Structure Modifications of Pinostrobin from Temu Kunci (Boesenbergia pandurata ROXB. SCHLECHT) and Their Analgesic Activity Based on in Silico Studies

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Submission date: 14-Apr-2023 03:46AM (UTC+0800)
Submission ID: 2063755946
File name: C-07_artikel.pdf (358.35K)
Word count: 3762
Character count: 19417

ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

Structure Modifications of Pinostrobin from Temu Kunci (*Boesenbergia pandurata* ROXB. SCHLECHT) and Their Analgesic Activity Based on in Silico Studies

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ABSTRACT:

Temu kunci (*Boesenbergia pandurata* ROXB. SCHLECHT) is one of Indonesia medicinal plants which contains essential oils and flavonoids and it has interesting pharmacological activities, such as antifungal, antibacterial, antioxidant, anti-inflammatory and anti-cancer. It also contains pinostrobin which potent as anti-inflammatory and analgesic activities through inhibition of COX-2 enzymes. This research was to obtain pinostrobin derivatives of acylation reactions between pinostrobin and acyl chloride derivatives. The structure modifications of pinostrobin were obtained by Schotten-Baumann method through nucleophilic substitution reactions between pinostrobin and acyl chloride derivatives. Their structure had analyzed using the spectrophotometric analysis (NMR, IR, and GC/MS). The investigation of structure modifications of pinostrobin (1) from this plant has demonstrated the presence of pinostrobin acetate (2) and new pinostrobin propionate (3). The 2 and 3 are derivatives of pinostrobin that can be synthesized using the Schotten-Baumann method to yield 84.3% and 73.9%, respectively. The results of in silico study between pinostrobin and pinostrobin acyl derivatives on the COX-2 receptor with a PDB code: 1PXX showed that pinostrobin RS value was -87.18kcal/mol, while pinostrobin propionate had a RS value of -98.61 kcal/mol. It can be predicted that the pinostrobin acyl derivative has greater analgesic activity than pinostrobin, so it is feasible to be developed and carried out research on its analgesic activity in vivo.

KEYWORDS: *Boesenbergia pandurata*, COX-2, in silico, pinostrobin, structure modification

INTRODUCTION:

Structure modification is a method used to obtain a novel drug with the desired several activities, such as increasing drug activity, reducing side effects or toxicity, increasing drug selectivity, and prolonging duration of effect. In addition, molecular modification will provide more economical cost, because to obtain a new drug with the desired activity, the experimental factor is suppressed as far as possible so that the synthesis pathway becomes shorter[1]. Protein-Ligand interactions play an important role in designing structural-based drugs. Several docking analysis focuses on several important interactions that operate at the molecular level. For example in structures that have seven-membered rings play an important role in holding molecules in place (binding) of the active site[2].

Received on 10.02.2020 Modified on 17.04.2020
Accepted on 04.06.2020
Research J. Pharm. and Tech. 2021; 14(4):2089-2094.
DOI: 10.52711/0974-360X.2021.00370

Pinostrobin is a flavonoid compound found in temu kunci (*Boesenbergia pandurata* Roxb. Schlecht) rhizome[3,4,5]. It is effective as an anti-inflammatory[6] and has analgesic activity, because it can inhibit COX-2 enzyme[7,8]. It is an enzyme responsible for prostaglandin synthesis involved in acute and chronic inflammatory pathologic processes[9]. Increasing analgesic activity of pinostrobin can be done by structure modified.

Esterification reaction is one of the most widely used reactions in the elderly as a basic chemical reaction in the synthesis of new compounds. In the synthesis of natural products, these reactions have a role in the protection or resolution of the kinetics of carboxylic acids and in the formation of lactones through intra-molecular reactions[10].

In 1895, Emil Fischer presented the first esterification reaction, by reacting alcohol and carboxylic acid with acid as reagents[11], but this reaction was difficult for phenol esterification. One method that uses phenol esterification is the Schotten-Baumann method. This method works by reacting a phenol with acyl chloride derivative through nucleophilic substitution with alkaline solvent as a catalyst[12].

MATERIALS AND METHODS:

General procedures:

In silico test was analysed by computer processor of intel core i7 with 8GB memory, ChemBioDraw ultra 12.0 program and Molegro Virtual Docker 5.5 program. The ^{1}H and ^{13}C-NMR spectra were performed on a JEOL ICS 400 MHz and 100 MHz, respectively, with a standard internal tetramethylsilane (TMS) to confirm the structure of synthesis results. The IR spectrum of pinostrobin was isolated from the meeting key and its derivatives were measured using PERKIN ELMER Spectrum One FTIR spectrometer in KBr pellets. Determination of the mass spectrum of pinostrobin isolated from key findings and its derivatives were obtained using GC/MS 5977B.

MATERIALS:

Pinostrobin (isolated compound from *Boesenbergia pandurata* Roxb. Schlecht), acetyl chloride (Aldrich), propionyl chloride (Sigma), tetrahydrofuran (Merck), ethyl acetate (Merck), methanol (Merck), hexane (Merck), triethylamine (Merck), chloroform (Merck), CMC-Na (Merck), diclofenac sodium (Dexa Medica) and glacial acetic acid 99.7% (Merck). In the in silico test, pinostrobin was used as a ligand and their modifications of 2 and 3 were stored in 2D and 3D. COX-2 with a PDB code: 1PXX was used as a receptor and downloaded from the Protein Data Bank (Fig.1).

Figure 1. Docking test of pinostrobin (1 in a) and pinostrobin derivatives (2 in b, and 3 in c) on COX-2 receptors with a PDB code of 1PXX receptor; - - - is H bond; - - - is steric interaction.

Plant materials:

The temu kunci rhizomes with 10 months harvest age were collected from Turen village, Malang, Indonesia, and voucher specimens were deposited at the Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia.

Pinostrobin isolation:

Temu kunci rhizomes were cleaned of impurities by washing with running water, then they were cut into small pieces and dried by oven at 50°C. The dried plants were finely powdered, weighed, and extracted. Gradually, the 2.0kg of dried powder of these rhizomes were extracted with 20 L *n*-hexane by maceration (3 times). The solvent residues were removed until 1/3 initial volume by a rotary evaporator then obtaining the crystalline isolates. This process was done by taking the precipitate crystals, dissolved with hot methanol and then placed in the refrigerator for 24 hours until in crystal form. The washing process was done 4 times to get white colored crystals, then dried in the oven with a temperature of 50°C and it obtained 38.7g (1.94% w/w) of pinostrobin (1) then it was used as a raw material of the synthesis process of pinostrobin acetate (2) and new pinostrobin propionate (3).

Synthesized of 2 and 3:

The synthesis procedure of pinostrobin derivatives compounds referred to modify Schotten-Baumann reaction[11,13]. The 11 mmol of 1 was mixed with 10mL tetrahydrofuran in a 250mL round bottom flask. Then it was added by 35mmol acetyl chloride solution in 10ml of tetrahydrofuran gradually at 5°C (ice bath) until run out and stirred by a magnetic stirrer. The mixture was added with 62 mmol triethylamine and let stand for 30 minutes at room temperature. The reaction was complete

when the spot of 1 had disappeared from the stain of silica gel plate 60 GF_{254} and obtained 2. The recrystallization process of **2** was performed using hot methanol. The residue on the filter paper was transferred into a beaker glass, then added with sufficient amount of methanol and placed on a heated magnetic stirrer (70-80°C) while stirring slowly and adding the solvent gradually until dissolved. The solution was filtered in hot conditions. The filtrate was left at room temperature until cool and then stored in the refrigerator for 24 hours (3 times). The formed crystal of 2 was filtered using a Buchner funnel and dried in an oven at a fixed temperature of 50°C, then weighed to determine the percentage by weight of the synthesis product. The same synthesis method was performed on new compound of 3 by mixing 11 mmol of 1 with 35 mmol propionyl chloride.

Table 1. Characteristic of IR spectrum of pinostrobin isolated from temu kunci and its derivatives

Vibration Type	Wave number (cm^{-1}) of compound		
	1	2	3
OH phenolic	3463.43	-	-
C=O ketone	1699.70	1676.27	1670.40
C=C aromatis	1660.70 1598.38	1617.13 1564.29	1620.32 1566.53
-C-OMe	1358.38 1239.30	1264.19 1246.71	1274.44 1250.63
C=O ester	-	1768.27	1763.44

Pinostrobin (1)

White crystalline, melting point: 98-99°C, R_f: 0.57 (*n*-hexane: ethyl acetate (5:1)), R_f: 0.69 (*n*-hexane: chloroform (2.5:4)), R_f: 0.74 (*n*-hexane: chloroform: ethyl acetate (4:2:1)), characteristic of IR spectrum: see Table 1. ^1H and ^{13}C NMR (400 MHz and 100 MHz) recorded in $CDCl_3$: see Table 2. MS: *m/z* for pinostrobin ($C_{16}H_{14}O_4$) 270.28; found: 270.1.

Table 2. Characteristic of ^1H and ^{13}C-NMR spectra (400 MHz and 100 MHz) of pinostrobin isolated from temu kunci and its derivatives, recorded in chloroform ($CDCl_3$) (δ in ppm)

Positions	1		2		3	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H(*J* in Hz)	δ_C
1	-	-	-	-	-	-
2	5.39 (dd, 12.8, 3.2)	79.33	5.45 (dd, 13.6, 2.4)	79.67	5.45 (dd, 14.0, 2.8)	79.67
3	3.07 (dd, 17.2, 12.8); 2.81 (dd, 17.2, 3.2)	43.48	3.02 (dd, 16.4, 13.6); 2.72 (dd, 16.4, 2.4)	45.15	3.01 (dd, 14.0, 16.5)	45.20
4	-	195.89	-	188.93	-	188.96
5	-	162.88	-	164.34	-	164.33
5-OH	12.03 (s)	-		-	-	-
6	6.07 (d, 3.2)	95.23	6.43 (d, 2.8)	104.88	6.43 (d, 2.8)	104.86
7	-	168.07	-	169.69	-	173.04
7-Ome	3.80 (s)	55.81	3.81 (s)	55.93	3.81 (s)	55.92
8	6.07 (d, 3.2)	94.38	6.28 (d, 2.8)	99.63	6.28 (d, 2.8)	99.58
9	-	164.23	-	165.59	-	165.57
10	-	103.23	-	108.03	-	108.14
11	-	-	-	151.94	-	152.12
12	-	-	2.38 (s)	21.25	2.66-2.74 (m)	27.74
13	-	-	-	-	1.29 (t)	8.82
1'	-	138.46	-	138.48	-	138.52
2'	7.39 (m)	126.25	7.39 (m)	126.27	7.40 (m)	126.25
3'	7.39 (m)	126.25	7.40 (m)	126.27	7.40 (m)	126.25
4'	7.40 (m)	128.99	7.40 (m)	128.99	7.42 (m)	128.98
5'	7.40 (m)	126.25	7.42 (m)	126.27	7.43 (m)	126.25
6'	7.42 (m)	126.25	7.43 (m)	126.27	7.44 (m)	126.25

Pinostrobin acetate (2):

Pale brown crystalline, melting point: 146-147°C, R_f: 0.34 (*n*-hexane: ethyl acetate (5:1)), R_f: 0.29 (*n*-hexane: chloroform (2.5:4)), R_f: 0.54 (*n*-hexane: chloroform: ethyl acetate (4:2:1)), characteristic of IR spectrum: see Table 1. ^1H and ^{13}C NMR (400 MHz and 100 MHz) recorded in $CDCl_3$: see Table 2. MS: *m/z* for pinostrobin acetate ($C_{18}H_{16}O_5$) 312.32; found: 312.1.

Pinostrobin propionate (3):

White bulk, melting point: 121-122°C, R_f: 0.40 (*n*-hexane: ethyl acetate (5:1)), R_f: 0.34 (*n*-hexane: chloroform (2.5:4)), R_f: 0.60 (*n*-hexane: chloroform: ethyl acetate (4:2:1)), characteristic of IR spectrum: see Table 1. ^1H and ^{13}C NMR (400 MHz and 100 MHz) recorded in $CDCl_3$: see Table 2. MS: *m/z* for pinostrobin propionate ($C_{19}H_{18}O_5$) 326.12; found: 326.1.

RESULTS AND DISCUSSION:

Binding drug interactions using docking studies is an essential part of computer-assisted drug design. The structure-based approach is a main role in the process of drug discovery. Designed compounds are examined for the ability of enzyme that play a role in certain therapies and identified as new lead compounds by molecular docking. The strongest compound chosen as lead on

structural modification is a new ligand with excellent binding ability[14]. The in silico method can be used to predict certain lead compounds against several activities such as hepatoprotector[2], cancer[5], gout[14], cardiovascular[14], jaundice[15], bacteria[16], virus[17], diabetes[18], and analgesic[9,12,19,20].

Zadorozhnii used the PASS-GUSAR software packages[19] and Chinchole used Auto Dock tool 1.5.6-Molinspiration shoftware[20] to estimate analgesic activity and acute toxicity of a predictive compound by linking inhibition to the COX-1 and COX-2 enzymes. Therefore, by using the Molegro virtual docker (MVD) software package, silico modeling of this enzyme inhibition has been carried out. MVD is a protein-ligand docking simulation program for docking simulations in fully integrated computing packages and applied to hundreds of different proteins. This model has docking performance that is similar to other docking programs such as AutoDock4 and AutoDock Vina and has four search algorithms and four original scoring functions[21]. The structure modified by addition acyl groups in 1 formed pinostrobin derivatives of 2 and new 3. The preliminary results using the ChemBioDraw Ultra 12.0 program showed that new compound of 3 had a lipophilic parameter (log P) value of 2.91 and a steric parameter molar refractivity (MR) value of 89.42. Then 1 had a log P value of 2.28 and a MR value of 75.29. Based on the preliminary results, it is necessary to conduct an analgesic activity study of pinostrobin that is isolated from temu kunci and pinostrobin derivatives.

Synthesis of two pinostrobin derivatives, 2 and 3, were done by reacting 11 mmol of 1 with 35 mmol acetyl chloride and propionyl chloride, respectively. Then they carried out in tetrahydrofuran as solvent with slow drop wise. The 62 mmol triethylamine (Et_3N) was added and evaporated. The reaction expressed in figure 2.

Figure 2. Synthesis reaction of pinostrobin derivatives

The phenol group of pinostrobin has a function as a nucleophile that attacks electrophilic carbon of the carbonyl group of acyl chloride derivatives. Tetrahydrofuran was chosen as the solvent because of its solubility and it is easy to evaporate. Drop wise technique was performed in an ice water bath to slow the reaction, regarding the high reactivity of acyl chloride. Triethylamine acted as a nucleophilic reaction catalyst. It neutralized the protons produced during esterification reaction. The latest step of synthesizing was recrystallized with hot methanol.

Based on the purity results, they obtained 1, 2, and 3. These results were proven by the presence of one spot on the thin layer chromatography (TLC) test using three eluents (see experimental), which have different polarity and also proven by determination of melting point with the value of 1-2°C[22]. So the synthesized compounds were 84.3% of **2** as white crystalline and 73.9% of **3** as white bulk (Fig. 3).

Figure 3. Chemical structure of 1, 2, and 3

The structures were confirmed using ^{1}H-NMR and ^{13}C-NMR in table 2. Based on their data, compounds 2 and 3 didn't have ^{1}H-NMR (δH: 12.03, 1H, s, 5-OH) as in 1. Then the ^{1}H-NMR data at δH 2.38 (s) and 1.29 (t) of 2 and 3 indicated the methyl group. The ^{13}C-NMR data at δC 151.95 and 152.12 of 2 and 3 indicated the carbonyl group at position 11. So the phenol group of 1 changed to ester group of 2 and 3 after synthesis reaction.

The absence of the -OH group (3463.43 cm^{-1}) and the presence of -C=O ester group (1768.27 cm^{-1} and 1763.44 cm^{-1}) indicated that the synthesis of pinostrobin derivatives had been formed (Table 1). The nucleophilic substitution reactions between the isolated pinostrobin from temu kunci with the acyl chloride derivatives obtained an ester bond. The mass spectra data of **1**, **2**, and **3** obtained the signal at *m/z* 270.1, 312.1, and 326.1 respectively (Fig. 4). So **1**, **2** and **3** were determined as pinostrobin, pinostrobin acetate and pinostrobin propionate, respectively. The pinostrobin propionate (**3**) is a new compound.

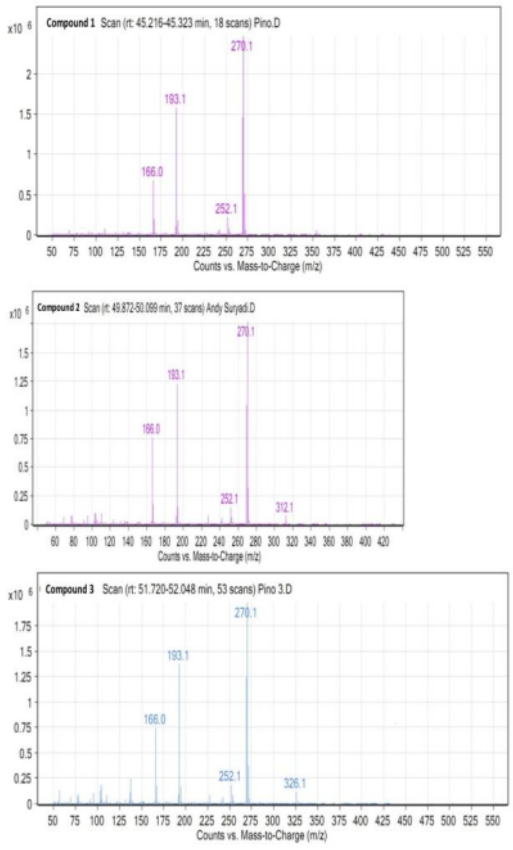

Figure 4. Spectrophotometry mass of 1, 2, and 3

It was also supported by the results of docking test between pinostrobin and pinostrobin derivatives on COX-2 receptors with a PDB code of 1PXX (Fig. 1)[22]. The re-rank score (RS) value of 1 was -87.18, while compound of 2 and 3 had a RS value of -90.27 and -98.61, respectively (Table 3), so it can be predicted that pinostrobin derivatives have better analgesic activity than pinostrobin.

Table 3. Docking score and ligand-amino acid residu interactions

Compounds	RS (kcal/mol)	Amino Acid Residues	
		Steric-Bond	Hydrogen-Bond
1	-87,18	Phe518; Val523; Leu352: Tyr355	Tyr355; Ser353
2	-90,27	Leu352; Met522; Ala527; Ser353	Arg120; Tyr355
3	-98,61	Leu352; Met522; Ala527	Arg120; Tyr355

Prostanoids (prostaglandin, prostacyclin, and thromboxane) are an enzyme COX which is responsible for the formation of important biological mediators. COX inhibition can cause symptoms of inflammation and pain. The mechanism of COX-2 formation is the conversion of arachidonic acid to prostaglandins (PGH2) mediated by COX. COX-2 is an enzyme induced by inflammatory and mitogenic stimuli resulting in increased PG synthesis in inflamed and neoplastic tissues. COX-2 selective inhibitors can be promising agents for cancer prevention and other treatments[23]. It related to developed risk of renal, CV and GI[24].

CONCLUSION:

Pinostrobin derivatives can be synthesized using an esterification reaction with the Schotten-Baumann method by reacting pinostrobin with acyl chloride derivatives (acetyl chloride and propionyl chloride) through nucleophilic substitution with ET_3N as a catalyst and both pinostrobin derivatives showed analgesic activity against the COX-2 receptor (PDB: 1PXX) that are higher than ponostrobin.

ACKNOWLEDGMENT:

This research was supported by Penelitian Unggulan Fakultas (PUF) 2018 granted by Faculty of Pharmacy Airlangga University.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6