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### **In vitro and in silico analysis of phytochemical compounds of 96% ethanol extract of semanggi (*Marsilea crenata* Presl.) leaves as a bone formation agent**

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Melanny Ika Sulistyowaty\*, Retno Widjowati, Galih Satrio Putra, Tutuk Budiati and Katsuyoshi Matsunami

# Synthesis, ADMET predictions, molecular docking studies, and *in-vitro* anticancer activity of some benzoxazines against A549 human lung cancer cells

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## Abstract

**Objectives:** This study aims to synthesize a series of benzoxazines (1–5) to be examined as an epidermal growth factor receptor (EGFR) inhibitor by *in-silico* study. The overexpression of EGFR causes the growth of normal lung cells to become uncontrollable, which may lead to cancer formation. We also conducted the absorption, distribution, metabolism, excretions and toxicity (ADMET) properties evaluation and also examined *in vitro* anticancer assay on human lung cancer cells line, which is A549.

**Methods:** Benzoxazines (1–5) were synthesized by reacting anthranilic acid and benzoyl chlorides. The structures of the compounds were determined with <sup>1</sup>H, <sup>13</sup>C-NMR, HRMS, UV and FT-IR spectrometric methods. Prediction of ADMET was using online pkCSM, and the molecular docking studies were using MVD with EGFR-TKIs as the target (PDB ID: 1M17). *In vitro* assay of anticancer activity was performed by MTT assay.

**Results:** Compounds 1–5 were successfully synthesized in good yields (71–84%). The ADMET prediction showed that benzoxazines are able to be absorbed through GIT, metabolized by CYP 450, and not hepatotoxic. The title

compounds have a greater MolDock Score than Erlotinib, and 3 has the highest activity against A549 compared with other benzoxazines, IC<sub>50</sub>=36.6 µg/mL.

**Conclusions:** Compound (3) more active as anticancer against Human cancer cells line compared with other benzoxazines.

**Keywords:** A549 cancer cell; ADMET prediction; benzoxazines; molecular docking; synthesis.

## Introduction

Lung cancer has the highest mortality case in the world among the other cancers. According to WHO data in 2018, a total of 26,095 people in Indonesia die from lung cancer each year, with 30,023 new cases, thus considered as a country with the highest cases in Southeast Asia [1]. Non-small cell lung cancer (NSCLC) is a type of lung cancer that often ensues nearly 75% all lung cancer cases. Many studies reported that NSCLC occurred due to the overexpression of epidermal growth factor receptor (EGFR) which caused the growth of normal lung cells to become uncontrollable [2]. In recent years, novel drugs known as EGFR-targeted therapies, or EGFR-tyrosine kinase inhibitors (TKIs), such as Gefitinib, Erlotinib, Afatinib and Osimertinib have succeeded in restraining the progression of lung cancer in some NSCLC patients [3].

Currently, several treatments for lung cancer are available, but a continuous treatment innovation is needed because some cases indicate the resistance to EGFR-tyrosine kinase inhibitors (TKIs) in some patients. One of the strategies undertaken by researchers to overcome cases of resistance to EGFR-TKIs, is first of all to combine the TKIs drug with several drugs that have other mechanisms such as Bortezomib, Everolimus, Bevacizumab, Tivantinib and Sorafenib. The second step is to create a new drug that has less side effects than the previous drug [4].

In the development of anticancer candidates, several studies found out that some compounds which possessed

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benzoxazine ring are able to inhibit the growth of A549 cell line (Figure 1) [5–9]. Based on the molecular docking results of benzoxazine ring to the PDB 1M17 receptor, it is predicted that it has ability to inhibit EGFR-TKIs, such as Erlotinib [6]. Therefore, our research aims were to synthesize derivatives of benzoxazine and carried out the computational tests on ADMET predictions and molecular docking on the EGFR receptors. In addition, we also conducted bioassays against A549 human lung cancer cells line.

## Materials and methods

### Synthesis of benzoxazines derivatives

All chemicals used were analytical grade and obtained from Sigma-Aldrich. Anthranilic acid (10 mmol) was dissolved in pyridine and benzoyl chloride (1.5 eq) was added wisely at 0 °C, then being stirred for an hour at room temperature. The progress of the reaction was conducted by TLC method, with *n*-hexane and ethyl acetate (1:1). When the reaction was completed, solution of sodium bicarbonate (10%) was poured to the mixture. The product was recrystallized from ethanol 96% [10, 11].

Characterizations of the benzoxazines were performed using various spectroscopic methods. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra measurements were conducted using Bruker Ultrashield 600 spectrometer at 600 and 150 MHz, MS spectra were measured in QSTAR XL Nano-Spray™ with ESI mode. FT-IR spectra were recorded by Jasco FT-IR 5300. Ultraviolet spectra were analyzed using Shimadzu UV-Vis Spectrophotometer 1800. In addition, melting point of the compound was determined using Fisher-John Electrothermal Mel-Temp without correction.

### ADMET prediction study

Benzoxazines (1–5) and Erlotinid were drawn using Marvin sketch and saved as a smile data. The data were then inputted to the online pkCSM website (<http://biosig.unimelb.edu.au/pkcsml/>) in order to obtain ADMET prediction data.

### Molecular docking study

*In silico* study was performed by using MVD (Molegro® Virtual Docker version 5.5) and MMFF94 was used to optimize the 3D geometry of the

compounds [12]. The benzoxazines and Erlotinid were docked into the active site of EGFR-TK domain (PDB ID: 1M17) [6, 13]. The validation of docking was performed by docking its native ligand (Erlotinid) into its active site EGFR-TK domain. The criteria of acceptance were the value of RMSD ≤ 2.0 Å. After validation docking process, benzoxazines were docked into active site of this receptor. The evaluation was carried out using MolDock score. Then, it was shown that the smaller the score, the more stable binding between ligand and receptor was [14].

### Bioassay against human lung cancer cell

A549 cell line was cultivated in an enhanced medium, which is the combination of DMEM (Dulbecco's modified Eagle's Medium), 10% heat inactive FBS (fetal bovine serum), Amphotericin B and Kanamycin. Three days-old cells were employed as test substance. One microliter of samples (1% in DMSO) and 99 μL of A549 cells (5 × 10<sup>3</sup> cells) were incubated at 37 °C for 72 h. After some steps of treatment, we measured the absorbance of the mixture by scanning it at λ: 540 nm with a 2,300 EnSpire Multimode plate reader, Perkin Elmer, Inc. The percentage (%) of the inhibition of cell growth was computed using Eq. (1).

$$\%inhibition = \left[ 1 - \frac{(A_{sample} - A_{blank})}{(A_{control} - A_{blank})} \right] \times 100 \quad (1)$$

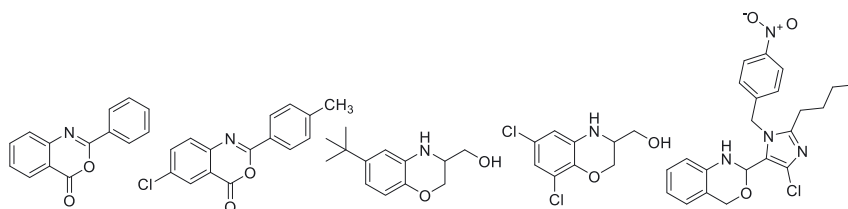
The evaluation was performed in triplicate and reported as mean ± SE [9].

## Results

### Synthesis

#### 2-(2-chlorophenyl)-4*H*-benzo-[1,3]-oxazin-4-one (2)

Obtained as white crystals, mp: 125–128 °C. FT-IR (KBr) cm<sup>-1</sup>: 1765 (C=O lactone); 1,620 and 1,474 (C=C aromatic); 3,040 (=C–H aromatic); 1,614 (C=N); 1,315 (C–N). UV (λ<sub>max</sub>): 216, 264, 306 nm. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>, δ) 8.28 (d, *J*=7.9 Hz, 1H), 7.91 (d, *J*=7.6 Hz, 1H), 7.87 (dd, *J*=8.1, 7.4 Hz, 1H), 7.73 (d, *J*=7.9 Hz, 1H), 7.59 (t, *J*=7.6 Hz, 1H), 7.54 (d, *J*=8.0 Hz, 1H), 7.51–7.44 (m, 1H), 7.41 (t, *J*=7.6 Hz, 1H). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>, δ) 159.39, 156.76, 146.64, 136.80, 133.67, 132.48, 131.61, 131.28, 130.51, 129.13, 128.77, 127.61, 127.04, 117.19, 77.16. HRMS-ESI (*m/z*)=280.0137 [M+Na]<sup>+</sup> (calcd. for C<sub>14</sub>H<sub>8</sub>O<sub>2</sub>NClNa: 280.0137).



**Figure 1:** Some benzoxazines which have ability on inhibiting the growth of A549 human lung cancer cells line.

### 2-(2,4-dichlorophenyl)-4H-benzo-[1,3]-oxazin-4-one (3)

Yielded as white crystals, mp: 141–143 °C. FT-IR (KBr)  $\text{cm}^{-1}$ : 1767 (C=O lactone); 1,623 and 1,476 (C=C aromatic); 3,090 (=C-H aromatic); 1,620 (C=N); 1,315 (C-N); 1,029 (C-O-C) and 772 (C-Cl). UV ( $\lambda_{\text{max}}$ ): 220, 280, 310 nm.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 8.30 – 8.25 (m, 1H), 7.90 (d,  $J=8.4$  Hz, 1H), 7.89 – 7.84 (m, 1H), 7.72 (d,  $J=8.1$  Hz, 1H), 7.62 – 7.57 (m, 1H), 7.56 (d,  $J=2.0$  Hz, 1H), 7.40 (dd,  $J=8.4, 2.0$  Hz, 1H).  $^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 159.15, 146.50, 138.24, 136.88, 134.70, 132.55, 131.29, 129.29, 128.82, 127.64, 127.51, 117.15, 77.16. HRMS-ESI ( $m/z$ )=313.9748  $[\text{M}+\text{Na}]^+$  (calculated for  $\text{C}_{14}\text{H}_7\text{O}_2\text{NCl}_2\text{Na}$ : 313.9746).

### 2-(3,4-dichlorophenyl)-4H-benzo-[1,3]-oxazin-4-one (4)

Yielded as white powders, mp: 166–169 °C. FT-IR (KBr)  $\text{cm}^{-1}$ : 1760 (C=O lactone); 1,621 and 1,474 (C=C aromatic); 3,090 (=C-H aromatic); 1,620 (C=N); 1,324 (C-N); 1,076 (C-O-); C-Cl (770). UV ( $\lambda_{\text{max}}$ ): 220, 244, 288, 302 nm.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 8.42 (d,  $J=1.9$  Hz, 1H), 8.26 (d,  $J=7.9$  Hz, 1H), 8.14 (dd,  $J=8.5, 2.0$  Hz, 1H), 7.86 (t,  $J=7.7$  Hz, 1H), 7.70 (d,  $J=7.8$  Hz, 1H), 7.60 (d,  $J=8.4$  Hz, 1H), 7.56 (t,  $J=7.6$  Hz, 1H).  $^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 159.12, 155.29, 146.69, 137.32, 136.95, 133.60, 131.02, 130.33, 130.23, 128.96, 128.92, 127.52, 127.39, 117.17. HRMS-ESI ( $m/z$ )=313.9748  $[\text{M}+\text{Na}]^+$  (calcd. for  $\text{C}_{14}\text{H}_7\text{O}_2\text{NCl}_2\text{Na}$ : 313.9746).

### 2-(4-methoxyphenyl)-4H-benzo-[1,3]-oxazin-4-one (5)

Yielded as white powders, mp: 150–152 °C. FT-IR (KBr)  $\text{cm}^{-1}$ : 1760 (C=O lactone); 1,621 and 1,474 (C=C aromatic); 3,090 (=C-H aromatic); 1,620 (C=N); 1,324 (C-N); 1,076 (C-O-); C-Cl (770). UV ( $\lambda_{\text{max}}$ ): 220, 250, 294, 306 nm.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 8.29 – 8.25 (m, 2H), 8.22 (dd,  $J=7.8, 1.1$  Hz, 1H), 7.80 (td,  $J=8.1, 1.5$  Hz, 1H), 7.67 – 7.63 (m, 1H), 7.48 (t,  $J=7.6$  Hz, 1H), 7.01 (d,  $J=8.9$  Hz, 2H), 3.90 (s, 3H).  $^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 163.31 (s), 159.80 (s), 157.17 (s), 136.49 (s), 130.30 (s), 128.57 (s), 127.71 (s), 126.94 (s), 122.60 (s), 116.76 (s), 114.17 (s), 55.52 (s). HRMS-ESI ( $m/z$ )=276.0632  $[\text{M}+\text{Na}]^+$  (calcd. for  $\text{C}_{15}\text{H}_{11}\text{O}_3\text{NNa}$ : 276.0631).

## ADMET prediction study

The absorption prediction of the title compounds by pkCSM application showed in Table 1 below:

The distribution prediction of benzoxazines using pkCSM application showed in Table 2 below:

The predictions of excretion of synthesized compounds using pkCSM application were shown in Table 3:

**Table 1:** Absorption prediction of compound 1–5 and Erlotinib.

Compounds	Lipinski Rule of Five	Human intestinal absorption, %	Caco2 permeability (log Papp in $10^{-6}$ cm/s)
1	✓	97.11	1.32
2	✓	95.36	1.33
3	✓	94.22	1.37
4	✓	95.15	1.38
5	✓	97.96	1.30
Erlotinib	✓	96.05	1.17

✓, Mr (Molecular weight)<500; HBA, Hydrogen bond acceptor $\leq$ 10; HBD, Hydrogen bond donor $\leq$ 5; Log<5; MR, molar refractivity=120–140 Å

The prediction of toxicity of compounds 1–5 using the application of pkCSM as described below in Table 4:

## Molecular docking study

The Molecular docking of the title compounds toward EGFR-tyrosine as shown Table 5 below:

Figure 2 illustrated the hydrogen bond and steric interaction of title compounds into the active site of EGFR-tyrosine in 2D and 3D as shown below:

The  $\text{IC}_{50}$  of benzoxazines 1–5 as shown in Table 6 below:

## Discussion

### Synthesis

Synthesis of the title compounds was started by dissolved anthranilic acid then added benzoyl chloride as described in Figure 3. Benzoxazines (1–5) were obtained in 60–84% yields. The synthesized compounds then being analysed their structures by using some method of spectrophotometry.

**Table 2:** Distribution prediction of benzoxazines and Erlotinib.

Compounds	Volume distribution	BBB permeability Log BB	CNS permeability Log PS
1	-0.12	0.35	-1.35
2	-0.03	0.32	-1.33
3	0.01	0.25	-1.32
4	0.07	0.3	-1.36
5	-0.01	0.35	-2
Erlotinid	0.07	-0.51	-3.40



**Table 3:** Metabolism and excretion prediction of the title compounds.

Compounds	Substrates		Inhibitors		Excretion mL/min/kg
	CYP 2D6	CYP 3A4	CYP 2D6	CYP 3A4	
1	–	✓	–	–	7.40
2	–	✓	✓	–	1.79
3	–	✓	–	–	1.50
4	–	✓	–	–	1.48
5	–	✓	–	–	7.13
Erlotinib	–	✓	–	✓	4.21

**Table 4:** Toxicity Prediction of benzoxazines 1–5 and Erlotinib.

Compounds	AMES toxicity	Hepatotoxicity	Maximal tolerated dose (human), mg/kg/day	Oral rat acute toxicity, mol/kg
1	–	–	1.37	1.72
2	–	–	1.08	1.84
3	–	–	0.68	1.99
4	–	–	0.80	2.00
5	–	–	1.02	2.03
Erlotinib	–	+	4.25	2.68

## ADMET prediction study

Based on the prediction of absorption by pkCSM application (Table 1), the title compounds and Erlotinid can be absorbed in the digestive tract (>90%). It happens because they meet the requirements of the Lipinski Rule of Five (MW<500, hydrogen bond donor <5, hydrogen acceptors <10, log P<5, molar refractivity between 40 and 130) [15, 16]. Not only that, all tested compounds have Caco2 permeability value of >0.9 which means it has high permeability. Caco2 cell lines are human epithelial colorectal adenocarcinoma cells which are cell monolayers that are often used as a human intestinal mucosa model as *in vitro* assay to predict oral drug absorption [16].

From the result of the distribution prediction using pkCSM application (Table 2), the tested compounds have moderate volume of distribution. It means that the total concentration of drugs circulating in blood plasma and tissues are the same. It is categorized as a small volume distribution if the value is less than  $-0.15 \log L/kg$  and as a large volume distribution if the value is  $>2.81 > 0.45 \log L/kg$  [16]. The benzoxazines derivatives are predicted to be able to penetrate BBB and enter the bloodstream in the brain because they have log BB value more of than 0.3 and log PS

of more than  $-2$ . On the other hand, Erlotinid is predicted not to be able to penetrate BBB and cannot enter the bloodstream in the brain because it has the log BB value of less than  $-0.1$  and Log PS of less than  $-3$ . The molecular weight of Erlotinib is also twice bigger compared to the synthesized compounds [16].

Benzoxazines are predicted to be able to penetrate BBB and enter the bloodstream in the brain because they are similar to narcotics class 1 [17, 18]. The starting material of benzoxazines was anthranilic acid, which is a precursor used in synthesizing narcotic-like compounds. There are several compounds classified as class 1 and often being misused as narcotic compounds which can be synthesized from anthranilic acid, namely Mecloqualone and Methaqualone. The structure of those compounds was similar to 1–5 [Figure 4].

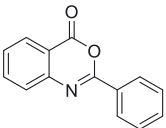
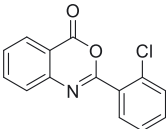
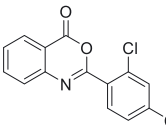
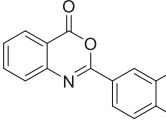
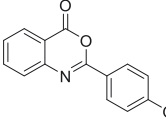
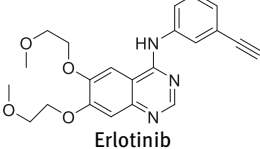
Cytochrome 450 is responsible for metabolizing most drugs. Most drugs are metabolized by two isoforms of cytochrome 450, namely CYP 2D6 and CYP 3A4. The knowledge about whether a drug is a substrate of CYP 2D6/CYP 3A4 or else will relate to the presence of inducer and inhibitor of both isoforms. This will have an impact on the fluctuations of drug's bioavailability [19]. Based on the prediction of metabolism by pkCSM application, benzoxazines (1–5) and Erlotinib compounds are CYP 3A4 substrates and are not CYP 2D6 substrates. It means that the presence of CYP 3A4 inducers has the potential to reduce blood levels of benzoxazines 1–5 and Erlotinid. However, the presence of CYP 3A4 inhibitors will create the opposite effect.

Based on the prediction of metabolism and excretion using pkCSM application (Table 3), the rate of drug clearance (total clearance) in the body is a combination of hepatic clearance (liver metabolism and biliary clearance) and renal clearance [16, 20]. The greater the total clearance, the faster the drug is excreted by the body. Compound 2, 3 and 4 have low total clearance rate ( $<2 \text{ mL/min/kg}$ ) compared to 1 and 5. This prediction is possible because benzoxazines 2, 3, and 4 contained halo-substitution (Cl atom) in benzene ring, so they are more difficult to be excreted by the body.

From data of the prediction of toxicity using the application of pkCSM (Table 4), benzoxazines 1–5 do not cause mutations. It is related to negative value of AMES toxicity predictions. The AMES test is widely used as a method for initial screening of mutagenic compound with the help of bacteria [16, 21]. The prediction results of pkCSM applications and mutagenic test of Erlotinib have been published as non-mutagenic compound, both by AMES test and by *in vitro* assay of mammalian mutation test [16, 22]. From the prediction of toxicity of pkCSM



**Table 5:** Molecular docking result of benzoxazines and their native ligand (Erlotinib).

Compound	Moldock score, Kcal/mol	Docked Pose	Hydrogen bond	Amino acids residues	Steric interaction	Amino acids residues
	$-65.89 \pm 0.07$	✓	1	Met 769	–	–
<b>1</b>						
	$-71.28 \pm 0.03$	✓	2	Met 769 Gln 767	–	–
<b>2</b>						
	$-73.29 \pm 0.05$	✓	1	Met 769	–	–
<b>3</b>						
	$-72.94 \pm 0.02$	✓	2	Lys 721 Met 769	–	–
<b>4</b>						
	$-68.86 \pm 0.06$	✓	1	Thr 766	3	Leu 694 Leu 768 Met 769
<b>5</b>						
	$-122.93 \pm 0.06$	✓	2	Thr 766 Met 769	2	Gly 695 Gln 767
Erlotinib						

application, the synthesized compounds are not hepatotoxic while Erlotinib causes hepatotoxicity. This result was in line with the fact that Erlotinib increases transaminases [16, 21].

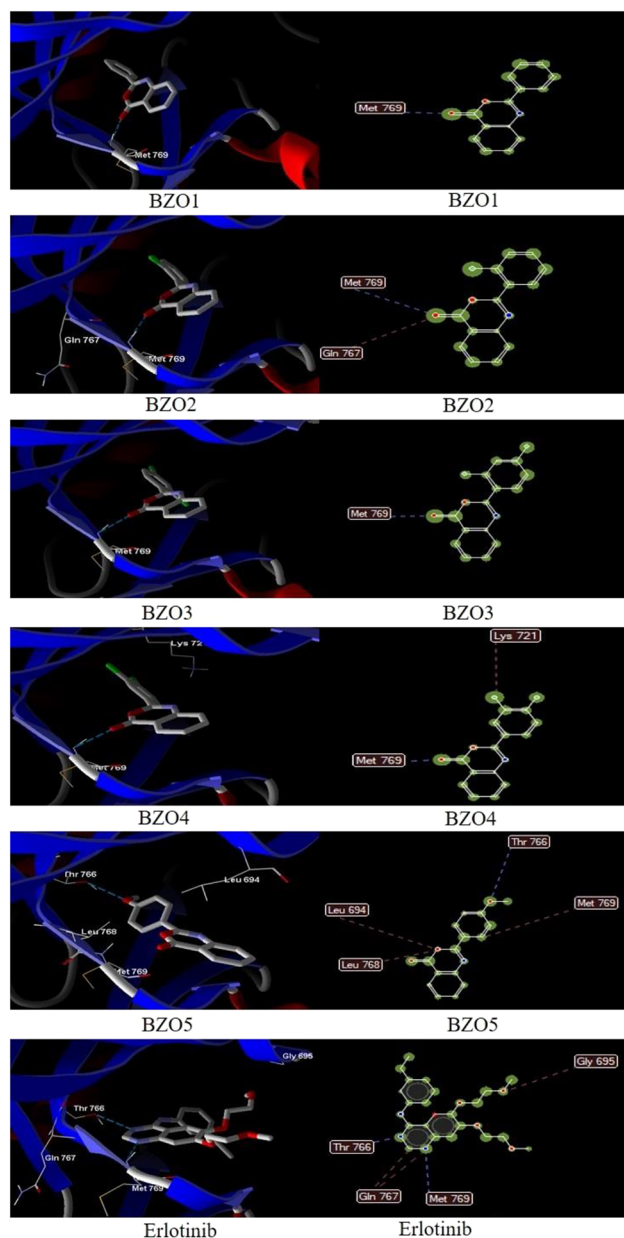
MTD is an estimated safe dose limit for humans. These data are very helpful for the initial dose given in phase 1 clinical trials. Prediction of MTD of compounds **1–5** is less than 3 mg/kg/day which is categorized as low [13]. Meanwhile, the MTD prediction of Erlotinib is more than 3 mg/kg/day which is categorized as high. The dose of Erlotinib used for NSCLC cases is 150 mg, which means that it does not exceed the prediction of the maximum tolerated dose [16, 21, 23].

From the prediction evaluation of oral rat acute toxicity, the LD50 results of the synthesized compounds are lower than Erlotinib. This can happen because

benzoxazines **1–5** have the same structure as Mecloqualone and Methaqualone with LD50 values of 250 mg/kg and 185 mg/kg [24]. Both compounds are narcotics drug class 1 which have a high potential for addiction with a potential effect of large lethality.

### Molecular docking study

Based on the results of the molecular docking study (Table 5), the most suitable predictor of binding with EGFR-TKs is Erlotinib as the native ligand. It has the lowest moldock score, which is  $-122.93 \pm 0.06$  Kcal/mol while benzoxazines **1–5** have moldock scores greater than Erlotinib. That means that the ability of benzoxazines in inhibiting the EGFR-TKI is not as great as Erlotinib.



**Figure 2:** Hydrogen bond (blue dotted) and steric interaction (red dotted) of 1–5 and Erlotinib into the active site of EGFR-tyrosine. Left side (3D); Right side (2D). *In-vitro* anticancer activity.

From Figure 2, Erlotinib has a hydrogen bond with the amino acid Thr 766, Met 769 and steric interaction with amino acid Gly 695, Gln 767. This interaction is predicted to be the most important, so that Erlotinib has low binding energy. The interaction of Erlotinib with the presence of hydrogen bonds (2.89 Å) from the N atom as a hydrogen

**Table 6:** IC<sub>50</sub> of the title compounds.

Compound	IC <sub>50</sub> , $\mu\text{g/mL}$	IC <sub>50</sub> , $\mu\text{M}$
1	74.3	>200
2	69.2	>200
3	36.6	125
4	>100	>200
5	>100	>200
Doxorubicin	1.46 ± 2.3	2.68
Erlotinib	–	–

acceptor with Met 769 gives a low free energy contribution, followed by the N atom as a hydrogen acceptor with Thr 766 with a distance of 2.93 Å [6, 11]. Compound 1, 2, 3 and 4 also have a hydrogen bond (2.62–3.20 Å) with the amino acid Met 769 and an O atom as a hydrogen acceptor but don't have a hydrogen bond with the amino acid Thr 766.

### *In vitro* anticancer activity

Based on the results of the *in vitro* evaluation on inhibiting the growth of A549 cell line using the MTT method (Table 6), the benzoxazines 1–5 possessed moderate activity as anticancer agent. Among the synthesized products, benzoxazine 3 had the greatest activity against A549 cell line, with the lowest IC<sub>50</sub> value of 36.6  $\mu\text{g/mL}$ , which is categorized as the low activity category [25]. Doxorubicin as a positive control *in vitro* had an IC<sub>50</sub> value of 2.68  $\mu\text{M}$  which is included in the strong activity category [25, 26]. The limitation of this *in vitro* examination was that we did not use erlotinib as a positive control, which is one of the drugs included in the NCCN Guideline for NSCLC cases [27]. In addition, the cytotoxic assay on the normal cell line to obtain the Selectivity Index (SI) value did not carried out because there was no tested compound with IC<sub>50</sub> values of <25  $\mu\text{M}$ .

### Conclusions

The derivatives of benzoxazine were synthesized in good yields (60–84%). The ADMET prediction resulted that the compounds were able to be absorbed through GIT, metabolized by CYP 450, and not hepatotoxic. From the result of *in vitro* evaluation and also *in silico* study, from the

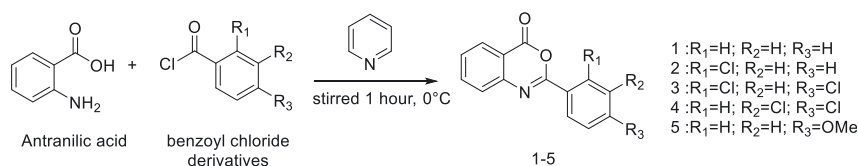


Figure 3: Synthesis of benzoxazines.

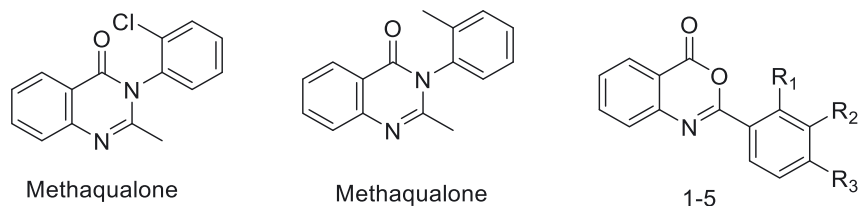


Figure 4: Chemical structures of Mecloqualone, Methaqualone and the synthesized compounds.

result of *in silico* and bioassay, compound **3** had strongly potential as anticancer activity compared other substituent, against human lung cancer cell line.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Not applicable.

**Ethical approval:** Not applicable.

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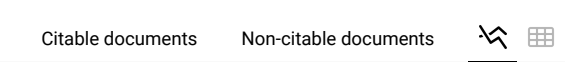
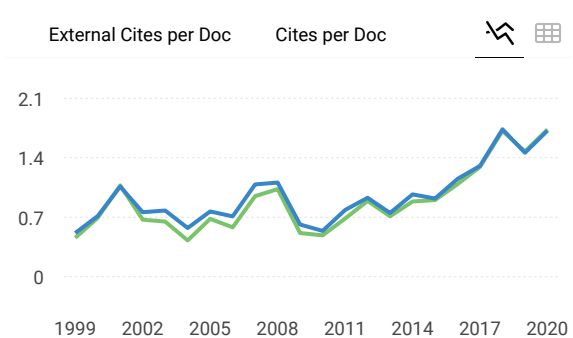
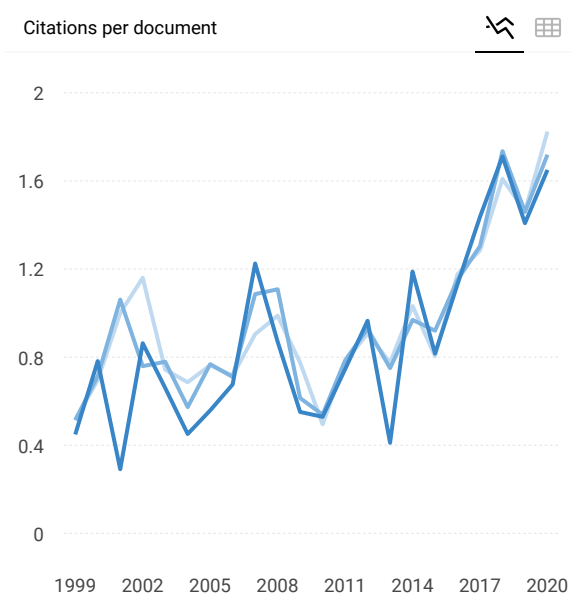
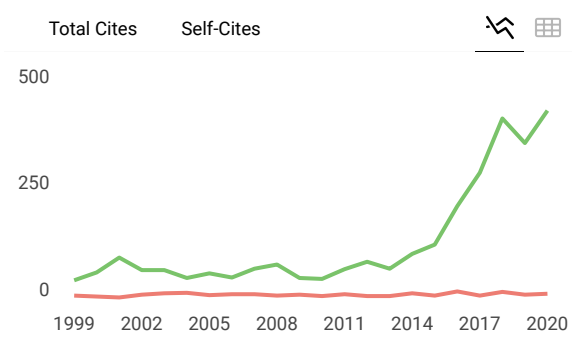
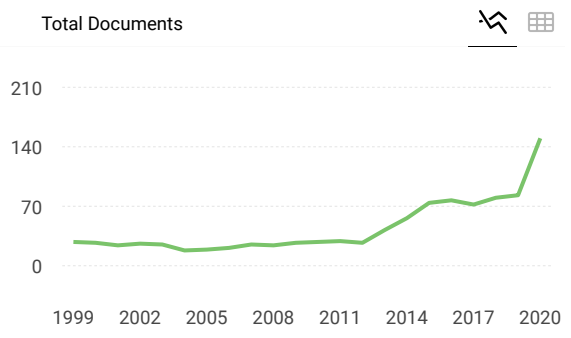
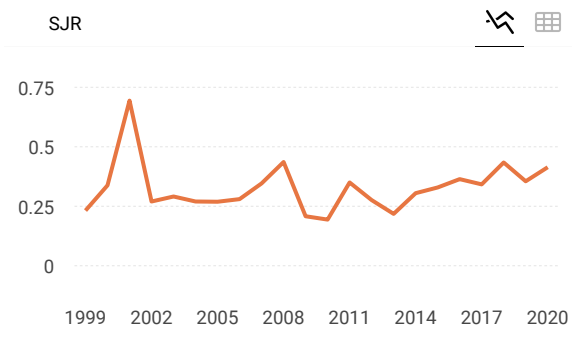
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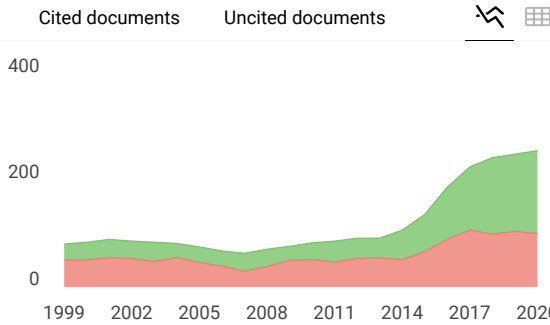
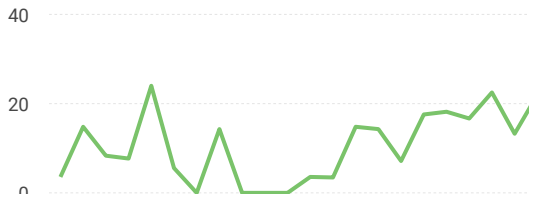
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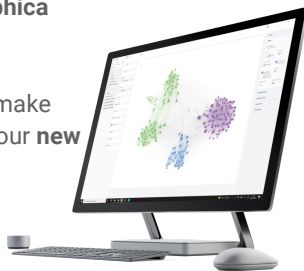
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