VI.2. MENDESAIN MOLEKUL ANTI SAR-Cov-2 MENGGUNAKAN 3E9S.PDB

1. Membuat folder dengan sistematika nama molekul_nama PDB, misalnya Boronhafagama2_3E9S atau BHFGM2_3E9S
2. Kopi beberapa file yang ada di folder validasi 3E9S dan pastekan di folder BHFGM2_3E9S seperti

   cmd.exe

   plants.exe

   mingwm.19.dll

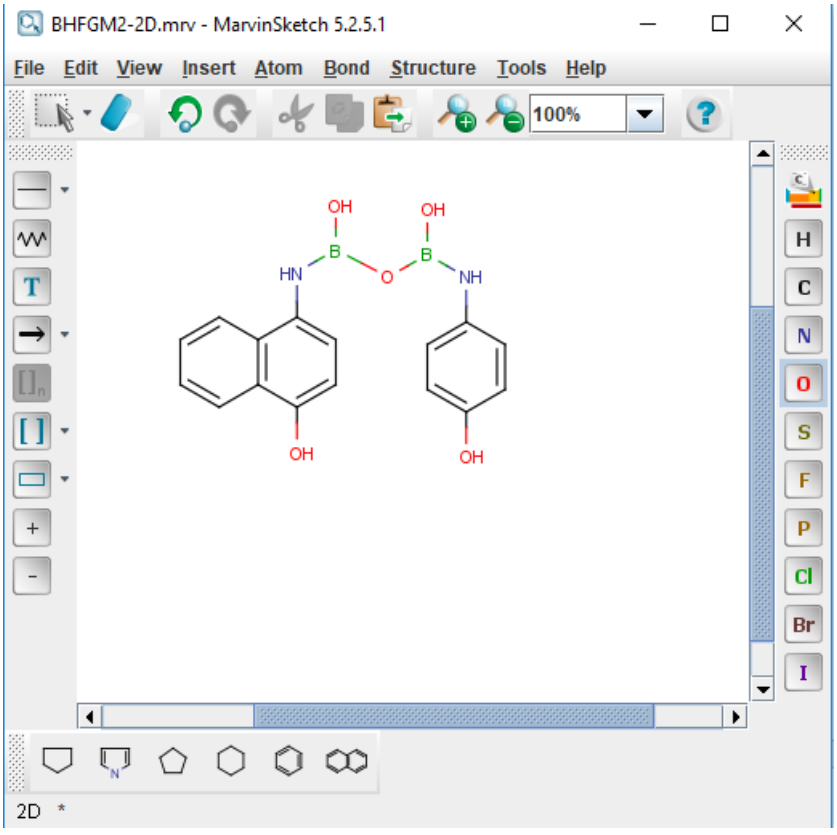
   pc_3e9s.txt

   protein.mol2

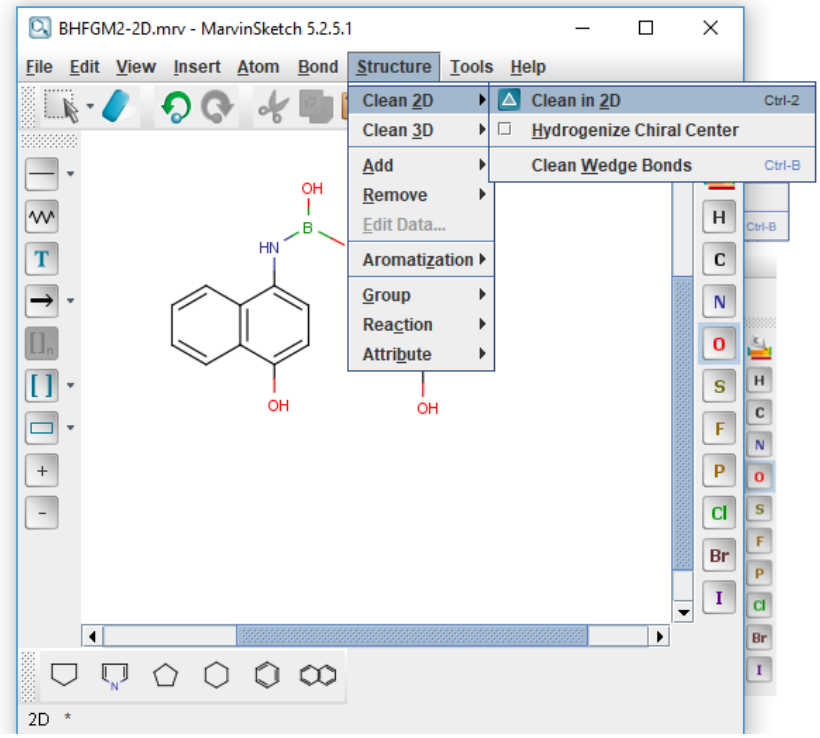
   ref_ligand.mol2

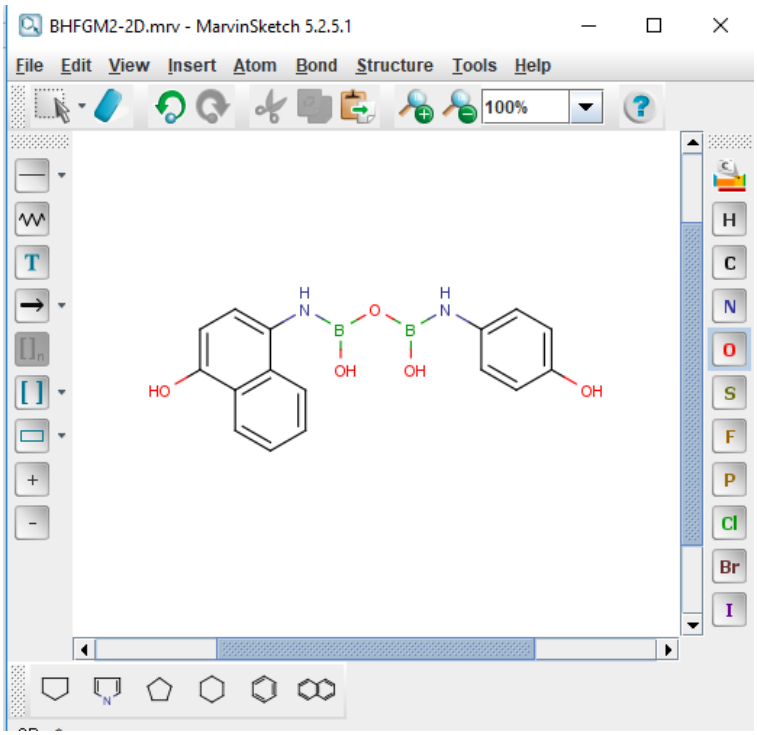
   Disini belum ada ligand.mol2 senyawa desain karena baru akan dibuat seperti pada poin 3 berikut

3. Menggambar molekul desain boronhafagama2

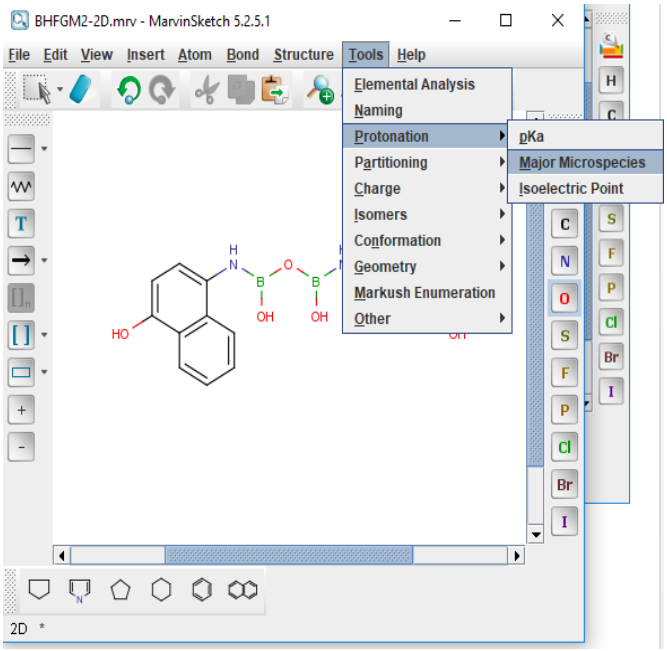


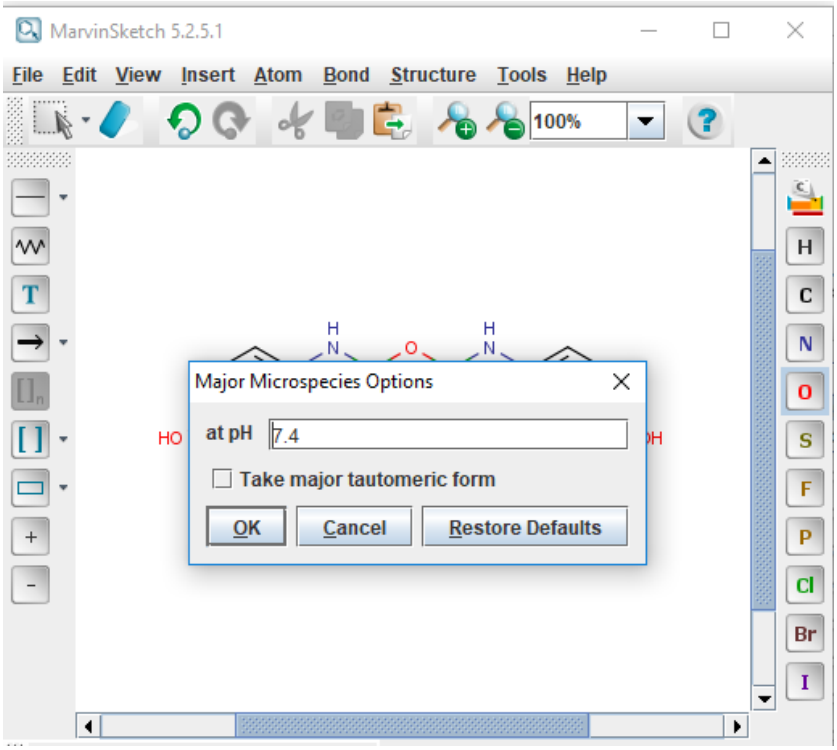
Untuk merapikan klik sktructure > clean in 2D



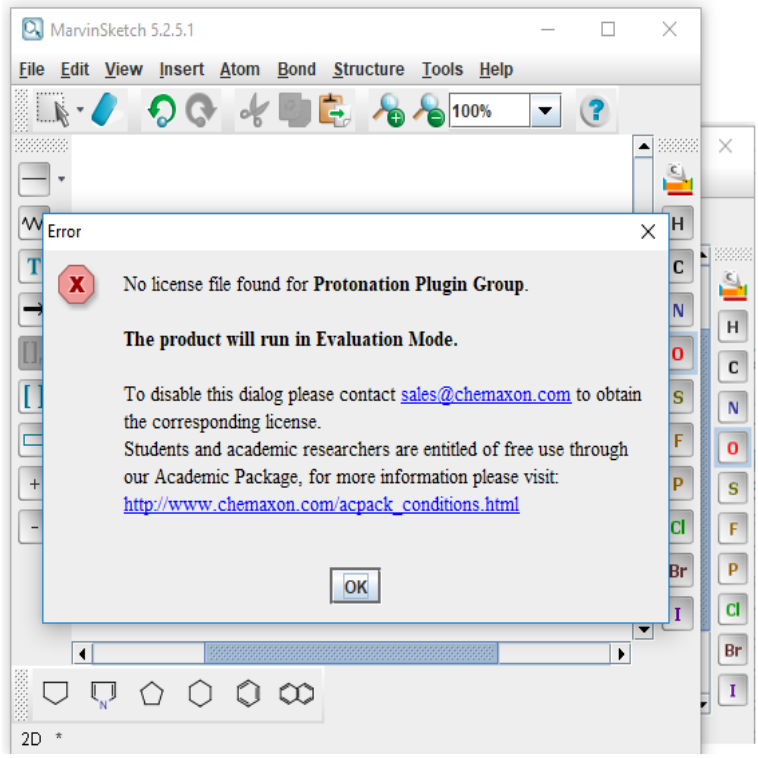


Membuat ligand2D.mrv (molekul dalam suasana pH tubuh 7.4) dari senyawa desain

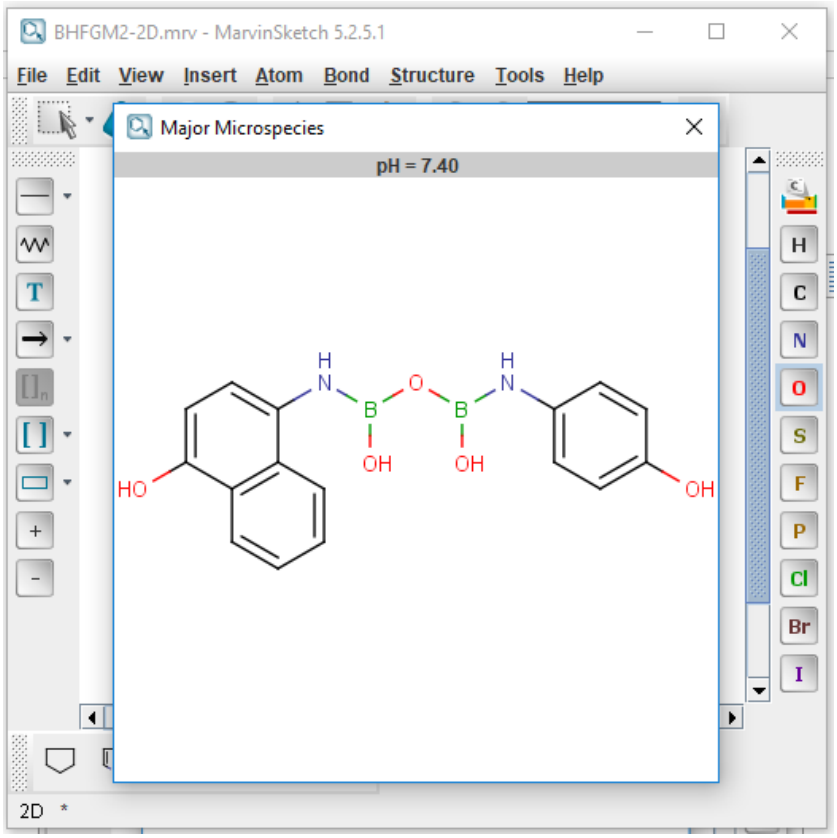




Ok akan muncul layar

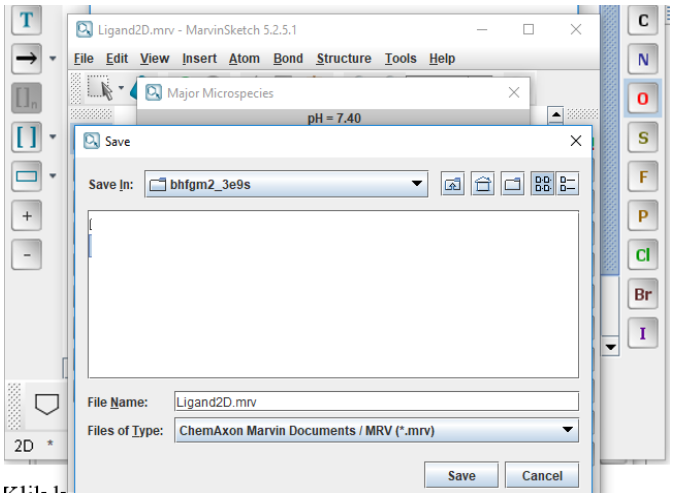


Setelah OK



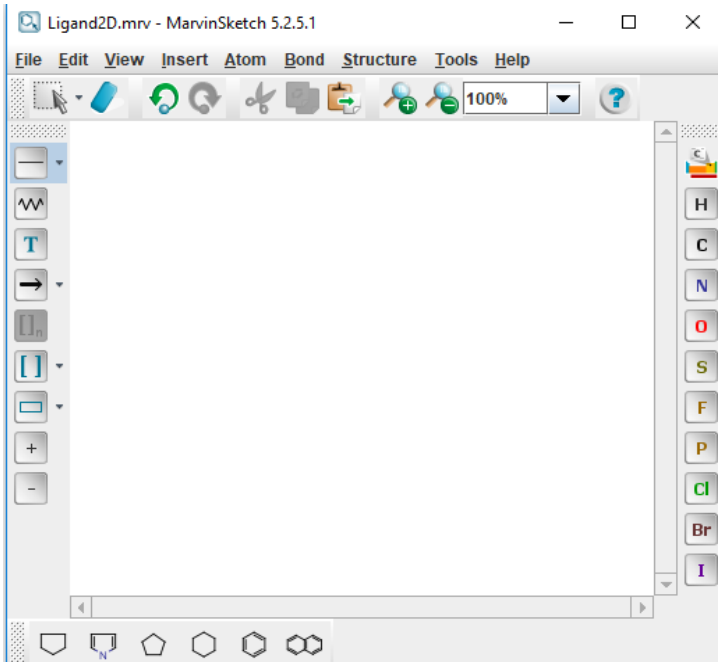
Klik kanan pada jendela baru > Save as ,

namai BHFGM2-2D.mrv

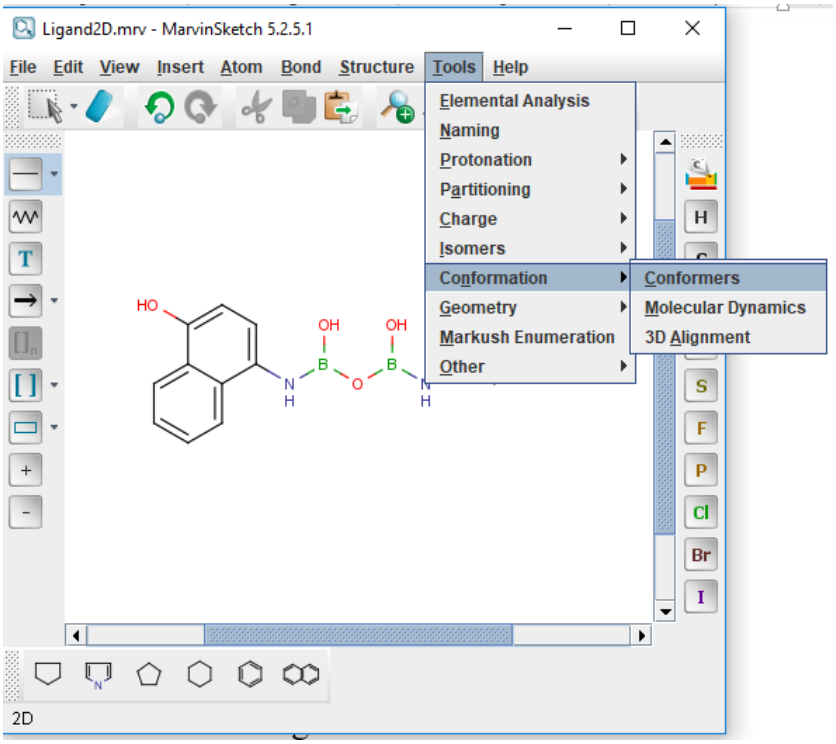


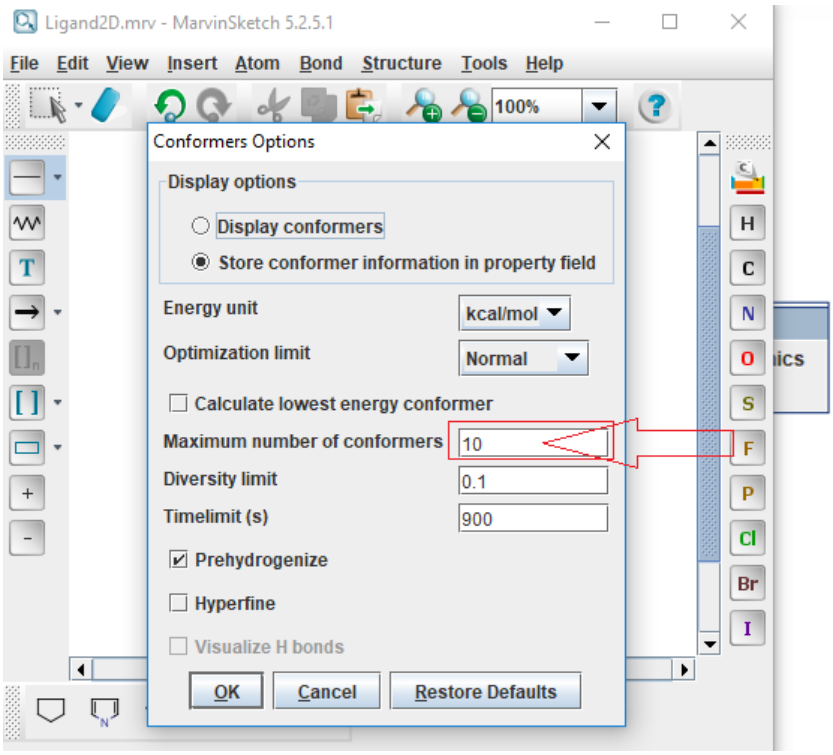
Klik Save

Bersihkan layar dengan File> New > clear Desk



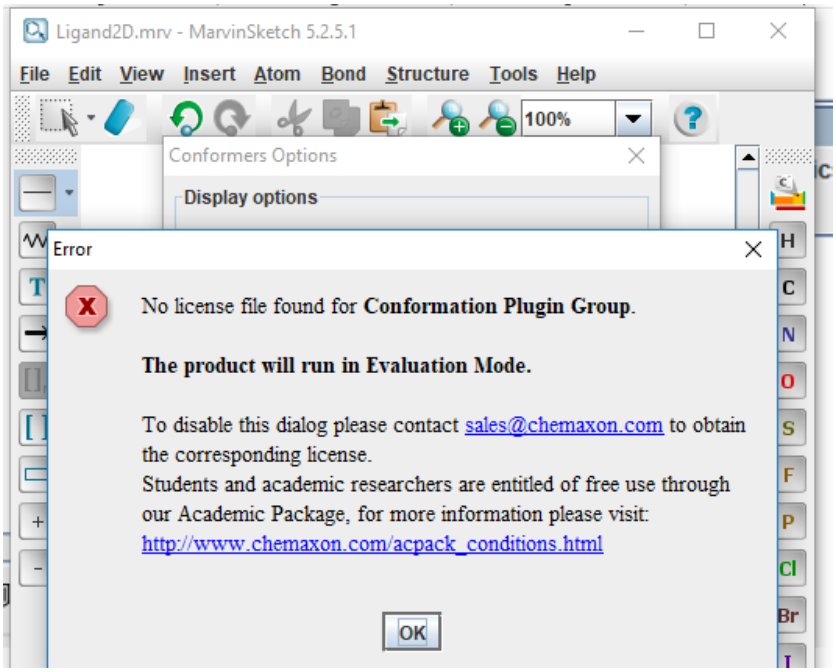
Load ligand2D.mrv



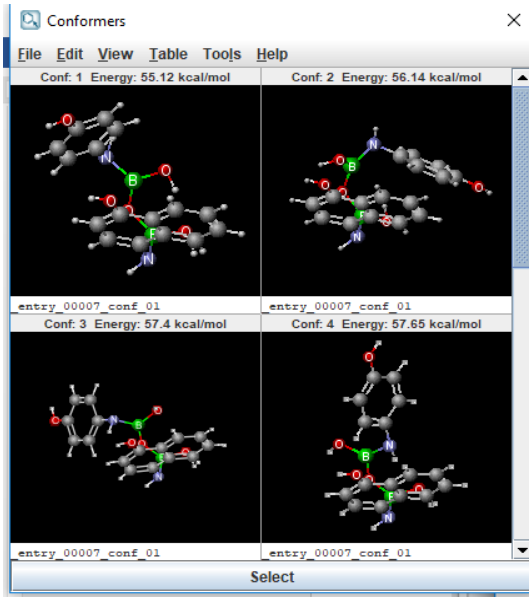


Disini Maximum number of conformers kita pilih 10 karena saat validasi juga menggunakan 10 conformer

Klik OK

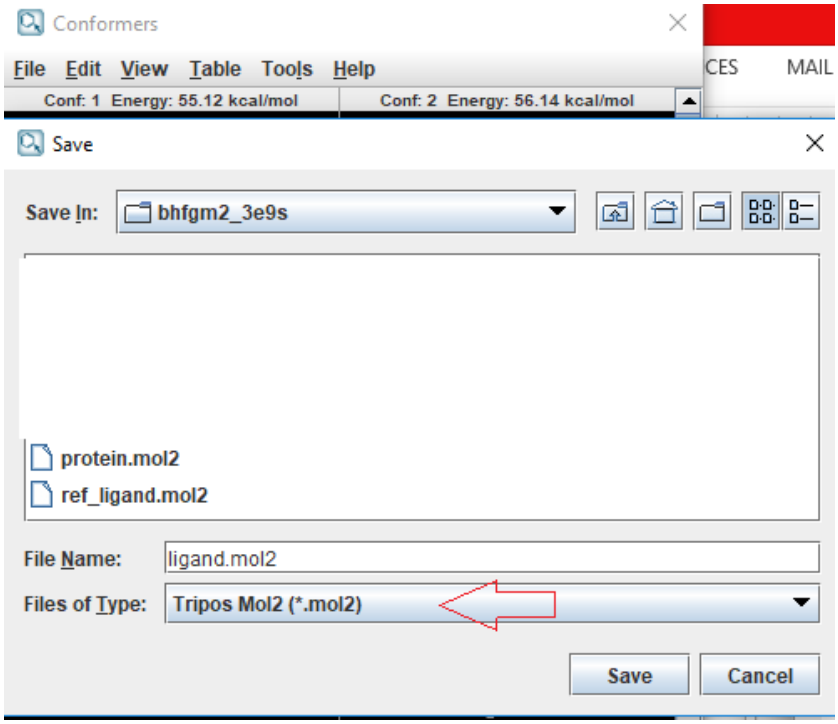


Klik OK jika minta lisensi



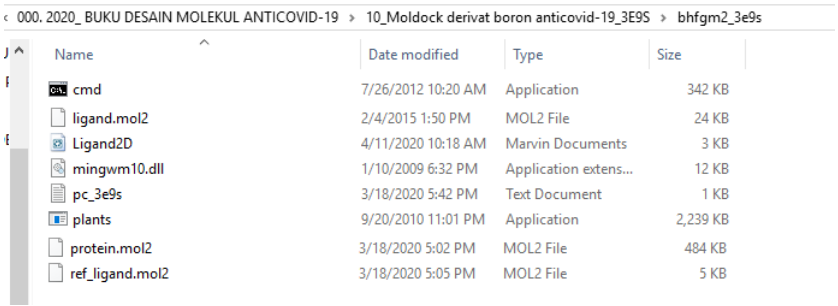
Disitu ada 10 conformer dan simpan sebagai ligand.mol2 , dengan cara File > Save as namai ligand.mol2

(ingat type file Tripos. Mol2)



Klik Save

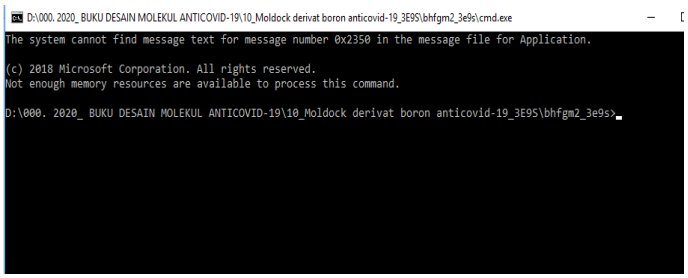
Sebelum running docking kita cek Folder tempat kita akan melakukan molecular docking



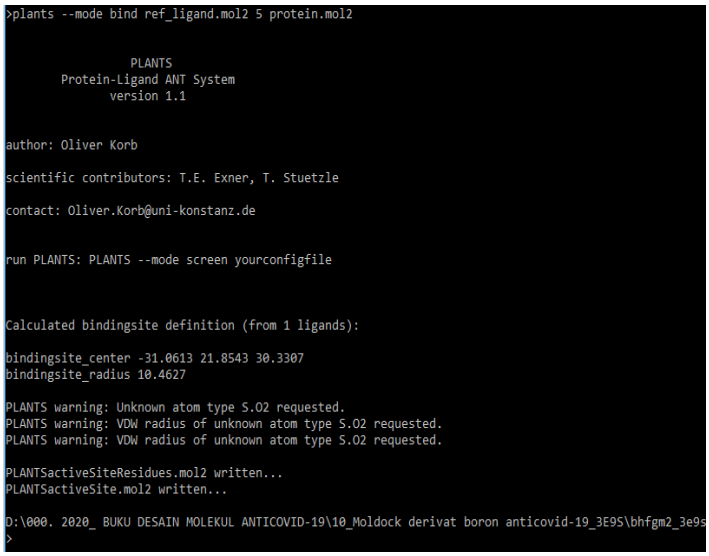
Jika ada file yang belum ada , dapat dikopi dari folder Validasi 3E9S dan di pastekan di folder boronhafagama2_3E9S.

Running docking molekul boronhafagama2 terhadap 3E9S.PDB

1. Buka cmd dengan double klik



Ketik plants –mode bind ref_ligand.mol2 5 protein.mol2 ENTER



Abaikan Warning selama molekul kita tidak mengandung gugus SO2

2. Lanjutkan dengan ketik

   plants –mode screen pc_3e9s.txt ENTER

D:\ \bhfgm2_3e9s>plants --mode screen pc_3e9s.txt

PLANTS

Protein-Ligand ANT System

version 1.1

author: Oliver Korb

scientific contributors: T.E. Exner, T. Stuetzle

contact: Oliver.Korb@uni-konstanz.de

run PLANTS: PLANTS --mode screen yourconfigfile

PLANTS warning: Unknown atom type S.O2 requested.

PLANTS warning: VDW radius of unknown atom type S.O2 requested.

PLANTS warning: VDW radius of unknown atom type S.O2 requested.

PLANTS info: CHO hydrogen found 315 HD2 HIS

PLANTS info: CHO hydrogen found 317 HE1 HIS

PLANTS info: CHO hydrogen found 774 HD2 HIS

PLANTS info: CHO hydrogen found 776 HE1 HIS

PLANTS info: CHO hydrogen found 821 HD2 HIS

PLANTS info: CHO hydrogen found 823 HE1 HIS

PLANTS info: CHO hydrogen found 1190 HD2 HIS

PLANTS info: CHO hydrogen found 1192 HE1 HIS

PLANTS info: CHO hydrogen found 1440 HD2 HIS

PLANTS info: CHO hydrogen found 1442 HE1 HIS

PLANTS info: CHO hydrogen found 2724 HD2 HIS

PLANTS info: CHO hydrogen found 2726 HE1 HIS

PLANTS info: CHO hydrogen found 2796 HD2 HIS

PLANTS info: CHO hydrogen found 2798 HE1 HIS

PLANTS info: CHO hydrogen found 3052 HD2 HIS

PLANTS info: CHO hydrogen found 3054 HE1 HIS

PLANTS info: CHO hydrogen found 4251 HD2 HIS

PLANTS info: CHO hydrogen found 4253 HE1 HIS

PLANTS info: CHO hydrogen found 4303 HD2 HIS

PLANTS info: CHO hydrogen found 4305 HE1 HIS

PLANTS info: CHO hydrogen found 4526 HD2 HIS

PLANTS info: CHO hydrogen found 4528 HE1 HIS

virtual screening progress: 1 of 1

current ligand: ligand.mol2 (entry 1)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -112.74

current ligand: ligand.mol2 (entry 2)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -114.72

current ligand: ligand.mol2 (entry 3)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -111.42

current ligand: ligand.mol2 (entry 4)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -114.22

current ligand: ligand.mol2 (entry 5)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -117.26

current ligand: ligand.mol2 (entry 6)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -113.11

current ligand: ligand.mol2 (entry 7)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -118.87

current ligand: ligand.mol2 (entry 8)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -111.09

current ligand: ligand.mol2 (entry 9)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -113.52

current ligand: ligand.mol2 (entry 10)

LIGAND DOFs: 16

PROTEIN DOFs: 4

Could not match: 18 19 17 13 -> B O.3 B N.3 bond type: 1

Could not match: 18 19 17 21 -> B O.3 B O.3 bond type: 1

Could not match: 17 19 18 14 -> B O.3 B N.3 bond type: 1

Could not match: 17 19 18 20 -> B O.3 B O.3 bond type: 1

Could not match: 19 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 21 17 13 1 -> O.3 B N.3 C.2 bond type: 1

Could not match: 21 17 13 32 -> O.3 B N.3 H bond type: 1

Could not match: 19 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 19 18 14 33 -> O.3 B N.3 H bond type: 1

Could not match: 20 18 14 7 -> O.3 B N.3 C.2 bond type: 1

Could not match: 20 18 14 33 -> O.3 B N.3 H bond type: 1

Simplex dimension: 20

Simplex dimension: 20

iterations : 453

starting optimization ...

problem dimension: 20

ATOMS / s: inf

EVAL / s: inf

optimization finished after 0.00s

best score: -116.59

total virtual screening time: 0.00s

Ligands skipped due to errors: 0

Ketik cd results ENTER

D:\ bhfgm2_3e9s>cd results

Ketik more bestranking.csv ENTER

D:\ \bhfgm2_3e9s\results>more bestranking.csv

TOTAL_SCORE,SCORE_RB_PEN,SCORE_NORM_HEVATOMS,SCORE_NORM_CRT_HEVATOMS,SCORE_NORM_WEIGHT,SCORE_NORM_CRT_WEIGHT,SCORE_RB_PEN_NORM_CRT_HEVATOMS,SCORE_NORM_CONTACT,EVAL,TIME

_entry_00001_conf_01,-112.735,-92.7352,-4.50941,-38.5549,-0.333607,-16.1852,-31.715,-4.02626,5450450,0

_entry_00002_conf_01,-114.72,-94.7199,-4.5888,-39.2337,-0.33948,-16.4701,-32.3938,-4.24889,5423839,0

_entry_00003_conf_01,-111.423,-91.423,-4.45692,-38.1061,-0.329724,-15.9968,-31.2662,-4.12678,5615312,0

_entry_00004_conf_01,-114.215,-94.2155,-4.56862,-39.0611,-0.337988,-16.3977,-32.2212,-4.07912,5497885,0

_entry_00005_conf_01,-117.264,-97.2636,-4.69055,-40.1036,-0.347008,-16.8353,-33.2637,-4.18799,5384567,0

_entry_00006_conf_01,-113.108,-93.1083,-4.52433,-38.6825,-0.334711,-16.2388,-31.8426,-4.1892,5354646,0

_entry_00007_conf_01,-118.867,-98.8673,-4.75469,-40.652,-0.351753,-17.0656,-33.8121,-4.24526,5495179,0

_entry_00008_conf_01,-111.089,-91.0894,-4.44358,-37.992,-0.328737,-15.9489,-31.1521,-3.96748,5598316,0

_entry_00009_conf_01,-113.516,-93.5162,-4.54065,-38.822,-0.335918,-16.2973,-31.9821,-4.05415,5501143,0

_entry_00010_conf_01,-116.586,-96.5856,-4.66343,-39.8717,-0.345001,-16.738,-33.0318,-4.16377,5562575,0

D:\ bhfgm2_3e9s\results>

Tandai dengan latar kuning conformer terstabil dan cari di folder results conformer tersebut untuk di kopi dan pastekan di folder bhfgm2_3E9S.PDB

Folder results berisi file bestranking yang dapat dibuka dengan excel

	TOTAL_SCORE	SCORE_RB_PEN	E_NORM_HEVA
2	_entry_00001_conf_01	-112.735	-92.7352
3	_entry_00002_conf_01	-114.72	-94.7199
4	_entry_00003_conf_01	-111.423	-91.423
5	_entry_00004_conf_01	-114.215	-94.2155
6	_entry_00005_conf_01	-117.264	-97.2636
7	_entry_00006_conf_01	-113.108	-93.1083
8	_entry_00007_conf_01	-118.867	-98.8673
9	_entry_00008_conf_01	-111.089	-91.0894
10	_entry_00009_conf_01	-113.516	-93.5162
11	_entry_00010_conf_01	-116.586	-96.5856

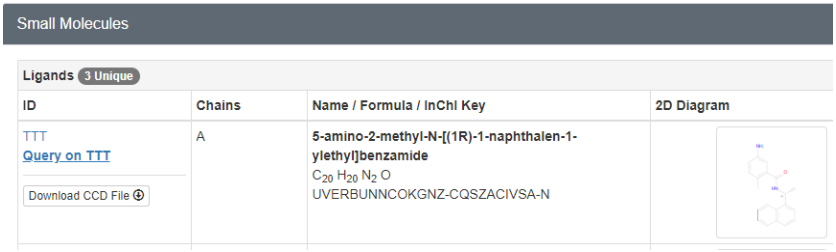
Kolom berlatar kuning merupakan hasil skor docking .

Jika dibandingkan dengan ref_ligand skor docking boronhafagama 2 sebagai berikut:

Konformasi dalam 3E9S.PDB	ref_ligand	Boronhafagama2
_entry_00001_conf_01	-111.466	-112.735
_entry_00002_conf_01	-110.561	-114.72
_entry_00003_conf_01	-111.048	-111.423
_entry_00004_conf_01	-110.509	-114.215
_entry_00005_conf_01	-109.992	-117.264
_entry_00006_conf_01	-110.134	-113.108
_entry_00007_conf_01	-111.064	-118.867
_entry_00008_conf_01	-111.069	-111.089
_entry_00009_conf_01	-110.761	-113.516
_entry_00010_conf_01	-109.735	-116.586
Rerata	-110.634	-114.352

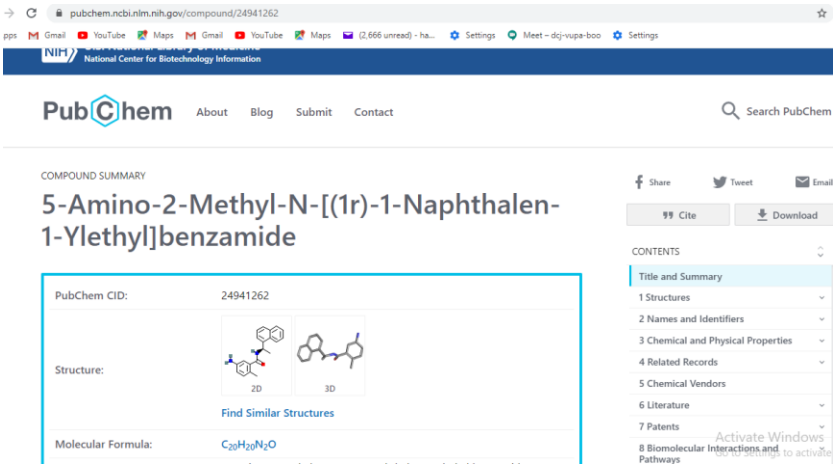
Dari skor terstabil dan skor rerata dapat disimpulkan bahwa boronhafagama2 lebih stabil berinteraksi dengan reseptor dalam kode 3E9S sehingga diprediksi boronhafagama3 lebih poten dibanding ref_ligand.

Mengenal ref_ligand

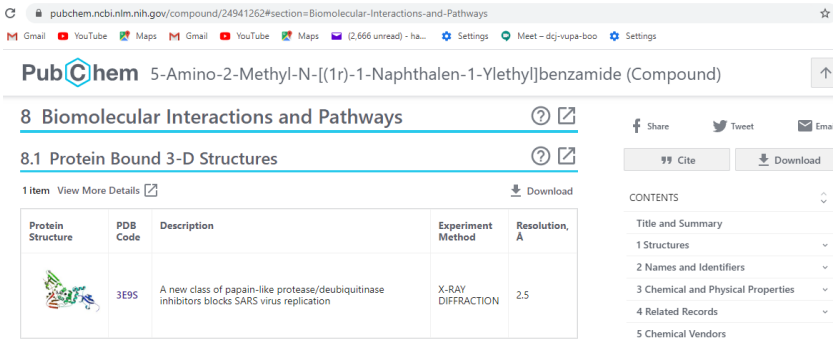


TTT atau 5-amino-2-methyl-N-[(1R)-1-naphthalen-1-ylethyl]benzamide dengan rumus molekul C_{20} H_{20} N_2 O dapat kita searching di PubChem

https://pubchem.ncbi.nlm.nih.gov/compound/24941262



Molekul reference ini sudah dipatenkan sebagaimana tercantum di web tersebut



Dalam paten disebut molekul TTT sebagai A new class of papain-like protease/deubiquitinase inhibitors blocks SARS virus replication (inhibitor deubiquitinase yang menghalangi replikasi virus SAR)