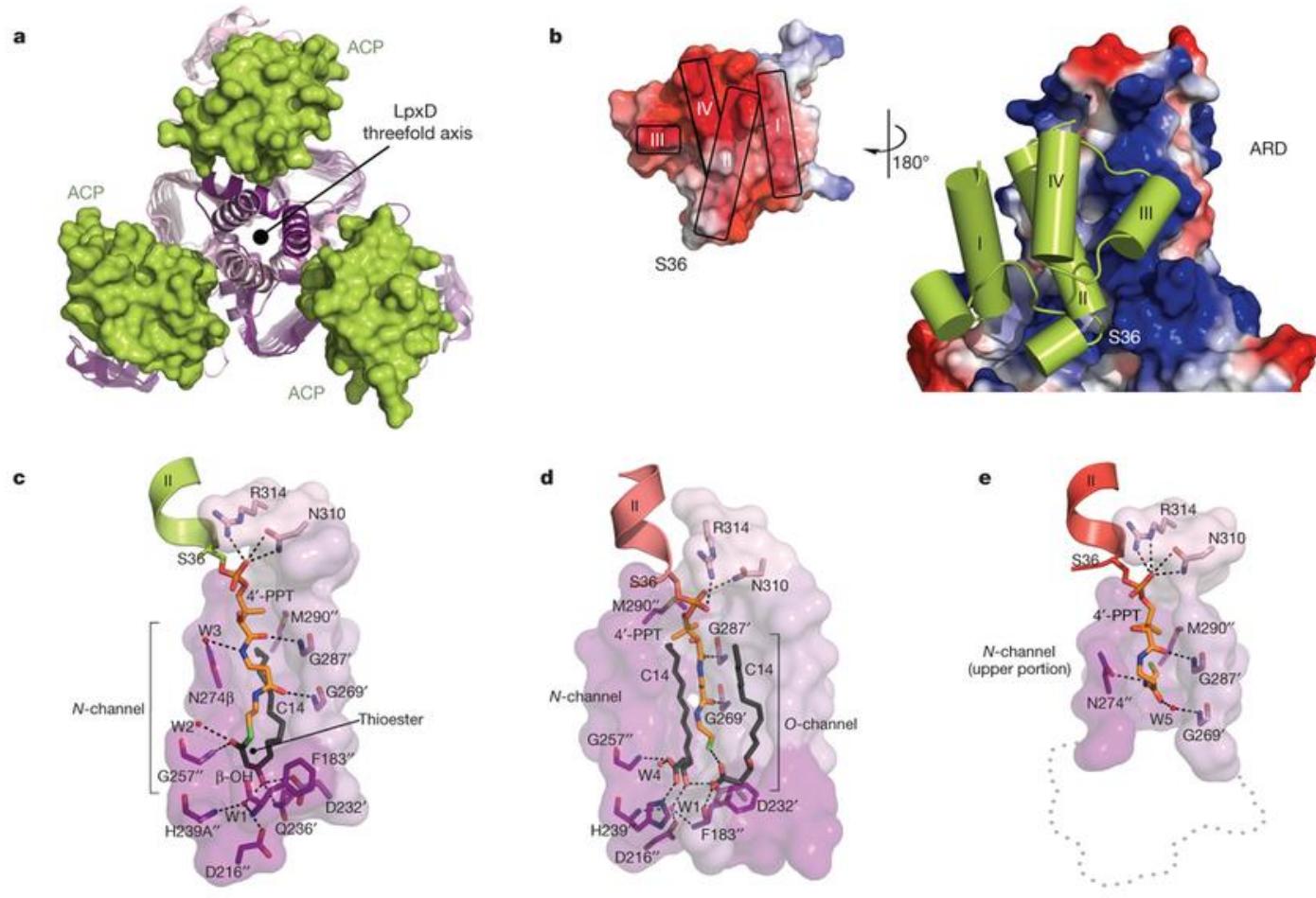
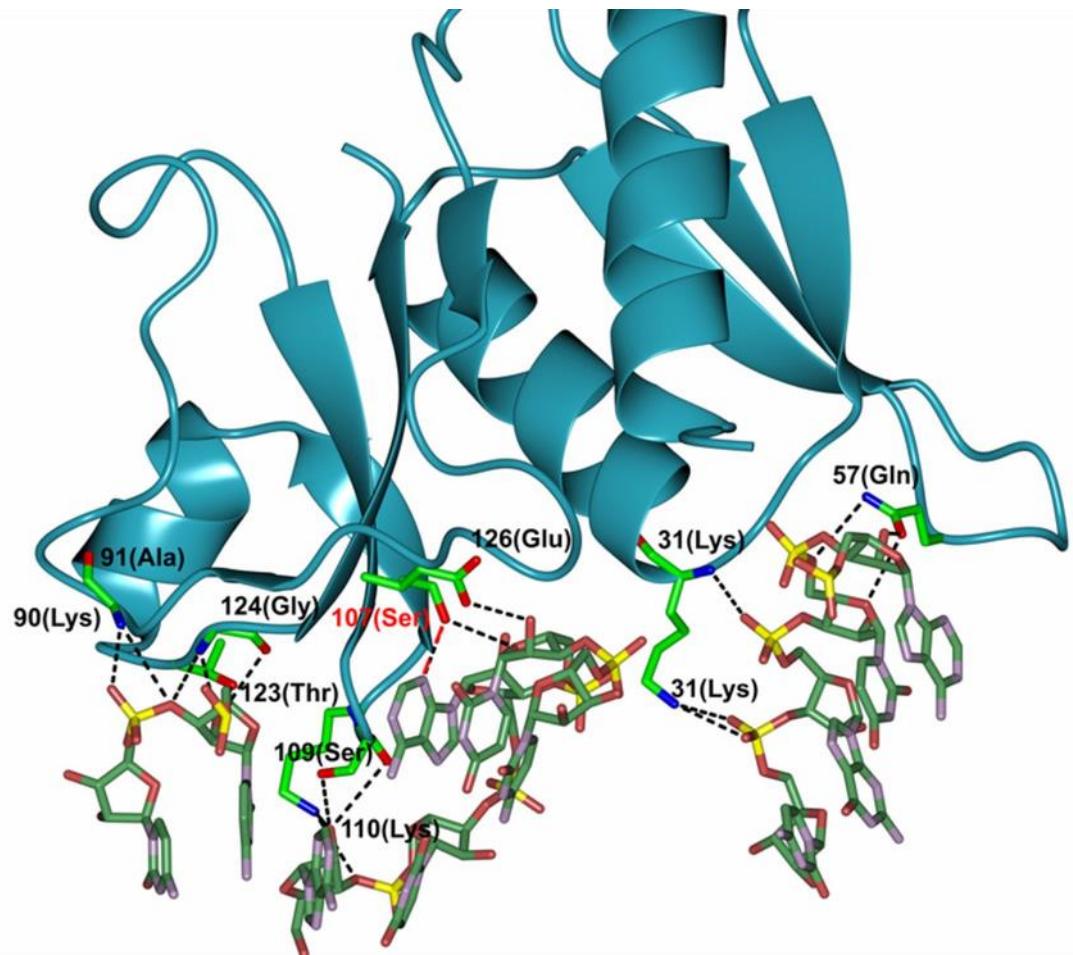


SUPRAMOLECULAR CHEMISTRY

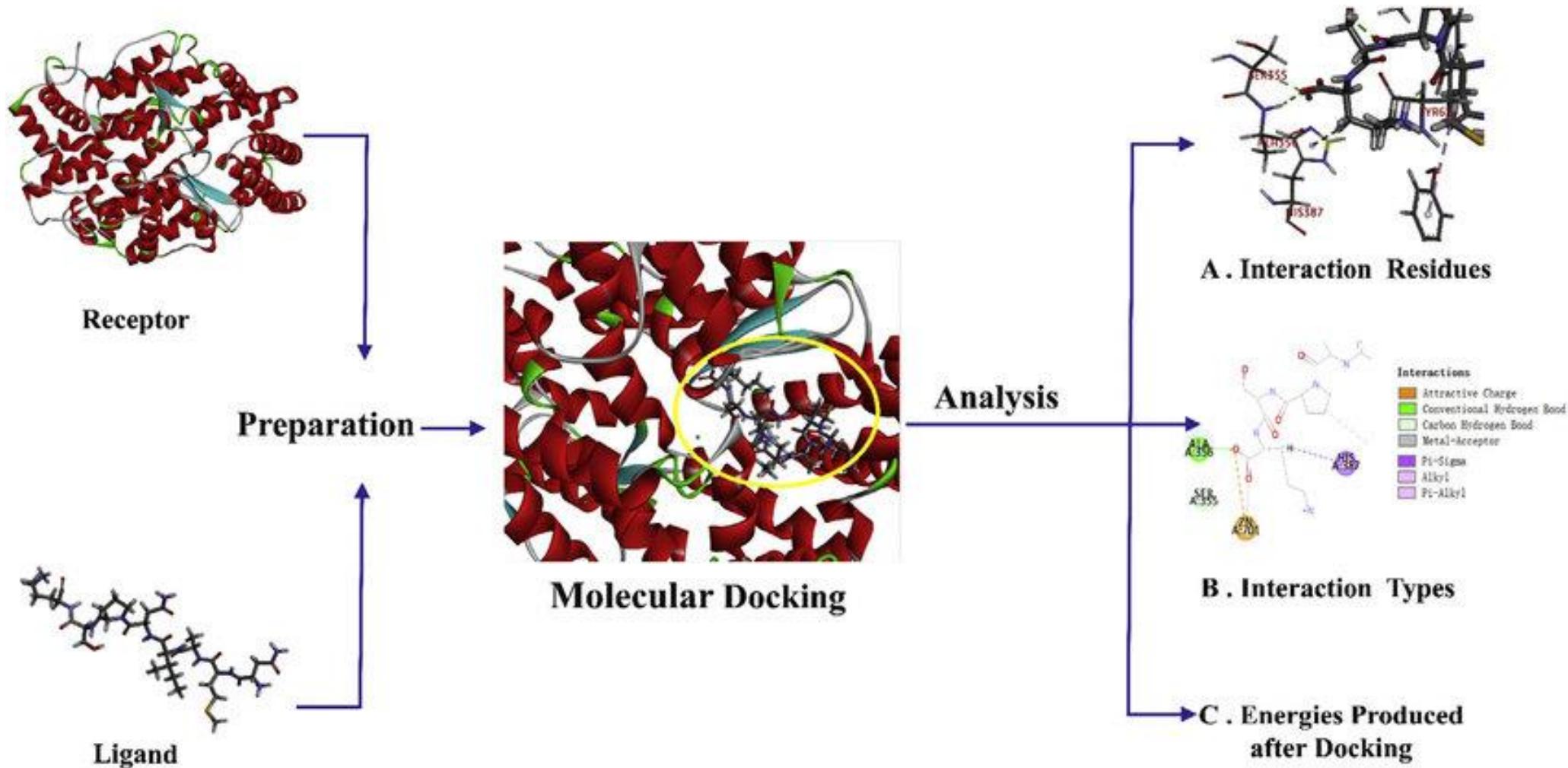
- ▶ Supramolecular chemistry deals with the chemistry of the **noncovalent bond** between molecules and/or ionic species.
- ▶ **Supramolecular chemistry** is the discipline covering “the chemistry of **molecular assemblies** and of the **intermolecular bond**” and deals with “organized entities that result from the **association** of two or more chemical species held together by intermolecular forces.”



Intermolecular interaction in protein system



Molecular Docking Procedure



Corona virus



- ▶ 2002: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)
- ▶ 2012: Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).
- ▶ 2019: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which causes infectious Covid-19 disease.

MOZAIK

Sumber : Bank Indonesia
& Riset tirto.id
NVL



SARS

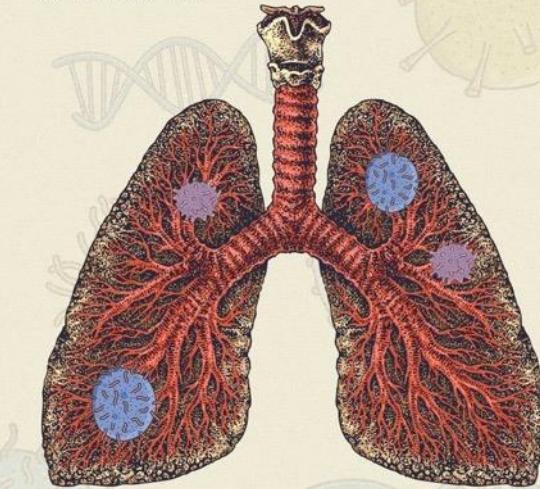
SEVERE ACUTE RESPIRATORY SYNDROME

SARS merupakan penyakit menular yang memengaruhi sistem pernapasan, disebabkan oleh virus corona SARS

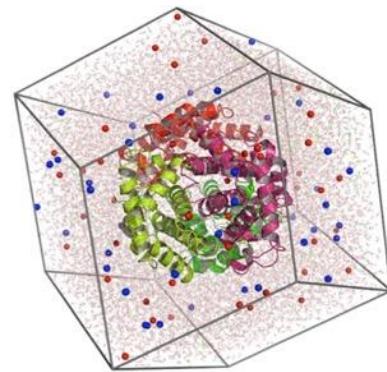
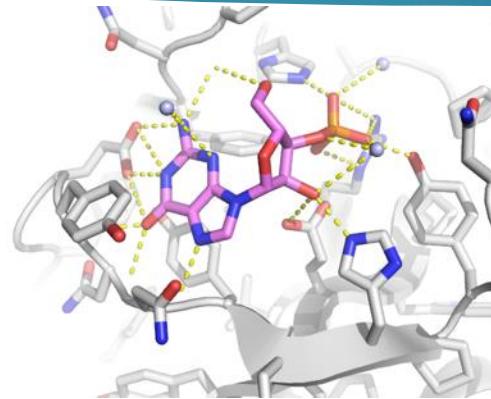
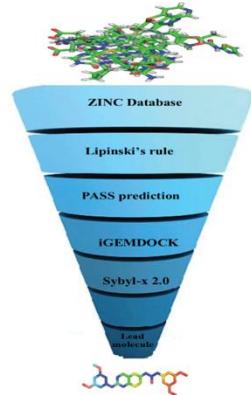
16 November 2002
Penyakit SARS pertama kali ditemukan di Kota Foshan, Provinsi Guangdong, Cina. Mulanya penyakit ini diidentifikasi sebagai kasus sindrom pernafasan

15 Maret 2003
WHO mengumumkan SARS sebagai ancaman kesehatan dunia

SARS-CoV dianggap sebagai penyakit zoonosis yang menyebar dari virus hewan (yang belum pasti) kelelawar lalu menyebar ke hewan lain, kemudian ke manusia



Research Process: Molecular Modelling of Anti-covid-19 Candidate from Indonesian Natural resources



Bioinformatics-driven **virtual screening**: PASS online can predict more than 300 pharmacological effects and biochemical mechanisms based on the structural formula of a substance.

The molecular docking study was conducted to analyze the interactions between the ligands and the targeted proteins, compared to the commercial drugs.

The molecular dynamics study was done to check the stabilities of complexes formed by the ligands and proteins.

Bioinformatics-driven virtual screening: Predictions of many biological activities based on the structural formula of a compound

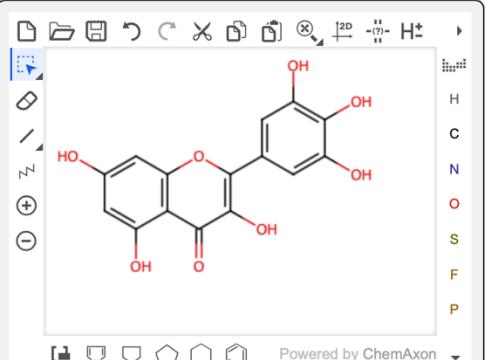
PASS online

harno Pranowo ([Log out](#)) [Go](#)

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[Predict new compound](#) [View old results](#) [View/change profile](#)

[SMILES](#) [MOL file](#) [Marvin JS](#)



Powered by ChemAxon

Predict

All Pa>Pi Pa>0,3 Pa>0,7 [ok](#)

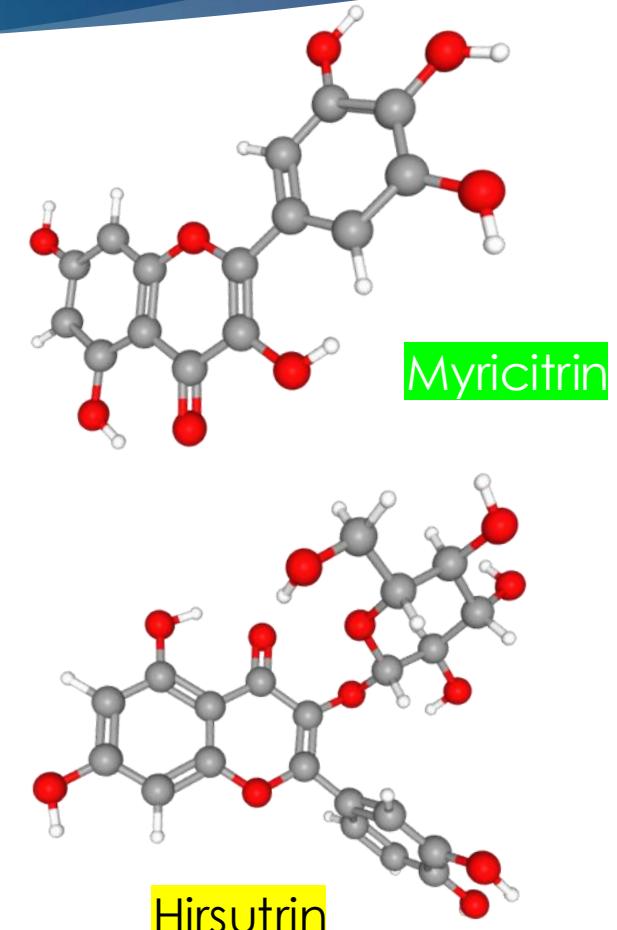
Pa	Pi	Activity
0,984	0,001	Chlordecone reductase inhibitor
0,969	0,002	HIF1A expression inhibitor
0,967	0,001	2-Dehydropantoate 2-reductase inhibitor

- ▶ The PASS (Prediction of Activity Spectra for Substances) online virtual screening web-server. PASS online can predict more than 300 pharmacological effects and biochemical mechanisms based on the structural formula of a substance.
- ▶ The prediction in the method using multilevel neighborhoods of atoms (MNA) descriptors is implemented in a Bayesian estimate-base algorithm (Varnek and Tropsha, 2008).
- ▶ The 3-dimensional structure of active compounds is downloaded from <http://www.knapsackfamily.com> and <https://pubchem.ncbi.nlm.nih.gov>.

Virtual Screening:

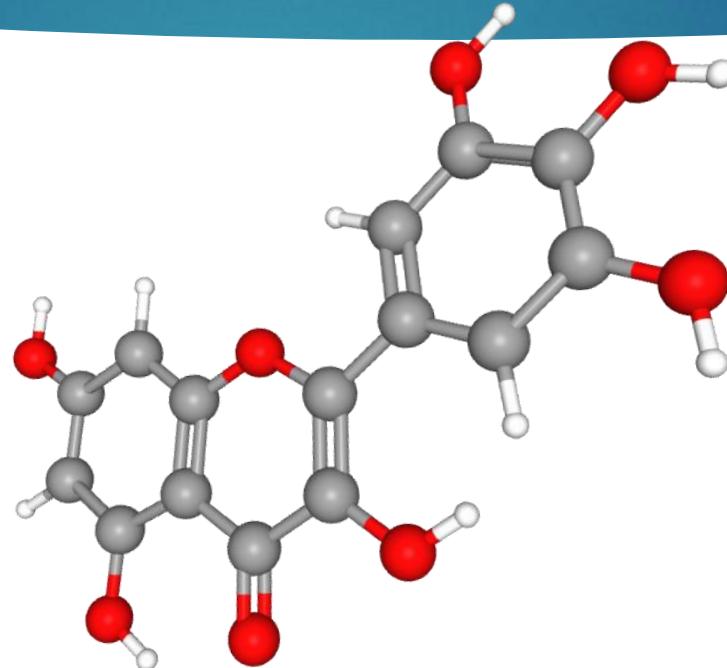
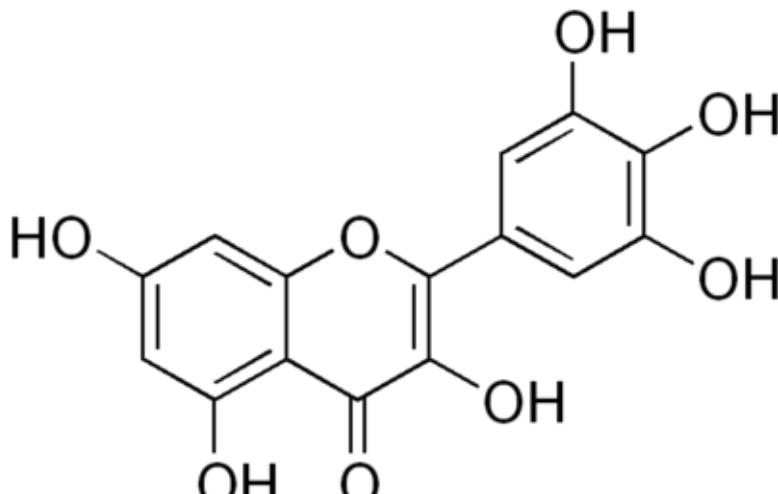
The top-ten of virtually screened natural compounds based on *Pa* (*protein-affinity*) values

Compound name	Pubchem ID	Pa value
Inosine	135398641	0.954
Rutin	5280805	0.907
Squalene	638072	0.817
Hirsutrin	5280804	0.801
Vitexin	5280441	0.753
Myricitrin	5281673	0.740
Asparagine	6267	0.732
Isoorientin	114776	0.725
Pectin	441476	0.721
Linalool	6549	0.711
Isoquercetin	5280804	0.709



Myricitrin

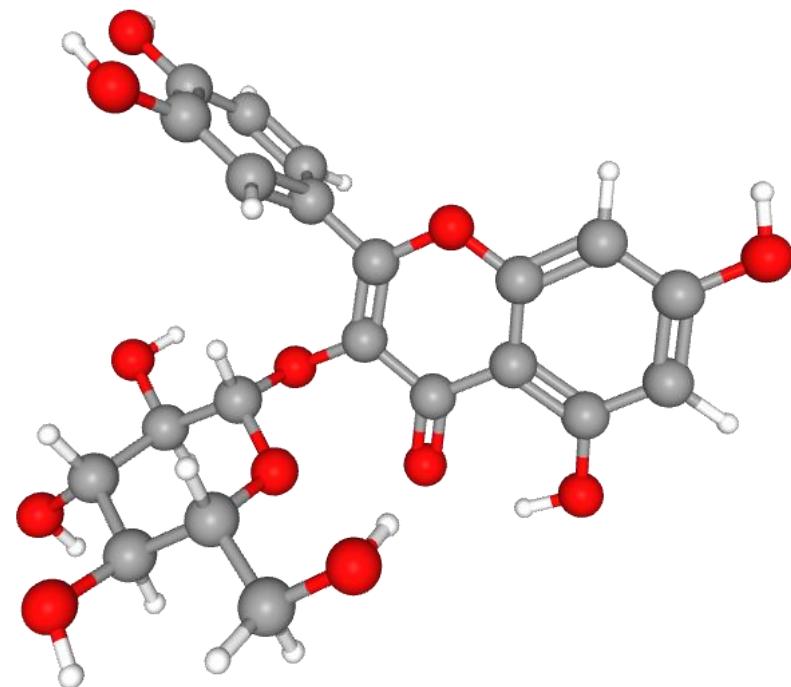
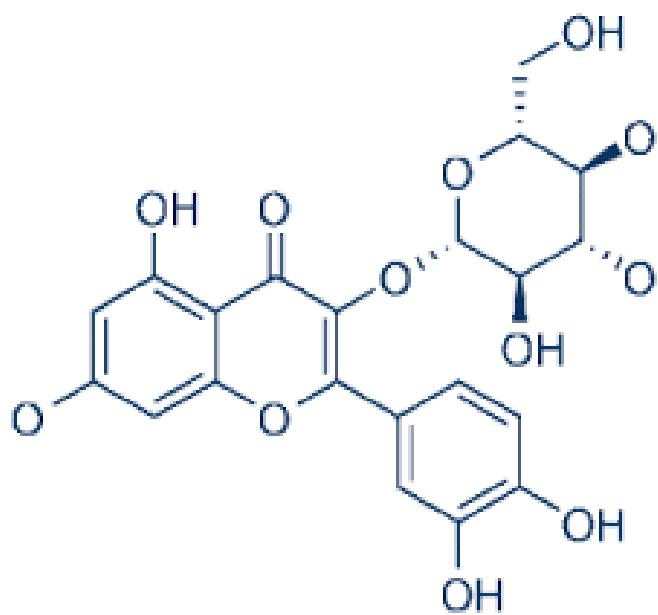
Another name	: Myricitroside
Species	: <i>Caesalpinia pulcherrima</i>
Local name	: Kembang Merak
Activity	: Antiviral (Influenza)



Compounds that can be used as anti-inflammatory, analgesic, anti-tumor, and anti-diabetic (Hwang and Chung, 2018). The presence of the 3,4,5-trihydroxyphenyl group plays an important role in its function as an inhibitor (Jo et al., 2020).

Hirsutrin

Another name : Isoquercitrin
Species : Casuarina equisetifolia
Local name : Cemara laut
Activity : Antiviral (Influenza)



Determination of the structure of ligands and receptor proteins:

1. Optimization of ligand structure with appropriate computational chemistry methods
2. Find the protein structures in the RCSB Protein data bank
3. Visualization of protein structure with Chimera

RCSB PDB Deposit Search Visualize Analyze Download Learn More Documentation MyPDB

181163 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

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PDB-101 Worldwide Protein Data Bank EMDDataResource NDB Worldwide Protein Data Bank Foundation

Celebrating 50 YEARS OF Protein Data Bank

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

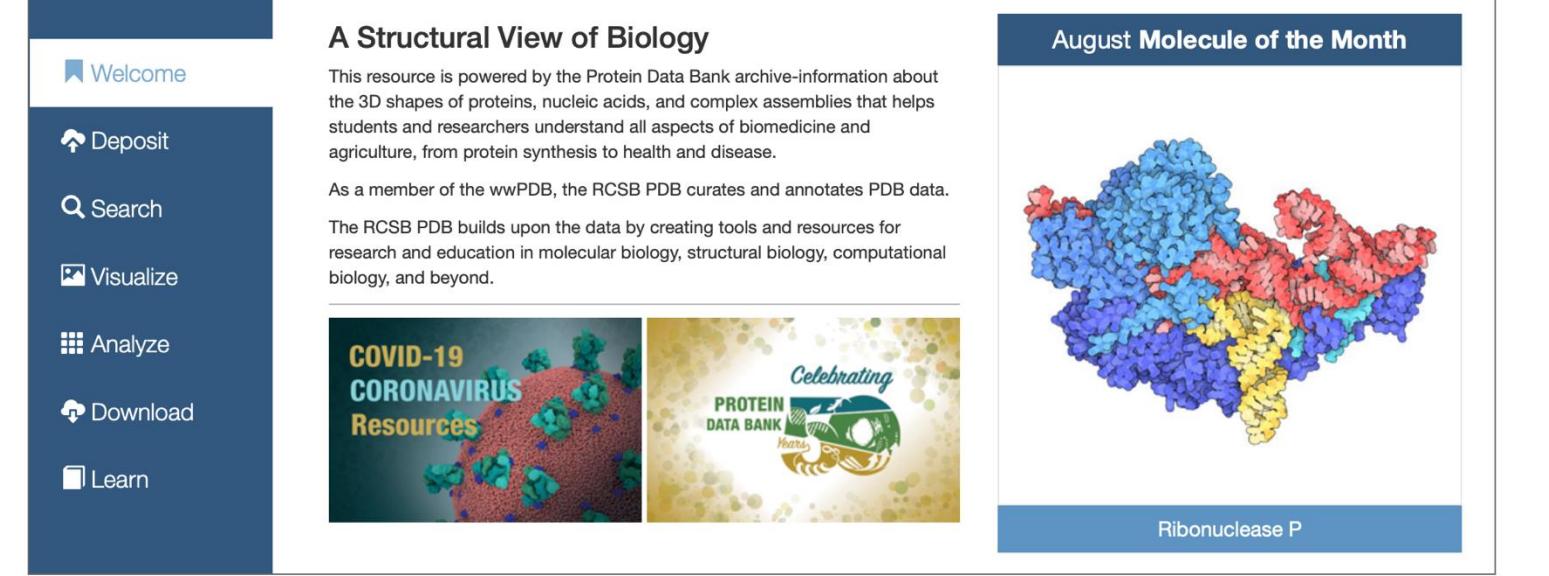
As a member of the wwPDB, the RCSB PDB curates and annotates PDB data. The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

COVID-19 CORONAVIRUS Resources

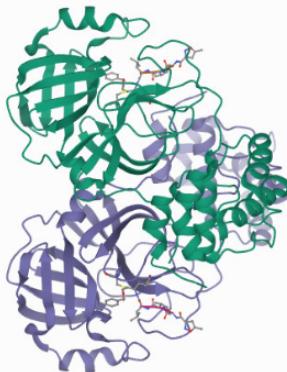
August Molecule of the Month

Ribonuclease P

Latest Entries As of Tue Aug 10 2021 Features & Highlights News Publications



Two SARS-CoV-2 proteins are used as the target in this research, they are the main protease (MPro) with PDB ID: 6W63 and the receptor-binding domain (RBD) with PDB ID: 6LZG which downloaded from www.rcsb.org.

[3D View](#)

6LU7

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The crystal structure of COVID-19 main protease in complex with an inhibitor N3

Liu, X., Zhang, B., Jin, Z., Yang, H., Rao, Z.

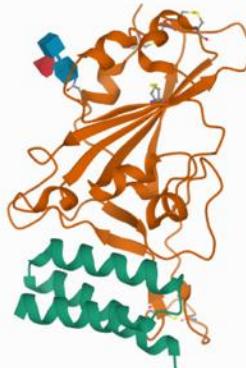
(2020) Nature 582: 289-293

Released 2020-02-05

Method X-RAY DIFFRACTION 2.16 Å

Organisms Severe acute respiratory syndrome coronavirus 2
synthetic construct

Macromolecule N-[(5-METHYLSOXAZOL-3-YL)CARBONYL]ALANYL-L-VALYL-N~1~-((1R,2Z)-4-(BENZYLOXY)-4-OXO-1-[(3R)-2-OXOPYRROLIDIN-3-YL]METHYL)BUT-2-ENYL)-L-LEUCINAMIDE (protein)
main protease (protein)

[3D View](#)

7JZU

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SARS-CoV-2 spike in complex with LCB1 (local refinement of the RBD and LCB1)

Park, Y.J., Veesler, D., Seattle Structural Genomics Center for Infectious Disease (SSGCID)

(2020) Science

Released 2020-09-23

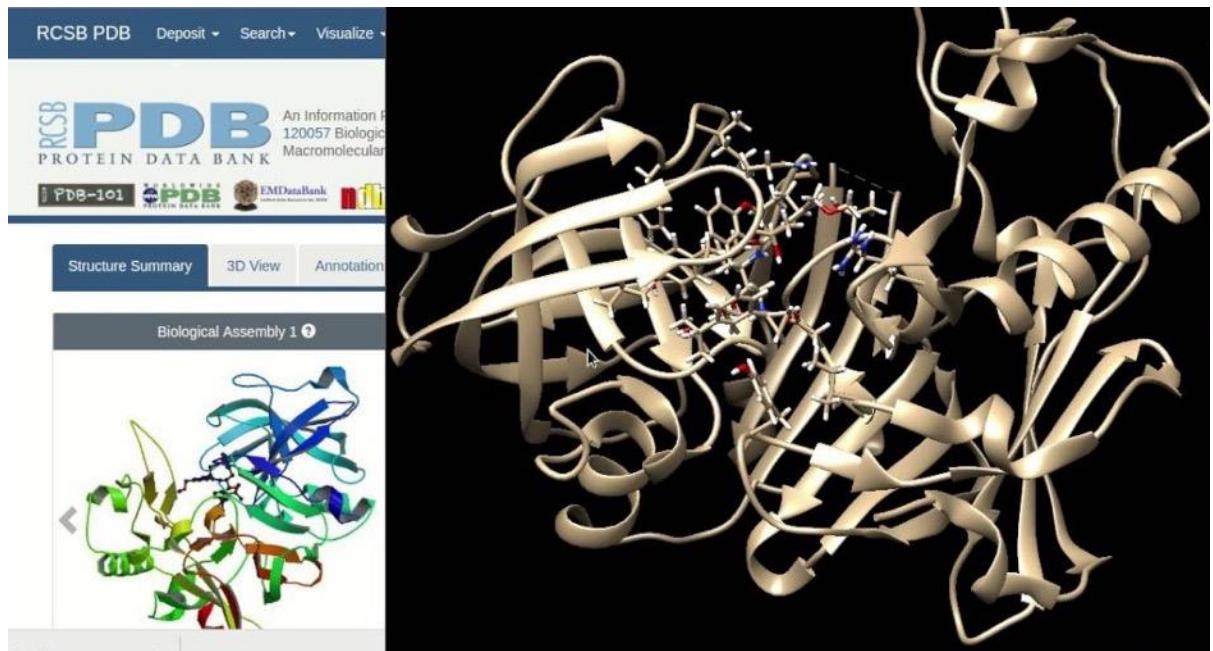
Method ELECTRON MICROSCOPY 3.1 Å

Organisms Severe acute respiratory syndrome coronavirus 2
synthetic construct

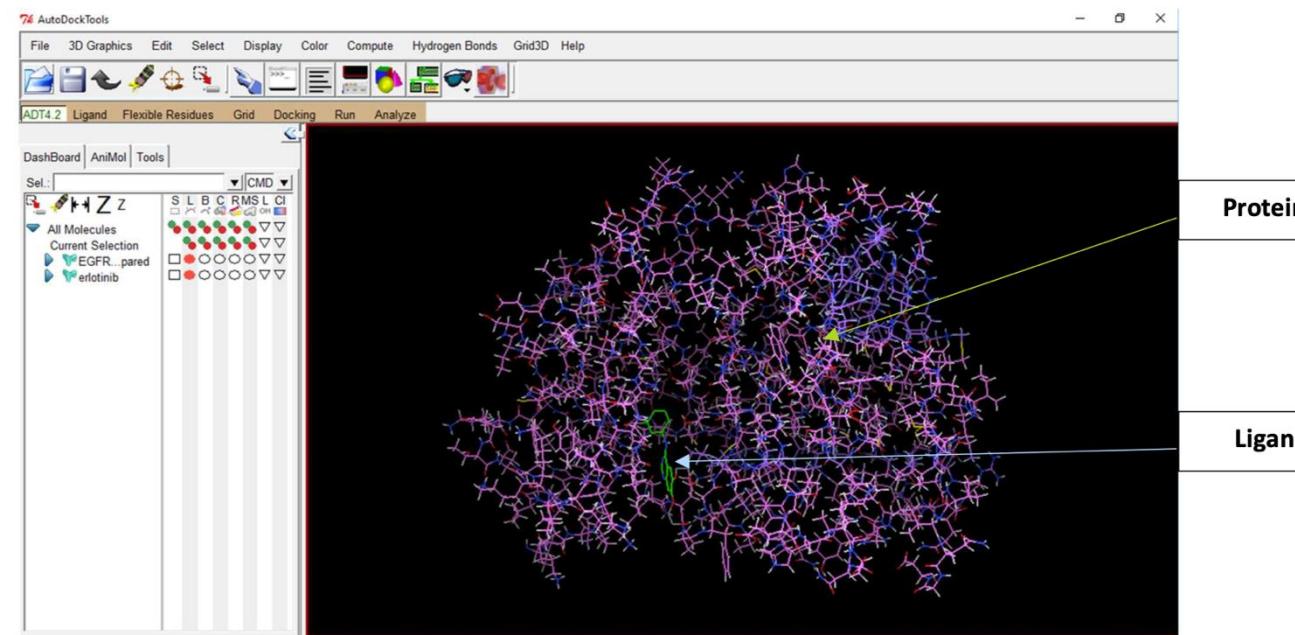
Macromolecule LCB1 (protein)
Spike glycoprotein (protein)

Unique branched monosaccharides FUC, NAG

Preparation Ligand-Receptor

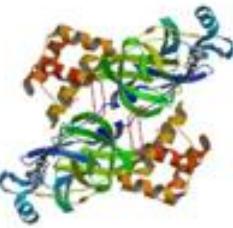


Molecular Docking Software



Ligand and protein preparation: Chimera

The molecular docking analysis: Autodock



6W63

[Download File](#) [View File](#)

Structure of COVID-19 main protease bound to potent broad-spectrum non-covalent inhibitor X77

Mesecar, A.D., Center for Structural Genomics of Infectious Diseases (CSGID)

To be published

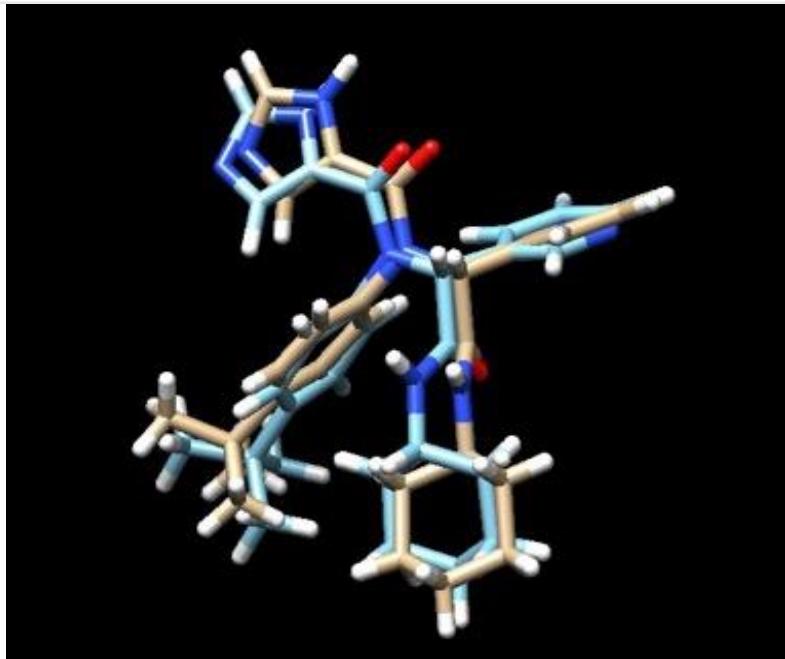
Released 2020-03-25

Method X-RAY DIFFRACTION 2.1 Å

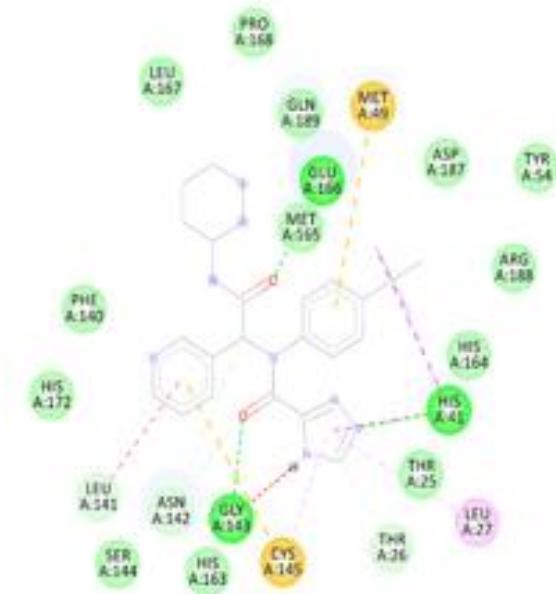
Organisms Severe acute respiratory syndrome coronavirus 2

Macromolecule 3C-like proteinase (protein)

Unique Ligands X77



Superimposition of redocked native ligand with crystallized structure in database, RMSD = 0.9



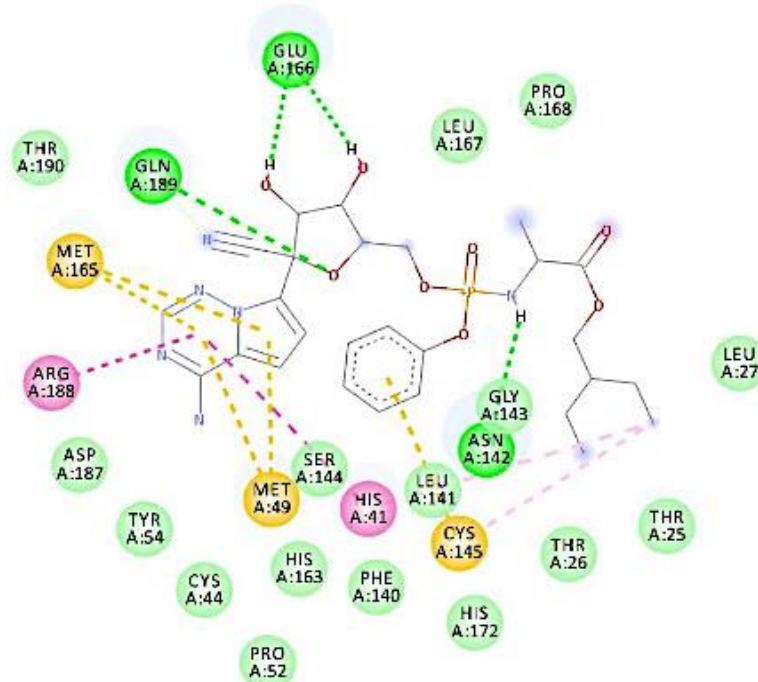
Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Unfavorable Donor-Donor
- Pi-Sigma

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

evaluated in molecular docking is the conventional hydrogen bond since this interaction is the most contributing to intermolecular interaction between the protein and ligand

Interaction between positive-control (remdesivir) and myricitrin against MPro



Interactions

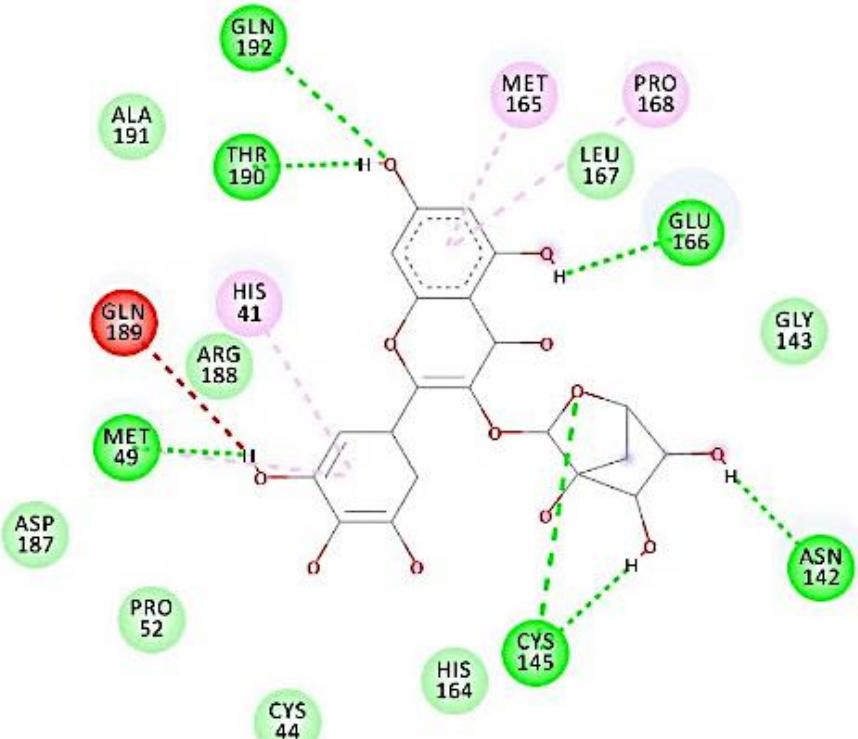
- █ van der Waals
- █ Conventional Hydrogen Bond
- █ Carbon Hydrogen Bond
- █ Pi-Sulfur

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

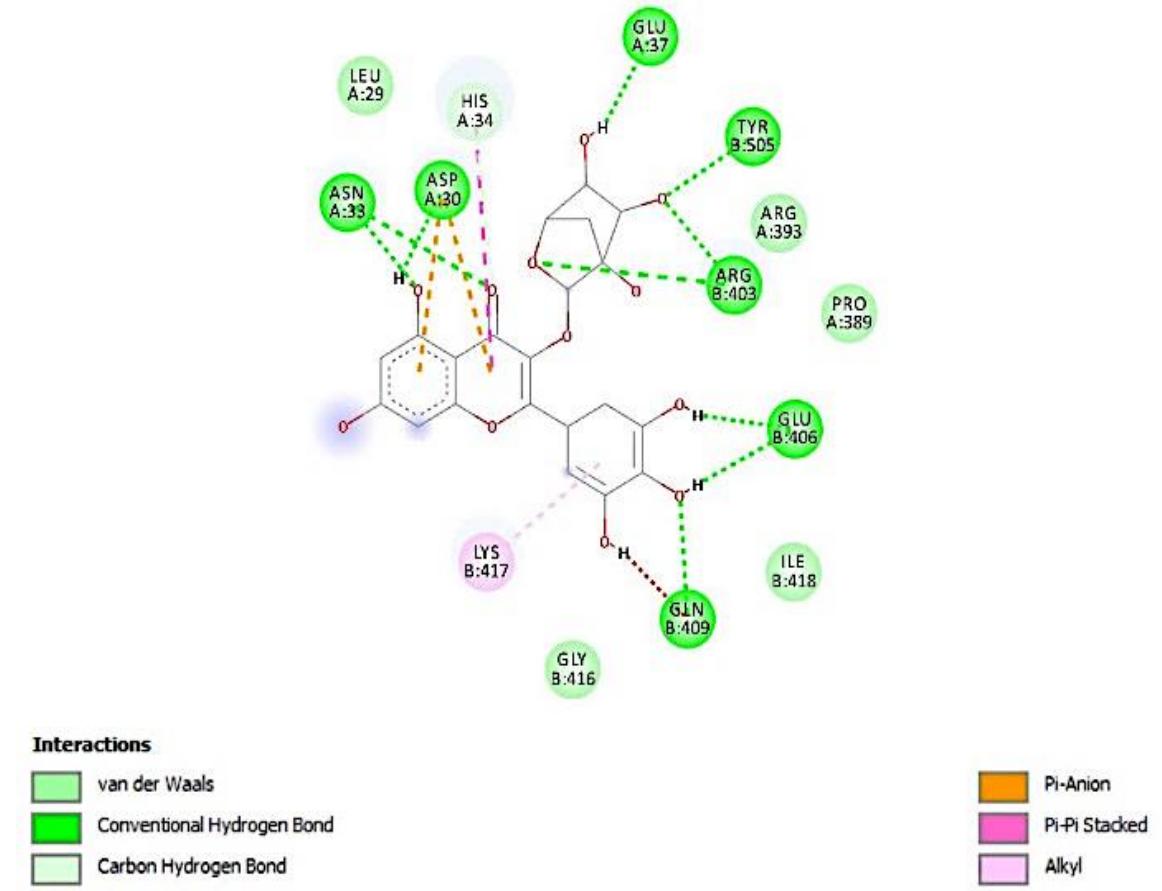
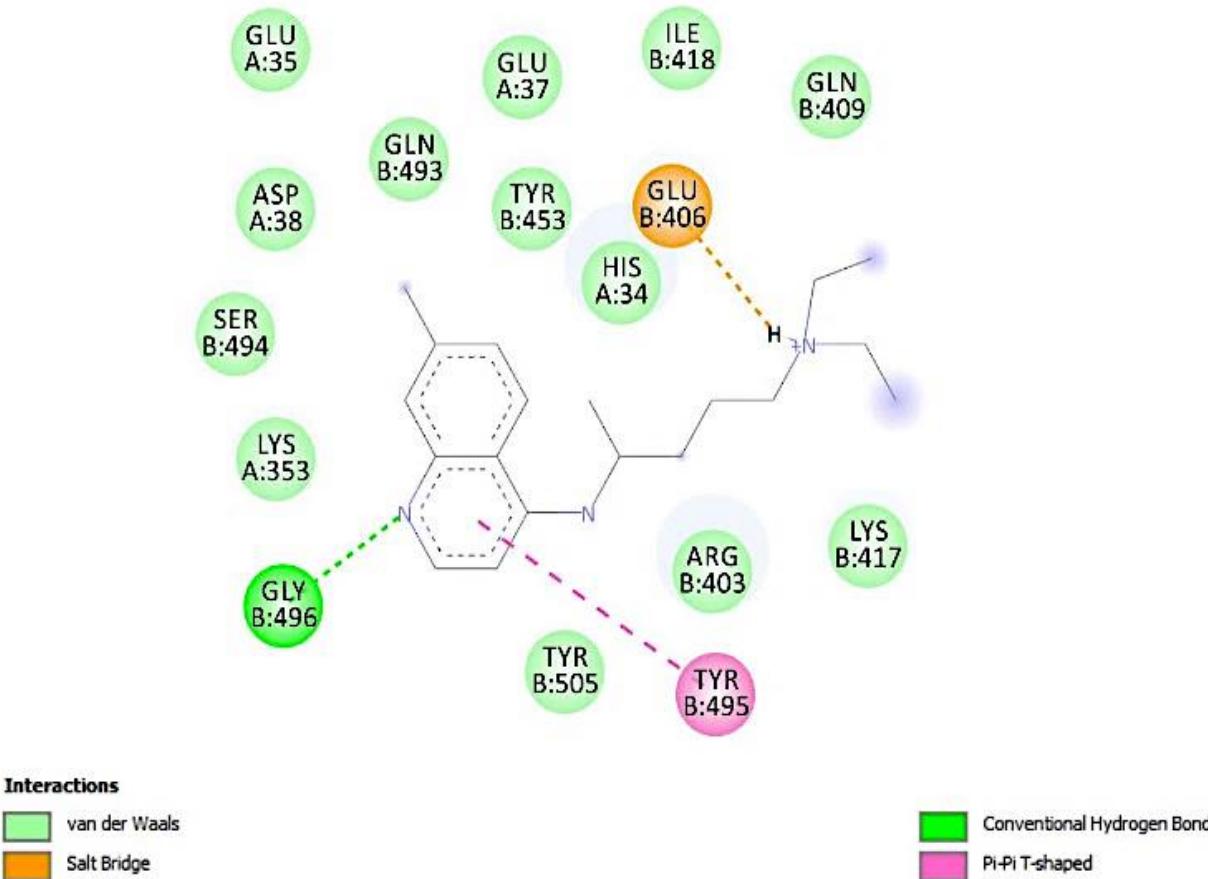
Interactions

- █ van der Waals
- █ Conventional Hydrogen Bond
- █ Unfavorable Donor-Donor

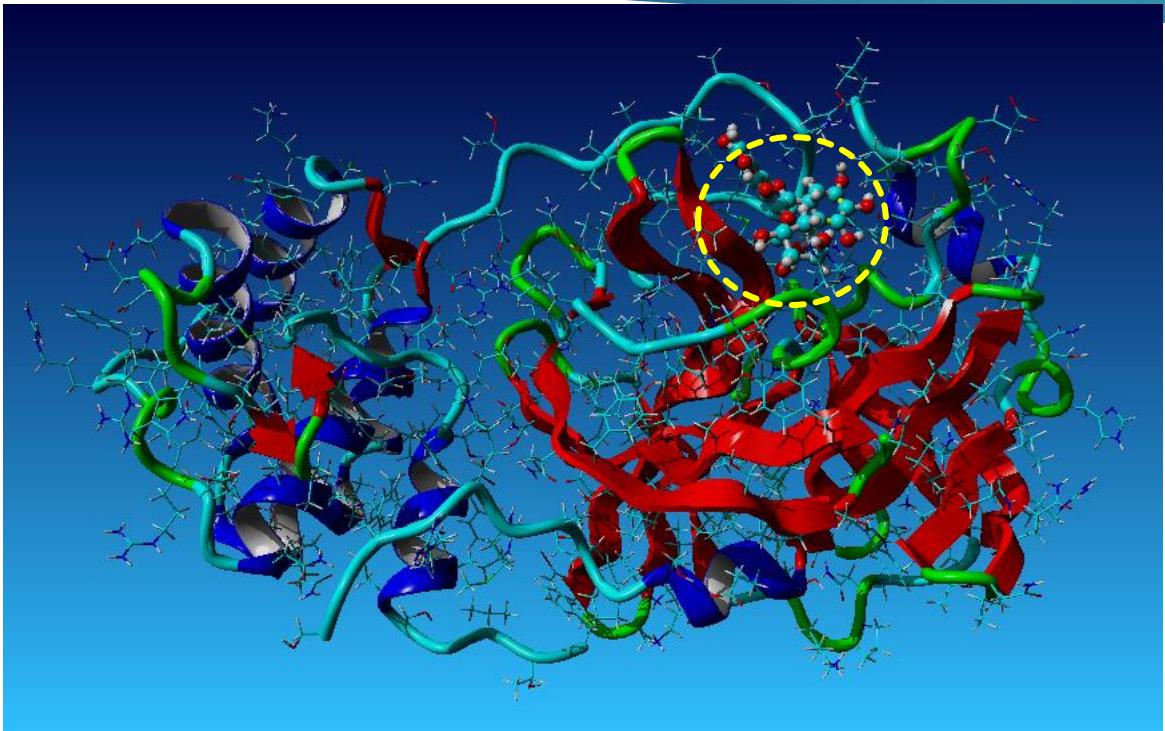
- █ Alkyl
- █ Pi-Alkyl



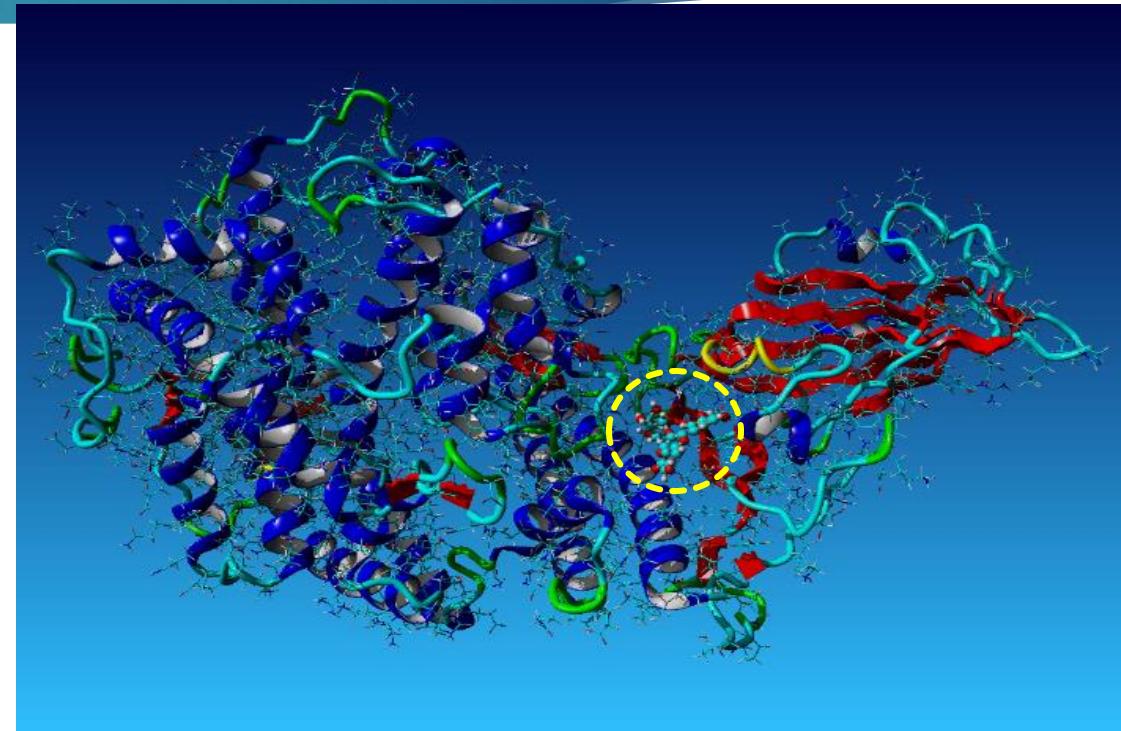
Interaction between positive-control (chloroquine) and myricitrin against RBD



Complexes between myricitrin with M^{pro} (a), RBD (b)



Myricitrin-M^{pro} (a)

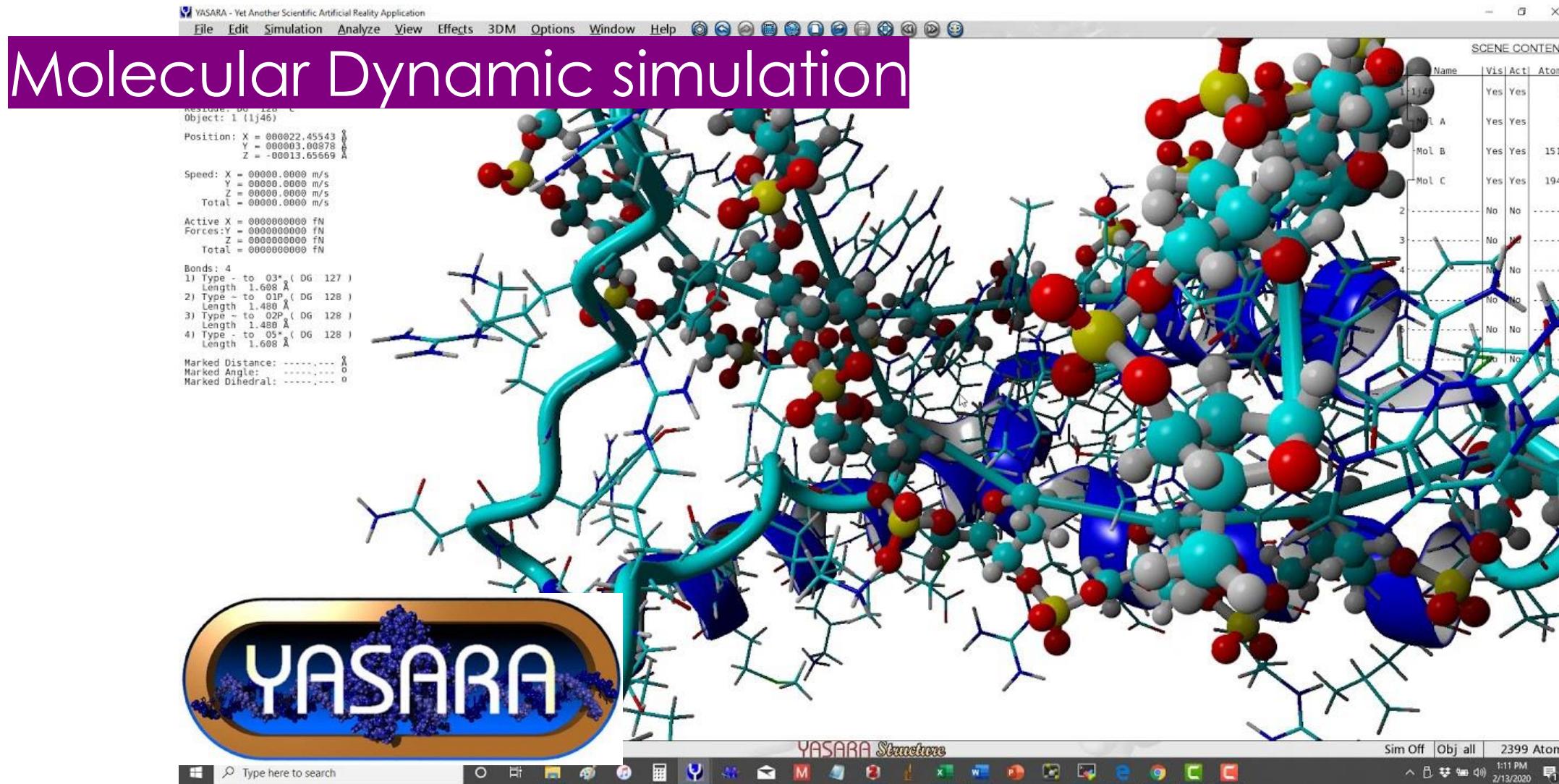


Myricitrin-RBD (b)

The results of molecular docking between proposed compounds and targeted proteins

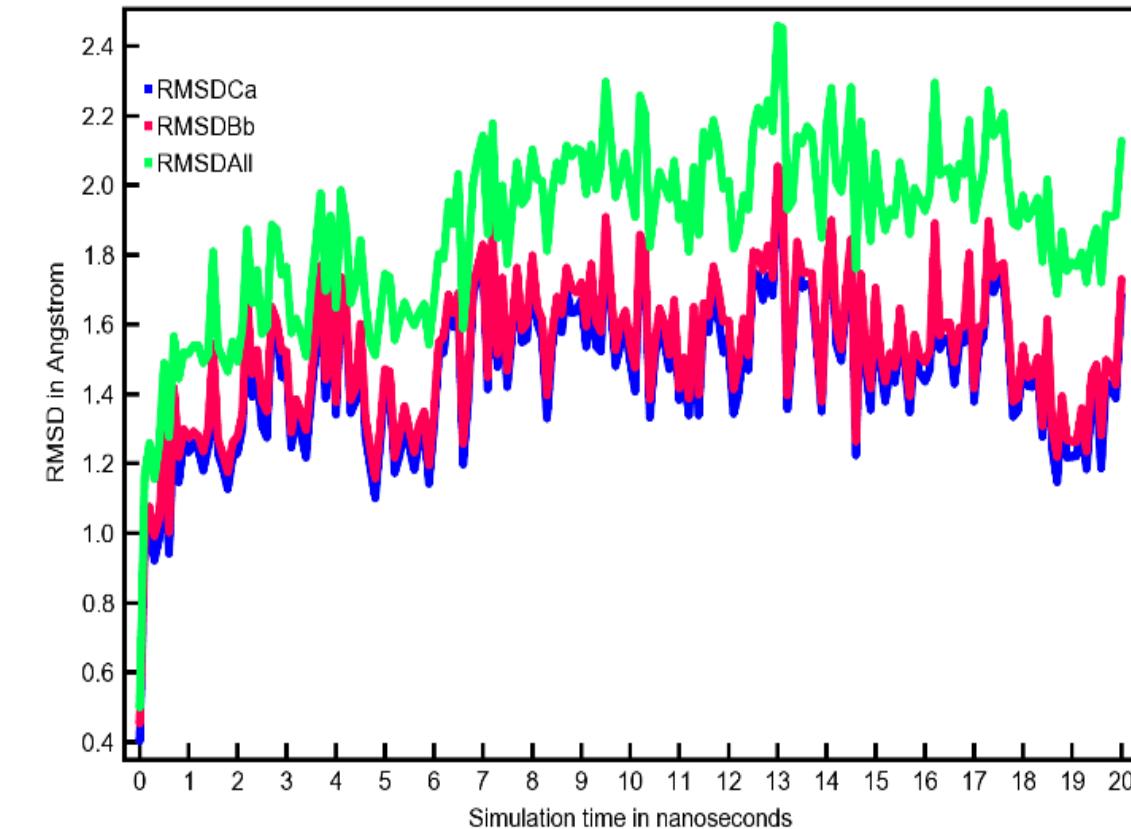
Ligand	Binding energy (kcal/mol)	
	M-Pro	RBD
Inosine	-5.84	-6.03
Vitexin	-8.08	-7.22
Hirsutrin	-8.88	-5.56
Myricitrin	-8.30	-9.24
Rutin	-9.27	-7.52
Squalene	-9.34	-6.52
Native	-5.86	-
Remdesivir	-7.11	-
Chloroquine	-	-7.20

Focus on :
Myricitrin and Hirsutin

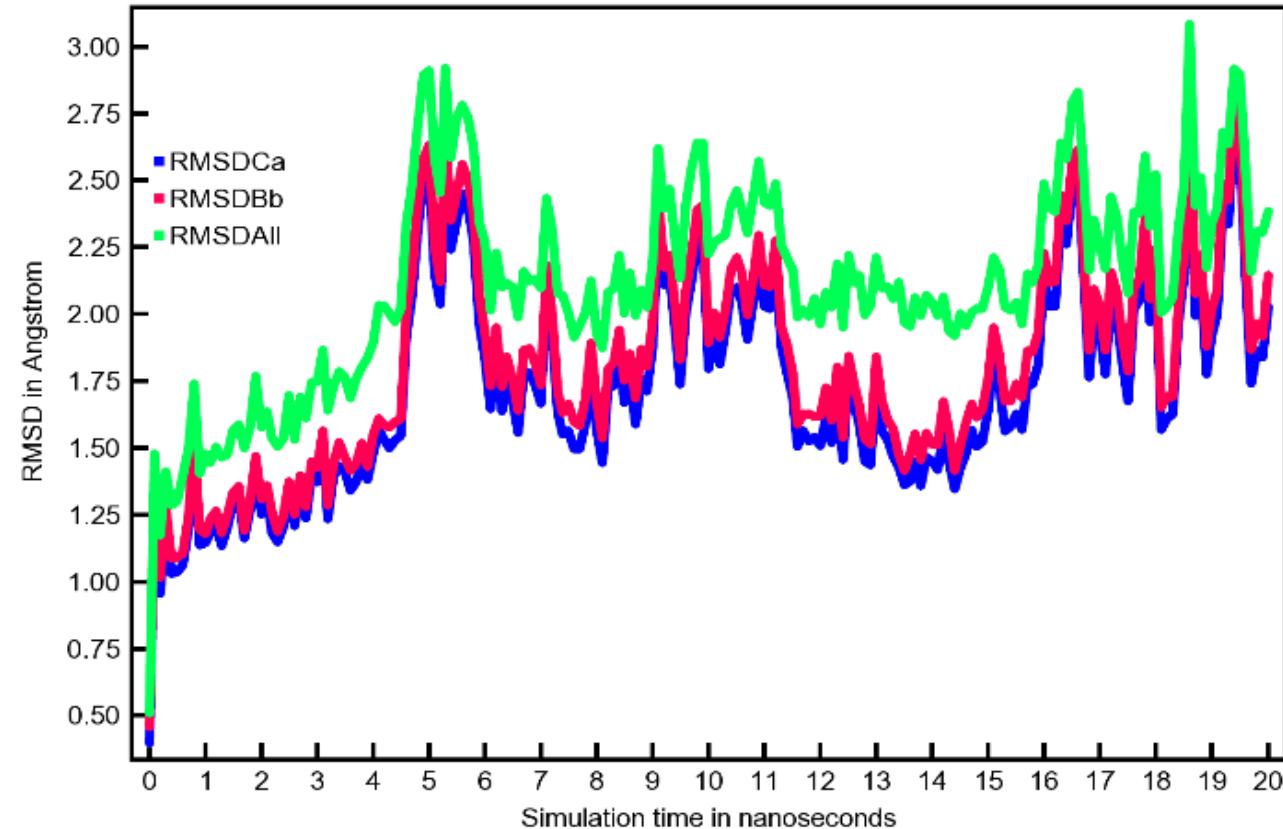


The best conformation resulted from molecular docking analysis was then simulated using the molecular dynamics method. The simulation was conducted on YASARA with a 7 Å extended simulation box, a 2 fs time step, and a total of 20 ns simulation time. Parameters that were analyzed in this step were the potential energy of the systems and the protein's RMSD values.

The profile of protein RMSD on the complex of M^{pro} and remdesivir and Myricitrin



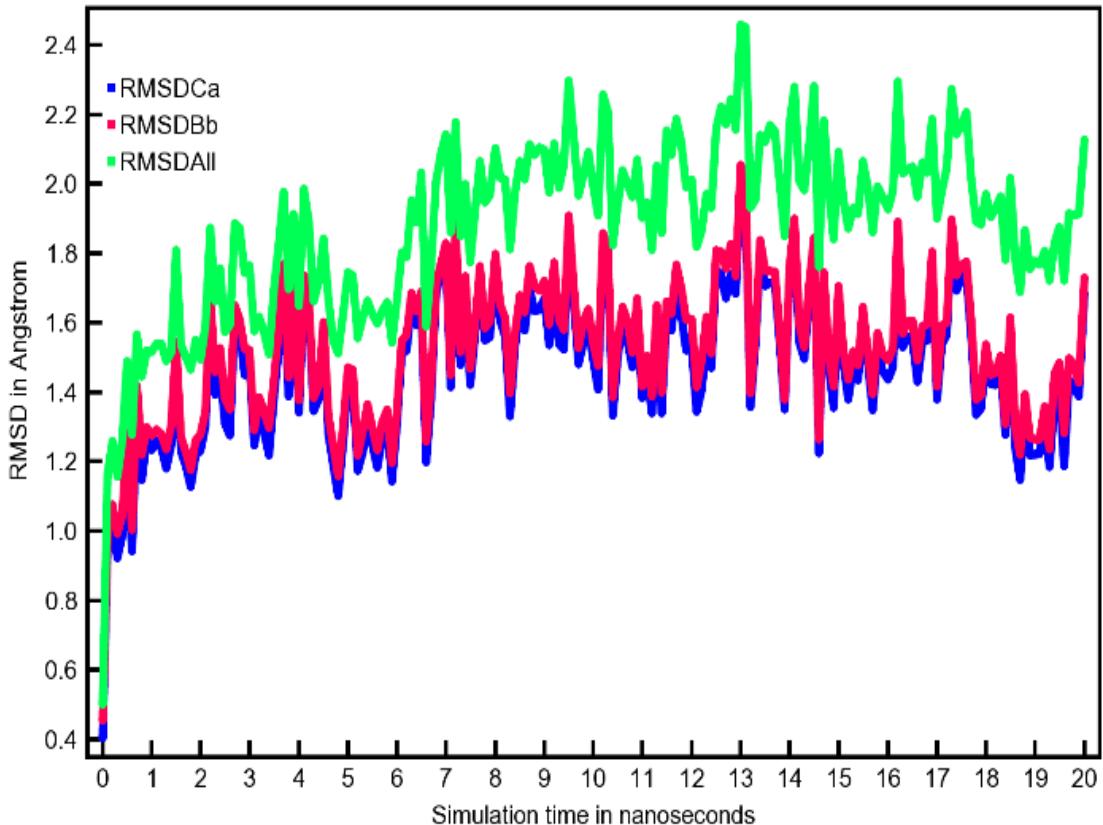
the complex of M^{pro} and remdesivir (a)



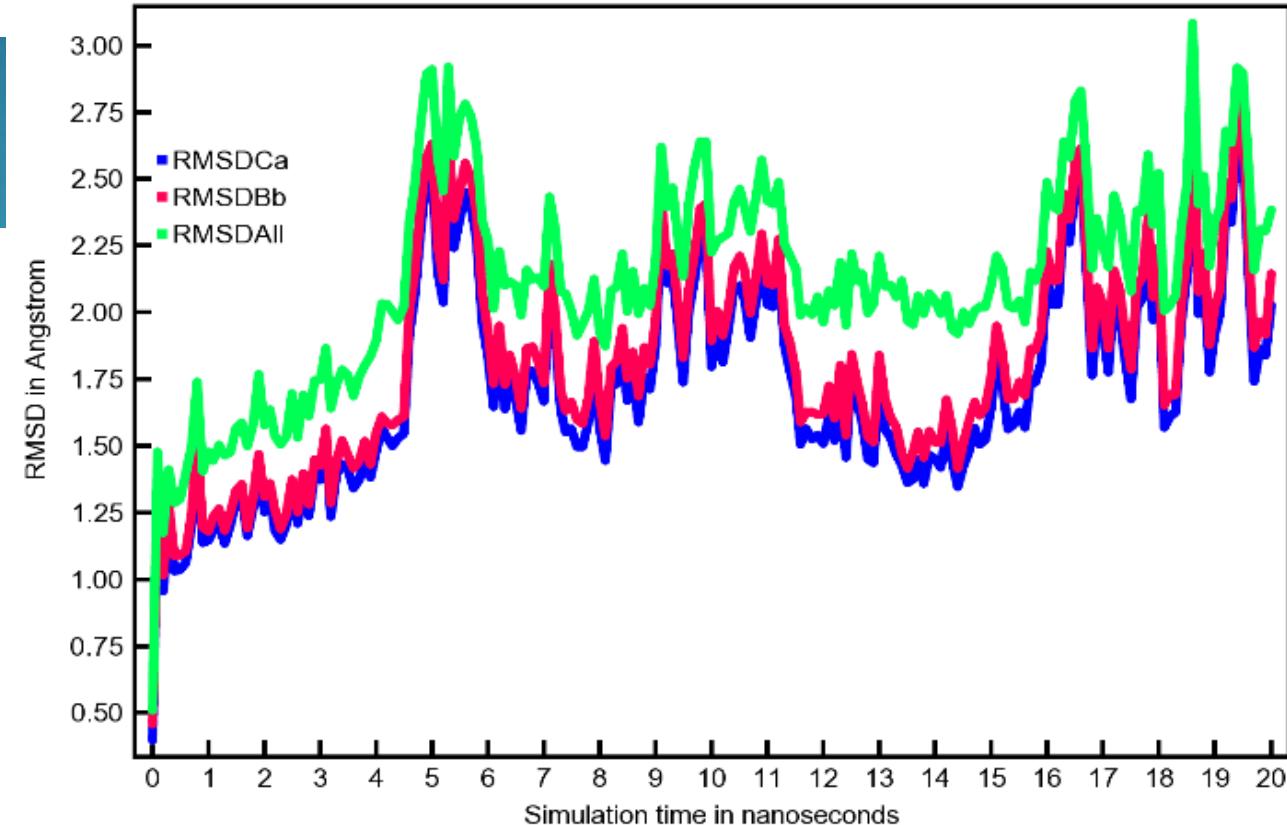
the complex of M^{pro} and myricitrin (b)

The RMSD profiles of the complexes are shown in Fig. 4, where both of the complexes of M^{pro} (Fig. 4 (a) and (b)) have a relatively low RMSD value, which is around 2 Å. This result is indicating that the complexes were stable along with the simulation.

The profile of protein RMSD on the complex of M^{pro} and remdesivir (c), the complex of RBD and myricitrin (d)



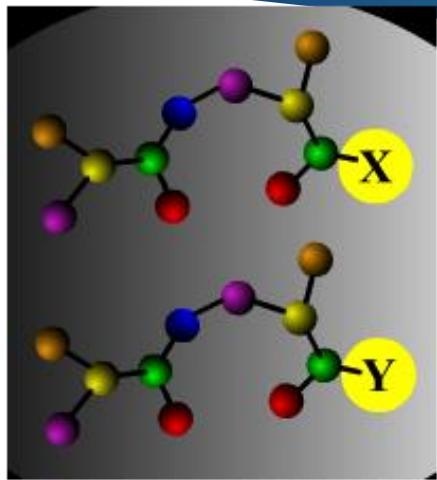
the complex of RBD and chloroquine (c)



the complex of RBD and myricitrin (d)

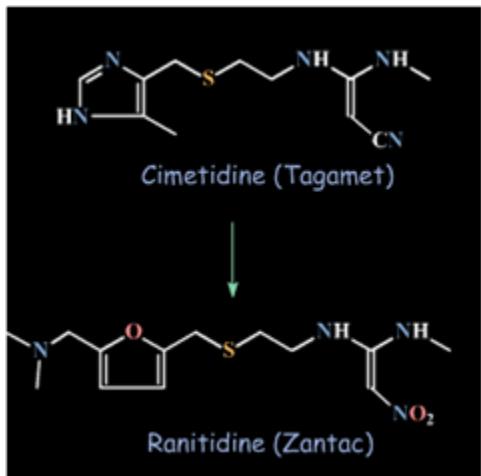
The overall RMSD value on the complex of RBD and myricitrin has a lower value. This fact is indicating that myricitrin formed more stabilizing interactions to the targeted protein comparing to chloroquine.

Molecular docking of some structurally modified compounds



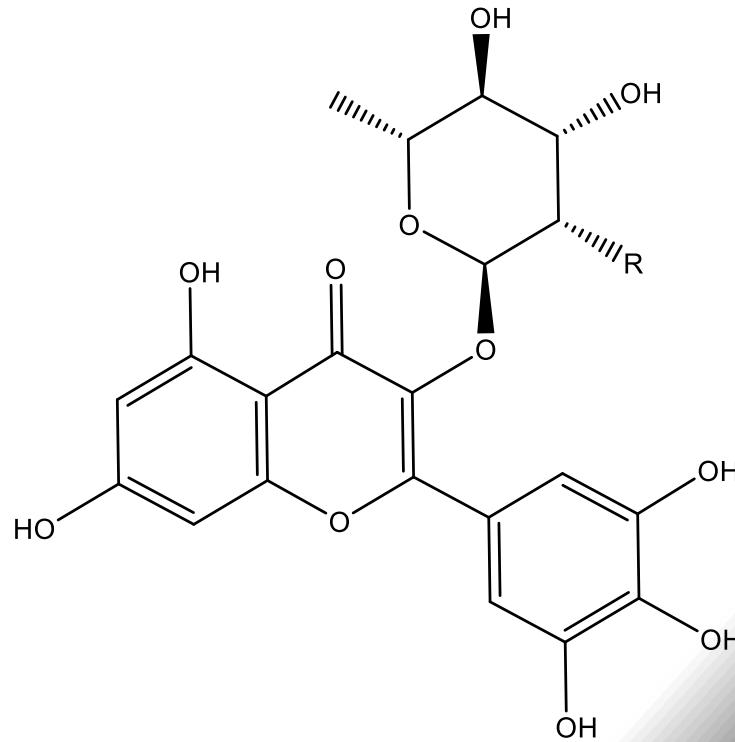
Chemical Modification

- Traditional method.
- An analog of a known, active compound is synthesized with a minor modification, that will lead to improved Biological Activity.
- Advantage and Limitation: End up with something very similar to what you start with.

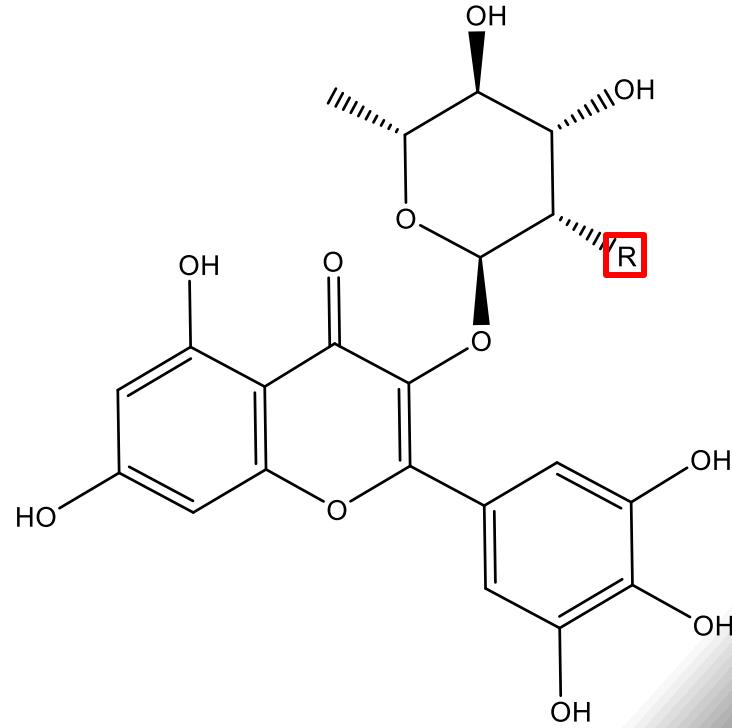


Molecular docking of some structurally modified compounds

Myricetin derivatives



- M^{pro} SARS-CoV-2 as protein reseptor
- Myricetin can be used as an inhibitor of SARS-Coronavirus because it can inhibit the helicase process of the coronavirus protein caused by inhibition of ATPase activity with an IC50 value of 2.71 M (Semwal et al., 2016)
- The hydroxyl group of myricetin gives good affinity results and is important in carrying out its function as an inhibitor (Jo et al., 2020)



No.	R
1.	H
2.	OCH ₃
3.	OC ₂ H ₅
4.	C ₂ H ₅
5.	C ₆ H ₅ OH
6.	COOH

Geometry Optimization
 GAUSSIA
N

DFT B3LYP
 6-31G (d,p)



Molecular docking

Autodock Tools

UCSF Chimera

PDB ID : 6W63

Discovery Studio



Molecular Dynamic Simulation

GROMO

S

GROMAC

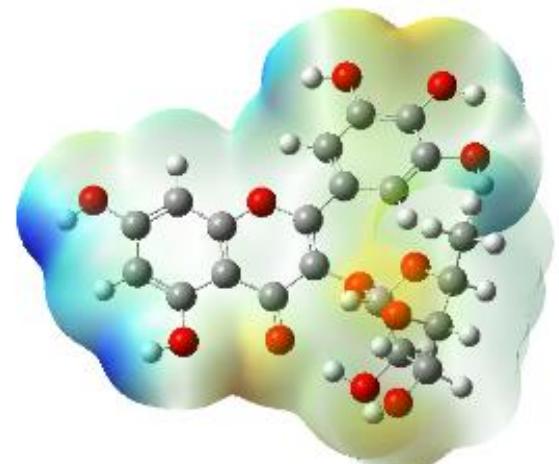
S

VMD

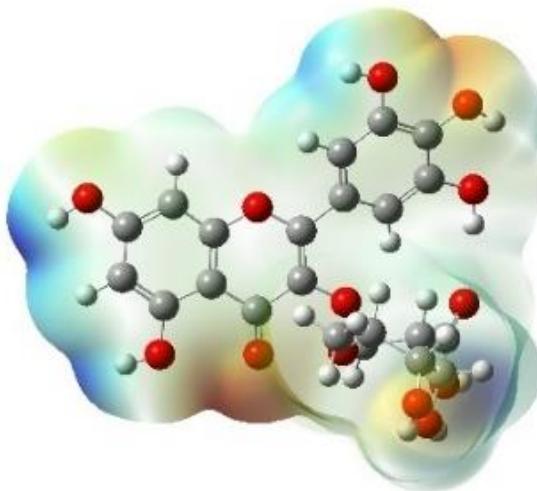
4 ns/2 fs

300 K, 1 atm

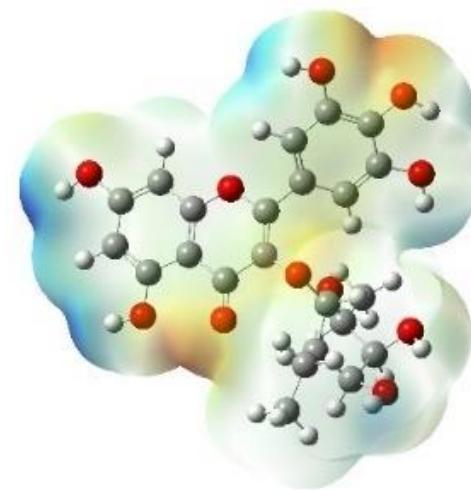
The result of geometry optimization (DFT/B3LYP/6-31G(d,p))



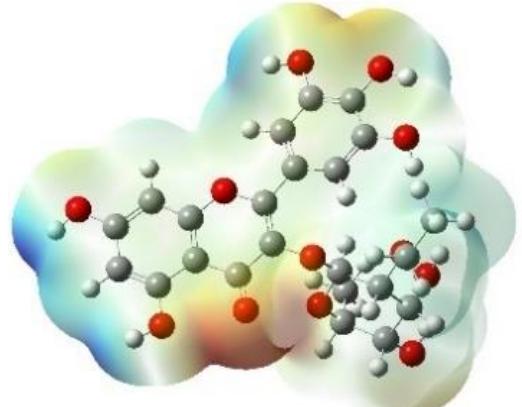
Myricitrin (M)



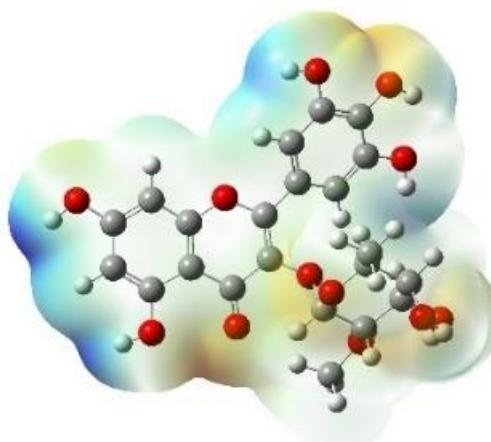
M-COOH



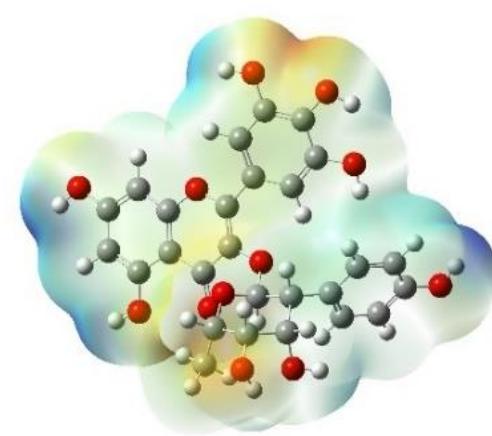
M-Et



M-OMe



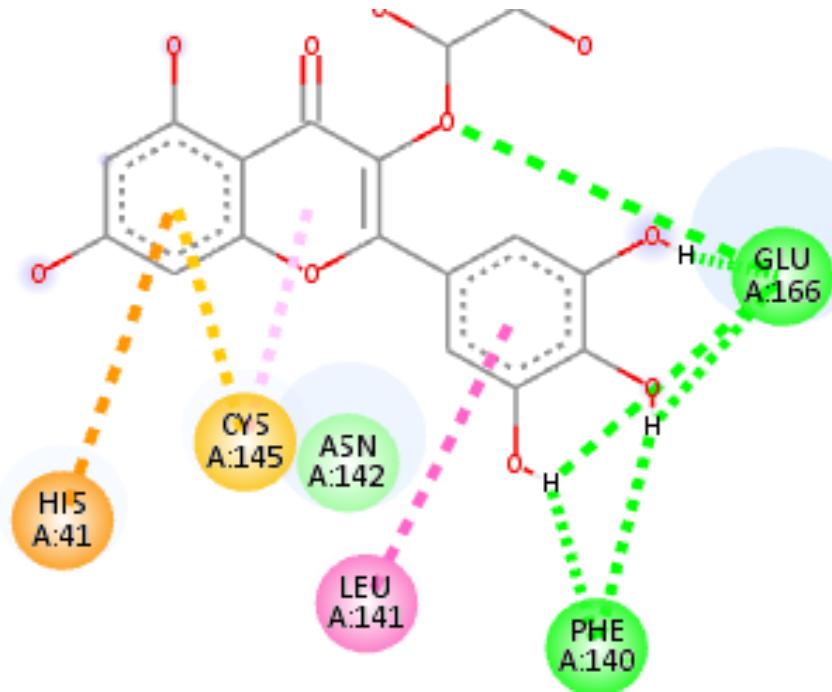
M-OEt



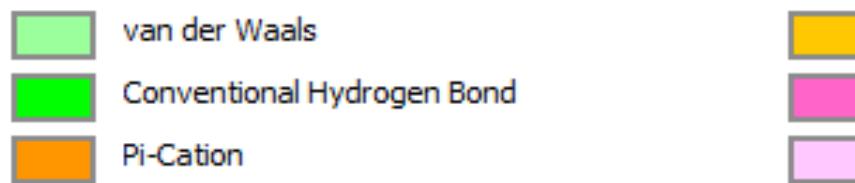
M-PhOH

Ligand	Binding energy (kcal/mol)	RMSD (Å)
-COOH	-3,08	2,37
-Et	-4,68	2,79
-H	-3,77	2,70
-OMe	-3,11	1,79
-OEt	-3,93	2,41
-PhOH	-4,71	2,60

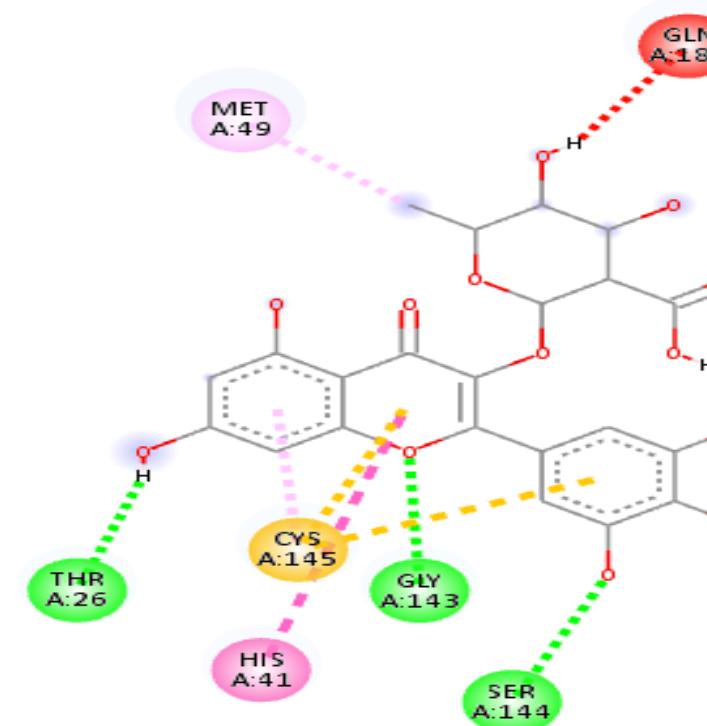
Cys 145 and His 41 as the main amino acids in the process of cell replication (Sepay et al., 2021).



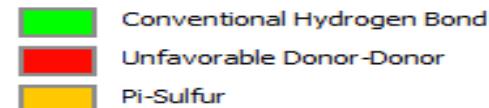
Interactions



Myricitrin (-3,77 cal/mol)



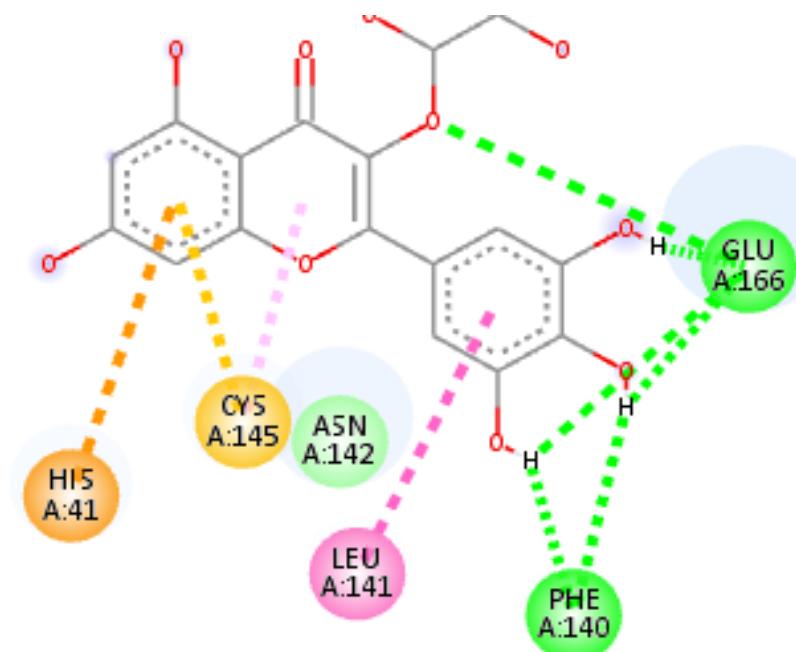
Interactions



Miricitrin-COOH (-3,08 kcal/mol)

Ser 144 and Glu 166 form hydrogen bonds with the -OH group on ring B. Glu 166 also forms hydrogen bonds with the -COOH group.

Cys 145 and His 41 as the main amino acids in the process of cell replication (Sepay et al., 2021).



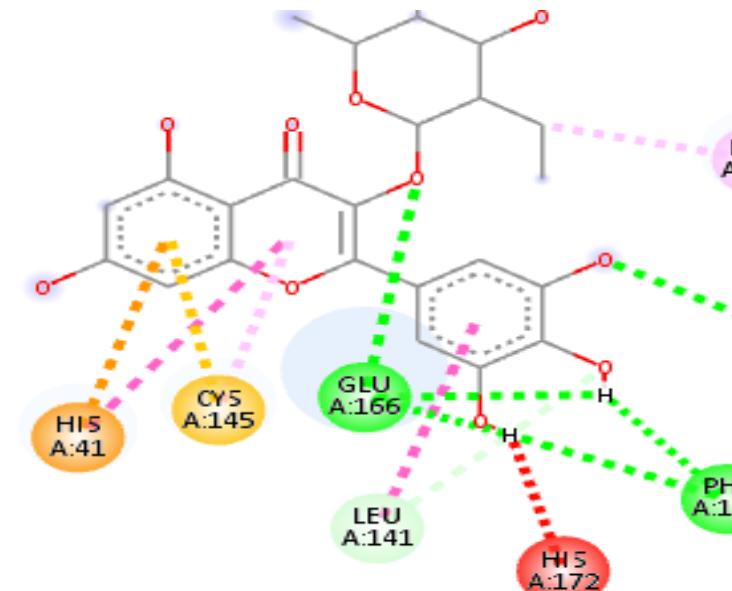
Interactions

- [Yellow Box] van der Waals
- [Green Box] Conventional Hydrogen Bond
- [Orange Box] Pi-Cation

Myricitrin (-3,77 kcal/mol)

Interactions

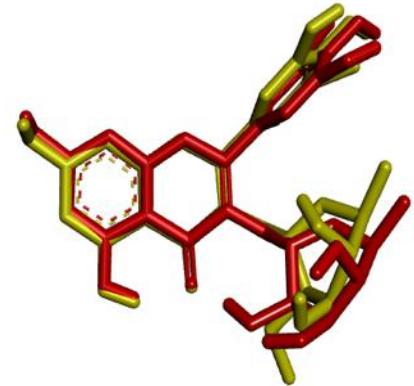
- [Green Box] Conventional Hydrogen Bond
- [Light Green Box] Carbon Hydrogen Bond
- [Red Box] Unfavorable Donor-Donor
- [Orange Box] Pi-Cation
- [Yellow Box] Pi-Sulfur



Myricitrin-Et -4,68 kcal/mol)

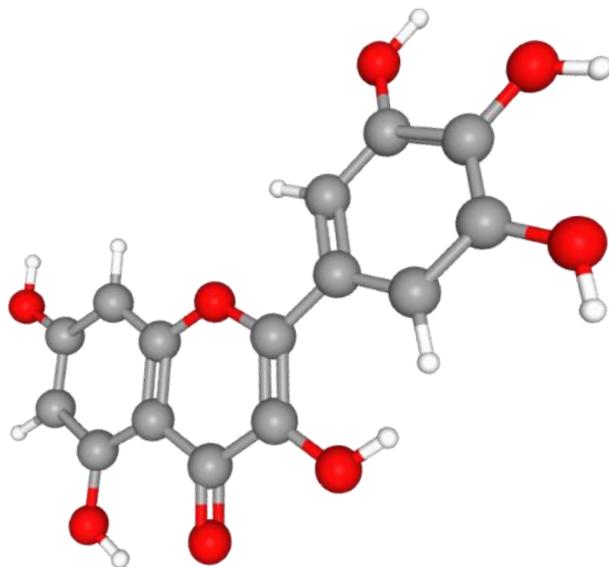
His 41 forms pi-cation interactions with ring A and pi-pi interactions with ring C. Cys 145 interacts with pi-sulfur with ring A and pi-alkyl with ring C. Hydrogen bonding interactions occur between the –OH group on ring B and the amino acids Asn 142, Phe 140, and Glu 166. Glu 166 also provides hydrogen bond interactions with atoms O which is between the C ring and the pyran group.

Type of interaction ligand-receptor

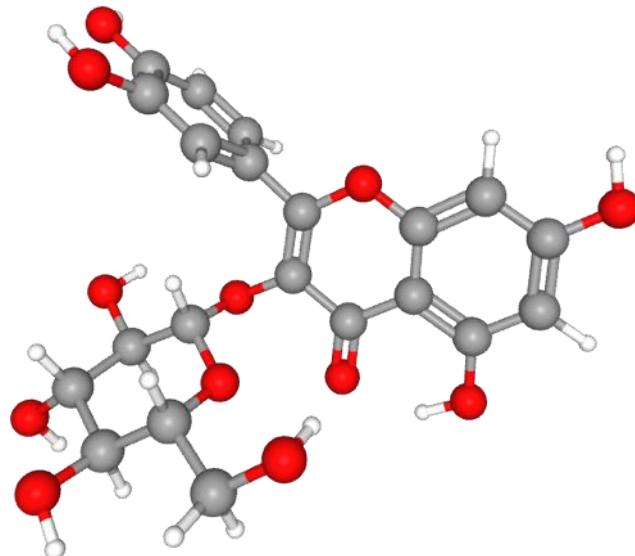


Ligand	Hydrogen bonding	Hydrophobic interaction	another interaction
X77	Glu 166, Gly 143, Thr 26, Leu 141, Asn 142	His 41, Leu 141, Met 165, Leu 127, Cys 145	His 41, Met 49, Cys 145, Gly 143
-H	Glu 166, His 41, Gln 192, Thr 190	Pro 168, Met 165	His 41, Glu 166, Cys 44, Met 49
-Et	Glu 166, Phe 140, Leu 141, Asn 142,	His 41, Leu 141, Met 165, Cys 145	His 41, Cys 145, His 172

Two compounds with different skeletal structures



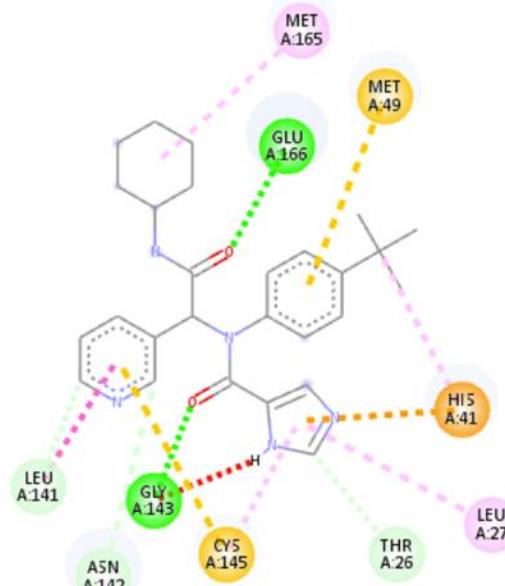
Myricitrin



Hirsutrin

Myricitrin and Hirsutrin are have more than one hydroxyl group which is already known had a powerful affinity to the active site of some proteins. Most of the hydrogen-bond interaction between the ligand to the protein was formed by the -OH group from the ligand and another -OH group or occasionally to the -NH group from the amino acid residues of the protein.

Molecular Docking Result of Native Ligand, Myricitrin and Myricitrin-etyl



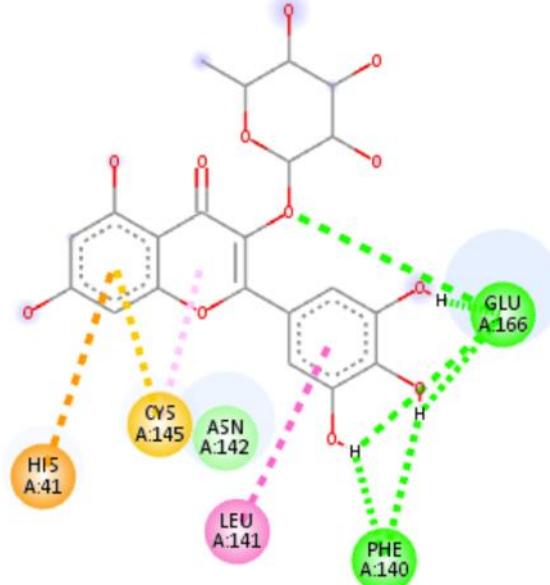
Interactions

- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Unfavorable Donor-Donor
- Pi-Cation
- Pi-Sulfur

Native Ligan (X77)

Binding Energy = -6,08 kkal/mol

RMSSD = 0,98



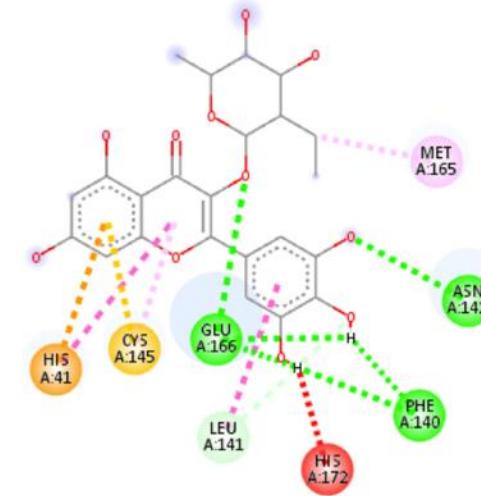
Interactions

- van der Waals
- Conventional Hydrogen Bond
- Pi-Cation

Myricitrin

Binding Energy = -3,05 kkal/mol

RMSSD = 2,08



Interactions

- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Unfavorable Donor-Donor
- Pi-Cation
- Pi-Sulfur
- Pi-Pi Stacked
- Amide-Pi Stacked
- Alkyl
- Pi-Alkyl

Myricitrin modifikasi Etil

Binding Energy = -4,68 kkal/mol

RMSSD = 2,79

Result of Molecular Docking of Native ligand, Myricitrin and Hirsutrin

Specific Interactions:

H-Bonding

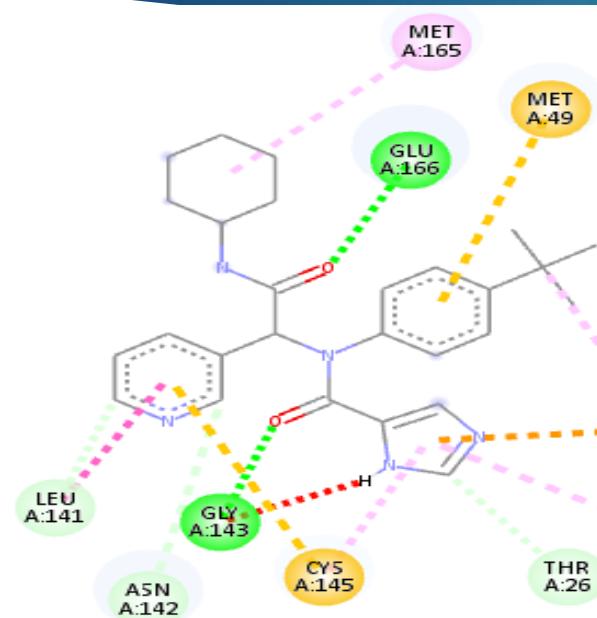
GLU 166, GLY 143

Pi-Sulfur

CYS 145

Alkyl, Pi-Alkyl

CYS 145

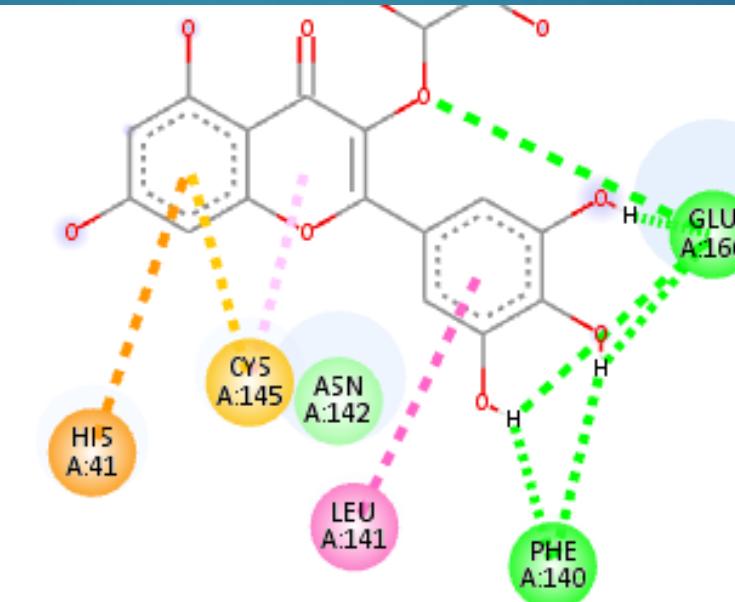


Interactions

- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Unfavorable Donor-Donor
- Pi-Cation
- Pi-Sulfur

Native Ligan (X77)

Binding Energy = -6,08 kcal/mol; RMSSD = 0,98

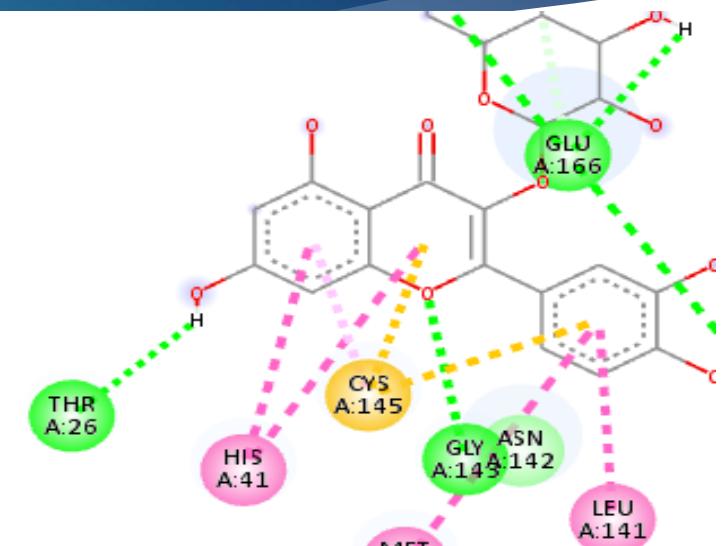


Interactions

- van der Waals
- Conventional Hydrogen Bond
- Pi-Cation

Myricitrin

Binding Energy = -3,05 kcal/mol; RMSSD = 2,08



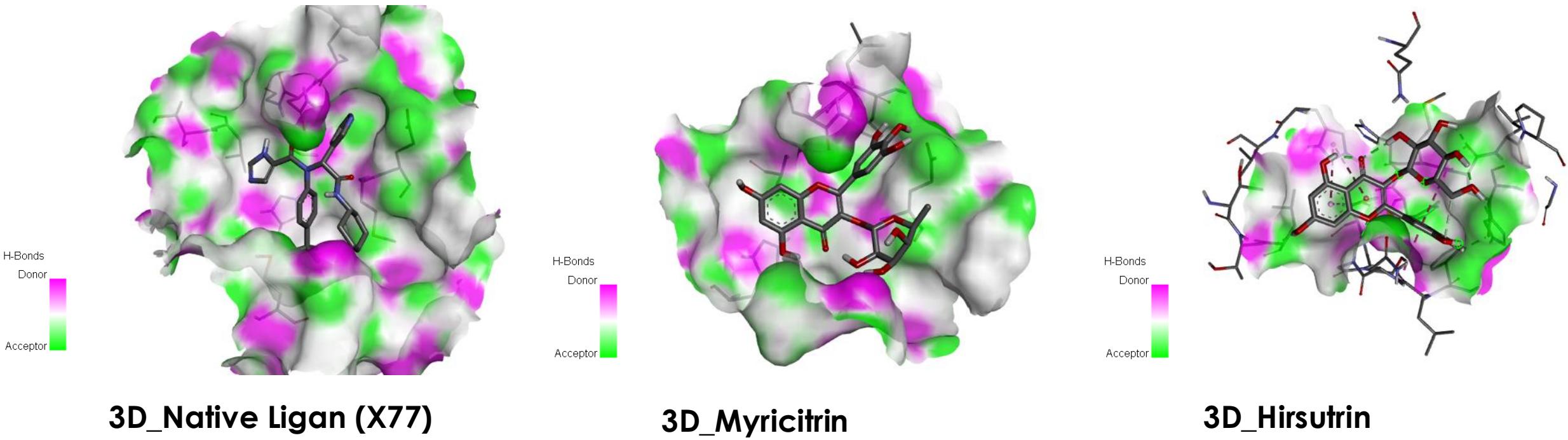
Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Pi-Sulfur

Hirsutrin

Binding Energy = -4,8 kcal/mol; RMSD = 2,8

Result of Molecular Docking of Native ligand, Myricitrin and Hirsutrin





MODELING OF NEW COMPOUNDS QUERSCETINO DERIVATIVES 3'-GLUCOSIDES AS SARS-COV-2 INHIBITORS USING A COMPUTATIONAL CHEMISTRY APPROACH

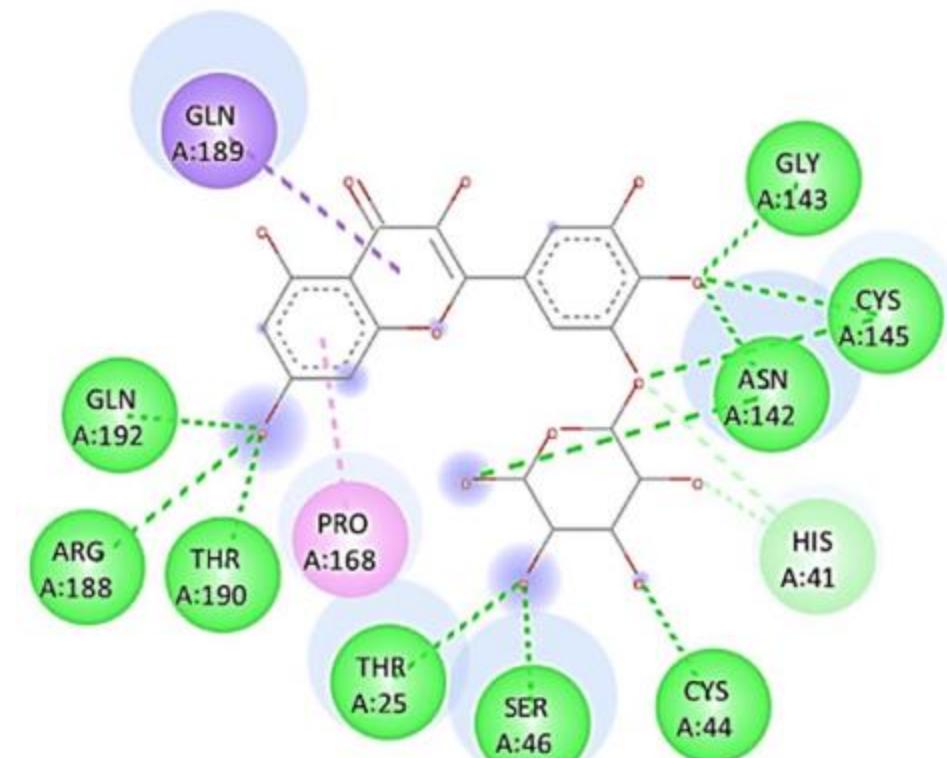
Table 1 Binding affinity of carotenoid and flavonoid compounds of *Pandanus conoideus* Lamk, reference flavonoids, and remdesivir against SARS-CoV-2 main protease (6YNQ)

Compound	Binding affinity
<i>Carotenoids</i>	
5,6-diepicapsokarpoxanthin	-7.5
Capsorubin	-6.8
Capsanthin 5,6-epoxide	-7.8
Capsanthin 3,6-epoxide	-7.1
Capsanthin	-7.1
Cryptocapsin	-7.5
β -cryptoxanthin 5,6-epoxide	-7.7
Cryptoxanthin	-7.0
<i>Flavonoids</i>	
4',6,6',8-tetrahydroxy-3-methoxy-flavon	-7.7
3,4',5-trihydroxy-7,3'-dimethoxy flavon	-7.5
Taxifolin 3-O- α -arabinopyranose	-8.8
Quercetin 3-O-glucose	-9.3
Quercetin 3-methyl-ether	-7.6
Quercetin	-7.8
Taxifolin	-8.4
Quercetin 3'-glucoside	-9.7
Rutin	-8.4
Astragalin	-8.2
Remdesivir	-7.5
Trifolin	-7.8



Buah Merah (*Pandanus conoideus* Lamk) - buah tradisional dari Papua

(Umar, future J Pharm Sci, 2021)

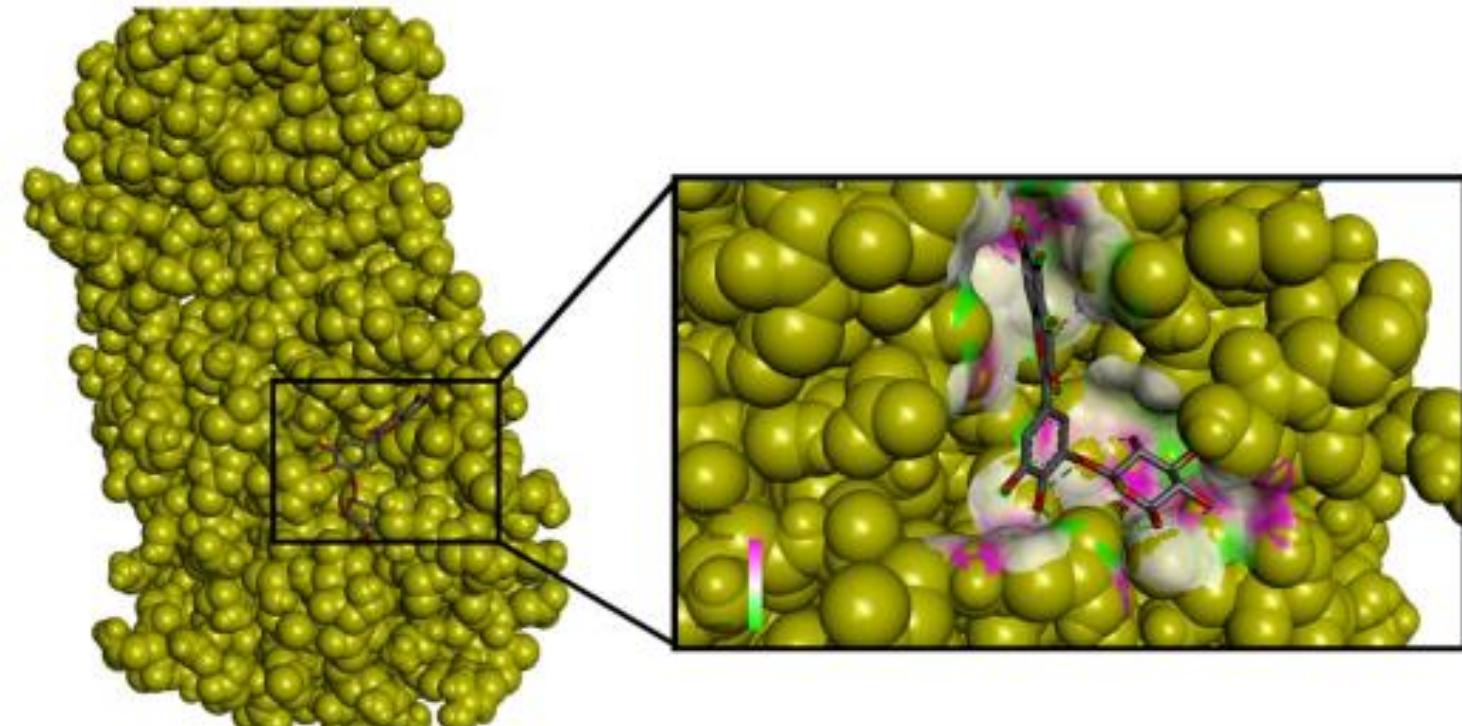


kuersetin 3'-
glukosida

Binding pocket of SARS-CoV-2 main protease (6YNQ) with quercetin 3'-glucoside

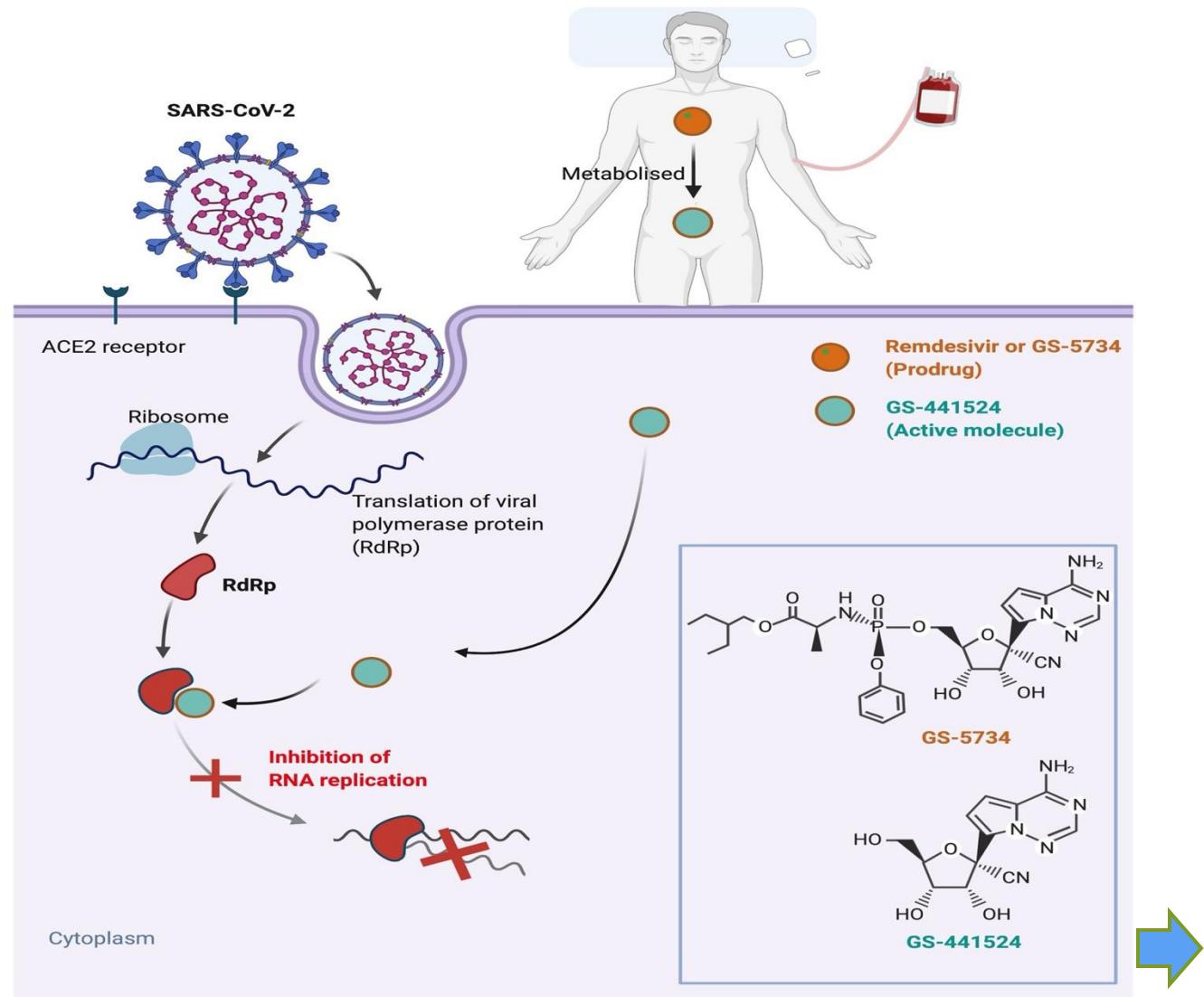
- Conventional Hydrogen Bond
- van der Waals
- Pi-Donor Hydrogen Bond
- Pi-Sigma
- Amide Pi-Stacked
- Pi-Pi T-shaped
- Pi-Alkyl
- Pi-Sulfur

(Umar, future J Pharm Sci, 2021)





- ▶ There are several drugs that have been used as Covid-19 therapy, including:
- ▶ Lopinavir
- ▶ Ribavirin
- ▶ Favipiravir
- ▶ Remdesivir
- ▶ Paxlovid

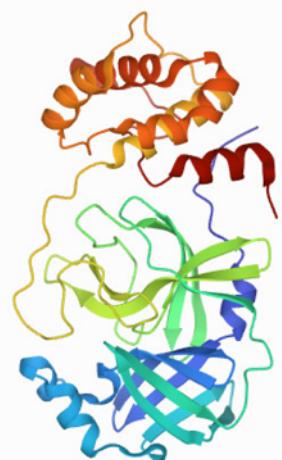


Rancangan Penelitian

a. Tahap Docking Molekul



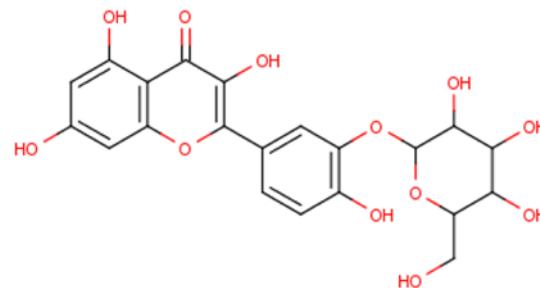
Mpro



RdRp



P1pro



kuersetin 3'-
glukosida

Perangkat
lunak
Yasara-
structure



b. Tahap Visualisasi

Perangkat
lunak
discovery
studio

c. Tahap simulasi dinamika molekul

Perangkat
lunak Yasara-
structure

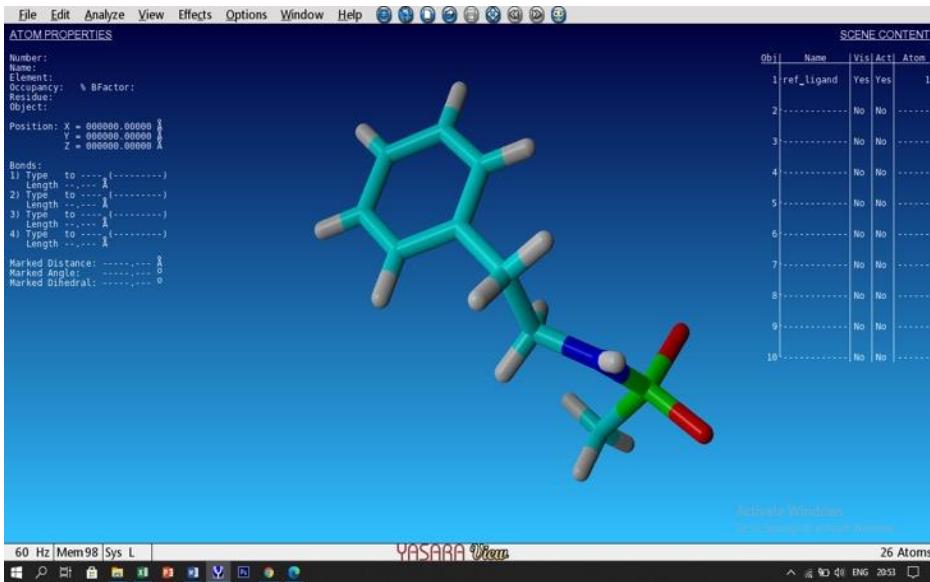
pH 7.4; T=
300K; selama
100 ns

d. Tahap prediksi sifat fisikokimia dan farmakokinetik

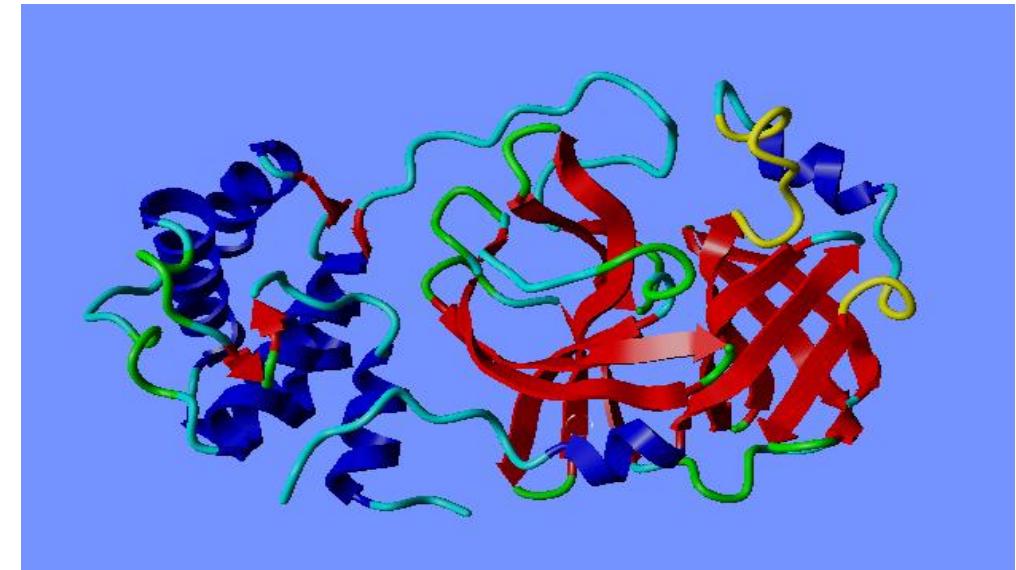
admetSAR, pkCSM

The docking process uses an empirical approach

Downloading of ligands and proteins and preparation of natural proteins and ligands
Mpro



Natural ligands



Protein PDB ID 5r7y

Various types of design compounds

Molecular docking score acquisition using an empirical approach for red fruit flavonoid compounds and the best derivative compounds

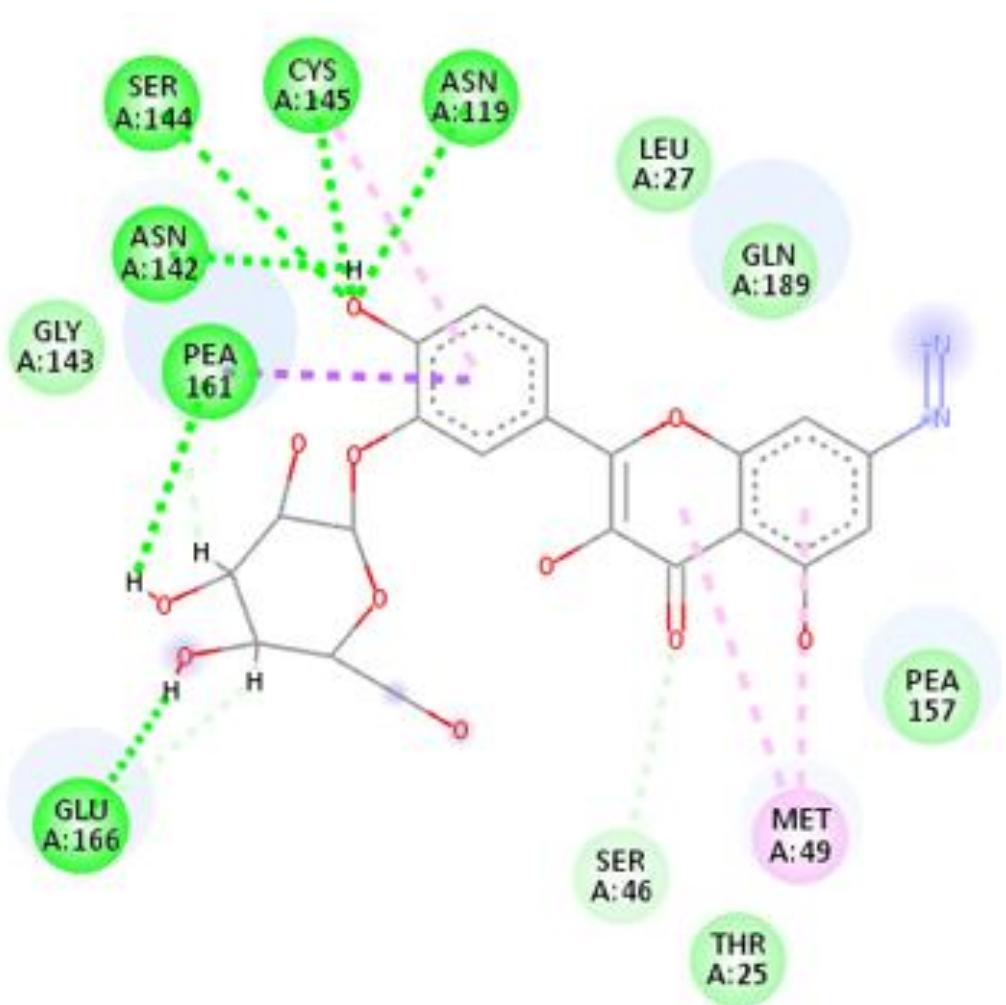
TOTAL_SCORE	4',6,6',8-tetrahydroxy- y-3-methoxy-flavon	3,4',5-trihydroxy- 7,3'-dimethoxy flavon	Taxifolin 3-O-a-arabinopyranose	Quercetin 3-O-glucose	Quercetin 3-methyl-ether	Quercetin	Taxifolin	Quercetin 3'-glucoside	Ligand native	sr133
konfigurasi 1	-65.523	-67.9959	-69.9759	-75.6083	-68.3748	-71.0852	-71.3893	-81.0989	-62.1894	-81.6272
konfigurasi 2	-63.0339	-68.2513	-73.5042	-77.8659	-67.2945	-70.8757	-71.39	-81.4962	-62.2087	-82.8828
konfigurasi 3	-63.757	-68.2197	-67.1485	-70.6126	-65.2553	-69.7717	-69.6986	-81.5977	-62.9091	-81.436
konfigurasi 4	-65.051	-69.0918	-72.4615	-90.5235	-64.777	-69.9294	-71.0389	-80.7138	-63.9732	-81.3204
konfigurasi 5	-63.6836	-66.953	-68.3386	-89.3681	-64.0305	-70.4564	-70.378	-80.6941	-62.3815	-81.3323
konfigurasi 6	-63.1803	-65.8605	-69.9827	-75.8069	-63.2378	-70.235	-71.3054	-81.0448	-62.2847	-82.7739
konfigurasi 7	-56.8431	-66.4742	-68.2007	-70.7654	-59.1718	-70.0603	-71.3796	-81.1935	-62.1535	-81.6123
konfigurasi 8	-57.1826	-65.7825	-71.2813	-75.7639	-57.8084	-69.6667	-71.4047	-80.6998	-62.4127	-83.0982
konfigurasi 9	-58.4303	-66.9462	-68.9111	-77.1664	-58.7558	-69.3805	-71.269	-81.4058	-62.2113	-81.2998
konfigurasi 10	-59.3612	-67.1521	-71.4496	-78.2352	-60.2136	-71.0199	-70.9518	-81.1598	-62.1175	-82.8047
Jumlah	-616.046	-672.7272	-701.2541	-781.7162	-628.9195	-702.4808	-710.2053	-811.1044	-624.8416	-820.1876
rata-rata	-61.6046	-67.27272	-70.12541	-78.17162	-62.89195	-70.24808	-71.02053	-81.11044	-62.48416	-82.01876
SD	3.300628182	1.093545296	2.034140798	6.741155375	3.711276029	0.595203524	0.563452699	0.331081605	0.570986852	0.762573831

The flavonoid compound in quercetin 3'-glucoside has the best average docking score.

The quercetin derivative compound 3'-glucoside with the code sr133 has a better docking score than all red fruit flavonoid compounds.

► Docking results for Mpro target

No	Ligand	Binding Energy (Kcal/mol)	Contacting receptor residues
1	4',6,6',8-tetrahydroxy-3-methoxy-flavon	-7.0620	A THR24 A THR25 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A HIS164 A MET165 A GLU166 A LEU167 A ARG188 A GLN189
2	3,4',5-trihydroxy-7,3'-dimethoxy flavon	-7.0170	A THR24 A THR25 A THR26 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A LEU141 A ASN142 A GLY143 A CYS145 A HIS163 A HIS164 A MET165 A GLU166
3	Taxifolin 3-O-a-arabinopyranose	-7.2700	A THR25 A THR26 A LEU27 A HIS41 A VAL42 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A MET165 A GLU166 A ASP187 A ARG188 A GLN189
4	Quercetin 3-O-glucose	-7.8410	A THR25 A THR26 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A MET165 A GLU166 A ARG188 A GLN189 A THR190
5	Quercetin 3-methyl-ether	-7.2820	A THR25 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS45 A HIS163 A MET165 A GLU166 A ARG188 A GLN189 A GLN192
6	Quercetin	-7.3950	A THR25 A HIS41 A VAL42 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A HIS163 A HIS164 A MET165 A GLU166 A ARG188 A GLN189 A THR190
7	Taxifolin	-7.1040	A THR25 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A HIS163 A HIS164 A MET165 A GLU166 A ARG188 A GLN189 A THR190
8	Quercetin 3'-glucoside	-8.0950	A THR24 A THR25 A THR26 A HIS41 A CYS44 A THR45 A SER46 A MET49 A PHE140 A LEU141 A ASN142 A GLY143 A SER144 A CYS145 A HIS163 A HIS164 A MET165 A GLU166 A HIS172 A ASP187 A GLN189
9	Ligand native	-4.8710	A THR24 A THR25 A THR26 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A GLY143 A CYS145
10	Remdesivir	-7.5200	A THR25 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A CYS145 A HIS163 A HIS164 A MET165 A GLU166 A LEU167 A PRO168 A ASP187 A GLN189 A THR190
11	Paxlovid	-7.3450	A THR24 A THR25 A THR26 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A HIS164 A MET165 A GLU166 A ASP187 A GLN189
12	SR133	-8.3370	A THR24 A THR25 A THR26 A LEU27 A HIS41 A CYS44 A THR45 A SER46 A MET49 A ASN142 A GLY143 A CYS145 A HIS163 A HIS164 A MET165 A GLU166 A LEU167 A PRO168 A ARG188 A GLN189 A THR190 A GLN192



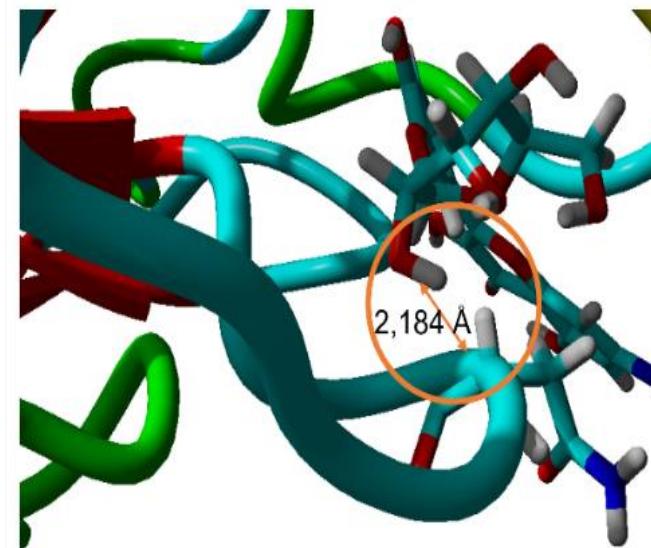
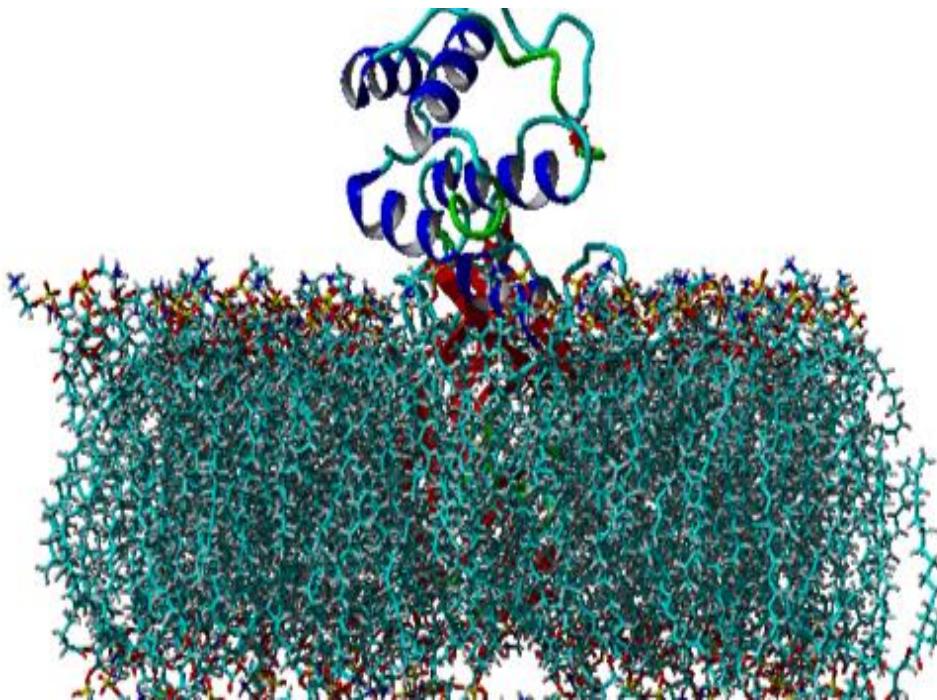
► Visualization of ligand-protein complexes for Mpro targets

Interactions

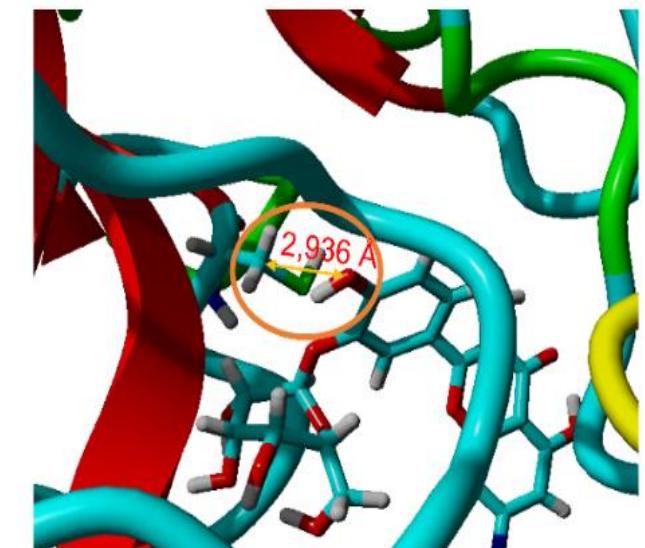
- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond

- Pi-Sigma
- Pi-Alkyl

MD Process for Mpro



(a)



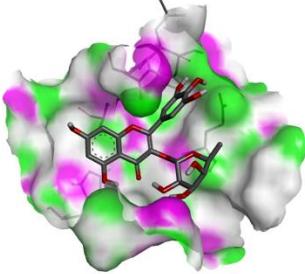
(b)

#Note:

- (a) The interaction between SR133 and Asn142
- (b) The interaction between SR133 and Cys145

Some publications:

- ▶ Oleate Epoxides Derived from Palm Oil as New Anticancer Agents: Synthesis, Cytotoxicity Evaluation, and Molecular Docking Studies Against FASN Protein, *Chinese Journal of Analytical Chemistry*, [Fatmayanti, B.R.](#), [Jumina](#), [Purwono, B.](#), ... [Pranowo, H.D.](#), [Sholikhah, E.N.](#) 2024, 9(17)
- ▶ Investigation on anticancer agent against cervical and colorectal cancer cell lines: One-pot synthesis, in vitro and in silico assays of xanthone derivatives; [Kurniawan, Y.S.](#), [Fatmasari, N.](#), [Pranowo, H.D.](#), [Sholikhah, E.N.](#), [Jumina, J.](#); *Journal of Applied Pharmaceutical Science*, 2024, 14(3), pp. 145–153
- ▶ [In silico Approach for Design, Synthesis and Biological Evaluation of Tioxanthone Derivatives as Potential Anticancer Agents](#) F Hermawan, J Jumina, HD Pranowo, EN Sholikhah, T Ernawati, *ChemistrySelect*, 2024.
- ▶ [Molecular docking and dynamics analysis of halogenated imidazole chalcone as anticancer compounds](#), , 2023 W Haryadi, HD Pranowo, *Pharmacia* 70 (2), 323-329



"Learning by Doing"
"Understanding by Teaching"
"Designing by Molecular Docking"