In Silico Study of Pyrazolylaminoquinazoline Toxicity by Lazar, Protox, and Admet Predictor

Supandi*, Yeni, Fajar Merdekawati
Department of Pharmacy, Faculty of Pharmacy and Sciences, UHAMKA, Jakarta, 13460, Indonesia.

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ABSTRACT
Pyrazolylaminoquinazoline is obtained from synthetic AZD4547 and can inhibit kinase activity in recombinant fibroblast growth factor receptor (FGFR) in vitro. The objective of this study was to obtain high activity and low toxicity pyrazolylaminoquinazoline derivatives in silico. The 2-dimensional structures were generated using the ChemDraw application. The Lazar application was used to predict endpoint carcinogenicity, maximum daily dose, and mutagenicity. The ProTox application was used for endpoint LD50 and toxicity classes, while the ADMET application was used for endpoint hepatotoxicity, with reproductive system disorders, and endocrine. Based on the scoring from the three software applications, two compounds were identified as being active against FGFR 2, with no carcinogenic or toxic effects on the liver, endocrine system, and the reproductive system, but they were predicted to have mutagenic effects. These compounds were V29 (N-(5-(3,5-dimethoxy phenethyl -1H-pyrazol-3-yl)-7(octahydro-2H-pyrido[1,2-a]pyrazine-2-yl) quinazoline-4-amine), with an IC50 of 0.2 ± 0.1 nM and a toxicity score of 1027, and V32 (N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-[(dimethylamino)piperidine-1-yl]quinazoline-4-amine), with an IC50 of 0.3 ± 0.1 nM and a toxicity score of 1024.

INTRODUCTION
Many bioactive compounds have been shown to have anticancer activity, but their uses are limited due to side effects and high toxic effects (Malchers et al., 2017). Nonetheless, toxicity can be assessed using computational resources (computational algorithms, software, and data) to organize, analyze, model, simulate, visualize, or predict chemical toxicity (Raies and Bajic, 2016). Predicted toxicity in silico is performed prior to in vitro and in vivo testing to minimize the number of test compounds and test animals in subsequent tests. Such in silico tests include Lazy Structure-Activity Relationships (Lazar), Prediction of Rodent Oral Toxicity (ProTox), and ADMET Predictor™.

Lazar is a useful tool to predict the toxic properties of chemical structures. It produces predictions for the query structure of the database with experimentally determined toxicity data in the quantitative QSAR (quantitative structure-activity relationship) statistical approach. The performance of the Lazar software model in the external validation dataset has an accuracy of 86% and a sensitivity of 78% in the carcinogenicity test, with 95% accuracy for the mutagenicity test (Helma, 2006).

ProTox is a web server for predicting small molecule oral toxicity in rodents. LD50 and toxicity classes are calculated on the basis of chemical compounds similar to those of toxic compounds. Researchers rely on known toxicity data to develop models that can predict the toxicity of new compounds. This web server calculates sensitivity, specificity, and precision for all considered toxicity classes, with values of 76%, 95%, and 75% (Drwal et al., 2014).

ADMET Predictor™ uses integrated sequences to examine how the molecular structure of a compound plays a role in absorption, distribution, metabolism, excretion, and toxicology. The classification accuracy qualitatively reaches 85–90%. The program has an intuitive user interface that allows visualization of the data (Hassan et al., 2013).

Pyrazolylaminoquinazoline derivative compounds can inhibit the fibroblast growth factor receptor (FGFR). Indeed, pyrazolilaminokuinazoline derivatives synthesized from AZD4547 have been shown to be effective, via targeting...
FGFR, against leukaemia in the KG-1 cell line (Gu et al., 2006),
gastric cancer in the KATO III cell line (Kunii et al., 2008),
bladder cancer in the RT112 cell line (Wang et al., 2014), and
lung cancer in the H1581 cell line (Malchers et al., 2017). The
IC₅₀ values ranged from 0.2–10 Nm, but their toxicity was not
determined. Therefore, this study aimed to predict the toxicity
of pyrazolylaminoquinazoline derivatives in silico using Lazar,
ProTox and ADMET Predictor™ applications. The results will
help in the selection of anticancer drugs with high activity, but low
toxicity prior to in vivo toxicity through preclinical testing. This is
particularly important as in vivo animal testing is limited by time,
ethical considerations, and a financial burden.

MATERIALS AND METHODS

Equipment and materials

The hardware used in this study was a PC with AMD
A8-7410 Quad Core 2.2-2.5 GHz specification, with 4 gigabytes
of DDR3 RAM and a Windows 10 Pro 64-bit operating system.
The software used were ChemDraw Pro 16.0 (http://scistore.
cambridgesoft.com/) under license code: 338-428260-4806,
pkCSM (http://biosig.unimelb.edu.au/pkcsm/), Open Babel GUI
(http://openbabel.org/wiki/Category:Installation), Lazar (https://
lazar.in-silico.ch/predict), ProTox (http://tox.charite.de/tox/), and
ADMET Predictor™ v8.0.4.62016 (http://simplusdownloads.com/
LicensingInstructions/AP8.html) with activation ID: 537-778-03-
08-2017-10-03-11-5095, Node Locked ID: CF9B5E81DD7C,
and License Model: FIXED. The pyrazolylaminoquinazoline
derivatives analyzed with IC₅₀ values according to Fan et al.,
(2016) are shown in Table 1.

Experimental procedure

The 2D structure of 37 pyrazolylaminoquinazoline
compounds was generated using the ChemDraw 2016 application.
All pyrazolylaminoquinazoline compounds were screened using
the pkCSM application to determine whether the compounds
met Lipinski’s Rule of Five. Compounds which did not meet
the maximum two endpoints of Lipinski’s Rule of Five were
eliminated. The toxicity of the screened pyrazolylaminoquinazoline
compounds was then predicted using Lazar for the carcinogenic
endpoint, maximum daily dose, and mutagenicity, the ProTox
application for LD₅₀ endpoint and toxicity classes, as well as the
ADMET Predictor application for hepatotoxicity endpoint, as well
as reproductive system disorders, and endocrine.

Table 1: Pyrazolylaminoquinazoline derivatives.

<table>
<thead>
<tr>
<th>No.</th>
<th>Comp. Code</th>
<th>Structure</th>
<th>IC₅₀ (nM)</th>
<th>Compound name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>V2</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>&lt;10</td>
<td>N4-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-ethylpiperazine-1-yl)-N2-((3-methylisoxazol-5-yl)methyl)quinazoline-2,4-diamine</td>
</tr>
<tr>
<td>2</td>
<td>V3</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>0.8 ± 0.2</td>
<td>N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-ethylpiperazine-1-yl) quinazoline-4-amine</td>
</tr>
<tr>
<td>3</td>
<td>V12</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>0.3 ± 0.1</td>
<td>N-(5-(2,6-dichloro-3,5-dimethoxyphenethyl)-1H-pyrazol-3-yl)-7-(4-ethylpiperazine-1-yl) quinazoline-4-amine</td>
</tr>
</tbody>
</table>
4  V13  29.9 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-ethylpiperazine-1-yl) quinoline-4-amine

5  V14  0.6 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-ethylpiperazine-1-yl)-2-methylquinazoline-4-amine

6  V15  0.5 ± 0.1  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-2-ethyl-7-(4-ethylpiperazine-1-yl) quinazoline-4-amine

7  V16  0.7 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-ethyl piperazine-1-yl)-2-propyl quinazoline-4-amine

8  V17  3.2 ± 0.5  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl) quinazoline-4-amine

9  V18  16.9 ± 0.2  5-chloro-N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl) quinazoline-4-amine
10  V19

N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-5-methoxy-quinazoline-4-amine

10.0 ± 0.2

11  V20

8-chloro-N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl) quinazoline-4-amine

4.8 ± 0.9

12  V21

N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-8-methoxy-quinazoline-4-amine

3.9 ± 0.1

13  V22

N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-8-(4-ethylpiperazine-1-yl) quinazoline-4-amine

4.3 ± 0.1

14  V23

N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-methylpiperazine-1-yl) quinazoline-4-amine

1.0 ± 0.2

15  V24

N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-iso propylpiperazine-1-yl) quinazoline-4-amine

0.6 ± 0.0
16. V25  
7-(4-cyclobutylpiperazin-1-yl)-N-(5-(3,5-dimethoxyphenethyl)-1H-pyrazol-3-yl) quinazoline-4-amine  
0.6 ± 0.1

17. V26  
N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-(2-methoxyethyl)piperazine-1-yl)-2-quinazoline-4-amine  
0.7 ± 0.2

18. V27  
N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-tosylpiperazine-1-yl) quinazoline-4-amine  
4.18 ± 0.1

19. V28  
N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(3,3-dimethylpiperazine-1-yl) quinazoline-4-amine  
0.9 ± 0.1

20. V29  
N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7(octahydro-2H-pyrido[1,2-a]pyrazine-2-yl) quinazoline-4-amine  
0.2 ± 0.1

21. V30  
N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-((3S,5R)-3,4,5-trimethyl piperazine-1-yl) quinazoline-4-amine  
0.2 ± 0.1
22  V31  0.7 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-methyl-1,4-diazepan-1-yl)quinazoline-4-amine

23  V32  0.3 ± 0.1  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-(dimethylamino)piperidin-1-yl)quinazoline-4-amine

24  V33  0.4 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(3-(dimethylamino)pyrrolidin-1-yl)quinazoline-4-amine

25  V34  0.8 ± 0.1  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(1-methylpiperidin-4-yl)quinazoline-4-amine

26  V35  0.87 ± 0.1  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(piperidin-1-yl)quinazoline-4-amine

27  V36  0.4 ± 0.1  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-morpholinoquinazoline-4-amine
28  V37  1.3 ± 0.3  N4-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-N7-(2-morpholinomethyl) quinazoline-4,7-diamine

29  V38  2.7 ± 0.2  N4-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-N7-(2-methoxyethyl) quinazoline-4,7-diamine

30  V39  0.9 ± 0.2  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(2-methoxyethoxy) quinazoline-4-amine

31  V40  0.73  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-methoxy-quinazoline-4-amine

32  V41  43.9  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-6-(2-methoxyethoxy) quinazoline-4-amine

33  V42  29.9  N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-6-(4-ethylpiperazin-1-yl) quinazoline-4-amine
Data analysis

The predictions were in the form of quantitative and qualitative data. Qualitative data were expressed in positive and negative statements, then expressed in the form of scoring, where a positive toxic score is 1 and a negative toxic score is 2. The data were scaled by summing all endpoints of the Lazar, ProTox, and ADMET predictions to obtain five compounds with the lowest toxicity, that is, the largest score. Five pyrazolylaminoquinazoline compounds were then selected which possessed high activity based on the in vitro test of Fan et al. (2016). The best compound was then obtained through the selected scoring model by comparing each compound with a low toxic effect, followed by the highest number of toxic negative endpoints. The next step selected two compounds with the highest activity and the lowest toxicity, by comparing the highest scores and the smallest IC\textsubscript{50} value among the five compounds.

RESULTS AND DISCUSSION

Lipinski’s Rule of Five

Lipinski’s Rule of Five helps to determine the level of absorption or permeability of lipid bilayers present in the human body, demonstrating 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 more than 5, the donor hydrogen bond is not more than 5, and the number of hydrogen bond acceptor is less than 10 (Lipinski et al., 2001). The results of the Lipinski’s Rule of Five calculations using pkCSM are presented in Table 2.

According to Table 2, all pyrazolylaminoquinazoline compounds met the Lipinski rule, so it can be predicted that all compounds have good absorptivity for oral medication. Veber et al. (2002) concluded that the lower molecular weight, log P,
hydrogen bond donors, and hydrogen bond acceptor, the higher the bioavailability of a candidate drug.

**Toxicity prediction**

Based on the results of Lazar, carcinogenicity test prediction of Carcinogenic Potency Database (CPDB) with Leave One Out (LOO) cross-validation of the compounds V14, V15, V18, V21, V25-V26, V29, V31, V34, V39-V43, and V46 is non-carcinogenic, but V40 has the highest non-carcinogenic probability, with probability values 0.0895 for hamster, 0.102 for house mouse and 0.108 for mouse. The higher the non-carcinogenic probability value, the higher the non-carcinogenic nature of a compound (Helma, 2006). Ranked from the highest to the lowest non-carcinogenic probability values, the compounds are V40, V46, V41, V21, V31, V39, V42, V29, V14, V15, V43, V26, V18, V34, and V25, while compounds V30, V32, V35, and V36 are carcinogens. Regarding the maximum daily dose prediction, the smaller the maximum dose, the more toxic the compound. The maximum daily dose could not be predicted for most compounds due to the lack of similar structures, except for compound V13, which was 7.57 mg/kg BW/day. According to the *in vitro* mutagenicity prediction (Ames test) from the Kazius/Bursi dataset using LOO cross-validation in the CPDB application domain, 35 compounds were predicted to have a risk of a mutagen. However, compound V29 had the lowest mutagen probability with a value of 0.0988. The lower the probability value of mutagen, the lower the mutagen property of a compound (Helma, 2006).

### Table 2: Lipinski’s Rule of Five Analysis Results.

<table>
<thead>
<tr>
<th>Comp. code</th>
<th>LogP (&lt;5)</th>
<th>Hydrogen Bond Donor</th>
<th>Hydrogen Bond Acceptor</th>
<th>Comp. code</th>
<th>LogP (&lt;5)</th>
<th>Hydrogen Bond Donor</th>
<th>Hydrogen Bond Acceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2</td>
<td>597.724</td>
<td>4.949</td>
<td>11</td>
<td>V20</td>
<td>409.877</td>
<td>4.552</td>
<td>7</td>
</tr>
<tr>
<td>V3</td>
<td>487.608</td>
<td>4.041</td>
<td>8</td>
<td>V21</td>
<td>405.458</td>
<td>3.908</td>
<td>7</td>
</tr>
<tr>
<td>V12</td>
<td>556.498</td>
<td>5.348</td>
<td>8</td>
<td>V22</td>
<td>487.608</td>
<td>4.041</td>
<td>8</td>
</tr>
<tr>
<td>V13</td>
<td>486.62</td>
<td>4.646</td>
<td>7</td>
<td>V23</td>
<td>473.581</td>
<td>3.651</td>
<td>8</td>
</tr>
<tr>
<td>V14</td>
<td>501.635</td>
<td>4.349</td>
<td>8</td>
<td>V24</td>
<td>501.635</td>
<td>4.429</td>
<td>8</td>
</tr>
<tr>
<td>V15</td>
<td>515.662</td>
<td>4.603</td>
<td>8</td>
<td>V25</td>
<td>513.646</td>
<td>4.573</td>
<td>8</td>
</tr>
<tr>
<td>V16</td>
<td>529.689</td>
<td>4.993</td>
<td>8</td>
<td>V26</td>
<td>517.634</td>
<td>4.573</td>
<td>9</td>
</tr>
<tr>
<td>V17</td>
<td>375.432</td>
<td>3.899</td>
<td>6</td>
<td>V27</td>
<td>613.744</td>
<td>4.718</td>
<td>9</td>
</tr>
<tr>
<td>V18</td>
<td>409.877</td>
<td>4.552</td>
<td>6</td>
<td>V28</td>
<td>487.608</td>
<td>4.087</td>
<td>8</td>
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<tr>
<td>V19</td>
<td>405.458</td>
<td>3.908</td>
<td>7</td>
<td>V29</td>
<td>513.646</td>
<td>4.573</td>
<td>8</td>
</tr>
<tr>
<td>V20</td>
<td>409.877</td>
<td>4.552</td>
<td>6</td>
<td>V30</td>
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<td>4.428</td>
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<tr>
<td>V21</td>
<td>405.458</td>
<td>3.908</td>
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<td>V31</td>
<td>501.635</td>
<td>4.429</td>
<td>8</td>
</tr>
<tr>
<td>V22</td>
<td>487.608</td>
<td>4.041</td>
<td>8</td>
<td>V32</td>
<td>487.608</td>
<td>4.039</td>
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<tr>
<td>V23</td>
<td>473.581</td>
<td>3.651</td>
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<td>V33</td>
<td>472.593</td>
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<td>V24</td>
<td>501.635</td>
<td>4.429</td>
<td>8</td>
<td>V34</td>
<td>501.635</td>
<td>4.429</td>
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<tr>
<td>V25</td>
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<td>V35</td>
<td>503.607</td>
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<td>V26</td>
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<td>3.667</td>
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<td>V27</td>
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<td>517.634</td>
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<td>V28</td>
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<td>V38</td>
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<tr>
<td>V29</td>
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<td>V39</td>
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<td>V40</td>
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<td>8</td>
<td>V41</td>
<td>487.608</td>
<td>4.041</td>
<td>8</td>
</tr>
</tbody>
</table>

Regarding acute oral toxicity, based on the ProTox results, V37 compound was of moderate toxicity (Hodge and Sterner, 2005), with a LD$_{50}$ value of 300 mg/kgBB and in class III Global Harmoni System (GHS) indicating that it could be toxic if swallowed (Drwal et al., 2014). Compound V34 had an LD$_{50}$ value of 3,550 mg/kgBB in class IV GHS IV toxicity class, indicating that they are dangerous if swallowed (Drwal et al., 2014). It belongs to class IV (50–500 mg/kgBB) according to Hodge and Sterner (2005), so it is harmful if swallowed. The thirty-three other compounds had LD$_{50}$ values between 380–1130 mg/kgBB and were class IV GHS IV toxicity class, indicating that they are dangerous if swallowed (Drwal et al., 2014). Furthermore, they were also class III (50–500 mg/kgBB) to grade IV (500–5000 mg/kgBB), which means they had moderate to mild toxicity (Hodge and Sterner, 2005).

Based on the results of ADMET Predictor, hepatotoxicity test, endocrine system toxicity, and repro toxicity, it can be seen that compounds V3, V14, V15, V23-V33, V35, V36, and V46 are predicted to have no toxic risk to liver function, the endocrine system, and the reproduction system. Hepatotoxicity predicts five increased serum enzymes for the diagnosis of liver damage, namely alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), aspartate transaminase/serum glutamate oxaloacetate transferase (AST/SGOT), and alanine transaminase/serum glutamate pyruvate transferase (ALT/SGPT). Hepatotoxicity prediction is issued by the Food and Drug Administration (FDA) on the side effects for human liver, based on two databases, the Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS). SRS data distinguishes three classes of compounds: inactive (RI < 3.0), slightly active (3.0 ≤ RI < 4.0), and active (RI ≥ 4.0). The ADMET Predictor sets the RI cut-off value at 3.0, therefore, the molecule with an RI < 3.0 is categorized as negative (normal) and with RI ≥ 3.0 as positive (not normal) in each enzyme (Hassan et al., 2013; Simulations Plus, 2016).
Table 3: Toxicity prediction results from Lazar, ProTox, and ADMET predictor.

<table>
<thead>
<tr>
<th>Comp. Code</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
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<th>N</th>
<th>O</th>
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<td>4</td>
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Based on the results of the scoring calculations of the three software applications in Table 3, the compound with the lowest toxicity has the highest average scores, which is V34, predicted to cause toxicity to LDH enzymes and V19, V20, and V40 predicted to be toxic to GGT and LDH enzymes. V43 is less effective than the best compound due to its high LD₅₀ value.
and predicted to be toxic to the liver. Therefore, further analysis is required by comparing the number of non-toxic endpoints for each compound.

From the analysis results, it is predicted that V14, V15, V25, V26, V29, V31 and V46 compounds have no carcinogenic, toxic effects on the liver, endocrine systems, and reproductive systems, but they are predicted to have mutagenic effects. The higher the LD\textsubscript{50} of a compound, the lower the toxic effect. V14, V15, and V29 compounds have an LD\textsubscript{50} of 1.000 mg/kgBW, V25, V31, and V46 have an LD\textsubscript{50} of 500 mg/kgBW, while V26 has an LD\textsubscript{50} of 380 mg/kgBW, so V26 compound was not selected for the lowest toxic effect.

The lowest mutagen effect has the smallest mutagenic probability value. V14, V15, V25, V29, V31 and V46 compounds have mutagenic probability values of 0.129, 0.125, 0.107, 0.0988, 0.159 and 0.127 respectively, so V31 was not selected for the lowest toxic effect. V14, V15, V25, V29, and V32 have the lowest toxicity with IC\textsubscript{50} values of 0.6 nM, 0.5 nM, 0.6 nM, 0.2 nM and 0.3 nM respectively.

CONCLUSION

The in silico applications, Lazar, ProTox, and ADMET, were used to predict the toxicity of anticancer pyrazolylaminoquinazolin compounds, revealing that the two compounds with the highest activity and the lowest toxicity were V29 (N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7(octahydro-2H-pyrido [1,2-a] pyrazine-2-yl) quinazoline-4-amine), with an IC\textsubscript{50} of 0.2 ± 0.1 nM and a toxicity score of 1027, and V32 (N-(5-(3,5-dimethoxy phenethyl)-1H-pyrazol-3-yl)-7-(4-(dimethylamino)piperidine-1-yl)quinazoline-4-amine) with an IC\textsubscript{50} of 0.3 ± 0.1 nM and a toxicity score of 1024.

AUTHORS CONTRIBUTIONS

All authors contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare.

REFERENCES


Raies AB, Bajic VB. In silico toxicology: computational methods for the prediction of chemical toxicity. WIREs Comput Mol Sci, 2016; 6:147-172.


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