Synthesis of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one and Their Biological Activity Against A549 Cancer Cell Line through Methionyl-tRNA Synthetase Inhibition Approach on *in-silico* Studies.

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Abstract :

Purpose: The research aims to synthesis of 1,3-benzoxazine ring and evaluated their anticancer activity against human lung cancer (A549) and also their molecular docking studies approach, through methionyl-tRNA synthetase inhibition.

Methodology: the successful of synthesis process, obtained 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one was evaluated by 1D NMR (^{1}H-NMR and 1^{3}C-NMR), FTIR and UV spectra. The biological anticancer activity was evaluated by MTT Assay against human lung cancer (A549). Molecular docking studies was performed by Molegro Virtual Docker (MVD) version 5.5 as a software. The molecule target was docked into the active side on Methionyl-tRNA Synthetase (MRS),that was downloaded from www.pdb.org with PDB; ID 1PG2.

Results: based on all spectra data (^{1}H-NMR, ^{13}C-NMR, FTIR dan UV) obtained 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one in very good yield (90 %±2%' n=6), their anticancer activity through MTT Assay Method against A549 Cancer Cell Line by triplicate, obtained IC_{50}= 65.43 ±2.7 µg/mL and the result of molecular docking studies their rerank score -76.04 Kcal/mol, more higher than its native ligand (-93.50 Kcal/mol).

Keywords : synthesis, anticancer, *in-silico*, MTT Assay, 1,3-benzoxazine ring

1.Introduction.

Cancer is the biggest health problem to human both in the developed and developing countries (Ferley et al., 2019). According to the World Health Organization (WHO) 2015, the top 10 diseases causing the most deaths worldwide, one of them is lung cancer. Lung cancer ranks fifth out of 10 deadly diseases in the world. Based on existing data from 2000-2015 there was an increase in mortality of around 12 million to 17 million people each year ((Pietrangelo & Holland, 2017; Kesuma et al., 2018). Based on this problem, many researchers have been trying to investigate medicines to treat cancer because all medicines to treat cancer still have so many side effects, some could develop other cancer type (Joseph et. al., 2008).

Benzoxazine are compounds that are quite interesting to study, in addition to their unique molecular structure (heterocyclic consist of atoms C,N and O), also because it is known that benzoxazine derivatives have various biological activities (Coppola, 1999). Several studies have reported benzoxazine derivatives have anticancer activity (Bharathkumar et al., 2015; Zilifdar et al., 2014; Rudyanto at. al., 2015; Putra et al., 2016). Some of research were reported 1,3-benzoxazine ring has potential anticancer activity on inhibiting the growth of lung cancer through Methionyl-tRNA Synthetase Inhibition (Bharathkumar et al., 2015). MRS is a group enzyme have a function for transferring a specific amino acid to cognate tRNA to form aminoacyl-tRNA. This enzyme play rule for carrying the respective amino acid to the site of protein synthesis to begin translation at the initiation codon (Katzung et al., 2009; Finkel et al., 2009; Lüllmann et al., 2000). Increasing activity of MRS was reported in many evidence human cancers cell therefore MRS to be one targeted some of drug discovery to reduce cancers cell survival, proliferation and metastasis.

In this research, we synthesized 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one, that were evaluated its activity against human lung cancer cells by *in-vitro study* through MTT Assay method and its *in-silico* study was determined by observing the energy binding of the compound while interacting with Methionyl-tRNA Synthetase (MRS). In signal transduction path of cancer, Methionyl-tRNA Synthetase (MRS) has an important role for the growth of cancer cells. Therefore by constructing compound which inhibited this enzyme, we have great opportunity to generate anticancer agents

2.Material and Method

2.1Synthesis

All chemicals (anthranilic acid, benzoyl chloride, $NaHCO_3$), solvents (Ethanol 90 %, ethyl acetate, n-henxane), and catalyst (pyridine) were purchased from commercial branded such as Sigma Aldrich and Merck. Reactions were monitored with TLC

silica gel 60, GF 254, 0.2 mm layer thickness was purchased from Merck. Mobile phase for TLC using n-hexane : ethyl acetate (1:1) and the spots were visualized under UV-ray (254 nm). Melting points was measured with an Electrothermal melting point apparatus innotech DMP-600. IR spectra was obtained using a Jasco FT-IR 5300 Perkin-Elmer spectrometer using KBr disks as media. 1D-NMR(^{1}H- NMR and ^{13}C-NMR) spectra were obtained on JEOL JNM-ECS 600 (^{1}H-NMR: 600 MHz, ^{13}C-NMR: 151 MHz). We used DMSO-d6 as solven for ^{1}H-NMR and ^{13}C-NMR analysis. Chemical shifts were measured relative to internal standard Tetramethylsilane TMS (d: 0). MS spectra was measured with a JEOL JMS 600 spectrometer by using the ESI methods.

Anthranilic acid (0.05 mol) was dissolved in 10 mL pyridine. Benzoyl chloride was dropped wisely at cool temperature (0°C) with constant stirring. After stirring for 1 hour at about room temperature (25 °C), add the saturated bicarbonate acid (10%). Addition of $NaHCO_3$ solution (10%) was continued until the effervescence due to the evolution of carbon-dioxide ceased. Add some purified water and separated solid phase and liquid phase using Buchner. The purification of the solid phase was carried out by recrystallization using ethanol 90 % : aceton (5:1) (Noolvi et al., 2011; Noolvi & Patel., 2013; Rajasekhar et al., 2016; Putra et al., 2017).

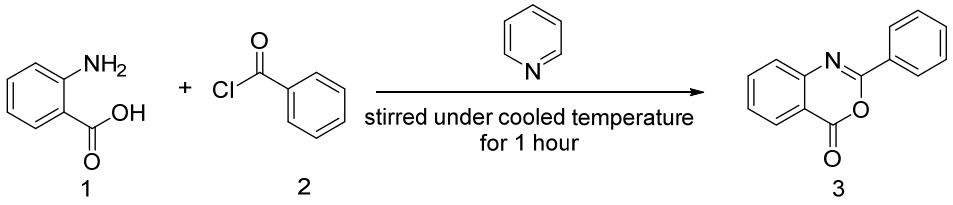


Figure 1. Synthesis of 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one from anthranilic acid (1) and benzoyl chloride (2)

2.2MTT Assay against Human lung cancer cells (A549).

Human lung cancer cells with code id A549 were got from Riken Cell Bank (Japan), and it was cultivated in an enhanced medium. The cell culture medium was used in this experiment was combination of 10% heat inactive FBS (Fetal Bovine Serum), DMEM (Dulbecco's modified Eagle's Medium), Amphotericin B (5.6 µg/mL) and Kanamycin (100µg/mL) both of antibiotics function to sterile the media, while 3 days-old cells was growth as test material. 1.00 µL of samples with the range of concentration 100-25 ppm (1% final concentration in DMSO solution) and 99.00 µL of A549 cells (5×103cells) were incubated with into a 96-well plate at 37°C for 3days or 72 hours. After removing medium and added 100.00 µL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), incubated for another 1.5 hours at CO2 incubator. Final step was replaced MTT solution with DMSO. The absorbance was scanned at λ540 nm with a 2300 EnSpire Multimode plate reader by PerkinElmer, Inc. We was used Doxorubicin as standard in positive control. The result of MTT Assay was performed in triplicate and reported as mean ± standard deviation.

2.3Molecular docking study

In-silico study was performed by using MVD (Molegro® Virtual Docker version 5.5).CS ChemBioDraw Ultra ver 11.0 (Cambridge Soft) was used to prepare compound 3 to building 3D chemical structure and to optimize their geometry structure were performed using MMFF94 energy (Thomas, 1996). Compound 3 was docked into the active side on Methionyl-tRNA Synthetase (MRS). MRS is a group enzyme have a function for transferring a specific amino acid to cognate tRNA to form aminoacyl-tRNA. They important play rule for carrying the respective amino acid to the site of protein synthesis to begin translation at the initiation codon. Increasing activity of MRS was reported in many evidence human cancers cell therefore the human MRS up-regulation in cancer renders it as a unique target and effective strategy to design inhibitors to reduce cancers cell survival, proliferation and metastasis (katzung et al., 2009; Bharathkumar et al., 2015). The structure of MRS enzyme (PDB ID: 1PG2) was downloaded from the Protein Data Bank (www.rcsb.org). The validation of docking was carried out by redocking its native ligand of the enzyme, namely 2-(6-amino-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol into its active site (Crepin et al., 2003). Criteria of acceptance is set with the value of Root Mean Square Deviation (RMSD) least than or equal 2.0 Å. After redocking process, the compound 3 was docked into active site of MRS enzyme. The binding affinity between ligand and enzyme (docking score) was evaluated using Rerank Score. Rerank score is one of the main parameters in molecular docking study. It is interaction energy between ligand and receptor, they was calculated base on external and internal ligand interaction with their receptor (Thomsen & Christensen., 2006). The smaller Rerank score value means the more stable ligand-receptor bonding, which predicted as a higher biological activity

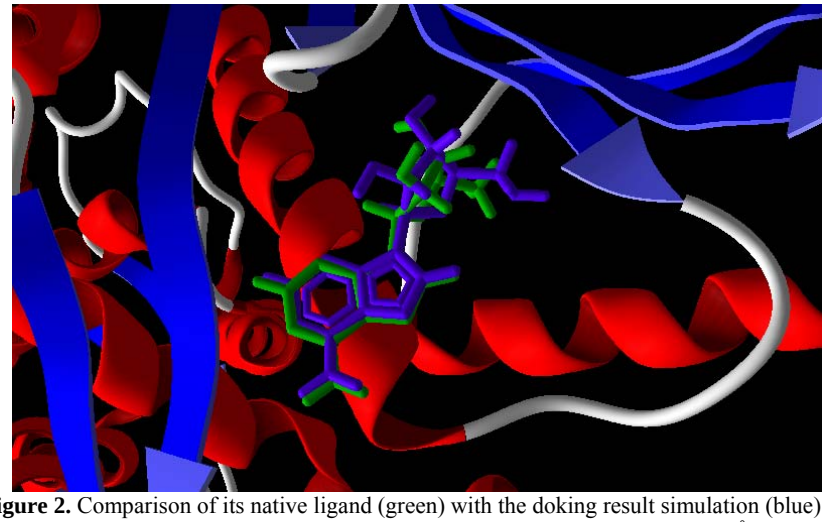


Figure 2. Comparison of its native ligand (green) with the doking result simulation (blue) by Molegro Virtual Docker (MVD) software Ver.5.5. The RMSD is 0.84Å

3.Result and Discussion

3.1 Synthesis

The reaction between anthranilic acid (1) and benzoyl chloride (2), they was dissolved in pyridine (free-water solvent) would be successfully synthesized and obtained 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one in very good yield (90 %±2%' n=6). The mechanism of this reaction consist of two steps. The first step for mechanism of reaction is amine functional group of (1) as nucleophile attacks carbonyl center of (2) via SN-acyl (addition following by elimination) see Figure 3. Pyridine as a catalyst plays a role in deprotonation process of the hydrogen atom of amine functional group. This yielded to a tetrahedral intermediate product which continue to form 3' shown at Figure 3. After that, the second step for mechanism of reaction is pyridine acted as deprotonating agent for carboxylic moiety of 3' to yield carboxylate anion which then proceeded to attack the resulting amide group intramolecularly (Noolvi et al., 2011; Noolvi & Patel., 2013; Putra et al., 2017). This cyclization resulted to a benzoxazine ring shown at Figure 4.

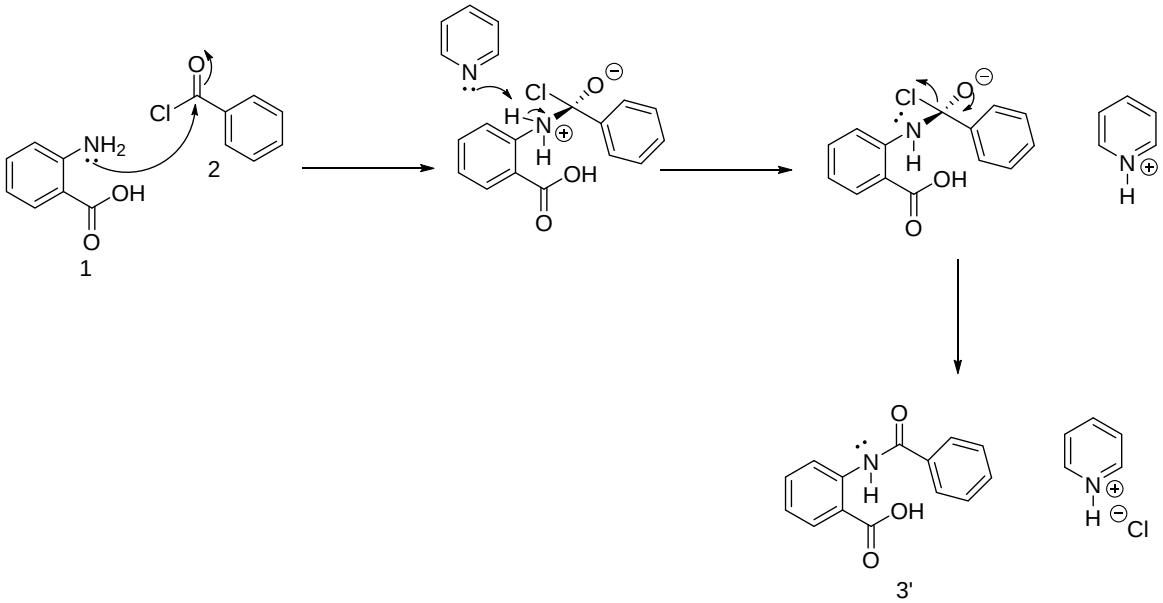


Figure 3. The first step for mechanism of reaction between anthranilic acid (1) and benzoyl chloride (2) to form 2-benzamidobenzoic acid (3')

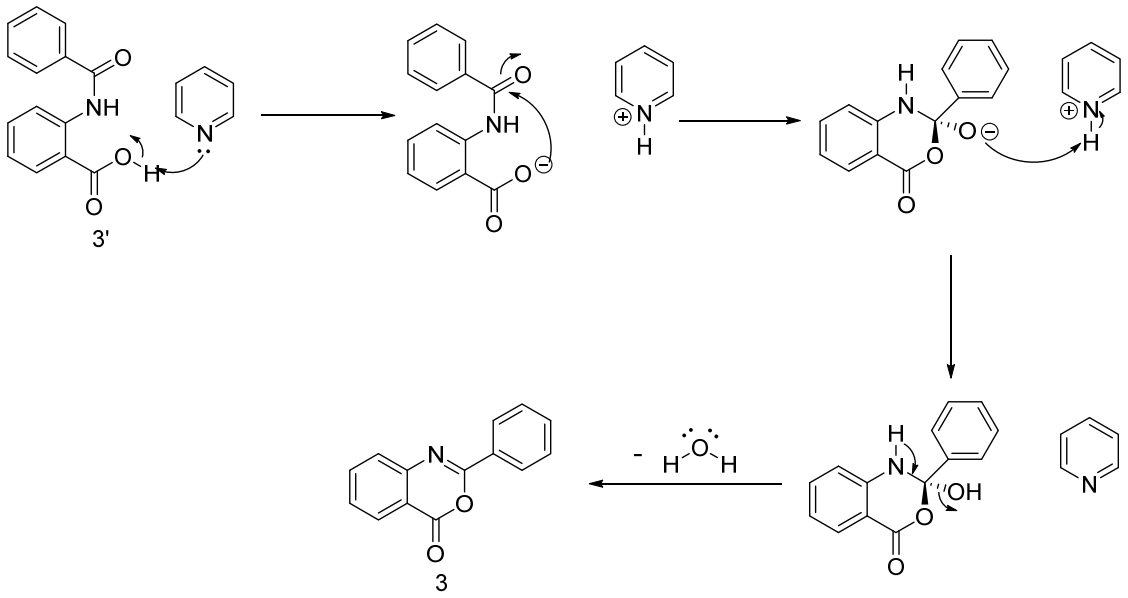


Figure 4. The second step for mechanism of reaction to form 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one

Determination of compound (3) was confirmed by 1D NMR (^{1}H-NMR, ^{13}C-NMR), MS, and IR spectral data. The 1H-NMR spectrum of compound (3) showed peaks in the aromatic region around δ 7.57-8.19 ppm, indicating the existence of 9 protons of aromatic ring shown at Figure 5. Meanwhile, ^{13}C-NMR similarly showed the presence of two aromatic rings shown at Figure 6. The total of carbon atom are 14. Furthermore, the presence of carbonyl fragment at δ 158.8 ppm and imine fragment at δ 156.4 ppm implied the formation of benzoxazine ring. Mass spectroscopy confirmed the compound 3 exhibited molecular weight of 224.07 ([M+H]+) shown at Figure 7, with mass deviation of 0.16 (< 5mmu) from theoretical molecular weight. The fragmentation result confirmed the molecular formula of $C_{14}H_9O_2N$. Ultimately, infrared spectrum data showed the formation of benzoxazine ring manifested in absorption band at 1764 cm^{-1} (C=O lactone bond) and 1614 cm^{-1} (-C=N bond) shown at Figure S8 (Pavia et al.,2009).

Detailed physicochemical and spectral data of the obtained compound of **2-phenyl-(4H) benzo[1,3]oxazin-4-one**
Obtained in white crystals, mp: 118-119°C. ^{1}H NMR (600 MHz, DMSO-d6) δ 8.18 (dd, J = 7.7, 1.7 Hz, 2H), 8.14 (dd, J = 7.8, 1.6 Hz, 1H), 7.93 (td, J = 7.7, 1.6 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.63 – 7.57 (m, 3H). The total of hydrogen atom are 9 atoms. ^{13}C-NMR (151 MHz, DMSO) δ 158.8, 156.4, 146.2, 136.8, 132.7, 130.0, 128.9 (2C), 128.5, 128.0, 127.8 (2C), 126.9, 116.9, The total of carbon atom are 14 atoms. FT-IR (KBr) cm-1 : 1764 (C=O lacton); 1599 and 1474 (C=C aromatic); 3040 (=C-H aromatic); 1614 (C=N); 1315 (C-N). ESI-MS m/z, [M+H]+=224. All these spectral data are in agreement with the structure of 2-phenyl-4*H*-benzo[1,3]oxazin-4-one

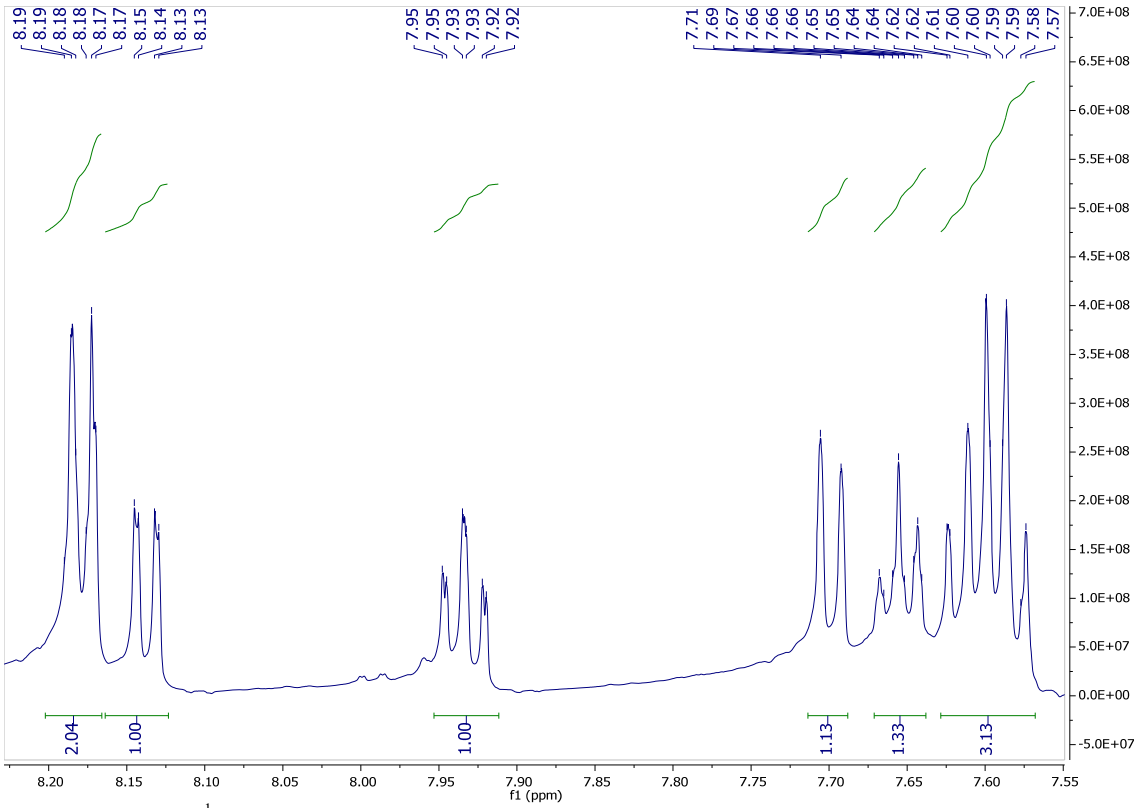


Figure 5. ^{1}H-NMR spectrum of 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one in (600 MHz, DMSO-d6)

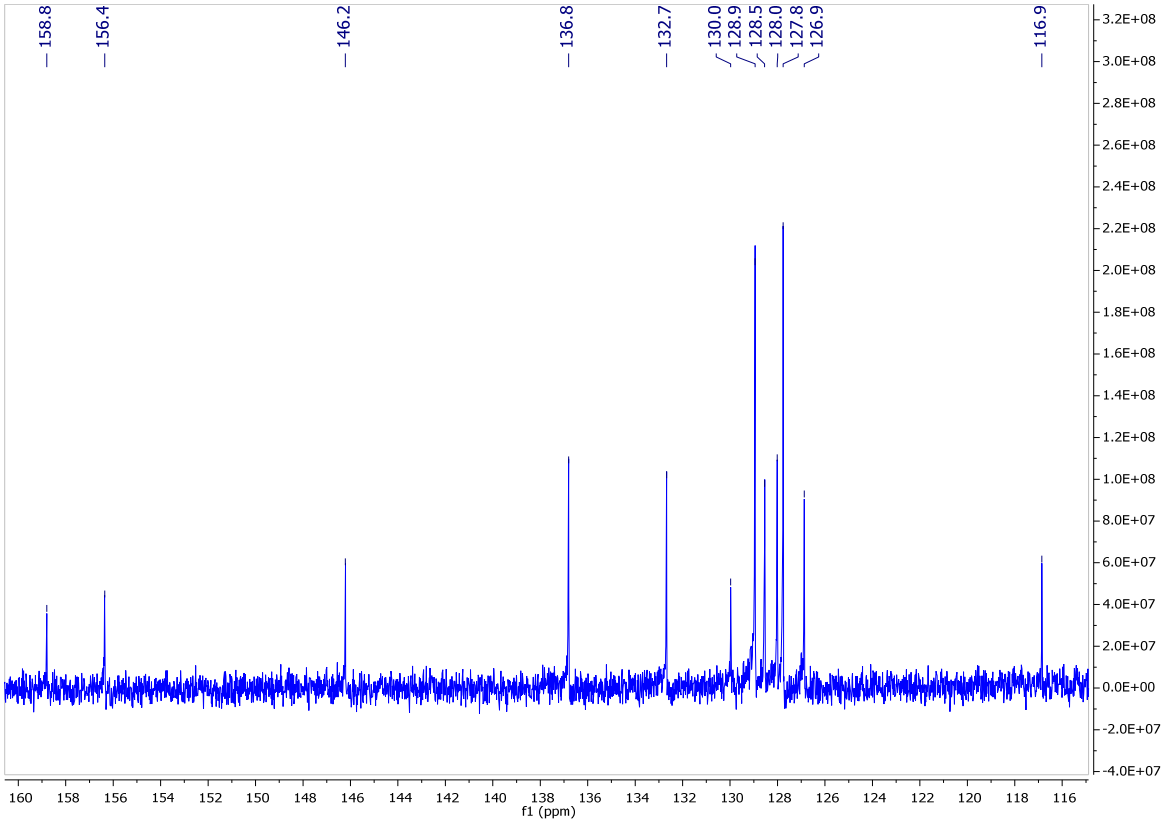


Figure 6. ^{13}C-NMR spectrum of 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one in (151 MHz, DMSO-d6)

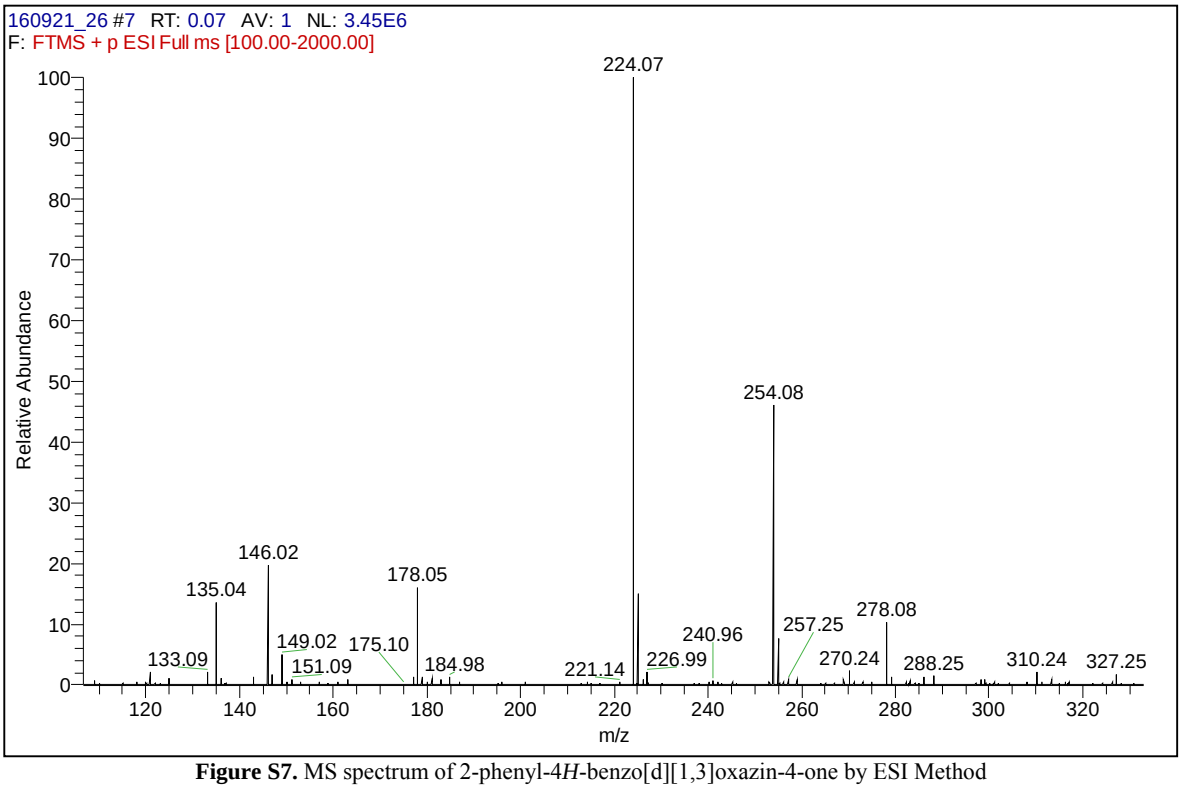


Figure S7. MS spectrum of 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one by ESI Method

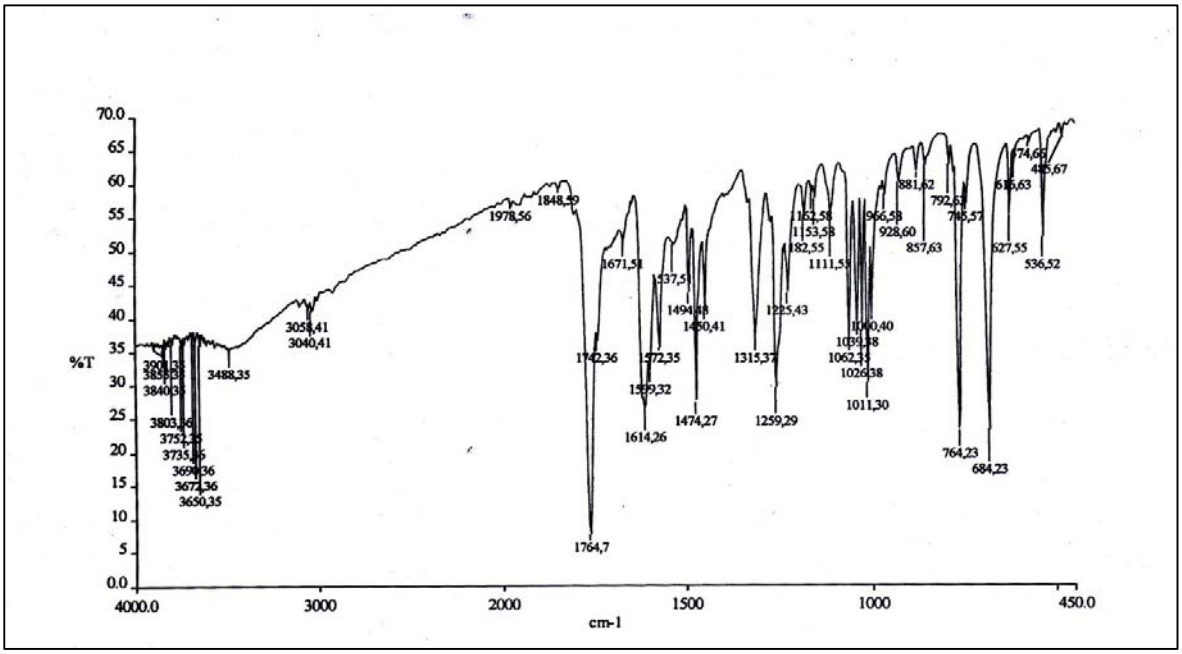


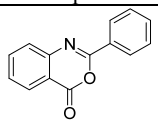
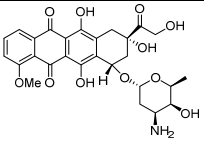
Figure 8. FT-IR spectrum of 2-phenyl-4*H*-benzo[d][1,3]oxazin-4-one in KBr pellet

3.2 Biological Assay

The result of MTT Assay against Human lung cancer cells (A549), compound (3) has anticancer activity with value of IC_{50} = 65.43 ±2.7 µg/mL as same as another research were reported by Bharathkumar et.al in 2015. Compound (3) have anticancer activity with IC_{50} value least than 100 µg/mL event though doxorubicin as positive control have IC_{50} value (14.61±2.3 µg/mL)

lower than compound (3) see table 1. The core structure of 1,3-benzoxazine ring was still believed have anticancer activity on inhibiting the growth of lung cancer although need optimize with another substituent to increasing potentially their activity.

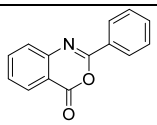
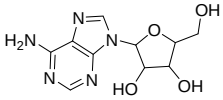
Tabel 1. The IC_{50} value of Human lung cancer cells (A549) growth inhibitory activity

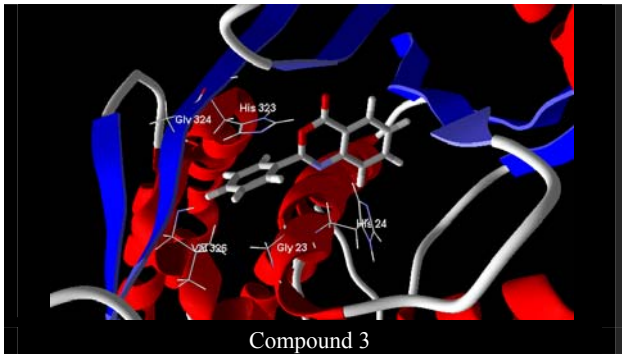
Compound	IC50 (µg/mL)
 3	65.43 ±2.7
 Doxorubicin as positive control	14.61±2.3

3.3 *In-silico* study

Based on molecular docking result (Table 2; Figure 9), it is shown that compound 3 has rerank score -76.04 ±0.03 Kcal/mol (n=3) more higher than its native ligand rerank score -93.48 ±0.07 Kcal/mol (n=3). Interaction between Compound 3 with Methionyl-tRNA Synthetase (MRS) showed just only steric interactions on residues such as Gly 23; His 24; His 323; Gly 324; Val 326. It is different with interaction between its native ligand with their enzyme, not only steric interactions (His 21 and Glu 27) but also it has hydrogen bond on amino acid residues such as Glu 27; His 28; Gly 294; Asp 296;Val 326, therefore rerank score of its native ligand more lower than compound 3, that means their native ligand more suitable interaction with MRS.

Tabel 2. Molecular docking result on Methionyl-tRNA Synthetase (MRS) active site

Compound	Rerank Score (Kcal/mol)	Doked Pose	Hydrogen Bond	Residual Involved	Steric Interaction	Residual Involved
 (3)	-76.04 ±0.03	√	-	-	5	Gly 23 His 24 His 323 Gly 324 Val 326
 (Native ligand)	-93.48 ±0.07	√	5	Glu 27 His 28 Gly 294 Asp 296 Val 326	2	His 21 Glu 27



Compound 3 Compound 3

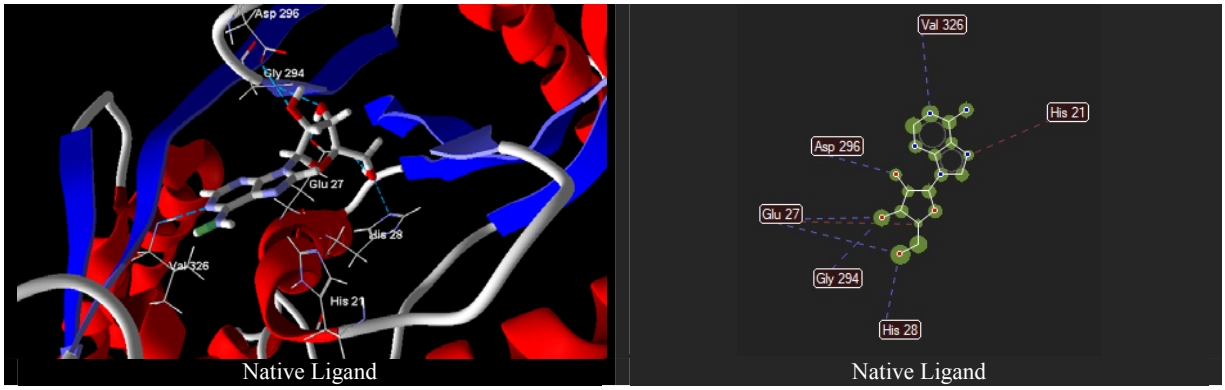


Figure 9. The Interaction between its native ligand and compounds 3 into active site Methionyl-tRNA Synthetase (MRS)

4. Conclusion

In this research we successfully synthesized 2-phenyl-4H-benzo[d][1,3]oxazin-4-one from starting material from anthranilic acid and benzoyl chloride in very good yields (90 %±2%' n=6). The compound of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one shown anticancer activity on inhibiting the growth of human lung cancer cell (A549) with IC_{50}= 65.43 ±2.7 µg/mL even though their anticancer activity lower than Doxorubicin, and also it has rerank score more higher than its native ligand when docked onto Methionyl-tRNA Synthetase (MRS) (PDB code:1PG2). On the other hand, we still believe if the core structure of 1,3-benzoxazine ring has anticancer activity on inhibiting the growth of lung cancer although they need optimize with another substituent to increasing potentially their activity.

Acknowledgement

We thank to Katsuyoshi Matsunami from Hiroshima University for helping us to obtained Human Lung Cancer cells A549 from Riken Cell Bank (Japan),

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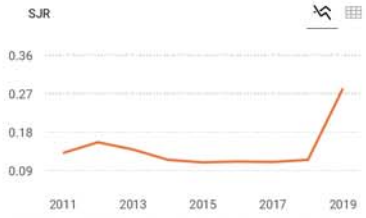

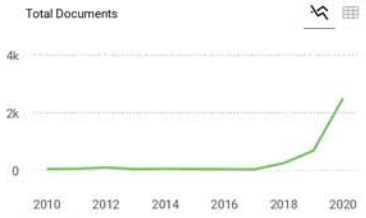

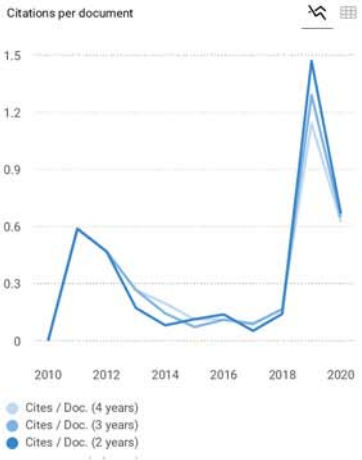

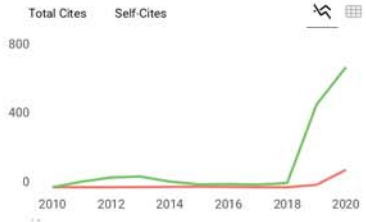

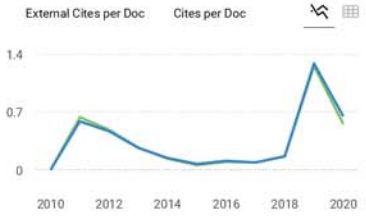

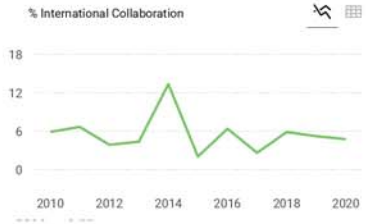

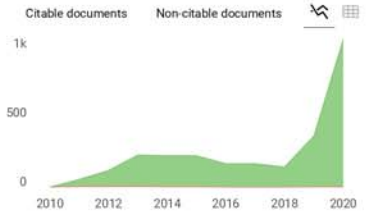

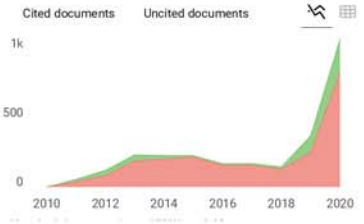

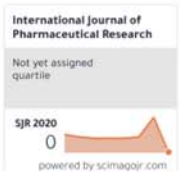

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ynthesis of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one and its Biological Activity Against A549 Cancer Cell Line through Methionyl-tRNA Synthetase Inhibition Approach on in-silico Studies.

Author: DINI KESUMA, GALIH SATRIO PUTRA , TEGAR ACHSENDO YUNIARTA, MELANNY IKA SULISTYOWATY, SISWANDONO , TUTUK BUDIATI

Abstract: Purpose: The research aimed to synthesis of 1,3-benzoxazinone ring and evaluated their anticancer activity against human lung cancer (A549) and also their molecular docking studies approach, through methionyl-tRNA synthetase inhibition. Methodology: The obtained 2-phenyl-4H-benzo[d][1,3]oxazin-4-one was evaluated by 1D NMR (1H-NMR and13CNMR), FTIR and UV spectra. The biological anticancer activity was evaluated by MTT Assay against human lung cancer (A549). Molecular docking studies was performed by Molegro Virtual Docker (MVD) version 5.5.The molecule target was docked into the active site on Methionyl-tRNA Synthetase (MRS),that was downloaded fromwww.pdb.org with PDB; ID 1PG2. Results: Based on the spectra data (1H-NMR, 13C-NMR, FTIR dan UV) 2-phenyl-4H-benzo[d][1,3]oxazin-4-one obtained was considered in very good yield (90 %±2%' n=6). Their anticancer activity throughout MTT assay method against A549 cancer cell line, showed the inhibitory concentration (IC50) of 65.43 ±2.7 µg/mL. Meanwhile the result from molecular docking studies indicated that their rerank score of -76.04 Kcal/mol was higher than its native ligand (-93.50 Kcal/mol). Conclusion: The compound 3 is potential to be developed as anticancer agent, so we need to optimize furthermore with another substituent to increase its activity toward A549 cell.

Keyword: Synthesis, anticancer, in-silico, MTT Assay, 1,3-benzoxazinone ring

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