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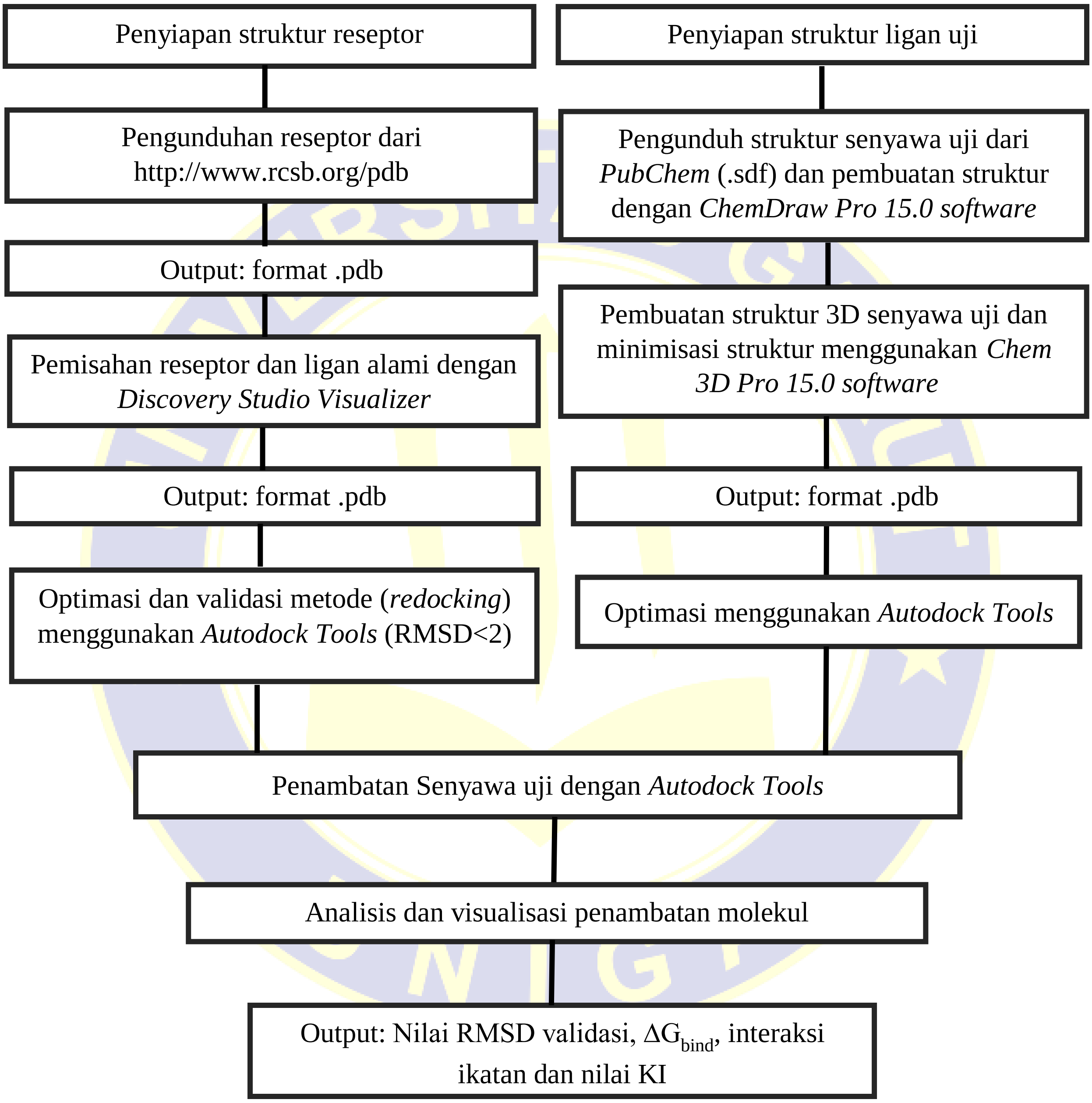
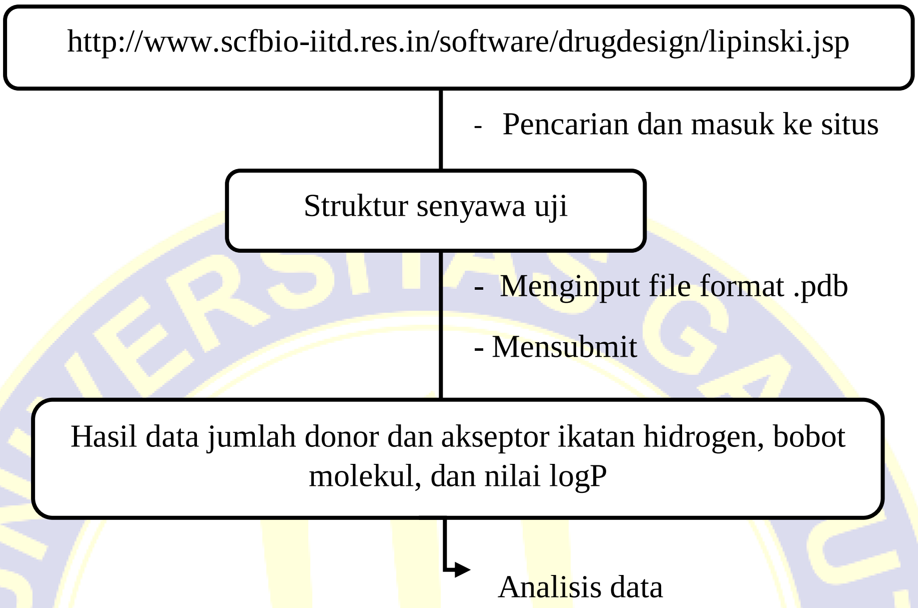
LAMPIRAN 1

ALUR PENELITIAN

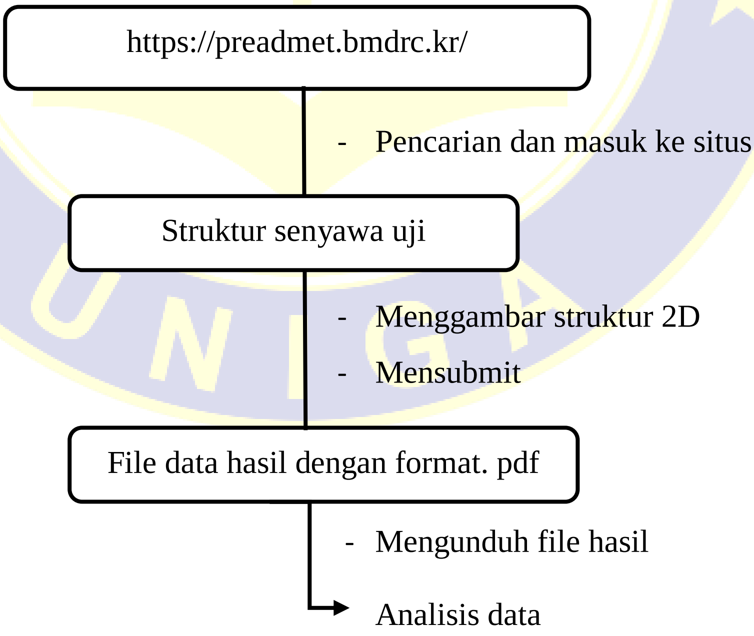


Gambar III.1 Alur penelitian penambatan molekul

LAMPIRAN 1
(LANJUTAN)



Gambar III.2 Analisis *lipinski's rule of five*



Gambar III.3 Analisis *pre-ADME* dan toksisitas

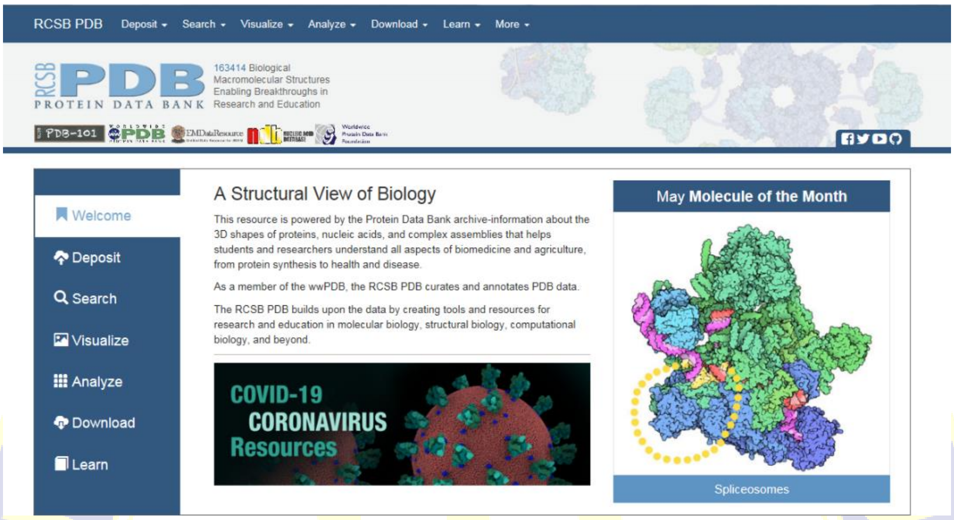
LAMPIRAN 2

TANAMAN AKAR PAKIS TANGKUR

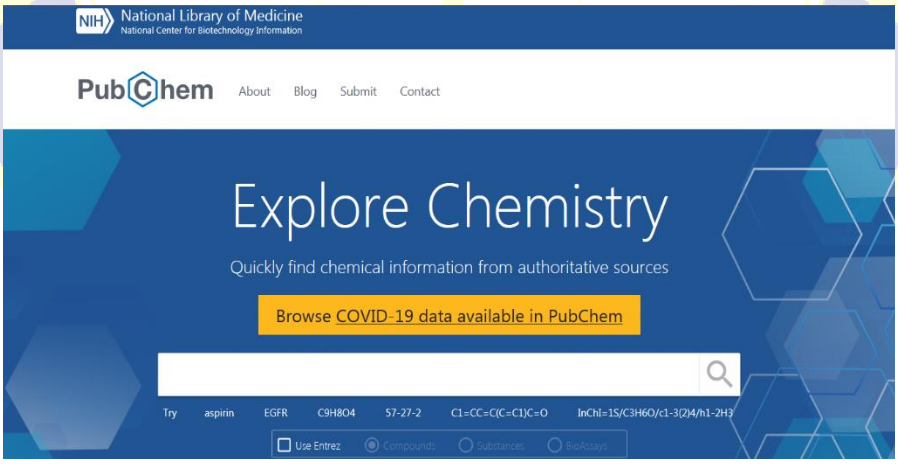
Gambar IV.1 Tanaman akar pakis tangkur (*Polypodium feei* METT)

LAMPIRAN 3

SITUS DAN APLIKASI

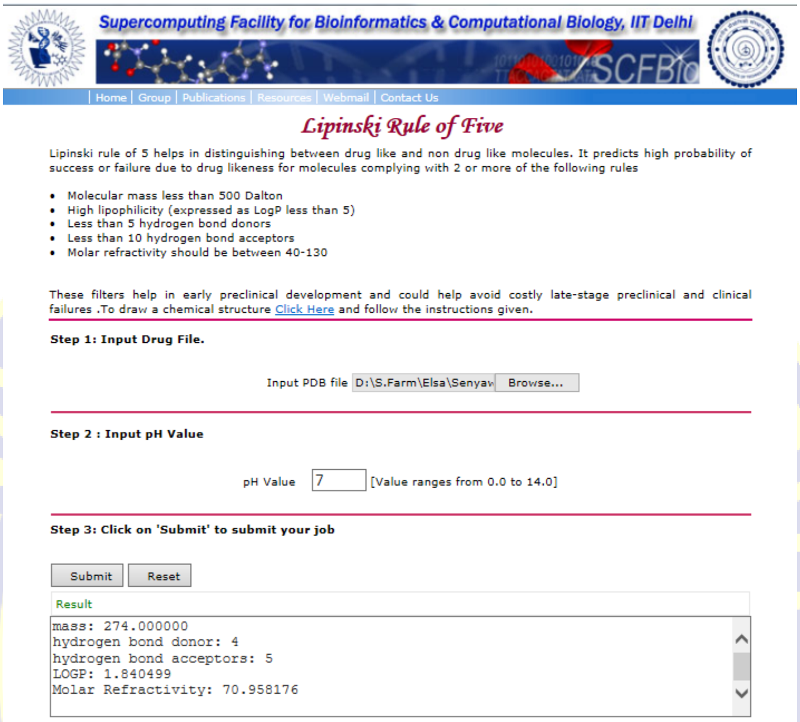


Gambar IV.2 Tampilan situs *Protein Data Bank* (PDB)

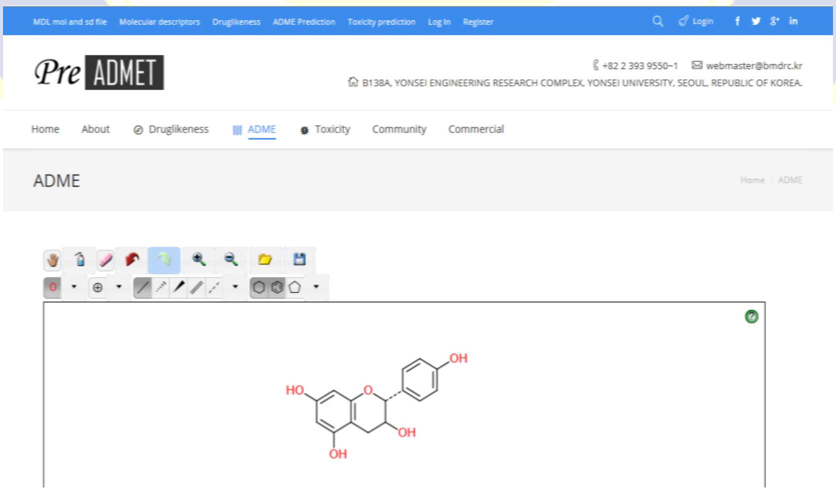


Gambar IV.3 Tampilan situs *pubchem*

LAMPIRAN 3
(LANJUTAN)

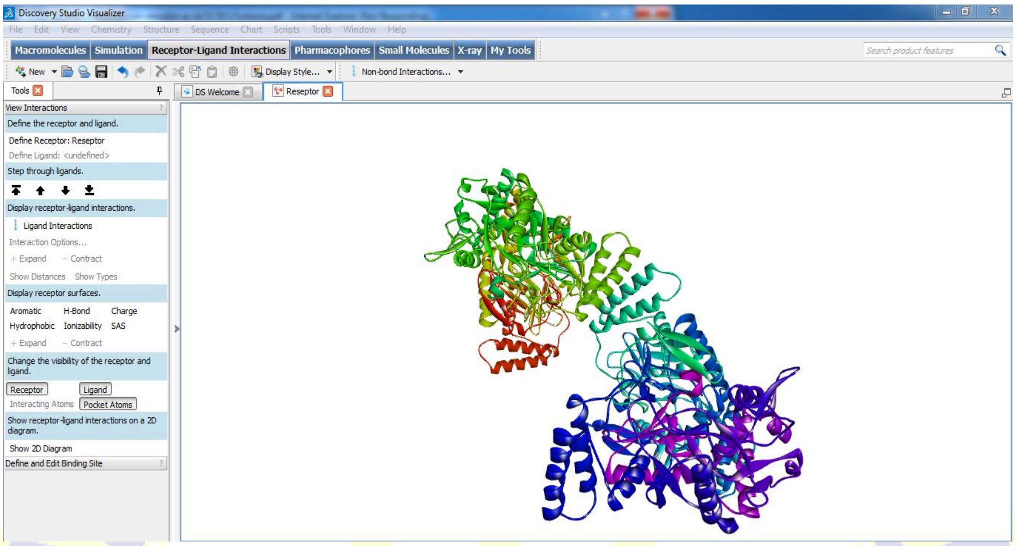


Gambar IV.4 Tampilan situs *lipinski rule of five*

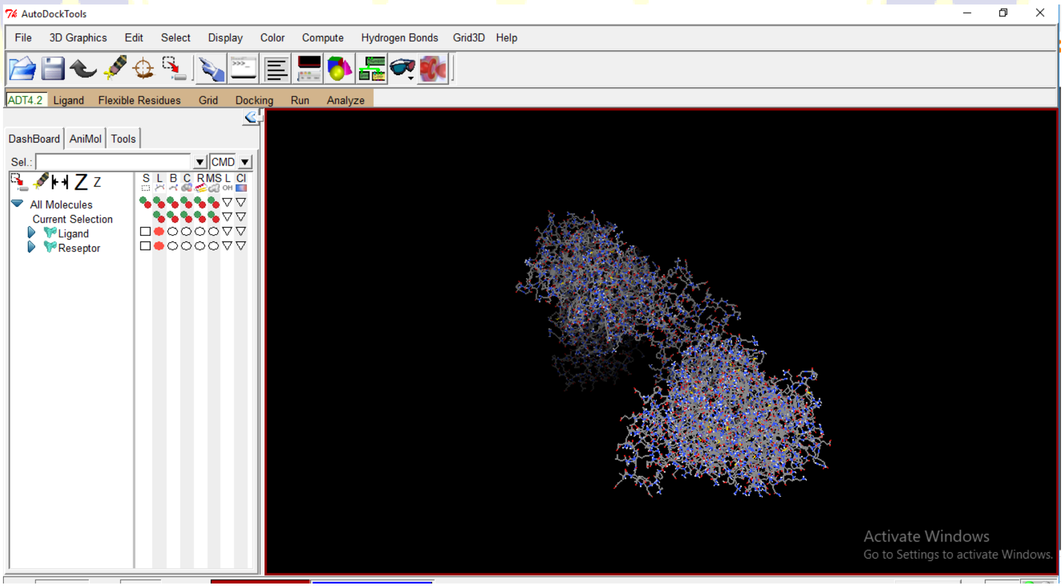


Gambar IV.5 Tampilan situs *pre-ADMET*

LAMPIRAN 3
(LANJUTAN)

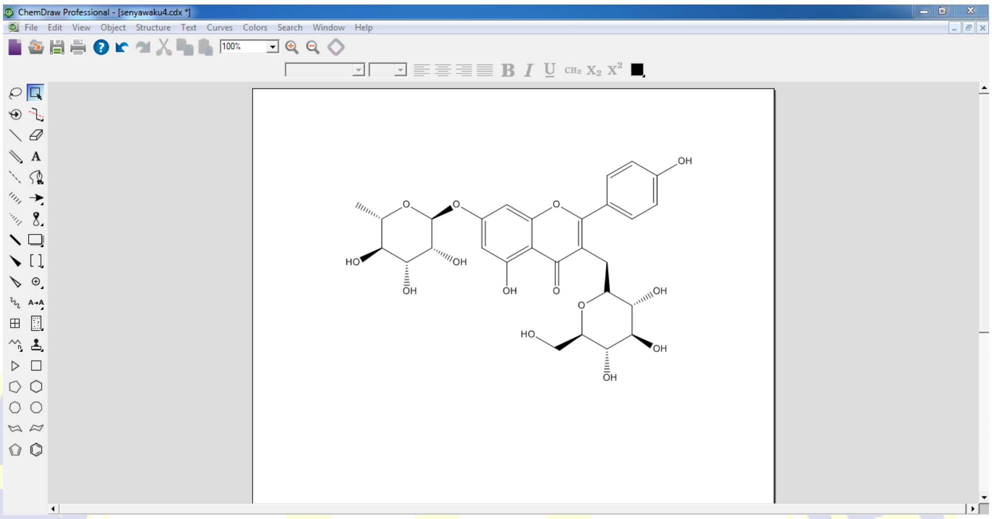


Gambar IV.6 Tampilan aplikasi *discovery studio visualizer*®

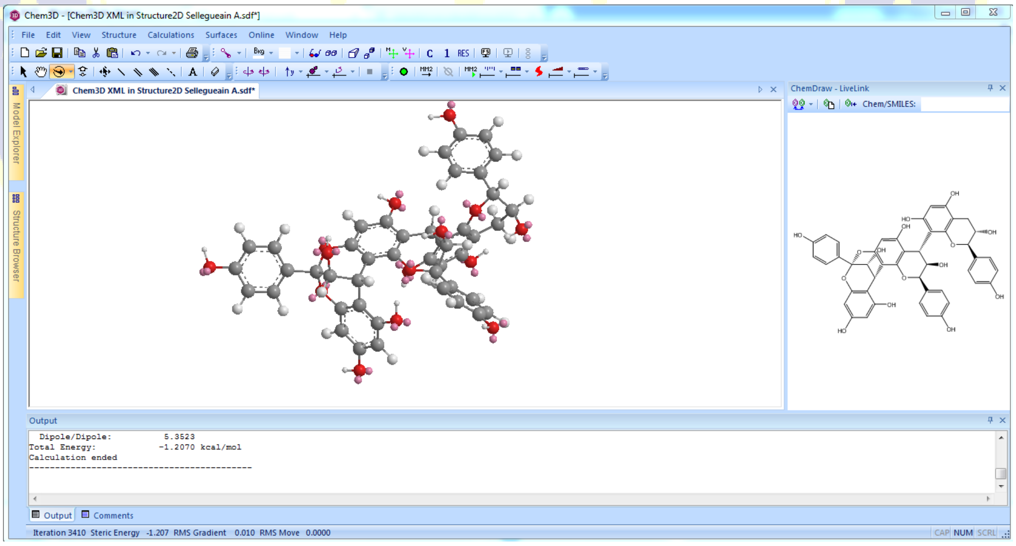


Gambar IV.7 Tampilan aplikasi *autodock tools*®

LAMPIRAN 3
(LANJUTAN)



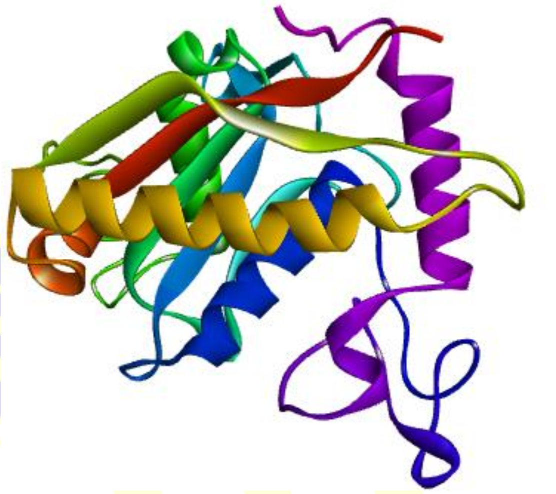
Gambar IV.8 Tampilan aplikasi *chemdraw office*®



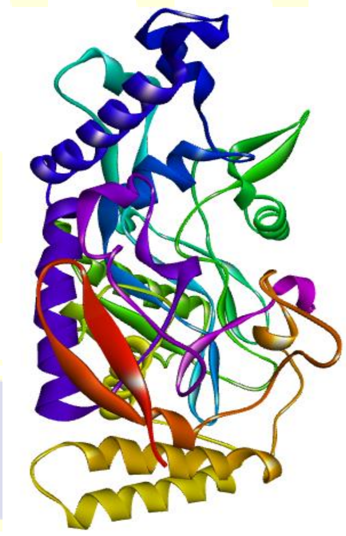
Gambar IV.9 Tampilan aplikasi *chem3D*®

LAMPIRAN 4

STRUKTUR 3D MAKROMOLEKUL



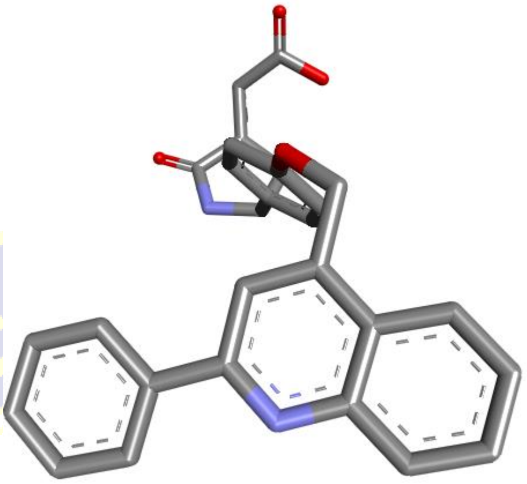
Gambar IV.10 Reseptor TNF-α dengan PDB ID 3EWJ



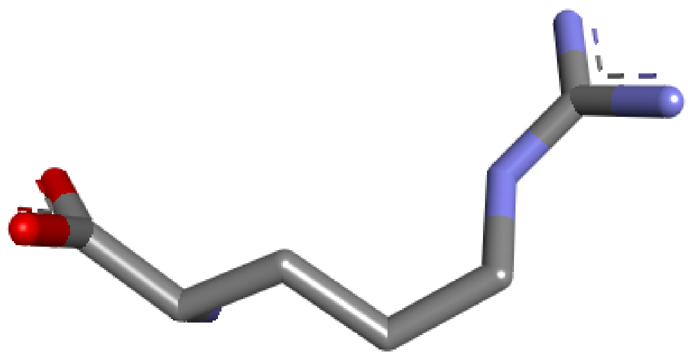
Gambar IV.11 Enzim iNOS dengan PDB ID 1NSI

LAMPIRAN 5

STRUKTUR 3D LIGAN ALAMI



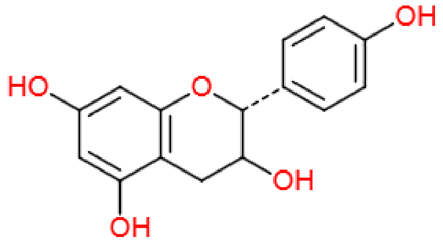
Gambar IV.12 Ligan alami dari reseptor TNF-α



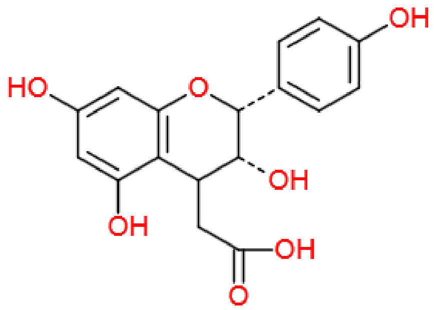
Gambar IV.13 Ligan alami dari enzim iNOS

LAMPIRAN 6

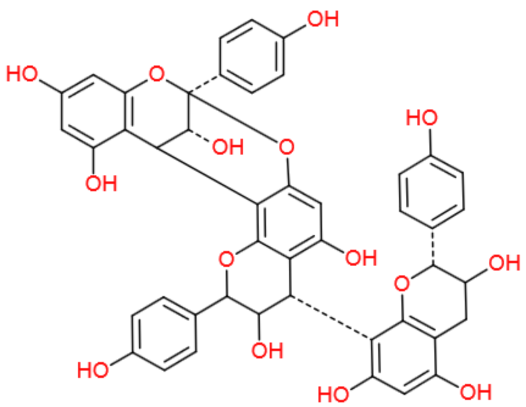
STRUKTUR 2D LIGAN UJI



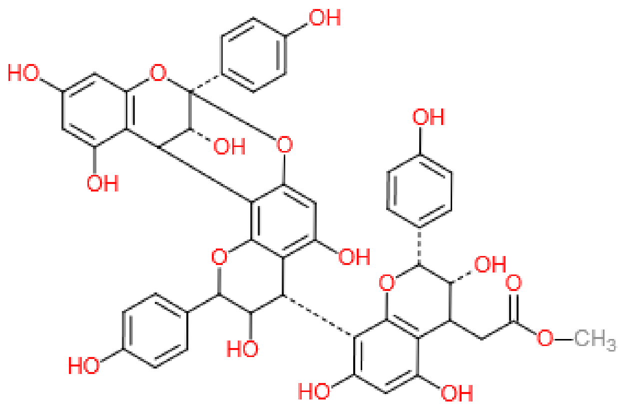
Gambar IV.14 (+)-afzelechin



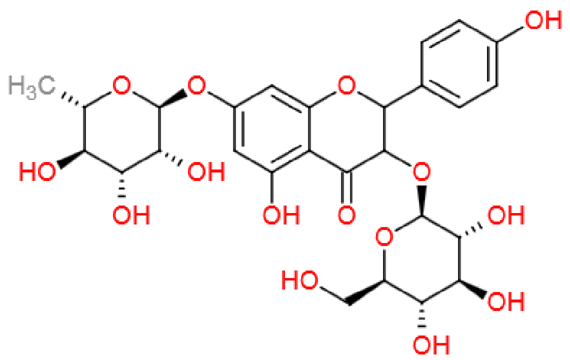
Gambar IV.15 3’-deoxydryopteric acid



Gambar IV.16 Selligueain A



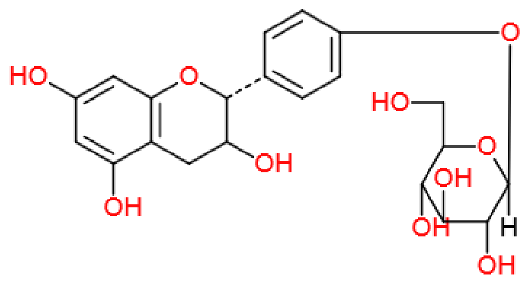
Gambar IV.17 Selligueain B



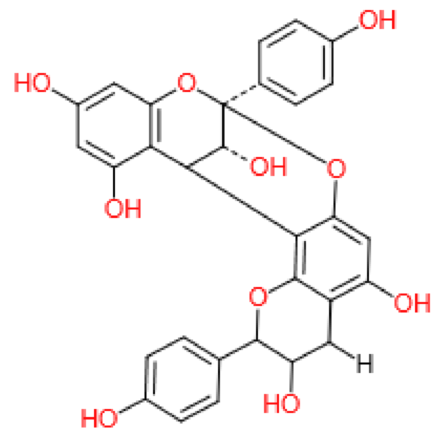
Gambar IV.18

Kaempferol-3-O-β-D-glukopyranoside-7-O-α-L-rhamnopyranoside

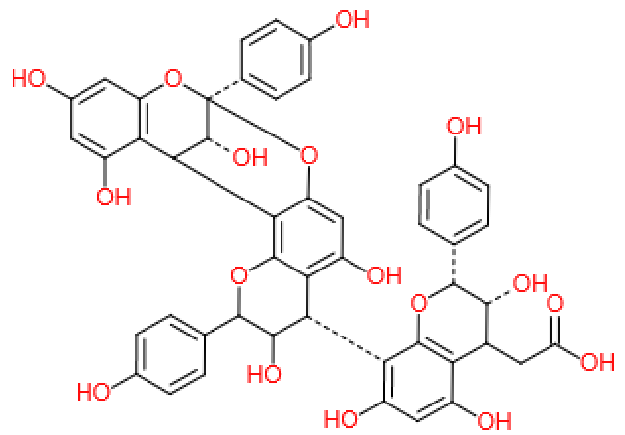
LAMPIRAN 6
(LANJUTAN)



Gambar V.19 (+)-afzelechin-O-β-4’D-glukopyranoside



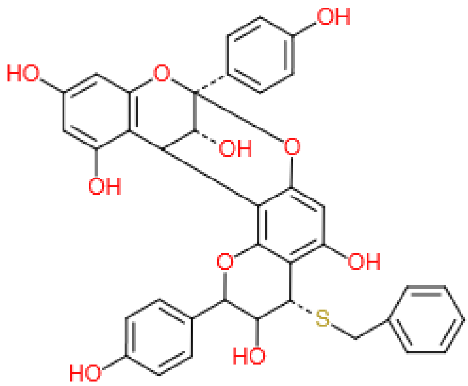
Gambar V.20 Geranin A



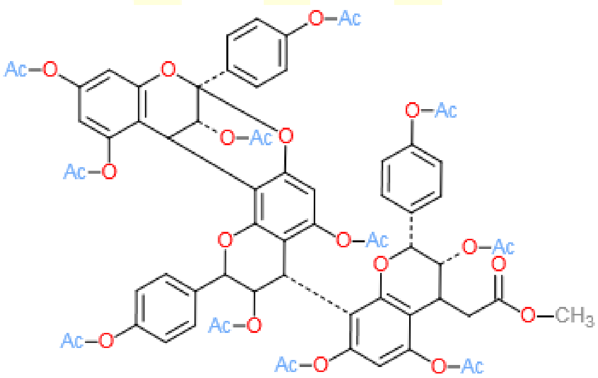
Gambar IV.21

2-((2R,3R)-3,5,7-trihydroxy-2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis(4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d]naphtho[1,2-g][1,3]dioxocin-10-yl) chroman-4-yl)aceticacid

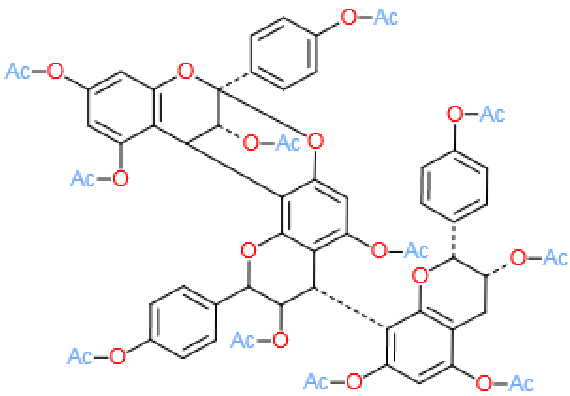
LAMPIRAN 6
(LANJUTAN)



Gambar IV.22
(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3]dioxocino[4,5-H]chromene-3,5,11,13,15-pentaol



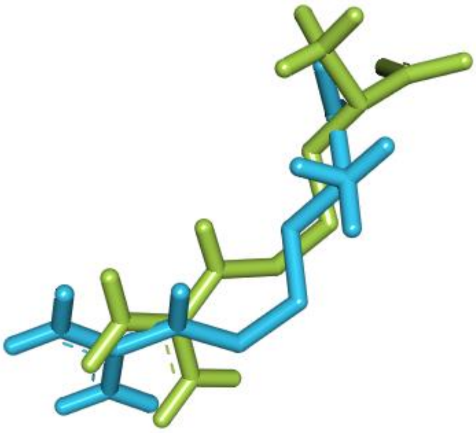
Gambar IV.23
Undecaacetate of epiafzelechin-(4β→8,2β→O→7)-epiafzelechin-(4β→8)-3'deoxydryopteric acid methyl ester



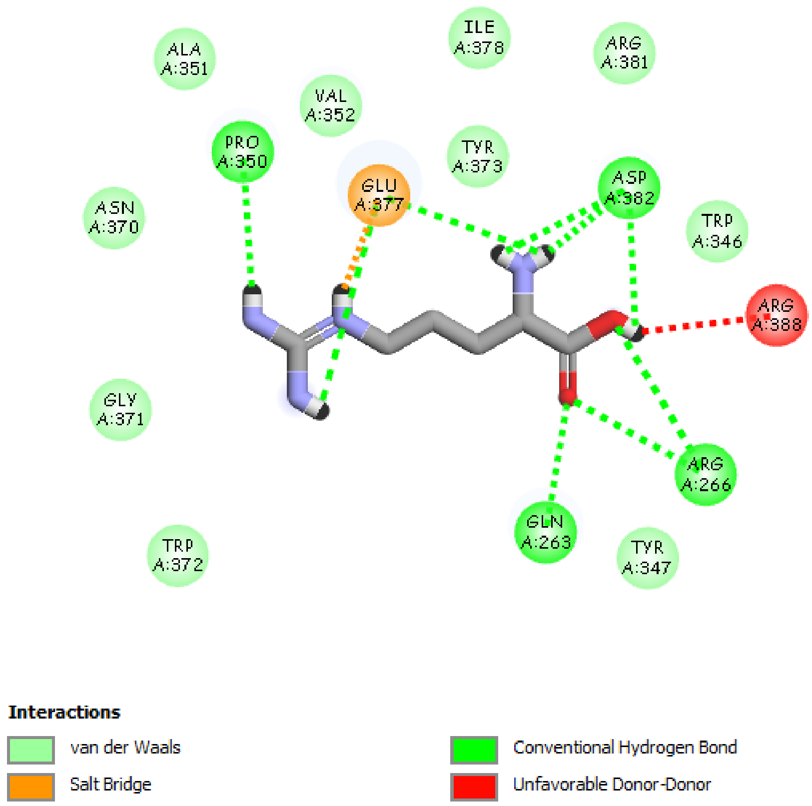
Gambar IV.24 Undeacetylepiafzelechin-(4β→8,2β→O→7)-epiafzelechin-(4β→8)-afzelechin

LAMPIRAN 7

VALIDASI METODE

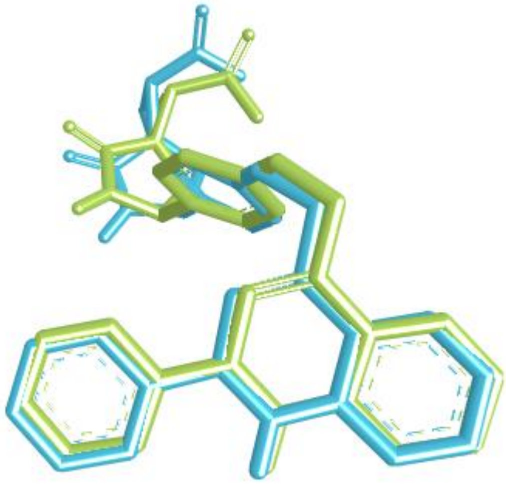


Gambar V.1 Hasil visualisasi tumpang tindih ligan alami dari enzim iNOS hasil kristalografi sinar-X (biru) dengan ligan hasil *redocking* (hijau)

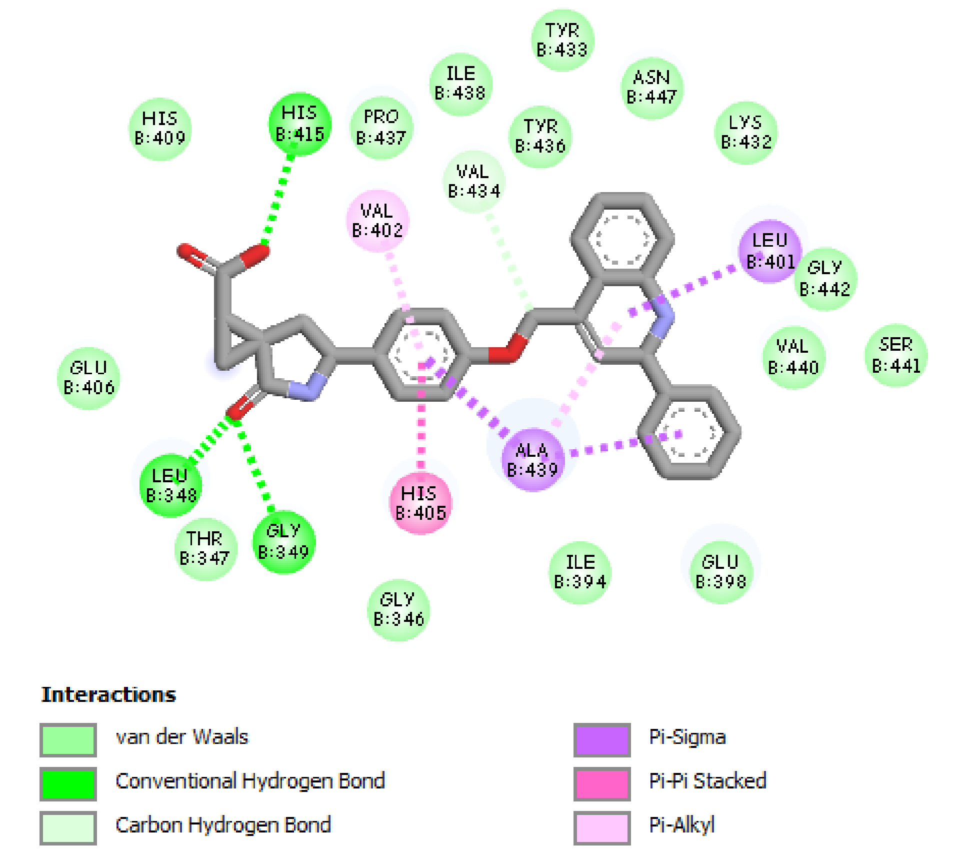


Gambar V.2 Hasil visualisasi interaksi ligan alami dengan enzim iNOS

LAMPIRAN 7
(LANJUTAN)



Gambar V.3 Hasil visualisasi tumpang tindih ligan alami dari reseptor TNF-α hasil kristalografi sinar-X (biru) dengan ligan hasil *redocking* (hijau)



Gambar V.4 Hasil visualisasi interaksi ligan alami dengan reseptor TNF-α

LAMPIRAN 7
(LANJUTAN)

Tabel V.1
Grid Box, *RMSD*, dan Nilai Energi Bebas Ligan Alami

Kode Reseptor	***Grid Box***	***RMSD* (Å)**	**Energi Bebas Ligan Alami**
1NSI	X : 9.756 Y : 64.46 Z : 15.994	1,817	-7,03
3EWJ	X : 48.607 Y : 30.91 Z : 43.381	0,681	-13,66

LAMPIRAN 8

HASIL PENAMBATAN MOLEKUL

Tabel V.2
Hasil Penambatan Molekul Ligan Alami dan Senyawa Uji pada Reseptor TNF-α

Ligan/Senyawa	Energi Bebas (Δ*G*) kkal/mol	KI (µM)	Jumlah Ikatan Hidrogen	Residu Asam Amino
Ligan Alami				
(1S,3R,6S)-4-oxo-6-{4-[(2-phenylquinolin-4-yl)methoxy]phenyl}-5-azaspirol[2.4]heptane-1-carboxylic acid	-13,66	9,76 x 10^{-5}	3	HIS B:415 LEU B:348 GLY B:349
Ligan Uji				
Geranin A	-8,65	0,453	2	TYR B:433 GLU B:406
Selligueain B	+80,64	-	5	GLY B:346 GLY B:349 GLU B:406 GLU B:398 ASN B:447
3'-deoxydryopteric acid	-8,02	1,32	6	PRO B:437 VAL B:434 VAL B: 440 TYR B:436 ILE B:438 GLU B:398
(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3]dioxocino[4,5-h]chromene-3,5,11,13,15-pentaol	-5,40	110,78	2	GLY B:349 PRO B:437

LAMPIRAN 8
(LANJUTAN)

Tabel V.2
Lanjutan

Ligan/Senyawa	Energi Bebas (ΔG) kkal/mol	KI (µM)	Jumlah Ikatan Hidrogen	Residu Asam Amino
Undecaacetyl epiafzelechin-(4β-8,2β-0-7)-epiafzelechin-(4β-8)-afzelechin	+598,81	-	1	THR B:347
Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	-10,83	0,011	7	ASN B:447 ILE B:438 TYR B:436 HIS B:405 GLU B:406 GLY B:349 THR B:347
(+)-afzelechin-O-β-4'-D-glucopyranoside	-10,38	0,025	5	VAL B:440 VAL B:434 PRO B:437 LEU B:348 GLY B:349
2-((2R,3R)-3,5,7-trihydroxy -2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis (4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d] naphtho[1,2-g][1,3]dioxocin-10-yl)chroman-4-yl)acetic acid	+52,34	-	7	GLY B:346 GLY B:349 GLU B:398 GLU B:406 PRO B:437 ASN B:447 VAL B:440

LAMPIRAN 8
(LANJUTAN)

Tabel V.2
Lanjutan

Ligan/Senyawa	**Energi Bebas (ΔG) kkal/mol**	**KI (μM)**	**Jumlah Ikatan Hidrogen**	**Residu Asam Amino**
Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteric acid methyl ester	+751,31	-	-	-
Selligueain A	+120,29	-	7	ASN B:447 ALA B:351 GLU B:406 GLY B:346 GLY B:349 PRO B:437 LEU B:401
(+)-afzelechin	-7,59	2,71	2	ILE B:438 PRO B:437

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(LANJUTAN)

Tabel V.3
Hasil Penambatan Molekul Ligan Alami dan Senyawa Uji pada Enzim iNOS

Ligan/Senyawa	Energi Bebas (Δ*G*) kcal/mol	KI (μM)	Jumlah Ikatan Hidrogen	Residu Asam Amino
Ligan Alami				
Arginine	-7,03	7,02	5	PRO A:350 ASP A: 382 ARG A:266 GLN A:263 GLU A:377
Ligan Uji				
Geranin A	**-7,79**	**1,95**	**2**	**ASP A:382** **ARG A:199**
Selligueain B	-2,38	17980	9	ILE A:201 PRO A:350 ARG A:381 ARG A:388 TYR A:373 TYR A:347 ASP A:382 TRP A:346 GLN A:263
3'-deoxydryopteric acid	**-7,40**	**3,77**	**4**	**TRP A:372** **PRO A:350** **PHE A:369** **ARG A:199**
(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3]dioxocino[4,5-h]chromene-3,5,11,13,15-pentaol	-6,59	14,80	2	ALA A:262 MET A:434

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Tabel V.3
Lanjutan

Ligan/Senyawa	**Energi Bebas (Δ*G*) kcal/mol**	**KI (µM)**	**Jumlah Ikatan Hidrogen**	**Residu Asam Amino**
Undecaacetyl epiafzelechin-(4β-8,2β-0-7)-epiafzelechin-(4β-8)-afzelechin	+569,52	-	4	MET A:374 TYR A:267 CYS A:200 ARG A:199
Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	-6,75	11,34	5	TRP A:372 CYS A:200 MET A:355 GLU A:377 GLY A:202
(+)-afzelechin-O-β-4'-D-glucopyranoside	**-9,20**	**0,179**	**9**	**GLU A:377** **ARG A:199** **ILE A:201** **TRP A:372** **TYR A:373** **TYR A:347** **GLN A:263** **ARG A:388** **ASP A:382**
2-((2R,3R)-3,5,7-trihydroxy -2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis (4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d] naphtho[1,2-g][1,3]dioxocin-10-yl)chroman-4-yl)acetic acid	-0,25	656120	7	PRO A:350 ILE A:201 TYR A:347 TYR A:373 ASP A:382 ARG A:388 GLN A:263

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(LANJUTAN)

Tabel V.3
Lanjutan

Ligan/Senyawa	**Energi Bebas (ΔG) kcal/mol**	**KI (µM)**	**Jumlah Ikatan Hidrogen**	**Residu Asam Amino**
Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteric acid methyl ester	+255,66	-	3	ASN A:283 ARG A:388 CYS A:200
Selligueain A	+11,47	-	5	MET A:434 PRO A:350 ALA A:262 ARG A:388 GLU A:377
(+)-afzelechin	**-7,28**	**4,62**	**4**	**ARG A:199** **TRP A:372** **PRO A:350** **PHE A:369**

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HASIL PENGUJIAN *LIPINSKI'S RULE OF FIVE*

Tabel V.4

Prediksi *Drug Likeness* Senyawa Akar Pakis Tangkur (*Polypodium feei* METT) Berdasarkan Aturan *Lipinski's Rule of Five*

Senyawa Uji	Donor Ikatan Hidrogen	Akseptor Ikatan Hidrogen	Bobot Molekul	Log P	Memenuhi Syarat/ Tidak
(+)-afzelechin	4	5	274	1,84	Memenuhi
Geranin A	7	10	544	3,38	Tidak memenuhi
Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	9	14	592	-1,48	Tidak memenuhi
3'-deoxydryopteric acid	5	7	332	1,86	Memenuhi
(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3]dioxocino[4,5-H]chromene-3,5,11,13,15-pentaol	7	10	652	5,67	Tidak memenuhi
Selligueain A	11	15	816	3,98	Tidak memenuhi
Selligueain B	11	16	886	5,44	Tidak memenuhi
Undecaacetyl epiafzelechin-(4β-8,2β-0-7)-epiafzelechin-(4β-8)-afzelechin	0	25	1276	8,80	Tidak memenuhi

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(LANJUTAN)

Tabel V.4
Lanjutan

Senyawa Uji	**Donor Ikatan Hidrogen**	**Akseptor Ikatan Hidrogen**	**Bobot Molekul**	**Log P**	**Memenuhi Syarat/ Tidak**
(+)-afzelechin-O-β-4'-D-glucopyranoside	7	10	436	-0,69	Tidak memenuhi
2-((2R,3R)-3,5,7-trihydroxy -2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis (4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d] naphtho[1,2-g][1,3]dioxocin-10-yl)chroman-4-yl)acetic acid	12	16	872	5,35	Tidak memenuhi
Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteric acid methyl ester	0	27	1348	8,91	Tidak memenuhi

Donor ikatan hidrogen : Tidak lebih dari 5

Akseptor ikatan hidrogen : Tidak lebih dari 10

Bobot molekul : Tidak lebih dari 500 g/mol

Log P : Tidak lebih dari 5

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HASIL PENGUJIAN *Pre-ADME*

Tabel V.5
Hasil Prediksi Profil Absorpsi dan Distribusi Senyawa Akar Pakis Tangkur (*Polypodium feei* METT)

No	Senyawa/Ligan	Absorpsi		Distribusi
		Caco-2 cell (nm sec-1)	HIA (%)	Protein Plasma Binding (%)
1	**Geranin A**	11,80[b]	73,11[a]	100,0[a]
2	Selligueain B	16,81[b]	48,56[b]	100,0[a]
3	**3'-deoxydryopteric acid**	13,87[b]	69,23[b]	87,44[b]
4	(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3]dioxocino[4,5-H]chromene-3,5,11,13,15-pentaol	17,64[b]	86,09[a]	100,0[a]
5	Undecaacetyl epiafzelechin-(4β-8,2β-0-7)-epiafzelechin-(4β-8)-afzelechin	21,02[b]	98,04[a]	100,0[a]
6	Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	6,99[b]	5,43[c]	40,36[b]
7	**(+)-afzelechin-O-β-4'-D-glucopyranoside**	2,40[c]	31,42[b]	65,20[b]
8	Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteric acid methyl ester	21,00[b]	98,13[a]	100,0[a]
9	Selligueain A	15,40[b]	54,23[b]	100,0[a]

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(LANJUTAN)

Tabel V.5
Lanjutan

No	Senyawa/Ligan	Absorpsi		Distribusi
		Caco-2 cell (nm sec-1)	**HIA (%)**	**Protein Plasma Binding (%)**
10	**(+)-afzelechin**	1,29[c]	80,41[a]	100,0[a]
11	2-((2R,3R)-3,5,7-trihydroxy -2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis (4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d] naphtho[1,2-g][1,3]dioxocin-10-yl)chroman-4-yl)acetic acid	16,73[b]	38,26[b]	100,0[a]

Keterangan: HIA (*Human Intestinal Absorpsi*) = (a) 70-100% *well absorbed*
(b) 20-70 *moderately absorbed*
(c) 0-20% *poorly absorbed*

In Vitro CaCo-2 *cell permeability* = (a) > 70 *higher permeability*
(b) 4-70 *medium permeability*
(c) < 4 *low permeability*

Plasma Protein Binding = (a) > 90% *strongly bound*
(b) < 90% *weakly bound*

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HASIL PENGUJIAN TOKSISITAS

Tabel V.6

Hasil Prediksi Toksisitas Senyawa Akar Pakis Tangkur (*Polypodium feei* METT)

No	Senyawa/Ligan	Mutagenik	Karsinogenik
		Mutagen / Non Mutagen	**(-) / (+)**
1	**Geranin A**	Non-Mutagen	Negatif
2	Selligueain B	Non-Mutagen	Negatif
3	**3'-deoxydryopteric acid**	Mutagen	Negatif
4	(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14-methanobenzo[7,8][1,3] dioxocino[4,5-h]chromene-3,5,11,13,15-pentaol	Non-Mutagen	Negatif
5	Undecaacetyl epiafzelechin-(4β-8,2β-0-7)-epiafzelechin-(4β-8)-afzelechin	Mutagen	Positif
6	Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	Non-Mutagen	Negatif
7	**(+)-afzelechin-O-β-4'-D-glucopyranoside**	Mutagen	Negatif
8	Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteric acid methyl ester	Mutagen	Positif
9	Selligueain A	Non-Mutagen	Negatif
10	**(+)-afzelechin**	Mutagen	Negatif

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(LANJUTAN)

Tabel V.6
Lanjutan

No	Senyawa/Ligan	Mutagenik	Karsinogenik
		Mutagen / Non Mutagen	**(-) / (+)**
11	2-((2R,3R)-3,5,7-trihydroxy -2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis (4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d] naphtho[1,2-g][1,3]dioxocin-10-yl)chroman-4-yl)acetic acid	Non-Mutagen	Negatif