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Synthesis, *In Vitro* Anticancer Activity and *In Silico* Study of some Benzylidene Hydrazide Derivatives

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Abstract. Some benzylidene hydrazides (**3a-e**) have been synthesized in three reaction steps from anthranilic acid in good yields, about 70-99%. The structures of the synthesized compounds were analyzed using spectroscopic methods. The compounds were evaluated its activity against human lung cancer, A549 cell line by MTT method and studied its molecular docking onto the protein tyrosine kinase (PDB ID: 1M17) by using Molegro® vs. 5.5. The data showed that N-(2-(2-(4-nitrobenzylidene)hydrazinecarbonyl)phenyl)benzamide (**3d**) which synthesized in 70% yield and has the highest activity on inhibiting the growth of A549 cell line with IC_{50} 10.9 µg/mL, which was linear with our *in silico* study. Compound **3d** has the smallest RS value -94.44 kcal/mol, lower than selected Ligand, Erlotinib.

Introduction

Cancer has become the leading cause of mortality number two worldwide. In 2018, it's estimated about 9.6 million people die because of cancer. Among several types of cancer, lung cancer is one of the most common cancers [1]. The cancer profile country from World Health Organization (WHO) data in 2014 showed that the incidence of lung cancer in Indonesia reached 34.696 cases and assumed to be the most life-threatening cancer as much 15.9% from 194.528 cases caused by cancer [2]. To date, many researchers have been trying to investigate medicines to treat cancer, but unfortunately that medicines still have so many side effects, where some could develop another cancer type [1]. Therefore, it needs further investigation to produce better drugs by conducting structure modification of drug candidates.

The *tyrosine kinase* is one of the kinases of the epidermal growth factor receptor (EGFR-TK) that has a primary role in signal transmission of cancer's pathway. The inhibition of this receptor can be a delightful challenge to cure cancer. As result, synthesis of EGFR-TK inhibitors is a feasible objective for the development of new anticancer therapy and erlotinib was accepted as EGFR-TK inhibitor for the non-small cell lung cancer treatment [3, 4].

In this work, we synthesized the derivatives of benzylidene hydrazide from anthranilic acid in multistep reactions. It is followed by an evaluation of the biological activity of the synthesized compounds against human lung cancer cells, A549 cells. We were also evaluating its molecular docking study to observe the resemblance of a ligand to its docking site through prediction of the energy of drug-receptor binding, which recognized as Rerank Score (RS) [5, 6].

Experimental Section

General. All chemicals are commercially available and purchased from registered suppliers. The ^{1}H- and ^{13}C-NMR spectra data of the compounds were measured on a Bruker Ultrashield 600 spectrometer at 600 MHz and 150 MHz, correspondingly. The molecular mass of the synthesized compounds was examined with a QSTAR XL NanoSpray™system. The accomplishment of the synthesis reactions was observed by using TLC method (Silica gel 60 F_{254} (E. Merck), with hexane:ethyl acetate (1.5:4) as eluent system. The melting point was determined on Electrothermal melting point equipment without correction. The IR and UV spectra were recorded on Jasco FT-IR 5300 and Perkin-Elmer Lambda EZ-201, respectively. *In silico* study was carried out using Molegro® Virtual Docker 5.5. The structures both 2D and 3D of the tested compounds and the ligand were determined using ChemBioDraw® Ultra 12.0. For biological evaluation, absorbance was assessed using a 2300 EnSpire Multimode plate reader (PerkinElmer, Inc.) at wavelength 540 nm.

Synthesis of 2-phenyl-4H-benzo-[1,3]-oxazin-4-one (1) and N-(2-(hydrazinecarbonyl) phenyl)-benzamide (2). Anthranilic acid (10 mmol) was dissolved in pyridine and a solution of benzoyl chloride (15 mmol) was added wisely at 0 °C, then being stirred for an hour at room temperature. After completion of the reaction by checking by TLC method, solution of bicarbonate acid (10%) was poured to the mixture until the bubble discharged. Filtered off the mixture and washed with distilled water and recrystallized from ethanol 96% to obtain **1** [7]. Compound **1** (4 mmol) was reacted with hydrazine hydrate (4 eq) in absolute ethanol. The mixture was refluxed for 3 hours. After being allowed to room temperature, it needed to be recrystallized from ethanol 96% to produce **2** [8].

Synthesis of N-(2-(2-benzylidenehydrazinecarbonyl)phenyl)benzamides (3a-e). Compound **2** (1 mmol) was dissolved in ethanol then added the proper benzaldehydes (2 eq) and few drops of concentrated HCl. The mixture was being stirred for 2 to 3 hours at room temperature. After completion of the reaction by checking using TLC method, added some solution of bicarbonate acid (10%) to the mixture until the bubble discharged. Filtered off the mixture and washed with distilled water and recrystallized from ethanol 96% to obtain **3a-e**.

N-(2-(2-benzylidenehydrazinecarbonyl)phenyl)benzamide (3a). Yield: 99%, m.p = 201-202 °C; ^{1}H NMR (600 MHz, DMSO) δ 12.13 (s, 1H), 11.96 (s, 1H), 8.59 (d, J = 8.3 Hz, 1H), 8.48 (s, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.6 Hz, 2H), 7.65 – 7.62 (m, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 7.0 Hz, 3H), 7.28 (s, 1H). ^{13}C NMR (150 MHz, DMSO) δ 165.04 (s), 164.57 (s), 149.16 (s), 139.37 (s), 134.42 (s), 134.04 (s), 132.64 (s), 132.12 (s), 130.39 (s), 128.93 (s, 2C), 128.88 (s, 2C), 128.61 (s), 127.59 (s, 2C), 127.19 (s, 2C), 123.14 (s), 121.07 (s), 120.46 (s). HRESIMS (m/z) = 366.1210 $[M+Na]^{+}$ (calculated for $C_{21}H_{17}O_2N_3Na$: 366.1213).

N-(2-(2-(4-(dimethylamino)benzylidene)hydrazinecarbonyl)phenyl)benzamide (3b). Yield: 91%, m.p = 260-261 °C; ^{1}H NMR (600 MHz, DMSO) δ 12.10 (s, 1H), 11.84 (s, 1H), 8.60 (d, J = 8.3 Hz, 1H), 8.32 (s, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.90 (d, J = 7.8 Hz, 1H), 7.75 – 7.60 (m, 4H), 7.56 (d, J = 8.8 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 2.98 (s, 6H). ^{13}C NMR (150 MHz, DMSO) δ 164.50 (s), 164.47 (s), 151.74 (s), 150.12 (s), 139.35 (s), 134.43 (s), 132.38 (s), 132.12 (s), 128.96 (s, 2C), 128.73 (s, 2C), 128.46 (s, 2C), 127.01 (s, 2C), 123.05 (s), 121.16 (s), 120.78 (s), 120.41 (s), 111.78 (s, 2C), 39.74 (s, 2C). HRESIMS (m/z) = 409.1639 $[M+Na]^{+}$ (calculated for $C_{23}H_{22}O_2N_4Na$: 409.1635).

N-(2-(2-(4-methoxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3c). Yield: 93%, m.p = 194-195 °C; ^{1}H NMR (600 MHz, DMSO) δ 12.00 (s, 2H), 8.58 (d, J = 8.2 Hz, 1H), 8.41 (s, 1H), 7.96 (d, J = 7.4 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.62 (dd, J = 18.9, 7.1 Hz, 4H), 7.28 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.9 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (150 MHz, DMSO) δ 164.79 (s), 164.51 (s), 161.10 (s), 149.07 (s), 142.08 (s), 139.33 (s), 134.41 (s), 132.52 (s), 132.12 (s), 128.96 (s, 2C), 128.54 (s), 127.03 (s, 2C), 126.55 (s), 123.10 (s), 120.94 (s), 120.44 (s), 114.60 (s), 114.40 (s, 2C), 55.33 (s). HRESIMS (m/z) = 396.1319 $[M+Na]^{+}$ (calculated for $C_{22}H_{19}O_3N_3Na$: 396.1319).

N-(2-(2-(4-nitrobenzylidene)hydrazinecarbonyl)phenyl)benzamide (3d). Yield: 70%, m.p = 243-244 °C; ^{1}H NMR (600 MHz, DMSO) δ 12.38 (s, 1H), 11.79 (s, 1H), 8.53 (d, *J* = 12.5 Hz, 2H), 8.29 (d, *J* = 7.9 Hz, 2H), 8.04 – 7.89 (m, 5H), 7.62 (dd, *J* = 26.1, 6.4 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO) δ 165.23 (s), 164.61 (s), 148.00 (s), 146.35 (s), 140.30 (s), 139.29 (s), 134.35 (s), 132.80 (s), 132.10 (s), 128.89 (s, 2C), 128.68 (s), 128.17 (s, 2C), 127.06 (s, 2C), 124.04 (s, 2C), 123.22 (s), 123.20 (s), 121.29 (s). HRESIMS (*m/z*) = 411.1062 $[M+Na]^+$ (calculated for $C_{21}H_{16}O_4N_4Na$: 411.1064).

N-(2-(2-(4-hydroxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3e). Yield: 76%, m.p = 254-255 °C; ^{1}H NMR (600 MHz, DMSO) δ 12.04 (s, 1H), 11.94 (s, 1H), 10.00 (s, 1H), 8.60 (d, *J* = 8.3 Hz, 1H), 8.37 (s, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.62 (ddd, *J* = 11.6, 10.9, 6.0 Hz, 6H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, DMSO) δ 164.72 (s), 164.50 (s), 159.74 (s), 149.55 (s), 139.36 (s), 134.43 (s), 132.13 (s), 129.15 (s, 2C), 128.95 (s, 2C), 128.51 (s), 127.03 (s, 2C), 125.00 (s), 123.10 (s), 123.08 (s), 120.89 (s), 120.39 (s), 115.78 (s, 2C). HRESIMS (*m/z*) = 382.1166 $[M+Na]^+$ (calculated for $C_{21}H_{17}O_3N_3Na$: 382.1162).

Biology Activity (Human lung cancer cell growth inhibition assay). This experiment was performed using A549 cell line, obtained from Riken (RCB3677) by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method. The procedure of this assay was referred to the reference without any modification. Doxorubicin was used as a positive control. All the tested compounds were prepared in DMSO solution. The cell growth inhibition was calculated using the following equation:

$$\% \text{ Inhibition} = [1 - (A_{\text{sample}} - A_{\text{blank}}) / (A_{\text{control}} - A_{\text{blank}})] \times 100 \quad (1)$$

IC_{50} was determined as the concentration of sample to inhibit 50% of the growth of cancer cells. The smaller the IC_{50} value of the compound compared to the standard compound, the higher activity of the compound to inhibit A549 cancer cells [9].

***In silico* study.** The receptor EGFR-TK (code: 1M17) and its comparative ligand (Erlotinib) were downloaded from Protein Data Bank (www.pdb.org). After gaining the crystal structure of 1M17 and its irreversible inhibitor, the receptor-ligand complexes were assessed in its active cavity [6]. The procedure of this evaluation based on the reference [10]. The RS obtained from *in silico* study can be interpreted as a prediction bonding interactions between drugs and its receptors. The smaller RS shows the level of synchronization between ligand-receptors' interactions, which is influenced by hydrogen bonds, hydrophobic interactions, and interactions electronic. The smaller the RS value, the more stable the bond between ligand and receptor. Therefore, strong interaction entailed high biological activity. It has been reported that the determination of the connection between a molecule and its docking protein engaged in signal transduction. This fact can be a tool to identify promising biological activity, in addition to possible mechanisms of action [11].

Results and Discussion

The derivatives of benzylidene hydrazide were synthesizing in multi-steps of reaction as summarized in the synthesis pathway (Fig. 1). Anthranilic acid was reacting with benzoyl chloride in the presence of pyridine, generated benzoxaxine **1** through nucleophilic substitution of an amino group from anthranilic acid to carbonyl group of benzoyl chloride and followed by condensation [10, 11]. Subsequent reaction with hydrazine hydrate produced compound **2**, which can be confirmed from the ^{1}H-NMR and its mass spectra. Conversion compound **2** into benzylidene hydrazides (**3a-e**) through adding of benzaldehyde and its derivatives using acid catalyst [12].

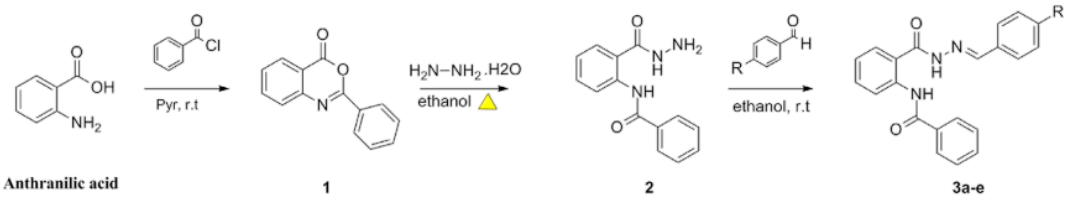
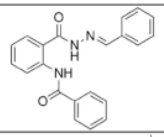
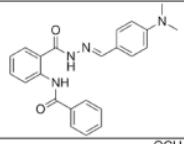
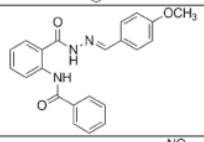
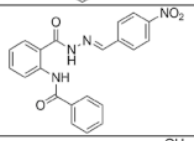
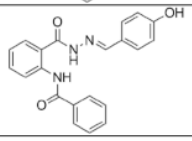


Figure 1. Synthesis pathway for the title compounds (**3a-e**)

Different groups at different positions on the aromatic ring will affect the percentage of the reaction. Drug candidates are often examined according to log *P*, it's because lipophilicity is one of major influential factors in a compound's absorption, distribution in the body, penetration across important membranes and biological barriers, metabolism, and excretion process. Based on 'Lipinski's Rule, the log *P* of a compound should be less than 5 [6]. The higher the log *P* value, the more lipophilic the active compound. All the synthesized compounds have log *P* less than 5. From Table 1, we can figure out the substituent, yields, and physical characterization of the product that resulted in this step reaction.

Table 1. Structure, yield, and physical properties of the benzylidene hydrazides

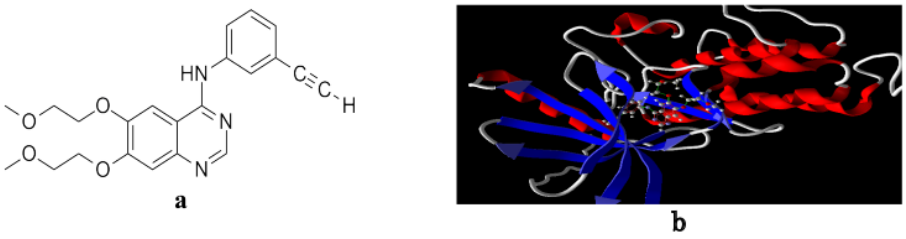
Compound	R	Structure	Yield (%)	MR	Log *P*
3a	H		99	343.39	4.17
3b	4-N(CH$_3$)$_2$		91	386.45	4.45
3c	4-OCH$_3$		93	373.41	4.04
3d	4-NO$_2$		70	388.38	3.22
3e	4-OH		76	359.39	3.78

The data of IR, ^{1}H-NMR, ^{13}C-NMR was employed for the determination of the chemical structure of products. In the region 1650-1637cm^{-1}, benzylidene hydrazides (**3a-e**) showed IR absorption band as sharp peak for C=O group [13]. H-NMR of compound **2** showed a single peak at 4.69, 10.20, 12,56 ppm of four protons, which attached the amine group and also multiplet peak from 7.16 to 8.67 ppm of nine protons of two benzenoid rings. H-NMR of compound benzylidene hydrazide **3a** showed single sharp peak at 11.96, 12.13 ppm of each one proton, which attached the amine group and also multiplet peak from 7.28 to 8.59 ppm of 15 protons of two benzenoid rings. The data from C-NMR of **3a** showed there are two carbons of carbonyl group at 164.6 and 165.0 ppm. H-NMR of compound benzylidene hydrazyde **3b** showed there was single peak as many six protons as two methyl groups at 2.98 and 39.7 ppm from C-NMR data. H-NMR of **3c** showed single sharp peak of

amine group's proton at 12.00 ppm as two protons and also singlet peak of methoxy group at 3.81 ppm. The data from C-NMR of **3c** showed there is **a** methoxy group at 55.5 ppm. Mass spectra of the products exhibited a molecular ion peak $M+Na^+$ at an *m/z* related to their molecular formula.

All the synthesized products were being assayed its ability to inhibit the growth of human lung cancer cells. The IC_{50} value of the compound was shown in Table 2. Among five synthesized benzylidene hydrazides, compound **3e** has the highest activity against A549 cancer cells with IC_{50} value 35.39 µg/mL. It can be assumed that nitro group at *para* position has the lowest hindrance to the related receptor of the cell. The benzylidene hydrazide **3a-c** showed very small activity against A549 cancer cells. The positive control has an IC_{50} value 14.61 µg/mL. The experiment was carried out by three times replication and represented as mean ± SE.

Molecular modeling is usually conducted to determine the affinity of a ligand to its docking site through the evaluation of the energy of drug-receptor binding. Receptor validation was performed by redocking native ligand Erlotinib with TKIs receptors with acceptance parameter, the Root Mean Square Deviation (RMSD)<2.0 Å. The RMDS value of the Erlotinib ligand redocking process with TKI was 1.17 Å. The N-(2-(2-benzylidenehydrazine-1-carbonyl)phenyl)benzamide was docked to the active site of the receptor's cavity, which occupied by Erlotinib. The 2- and 3-dimensional structure of Erlotinib and the ribbon structure of tyrosine kinase 1M17 was shown in Fig. 2.



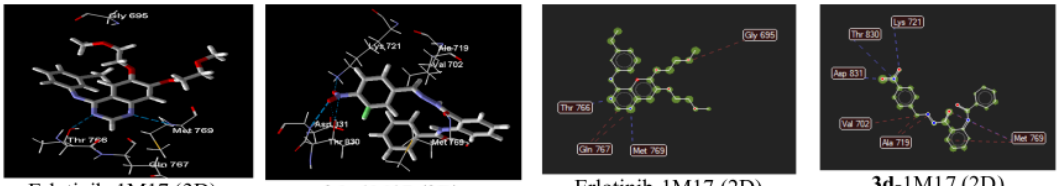
a **b**

Figure 2. **(a)** 2D structure of Erlotinib. **(b)** Ribbon structure of Tyrosine kinase 1M17 and Erlotinib

Table 2. The IC_{50} value and Rerank score of the title products

Compound	IC_{50} (µg/mL)	Rerank score (kcal/mol)
3a	90.88 ±1.2	-79.10
3b	>100	-78.52
3c	93.52±4.3	-80.84
3d	35.39±2.5	-94.44
3e	36.08±2.2	-84.88
Positive control	14.61±2.3	not tested
Ligand	not tested	-85.90

The existence of proton acceptors such as N and O of nitro group in *para* position of **3d** causes hydrogen bond interactions, which occur on the active site of the TKs receptor, which decreased the rerank score on the docking results. From Table 2, compounds **3d** has RS value -94.44 kcal/mol, lower than erlotinib (RS value -85.90 kcal/mol). Other synthesized compounds have RS value range of -80.84 to -67.94 kcal/mol which is higher than RS of erlotinib. From Fig. 3, the native ligand inhibited TKIs receptors with hydrogen bonds on amino acid residues Thr 766 and Met 769 and steric interactions on Gly 695 and Gln 767 from TKIs receptors. The compound **3d,** which has hydrogen bonding and steric interaction to the receptor of amino acid's residues: Met 769, Lys 721, Thr 830, Asp 831, Met 199 and Glu 219. The docking results proved that benzylidene hydrazide **3d** has the highest anticancer activity than any other tested compounds. From Table 2, it can be concluded that RS value of the evaluated compounds has a linear correlation with the IC_{50} value against human lung cancer cell, A549.



Erlotinib-1M17 (3D) **3d** -1M17 (3D) Erlotinib-1M17 (2D) **3d**-1M17 (2D)

Figure 3. Interaction of Erlotinib and compound **3d** with receptor 1M17 in 2D and 3D structure

Summary

We have generated five compounds of benzylidene hydrazides, which differ only in one functional group in the *para* position in good yields. The molecular docking study of these derivatives showed **3d** has the highest RS value and also the highest activity on inhibiting the growth of A549 cell. Therefore, benzylidene hydrazides can be elaborated furthermore to be new medicine for lung cancer.

Acknowledgments

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