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New fluorinated chalcone and pyrazoline analogs: Synthesis, docking, and molecular dynamic studies as anticancer agents

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ABSTRACT

Introduction: Some of chalcone and pyrazoline analogs are known to have a good potency as anticancer agents. The objective of this study is to observe the potency of these compounds as anticancer against epidermal growth factor receptor (EGFR) tyrosine kinase domain using molecular docking and molecular dynamic (MD). **Method:** The fluorinated chalcone and pyrazoline derivatives were successfully synthesized under microwave irradiation. **Result and Conclusion:** Hydrogen bonding, van der Waals, and electrostatic interaction were assumed to be enhancing the biological activity of those compounds. Compound 1 and compound 2 showed a good potential against EGFR tyrosine kinase, and it can be used and chosen as the reference for the next stage in drug design, whereas compound 3 has another mode of action against EGFR tyrosine kinase.

INTRODUCTION

Cancer is the leading cause of death in the world, and it is becoming a serious problem of human health. This disease begins in the cell of the body which is characterized by uncontrolled, uncoordinated, and undesirable cell division [1].

Epidermal growth factor receptor (EGFR) is a receptor of tyrosine kinases that play essential roles in both normal physiological conditions and cancerous conditions [2]. EGFR was also the first receptor that provided evidence for a relationship between receptor overexpression and cancer. EGFR is expressed in a variety of human tumors, including those in the lung, head and neck, colon, pancreas, breast, ovary, bladder and kidney, and in gliomas. EGFR expression and cancer prognosis have been investigated in many human cancers. Although there some discrepancies have been reported, patients with tumors that show high expression of EGFR tend to have a poorer prognosis in general [2].

Fluorine is an important element in medicinal and industrial chemistry. It has applications in a wide range of industries, such as pharmaceuticals and agrochemicals [3,4]. The uniqueness of fluorine properties, making fluorinated organic compounds to be an attractive option to modulate biological activity and enhance ADME properties [5,6]. The fluorine can modify the p*K*a of neighboring groups, affect lipophilicity (log P), hydrogen bonding and other binding interactions, and in many cases block pathways leading

to rapid metabolization of the drug, thereby increasing its bioavailability [7].

In the past decade, in view of the unique of organic compounds containing fluorine and the influence of fluoro substituent on the biological activities, several previous workers have reported the synthesis some fluorinated chalcone and pyrazoline analogs and studied their broad spectrum of biological activities. Some fluorinated pyrazolines have been synthesized by reacting fluorinated chalcones with phenylhydrazine [8,9] or thiosemicarbazide [10,11]. Numerous pyrazoline derivatives have been found to possess considerable biological such as antimicrobial, anti-inflammatory, antidepressant, and anticancer effects [12]. Among the reported activities, it is important to note that pyrazolines are not only useful in the treatment of various cancer types, including brain, bone, mouth, esophagus, stomach, liver, bladder, pancreas, cervix, lung, breast, colon, rectum, and prostate cancers but also some of them act as cancer chemopreventive agents [13].

Thus far, there are not so many reports on computational for discovering new agent against cancer (i.e., EGFR tyrosine kinase). This study was conducted to synthesize new fluorinated chalcone and pyrazoline analogs for then can be used as anti-EGFR tyrosine kinase agent with the aid of molecular docking and molecular dynamic (MD) simulation.

MATERIALS AND METHODS

General Information for the Synthesis of Fluorinated Chalcone and Pyrazoline

The materials used including 1-acetylnaphthalene, 2-fluorobenzaldehyde, sodium hydroxide, hydrochloric acid, hydrazine hydrate, phenyl hydrazine, glacial acetic acid, universal indicator, and some organic solvents, such as ethanol, *n*-hexane, and ethyl acetate, were produced by Merck. The synthesis reactions were carried out in an ace pressure tube using a Samsung ME109F domestic microwave oven. Melting point was determined on a Fisher–Johns apparatus (Fisher Scientific, Waltham, MA, USA) (uncorr). Thin-layer chromatography (TLC) analysis was carried out using GF_{254} (Merck Millipore, Darmstadt, Germany) under ultraviolet (UV) Lamp 254/366 nm (CamagTM, Camag Chemie-Erzeugnisse & Adsorptionstechnik AG, Muttenz, Switzerland). UV spectra were recorded on GenesysTM 10S UV-visible spectrophotometer (Thermo ScientificTM, Waltham, MA, USA). Fourier transform infrared (FTIR) spectra were recorded in KBr powder on a Shimadzu® FTIR Prestige-21 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Mass spectral data were recorded on LC-HRMS Mariner BiospectrometryTM (Applied Biosystems, Foster City, CA, USA). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectral data were recorded on an Agilent® (Agilent Technologies, Santa Clara, USA) at 500 MHz and 125 MHz, respectively.

General Procedure for Preparation of Fluorinated Chalcone (Compound 1)

As much as 5 mmol 1-acetylnaphthalene and 5 mmol 2-fluorobenzaldehyde were dissolved in 2.5 mL ethanol. Then, 5 mL sodium hydroxide 0.5 N was added into the mixture. The mixture was irradiated using a domestic microwave oven (180 W) for 3 min. The reaction was monitored every 1 min of irradiation by TLC. After the reaction was completed, the mixture was cooled for 20 h and then neutralized by adding hydrochloric acid 1N to afford a precipitate. The precipitate was filtered *in vacuo*, washed by distilled water, cold *n*-hexane, and allowed to dry in a desiccator to get pure compound.

General Procedure for Preparation of Fluorinated Pyrazolines (Compound 2 and 3)

Some 1 mmol of compound 1 was dissolved in 10 mL ethanol. Then, 11 mmol hydrazine hydrate or phenyl hydrazine and 5 drops glacial acetic acid were added. The mixture was irradiated using a domestic microwave oven (180 W) for 2 min. The reaction was monitored every 1 min of irradiation by TLC. After the reaction was completed, the mixture was cooled to afford a precipitate. The precipitate was filtered *in vacuo*, washed by distilled water, cold *n*-hexane, and allowed to dry in a desiccator to get pure compound. The scheme for synthesize fluorinated chalcone and pyrazoline analogs is presented in Figure 1.

Molecular Docking and MD Simulation

Preparation of the protein

Molecular docking was conducted using AutoDock 1.5.4 software packages. In this study, the protein was prepared by retrieving the three-dimensional crystal structure of the tyrosine kinase, that is, breast cancer from the protein data bank (PDB ID: 1M17), and it was used as the macromolecule for molecular docking. This protein must be kept in rigid. For then, all hydrogen atoms were added, merging non-polar hydrogen atoms, checking and repairing missing atoms, adding Gasteiger charges, checking and fixing total charges on residues, and assigning atom types to the protein structure. Autogrid 4 software was used to generate a grid box of the protein structure with default atom types (carbon, hydrogen, oxygen, and nitrogen), grid spacing of 0.35 Å, dimensions of 122 × 116 × 120 points along the x, y, and z axes and centered on the protein for the docking.

Preparation of the ligand

These nine compounds as depicted in Figure 2 were used as the ligands and drawn using ChemDraw. These ligands must be kept in flexible. All the ligands were required to minimize the energies for then the minimized structures were subsequently prepared with the detected root of torsion and number of torsions for flexible-ligand docking using Autodocktools 1.5.4 software.

Analyzing and Output Visualization

Based on the docking scores, the docking poses were ranked. The scoring function in AutoDock was used to predict the binding affinity of one ligand to the receptor molecule. The conformation with the lowest binding affinity was selected for further analysis after the docking process. The molecular visualization of the docked complexes was performed using the Biovia Discovery Studio Visualizer.

MD Simulation

Nano scale MD Program; v 2.9 was used for the modeled protein for then the all files were generated using visual MD [10]. The

protein was solvated with a TIP3P water box with a 2.0 Å layer of water for each direction of the coordinate structure and a CHARMM (Chemistry at Harvard Macromolecular Mechanics) was used as a force field.

RESULTS AND DISCUSSION

Synthesis of Fluorinated Chalcones and Pyrazolines

Compound 1

Pale yellow solid in 92% yield; Mp = 41-42°C; UV (MeOH), λ_{max} (nm): 219 and 295; FTIR (KBr), $\bar{\upsilon}$ (cm^{-1}): 3060, 1663, 1594, 1507, 1228; ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 8.36 (d, 1H), 8.16 (d, 1H, J = 13.5, 7.5 Hz), 8.03 (dt, 3H, J = 9.5, 7.5 Hz), 7.71 (d, 1H$_\beta$, J = 16.5 Hz), 7.65 (d, 1H$_\alpha$, J = 16.5 Hz), 7.62 (m, 3H), 7.51 (dd, 1H, J_a = 13.5, 7.5 Hz), 7.30 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 195.1, 161.2 (d, $^1J_{C\text{-}F}$ = 250 Hz), 136.6 (d, $^3J_{C\text{-}F}$ = 3.87 Hz), 133.8, 133.2 ($^3J_{C\text{-}F}$ = 8.75 Hz), 132.6, 130.2, 129.7 (d, $^4J_{C\text{-}F}$ = 2.25 Hz), 129.06 (d, $^4J_{C\text{-}F}$ = 3.37 Hz), 129.05, 128.6, 128.1, 127.01, 125.6, 125.5 (d, $^3J_{C\text{-}F}$ = 3.37 Hz), 125.3, 122.5 (d, $^2J_{C\text{-}F}$ = 11.00 Hz), 116.5 (d, $^3J_{C\text{-}F}$ = 21.62 Hz); HRMS (ES+): m/z $[M+H]^+$ calculated for $C_{19}H_{14}OF$: 277.1029, found: 277.1023.

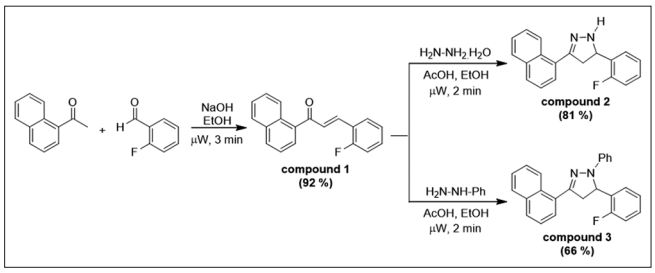

Figure 1: Scheme for synthesize the fluorinated chalcone and two pyrazoline analogs

Compound 2

White solid in 81% yield; Mp = 82-84°C; UV (MeOH), λ_{max} (nm): 229 and 315; FTIR (KBr), $\bar{\upsilon}$ (cm^{-1}): 3298, 3047, 2933, 1589, 1486, 1347, 1225; ^{1}H-NMR (500 MHz, CD_3OD), δ (ppm): 9.01 (dd, 1H, J = 9.5 and 1.5 Hz), 7.61 (m, 2H), 7.59 (dd, 1H, J = 7.0 and 1.0 Hz), 7.53 (m, 3H), 7.32 (m,1H, H-4'), 7.20 (dt, 1H, J = 7.0 and 0.5 Hz), 7.13 (ddd, 1H, J = 9.5, 8.5 and 1.0 Hz), 5.23 (t, 1H, H$_x$, J_{xb}= 10.0 Hz, J_{xa}= 10.0 Hz), 3.72 (dd, 1H, H$_b$, J_{ba}= 16.5 Hz, J_{bx}= 10.5 Hz), 3.20 (dd, 1H, H$_a$, J_{ab}= 16.0 Hz, J_{ax}= 9.5 Hz); ^{13}C NMR (125 MHz, CD_3OD), δ (ppm): 162.03 ($^1J_{C\text{-}F}$= 243 Hz), 153.96, 134.14, 130.71, 129.55, 129.11, 128.85 ($^3J_{C\text{-}F}$= 8,25 Hz), 128.10, 127.44 ($^3J_{C\text{-}F}$= 4,25 Hz), 126.53, 126.43, 126.33, 125.65, 124.57,

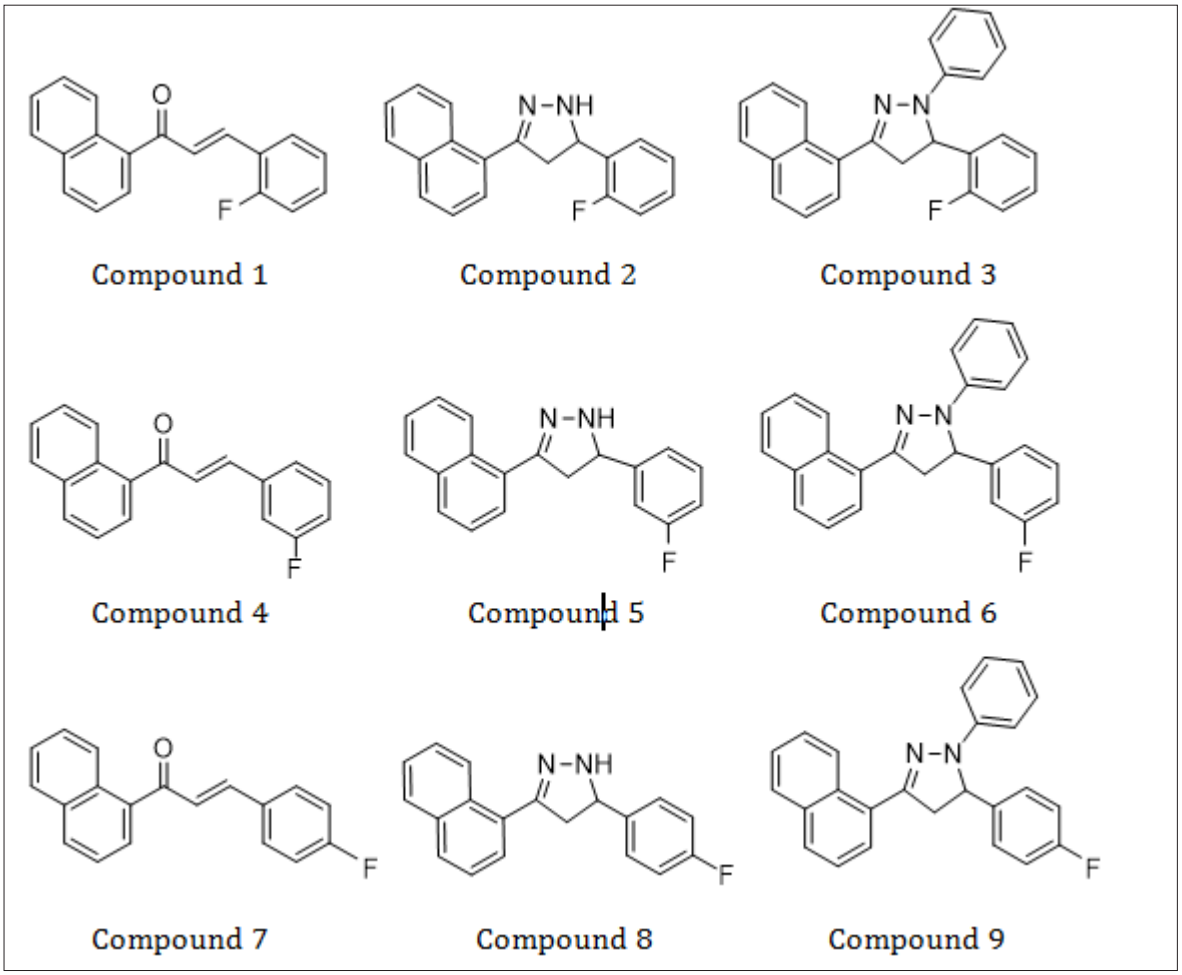

Figure 2: Structure of the ligands. Compound 1, 2, 3 with R is F in ortho position, Compound 4, 5, 6 with R is F in meta position, Compound 7, 8, 9 with R is F in para position

124.16 ($^4J_{C-F}$= 3,5 Hz), 114.94 ($^2J_{C-F}$= 21,75 Hz), 56.71 ($^3J_{C-F}$= 2,25 Hz), 42.54; HRMS (ES+): m/z $[M+H]^+$ calculated for $C_{19}H_{16}N_2F$: 291.1298, found: 291.1288.

Compound 3

Yellow solid in 81% yield; Mp = 174-176°C; UV (MeCN), λ_{max} (nm): 213 and 377; FTIR (KBr), $\bar{\upsilon}$ (cm^{-1}): 3065, 2898, 1598, 1499, 1341, 1227; ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 9.47 (d, 1H, *J* = 8.5 Hz), 7.94 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.61 (t, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.33 (m, 1H), 7.26 (m, 1H), 7.24 (m, 2H), 7.23 (m, 1H), 7.06 (d, 2H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 6.78 (t, 1H, *J* = 7 Hz), 5.70 (dd, 1H, H_x, J_{xb} = 12 Hz, J_{xa} = 6 Hz), 4.21 (dd, 1H, H_b, J_{ba} = 17 Hz, J_{bx} = 12 Hz), 3.40 (dd, 1H, H_a, J_{ab} = 17 Hz, J_{bx} = 6 Hz); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 160.04 (d, $^1J_{C-F}$ = 238 Hz), 148.76, 144.51, 134.19, 130.26, 130.07 (d, $^3J_{C-F}$ = 8,75 Hz), 130.01, 129.64, 129.21, 129.07 (d, $^2J_{C-F}$ = 13,75 Hz), 128.55, 128.32 (d, $^3J_{C-F}$ = 3,75 Hz), 128.07, 127.90, 127.20, 126.60, 125.79, 125.38 (d, $^4J_{C-F}$ = 3,75 Hz), 119.43, 116.51 (d, $^2J_{C-F}$ = 21,25 Hz), 113.23, 56.50 (d, $^3J_{C-F}$ = 2,5 Hz), 44.48; HRMS (ES+): m/z $[M+H]^+$ calculated for $C_{25}H_{20}N_2F$: 367.1611, found: 367.1607.

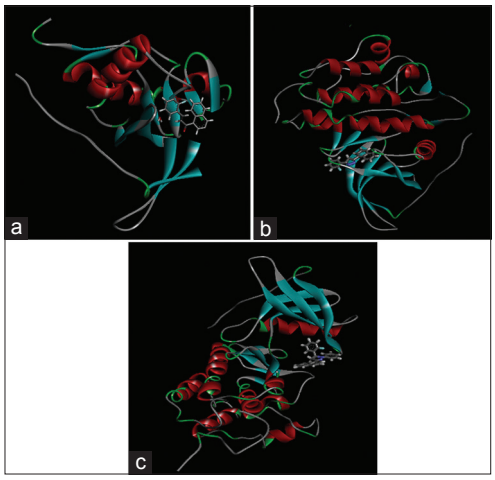

Figure 3: Spatial arrangement of the binding site for (a) compound 1 (b) compound 2 (c) compound 3

Molecular Docking

Molecular docking has become an increasingly important tool in drug discovery and molecular docking also can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes [11].

For ortho position, the lowest docked energy values were used to select the best poses of the docking results. Two of these compounds were observed to align in similar manner orientation around the active site of the protein. Unfortunately, compound 3 has another mode of interaction.

Compound 1 was observed to display important hydrogen bonding between carbonyl of the ligand with residue Met769. Asp831 shown interaction with the ligand through van der Waals interaction suggesting the importance of the residue in the formation of Van der Waals pocket. In addition, compound 1 was also able to build the hydrophobic interaction with

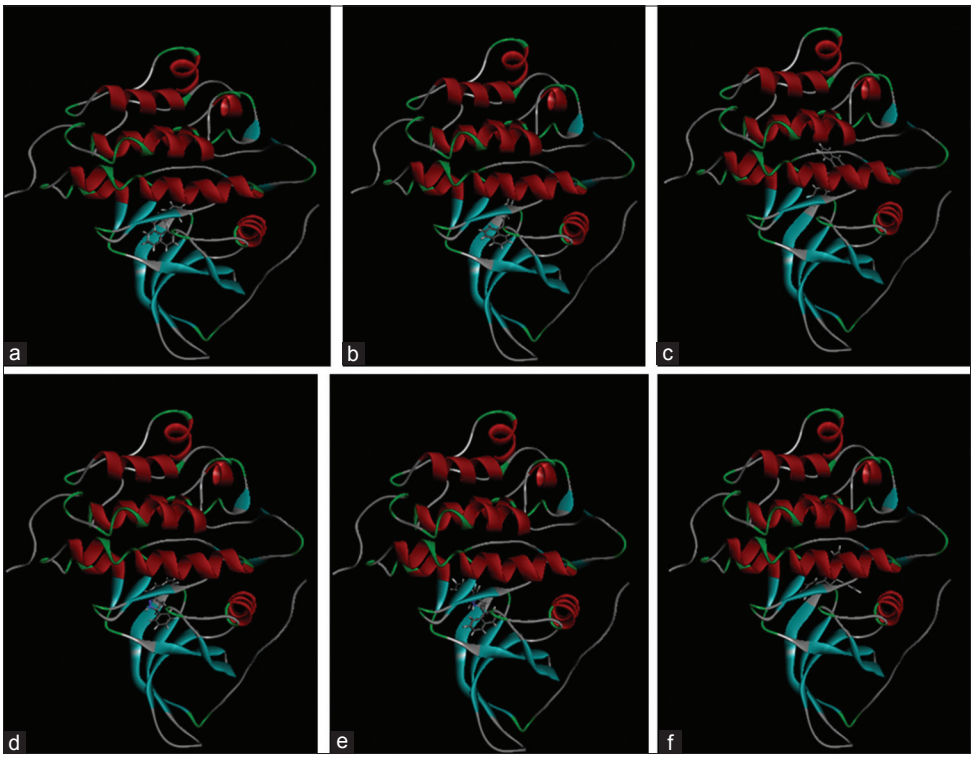

Figure 4: Spatial arrangement of the binding site for (a) compound 4 (b) compound 5 (c) compound 6 (d) compound 7 (e) compound 8 (f) compound 9

Table 1: Docking output

No	Molecule	Estimated free energy of binding (kcal/mol)	Estimated inhibition of constant (μM)	Interaction		
				H-bond	Van der Waals	Hydrophobic interaction
1	Compound 1	−7.85	11.83	Met769	Asp831	Lys721
2	Compound 2	−8.12	10.95	Met769	Asp831	-
3	Compound 3	−5.34	23.78	Phe669	Glu734; Asp813	Lys730; Lys851
4	Compound 4	−4.23	26.90	Phe669	Asp831;	Lys721
5	Compound 5	−4.36	27.04	-	Asp813; Asp831	Arg817; Lys851
6	Compound 6	−5.67	22.89	-	Asp831	Arg817
7	Compound 7	−6.89	20.76	-	Asp831	Lys721
8	Compound 8	−6.50	19.89	-	Asp831	Lys721
9	Compound 9	−5.56	18.98	-	Asp813; Asp831	Lys721

Table 2: Interaction of the ligand with the amino acid through molecular dynamic simulation at 300 K

Ligand	MD 300K
Compound 1	Leu694, Phe699, Val702, Met769, Pro770, Asp776
Compound 2	Leu694, Phe699, Val702, Leu820
Compound 3	Phe699, Ala668, Lys730, Glu734, Gly833, Lys851
Compound 4	Phe699, Ala668, Lys730, Leu820
Compound 5	Leu694, Phe600, Val702, Pro770
Compound 6	Leu694, Ala668, Asp776
Compound 7	Leu694, Ala668, Asp776, Pro770
Compound 8	Ala668, pro770, Asp776, Met769
Compound 9	Phe669, Val702, Glu734, Gly833

Table 3: Binding free energy of the ligand

No	Ligand	Binding free energy (kcal/mol)
1	Compound 1	−7.85
2	Compound 2	−8.12
3	Compound 3	−5.34
4	Compound 4	−4.23
5	Compound 5	−4.36
6	Compound 6	−5.67
7	Compound 7	−6.89
8	Compound 8	−6.50
9	Compound 9	−5.56

Lys721. Wala *et al* [12]. reported that this protein with anticancer drugs formed a hydrogen bond with the residue Met769, in addition this protein also made a van der Waals interaction with Asp831 [13]. Based on this, probably the reason compound 1 can be assumed as active compound. The spatial arrangement of the compound 1 is shown in Figure 3.

Another compound assumed as the active compound is compound 2. From the docking results, compound 2 showed to have one hydrogen bonding and also one van der Waals interaction with the important amino acid. The hydrogen

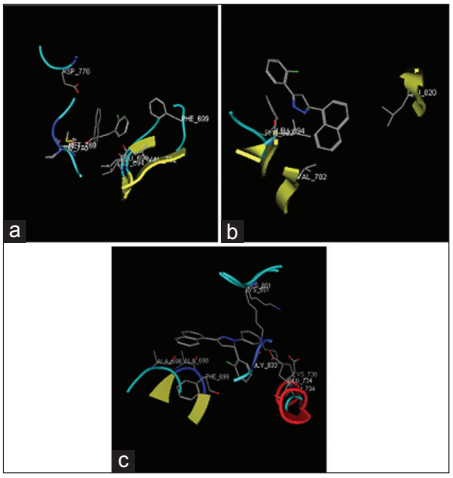

Figure 5: Visualization of the binding mode from MD simulation (a) compound 1 (b) compound 2 and (c) compound 3

bonding is constructed between nitrogen of ligand with residue Met769. Van der Waals interaction was also observed with the important residue Asp831. The binding interaction is shown in Figure 3.

From the docking results, compound 3 is shown another mode of interaction with the protein. There are two van der Waals interactions; unfortunately, the interaction was build with the unimportant residues Glu734 and Asp813. Two hydrophobic interactions were also observed with the unimportant residues Lys730 and Lys851. In addition, hydrogen bonding was constructed between the benzyl ring with the residue Phe699. Although this compound has many interactions, if the interaction were not with the important residue (i.e. active site), this compound can be assumed as not active compound [14]. The major interaction between tyrosine kinase protein with the active anticancer is the important hydrogen bond with the residue Met769 [12] and van der Waals interaction with the residue Asp831 [13]. In our case, two of these compounds (i.e. compound 1 and 2) interact well with these residues through hydrogen bonding but also via van der Waals or hydrophobic interaction. Presumably, these two compounds can be used as new active agents against cancer.

The interaction of the ligands with the amino acid is shown in Table 1.

All compounds in meta and para are seemed to be moderate compounds. From the spatial arrangement, no hydrogen bonds were observed for all the compounds (compound 4-compound 9). These compounds only interact with the important residue Asp831 through van der Waals interaction and Lys721 through hydrophobic interaction. The interaction of the ligands with the amino acid is presented in Table 1 and the spatial arrangement is depicted in Figure 4.

MD

MD simulation was carried out on these nine compounds to further explore the ligand-receptor interaction (Huiding *et al*., 2015) [15]. In this study, docking and MD simulation are combined to see the interaction between the ligand as an inhibitor to the enzyme complex. To evaluate the stability of the MD simulation, the properties (i.e., H-bond) of each complex was inspected. Hydrogen bonding interaction is quite important in the binding between ligand and receptor [16]. In this study, the MD simulations were performed at temperature 300 K to see the affinity of the ligand to the binding site. In general, the conformations two of these ligands (i.e., compound 1 and compound 2) are maintained to binding with the important residues as presented in Figure 5 and Table 2.

It can be observed that two of these ligands (i.e., compound 1 and compound 2) during the docking process have hydrogen bond with the important residue Met769, van der Waals interaction with Asp831. For MD simulation, at the temperature 300 K show that at the end of the simulation, these two ligands seem lost their ability but still has interaction through hydrogen bonding with the important residues, that is, Met769 and Asp831.

Table for binding free energy of MD simulation is presented in Table 3. Currently, drug as EGFR inhibitors such as gefitinib, erlotinib, and lapatinib are members of a class of potent and selective inhibitors of the human EGFR (HER) family of tyrosine kinases that have been developed to treat patients with tumors with defined genetic alterations of the HER tyrosine kinase domain.

CONCLUSION

Nine new chalcone and pyrazolines were successfully synthesized. Docking studies were performed to evaluate the effects of chalcones against breast cancer. Docking study and MD simulation showed the binding affinity of two pyrazoline chalcone derivatives (i.e. compound 1 and compound 2) to be within the enzyme binding pockets with relatively constructed the hydrogen bond and van der Waals interaction with the important residue for these compounds can be used as potential candidates for second generation drug discovery.

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