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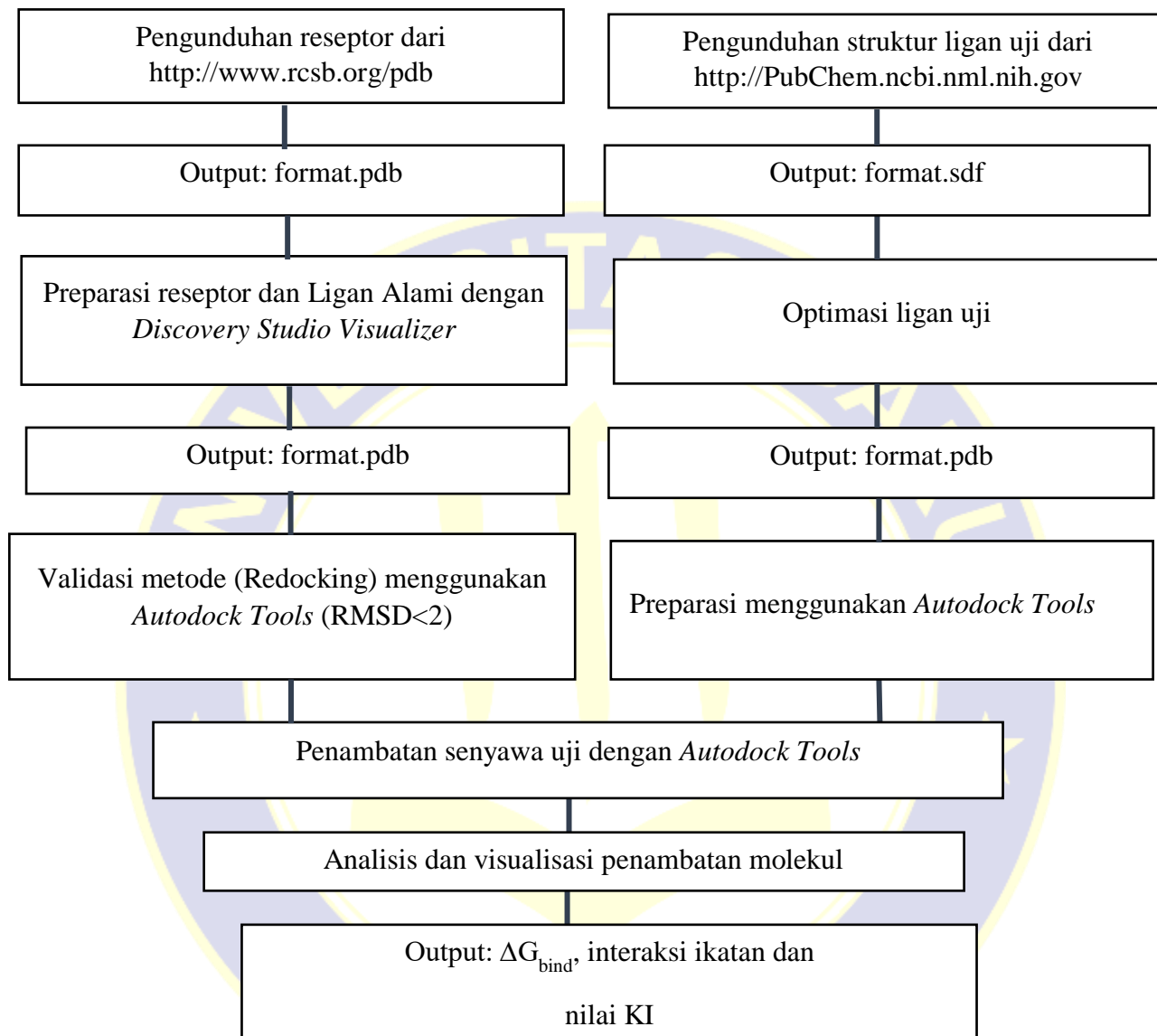
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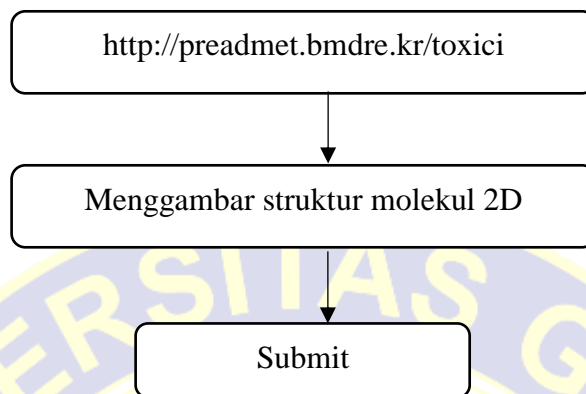


LAMPIRAN 1
ALUR PENELITIAN

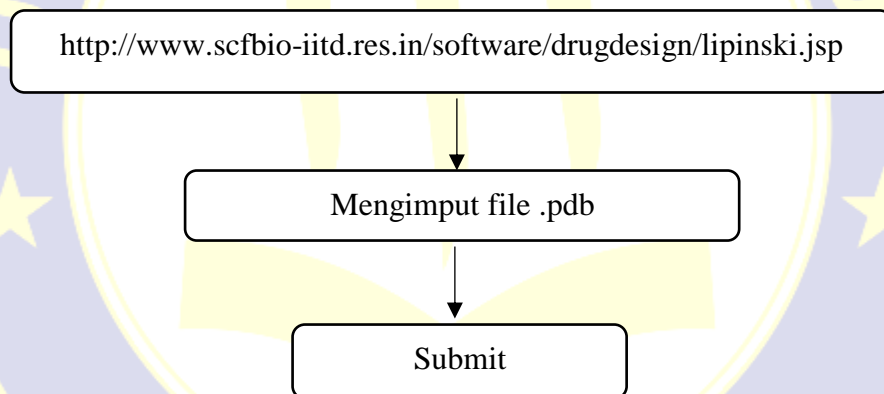


Gambar III.1 Alur penelitian

**LAMPIRAN 1
(LANJUTAN)**



Gambar III.2 Analisis *pre*-ADME dan toksisitas



Gambar III.3 Analisis *lipinski's rule of five*

LAMPIRAN 2
AKAR PAKIS TANGKUR

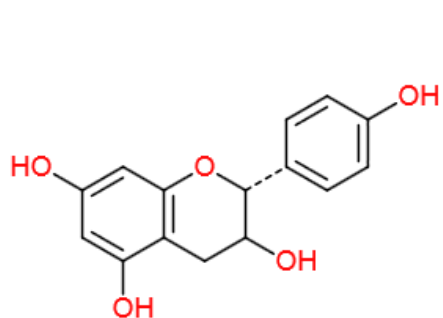


Gambar IV.1 Tanaman akar pakis tangkur

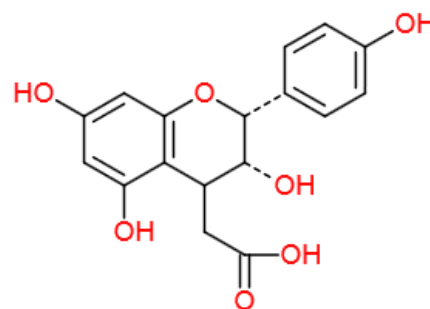


LAMPIRAN 3

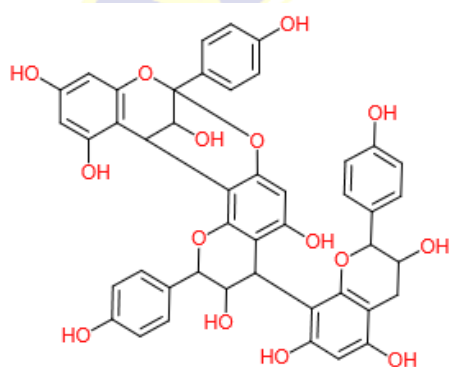
STRUKTUR 2D SENYAWA UJI



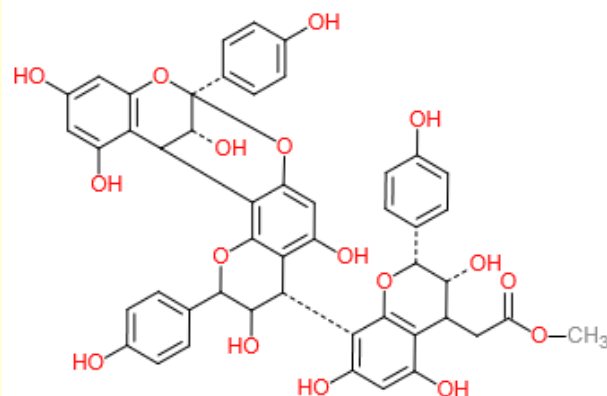
Gambar IV.2 (+)-afzelechin



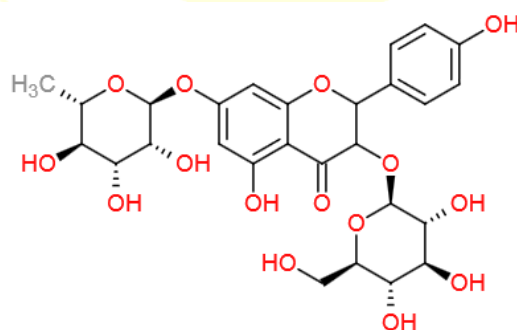
Gambar IV.3 3'-deoxydryopteretic acid



Gambar IV.4 Selligueain A



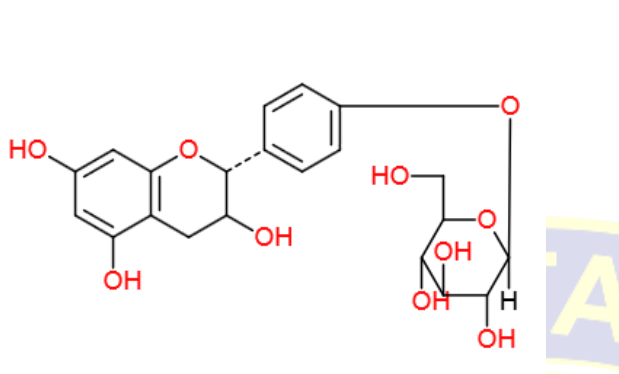
Gambar IV.5 Selligueain B



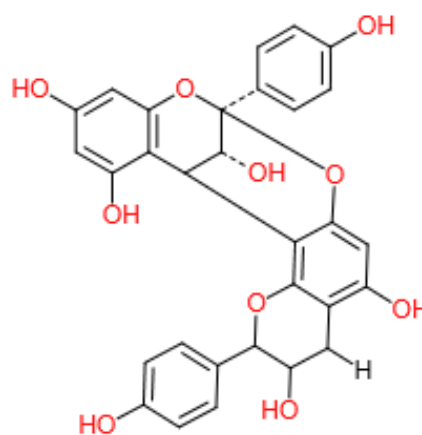
Gambar IV.6

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

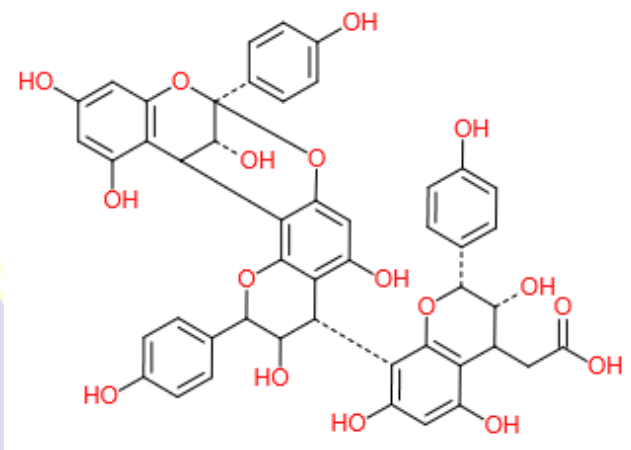
**LAMPIRAN 3
(LANJUTAN)**



Gambar IV.7 (+)-afzelechin-O- β -4'-D-glukopyranoside



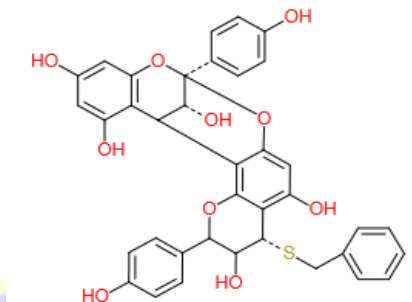
Gambar IV.8 Geranin A



Gambar IV.9

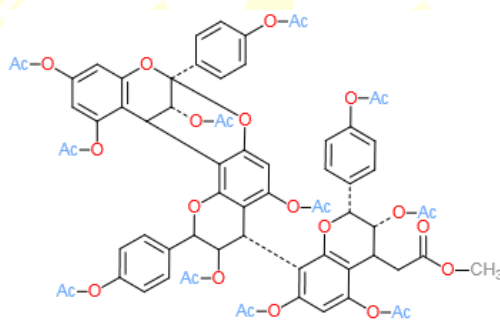
2-((2R,3R)-3,5,7-trihydroxy-2-(4-hydroxyphenyl)-8-((6R,10R,15R)-1,3,9,11,15-pentahydroxy-6,12-bis(4-hydroxyphenyl)-11,12,13,14-tetrahydro-10H-6,14-methanobenzo[d]naphtho[1,2-g][1,3]dioxocin-10-yl) chroman-4-yl)acetic acid

**LAMPIRAN 3
(LANJUTAN)**



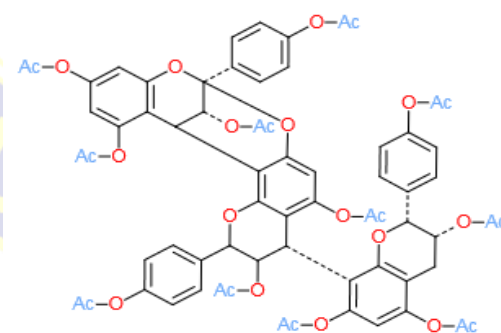
Gambar IV.10

(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



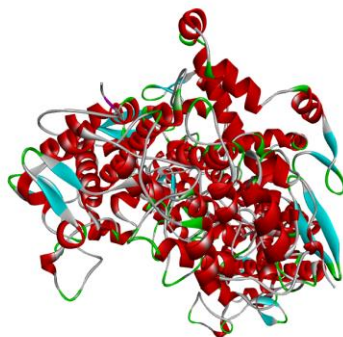
Gambar IV.11

Undecaacetate of epiafzelechin-(4 β →8,2 β →O→7)-epiafzelechin-(4 β →8)-3'deoxydryopteris acid methyl ester

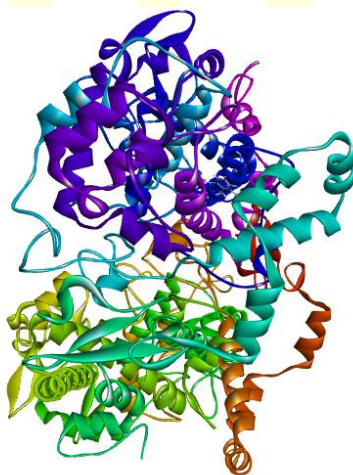


Gambar IV.12 Undeacetylepiafzelechin-(4 β →8,2 β →O→7)-epiafzelechin-(4 β →8)-afzelechin

LAMPIRAN 4
STRUKTUR 3D MAKROMOLEKUL

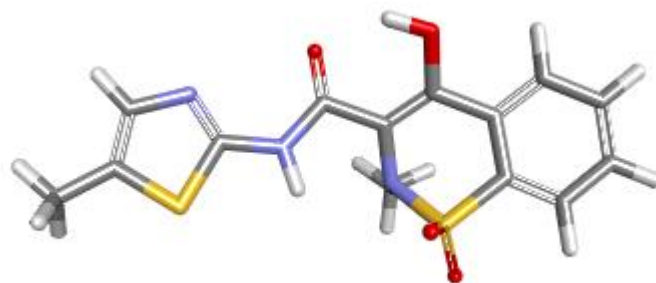


Gambar IV.13 Reseptor COX-1 dengan PDB ID 4O1Z

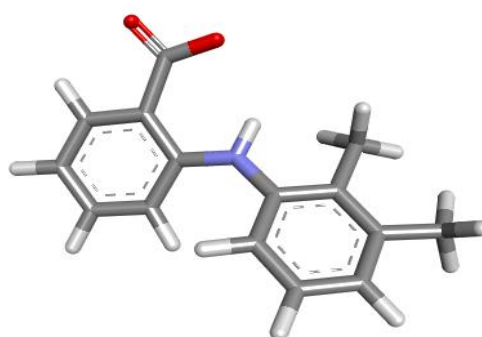


Gambar IV.14 Reseptor COX-2 dengan PDB ID 5IKR

LAMPIRAN 5
STRUKTUR 3D LIGAN ALAMI



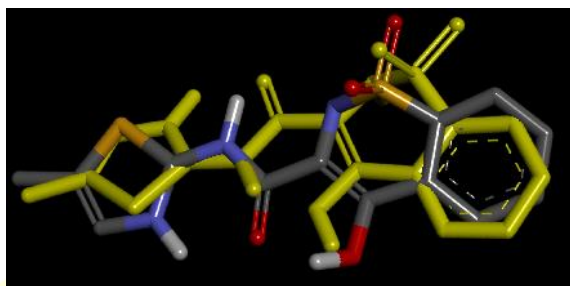
Gambar IV.15 Ligan alami reseptor COX-1 (*Meloxicam*)



Gambar IV.16 Ligan alami reseptor COX-2 (*Asam Mefenamat*)

LAMPIRAN 6

VALIDASI METODE

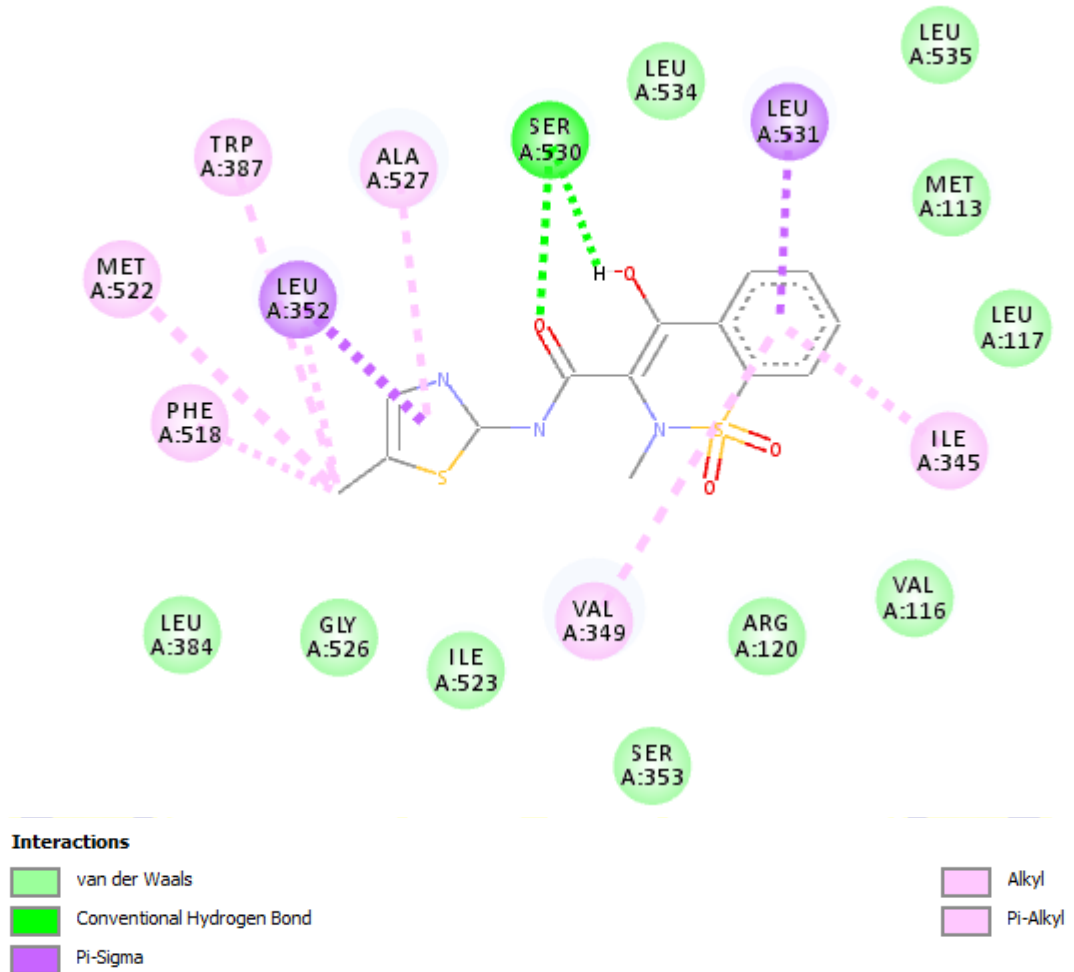


Gambar V.1 Hasil visualisasi tumpang tindih ligan alami dari reseptor COX-1 dari hasil kristalografi sinar-X (abu) dengan ligan hasil *redocking* (kuning)

Tabel V.1
Grid Box, RMSD, Nilai Energi Ikatan Ligan Alami

Kode Reseptor	Grid Box	RMSD (Å)	Nilai Energi Ikatan Ligan Alami
4O1Z	X: 251.485 Y: 107.183 Z: 4.561	1,262	-8,74

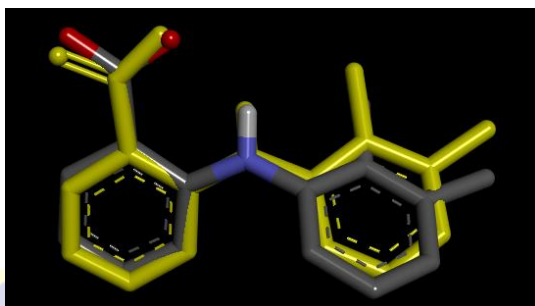
LAMPIRAN 6 (LANJUTAN)



Gambar V.2 Hasil visualisasi interaksi ligan alami dengan reseptor COX-1

UNIGA

**LAMPIRAN 6
(LANJUTAN)**

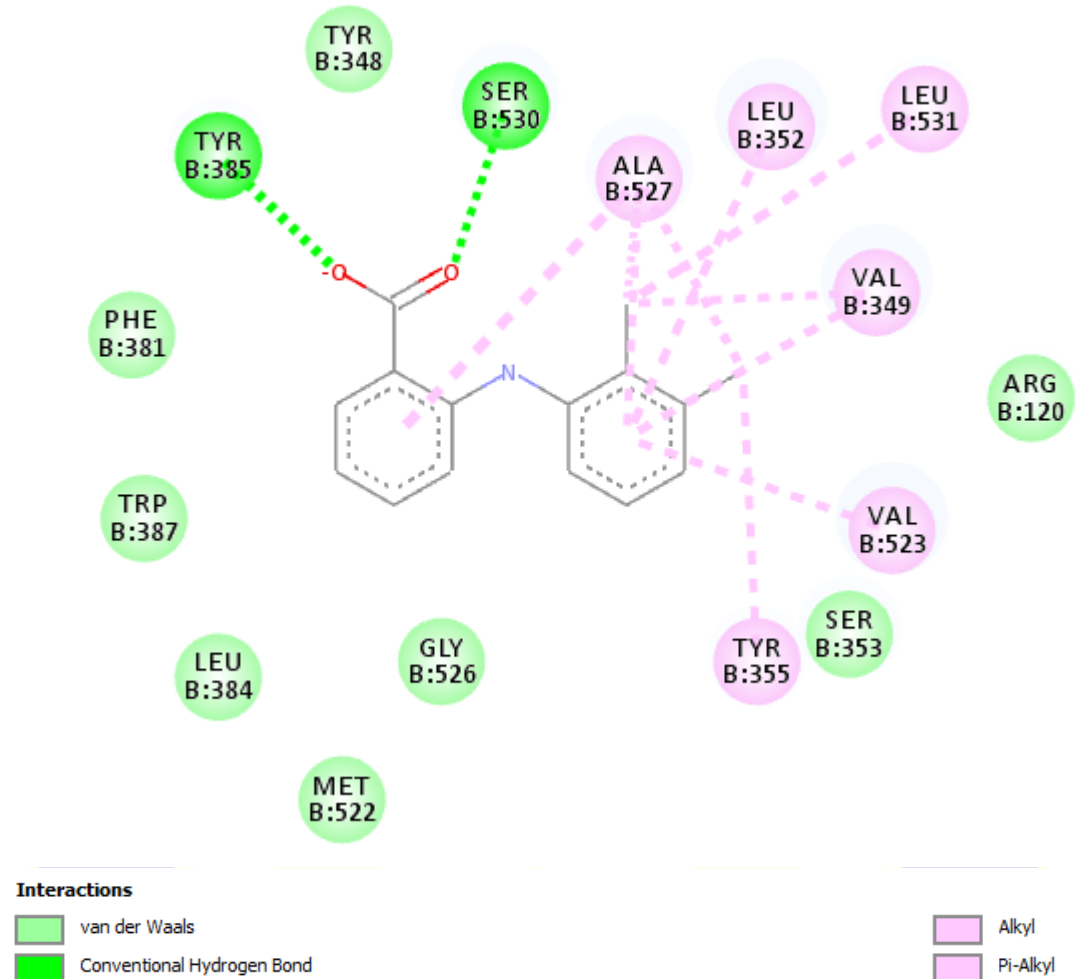


Gambar V.3 Hasil visualisasi tumpang tindih ligan alami dari reseptor COX-2 dari hasil kristalografi sinar-X (abu) dengan ligan hasil *redocking* (kuning)

Tabel V.2
Grid Box, RMSD, Nilai Energi Ikatan Ligan Alami

Kode Reseptor	Grid Box	RMSD (Å)	Nilai Energi Ikatan Ligan Alami
5IKR	X: 40.741 Y: 38.189 Z: 85.878	0,537	-7,18

LAMPIRAN 6 (LANJUTAN)



Gambar V.4 Hasil visualisasi interaksi ligan alami dengan reseptor COX-2

UNIGA

LAMPIRAN 7

HASIL PENAMBATAN MOLEKUL

Tabel V.3

Nilai Ikatan Energi dari Ligan Alami dan Senyawa Uji Pada Reseptor COX-1

No	Senyawa/Ligan	Energi Ikatan (ΔG) kcal/mol	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
1.	Ligan Alami (<i>Meloxicam</i>)	-8.74	1	SER A:530	391.95
2.	Geranin A	-8.99	6	ARG A:120 ALA A:527 VAL A:349 TYR A:385 SER A:530 ILE A:523	255.79
3.	(+)-afzelechin	-7.56	2	METT A:522, TYR A: 355	2.880
4.	(+)-afzelechin-O- β -4'D-glukopyranoside	-6.56	2	ILE A:345 TYR A:385	15.430
5.	3'-deoxydryopteris acid	-5.86	3	ARG A:120 VAL A:349 SER A 530	50.410
6.	<u>Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside</u>	-0.30	2	MET A:522 LYS:360	604.280.000
7.	(4S,8S,15R)-4-(benzylthio)-2,8-bis(4-hydroxyphenyl)-3,4-dihydro-2H,14H-8,14methanobenzo[7,8][1,3]dioxin o[4,5-h]chromene-3,5,11,13,15-pentaol	+8.75	2	ILE A:523 TYR A:355	-
8.	Selligueain A	+228.31	2	ILE A:345 VAL A:116	-
9.	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]dioxin-10-yl)chroman-4-yl)acetic acid.(7-9)	+370.39	-	-	-

**LAMPIRAN 7
(LANJUTAN)**

**Tabel V.3
Lanjutan**

No	Senyawa/Ligan	Energi Ikatan (ΔG) kcal/mol	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
10.	<u>Selligueain B</u>	+402.16	-	-	-
11.	Undecaacetyl <u>epiafzelechin</u> -(4 β -8,2 β -0-7)-epiafzelechin-(4 β -8)- <u>afzelechin</u>	+579.70	1	LYS A:360	-
12.	Undeca acetate of epiafzelechin-(4 β →8, 2 β →O→7)-epiafzelechin-(4 β →8)-3'-deoxydryopteris acid methyl ester	+3.11e+00 3	1	SER A:530	-

**LAMPIRAN 7
(LANJUTAN)**

Tabel V.4
Nilai Ikatan Energi dari Ligan Alami dan Senyawa Uji Pada Reseptor COX-2

No	Senyawa/Ligan	Ikatan Energi (ΔG) kcal/mol	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
1.	Ligan Alami (Asam mefemanat)	-7.17	2	SER B:530 TYR B:385	5.570
2.	(+)-afzelechin	-7.91	6	SER B:530 PHE B:518 GLN B:192 HIS B: 90 SER B:353 TYR B:355	1.600
3.	3'-deoxydryopteris acid	-5.38	3	SER B:530 ARG B:120 MET B:522	112.920
4.	(+)-afzelechin-O- β -4'D-glucopyranoside	-5.00	1	SER B:530	217.870
5.	<u>Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside</u>	-3.20	2	TYR B:355 LEU B:531	4.500.000
6.	Geranin A	+0.10	1	TYR B:355	-
7.	(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	+14.77	2	SER B:352 GLY B:526	-
8.	<u>Selligeanin B</u>	+200.02	3	MET B:522 GLN B:192 VAL B:523	-
9.	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.(7-9)	+249.16	2	SER B:530 VAL B:344	-

**LAMPIRAN 7
(LANJUTAN)**

**Tabel V.4
Lanjutan**

No	Senyawa/Ligan	Ikatana Energi (ΔG) kcal/mol	Jumlah Ikatan Hidrogen	Residu Asam Amino	KI (nM)
10.	Selligueain A	+314.24	-	-	-
11.	Undeca acetate of epiafzelechin-(4 β →8, 2 β →O→7)-epiafzelechin-(4 β →8)-3'-deoxydryopteris acid methyl ester	+1.59e+003	1	VAL B:525	-
12.	Undecaacetyl epiafzelechin -(4 β -8,2 β -0-7)-epiafzelechin-(4 β -8)-afzelechin	+3.29e+003	1	HIS B:90	-

LAMPIRAN 8

PREDIKSI DRUG LIKENESS BERDASARKAN ATURAN *LIPINSKI'S**RULE OF FIVE*

Tabel V.5

Sifat Fisiko kimia Senyawa yang Terkandung Didalam Akar Pakis Tangkur
Berdasarkan Aturan *Lipinski's Rule of Five*

Senyawa Uji	Donor Ikatan Hidrogen	Akseptor Ikatan Hidrogen	Bobot Molekul (Dalton)	LogP	Memenuhi Syarat/Tidak
(+)-Afzelechin	4	5	274	1,84	Memenuhi
Geranin A	7	10	544	3,38	Tidak memenuhi
3'-deoxydryopteris acid	5	7	332	1,86	Memenuhi
<u>Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside</u>	9	14	592	-1,48	Tidak 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
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.(7-9)	12	16	872	5,35	Tidak memenuhi

**LAMPIRAN 8
(LANJUTAN)**

**Tabel V.5
Lanjutan**

Senyawa Uji	Donor Ikatan Hidrogen	Akseptor Ikatan Hidrogen	Bobot Molekul (Dalton)	LogP	Memenuhi Syarat/Tidak
Selligueain A	11	15	816	3,98	Tidak memenuhi
Selligueain B	11	16	886	5,44	Tidak memenuhi
(+)-afzelechin-O- β -4'D-glukopyranoside	7	10	436	-0,69	Tidak memenuhi
Undeca acetate of epiafzelechin-(4 β →8, 2 β →O→7)-epiafzelechin-(4 β →8)-3'-deoxydryopteris acid methyl ester	0	27	1348	8,91	Tidak memenuhi
Undecaacetyl epiafzelechin-(4 β -8,2 β -0-7)-epiafzelechin-(4 β -8)-afzelechin	0	25	1276	8,80	Tidak memenuhi

Keterangan: Berat Molekul tidak lebih dari 500 Dalton

Donor ikatan hidrogen tidak lebih dari 5

Akseptor ikatan hidrogen tidak lebih dari 10

Log P tidak lebih dari 5

LAMPIRAN 9

HASIL PENGUJIAN PreADME

Tabel V.6
Uji PreADME (Absorpsi dan Distribusi)

No	Senyawa/Ligan	Absorpsi		Distribusi
		Caco-2 cell (nm sec-1)	HIA (%)	Protein Plasma Binding (%)
1	(+)-Afzelechin	1,29	80,41	100,0
2	Geranin A	11,80	73,11	100,0
3	3'-deoxydryopteris acid	13,87	69,23	87,44
4	(+)-afzelechin-O-β-4'D-glukopyranoside	2,40	31,42	65,20
5	Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	6,99	5,43	40,36
6	(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	86,09	100,0
7	<u>Selliguaein B</u>	16,81	48,56	100,0
8	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.(7-9)	16,73	38,26	100,0
9	Selliguaein A	15,40	54,23	100,0
10	Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteris acid methyl ester	21,00	98,13	100,0

**LAMPIRAN 9
(LANJUTAN)**

**Tabel V.6
Lanjutan**

No	Senyawa/Ligan	Absorpsi		Distribusi
		Caco-2 cell (nm sec-1)	HIA (%)	Protein Plasma Binding (%)
11	Undecaacetyl epiafzelechin-(4 β -8,2 β -0-7)-epiafzelechin-(4 β -8)-afzelechin	21,02	98,04	100,0

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

In Vitro CaCo-2 cell permeability = > 70 *higher permeability*
 4-70 *medium permeability*
 < 4 *low permeability*

Plasma Protein Binding = > 90% *strongly bound*
 < 90% *weakly bound*

LAMPIRAN 10

UJI TOKSISITAS

Tabel V.7
Uji Toksisitas

No	Senyawa/Ligan	Ames Test	Karsinogenik
		Mutagen / Non-Mutagen	(-) / (+)
1	(+)-Afzelechin	Mutagen	(-)
2	Geranin A	Non-Mutagen	(-)
3	3'-deoxydryopteris acid	Mutagen	(-)
4	(+)-afzelechin-O-β-4'D-glukopyranoside	Mutagen	(-)
5	<u>Kaempferol-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside</u>	Non-Mutagen	(-)
6	(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	(-)
7	<u>Selliguaein B</u>	Non-Mutagen	(-)
8	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.(7-9)	Non-Mutagen	(-)
9	Selliguaein A	Non-Mutagen	(-)
10	Undeca acetate of epiafzelechin-(4β→8, 2β→O→7)-epiafzelechin-(4β→8)-3'-deoxydryopteris acid methyl ester	Mutagen	(+)

LAMPIRAN 10
(LANJUTAN)

Tabel V.7
Lanjutan

No	Senyawa/Ligan	Ames Test	Karsinogenik
		Mutagen / Non- Mutagen	(-) / (+)
11	Undecaacetyl epiafzelechin -(4 β -8,2 β -0-7)-epiafzelechin-(4 β -8)-afzelechin	Mutagen	(+)

