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SYNTHESIS OF DIHYDROPYRIMIDINONE DERIVATIVES AND CYTOTOXIC ACTIVITY TEST AGAINST T47D CANCER CELLS

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ABSTRACT

Dihydropyrimidinone (DHPM) derivatives are heterocyclic compounds known for a variety of biological activities including anticancer properties. The Mitsunobu reaction was used in this study to synthesize a new DHPM derivative, ethyl 4-(4-isopropoxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (compound B2), and assess its cytotoxic activity against T47D breast cancer cells. Compound B2 was synthesized from ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (compound M1) using multicomponent reactions (MCR) and the Mitsunobu reaction with isopropyl alcohol as the pronucleophile. Compound B2 was characterized using melting point test, FTIR and LC-MS spectroscopy, which confirmed its structure, functional groups, and molecular weight of 334.13 g/mol. MTT assay was used to evaluate cytotoxic activity. Compound B2 had an IC50 value of 205.71 µg/mL, indicating weak cytotoxicity, whereas doxorubicin had an IC_{50} value of 3.33 µg/mL. Despite the low cytotoxicity of compound B2, this synthesis sheds light on the development of DHPM derivatives with potential anticancer properties. The results showed that the Mitsunobu reaction is useful for modifying DHPM derivatives and highlights the need for further optimization to improve cytotoxic potency.

Keywords: Dihydropyrimidinone, Mitsunobu, Cytotoxicity, T47D

INTRODUCTION

Dihydropyrimidinone (DHPM) derivatives are heterocyclic compounds synthesized via multi-component reactions such as the Biginelli reaction. Dihydropyrimidinones are multifunctional scaffolds that exhibit diverse biological activities, such as antibacterial (Fauzi Saifudin and Rullah, 2023), antifungal (Chhillar et al., 2006; Tiwari et al., 2006), antihyperglycemic (Bhosle et al., 2015), anti-inflammatory (Shaikh and Meshram, 2015), and anticancer (Fauzi, Saifudin, and Rullah, 2023) activities. Dihydropyrimidinones are heterocyclic compounds with a pyrimidine group on the nucleus ring. Dihydropyrimidinone compounds are products of reactions involving aldehydes, ethyl acetoacetate, and urea or thiourea (Kaur et al., 2017). Mitsunobu converts alcohols to esters by combining acids/pronucleophiles. The Mitsunobu reaction uses phosphine (triphenylphosphine) and azodicarboxylate (diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD)) (Munawar et al., 2022; Beddoe et al., 2018).

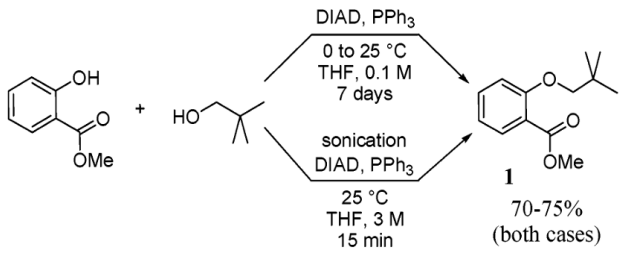

Figure 1. Mitsunobu reaction (Lepore and He, 2003)

Cancer is caused by genetic or epigenetic changes in somatic cells, which result in abnormal cell growth and spread throughout the body. Cancer is part of neoplasm (Saini et al., 2020; Sitki-Copur, 2019). The T47D cell line is widely used for cytotoxic testing because of its ease of handling cultured cells, good replication ability, and good homogeneity (Pascayantri et al., 2021).

MTT assay has been used to evaluate the cytotoxicity of various substances, including herbal extracts and chemicals (Vajrabhaya and Korsuwannawong, 2018). The principle underlying this assay is the reduction of MTT tetrazolium salt, which has a yellow color and is water-soluble to purple formazan crystals that are insoluble in water, by introducing metabolically active cells (Buranaamnuay, 2021). Formazan crystals require additional substances such as dimethyl sulfoxide (DMSO) to dissolve purple formazan crystals. The absorbance value of the dissolved formazan crystals measured using ELISA at a wavelength of 595 nm can be indicated by the Optical Density (OD). The absorbance value indicates the level of cell proliferation as a manifestation of cellular immunity (Ghasemi et al., 2021; Stockert et al., 2018).

Therefore, researchers have synthesized dihydropyrimidinone-derived compounds with ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydroprimidine-5-carboxylate or compound M1 (**Figure 2**) using the MCR method. Compound M1 reacts via the Mitsunobu reaction to produce a new compound, ethyl 4-(4-isopropoxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate or compound B2 (**Figure 3**).

RESEARCH METHODS

Equipment and Materials

The equipment used hotplate stirrer (Cimarec), vacuum Buchner, waterbath (Memmert), sonicator (Branson), vortex (Barnstead), melting point (Electrothermal), FTIR ATR (Perkin Elmer L1600300 Spectrum Two LiTa), LC-MS (Waters Corporation Floats), incubator CO^{-}_{2} (Binder), Microscop (Olympus CKX41) and ELISA Reader (Epoch).

The material used were 4-hydroxy-3,5-dimethylbenzaldehyde (Sigma Aldrich), urea, ethyl acetoacetate (Merck), isopropyl alcohol (Merck), DMSO (Merck), triphenylphosphine (PPh3) (Merck), THF (Merck), ethanol (Merck), diisopropyl azocarboxylate (DIAD) (Sigma Aldrich), distilled water (Sungai Budi), doxorubicin, RPMI, MTT, Phosphate Buffered Saline (PBS), Sodium Dodecyl Sulphate (SDS), and T47D cells obtained from the Pharmaceutical Biology Laboratory, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta.

Research Procedure

1. Synthesis of Compound M1

   The synthesis of M1 followed the procedure from (Fauzi, Saifudin, and Rullah, 2023), mixed 4-hydroxy-3,5-dimethyl benzaldehyde (3 g), urea (2.4 g), and ethyl acetoacetate (5.2 g) and refluxed at 80 °C for 1 h. The precipitate (crystal) was washed with 100 mL cold distilled water and filtered on a vacuum Buchner. The sample was stored in a porcelain cup and dried in an exicator.
2. Mitsunobu Reaction of Compound B2

Mix M1 sample (100 mg, $6.558x10^{-2}$ mmol), isopropyl alcohol (258 mg, 4.30 mmol), tryphenylphosphine (18 mg, $6.891x10^{-2}$ mmol), and tetrahydrofuran 1 mL into a flacon that has been washed using isopropyl alcohol. Sonicate using sonicator (Branson) the sample for 10 minutes, then add 13.7 µl DIAD and sonicate for 50 minutes at 55 °C. After cooling, the samples were placed in a refrigerator for 1 day. The sample was then placed in a waterbath (Memmert) and heated at 55°C for 30 minutes (Lepore and He, 2003).

3. Melting Point Test

   Put in B2 sample into a capillary tube. The capillary tube was then placed in the hole of the melting point device (electrothermal). The changes in the sample from the initial temperature change to the final temperature when the sample melts were observed (Fauzi, Saifudin and Rullah, 2023).

4. FTIR Test

   Prepare the B2 sample and dissolve it in DMSO in Eppendorf tubes. Read the B2 sample on FTIR (Perkin Elmer L1600300 Spectrum Two LiTa) to find out the spectrum. Then analyze the results of the FTIR (Fauzi, Saifudin and Rullah, 2023).

5. LC-MS Test

   Put in 5 mg of B2 sample then add it with DMSO up to 10 mL in a volumetric flask. The sample (20 µL) was dissolved and added to 10 mL DMSO in a volumetric flask. The sample that was prepared using LC-MS (Waters Corporation Floats) was read. Results of LC-MS (Fauzi Saifudin and Rullah, 2023).

6. MTT Assay Procedure

   a. Preparation of Test Solution

      Weigh 5 mg of the B2 sample was weighed and add it with DMSO to 50 µL of DMSO in an Eppendorf tube. The vortex was vortexed (Barnstead) to prepare a stock solution with a concentration of 100.000 µg/mL. A substock solution of 1.000 µg/mL from the 100.000 µg/mL stock solution. The B2 sample was diluted from the substock in RPMI medium at concentrations of 200, 100, 50, 25, 12.5, 6.25, and 3.125 µg/mL. Dilute Doxorubicin in RPMI media with series of concentration: 10; 5; 2,5; 1,25; 0,625; 0,3125; and 0,156225 µg/mL. The media content was removed from the wells. Next, 100 µL of PBS was added to each well. The PBS was removed from the wells. Add doxorubicin and B2 samples were added to each well. Add 100 µL of RPMI media to the cell and media control wells. Incubate in incubator CO^{-}_{2} (Binder) at 37 °C for 24 hours (Fauzi Saifudin and Rullah, 2023).

   b. MTT Assay Testing

      T47D cell growth was observed on an incubated plate. Then, the contents of the well were removed. Add 100 µL PBS to each well and then remove it. Add 1 mL MTT and add RPMI media up to 10 mL. Next, 100 µL was added to each well. The mixture was then incubated at 37 °C for 24 hours. Cell growth was observed under a microscope. Next, 100 µL of SDS was added to each well. The samples were placed at room temperature for 24 hours. The absorbance was read on an ELISA Reader (Epoch) at a wavelength of 595 nm. Analysis of the calculation of the reading results (Fauzi, Saifudin and Rullah, 2023).

Data Analysis

The percentage of living cells (% cell viability) was calculated using equation (1):

$$\% \text{ cell viability} = \frac{(\text{absorbance of treatment} - \text{absorbance of media control})}{(\text{absorbance of cell control} - \text{absorbance of media control})} \; x\; 100\%$$

The IC_{50} value based on the relationship between the concentration and % cell viability was calculated using Equation (2):

$$y = a \pm bx$$

RESULTS AND DISCUSSION

This DHPM derivative synthesis research aims to synthesize new compounds from compound M1 with isopropyl alcohol using the Mitsunobu reaction method, to determine the cytotoxic activity of compound B2 against T47D cancer cells, and to increase the activity of T47D cells as an anticancer agent. DHPM derivatives were chosen because of their potential anticancer activities (Fauzi, Saifudin and Rullah, 2023).

Compound M1 was synthesized using the MCR (Multicomponent Reaction) method (**Figure 2**). Multicomponent reactions (MCRs) are theoretically useful in organic reactions, where three or more starting materials react to form the desired product (Kaur et al., 2017). Synthesis of dihydropyrimidinone derivatives using the Multicomponent Reaction (MCR) method is a convenient and efficient approach for the synthesis of complex molecules (Zhong, 2022).

Compound M1 was synthesized by reflux at 80°C. Temperatures above 80°C immediately cause reactions and produce solid products (Fauzi, Saifudin and Rullah, 2023). This temperature was used to increase the reaction speed. An increase in the reaction temperature will increase the energy of the molecules and cause them to collide with each other. Therefore, the number of molecules with sufficient energy to carry out the reaction also increases. This will make the reaction occur more rapidly. During reflux, the reaction mixture is stirred to increase the frequency of collisions between molecules so that the kinetic energy of the molecules and reaction speed increase (Ritmaleni et al., 2011). The reflux product was washed using cold distilled water which aims to neutralize the pH of the residue produced after the reflux process. This is important to ensure that the pH conditions are within the appropriate range for further analysis and prevent unwanted chemical reactions in the next step (Ischak, Fazriani and Botutihe, 2021).

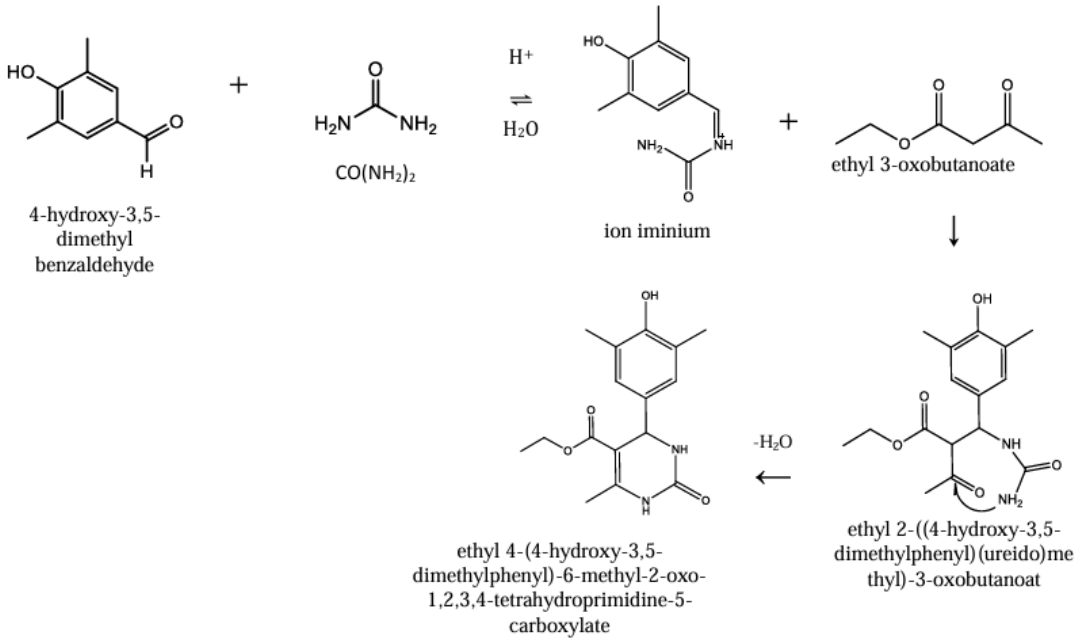

Figure 2. Synthesis Compound M1

According to Fauzi et al. (2023), reaction M1 (**Figure 2**) begins when the nucleophilic bond is attacked by the amine group of the urea on the aldehyde carbon. As a result, positive imine ions are formed because electrophiles are easily attacked by ethyl acetoacetate. The last phase of the reaction is the formation of a ring due to the addition of an amide to the carbonyl carbon of ethyl acetoacetate. Compound M1 reacts with the Mitsunobu method (**Figure 3**) with the addition of isopropyl alcohol to increase the ability of the compound to penetrate the membrane owing to its polarity (Ridwan and Wahyuni, 2015).

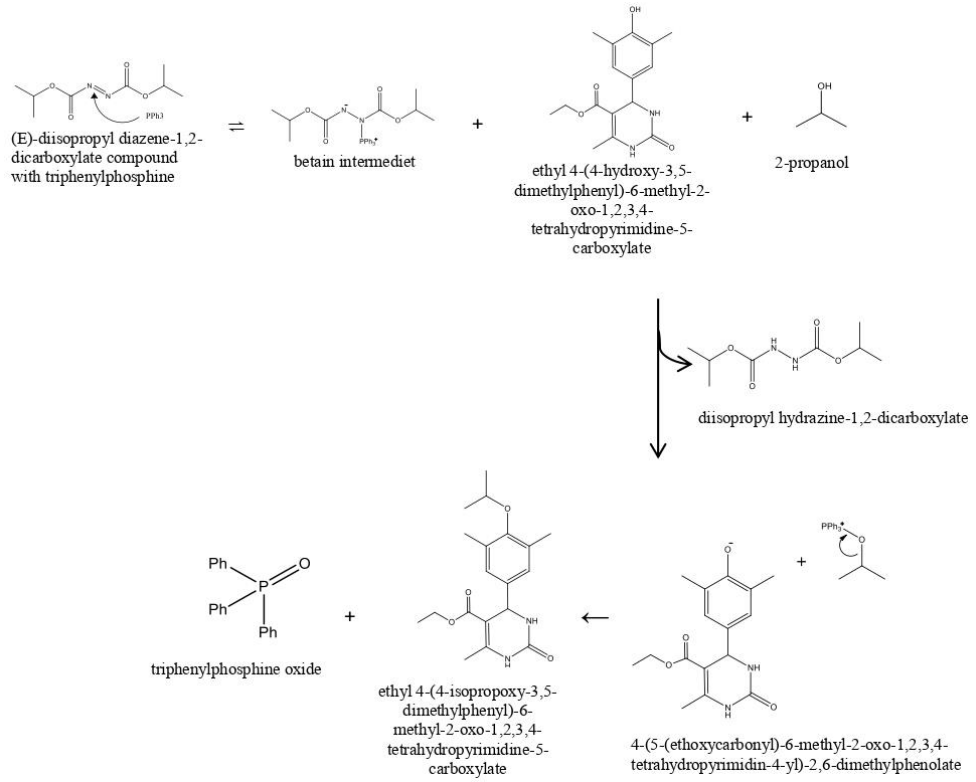

Figure 3. Mitsunobu Reaction of Compound B2

In the reaction of compound B2, the use of isopropyl alcohol which is a pronucleophile was chosen in the Mitsunobu reaction because its polar nature makes it more effective in reactions that require hydrogen bonding. In addition, isopropyl alcohol has a low melting point (-89°C) and high boiling point (82.6°C), which makes it possible to better control the reaction temperature. These properties also facilitate separation and purification of the final product (Helmenstine, 2021). In the reaction of compound B2, the free electron pair on PPH_3 attacks the DIAD compound to produce betaine intermediates. The betaine intermediate compound deprotonates the hydroxyl group of the M1 compound. The O group in isopropyl alcohol has a free electron pair that attacks PPh_3. Thus, compound B2 and its by-products in the form of PPh_3O were formed.

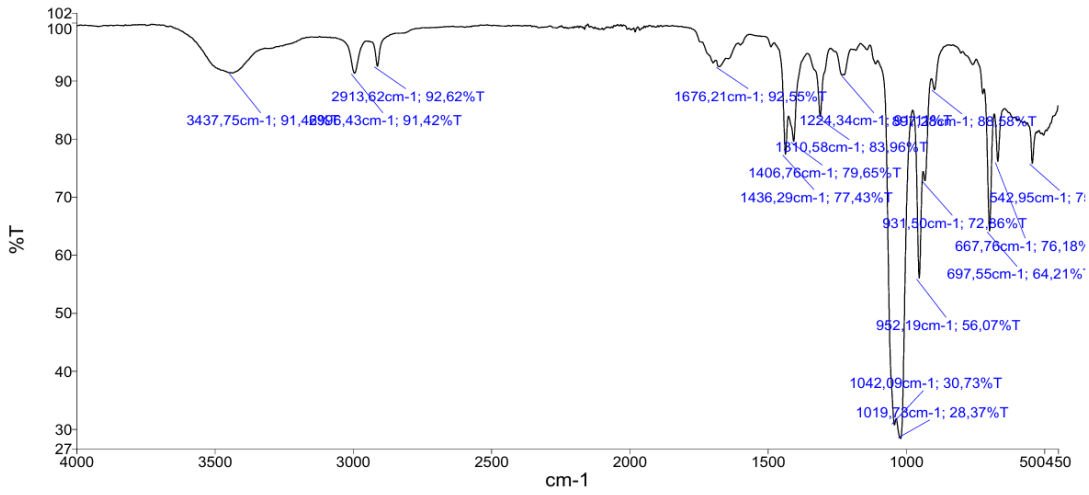

Figure 4. IR Spectra of Compound B2

In the synthesis of the compounds, characterization of the melting point test, FTIR Spectroscopy, and LC-MS Spectroscopy were used. FTIR spectroscopy was used in the

synthesis of organic compounds to monitor the synthesis process and identify the synthesis products. FTIR spectroscopy helps to determine the success of the synthesis products (Nurhamidah et al., 2024). FTIR is an instrument that can be used to detect functional groups, identify compounds, and analyze mixtures of analyzed samples without damaging them. The infrared region in the electromagnetic wave spectrum ranges from 14, 000 cm-1 to 10^{-1} (Sari and Fajri, 2018). In the FTIR analysis, compound B2 identified a peak in the wavenumber region of 3437.27 cm^{-1} which indicates the presence of NH bonds (Pavia et al., 2001). The peak at 1676.21 cm^{-1} indicates the C=O bond. Furthermore, the peak at 2996.43; 2913.62; 1436.29; 1406.76; 952.19; 931.50; 897.28; 697.55; 667.76; 542.95 cm^{-1} indicates the presence of CH bonds. While the peaks of 1310.58; 1224.34; 1042.09; 1019.73 cm^{-1} showed CO bonds.

The result of the melting point test of the B2 sample was 190-220 ^{o}C. LC-MS testing was used to provide information on the molecular weight, structure, identity, and quantity of specific sample components. Compounds are separated based on their relative interactions with a chemical layer of particles (stationary phase) and elution of the solvent through the column (mobile phase) (Mangurana, Yusnaini, and Sahidin, 2019). The results of the LC-MS analysis of the B2 sample showed a molecular weight of 334.13. This value is smaller than the theoretical molecular weight value of 346.42. This is because the chemical reactions that occur during the synthesis of a compound may result in the loss of hydrogen atoms. For example, if a compound undergoes deprotonation or reacts with an oxidizing agent, the NH group may lose hydrogen.

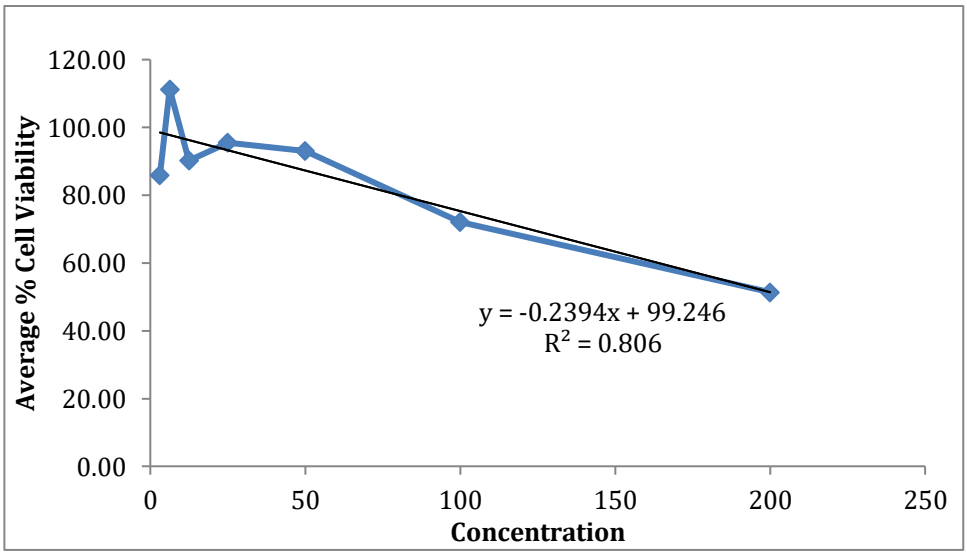

Figure 5. Concentration vs Average % Cell Viability in T47D

Cytotoxic activity was tested using the T47D cell line. The T47D cell line is a cancer cell model that is widely used in research, and this cell line has a morphology similar to that of epithelial cells. T47D cells express mutants of the tumor suppressor gene p53 protein, which plays a role in cell cycle regulation and regulation of apoptosis (cell death). In addition, the p53 protein is sensitive to the stimulant effects of estradiol because it often undergoes mutations in cancer patients (Susanty and Rahim, 2023). The American National Cancer Institute categorizes the cytotoxic of a substance based on its IC_{50} value. A material is said to have very strong cytotoxicity if the IC_{50} value is ≤ 20 µg/mL, moderate if the IC_{50} value is 21-200 µg/mL, weak if the IC_{50} value is 201-500 µg/mL, and nontoxic if the IC_{50} value is ≥ 500 µg/mL (Sajjadi et al., 2015). Based on data from Fauzi et al. (2023), ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydroprimidin-5-carboxylate cytotoxic activity in T47D cells gave good results, with an IC_{50} of 90.4 µg/mL classified as a moderate category. The results of the development using the Mitsunobu reaction method were less than optimal. According to Sajjadi et al. (2015), the results of this study showed a

weak IC_{50} value on T47D cells is 205.71 µg/mL which was classified as a weak category. The positive control doxorubicin showed an IC_{50} value of 3.33 µg/mL was classified as a very strong category. The results of research conducted using the Mitsunobu reaction did not show an increase in anticancer activity. This is because the alkylation process on isopropyl alcohol can reduce polarity, which causes the solubility to decrease (Ridwan and Wahyuni, 2015).

CONCLUSION

In this study, dihydropyrimidinone-derived compounds, ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydroprimidin-5-carboxylate (compound M1), were synthesized using the MCR method. The synthesis results were developed using the Mitsunobu reaction method to produce a new compound, ethyl 4-(4-isopropoxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (compound B2). Compound B2 was carried out cytotoxic test using T47D cells, with an IC_{50} value of 205.71 µg/mL which is classified as a weak category.

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If deemed necessary, such as for funders, technicians, and discussion partners, this can be written in this section.

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