SYNTHESIS METHYL NITROPHENYL ACRYLATE AND CYTOTOXIC ACTIVITY TEST AGAINST P388 LEUKEMIA CELLS

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ABSTRACT

Synthesis of methyl nitrophenyl acrylate via modification of methyl trans-cinnamate had been done to improve its biological activity. The reaction of methyl trans-cinnamate with nitrating agent gave methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate with an ortho/para ratio of 1:8. Its structure was confirmed with ^{1}H-NMR, ^{13}C-NMR, FTIR, GC-MS. Biological activity of methyl 3-(4-nitrophenyl)acrylate and methyl 3-(2-nitrophenyl)acrylate assays was performed on Cancer cells against P388 Murine Leukemia with IC_{50}= 7.98 µg/mL, IC_{50} = 27.78 µg/mL.

Keywords: *nitration; methyl trans-cinnamate; methyl 3-(2-nitrophenyl)acrylate; 3-(4-nitrophenyl)acrylate, P388 leukemia cells*

ABSTRAK

Sintesis metil nitrofenil akrilat melalui modifikasi metil trans-sinamat telah dilakukan untuk meningkatkan aktivitas biologinya. Reaksi metil trans-sinamat dengan nitrating agen memberikan metil 3-(2-nitrofenil)akrilat dan metil 3-(4-nitrofenil)akrilat dengan rasio orto/para 1:8. Strukturnya dikonfirmasi dengan ^{1}H-NMR, ^{13}C-NMR, FTIR, GC-MS. Pengujian aktivitas biologis senyawa metil 3-(4-nitrofenil)akrilat dan metil 3-(2-nitrofenil)akrilat dilakukan terhadap sel-sel kanker P388 murine Leukemia dengan nilai IC_{50} = 7,98 µg/mL, IC_{50} = 27,78 µg/mL.

Kata Kunci: *nitrasi; metil trans-sinamat; metil 3-(2-nitrofenil)akrilat; metil 3-(4-nitrofenil)akrilat; sel leukemia P388*

INTRODUCTION

Nitration of aromatic compound is the fundamental reaction of great industrial importance. The universal nature of aromatic nitration has shown the reaction's simplicity, efficacy, and usefulness in both the chemical and pharmaceutical industries [1]. There are many nitro aromatics that are utilized and acted as a wide range of useful materials such as plastics, dyes, pharmaceutical, perfumes and also they were keys as organic intermediates [2]. Therefore nitration of hydrocarbons, particularly of aromatic compounds, is properly one of the most widely studied organic reactions [3]. The introduction of a nitro group into an aromatic compound is commonly performed in strongly acidic polar media [4]. Mono-nitration of aromatics was achieved in a two-phase system using phase-transfer catalyst. Nitration conditions were determined through several parameters such as temperature, reaction time, type and amount of phase transfer catalyst, and nitrification strength of the nitro-sulfuric acid [5]. However, many of these reactions have been carried out in the presence of protic and Lewis acids, most suffer from drawbacks such as region-selectivity issues, over nitration, and competitive oxidation of substrates [6].

Several methods have reported that nitration is used in a number of ways such as the use of *N*-bromosuccinimide and silver nitrate as a convenient reagent system for the nitration of aromatic compounds under neutral [6-7], nitration of aromatic compounds with NO_2/air catalyzed by sulfonic acid-functionalized ionic liquid under solvent-free [8], ipso-nitration reaction using the Crivello's reagent [9], using bismuth nitrate and acetic anhydride as nitration agent [10], nitrate salt under hydrothermal conditions [11], using Bismuth nitrate pentahydrate BN [12], with bismuth nitrate pentahydrate (BN) in [bmim][PF_6] or [bmim][BF_4] imidazolium ionic liquid [13], through acidic ionic liquid modified silica gel [14], and the nitration of alkanes with NO_2 into nitro-alkanes [15].

Herein, we used the most common nitrating reagent, a simple and efficient approach a mixture of

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concentrated fuming nitric acid with sulfuric acid, for the nitration of methyl *trans*-cinnamate. Methyl *trans*-cinnamate is a fragrance ingredient used in many applications such as flavoring, pharmaceuticals, and fragrance compounds. It might be found in dairy product, candy, bakery product, cosmetics, shampoos, soap, fine fragrances, and pharmaceuticals industries [16]. Recently, the studies have demonstrated that methyl *trans*-cinnamate possesses antimicrobial activity; it is a tyrosinase inhibitor and also has an inhibitory effect on adipogenesis [17-18].

In this paper, we tried to modify methyl *trans*-cinnamate using nitration reaction to improve its biological activity. The distribution of the *ortho/para* ratio in electrophilic aromatic substitution of activated mono-substituted benzenes still continues to be studied. Nitration of aromatic benzene derivatives with electron donating substituent leads to substitution at the *o*- and *p*-position according to a statistical distribution. Lazslo demonstrated that phenol can be nitrated in trihydrated cupric nitrate supported on montmorillonite/acetic anhydride/CCl_4 resulted 92% yield with *ortho/para* ratio of 13:3 [19]. The *ortho* orientation nitration of phenol was revealed by using a surfactant suspended in acetonitrile treated by nitronium tetrafluoroborate which gave *ortho/para* ratio of 19:0. Another papers showed that a high *ortho/para* ratio of 3:0 in the nitration of anisole with benzoyl nitrate in acetonitrile [20].

Chemical active compounds from plants have been proven to be a valuable source of novel anticancer drugs for the treatment of various types of leukemia. Discovery of drugs in the last century, such as cisplatin, have a high success rate in patients with leukemia although patients must often tolerate unpleasant side effects. There are mainly three types of Murine leukemia virus: (1) Moloney murine leukemia virus, (2) Abelson murine leukemia virus, and (3) Feline leukemia virus [21]. Isolation of active compounds from different plant sources is still being conducted for the development of new drug compounds which are having activity against murine leukemia. The objective of this research was to improve the bioactivity of methyl *trans*-cinnamate in term of its ability to inhibit P388 leukemia cancer cells through nitration reaction.

EXPERIMENTAL SECTION

Materials

All reactions were carried out under a static argon atmosphere. All solvents were dried and distilled according to standard procedure [22]. Analytical thin layer chromatography (TLC) was performed on Merck silica gel plates (Kiesel gel $60F_{254}$ 0.25 mm) and preparative TLC was carried out on Merck silica gel plates (Kiesel gel $60F_{254}$ 0.5 mm). Silica gel column chromatography was carried out on Daisogel IR-60. Methyl *trans*-cinnamate was used as starting material for the synthesis of methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate. Methyl *trans*-cinnamate was obtained from isolation of galangal oil and the identification of structure was carried out using ^{1}H-NMR, ^{13}C-NMR, GC-MS. Sulfuric acid was used as catalyst while nitric acid was used a nitrating agent. Lastly *n*-hexane and ethyl acetate were used as solvent for column chromatography. MTT, RPMI, PBS, DMSO were used in anti-cancer bioassays, P388 leukemia cells.

Instrumentation

^{1}H and ^{13}C-NMR spectra were recorded on JEOL 1NM–LA for 500 MHz in deuterio chloroform unless otherwise specified. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (δ 0.00) or $CHCl_3$ (δ 7.26) for ^{1}H-NMR and δ 77.0 for ^{13}C-NMR as internal standard, and coupling constant are reported in Hertz. The results from synthesis reaction were identified by using *Gas Chromatography Mass Spectrometer* (GCMS-QP2010 Shimadzu). Organic solvent was dried by using *vacuum rotary evaporator* (BUCHI *Water Bath* B-480). IR spectra were obtained on Shimadzu IRPrestige-21. Analyses of anti-cancer was used ELISA reader at a wavelength of 550 nm.

Procedure

Isolation of methyl trans-cinnamate

Methyl cinnamates was obtained from isolation of *Alpinia malaccensis* using hydrodistillation method. The essential oil of *A. malaccensis* was acquired by repeated extraction, crystallization, and filtration. The resulting of methyl cinnamate crystal was dried under low temperature to get 55% yield. Methyl *trans*-cinnamate was elucidated with ^{1}H-NMR, ^{13}C-NMR, GC-MS.

Nitration of methyl trans-cinnamate

Methyl *trans*-cinnamate (0.0297 mol) was added into mixture of H_2SO_4 (0.0462 mol) and HNO_3 (0.0462 mol). The mixture was stirred in an oil bath at 50 °C and the progress of the reaction was monitored by TLC. At the end of the reaction, the resulting mixture was work up with ethyl acetate/water. The filtrate was washed with water (2 x 10 mL), and dried over with Na_2SO_4 and evaporated. The product was purified by column chromatography with the use of ethyl acetate-hexane (2:1) as eluent solvent. The reaction of methyl *trans*-cinnamate with nitrating agent gave methyl 3-(2-

nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate with an *ortho/para* ratio of 1:8, 60% yield for *para* and 7.5% yield for *ortho*. All products were characterized by ^{1}H-NMR, ^{13}C-NMR, GC-MS and FT-IR and mass spectra data.

Anti-cancer bioassay

MTT method. Toxicity test was done by using MTT method (3-(4,5-dimethyltiazol-2-yl)-2,5-difeniltetrazolium bromide. Cytotoxicity test was performed on P388 leukemia cells.

The growth of cell cultures. Stock cell cultures in medium RPMI-1640 serum (PBS) was incubated at 37 °C with a flow of 5% CO_2 for 24 h and observed under an inverted microscope. If there were cells attached to the walls of flasks, the medium were removed and replaced with new serum medium, then incubated at 37 °C primarily to the flow of 5% CO_2 until confluent growth. Refurbishing the medium continued until the number of cells obtained sufficient for testing.

Preparation of cells to be tested. Once the number of cells to be tested was sufficiently adequate, cell medium was discarded. Lastly cells were washed and added to RPMI medium. Cells were transferred into a sterile tube and then centrifuged at 1200 rpm for 5 min. Supernatant was discarded, the cell sediment was added into RPMI 1640 (Sigma Chemical Co.) containing 10% FBS (Sigma Chemical Co.). Cell suspension was taken then the cell density was calculated using hemocymeter under a microscope. The number of cells was calculated by counting: (the number of cells in four chambers x 103 cells/mL)/4. The number of cells that had been known then was made as dilutions of the cells with medium RPMI-serum to obtain cell 2 x 104 cells/mL cell suspensions.

Cytotoxicity test. Cells with the number 1 – 2 x 104 cells/wells in RPMI 1640 culture medium was distributed in 96 wells plate and incubated in a CO_2 incubator (5%) at 37 °C for 24 h to adapt and stuck to the bottom wells. The next day the media was taken, washed by using FBS and then added 100 mL of culture medium containing DMSO or sample and incubated for 48 h. At the end of incubation, culture media containing the sample was removed, washed with 100 mL of FBS. Into each of the wells was added 100 mL of culture medium containing MTT 5 mg/mL. The culture medium was incubated for 4 h at 37 °C. Living cells interacted with MTT to form purple formazan crystals. After 4 h the media containing MTT was removed, washed with FBS and then added a solution of 200 mL isopropanoate to dissolve the formazan crystals. In order to dissolve formazan, it was incubated at room temperature for 12 h and then read with ELISA reader at a wavelength of 550 nm. Then it was proceeded to determine the equation of the regression line and to determine its IC_{50} (concentration that causes the death of 50% of the population of cells

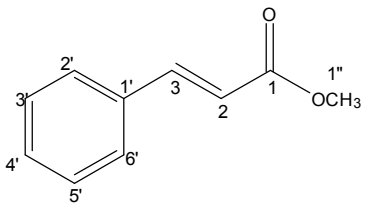

Fig 1. Structure of Methyl *trans*-cinnamate

Table 1. The ^{1}H-NMR and ^{13}C-NMR Data for methyl *trans*-cinnamate in $CDCl_3$

Position	Chemical Shift (δ, J in Hz)	
	^{1}H-NMR	^{13}C-NMR
1’	-	134.5
2’	7.52 (1H, *d*, J=5.8 Hz)	128.2
3’	7.38 (1H, *t*)	129.1
4’	7.38 (1H, *t*)	130.5
5’	7.38 (1H, *t*)	129.1
6’	7.52 (1H, *d*, J=5.8 Hz)	128.2
3	7.68 (1H, *d*, J=16 Hz)	145.1
2	6.46(1H, *d*, J=16 Hz)	117.9
1	-	167.6
1”	3.86 (3H, *s*)	51.9

RESULT AND DISCUSSION

Isolation of Methyl Trans-cinnamate

We isolated methyl *trans*-cinnamate compound from *A. malacensis*. The structure of methyl *trans*-cinnamate is shown in Fig. 1. The process of isolation of Methyl *trans*-cinnamate from galangal oil produced white crystals with a yield of 55% however it is only 2.4%, overall, from the raw material. Identification of methyl *trans*-cinnamate was performed using melting point, GC-MS and ^{1}H-NMR, ^{13}C-NMR. The identification of the melting point of methyl *trans*-cinnamate showed that the crystal melts at a temperature of 36 °C. Analysis by gas chromatography-mass spectroscopy (GC-MS) showed a peak at 5.6 min retention time and molecular weight 162.1 g/mol (Fig. 2).

From Table 1, ^{1}H-NMR data of methyl *trans*-cinnamate, there is one methoxy methyl ester group that gave signals chemical shift at 3.86 ppm (3H) as *singlet* form. Chemical shift at 6:46 ppm (1H)-shaped doublet have a relationship with a peak chemical shift at 7.68 ppm (1H)-shaped doublet, with coupling constant values (J) were equal: 16.2 Hz. The chemical form found was olefins with *trans*-configuration. For other protons at chemical shifts around 7 ppm (5H), it was protons of benzene with mono substitution. Chemical shift of 167.6 ppm at ^{13}C-NMR spectra indicate that this compound had the ester group.

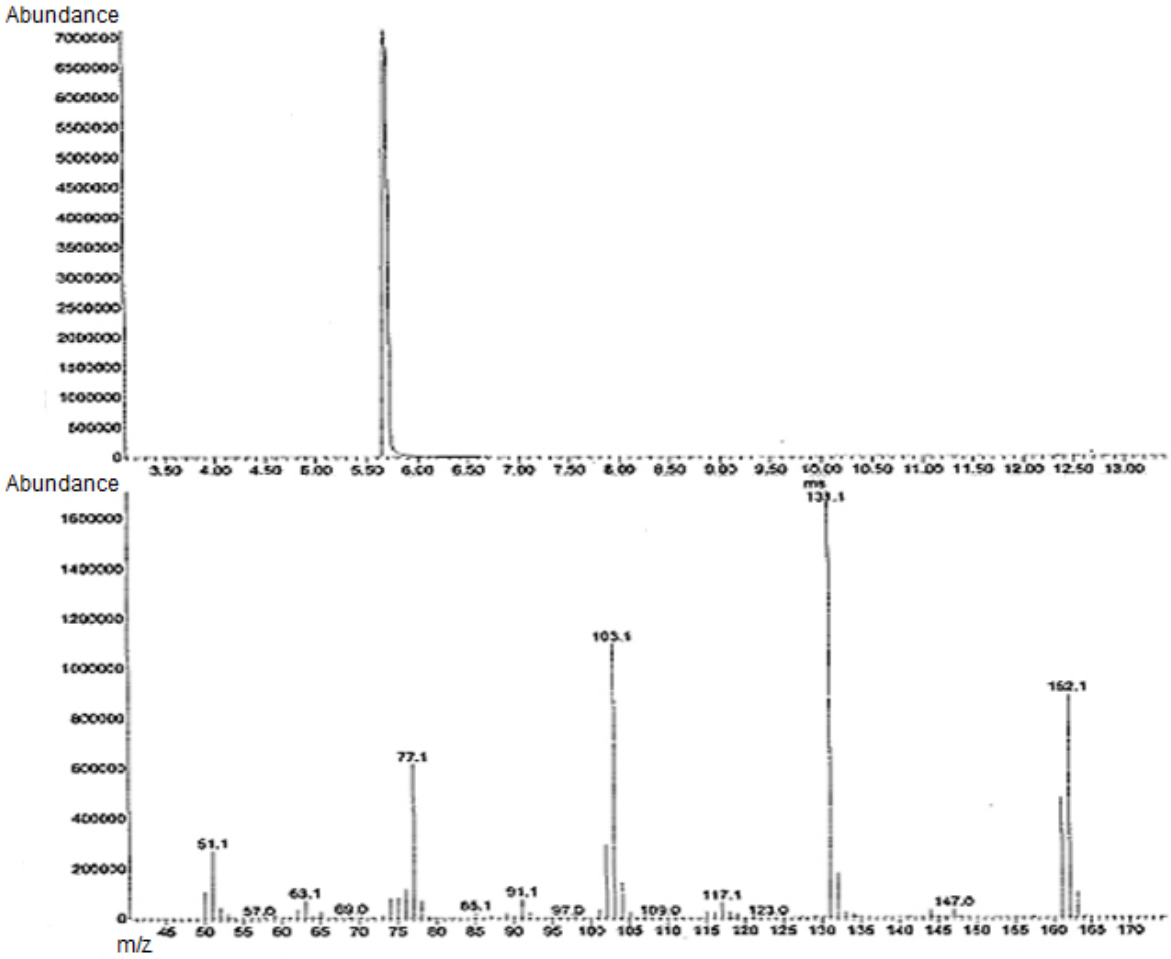

Fig 2. GC-MS Spectra of Methyl *trans*-Cinnamate

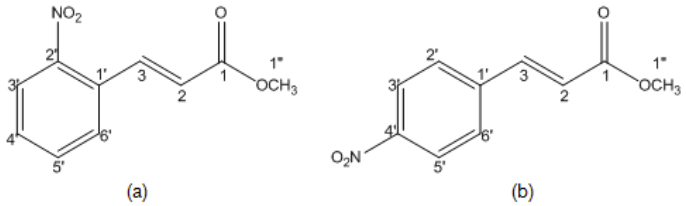

Fig 3. (a) Structure of Methyl 3-(2-nitrophenyl)acrylate (b) Structure of Methyl 3-(4-nitrophenyl)acrylate

Chemical shift of 51.9 ppm showed that it was sp^3 carbon (methyl). Chemical shifts were 117.9 and 145.1 ppm alkene (sp^2 carbon).The presence of a quaternary carbon aromatic compound was represented by the chemical shift of the signal at 134.5 ppm. Meanwhile, the chemical shift of 120 ppm was an aromatic carbon. On the chemical shift 128.3 and 129.1 ppm the peak was twice as high so this indicates that there were two carbons that had the same chemical environment. The ^{1}H-NMR and ^{13}C-NMR Data for methyl *trans*-cinnamate is shown in Table 1.

Synthesis of Methyl 3-(2-nitrophenyl)acrylate, Methyl 3-(4-nitrophenyl)acrylate and its Elucidation Structures

Modification of methyl *trans*-cinnamate through nitration process aims to create bioactivity ability against cancer cells. Herein, the nitration of the methyl trans-cinnamate compounds was used and general process that was already done. The reaction of methyl *trans*-cinnamate with nitrating reagent gave methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl) acrylate with an *ortho/para* ratio of 1:8. Identification of product was performed using melting point, GC-MS, FT-IR and ^{1}H-NMR, ^{13}C-NMR. The structure of methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl) acrylate is shown in Fig. 3.

The identification of the melting point of methyl 3-(2-nitrophenyl)acrylate showed that the crystal melts at temperature of 42 °C while methyl 3-(4-nitrophenyl) acrylate was melting at 121 °C. Analysis done by GC-MS (Fig. 4) found that methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate had a molecular

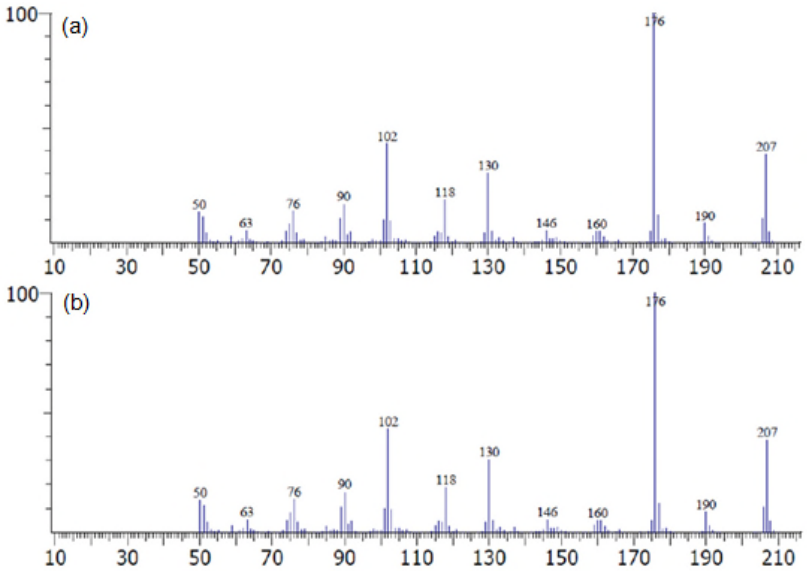

Fig 4. GC-MS Spectra of (a) Methyl 3-(2-nitrophenyl)acrylate (b) Methyl 3-(4-nitrophenyl)acrylate

Table 2. The ^{1}H-NMR and ^{13}C-NMR Data for (a) Methyl 3-(2-nitrophenyl)acrylate (b) Methyl 3-(4-nitrophenyl) acrylate in $CDCl_3$

Position	Chemical Shift (δ, J in Hz)			
	(a) Methyl 3-(2-nitrophenyl)acrylate		(b) Methyl 3-(4-nitrophenyl)acrylate	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1'	-	128.8	-	140.6
2'	-	148.8	7.68 (1H, *d*, J=7 Hz)	128.8
3'	8.04 (1H, *d*, J= 7 Hz)	124.4	8.24 (1H, *d*, J=7 Hz)	124.4
4'	7.55 (1H, *td*, J= 7Hz; J=2.6 Hz)	129.3	-	148.7
5'	7.55 (1H, *td*, J= 7Hz; J=2.6 Hz)	133.7	8.24 (1H, *d*, J=7 Hz)	124.4
6'	8.04 (1H, *d*, J= 7Hz)	128.8	7.68 (1H, *d*, J=7 Hz)	128.8
3	8.10 (1H, *d*, J=16 Hz)	140.4	7.73 (1H, *d*, J=16 Hz)	142.1
2	6.38 (1H, *d*, J=16 Hz)	123.0	6.58 (1H, *d*, J=16 Hz)	122.2
1	-	166.4	-	166.7
1"	3.83 (3H, *s*)	52.2	3.83 (3H, *s*)	52.3

weight of M^+ = 207, with fragmentation of m/z 176, 130, 102, 76, and 50. The highest peak, with m/z of 176, was a fragmentation that occurs with abundance, i.e. 100%. Parent peak was located at $[M^+]$ = 207.

Measurements with FTIR spectra provided information regarding functional groups. FTIR spectra data of methyl 3-(2-nitrophenyl)acrylate (Fig. 5) explained that the ribbon at wave number 1722 cm^{-1} was specific to stretching vibration absorption of carbonyl group C=O while bands along the range of 1346-1290 cm^{-1} were vibrational C-O absorptions. Uptake of both indicated the presence of an ester. Specific uptake of stretching vibration between atoms C-H bonds in aromatic group was contained in the wave number 3088-3024 cm^{-1}. For aromatic group, C=C aryl was shown in wave numbers 1637-1568 cm^{-1}. While the aliphatic C-H bonds present in absorption wave numbers 2953-2850 cm^{-1}. NO_2 groups were shown in wave numbers 1517 cm^{-1} and 1431 cm^{-1}. Although FTIR spectra data of methyl 3-(4-nitrophenyl)acrylate (Fig. 5) described that wave number 1724 cm^{-1} was specific to stretching vibration absorption of carbonyl group C=O and at 1348-1313 cm^{-1} bands were vibrational C-O absorption. Uptake of both indicated the presence of an ester. Specific uptake of stretching vibration between atoms C-H bonds in aromatic group was contained in the wave number 3107-3014 cm^{-1}. For aromatic group C=C aryl, it was shown that the wave numbers are 1639-1595 cm^{-1}. While the aliphatic C-H bonds present in absorption wave numbers 2956–2833 cm^{-1}. And NO_2 groups were shown in wave numbers 1512 cm^{-1} and 1429 cm^{-1}.

Interpretation of ^{1}H-NMR spectrum of methyl 3-(2-nitrophenyl)acrylate (Table 2) gave signals of chemical shift at 3.83 ppm (3H) as *singlet form* from methyl ester. Double bonds (olefins) of methyl 3-(2-nitrophenyl)acrylate gave signals of chemical shift at 6.38 ppm (1H, *d*, J=16 Hz) and 8.10 ppm (1H, *d*, J=16 Hz). Value of coupling constant indicated that the two protons had *trans*-configuration. The aromatic signals

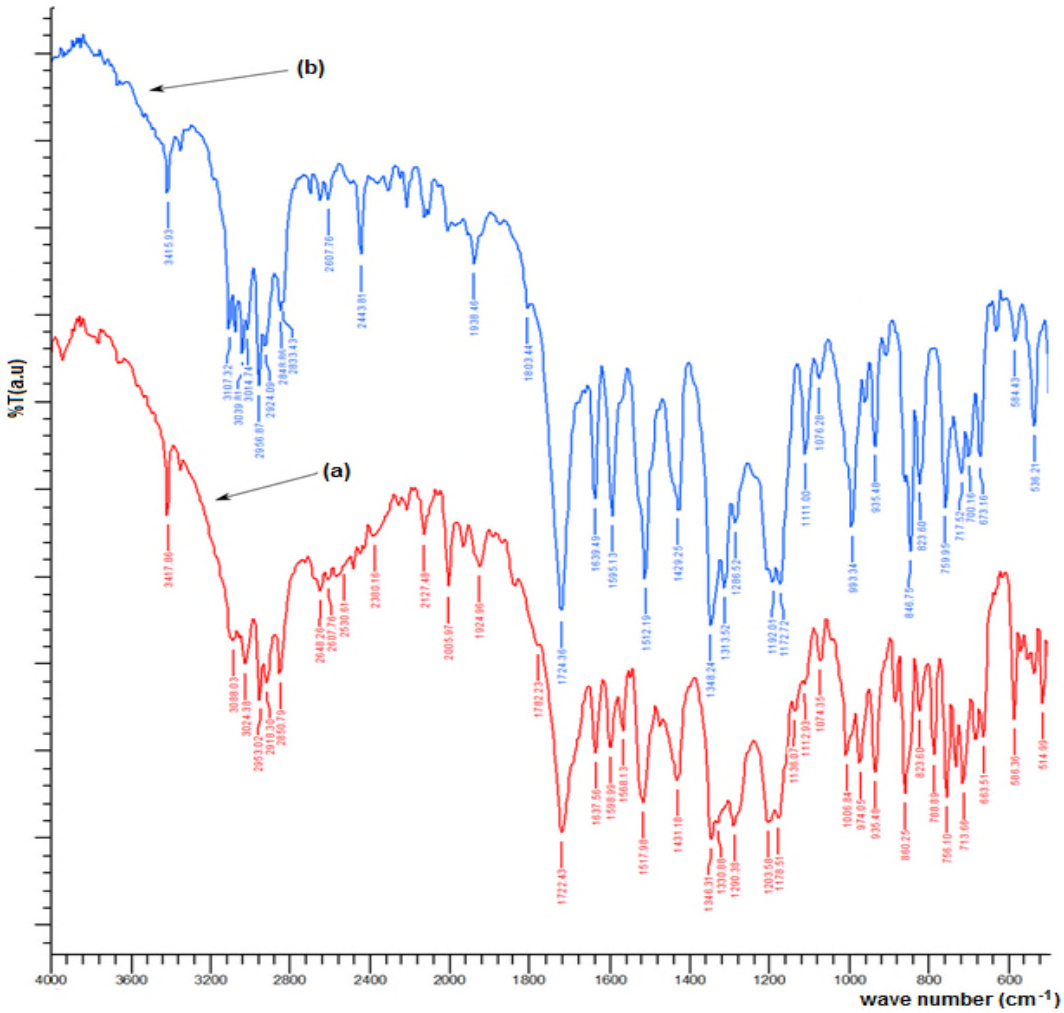

Fig 5. FTIR Spectra of (a) Methyl 3-(2-nitrophenyl)acrylate and (b) Methyl 3-(4-nitrophenyl) acrylate

were shown in the chemical shift at 7.55 ppm *triplet of doublets* with coupling constants of 7.15; 2.60 Hz for H4' and H5'. Chemical shift at 8.04 ppm was *doublet* with a coupling constant 7:15 Hz for H3' or H6' having *ortho* coupling with H4' or H5'. In the chemical shift around the values of 7.6-7.7 ppm, there were 2 overlapping signals that were integrated so that the 2H of ^{1}H-NMR spectrum indicated that the signals have 4 protons. Identification of structures using ^{13}C-NMR (Table 2), carbon carbonyl was shown in the chemical shift at the position of 166.4 ppm. Carbon methyl ester was shown in the chemical shift at the position of 52.2 ppm. Carbon-olefin was shown on ^{13}C-NMR chemical shift of 123.0 and 140.4 ppm. Chemical shift in the position of 128.8 ppm indicated the presence of a quaternary carbon of aromatic compounds (H4'). For carbon of other aromatic compounds, the chemical shift was between 110-150 ppm.

Elucidation of ^{1}H-NMR spectrum of methyl 3-(4-nitrophenyl)acrylate (Table 2) gave signals of chemical shift at 3.83 ppm (3H) as *singlet* form from methyl ester. Double bonds (olefins) of methyl 3-(4-nitrophenyl)acrylate gave signals of chemical shift at 6.58 ppm (1H, *d*, J=16 Hz) and 7.73 ppm (1H, *d*, J=16 Hz). Value of coupling constant indicates that the two protons had *trans* configuration. From the ^{1}H-NMR spectrum, there were two doublet signals at chemical shifts of 7.68 and 8.24 ppm respectively, integrated to 2 protons with coupling constant of 7.15 Hz. This signal pattern indicated that two equivalent protons have *ortho* coupling with 2 other equivalent protons, H2' to H6' and H3' to H5'. Identification of carbons structures using ^{13}C-NMR (Table 2), carbon carbonyl was shown in the chemical shift of 166.6 ppm. Carbon methyl ester was shown in the chemical shift of 52.3 ppm. Carbon-olefin was shown on ^{13}C-NMR chemical shift of 122.3 and 142.1 ppm. Chemical shift in the position of 140.6 ppm indicated the presence of a quaternary carbon of aromatic compounds (H4'). Other aromatic carbons had chemical shift about 110-150 ppm. On the

chemical shift of 124.4 and 128.8 ppm, the peak at 128.8 was twice as high as the peak at 124.4 which indicated that there were two shifts of carbon that had the same value as the same chemical environment, i.e C3' with C5' to C2' and C6'. At the chemical shift of 148.7 ppm, one hydrogen atom was missing, namely the C4' position. This suggested that the H atom at the C4' atom of the aromatic was substituted with another group, in this case substituted with nitro groups.

The ^{1}H-NMR and ^{13}C-NMR data for methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate is shown in Table 2.

Bioactivity of Methyl 3-(4-nitrophenyl)acrylate

Cytotoxicity test was used to find out potential anticancer properties of methyl 3-(4-nitrophenyl)acrylate. Cytotoxicity tests of methyl 3-(4-nitrophenyl)acrylate was conducted with MTT method. The assay was based on the capacity of mitochondrial dehydrogenase to convert the tallow water-soluble substrate MTT into dark blue formazan product which was insoluble in water. Cell mortality data could be used to determine the IC_{50}. Test anticancer activity against murine leukemia P388 cells by using methyl *trans*-cinnamate resulted of IC_{50} = 20.35 µg/mL while methyl 3-(4-nitrophenyl) acrylate compound resulted of IC_{50} = 7.98 µg/mL and methyl 3-(2-nitrophenyl)acrylate compound resulted of IC_{50} = 27.78 µg/mL. This value indicated that there was an increase in the bioactivity after methyl *trans*-cinnamate modified through nitration process and potentially active as anticancer**.**

CONCLUSION

Modification of methyl *trans*-cinnamate through nitration process gave methyl 3-(2-nitrophenyl)acrylate and methyl 3-(4-nitrophenyl)acrylate with an *ortho/para* ratio of 1:8. Biological activity test performed on methyl 3-(4-nitrophenyl)acrylate against murine leukemia P388 cancer cells resulted of IC_{50} = 7.98 µg/mL and IC_{50} = 27.78 µg/mL for methyl 3-(2-nitrophenyl)acrylate.

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