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## *N*-(2-(2-Benzylidenehydrazinecarbonyl)phenyl)benzamides: Synthesis, Cytotoxic, Antioxidant Activity and Molecular Docking Studies

Melanny Ika Sulistyowaty<sup>1</sup>, Galih Satrio Putra<sup>2</sup>, Wang Zhichao<sup>3</sup>, Tutuk Budiati<sup>4</sup>

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**Abstract:** This study's purpose was to continue our research by acquiring novel anticancer candidates, the derivatives of *N*-(2-(2-benzylidenehydrazinecarbonyl)phenyl)benzamide. The benzamides were synthesized from the starting material, anthranilic acid. The products were examined for their antioxidant activity and bioactivity against human lung cancer in cell line A549. This study also reported the molecular interaction with tyrosine kinase (PDB ID: 1M17) by *in silico* method. The synthesis was conducted in three reaction steps, consisting of nucleophilic substitution, dehydration reaction, and nucleophilic addition. *In vitro* anticancer activity of the compounds was examined in the A549 cell line by using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) method. Free radical scavenger activity of these compounds was also evaluated by DPPH (2,2,1-diphenyl-1-picrylhydrazyl) assay. The virtual molecular docking study was performed using Molegro® version 5.5. The derivatives of *N*-(2-(2-benzylidenehydrazinecarbonyl)phenyl)benzamide were synthesized in good yields. Among the synthesized compounds, *N*-(2-(2-(2-hydroxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (**3c**) had the highest activity in terms of inhibiting the growth of the A549 cell line, with IC<sub>50</sub> of 10.88 ± 0.82 µg/mL, which was linear with the docking result. Meanwhile, *N*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (**3f**) possessed the highest antioxidant activity, with IC<sub>50</sub> of 37.23 ± 3.76 µg/mL.

**Keywords:** synthesis, benzamides, cancer, antioxidant, PDB ID 1M17, A549.

## *N*-(2-(2-苯甲撑脒基羰基)苯基)苯甲酰胺的合成·細胞毒性·抗氧化活性和分子對接研究使用结构偏最小二乘方程的影响巴厘岛社会响应地震信息的因素

**摘要:** 這項研究的目的是通過獲得新的抗癌候選物 *N*-(2-(2-苄叉脒基羰基)苯基)苯甲酰胺的衍生物來繼續我們的研究。苯甲酰胺由原料鄰氨基苯甲酸合成。檢查產物在細胞系一種 549 中的抗氧化活性和對人肺癌的生物活性。該研究還通過計算機方法報導了與酪氨酸激酶 (PDB ID: 1M17) 的分子相互作用。合成在三個反應步驟中進行, 包括親核取代, 脫水反應和親核加成。使用 MTT (3-(4,5-二甲基噻唑-2-基)-2,5-二苯基-四唑溴化物) 方法在一種 549 細胞系中檢查了化合物的體外抗癌活性。還通過 DPPH (2,2,1-二苯基-1-苦瓜酰肼) 分析評估了這些化合物的自由基清除劑活性。虛擬分子對接研究使用 5.5 版進行。以良好的產率合成了 *N*-(2-(2-亞苄叉脒基羰基)苯基)苯甲酰胺的衍生物。在合成的化合物中, 就抑制一種 549 細胞系的生長而言, *N*-(2-(2-(2-(2-羥基苄叉基)脒基)羰基)苯基)苯甲酰胺 (**3c**) 的活性最高, 我知道了 50 為 10.88±0.82 微克/毫升, 與對接結果呈線性關係。同時, *N*-(2-(2-(2-(4-羥基-3-甲氧基亞苄基)脒基)羰基)苯基)苯甲酰胺 (**3f**) 具有最

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高的抗氧化活性，我知道了 50 為  $37.23 \pm 3.76$  微克/毫升巴厘岛是一个容易发生板块碰撞活动和弗洛雷斯登高断裂俯冲过程中产生的反吹地震的地区。巴厘岛东北部弗洛雷斯上升断层的地质结构引发了一场大地震，随后海啸席卷了巴厘岛南部和北部。鉴于巴厘岛发生地震的可能性巨大，有必要采取战略措施来衡量面对地震的社区准备水平。并为来巴厘岛旅游的游客提供信息。社区准备也是确保游客安全和舒适的一部分。这项研究将调查影响巴厘岛人民准备应对气象，气候和地球物理局发布的地震信息的因素。数据分析使用结构方程模型-偏最小二乘（扫描电镜）方法。结果表明，风险信念，社区参与，批判意识，信念，地震知识，地震经验，参与灾害教育和培训以及关于减灾的知识对巴厘岛的巴厘岛人的备灾产生了积极的影响。面对地震灾害。

**关键词：**合成，苯甲酰胺，癌症，抗氧化劑，PDB ID 1M17，一种 549 地震，准备，结构方程建模，偏最小二乘。

## 1. Introduction

Our previous study revealed that the derivatives of benzylidenehydrazide with a polar substituent, such as those with a hydroxyl and nitro group at *p*- position, were capable of being further developed as an anticancer drug [1]. In this research, several compounds with a certain functional group at another position were synthesized to determine their activity with respect to inhibiting the growth of the human lung cancer cell line, and their antioxidant activity and drug-receptor binding energy was evaluated through an *in silico* experiment.

The starting material used in this study was anthranilic acid, which is regarded as a good pharmacophore agent. This compound is regularly used in drug discovery design [2], [3]. The *N*-(2-(2-benzylidenehydrazinecarbonyl)phenyl)benzamides were synthesized by reacting anthranilic acid with benzoyl chloride with the presence of pyridine as basic catalyst in room temperature. After two subsequent reactions, the products were obtained in 70-90 % yields.

In the last decade, quinazolines have appeared as a useful scaffold for the inhibition of various receptor tyrosine kinases. In the signal transduction path of cancer, the tyrosine kinases have a vital role. The most commonly investigated of these is the epidermal growth factor receptor (EGFR). Jiao *et al.* reported EGFR as a cell surface receptor that performs an essential task in regulating survival and apoptosis of epithelial cells and tumors of epithelial cell origin. Overexpression of EGFR and its ligands exists in some epithelial tumor cells, including lung cancer, especially non-small-cell lung carcinoma (NSCLC) [4], [5]. Some studies presented a series compounds containing quinazoline and ring-opened quinazolines as EGFR inhibitors [6], [7].

In this research, the synthesized compounds (3a-3f) were evaluated to ascertain their free radical scavenging capacity, their activity against human lung cancer cell line by *in vitro* study, and also its molecular docking characteristics by observing the energy of the synthesized compounds when bonding with tyrosine kinase (TK) receptor. To the best of our knowledge, *N*-(2-(2-(3-nitrobenzylidene)hydrazine-carbonyl)phenyl)-benzamide (3b) and *N*-(2-(2-(2-methoxybenzylidene)hydrazine-carbonyl)phenyl)-benzamide (3e) have not yet been reported. Therefore, this study is reporting synthesis of *N*-(2-(2-(3-nitrobenzylidene)hydrazine-carbonyl)phenyl)-benzamide (3b) and *N*-(2-(2-(2-methoxybenzylidene)hydrazine-carbonyl)phenyl)benzamide for the first time, and their activity as anticancer is evaluated by conducting an *in silico* study and against A549 cancer in an *in vitro* experiment.

## 2. Materials and Method

### 2.1. Synthesis of the Title Compounds

#### 2.1.1. Synthesis of Compounds 1 and 2

Benzoyl chloride (15 mmol) was added drop by drop at 0°C into anthranilic acid (10 mmol) solution in pyridine. After stirring for 60 minutes at 30°C, saturated bicarbonate acid was added. The purification was carried out by recrystallization using ethanol [8-10]. For the next reaction, compound 1, namely 2-phenyl-4H-benzo-[1,3]-oxazin-4-one (4 mmol) was dissolved in ethanol, and hydrazine hydrate (16 mmol) was added and refluxed for 3 hours. Compound 2 (*N*-(2-(hydrazinecarbonyl)phenyl)-benzamide) was purified by ethanolic recrystallization [1], [11].

### 2.1.2. Synthesis of *N*-(2-(2-benzylidenehydrazine-carbonyl) phenyl)-benzamides (3a-3f)

Each of the appropriate benzaldehyde (*o*-NO<sub>2</sub> benzaldehyde, *m*-NO<sub>2</sub> benzaldehyde, *o*-OH benzaldehyde, *m*-OH benzaldehyde, *o*-OCH<sub>3</sub> benzaldehyde, and vanillin) (2 mmol) was mixed with the ethanolic solution of Compound 2 (0.5 eq). A few drops of concentrated HCl were added to the mixture, and the reaction proceeded for 3 hours at room temperature. Collected solid products were recrystallized from ethanol.

All the structures of synthesized compounds were characterized using the spectroscopy method. The NMR (Nuclear Magnetic Resonance) spectra data were measured on a Bruker Ultrashield 600 spectrometer with *d*-DMSO (deuterated-Dimethyl sulfoxide) as the solvent and reported in chemical shift (ppm) and coupling constant (*J*) in hertz for <sup>1</sup>H-NMR. The MS (Mass Spectrometry) data of products were determined using the QSTAR XL NanoSpray™ system by the electrospray ionization (ESI) method. Melting points were tested on electrothermal melting point equipment and corrected. The IR data were recorded on an FT-IR Perkin-Elmer Spectrum One spectrometer. The UV-vis spectra of the compounds were determined with the UV-Vis HP 8452A Spectrophotometer.

## 2.2. Biological Activity Evaluations of the Tested Compounds

### 2.2.1. DPPH Assay

Antioxidant activity of the tested compounds was observed by employing the DPPH assay. The absorbance of 99 μL of compounds dissolved in 99 μL of MeOH was determined at 515 nm as blank. Next, 100 μL of a 200 μM DPPH solution was mixed with each well. The mixture was incubated at 25°C for half an hour in a dark room. Then, the absorbance of the mixture was measured with a multiplate reader. As a positive control, we used Trolox. The equation below was applied to estimate the percentage inhibition of each compound. The IC<sub>50</sub> values were calculated based on three independent experiments [12].

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

### 2.2.2. Cytotoxicity Evaluation

The human lung cancer cell line (A549) was cultivated in an enhanced medium. The cell culture medium used in this experiment was a combination of DMEM (Dulbecco's modified Eagle's medium), 10% heat inactive FBS (Fetal Bovine Serum), Amphotericin B (5.6 μg/mL), and Kanamycin (100 μg/mL), while 3 day-old cells were employed as test material. A total of 1 μL of samples (1% final concentration in the DMSO solution) and 99 μL of A549 cells (5 × 10<sup>3</sup> cells) were

incubated at 37°C for 72 hours. After removing the medium, 100 μL of MTT was added and then incubated for another 1.5 hours in a CO<sub>2</sub> incubator. Next, 100 μL DMSO was added to each well after removing the MTT solution. The absorbance of the mixture was scanned at a wavelength of 540 nm with a 2300 EnSpire Multimode plate reader by Perkin Elmer, Inc. Doxorubicin was utilized as a positive control. The percentage (%) inhibition of cell growth was estimated using equation (1). The evaluation was performed in triplicate and reported as mean ± SE [13], [14].

## 2.3. Virtual Molecular Docking Study

In this work, the virtual molecular docking study was performed using ChemBioDraw® Ultra 12.0 for the 2D and 3D structures of the compound. To screen their molecular interaction with the selected receptor, we utilized Molegro® Virtual Docker 5.5. The epidermal growth factor receptor tyrosine kinase (ID 1M17) and ligand Erlonitib were obtained from PDB (Protein Data Bank) [23]. After validating the ligand-receptor binding site with an acceptable parameter, the title compounds were docked to the receptor's active site following the determination of some values, such as the rerank score (RS) and the environment of the interaction (hydrogen bonding and steric interaction). The acceptance parameter for receptor validation is a root mean square deviation (RMSD) value less than 2.0 Å. RS is one of the main parameters of the *in silico* study. It is the interaction energy between the ligand and the receptor. A smaller RS value implies a more stable ligand-receptor binding, which predicts a higher biological activity [15], [16].

## 3. Results and Discussion

### 3.1. Synthesis

Synthesis of *N*-(2-(2-benzylidenehydrazine-carbonyl) phenyl)-benzamides was initiated by reaction with anthranilic acid and benzoyl chloride. After obtaining Compound 1, hydrazine hydrate was added, thus yielding benzamide 2 (99%). This was followed by stirring Compound 2 and the benzaldehydes, resulting in a 73–99% yield of 3a–3f. The synthetic scheme of *N*-(2-(2-benzylidenehydrazine-carbonyl) phenyl)-benzamides is shown below (Figure 1).

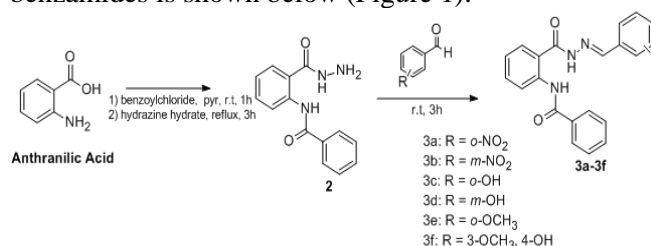


Fig. 1 Synthesis of *N*-(2-(2-benzylidenehydrazine-carbonyl)phenyl)benzamides (3a-3f)



The structures of the synthesized compounds were in agreement with the  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , IR, and MS spectra data. All the spectra of the products are reported below:

*N*-(2-(2-(2-nitrobenzylidene)hydrazinecarbonyl)phenyl)benzamide (3a)

$^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 12.45 (s, 1H), 11.86 (s, 1H), 8.90 (s, 1H), 8.55 (d,  $J = 8.2$  Hz, 1H), 8.16 (d,  $J = 7.7$  Hz, 1H), 8.09 (d,  $J = 8.1$  Hz, 1H), 7.94 (dd,  $J = 20.0, 7.5$  Hz, 3H), 7.83 (t,  $J = 7.5$  Hz, 1H), 7.72 – 7.57 (m, 5H), 7.29 (t,  $J = 7.5$  Hz, 1H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 165.2, 164.6, 148.3, 144.2, 139.3, 134.4, 133.7, 132.8, 132.1, 130.9, 128.7, 128.5, 128.9, 128.9, 128.0, 127.0, 127.0, 124.7, 123.1, 121.2, 120.3. HRESIMS ( $m/z$ ) = 411.1062 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{21}\text{H}_{16}\text{O}_4\text{N}_4\text{Na}$ : 411.1064).

*N*-(2-(2-(3-nitrobenzylidene)hydrazinecarbonyl)phenyl)benzamide (3b)

$^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 12.37 (s, 1H), 11.80 (s, 1H), 8.57 (s, 2H), 8.53 (d,  $J = 8.3$  Hz, 1H), 8.29 (d,  $J = 8.0$  Hz, 1H), 8.18 (d,  $J = 7.6$  Hz, 1H), 7.96 (d,  $J = 7.3$  Hz, 2H), 7.92 (d,  $J = 7.7$  Hz, 1H), 7.77 (t,  $J = 7.9$  Hz, 1H), 7.65 (dd,  $J = 10.6, 7.2$  Hz, 2H), 7.60 (t,  $J = 7.3$  Hz, 2H), 7.30 (t,  $J = 7.6$  Hz, 1H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 165.2, 164.6, 148.2, 146.5, 146.5, 139.2, 135.8, 134.35, 133.56, 132.75, 132.11, 130.53, 128.92, 128.92, 128.71, 127.06, 127.06, 124.50, 123.23, 121.28, 121.05. HRESIMS ( $m/z$ ) = 411.1062 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{21}\text{H}_{16}\text{O}_4\text{N}_4\text{Na}$ : 411.1064).

*N*-(2-(2-(2-hydroxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3c) [17]

Yield: 73%, m.p = 230-231°C; IR (KBr): 3451, 1655, 1604, 1285, 749. UV/Vis  $\lambda_{\text{max}}$  (EtOH): 332, 232, 206 nm.  $^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 12.31 (s, 1H), 11.89 (s, 1H), 11.12 (s, 1H), 8.69 (s, 1H), 8.56 (d,  $J = 8.3$  Hz, 1H), 7.98 – 7.94 (m, 2H), 7.93 (d,  $J = 7.8$  Hz, 1H), 7.64 (t,  $J = 7.7$  Hz, 2H), 7.60 (ddd,  $J = 6.8, 4.3, 2.5$  Hz, 3H), 7.30 (dd,  $J = 14.6, 7.2$  Hz, 2H), 6.93 (dd,  $J = 15.4, 7.9$  Hz, 2H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 164.7, 164.6, 157.4, 148.9, 139.3, 134.4, 132.7, 132.1, 131.7, 129.2, 128.9, 128.9, 128.6, 127.0, 127.0, 123.2, 121.2, 120.2, 119.4, 118.7, 116.4. HRESIMS ( $m/z$ ) = 382.1159 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{21}\text{H}_{17}\text{O}_3\text{N}_3\text{Na}$ : 382.1162).

*N*-(2-(2-(3-hydroxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3d) [18], [19]

Yield: 99%, m.p = 238-239°C; IR (KBr): 3466, 1637, 1535, 1298, 760. UV/Vis  $\lambda_{\text{max}}$  (EtOH): 312, 216 nm.  $^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 12.06 (s, 1H), 11.95 (s, 1H), 9.65 (s, 1H), 8.58 (d,  $J = 8.3$  Hz, 1H), 8.37 (s, 1H), 7.96 (d,  $J = 7.4$  Hz, 2H), 7.67 – 7.60 (m, 4H), 7.28 (dd,  $J = 16.7, 8.1$  Hz, 2H), 7.23 (s, 1H), 7.13 (d,  $J = 7.4$  Hz, 1H), 6.86 (d,  $J = 8.0$  Hz, 1H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 164.9, 164.5, 157.7, 149.2, 139.3, 135.3, 134.4, 132.6, 132.1, 129.9, 128.9, 128.6, 127.0, 123.1, 121.0, 120.4, 119.0, 117.7, 112.8.

HRESIMS ( $m/z$ ) = 382.1164 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{21}\text{H}_{17}\text{O}_3\text{N}_3\text{Na}$ : 382.1162).

*N*-(2-(2-(2-methoxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3e)

Yield: 93%, m.p = 233-234°C; IR (KBr): 3466, 3236, 1650, 1525, 1251, 758. UV/Vis  $\lambda_{\text{max}}$  (EtOH): 332, 278, 206 nm.  $^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 12.11 (s, 1H), 12.04 (s, 1H), 8.84 (s, 1H), 8.60 (d,  $J = 8.3$  Hz, 1H), 7.97 (d,  $J = 7.6$  Hz, 2H), 7.92 (dd,  $J = 19.8, 7.7$  Hz, 2H), 7.62 (dd,  $J = 19.1, 7.8$  Hz, 4H), 7.44 (t,  $J = 7.8$  Hz, 1H), 7.27 (t,  $J = 7.6$  Hz, 1H), 7.12 (d,  $J = 8.4$  Hz, 1H), 7.04 (t,  $J = 7.5$  Hz, 1H), 3.87 (s, 3H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 164.9, 164.5, 157.9, 144.7, 139.4, 134.4, 132.6, 132.1, 131.9, 131.9, 128.9, 128.9, 128.6, 128.6, 127.0, 127.0, 125.6, 123.0, 122.0, 120.9, 120.8, 111.9, 55.7. HRESIMS ( $m/z$ ) = 396.1312 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{22}\text{H}_{19}\text{O}_3\text{N}_3\text{Na}$ : 396.1319).

*N*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinecarbonyl)phenyl)benzamide (3f) [19]

Yield: 75%, m.p = 298-299°C; IR (KBr): 3466, 1634, 1517, 1282, 757. UV/Vis  $\lambda_{\text{max}}$  (EtOH): 334, 276, 206 nm.  $^1\text{H-NMR}$  (600 MHz, DMSO- $d_6$ ,  $\delta$ ) 11.98 (s, 1H), 11.95 (s, 1H), 9.61 (s, 1H), 8.58 (d,  $J = 8.3$  Hz, 1H), 8.36 (s, 1H), 7.98 – 7.94 (m, 2H), 7.90 (d,  $J = 7.8$  Hz, 1H), 7.65 – 7.57 (m, 4H), 7.34 (s, 1H), 7.28 (d,  $J = 7.5$  Hz, 1H), 7.12 (d,  $J = 8.1$  Hz, 1H), 6.87 (d,  $J = 8.0$  Hz, 1H), 3.84 (s, 3H).  $^{13}\text{C-NMR}$  (151 MHz, DMSO- $d_6$ ,  $\delta$ ) 164.7, 164.5, 149.8, 149.3, 148.1, 139.3, 134.4, 132.4, 132.1, 128.9, 128.9, 128.5, 127.0, 127.05, 125.4, 123.1, 122.5, 121.0, 120.6, 115.5, 109.2, 55.6. HRESIMS ( $m/z$ ) = 412.1271 [ $\text{M}+\text{Na}$ ] $^+$  (calculated for  $\text{C}_{22}\text{H}_{19}\text{O}_4\text{N}_3\text{Na}$ : 412.1268).

### 3.2. Biological Activity

The title compounds were evaluated for their antioxidant activity, and the results showed that the compound *N*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinecarbonyl)phenyl)benzamide was the most active among the tested compounds (Figure 2). The synthesized compounds 3c, 3d, and 3f showed almost 100% inhibitory effect at sample concentration 100  $\mu\text{g}/\text{mL}$  against A549 cancer cell line (Figure 3).

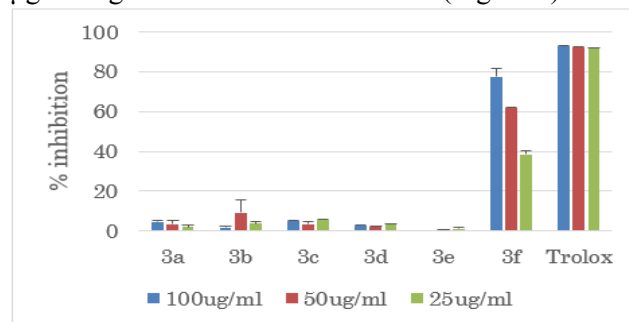


Fig. 2 DPPH Radical Scavenging Assay of *N*-(2-(2-benzylidenehydrazine-carbonyl)phenyl)benzamides and Trolox as positive control

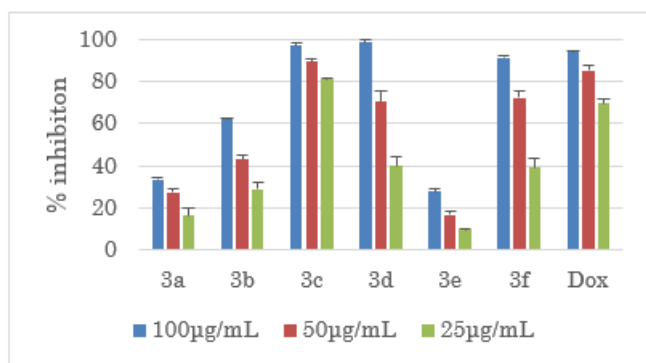


Fig. 3 A549 Growth Inhibitory Assay of *N*-(2-(2-benzylidenehydrazine-carbonyl)phenyl)benzamides and doxorubicine (dox) as positive control

The bioactivities of *N*-(2-(2-Benzilidenehydrazine carbonyl) phenyl) benzamides (3a-3f) are displayed in Table 1.

Table 1 The  $IC_{50}$  values of synthesized compounds

Comp.	DPPH $IC_{50}$ ( $\mu\text{g/mL}$ )	A549 Cytotoxicity $IC_{50}$ ( $\mu\text{g/mL}$ )	Cytotoxicity Classification [20-22]
3a	>100	>100	Inactive
3b	>100	68.82 $\pm$ 2.36	Low activity
3c	>100	10.88 $\pm$ 0.82	Good activity
3d	>100	33.35 $\pm$ 5.52	Moderate activity
3e	>100	>100	Inactive
3f	37.23 $\pm$ 3.76	33.21 $\pm$ 3.52	Moderate activity
Trolox	7.30 $\pm$ 0.39	-	-
Doxoru-bicine	Not tested	0.48 $\pm$ 0.02	Excellent activity

Compounds 3a-3f were evaluated for their DPPH radical scavenging activities. As shown in Table I, compound 3f displayed very potent radical scavenging activities ( $IC_{50}$ : 37.23  $\pm$  3.76  $\mu\text{g/ml}$ ) when compared with the standard agent, Trolox ( $IC_{50}$ : 7.30  $\pm$  0.39  $\mu\text{g/ml}$ ). The remaining products did not show significant free radical scavenging properties ( $IC_{50}$  >100  $\mu\text{g/ml}$ ). These results imply that the radical scavenging activity of 3f may be related to the presence of hydroxyl moieties at the para position.

Based on the MTT assay results, the title compound with NO- and CH<sub>3</sub>O- group in the *ortho* and *meta*-positions had no activity against the A549 cell line. Compound 3c has the smallest  $IC_{50}$  value of about 10.88  $\mu\text{g/mL}$  (good cytotoxicity activity). This means that 3c has the highest activity in inhibiting the growth of the human lung cancer line among all the products. The  $IC_{50}$  value of the positive control doxorubicin was 0.48  $\pm$  0.02  $\mu\text{g.ml}$  (Excellent/potent cytotoxicity activity). Table I shows the  $IC_{50}$  value of the synthesized compounds. The results are reported as the mean value from three replication experiments ( $\pm$  SE).

### 3.3. Molecular Docking Study

The purpose of the molecular docking study was to find out the affinity of a ligand to its docking site by examining the energy of drug-receptor binding. Receptor validation was carried out by redocking erlotinib with TK receptors as a native ligand. The RMSD value of the erlotinib with TK receptors was 1.17 Å. Figure 4 shows the superposition of the docked and co-crystallized ligands.

The *in silico* study of the derivatives of *N*-(2-{2-benzylidenehydrazinecarbonyl}phenyl)benzamide are

explained in Table 2 and Figure 5. The RS value of the ligand erlotinib was -85.90 kcal/mol.

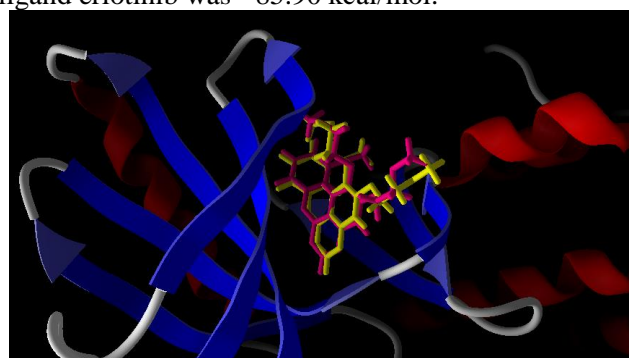


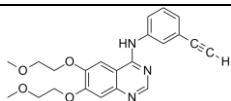
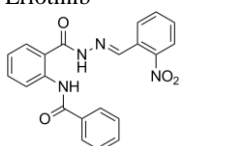
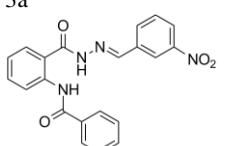
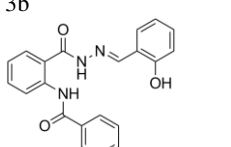
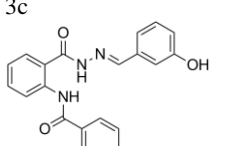
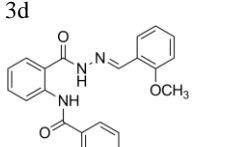
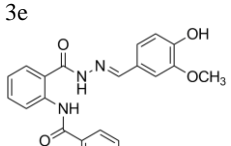
Fig. 4 Superposition of co-crystallized ligand and docked conformation, yellow represent the co-crystallized ligand and purple the re-docked conformation of the ligand with Molegro Virtual Docker (MVD) Ver.5.5

A compound with the lowest predicted RS value is considered the most active. The compound 3c had an RS value lower than erlotinib and the lowest one among all products, -91.09 kcal/mol. The *in vitro* data compound 3c had the highest activity against A549. This prediction corresponds to the *in silico* study of the compound. Erlotinib inhibited the TK receptors by making the hydrogen bonds with amino acid residues Met-769 and Thr-766. It also had steric interactions with amino acid residues Gln-767 and Gly-695.

*N*-(2-{2-[2-hydroxybenzylidene]hydrazinecarbonyl}phenyl)benzamide inhibited the TK receptors by forming hydrogen bonds with amino acid residues Met-769 and Thr-766, as erlotinib did, but also formed bonds with Ala-719 and Lys-721. The steric interactions of 3b occurred between amino acid residues Lev-768 and Met-769 with the TK receptors.

The results of the correlation between the Re-Rank scores and the experimental values are given in Table 2.

Table 2 Molecular Docking Study of Erlotinib and the Title Compounds

Compounds	RS (kcal/mol)	Hydrogen bond	Residues involved	Steric interaction	Residues involved
 Erlotinib	-85.90	2	Thr 766; Met 769	2	Gly 695, Gln 767
 3a	-86.55	2	Thr 766; Met 760	4	Val 702, Ala 719, Leu 768, Met 769
 3b	-86.55	3	Lys 721, Met 769, Thr 830	2	Leu 768, Met 769
 3c	-91.09	2	Thr 830, Met 769	2	Leu 768, Met 769
 3d	-88.52	4	Ala 719, Thr 766, Lys 721, Met 769	2	Leu 768, Met 769
 3e	-72.23	2	Thr 766, Met 769	3	Lys 721, Leu 768, Met 769
 3f	-84.88	1	Thr 766	6	Leu 694, Phe 699, Val 702, Ala 719, Gln 767 Thr 830

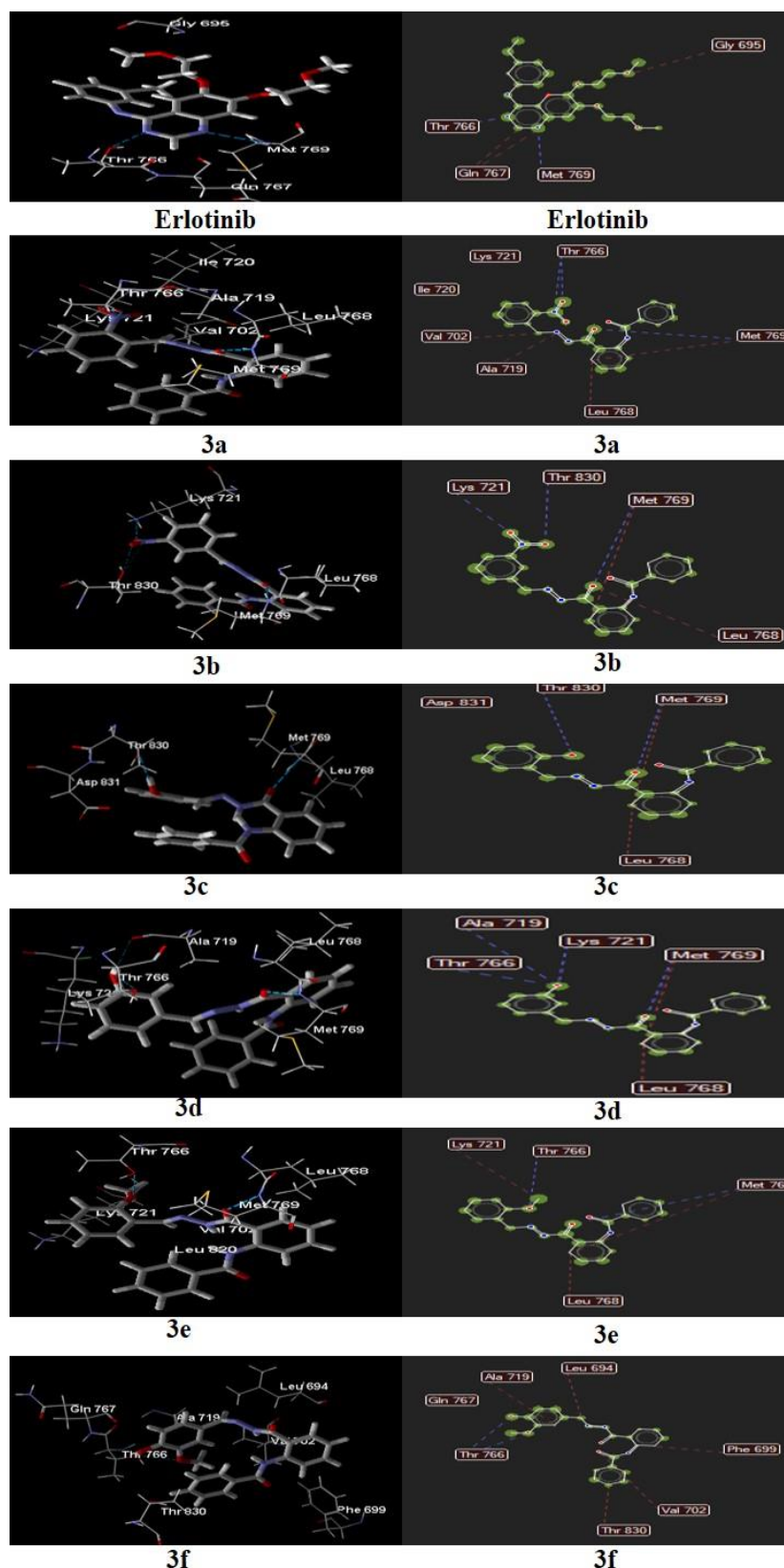


Fig. 5 3D Interactions (left) dan 2D Interactions (right) of Ligand and Benzamides 3a-3f with receptor 1M17 (Blue dotted line indicates hydrogen bond, while red dotted lines indicates steric interaction)

## 4. Conclusion

In this report, we have synthesized six compound derivatives of *N*-(2-{2-benzylidenehydrazinyl}phenyl)benzamide (3a-3f) with good yields (73–99%). The synthesis of the

two compounds (3b and 3e) is considered to be the first reported. The compound that has a hydroxyl group in *ortho*- position showed the highest growth inhibition activity on the human lung cancer cell line (A549) and also had the lowest RS score when docked onto TK receptor (PDB code: 1M17), which was better than its

original ligand, erlotinib. *N*-(2-{2-[4-hydroxy-3-methoxybenzylidene]hydrazinecarbonyl}phenyl)benzamide had the highest activity as an antioxidant based on its DPPH assay and its moderate activity in inhibiting A549 cells. Therefore, these compounds can be developed as anticancer candidates.

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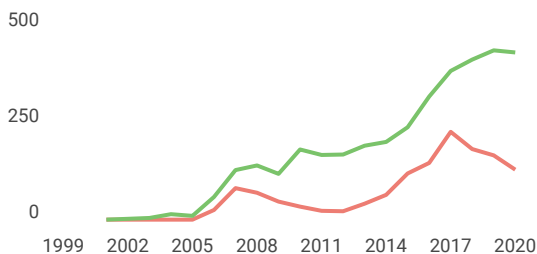
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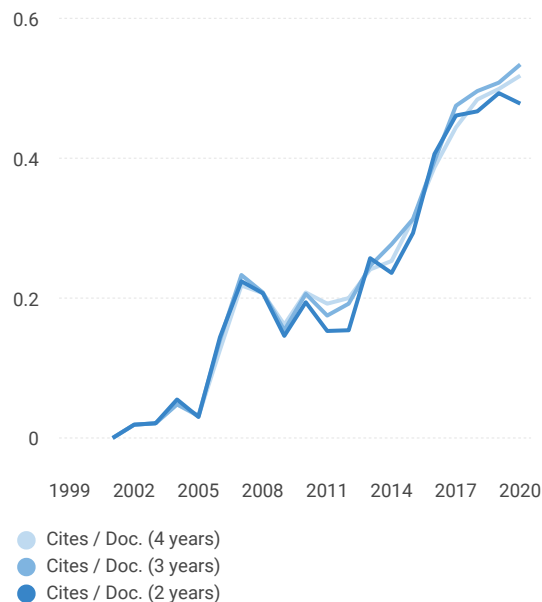
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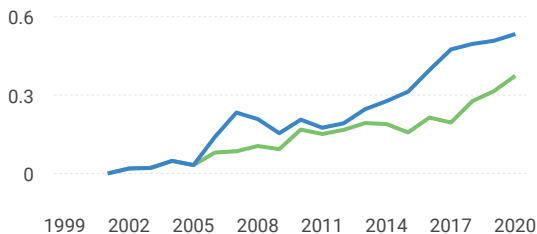
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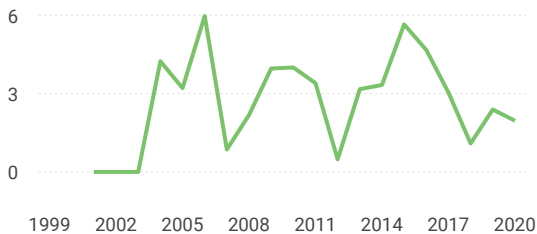
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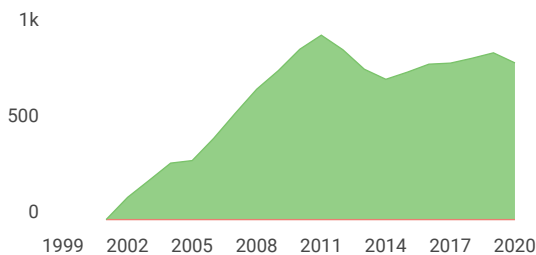
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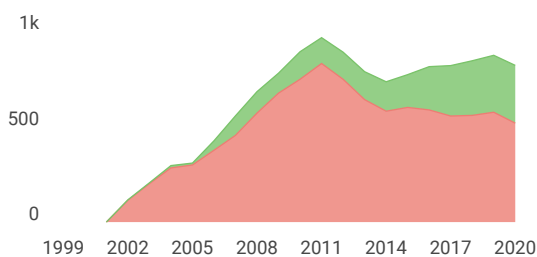
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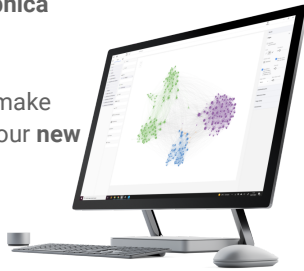
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