LEMBAGA PENELITIAN DAN
PENGABDIAN KEPADA MASYARAKAT

INSTITUT TEKNOLOGI BANDUNG - 2014

QSAR and *In Silico* study of Curculigoside A Derivative Isolated from Rhizome of Congkok (*Curculigo orchioides*) as Anti-cancer Candidate

Daryono Hadi Tjahjono

Department of Pharmacochemistry
School of Pharmacy

Institut Teknologi Bandung

Introduction

Cancer is a disease caused by an abnormal growth of tissue due to loss of cell control mechanisms

a number of natural compounds have been reported to have anticancer activity, but their mechanism has not been well described

The interaction of ***Curculigoside A*** and ***its aglycone*** with related receptors were studied by molecular modeling

Method

The docking simulation were performed using seven different molecular targets involved in cell cycle, cell growth, and DNA replication, i.e., cyclin-dependent protein kinase 2 (CDK-2), cyclin-dependent protein kinase 6 (CDK-6), DNA topoisomerases I and II, B-cell lymphoma 2 (Bcl-2), vascular endothelial growth factor receptor 2 (VEGFR-2), and G-Quadruplexes of telomere

Determine the atomic and molecular variables (***descriptors***) which affect anticancer activity of curculigoside A derivatives by **QSAR**

The new designed curculigoside A derivatives which have better anti-cancer activity and more selective and safer than the lead compound will be subject as candidate for further investigation (for synthesis and *in vitro* study)

Objectives

The present study aims to obtain information about pharmacofore of curculigosida A and its derivatives which have a role in anti-cancer activity, and to analyze its interaction with related receptors. It is also proposed to obtain new curculigoside derivatives which have high activity and low toxicity, and feasible to be synthesized.

Research Method

QSAR STUDY

Molecular Modelling
- *Hyperchem v8.0*

Optimization Geometry (*Ab initio*)
- *Hyperchem V8.0*

Descriptors calculation
- *HyperChem v8.0, Molecular Operating Environment (MOE 2009.10)*

Analysis of QSAR equation
- *SPSS Statistics 21.0*

Validation of QSAR equation
- *SPSS Statistics 21.0, Microsoft Excel*

Modification of Curculigoside A

Molecular Modelling

- *Hyperchem V8.0*

Geometri Optimization

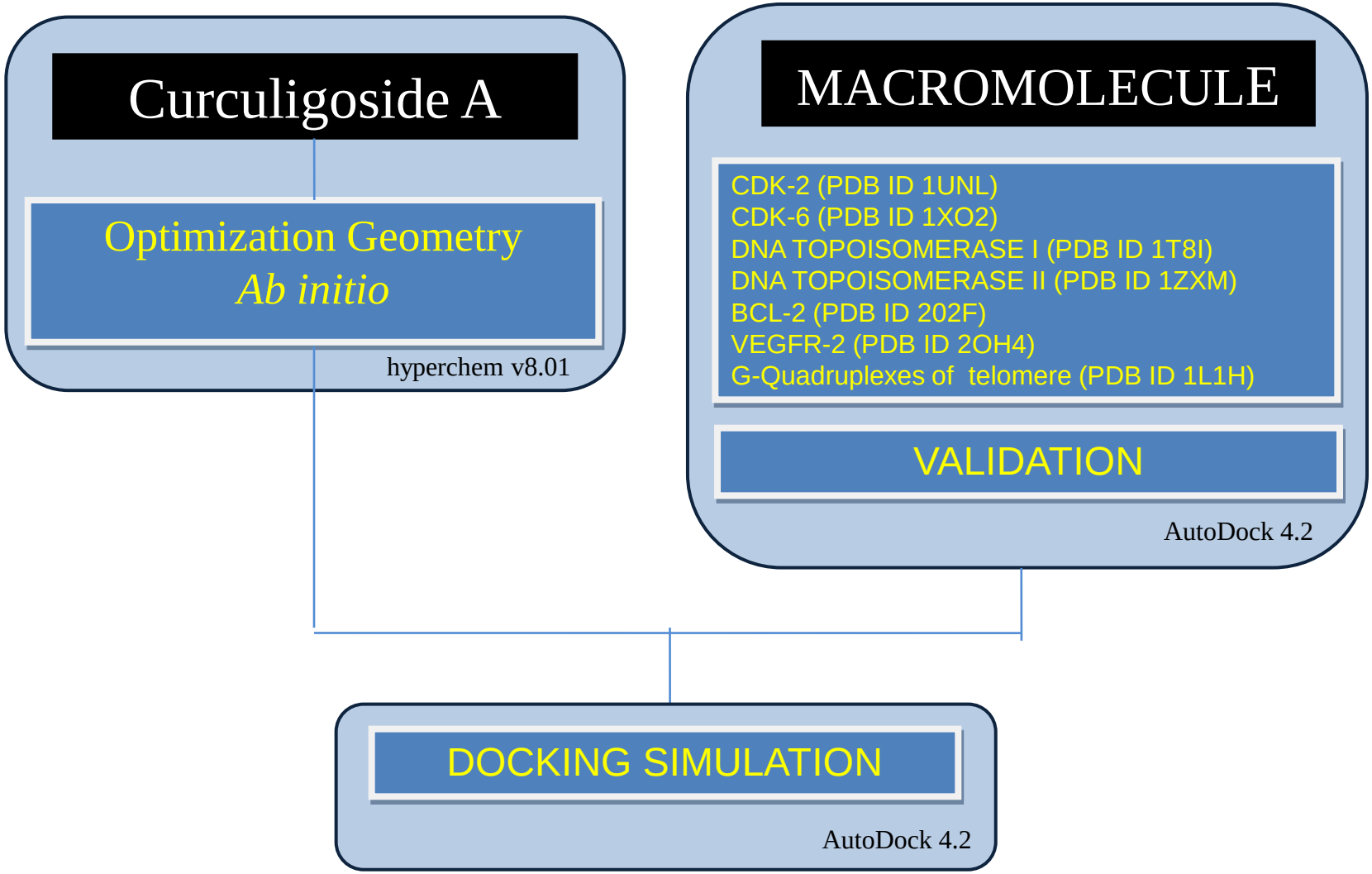
- *Hyperchem V8.0*

Descriptors calculation

HyperChem v8.0, Molecular Operating Environment (MOE 2009.10)

Prediction of IC_{50}

- *Microsoft Excel*


Curculigoside A
Optimization Geometry
Ab initio
hyperchem v8.01
MACROMOLECULE
CDK-2 (PDB ID 1UNL)
CDK-6 (PDB ID 1XO2)
DNA TOPOISOMERASE I (PDB ID 1T8I)
DNA TOPOISOMERASE II (PDB ID 1ZXM)
BCL-2 (PDB ID 202F)
VEGFR-2 (PDB ID 2OH4)
G-Quadruplexes of telomere (PDB ID 1L1H)
VALIDATION
AutoDock 4.2
DOCKING SIMULATION
AutoDock 4.2

RESULT AND DISCUSSION

Tabel 1: Parameters of binding interaction of the natural ligand with their receptor

No	RECEPTORS	PDB ID	LIGAND	RMSD	ΔG (kcal/mol)	Ki (M)
1	CDK-2	2A4L	Roscovitine	1.364	-7.37	3.98×10^{-6}
2	CDK-6	1XO2	Fisetin	0.954	-10.05	4.32×10^{-8}
3	VEGFR-2	2OH4	GIG	0.679	-12.4	8.09×10^{-10}
4	BCL-2	202F	LIO	0.821	-11.09	7.43×10^{-9}
5	Topoisomerase I	1T8I	EHD	0.806	-8.56	5.27×10^{-7}
6	Topoisomerase II	1ZXM	ANP	1.687	-11.63	3.00×10^{-9}
7	G-Quadruplexes of telomere	1L1H	PYN	1.615	-11.82	2.18×10^{-9}

Table 2: Binding energies and inhibition constant of Curculigoside A and tts aglycone to some receptors

		Curculigoside A		Aglycone	
No	Receptors	Binding energy (kcal/mol)	Ki (μM)	Binding energy (kcal/mol)	Ki (μM)
1	CDK-2	-7.04	6.86	-6.62	14.01
2	CDK-6	-8.09	1.18	-7.37	3.95
3	BCl-2	-5.04	201.12	-6.64	13.51
4	VEGFR	-7.00	7.43	-6.84	9.76
5	Topoisomerase I	-6.55	15.88	-6.30	23.95
6	Topoisomerase II	-7.23	4.99	-6.68	12.71
7	G-Quadruplexes of Telomere	-6.93	8.38	-7.69	2.31

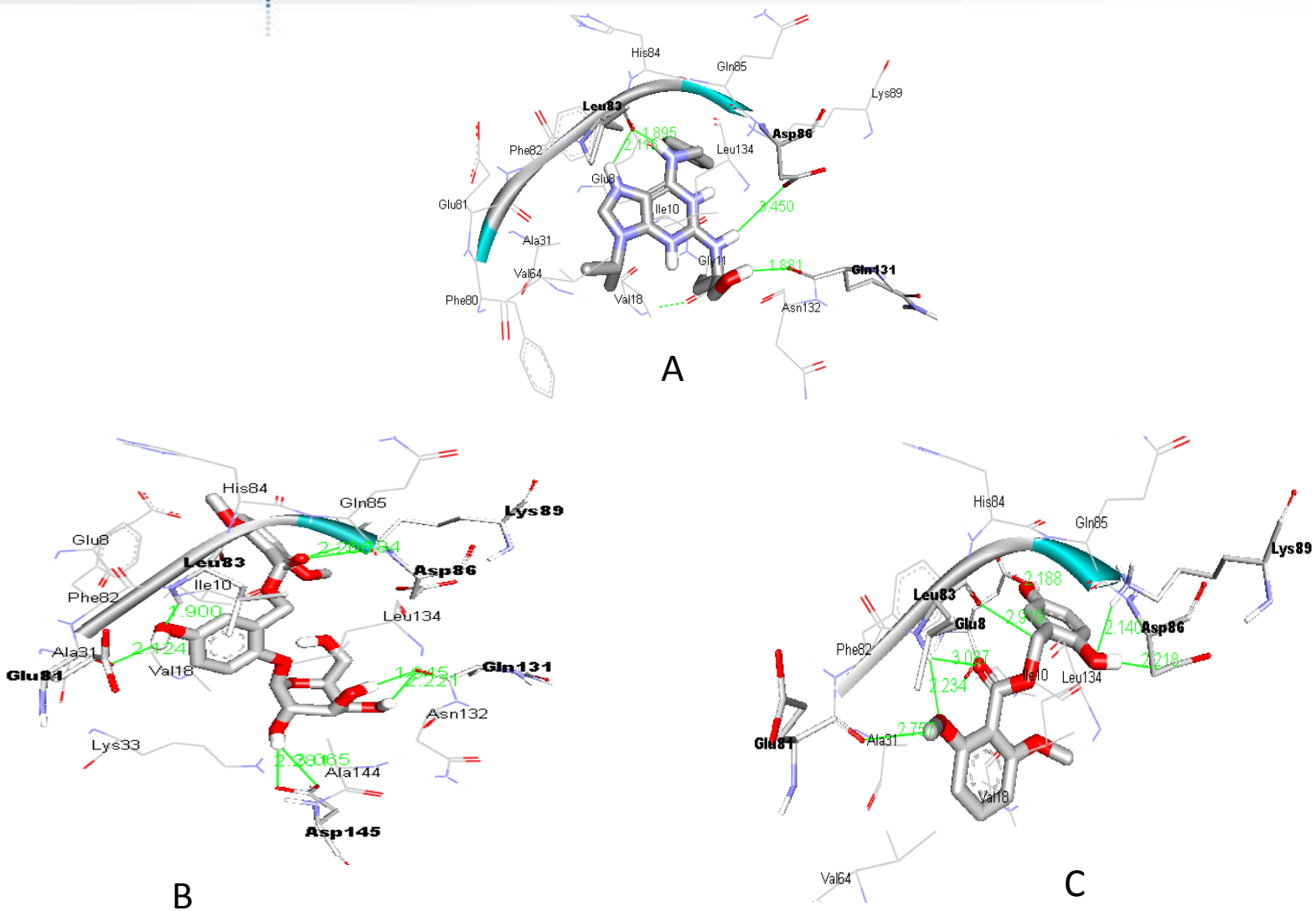
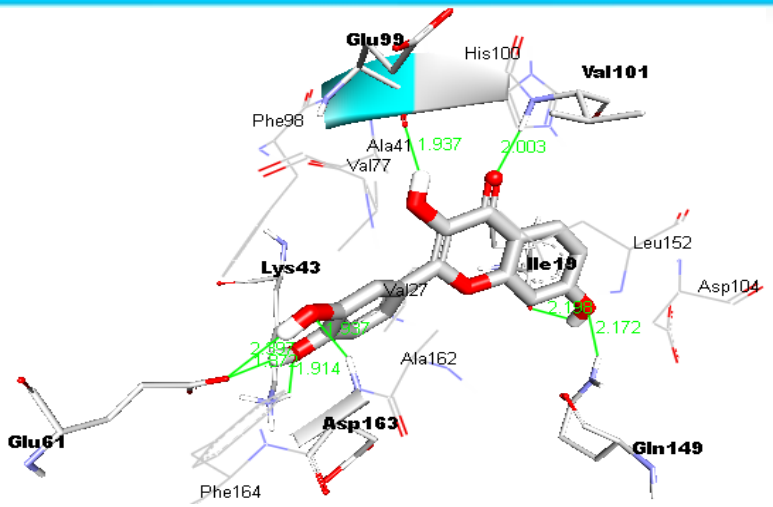
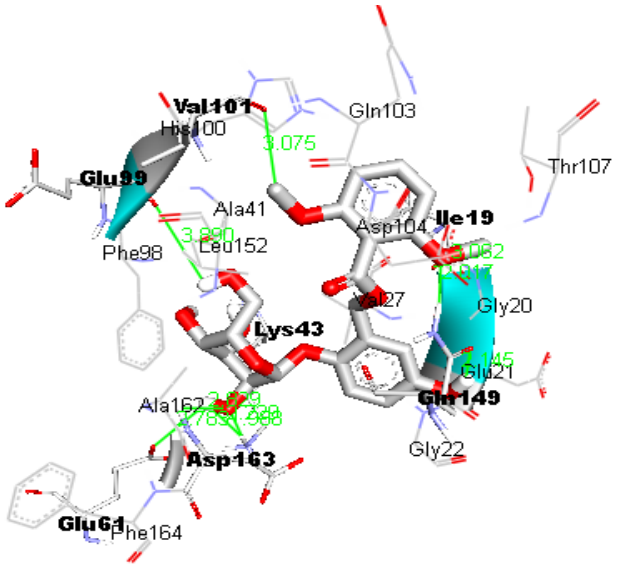


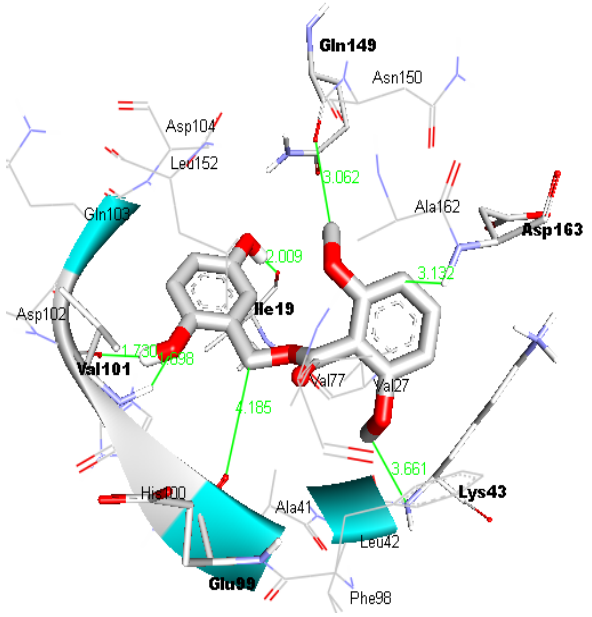
Fig.1: Binding interaction between CDK-2 with (A) Roscovitine; (B) Curculigoside A; (C) Aglycone of cuculigoside A



A



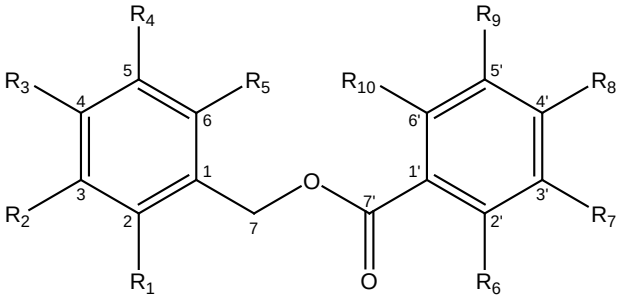
B



C

Fig.2: Docking position of CDK-6 with the ligands (A) Fisetin; (B) Curculigoside A; (A) Aglycone of cuculigoside A

Tabel 3. IC_{50} prediction of the curculigosid A derivatives



No	Senyawa	R1	R2	R3	R4	R6	R7	R8	R9	R10	IC_{50}Prediksi (µg/mL)
1	1	OH	H	H	OH	OCH_3	H	H	H	OCH_3	0.4465
2	2	H	OH	H	OH	OCH_3	H	H	H	OCH_3	0.5864
3*	**3**	**H**	**OH**	**H**	**OH**	**H**	**OH**	**H**	**OH**	**H**	**0.3529**
4	4	OH	H	H	OH	H	OH	H	OH	H	0.4650
5	5	OH	H	H	OH	OCH_3	H	Cl	H	OCH_3	0.06710
6	6	OH	H	Cl	OH	OCH_3	H	Cl	H	OCH_3	0.02590
7	7	OH	H	Cl	OH	OCH_3	H	H	H	OCH_3	0.1594
8	8	OH	Cl	Cl	OH	OCH_3	H	Cl	H	OCH_3	0.0062
9	9	OH	H	Cl	OH	OCH_3	Cl	Cl	H	OCH_3	0.0021
10	10	OH	H	Cl	OH	OCH_3	H	Cl	Cl	OCH_3	0.0023
11	11	OH	Cl	Cl	OH	OCH_3	H	H	H	OCH_3	0.0335
12	12	OH	H	H	OH	OCH_3	Cl	Cl	H	OCH_3	0.0066
13	13	OH	H	H	OH	OCH_3	H	Cl	Cl	OCH_3	0.0072
14	14	OH	Cl	H	OH	OCH_3	H	Cl	H	OCH_3	0.0197
15	15	OH	CF_3	Cl	OH	OCH_3	H	H	H	OCH_3	2.9638E-06
16	16	OH	H	H	OH	OCH_3	CF_3	Cl	H	OCH_3	1.2504E-06
17	17	OH	CF_3	H	OH	OCH_3	H	Cl	H	OCH_3	2.8525E-06
18	18	OH	H	Cl	OH	OCH_3	CF_3	H	H	OCH_3	3.4757E-06
19	19	OH	CF_3	Cl	OH	OCH_3	H	Cl	H	OCH_3	8.3217E-07
20	20	OH	H	Cl	OH	OCH_3	CF_3	Cl	H	OCH_3	4.085E-07
21	21	OH	CF_3	NO_2	OH	OCH_3	H	H	H	OCH_3	2.6178E-09
22	22	OH	H	H	OH	OCH_3	CF_3	NO_2	H	OCH_3	1.8991E-09
23	23	OH	H	Cl	OH	OCH_3	CF_3	NO_2	H	OCH_3	7.3778E-10
24	24	OH	CF_3	NO_2	OH	OCH_3	H	Cl	H	OCH_3	7.3671E-10
25*	**25**	**OH**	**H**	**NO_2**	**OH**	**OCH_3**	**CF_3**	**NO_2**	**H**	**OCH_3**	**2.4459E-11**
26	26	OH	H	NO_2	OH	H	H	NO_2	H	H	0.0003
27	27	H	OH	NO_2	OH	H	OH	NO_2	OH	H	4.2383E-08
28	28	OH	H	H	OH	H	H	NO_2	H	H	0.0061
29	29	OH	H	H	OH	H	OH	NO_2	OH	H	0.0004
30	30	H	OH	H	OH	H	OH	NO_2	OH	H	0.1166

Conclusion

- *Curculigoside A* and its derivative can interact with the binding site of studied cancer receptors.
- Interaction of *curculigoside A* and its aglycone with CDK-2 and CDK-6 showed better binding interactions than those of other receptors as shown by their free binding energy of –7.04 kcal/mol and –8.04 kcal/mol to curculigoside A and –6.62 kcla/mol and –7.37 kcal/mol to its aglycone, respectively.
- Upon interaction with CDK-2, *curculigoside A* forms hydrogen bonds to Glu81, Leu83, Asp86, Lys89, Gln131, Asp145 and CDK-6 with Ile19, Lys43, Glu61, Val101, Gln149, Asp163
- They have the same pattern of hydrogen bonds with the known binding ligands (*roscovitine* and *fisetin*) for CDK-2 and CDK-6, respectively.
- The best QSAR equation for anticancer activity of aglycone of curculigoside A derivatives defined by SPSS 19.0 is: $\log IC_{50}$ = – 4,805 (± 1,246) + 1.486 (± 0.593) + AM1_LUMO 0.726 (± 0.132) logS – 4.10^{-5} (± 23.10^{-5}) AM1_E + 23.10^{-5} (± 5.797.10-6) AM1_Eele + 2.2323 (± 0.327) mr, [AM1_LUMO = LUMO energy; logS = logarithm of solubility; AM1_E = total energy; AM1_Eele = electronic energy, and mr = molar refractivity].
- The modification of aglycone curculigoside A based on pharmacofore analysis and Topless scheme, suggested a number of new compounds to be synthesized, and the 3,5-dihydroxybenzyl-3,5-dihydroxybenzoate (compound **3**) and 2,5-dihydroxy-4-Nitrobenzyl-2,6-dimethoxy-4-nitro-3-(trifluoromethyl) benzoate (compound **25**) was predicted to have better anticancer activity than that of aglycone curculigosida A with IC_{50} (theoretical) of 0.35 and $2{,}45.10^{-11}$ µM, respectively.

References

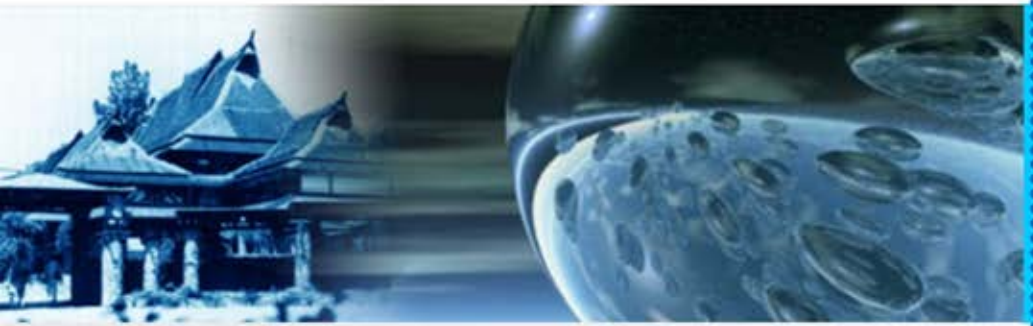
1. Boyle, P. and Levin, B., World Cancer Report. International Agency for Research on Cancer (WHO) 2008.
2. Dai Y, Grant S. Cyclin-dependent kinase inhibitors. *Curr Opin Pharmacol* 2003; **3**:362–370.
3. Huwe A, Mazitschek R, Giannis A. Small molecules as inhibitors of cyclin-dependent kinases. *Angew Chem Int Ed Engl* 2003; **42**: 2122–2138.
4. Wang, J.C. Recent studies of DNA topoisomerases. *Biochim. Biophys. Acta* 1987; **909**: 1-9
5. Vosberg, H.P. DNA topoisomerases: Enzymes that control DNA conformation. *Curr.* Top. *Microbiol. Immunol.* 1985; **114**: 19-102.
6. Alessi F, Quarta S, Savio M, Riva F, Rossi L, Stivala LA, Scovassi AI, Meijer L, Prosperi E. The cyclin-dependent kinase inhibitors olomoucine and roscovitine arrest human fibroblasts in G1 phase by specific inhibition of CDK2 kinase activity. *Exp Cell Res* 1998; **245**: 8–18
7. Meijer L, Borgne A, Mulner O. Biochemical and cellular effects of roscovitine, a potent and selective inhibitor of the cyclin-dependent kinases cdc2, cdk2 and cdk5. *Eur J Biochem* 1997; **243**: 527–536
8. Koff A, Giordano A, Desai D, Yamashita K, Harper JW, Elledge S, Nishimoto T, Morgan DO, Franza R, Roberts JM. Formation and activation of a cyclin E-Cdk2 complex during the G1 phase of the human cell cycle. *Science* 1992; **257**:1689-1694
9. Girard, F., Strausfeld, U., Fernandez, A. and Lamb, N.J.C. Cyclin A is required for the onset of DNA replication in mammalian fibroblasts. *Cell* 1991; **67**: 1169-1179.
10. Hinds P.W., Mittnacht S., Dulic V., Arnold A. Reed S. I., and Weinberg R. A.: Regulation of Retinoblastoma Protein Funktion by Ectopic Expression of Human Cyclins. *Cell* 1992; **70**: 993-1006.

Publications (Research Out put)

- Nursamsiar, Ida Musfiroh, Muchtaridi, Slamet Ibrahim, D.H. Tjahjono, "Interaction study of curculigoside A and its aglycone as cyclooxygenase inhibitors using computational modelling", *International Journal of Pharmacy and Pharmaceutical Sciences*, 2013, **5**, 702-705.
- Nursamsiar, Slamet Ibrahim S, Daryono H Tjahjono, *In silico* study of the interaction of curculigoside a from congkok (*Curculigo orchioides*) with various cancer receptors, *6th Asian Association of Schools of Pharmacy Conference* (AASP-6), 14-17 November 2013, Singapore.
- Hubungan Kuantitatif Struktur dan Aktifitas Senyawa Turunan Aglikon *Curculigosida A* sebagai Antikanker**,** Nursamsiar, Slamet Ibrahim, Daryono H Tjahjono (*manuscript submitted to Jurnal Farmasi Indonesia; in Indonesian*)

Acknowledgment

- **This research was supported by ASAHI GLASS FOUNDATION**



LEMBAGA PENELITIAN DAN
PENGABDIAN KEPADA MASYARAKAT

INSTITUT TEKNOLOGI BANDUNG

Terima Kasih

Hatur Nuhun

Thank You