Pharmaciana
Vol.8, No.2, Nov 2018, Page. 205-216
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v8i2.9508

In silico toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds by using Toxtree, pkCSM and preADMET

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Submitted: 05-04-2018 ***Reviewed: 05-06-2018*** ***Accepted: 02-11-2018***

ABSTRACT

The 1-phenyl-1-(quinazolin-4-yl) ethanol compounds are alkaloids of quinozoline class found in many *Hydrangeaceae* families. A survey revealed that most of the identified quinazoline derivatives have anticancer activity. Toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanols compounds were performed to obtain the best three compounds with high activity and the lowest toxicity. Toxicity prediction was conducted using Toxtree, pkCSM and PreADMET. The 2D structure of compounds were formed using ChemDraw. The decision tree approach was used in Toxtree application with endpoints including Cramer rules, Kroes TTC, carcinogenicity (genotoxic and non genotoxic) and in vitro mutagenicity. Graph based signature was used in pkCSM application with endpoints including mutagenicity, maximum daily dose, LD_{50} and hepatotoxicity. In PreADMET application, a method based on drugs similarity and ADMET properties was used with endpoints including mutagenicity, carcinogenicity to rat and mice. The results of data analysis showed that the best three anticancer compounds that have high activity and the lowest toxicity are compounds 14, 16 and 19.

Keywords: toxicity prediction, in silico, 1-phenyl-1-(quinazolin-4-yl) ethanol compounds, Toxtree, pkCSM, PreADMET

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INTRODUCTION

Cancer is a chronic disease that causes death number two in the world. In 2012, cancer is responsible for the deaths of around 8.2 million people worldwide. The cases of cancer can increase up to 50% in 2020 (Parameshwar *et al.*, 2016). The high number of deaths caused by cancer led to studies on anticancer compounds expand.

The 1-phenyl-1-(quinazolin-4-yl) ethanol compounds are alkaloids of quinazolin group which are widely present in *Hydrangeaceae* family (Ajani *et al.*, 2016). The most of quinazolin derivatives have been identified as having biological activities such as anticancer, antioxidant, antiviral, anticonvulsant, antiinflammatory, antituberculous, anti-HIV, analgesic, and antimicrobial (Faraj *et al.*, 2014). Kuroiwa *et al.* (2015) have conducted a Quantitative Structure and Activity Relationships (QSAR) study and in vitro testing of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds. The in vitro testing result of cell line A549 (lung) obtained a value of biological activity of IC_{50} which showed that 1-phenyl-1-(quinazolin-4-yl) ethanol compounds have potential as anticancer. The compounds have an anticancer mechanism through the binding of tubulin which binds to colchicine. It inhibits the binding of tubulin molecule and microtubule resulting polymerization in microtubules or failure of microtubule formation in cancer cells.

In silico toxicity prediction is a type of toxicity assessment using computational resources (algorithms, softwares and data) to organize, analyze, modeling, simulate, visualize, or predict chemical toxicity (Raies and Bajic, 2016). In silico toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds was performed using Toxtree, pkCSM, and preADMET.

Toxtree is designed to estimate toxic hazards using decision tree approach. Decision tree uses the method based on Structural Alerts (SA) and QSAR. The method has a role to designate the potential of toxic chemicals (Benigni *et al.*, 2008). The performance of Toxtree in the external validation dataset showed an accuracy of 70% and a sensitivity of 78.3% in the carcinogenicity test and an accuracy of 78% for the mutagenicity test (Valerio, 2009). Toxtree represents endpoints of different toxicities, i.e. Cramer rule, Kroes TTC, carcinogenicity (genotoxic and non genotoxic) and in vitro mutagenicity (Ames test).

PkCSM (Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures) is a method for predicting and optimizing pharmacokinetic properties and toxicity properties. It use graph-based signatures approach. pkCSM adapted the cut off scanning concept to develop a predictive model of ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) properties for drug development. The performance of pkCSM software in the external validation dataset showed an accuracy of 83.8% in the mutagenicity test. There are several endpoints of pkCSM i.e. LD_{50}, ames test, maximum daily dose, and hepatotoxic (Pires *et al*., 2015).

PreADMET (Prediction of ADME/Tox) developed a fast and reliable method to predict the similarity of drugs and ADMET properties. This application can calculate more than 900 molecular descriptors including constitutional, topological, electrostatic, physico-chemical and geometric descriptor to predict ADME (Absorption, Distribution, Metabolism, Excretion) properties. PreADMET collects databases containing ADME and toxicities data to train physiologically-based pharmacokinetics model tissues and toxicity predictions. PreADMET provided 62.5% accuracy and 52.2% sensitivity for carcinogenicity test (Zhang *et al.*, 2017). PreadMET predicts toxicity based on Ames mutagenity parameters. The actual value of the prediction is "positive" or "negative". The carcinogenicity is predicted based on the structure results which is constructed from NTP (National Toxicology Program) data and US FDA (US Food and Administration). It is the result of in vivo carcinogenicity test in rat for two years (Riju *et al.*, 2010).

Many of bioactive compounds have been shown anticancer activity but their utilization is limited due to their side effects and high toxic effects, that are very dangerous and life-threatening effect (Priyanto, 2015). Therefore, in silico toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds was performed before in vitro and in vivo testing to minimize the number of test compounds and test animals in the following tests.

MATERIALS AND METHODS

Materials

The softwares used in this research were ChemDraw 2016 (http: //scistore.cambridgesoft.com/) (License Code: 338-284099-4415), Openbabel GUI 2.4.1 (https://sourceforge.net), pkCSM (http://biosig.unimelb.edu.au/pkcsm), Toxtree version 2.6.6 (http: //toxtree.sourceforge. net /) and preADMET (http://preadmet.bmdrs.kr). The materials used in this research were the 2D structures and IC_{50} value of 44 compounds of 1-phenyl-1-(quinazolin-4-yl) ethanol which have been synthesized by Kuroiwa *et al.,* (2015). IC_{50} value of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds are presented in Table I.

Table I. IC_{50} of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds (Kuroiwa *et al.*, 2015)

Compound Number	Name of The Compounds	IC_{50} (µM)	Compound Number	Name of The Compounds	IC_{50} (µM)
1a	1-(4-methoxyphenyl)-1-(quinazolin-4-yl)ethan-1-ol	0.27	9	1-(2-chloroquinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	2.0
1b	1-(4-fluorophenyl)-1-(quinazolin-4-yl)ethan-1-ol	>25	14	1-(4-methoxyphenyl)-1-(2-methylquinazolin-4-yl)ethan-1-ol	0.053
1c	1-(4-chlorophenyl)-1-(quinazolin-4-yl)ethan-1-ol	>25	15	1-(2-cyclohexylquinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	0.1
1d	1-(quinazolin-4-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol	>25	16	1-(4-methoxyphenyl)-1-(2-(trichloromethyl)quinazolin-4-yl)ethan-1-ol	0.038
1f	1-(4-ethoxyphenyl)-1-(quinazolin-4-yl)ethan-1-ol	0.30	17	1-(2-chloroquinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	0.027
1g	1-(4-(tert-butoxy)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	>25	18	(R)-4-(1-hydroxy-1-(4-methoxyphenyl)ethyl)quinazolin-2(1H)-one	>25
1h	1-(quinazolin-4-yl)-1-(4-(trifluoromethoxy)phenyl)ethan-1-ol	>25	19	(R)-1-(4-methoxyphenyl)-1-(2-methoxyquinazolin-4-yl)ethanol	0.058
1i	1-(3-methoxyphenyl)-1-	>25	20	(R)-1-(2-ethoxyquinazolin-4-	0.34

Compound Number	Name of The Compounds	IC_{50} (µM)	Compound Number	Name of The Compounds	IC_{50} (µM)
	(quinazolin-4-yl)ethan-1-ol			yl)-1-(4-methoxyphenyl)ethanol	
1j	1-(3,4-bis(methoxymethoxy)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	20	21	(R)-1-(4-methoxyphenyl)-1-(2-propoxyquinazolin-4-yl)ethanol	1.2
1k	1-(3,4-dimethoxyphenyl)-1-(quinazolin-4-yl)ethan-1-ol	21	22	1-(2-(allyloxy)quinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	0.41
1l	1-(quinazolin-4-yl)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol	>25	23	(R)-1-(2-(cyclohexyloxy)quinazolin-4-yl)-1-(4-methoxyphenyl)ethanol	3.3
1m	1-(3-(benzyloxy)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	>25	24	(R)-1-(4-methoxyphenyl)-1-(2-methoxyquinazolin-4-yl)ethanol	0.067
1n	3-(1-hydroxy-1-(quinazolin-4-yl)ethyl)phenol	>25	25	(R)-1-(2-(dimethylamino)quinazolin-4-yl)-1-(4-methoxyphenyl)ethanol	0.21
1o	1-(4-(methylamino)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	4.1	26	(R)-1-(2-(cyclohexylamino)quinazolin-4-yl)-1-(4-methoxyphenyl)ethanol	2.7
1p	1-(4-(dimethylamino)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	1.3	27	(R)-1-(4-methoxyphenyl)-1-(2-(piperidin-1-yl)quinazolin-4-yl)ethanol	2.7
1q	1-(4-(methylthio)phenyl)-1-(quinazolin-4-yl)ethan-1-ol	0.34	28	(R)-1-(4-methoxyphenyl)-1-(2-(4-methylpiperazin-1-yl)quinazolin-4-yl)ethanol	19
4a	(4-methoxyphenyl)(quinazolin-4-yl)methanone	20	29	(R)-1-(4-methoxyphenyl)-1-(2-morpholinoquinazoli	0.17

Compound Number	Name of The Compounds	IC_{50} (µM)	Compound Number	Name of The Compounds	IC_{50} (µM)
				n-4-yl)ethanol	
4f	(4-ethoxyphenyl)(quinazolin-4-yl)methanone	>25	30	(R)-1-(2-(4-(4-fluorophenyl)piperazin-1-yl)quinazolin-4-yl)-1-(4-methoxyphenyl)ethanol	1.9
5	1-(4-methoxyphenyl)-1-(quinazolin-4-yl)propan-1-ol	1.8	31	(1R)-1-(4-methoxyphenyl)-1-(2-(thiophen-3-yl)quinazolin-4-yl)ethanol	0.035
6	(4-methoxyphenyl)(phenyl)(quinazolin-4-yl)methanol	9.8	32	(R)-1-(2-(4-chlorophenyl)quinazolin-4-yl)-1-(4-methoxyphenyl)ethanol	0.40
7	2,2,2-trifluoro-1-(4-methoxyphenyl)-1-(quinazolin-4-yl)ethan-1-ol	1.1	33	1-(2-(2-chlorophenyl)quinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	0.78
8	(4-methoxyphenyl)(quinazolin-4-yl)methanol	>25	34	1-(2-(3-chlorophenyl)quinazolin-4-yl)-1-(4-methoxyphenyl)ethan-1-ol	2.1

Methods

The 2D structures of 44 compounds of 1-phenyl-1-(quinazolin-4-yl) ethanol were prepared using ChemDraw 2016. The 1-phenyl-1-(quinazoline-4-yl) ethanol compounds were screened using pkCSM to find out whether the compounds conform the Lipinski's rule of Five. The unconform compounds maximum 2 endpoints of Lipinski's rule of Five were eliminated. The toxicity of screened 1-phenyl-1-(quinazolin-4-yl) ethanol compound were predicted using Toxtree, pkCSM and PreADMET. The endpoints selected in Toxtree were Cramer rule, Kroes TTC decision tree, carcinogenicity (genotox and non genotox) mutagenicity rule base by ISS, and in vitro mutagenicity (Ames test) alerts by ISS. Open Babel GUI is used in pkCSM to create a compound SMILE format. The selected endpoint in pkCSM were Ames Toxicity, Maximum Tolerated Dose, Rat Acute Oral Toxicity (LD_{50}) and hepatotoxicity. The selected endpoints in PreADMET were Ames Test and Rodent Carcinogenicity (Mice and Rat).

Data Analysis

The toxicity prediction results of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds were quantitative and qualitative data. Qualitative data were expressed in positive and negative statements. Then made in the form of scoring, where the positive toxic score was 1 and negative toxic scored was 2. The data analysis used the scoring model by summing all endpoints of Toxtree, pkCSM and PreADMET to obtain five compounds with the lowest toxicity effect (largest score). Then five of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds which have high activity based on in

vitro test of Kuroiwa *et al.* (2015) against cell line A549 (lung) were selected. The best compound is obtained through the selected scoring model by comparing any compounds having a low toxic effect and followed by the most amount of toxic negative endpoints. The next step for getting the three compounds that have the highest activity with the lowest toxicity was comparing the highest scores and the smallest IC_{50} values among the five compounds.

RESULTS AND DISCUSSION

Lipinski's rule of five calculations

The Lipinski's rule of five calculations were performed to determine the degree of absorption or permeability of compounds against lipid bilayers in the human body. The Lipinski rule is a parameter that demonstrates the oral bioavailability of a compound. Good bioavailability will satisfy the Lipinski rule where the maximum molecular weight of the compound is 500, the log P is not greater than 5, the hydrogen bond donor is less than 5, and hydrogen bond acceptor is less than 10 (Lipinski *et al.*, 2012). The results of Lipinski's rule of Five calculations using pkCSM are presented in Table II.

Table II. Results of Lipinski's Rule of Five calculation

Compound Number	Molecular Weight	Log P	Hydrogen Bonds Acceptor	Hydrogen Bonds Donor
1a	280.327	2.8942	4	1
1b	268.291	3.0247	3	1
1c	284.746	3.5390	3	1
1d	318.298	3.9044	3	1
1f	294.354	3.2843	4	1
1g	322.408	4.0629	4	1
1h	334.297	3.7842	4	1
1i	280.327	2.8942	4	1
1j	370.405	2.8510	7	1
1k	310.353	2.9028	5	1
1l	342.351	1.8413	7	2
1m	356.425	4.4646	4	1
1n	266.300	2.5912	4	2
1o	295.386	3.5634	4	2
1p	293.370	2.9516	4	1
1q	296.395	3.6075	4	1
4a	264.284	2.8694	4	0
4f	278.311	3.2595	4	0
5	294.354	3.2843	4	1
6	294.354	3.2843	4	1
7	334.297	3.4366	4	1
8	266.300	2.7201	4	1
9	310.353	2.9028	5	1

Compound Number	Molecular Weight	Log P	Hydrogen Bonds Acceptor	Hydrogen Bonds Donor
14	294.354	3.2026	4	1
15	362.473	4.9419	4	1
16	397.689	4.7209	4	1
17	314.772	3.5476	4	1
18	296.326	2.1875	4	2
19	310.353	2.9028	5	1
20	324.380	3.2929	5	1
21	338.407	3.6830	5	1
22	352.434	4.0951	5	1
23	378.472	4.6057	5	1
24	326.421	3.6161	5	1
25	323.396	2.9602	5	1
26	377.488	4.6388	5	2
27	363.461	3.8845	5	1
28	378.476	2.6460	6	1
29	365.433	2.7308	6	1
30	458.537	4.3599	6	1
31	362.454	4.6227	5	1
32	390.870	5.2146	4	1
33	390.870	5.2146	4	1
34	390.870	5.2146	4	1

Based on results of Lipinski's Rule of Five calculations, all of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds conform Lipinski's rule. All compounds were predicted having good absorptivity for an oral medication (Wulandari and Kristin, 2010). Based on research conducted by Veber *et al*. (2002) concluded that a compound with lower molecular weight, log P, hydrogen bond donor, and hydrogen bond acceptor has the higher bioavailability.

Toxicity predictions

The results of toxicity prediction by Toxtree, pkCSM and PreADMET are presented in Table III.

Table III. Results of toxicity prediction by Toxtree, pkCSM and PreADMET

Compound Number	A	B	C	D	E	F	G	H	I	J	K	L	Scoring
1a	1	1	2	2	2	2	1.273	2.079	2	1	2	2	20.352
1b	1	1	2	1	2	1	1.330	2.016	2	1	1	2	17.346
1c	1	1	2	2	2	1	1.225	1.973	2	2	1	2	19.198
1d	1	1	2	2	2	2	1.072	2.223	1	2	1	2	19.295
1f	1	1	2	2	2	1	2.323	1.870	2	1	2	2	20.193
1g	1	1	2	2	2	2	-1.119	2.007	1	2	2	2	17.888

Compound Number	A	B	C	D	E	F	G	H	I	J	K	L	Scoring
1h	1	1	2	2	2	2	-1.127	2.295	2	1	2	2	18.168
1i	1	1	2	2	2	2	1.849	1.834	2	1	1	2	19.683
1j	1	1	2	2	2	2	3.034	2.204	2	2	2	2	23.238
1k	1	1	2	2	2	2	1.766	2.269	1	2	2	2	21.035
1l	1	1	2	2	2	2	2.265	1.906	1	2	2	2	21.171
1m	1	1	2	2	2	1	2.265	2.466	1	1	1	2	18.731
1n	1	1	2	2	2	2	1.442	2.147	2	1	1	2	19.589
1o	1	2	1	2	1	2	1.528	2.367	2	2	1	2	19.895
1p	1	2	1	2	1	2	1.442	2.147	2	2	1	2	19.589
1q	1	1	2	2	2	2	2.094	1.804	2	1	1	2	19.898
4a	1	1	2	2	2	2	1.879	2.294	2	1	2	2	21.173
4f	1	1	2	2	2	1	4.188	2.245	2	1	2	2	22.433
5	1	1	2	2	2	2	1.227	2.116	2	2	2	2	21.343
6	1	1	2	2	2	1	2.275	2.996	1	2	2	2	21.271
7	1	1	2	2	2	2	1.259	2.275	2	1	2	2	20.534
8	1	1	2	2	2	2	1.164	1.980	2	1	2	2	20.144
9	1	1	2	2	2	2	2.565	2.525	1	2	2	2	22.090
14	1	1	2	2	2	2	1.361	2.525	2	2	2	2	21.886
15	1	1	2	1	2	2	-1.349	2.179	1	2	2	2	16.830
16	1	1	2	2	2	2	1.432	2.641	2	2	2	2	22.073
17	1	1	2	2	2	2	1.208	2.270	1	2	2	2	20.478
18	1	1	2	2	2	2	2.005	2.139	2	1	1	2	20.144
19	1	1	2	2	2	2	1.503	2.189	2	2	2	2	21.692
20	1	1	2	2	2	2	1.496	2.237	1	2	2	2	20.733
21	1	1	2	2	2	2	3.169	2.091	1	2	2	2	22.260
22	1	1	2	2	2	2	2.606	2.231	2	1	2	2	21.837
23	1	1	2	2	2	2	1.334	2.472	1	2	2	2	20.806
24	1	1	1	2	2	2	1.337	2.170	2	2	2	2	20.507
25	1	2	1	2	1	2	1.170	2.141	1	2	2	2	19.311
26	1	1	2	2	2	2	-1.462	2.539	1	2	2	2	18.077
27	1	1	2	2	2	2	-1.459	2.326	1	2	2	2	17.867
28	1	1	2	2	2	2	1.288	2.617	1	2	1	2	19.905
29	1	1	2	2	2	2	-1.049	2.245	1	2	2	2	18.196
30	1	1	2	2	2	2	1.119	2.541	1	2	2	2	20.660
31	1	1	2	1	2	1	2.512	2.289	1	2	2	2	19.801
32	1	1	2	1	2	1	2.576	2.397	1	2	2	2	19.973
33	1	1	2	1	2	1	2.600	2.424	1	2	2	2	20.024
34	1	1	2	1	2	1	2.431	2.431	1	2	2	2	16.862

Information:

1= Positive toxic
2= Negative toxic
A= Cramer rule Toxtree
B= Kroes TTC Toxtree
C= Carcinogenicity genotox Toxtree
D= Carcinogenicity non genotox Toxtree
E= In vitro mutagenicity (*Ames test*) Toxtree
F= Mutagenicity (*Ames test*) pkCSM
G= Maximum daily dose pkCSM (mg/kg/day)
H= Rat Acute Oral Toxicity (LD_{50}) pkCSM (mol/kg)
I= Hepatotoxicity pkCSM
J= Mutagenicity (*Ames Test*) PreADMET
K= Carcinogenicity to rat PreADMET
L= Carcinogenicity to mice PreADMET

Table IV. Classification of the compounds based on their toxicity

Toxicity	Compound
High toxicity risk (Cramer rules Toxtree)	1a, 1b, 1c, 1d, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1p, 1q, 4a, 4f, 5, 6, 7, 8, 9, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34
High toxicity risk (Kroes TTC Toxtree)	1a, 1b, 1c, 1d, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1q, 4a, 4f, 5, 6, 7, 8, 9, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33 and 34
Carcinogen genotox Toxtree	1o, 1p, 24 and 25
Carcinogen non genotox Toxtree	1b, 31, 32, 33 and 34
In vitro mutagen (Ames test) Toxtree	1o, 1p, 25 and 26
Mutagen (Ames test) pkCSM	1b, 1c, 1f, 1m, 4f, 6, 31, 32, 33 and 34
The lowest maximum daily dose pkCSM	26
The lowest rat acute oral toxicity (LD50) pkCSM	1q
Hepatotoxic pkCSM	1d, 1g, 1k, 1l, 1m, 6, 9, 15, 17, 20, 21, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34
Mutagen (Ames Test) PreADMET	1a, 1b, 1f, 1h, 1i, 1m, 1n, 1q, 4a, 4f, 7, 8, 18 and 22
Carcinogen to rat PreADMET	1b, 1c, 1d, 1i, 1m, 1n, 1o, 1p, 1q, 18 and 28

According to Table III and Table IV, in the Cramer rule Toxtree, all of 1-phenyl-1-(quinazolin-4-yl) ethanol compound derivatives are class 3 (score 1) which have a high toxicity risk. It means the high concentrations of the 1-phenyl-1-(quinazolin-4-yl) ethanol compounds are not guaranteed for the safety in their use. Based on the Kroes TTC endpoint, 41 compounds are positively at high risk bacause their exposure limits more than 0.15 µg/day (score 1). While compounds 1o, 1p, and 25 have no a significant risks (score 2). The risk can be reduced if given at or below 0.15 µg/day with a threshold value of 86-97%. Based on the predictions of carcinogenicity (genotoxic and non genotoxic), compounds 1o, 1p, 24, and 25 are genotoxic carcinogenic (score 1) whereas compounds 1b, 31, 32, 33, and 34 are non-genotoxic carcinogenic (score 1). Genotoxic carcinogens cause irreversible genetic damage or mutations by binding to DNA. Non-genotoxic carcinogens or epigenetics not bind covalently to DNA do not cause DNA damage directly and generally negative for mutagenicity tests. Based on in vitro mutagenicity (Ames test) predictions, compounds 1o, 1p, 25, and 26 have risk as mutagen (score 1), while 40 other compounds have no risk as mutagen (score 2).

Compound 6 has the highest value of LD_{50} endpoint of 2.996 mol/kg. Compound 4f has the highest value at the maximum daily dose endpoint of 4.188 mg/kg/day. The higher maximum daily dose and LD_{50} value in the acute toxicity test of the compound, the compound will not have toxic effect on the mice. Based on the mutagenicity endpoint of pKCSM, the compounds 1b, 1c, 1f, 1m, 4f, 6, 31, 32, 33 and 34 are mutagenic (score 1) whereas the other compounds are non-mutagenic (score 2). The last parameter of pkCSM is hepatotoxic. There are 22 hepatotoxic compounds (score 1) and 22 non-hepatotoxic compounds (score 2).

At the Ames test endpoint of PreADMET, there are 14 mutagenic compounds (score 1) and 30 other compounds are non-mutagenic compounds (score 2). The positive test results on Ames test indicate that the compound is mutagenic and has the possibility as carcinogenic. In the prediction of carcinogenicity in rat produced 11 carcinogenic positive compounds (score 1) and 33 other compounds are negative carcinogenic (score 2). While in the prediction of carcinogenicity in mice, all of compounds are not carcinogenicity (score 2).

In the study of Kuroiwa *et al.* (2015) obtained compounds 14, 16, 17, 19 and 31 which have the best activity with IC_{50} 0.053 μM, 0.038 μM, 0.027 μM, 0.058 μM and 0.035 μM on cell line A549 (lung). The results of the toxicity prediction showed the five compounds having the lowest toxicity (largest scores), i.e. compounds 1j, 5, 14, 16 and 19. Compound 31 was not selected because of hepatotoxic, non-genotoxic and mutagenic carcinogens. While the compound 17 was not selected because of hepatotoxic. Compounds 1j, 5, 14, 16 and 19 are negative genotoxic carcinogens and non-genotoxic carcinogens, in vitro mutagenicity (Ames test), hepatotoxicity, and carcinogenicity in mice and rat. The highest maximum daily dose value among the five compounds is compound 1j, that is 3.034 mg/kg/day while the highest LD_{50} value is compound 16, that is 2.642 mol/kg.

Based on in vitro test results Kuroiwa *et al.* (2015) compounds 1j, 5, 14, 16 and 19 have IC_{50} values of 20 μM, 1.8 μM, 0.053 μM, 0.038 μM and 0.058 μM. The compound with smaller IC_{50} is a compound that has higher activity as anticancer. Compounds 1j and 5 are not selected because they have a lower activity value compared to the other three compounds. Compounds that have small IC_{50} values with low toxicity effects, i.e. compounds 14, 16 and 19.

CONCLUSION

In the toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds using Toxtree, pkCSM and preADMET, three anticancer compounds have the highest activity in A549 cell (lung) and lowest toxicity i.e. compounds 14, 16 and 19. Compound 14 has IC_{50} of 0.053 μM and toxicity score of 21.886. Compound 16 has IC_{50} of 0.038 μM and toxicity score of 22.073. Meanwhile, compound 19 has IC_{50} of 0.058 μM and toxicity score of 21.692.

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