DAFTAR PUSTAKA

1 P. Khairunnisa, *Pengembangan Dan Validasi Metode Uji Aktivitas Inhibitor α-Amilase Dari Ekstrak Metanol Daun Kopi Secara In Vitro*. 2017.

2 R. Khairani, "Prevalensi diabetes melitus dan hubungannya dengan kualitas hidup lanjut usia di masyarakat," vol. 26, no. 1, 2007.

3 nur aisyah syafitri s. dkk, "untuk penderita diabetes mellitus dan hipertensi di desa minanga kecamatan bambang kabupaen mamasai nventarisasi tanaman obat tradisional," pp. 26–32.

4 M. Naveed *et al.*, "Biomedicine & Pharmacotherapy Chlorogenic acid (CGA): A pharmacological review and call for further research," *Biomed. Pharmacother.*, vol. 97, no. August 2017, pp. 67–74, 2018, doi: 10.1016/j.biopha.2017.10.064.

5 ITIS, "Integrated Taxonomy information system," 2020. .

6 Nuraeni.D, *Aneka Manfaat Biji-Bijisn*. 2011.

7 S. Shiyan, H. Herlina, D. Arsela, and E. Latifa, "Aktivitas Antidiabetes Ekstrak Etanolik Daun Kopi Robusta (Coffea canephora) Pada Tikus Diabetes Tipe 2 Yang Diberi Diet Lemak Tinggi Dan Sukrosa," *J. Farm. Sains dan Prakt.*, vol. 3, no. 2, pp. 39–46, 2017, doi: 10.31603/pharmacy.v3i2.1730.

8 H. Bhatt, S. Saklani, and K. Upadhayay, "Anti-oxidant and anti-diabetic activities of ethanolic extract of Primula Denticulata Flowers," *Indones. J. Pharm.*, vol. 27, no. 2, pp. 74–79, 2016, doi: 10.14499/indonesianjpharm27iss2pp74.

9 R. R. Tjandrawinata, “Patogenesis Diabetes Tipe 2 : Resistensi Defisiensi Insulin,” *Dexa Medica Gr.*, no. February, pp. 1–4, 2016.

10 B. Prianto, “Pemodelan Kimia Komputasi,” *Ber. Dirgant.*, vol. 8, no. 1, p. 4, 2007.

11 Situs, “Pre-Admet.” [Online]. Available: https://preadmet.bmdrc.kr/ADME/.

12 K. E. Saputri, N. Fakhmi, E. Kusumaningtyas, D. Priyatama, and B. Santoso, “Docking Molekular Potensi Anti Diabetes Melitus Tipe 2 Turunan Zerumbon Sebagai Inhibitor Aldosa Reduktase Dengan Autodock-Vina,” *Chim. Nat. Acta*, vol. 4, no. 1, p. 16, 2016, doi: 10.24198/cna.v4.n1.10443.

13 W. Agustina, E. Susanti, N. Yunita, and S. Yamtinah, “Chem Office,” *Uniersitas Sebel. Maret*, 2018.

14 M. A. Setiajid, “Analisis Dinamika Molekuler Hasil Penambatan Molekul Kompleks Siklooksigenase-2 Dengan Kuinazolinon Tersubstitusi Sulfonamida Atau Analisis Dinamika Molekuler Hasil Penambatan Molekul Kompleks Siklooksigenase-2 Dengan,” vol. 4, p. 10, 2012.

15 Siswandono, *Prinsip-Prinsip Rancangan Obat*. 1998.

16 Ariandi, “Pengenalan Enzim Amilase (Alpha-Amylase) dan Reaksi Enzimatisnya Menghidrolisis Amilosa Pati Menjadi Glukosa,” *J. Din.*, vol. 07, no. 1, pp. 74–82, 2016.

17. J. Dong *et al.*, "Admetlab: A platform for systematic ADMET evaluation based on a comprehensively collected ADMET database," *J. Cheminform.*, vol. 10, no. 1, pp. 1–11, 2018.

18. R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth, "The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree," *Heal. San Fr.*, 2008.

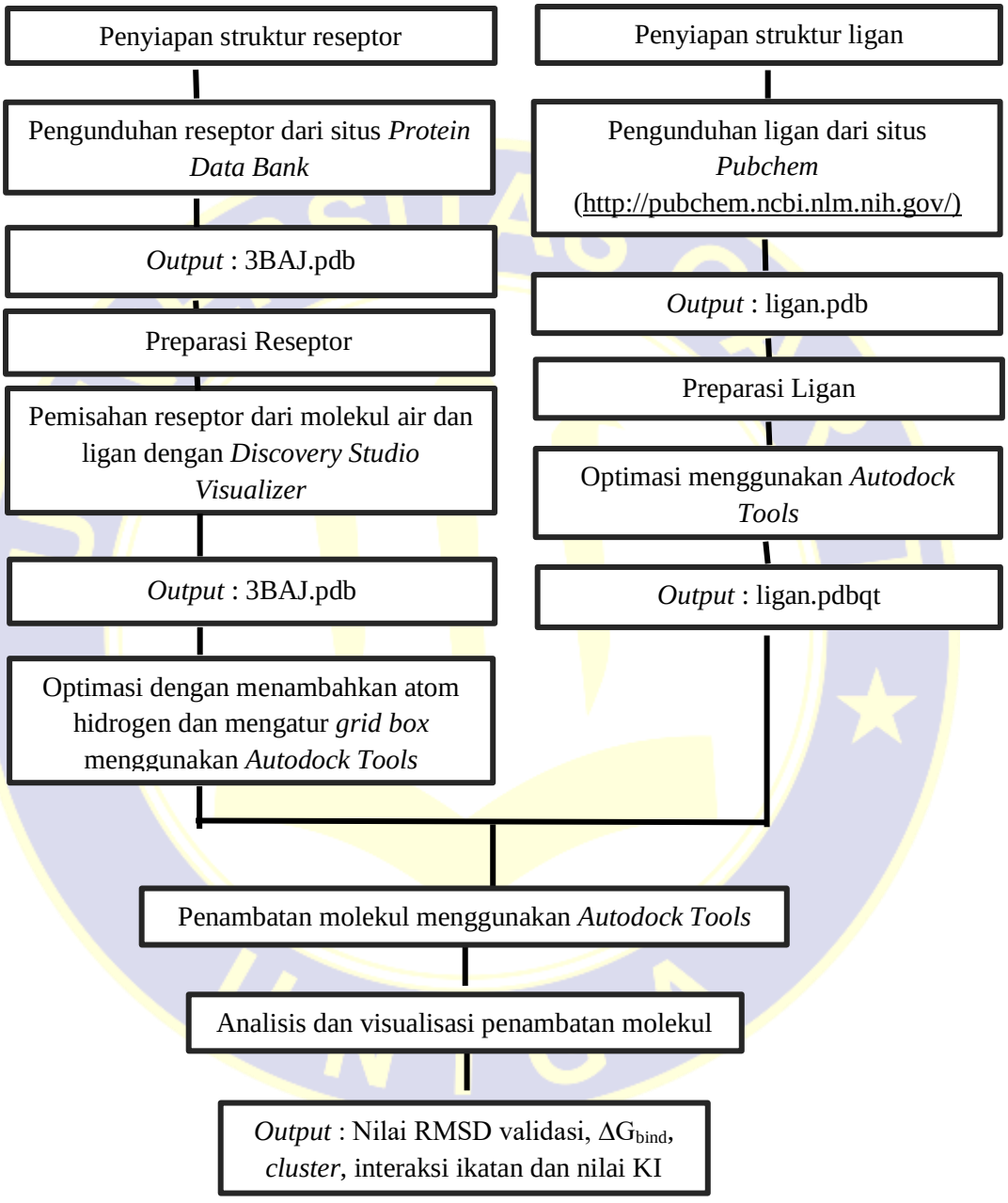
LAMPIRAN 1

BIJI KOPI HIJAU ROBUSTA (*Coffea canephora*)

Gambar II.1 Biji kopi hijau robusta (*Coffea canephora*)

LAMPIRAN 2

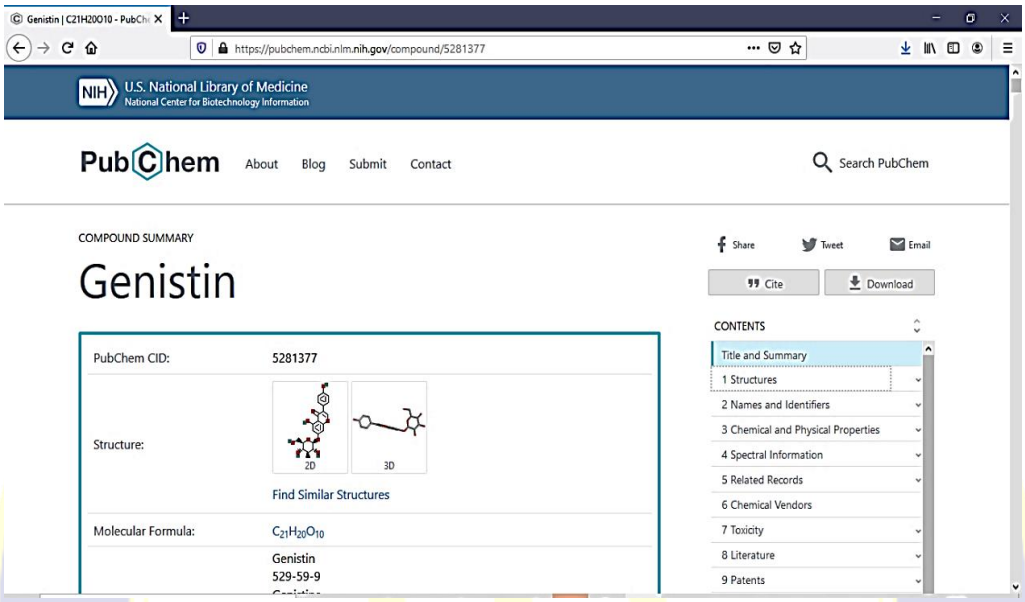
ALUR PENELITIAN



Gambar III.1 Skema alur penelitian penambatan molekul dari reseptor HPAA

LAMPIRAN 3

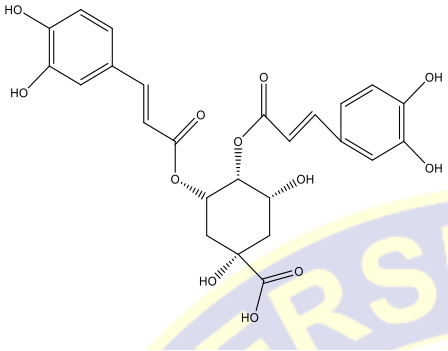
SITUS pubChem



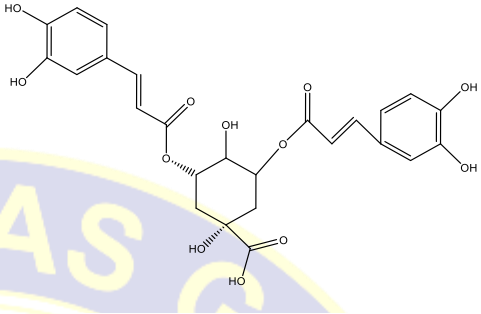
Gambar II.2 Situs pubChem

LAMPIRAN 4

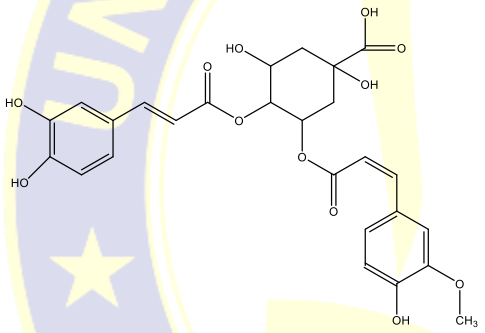
SENYAWA BIJI KOPI HIJAU ROBUSTA (*Coffea canephora*)



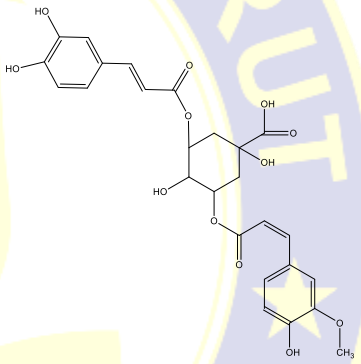
a. 3,4-O-Dicaffeoylquinic Acid Malonyl



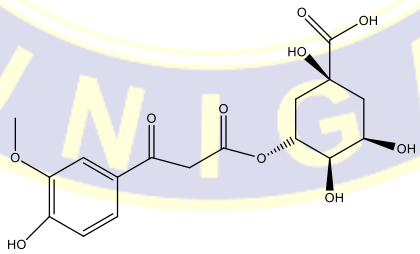
b. 3,5-O-Dicaffeoylquinic Acid Malonyl



c. 3-feruloyl-4-caffeoylquinic acid



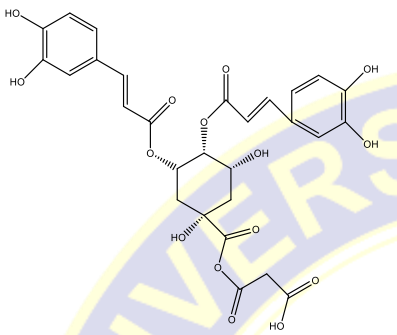
d. 3-feruloyl-5-caffeoylquinic



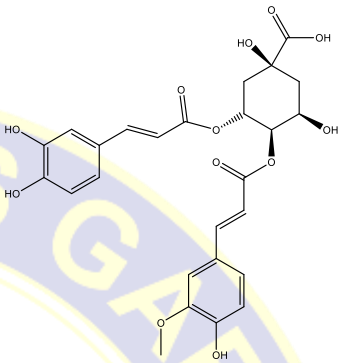
e. 3-O-feruloylquinic

LAMPIRAN 4

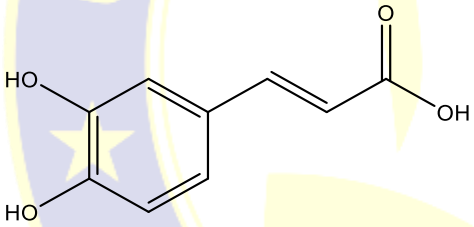
(LANJUTAN)



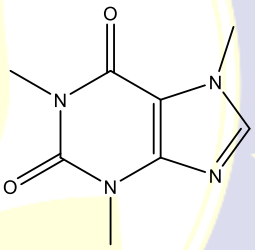
f. 4,5-O-dicaffeoylquinic acid



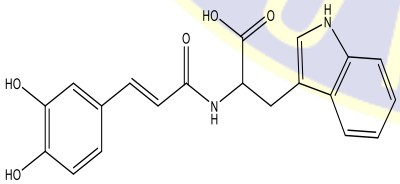
g. 4-O-feruloyl-5-caffeoylquinic acid



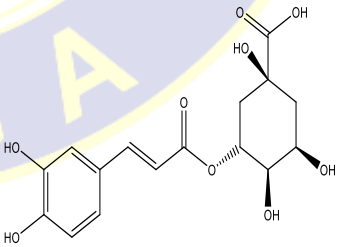
h. Caffeic Acid



i. Caffeine



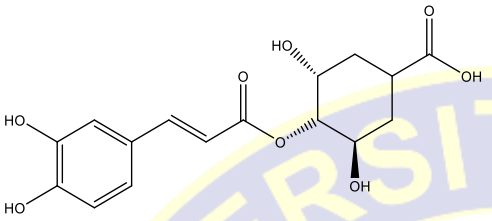
j. N-Caffeoyltryptophan



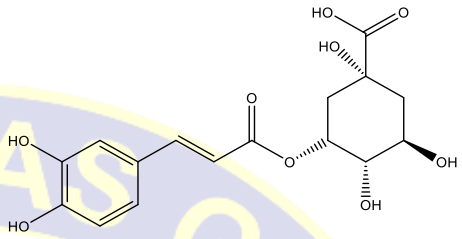
k. Chlorogenic Acid

LAMPIRAN 4

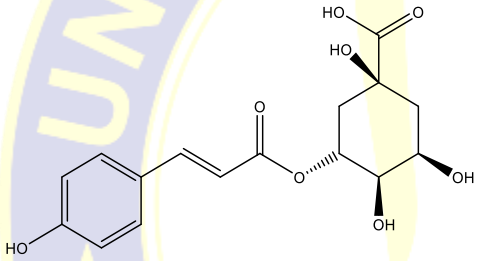
(LANJUTAN)



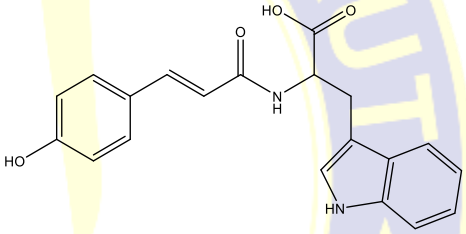
l. Cryptochlorogenic Acid



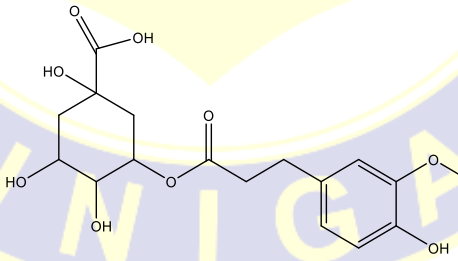
m. Neochlorogenic Acid



n. p-coumaroylquinic acid



o. p-coumaroylquinic-N-tryptophan

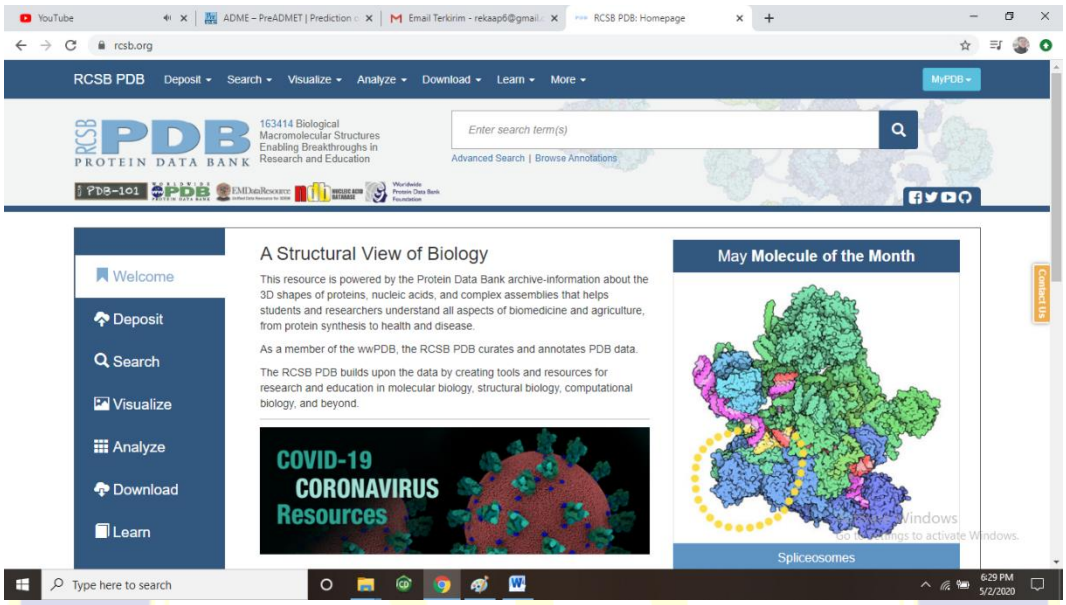


p. 5-O-feruloylquinic acid

Gambar IV.1 Senyawa biji kopi hijau robusta (*coffea canephora*)

LAMPIRAN 5

SITUS PDB (PROTEIN DATA BANK)



Gambar II.3 Situs PDB (Protein Data Bank)

LAMPIRAN 6

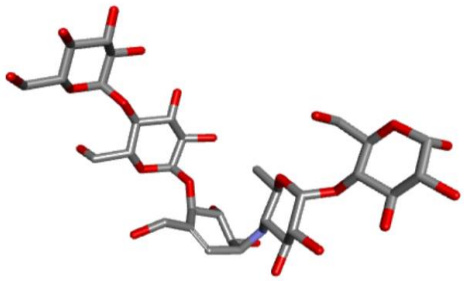
STRUKTUR 3D RESEPTOR

Reseptor 3D *human pancreatic alpha amylase (3BAJ)*

Gambar III.2 Struktur 3D reseptor

LAMPIRAN 7

LIGAN ALAMI



3BAJ

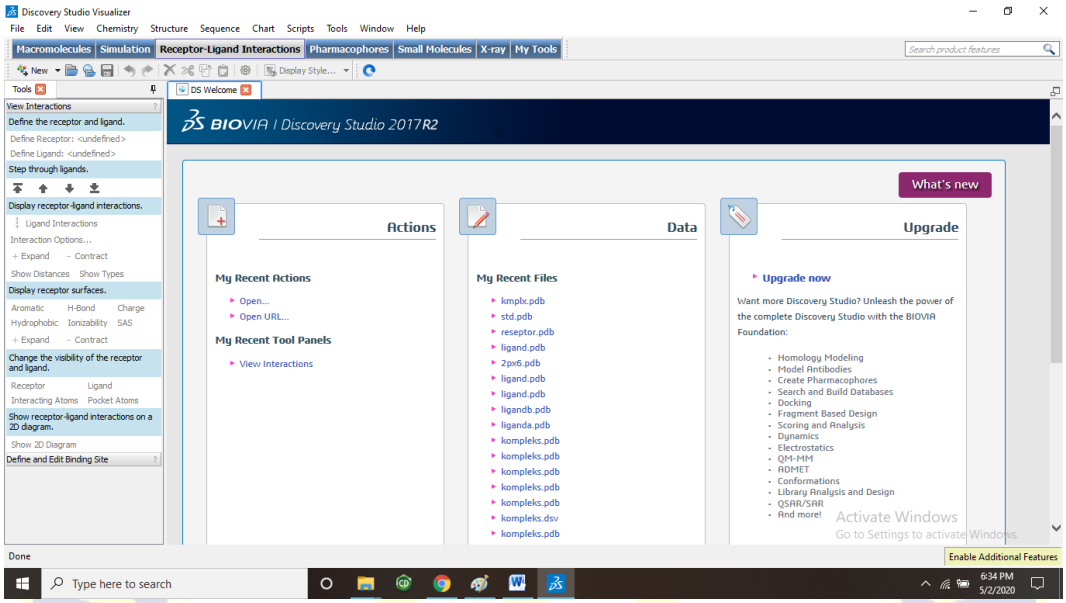
Ligan alami dari reseptor *human*

Pancreatic alpha amylase

Gambar IV.2 Ligan alami

LAMPIRAN 8

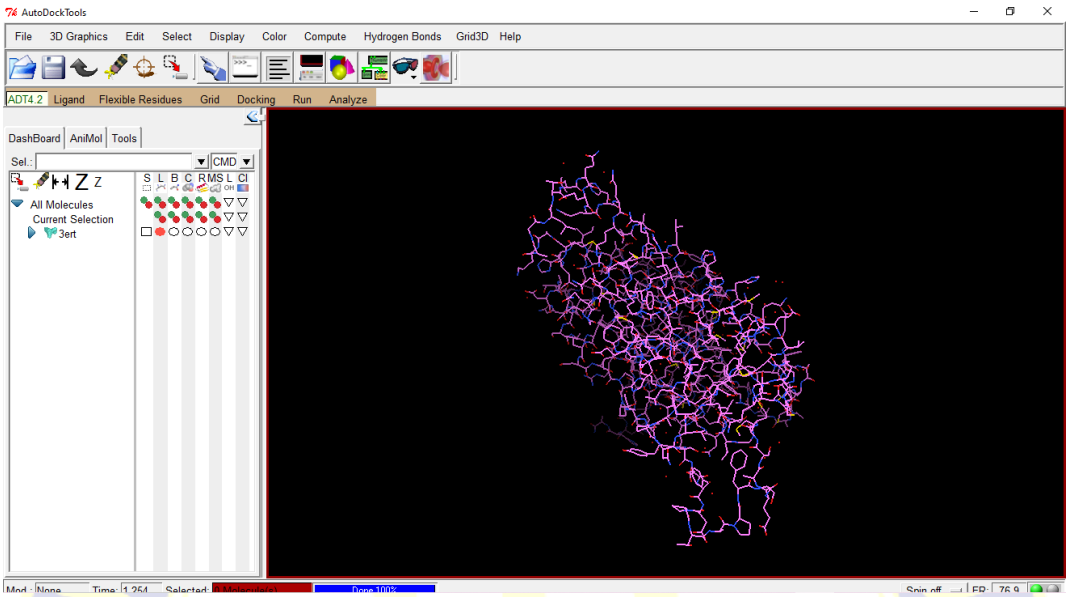
PERANGKAT LUNAK *DISCOVERY STUDIO VISUALIZER*



Gambar IV.3 Perangkat lunak *Discovery Studio Visualizer*

LAMPIRAN 9

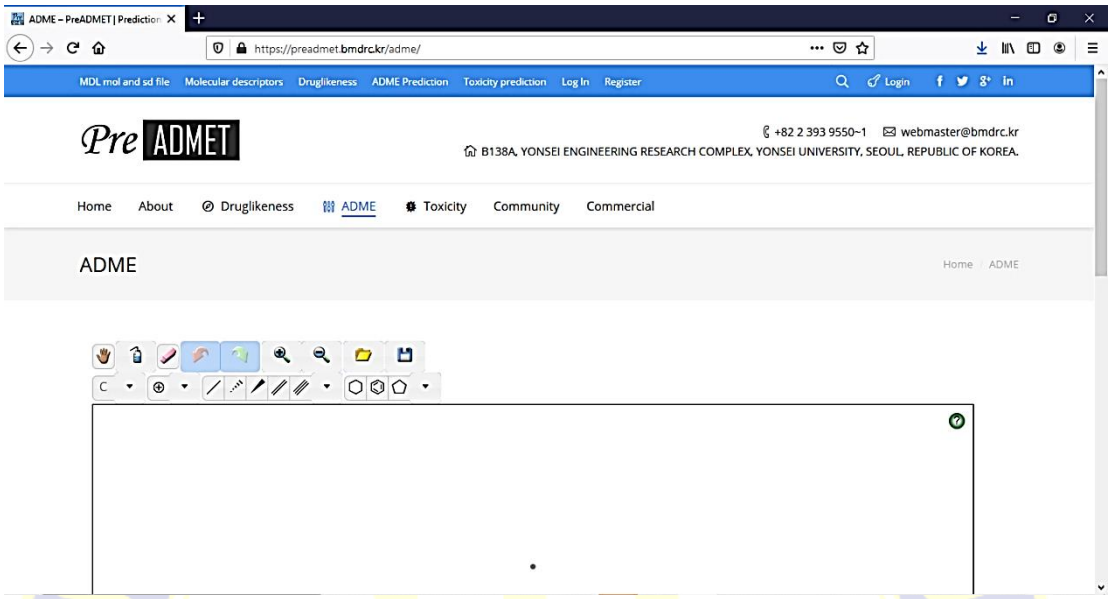
PERANGKAT LUNAK AUTODOCK TOOLS



Gambar IV.4 Perangkat lunak Autodock Tools

LAMPIRAN 10

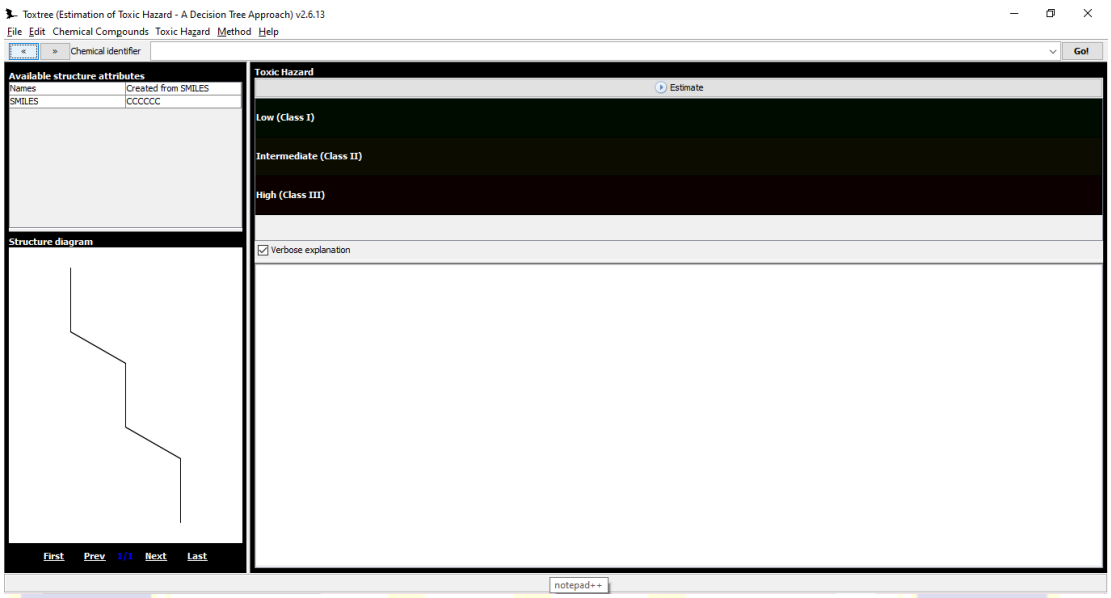
SITUS *PRE-ADMET*



Gambar II.4 Situs *pre-admet*

LAMPIRAN 11

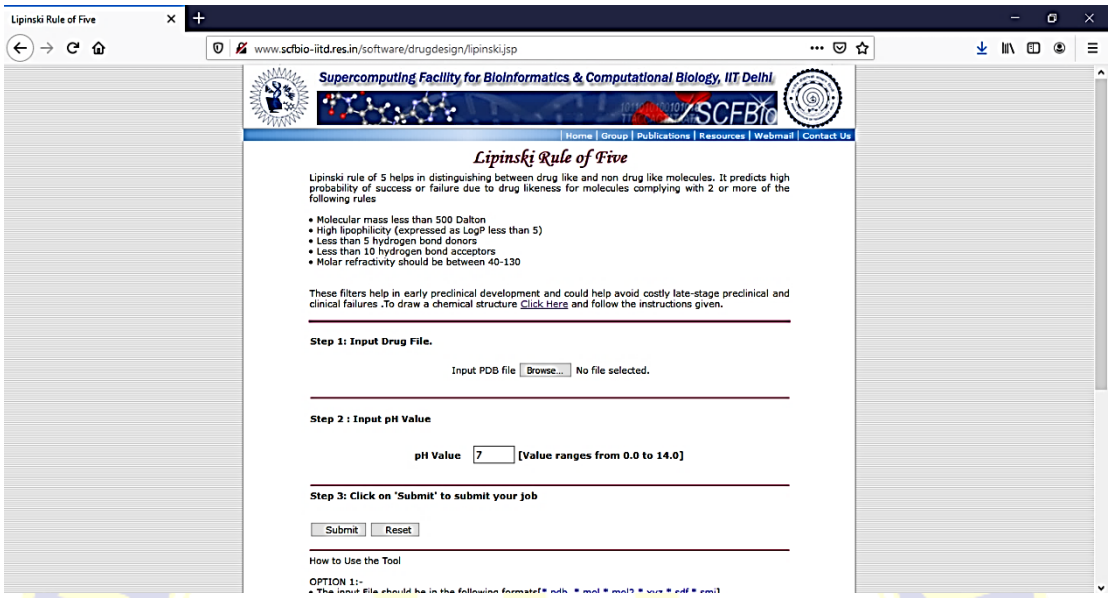
PERANGKAT LUNAK TOXTREE



Gambar IV.5 Perangkat lunak Toxtree

LAMPIRAN 12

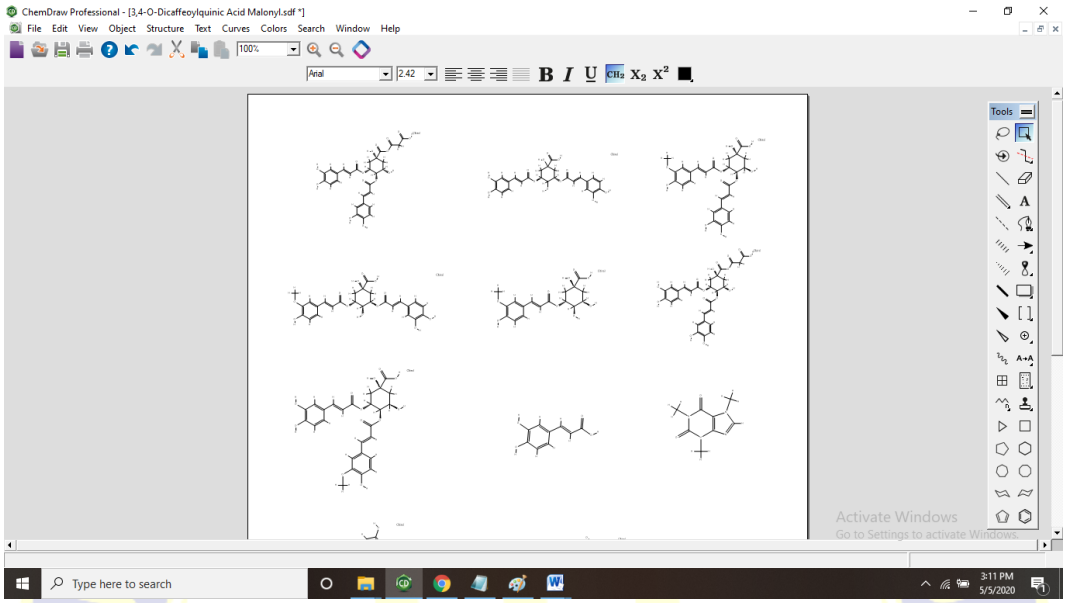
SITUS *LIPINSKI'S RULE OF FIVE*



Gambar I1.5 Situs *lipinski's rule of five*

LAMPIRAN 13

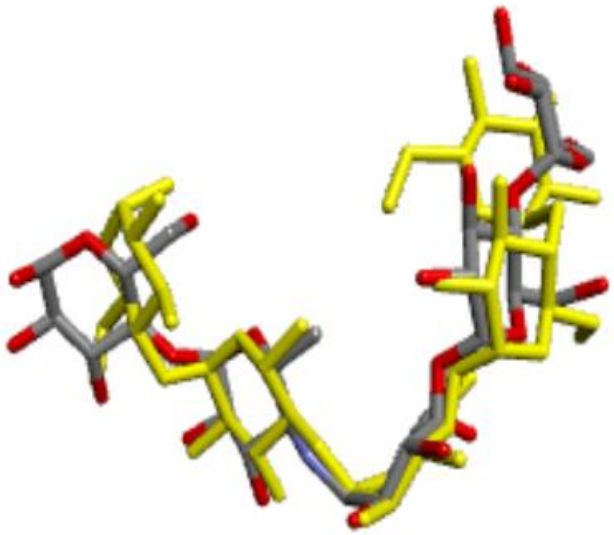
PERANGKAT LUNAK *CHEM DRAW*



Gambar IV.6 Perangkat lunak *Chem Draw*

LAMPIRAN 14

HASIL VALIDASI



Visualisasi tumpang tindih ligan alami dengan ligan hasil *redocking* dari reseptor *Human Pancreatic Alpha Amylase*

Gambar V.1 Hasil validasi

4

LAMPIRAN 14
(LANJUTAN)

Tabel V.1
Hasil Redoking Reseptor *3BAJ*

Reseptor	**Grid Box**	**RMSD**	**ΔG (Energi Bebas)**
3BAJ	x : 8.652 y : 15.387 z : 40.189	1.325 Å	-11.08

LAMPIRAN 15

HASIL PENAMBATAN MOLEKUL

Tabel V.2
Hasil Penambatan Senyawa Aktif dari Tanaman Kopi Hijau Robusta (*Coffea canepghora* (L.) dengan Reseptor *3BAJ*

No	Senyawa / Ligan	Ikatan Energi Bebas (ΔG)	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
1	Ligand Alami 3BAJ	-11.08	11	THR163, LYS200, GLY306, ALA307, ASP300, GLU233, GLN63, TRP59, TRY62, HIS299, ARG195	7.52(nM)
2	3,4-O-Dicaffeoyl quinic Acid Malonyl	-6.02	3	ILE235, GLU233, HIS20	38.93 uM
3	3,5-O-Dicaffeoyl quinic Acid Malonyl	-5.48	3	HIS305, GLU233, HIS20	96.01 uM
4	3-O-feruloyl-4-caffeoylquinic acid	-5.78	3	LYS200, ASP300, HIS299	57.76 uM

LAMPIRAN 15

(LANJUTAN)

Tabel V.2
Lanjutan

No	Senyawa / Ligan	0p0Ikatan Energi (ΔG)	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
5	3-O-feruloyl-5-caffeoylquinic acid	-6.49	6	HIS20, ALA198, ASP197, ARG195, HIS299, TYR62	17.46 uM
6	3-O-feruloylquinic acid	-5.19	5	HIS20, TRY151, LYS200, ASP300, HIS299	155.62 uM
7	4,5-O-dicaffeoylquinic acid	-5.57	4	LYS200, ALA307, GLY306, ASP197	82.47 uM
8	4-O-feruloyl-5-caffeoylquinic acid	-6.52	5	HIS20, HIS101,TRY62, ASP300,HIS299	16.50 uM
9	Caffeic Acid	-4.26	3	TRY151, LYS200, HIS20	755.22 uM

LAMPIRAN 15

(LANJUTAN)

Tabel V.2
Lanjutan

No	Senyawa / Ligan	0p0Ikatan Energi (ΔG)	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
10	Caffeine	-4.52	3	TTY151, ILE235, GLU233	483.77 uM
11	N-Caffeoyltryptophan	-6.17	5	ILE235, ASP197, HIS350, ASP300	29.88 uM
12	Chlorogenic Acid	-5.84	3	ASP197, ALA307, ASP300	52.77 uM
13	Cryptochlorogenic Acid	-6.00	3	HIS350, ASP197, HIS299	39.97 uM
14	5-O feruloylquinic acid	-4.97	3	HIS20, ASP300, HIS299	227.25 uM

LAMPIRAN 15

(LANJUTAN)

Tabel V.2
Lanjutan

No	Senyawa / Ligan	0p0Ikatan Energi (ΔG)	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
16	p-coumaroylquinic acid	-5.67	4	HIS299, ASP197, ASP300, LYS200	69.76 uM
17	p-coumaroylquinic-N-tryptophan	-6.30	7	GLU233, HIS299, ASP300, LYS200, HIS210, TYR151, HIS350	24.03 uM

LAMPIRAN 16

HASIL PENGUJIAN PREADMET

Tabel V.3
Hasil Uji Pre-ADMET

No	Nama Ligan	Absorbsi		Distribusi
		CaCo-2 (nm. Sec-1)	HIA (%)	PPB (%)
1	3,4-O-Dicaffeoylquinic Acid Malonyl	19.53	23.12	87.77
2	3,5-O-Dicaffeoylquinic Acid Malonyl	19.32	23.12	86.05
3	3-feruloyl-4-caffeoylquinic acid	18,66	39.17	80.29
4	3-feruloyl-5-caffeoylquinic acid	19.76	66.82	87.87
5	3-O-feruloylquinic acid	17.52	34.18	41.13
6	4,5-O-dicaffeoylquinic acid	19.55	23.13	86.7
7	4-O-feruloyl-5-caffeoylquinic acid	19.15	39.17	80.82
8	Caffeic Acid	21.11	82.30	40,29
9	Caffeine	21.26	93.82	14.07
10	N-Caffeoyltryptophan	17.43	79.28	92.19
11	Chlorogenic Acid	18,71	20.43	41.96
12	Cryptochlorogenic Acid	19.31	29,77	50.33
13	Neochlorogenic Acid	17.43	29.77	47.03
14	5-O-feruloylquinic acid	18.66	37.11	44.54
15	p-coumaroylquinic acid	18.71	20.42	41.96
16	p-coumaroylquinic-N-tryptophan	19.41	86.86	97.24

Keterangan: *in vitro CaCo-2 cell permeability (nm. Sec^{-1}): >70 higher permeability, 4-70 medium permeability, <4 low permeability; % human intestinal absorption (%HIA): 70-100% well absorbed, 20-70% moderately absorbed, 0-20% poorly absorbed; %plasma protein binding: >90% strongly bound, <90% weakly bound.*

LAMPIRAN 17

HASIL PENGUJIAN TOKSISITAS

Tabel V.4
Hasil Pengujian Toksisitas

No	Ligan	Cramer rules	Benigni/bosarulebase	Kroes TTC decission tree
1	3,4-O-Dicaffeoylquinic Acid Malonyl	3	8,9	1
2	3,5-O-Dicaffeoylquinic Acid Malonyl	3	8,9	1
3	3-feruloyl-4-caffeoylquinic acid	3	8,9	1
4	3-feruloyl-5-caffeoylquinic acid	3	8,9	1
5	3-O-feruloylquinic acid	2	8,9	1
6	4,5-O-dicaffeoylquinic acid	3	8,9	1
7	4-O-feruloyl-5-caffeoylquinic acid	3	8,9	1
8	Caffeic Acid	1	8,9	1
9	Caffeine	3	8,9	1
10	N-Caffeoyltryptophan	3	8,9	1
11	Chlorogenic Acid	2	8,9	1
12	Cryptochlorogenic Acid	1	8,9	1
13	Neochlorogenic Acid	2	8,9	1
14	5-O-feruloylquinic acid	2	8,9	1
15	p-coumaroylquinic acid	2	8,9	1
16	p-coumaroylquinic-N-tryptophan	3	8,9	1

Keterangan: *Cramer rules 1 Low class, 2 Intermediet class, 3 Hight class. Benigni/bose rulebase 2 (structural alert for non genotoxic carcinogenicity), 8 (negative for genotoxic carcinogenity), 9 (negative for non-genotoxic carcinogencity),. Kroes TTC decision tree 1(Subtance would not be expected to be a safety concern).*

LAMPIRAN 18

HASIL PREDIKSI BIOAVAILIBILITAS

Tabel V.5

Hasil Prediksi Bioavalibilitas

No	Ligan	BM	Log P	Ikatan Hidrogen		Keterangan
				Donor	Akseptor	
1	3,4-O-Dicaffeoylquinic Acid Malonyl	516	-0.269	7	9	Tidak Memenuhi Syarat
2	3,5-O-Dicaffeoylquinic Acid Malonyl	516	-0.91	7	9	Tidak Memenuhi Syarat
3	3-feruloyl-4-caffeoylquinic acid	530	0.175	6	9	Tidak Memenuhi Syarat
4	3-feruloyl-5-caffeoylquinic acid	530	0.355	6	9	Tidak Memenuhi Syarat
5	3-O-feruloylquinic acid	368	-1.433	5	7	Tidak Memenuhi Syarat
6	4,5-O-dicaffeoylquinic acid	602	-0.163	7	11	Tidak Memenuhi Syarat
7	4-O-feruloyl-5-caffeoylquinic acid	530	0.179	6	9	Tidak Memenuhi Syarat
8	Caffeic Acid	180	0.976	3	3	Memenuhi Syarat
9	Caffeine	194	-0.04	0	4	Memenuhi Syarat
10	N-Caffeoyltryptophan	366	1.971	5	5	Memenuhi Syarat
11	Chlorogenic Acid	354	-1.879	6	7	Tidak Memenuhi Syarat
12	Cryptochlorogenic Acid	354	-1.4	6	7	Tidak Memenuhi Syarat
13	Neochlorogenic Acid	354	-.1875	6	7	Tidak Memenuhi Syarat
14	5-O-feruloylquinic acid	370	-1.49	5	7	Memenuhi Syarat
15	p-coumaroylquinic acid	338	-1.282	5	6	Memenuhi Syarat
16	p-coumaroylquinic-N-tryptophan	338	-1.275	5	6	Memenuhi Syarat

Keterangan: BM (Berat molekul) <500 Dalton, Log P <5, Donor ikatan hidrogen <5 dan Akseptor ikatan hidrogen <10.

LAMPIRAN 19

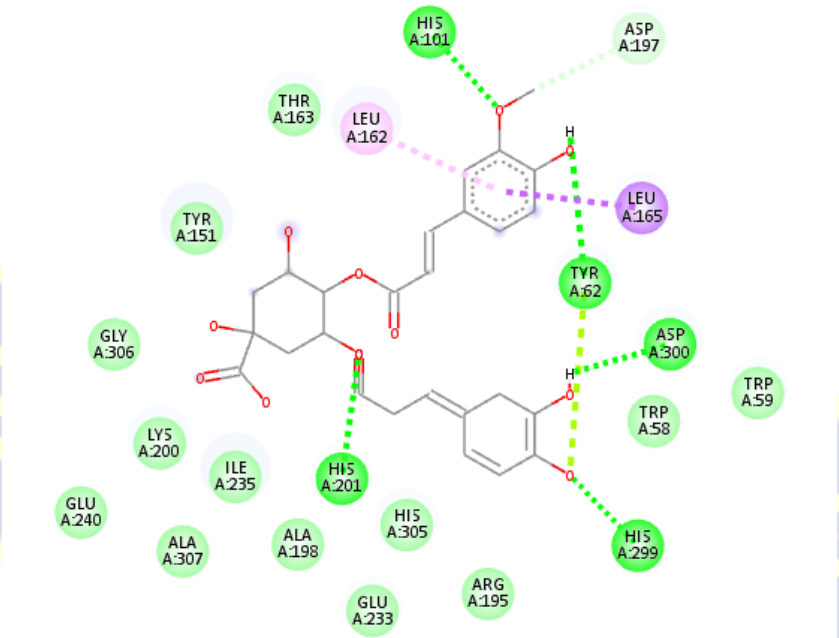
RESEPTOR 3D

Visualilasi reseptor dengan senyawa aktif terbaik *4-0-feruloyl-5-caffeoylquinic acid*

Gambar V.2 Visualilasi reseptor dengan senyawa aktif terbaik

LAMPIRAN 20

INTERAKSI ASAM AMINO



Interaksi *4-0-feruloyl-5-caffeoylquinic acid* terhadap reseptor 3BAJ

Gambar V.3 Interaksi residu asam amino