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Short Communication

Synthesis *N*-(4-methoxybenzoyl)-*N*'phenylurea and the central nervous system depressant test

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ABSTRACT

Synthesis the new compound *N*-(4-methoxybenzoyl)-*N*'phenylurea has been done. The Schotten Baumann method was used for the reaction between *N*'phenylurea and 4-methoxybenzoyl chloride. The CNS depressant activity test was done for the *N*-(4-methoxybenzoyl)-*N*'phenylurea compound by Barbituric Sleeping Time (BST) method and compared with bromisoval as the standard compound and also with the parent compound *N*-benzoyl-*N*'phenylurea. The compound yield was 73,24% , had a white crystal and gave one spot in Thin Layer Chromatography with two different eluents. The compound melting point was different from the *N*'phenylurea and showed greater. The structure identification from the new compound was analysed by UV, IR, ^{1}-HNMR and MS, the result showed that the new compound was *N*-(4-methoxybenzoyl)-*N*'phenylurea. The CNS depressant activity test from *N*-(4-methoxybenzoyl)-*N*'phenylurea had a greater activity if compare with the standard compound bromisoval and also with the parent compound *N*-benzoyl-*N*'phenylurea.

Keywords: *N*-(4-methoxybenzoyl)-*N*'phenylurea; Synthesis; CNS depressant activity test

INTRODUCTION

The experiment to looking for the new compound which has the specific activity of pharmacological effect is a challenge in this period. In the health sector the development in the availability of a new molecule of drug is needed with further research to develop the structure of existing drug molecules or searching and finding new drug molecule which could be the candidate compounds that have potent pharmacological activity [12]. The chemical synthesis is one of the process to obtain a new compound that has the potential pharmacological effect as a new drug molecul candidate, of course with the new expectation that the new molecul drug compound relatively pure and has higher pharmacological activity than the parent compound [4,7]. All the world and in Indonesia exactly known about urea which is a chemical compound and produced by the chemical industry. The use of urea compound in the world and also in Indonesia was limited as the fertilizer of the plants, it turns out on further development of one of the urea derivative compound that have pharmacological activity as a central nervous system depressant drug, namely bromisoval. This compound is used as a depressant of the central nervous system when the barbiturate derivatives are no longer effective as a depressant of the central nervous system [5,6]. The ureide acyclic structure ($OCNH_2CONH_2$) is existence on bromisoval compound and also on the barbiturate compounds that show pharmacological activity as a depressant of the central nervous system. Some researchers have succeeded in making urea derivatives which have pharmacological activity as a depressant of the central nervous system. Reksohadiprojo, 1981, has succeeded in making urea derivative compound namely isovalerilurea which also has a group pharmacophore ureide acyclic structure that have pharmacological activity as a depressant of the central nervous system [10]. Other researchers, Tjiptasurasa, 1991, has managed to create another instance of the urea compound bromasilurea which also has activity as a depressant of the central nervous system because of the compound also have a group pharmacophore ureide acyclic structure [15]. Siswandono, 1999has managed to make the benzoilurea derivatives contained therein pharmacophore acyclic ureide structure also have pharmacological activity as a depressant of the central nervous system [13]. Suzanna, in 2004, managed to make the new compound of urea derivative benzoiltiourea who also have pharmacological activity as central nervous system depressant compound, it is also because of the group pharmacophore ureide acyclic

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structure.[14] Further development of the urea derivatives is to try to create a new instance of the compound *N*-(4-methoxybenzoyl)-*N*'phenylurea which also has pharmacophore ureide acyclic structure so that the compound is also expected to have pharmacological activity as a central nervous system depressant compound. The synthesis method used to make urea derivative compounds mentioned above are using the Schotten Baumann method which is has reaction principle between the amine group with the carbonyl group to form a carbamide compound [8,17]. To test the depressant activity of the central nervous system implemented by the Barbituric Sleeping Time (BST) method which consists of two steps, first is the determination of the timing of the peak activity and second is the potentiation test of the compound [1,16,18].

EXPERIMENTAL WORK

Synthesis of the *N*-(4-methoxybenzoyl)-*N*'phenylurea compound: To make a urea derivative compound become the carbamide compound a method such as the Schotten Baumann method is needed because the reaction of the synthesis of the carbamide compound formation in one stage proccess [8,16]. Bambang Tri Purwanto, 1991, it has successfully created ampicillin derivative compounds namely *p*-bromobenzoilampisilin using Schotten Baumann method, by reacting between ampicillin compound with *p*-bromobenzoylchloride compound [2]. Bambang Tri Purwanto, 2012, has successfully too on synthesized *N*-benzoyl-*N*'phenylurea using Schotten Baumann method, by reacting between *N*'phenylurea with benzoyl chloride compound [3]. Siswandono, 1999, has made a new compound namely *N*-benzoylurea, also using the Schotten Baumann method which was reacted the urea compound with benzoyl chloride [13]. In the synthesis of the *N*-(4-methoxybenzoyl)-*N*'phenylurea compound was made through the reaction between 4-methoxy-benzoyl chloride compound (0.150 mol) and *N*'phenylurea compound (0.125 mol) stirred and slowly mixed at a temperature of 0 - 5^{o} C. Then done stirring for 60 minutes at room temperature. The next step is heating the mixture (refluxed) at a temperature of 70^{o} C for 8 hours. Then added to a solution of saturated sodium bicarbonate, washed with water and then do recrystalization with hot methanol [8,18].

Structural characterization of the compound was carried out on the next stage with a variety of instruments, which can be proved that the compound which was synthesized has been successfully created [9,11].

The depressant activity test of the central nervous system: The method of the depressant activity test on the central nervous system is Barbituric Sleeping Time (BST), because this method is a standard method in the test of the depressant activity of the central nervous system. BST method consists of two stages, first the determination of the timing of the peak activity of the compound, which is to looked for the longest sleep time of the experimental animals, the second was the potentiating of the compound at the time of peak activity by giving compound thiopental induction [1,16,18]. The experimental animals which used were white mice (*Mus musculus*) aged 2-3 months, had weigh between 20-30 g, BLAB C strain, without physical disabilities, and acquired from the animals laboratory Airlangga University.

In the depressant activity test of the central nervous system the compound *N*-(4-methoxybenzoyl)-*N*'phenylurea on the first stage is the determination of the peak activity time starts from minutes to 15, 30, 45, 60, 75, 90 and 120 by using a single dose. The next stage is the determination of the potentiation test using 5 different doses (10, 25, 50, 100 and 200 mg / kg BW) were administered by intraperitoneal routes. Bromisoval used as a standard compound with the same dose, whereas the inducer compound is used thiopental sodium injection. The *N*-benzoyl-*N*'phenylurea was used as the parent compound.

RESULT AND DISCUSSION

The compound had been synthesized was white needle-shaped crystals with a yield gain of 73.24 %, and it indicates that the method of Schotten Baumann was an elected method of the synthesis.
In the first step to prove that the compound had been synthesized, a thin-layer chromatography test by using 2 different solvents (hexane: acetone = 4: 2 and hexane: ethyl acetate = 4: 2) gave a single spot with different Rf and it showed a different Rf from *N*'phenylurea. The above showed that the target compound which was synthesized have been formed and relatively pure. In the next step, the melting point analysis test from the compound which was synthesized has a melting point 195^{o}C and it was different from the *N*'phenylurea compound which have melting point 145^{o}C. In this test has been proven that the compound synthesized have been formed and has a relatively of purity because there were no other impurities in it. The structure identification of the compound was synthesized performed by ultraviolet spectrophotometer, Infrared, ^{1}-HNMR and mass spectrometer. The compound synthesized, UV (methanol solvent): λmaks (nm) = 252; IR (pellet KBr): 3446 cm^{-1} (NH secondary), 1685 cm^{-1}; 1603

cm^{-1} (-CO), 1538;1515 cm^{-1} (C = C arom); ^{1}-H-NMR (DMSO-d_6 solvent): 6.90 to 8.10, m, (C_6H_5), 12.00 to 13.00,d,(NH), 3.70-4.10,s,(OCH_3); MS (EI): 270 $(M)^+$, 151 $(C_6H_5NH)^+$. The compound from *N*'phenylurea, UV (methanol solvent): λmaks (nm) = 204, 238; IR (pellet KBr): 3428 cm^{-1} (NH primary), 1655 cm^{-1} (CO), 1553 cm^{-1} (C = C aromatic); ^{1}-H-NMR (DMSO-d_6 solvent): 6.80 to 8.00, m, (C_6H_5), 5.60, s, (NH), 6.20, s, (NH), 8.60, s, (NH_2).

In the structure identification with a variety of instruments the structure from the compound which was synthesized have different with the *N*'phenylurea compound, especially on the number of hydrogen atoms contained in the *N*'phenylurea compound (^{1}-HNMR) and presence of 2 peaks from the carbonyl group (IR). On the characterization of the structure of the mass spectrometer showed that the synthesized compound have a molecular weight of 240 intact and the structure identification showed that suitable with that was shown on the literature so it can be ascertained that the compound had been synthesized have formed [9,11],. The structure from the compound have been synthesized can be seen on figure 1.

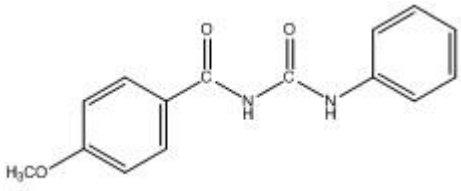

Figure 1 : The structure of the *N*-(4-methoxybenzoyl)-*N*'phenylurea

The depressant activity test of the central nervous system on the early stage, the compound which was synthesized had a peak activity at 30 minutes to the longest time sleeping mice, while the peak activity time for bromisoval 60 minute sleep mice showed the longest time. To test the inducer compound potentiation with thiopental, which was by routes with 5 different doses can be seen in Figure 2 below.

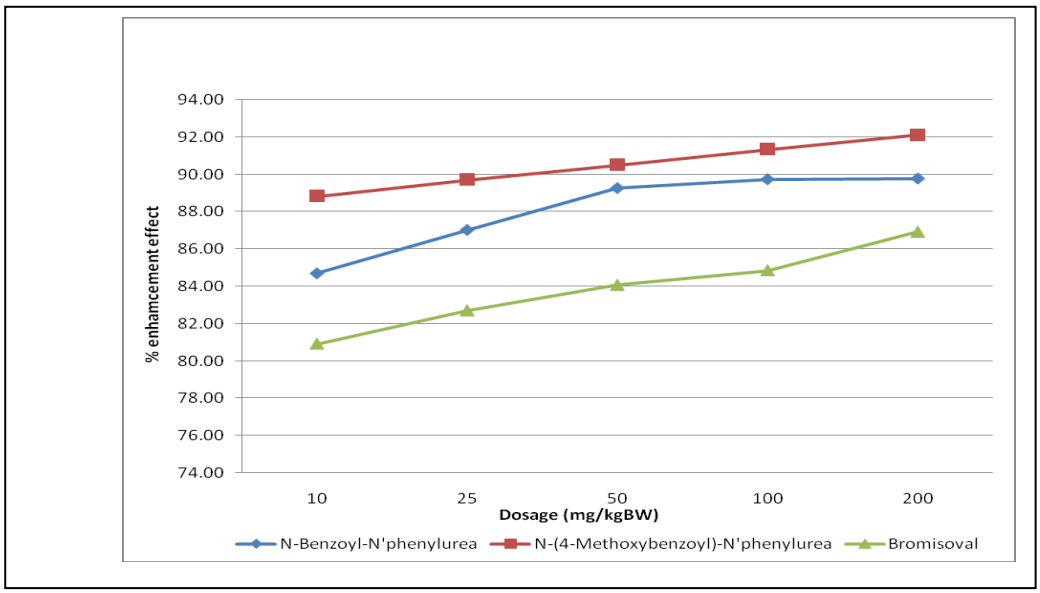

Figure 2: The central nervous system depressant activity test of *N*-benzoyl-*N*'phenylurea; *N*-(4-methoxybenzoyl)-*N*'phenylurea and bromisoval

Based on the figure 2 shows that the activity of the compound *N*-(4-methoxybenzoyl)-*N*'phenylurea has the depressant activity of the central nervous system higher than the standard compound bromisoval at the same dose, also higher than the parent compound *N*-benzoyl-*N*'phenylurea, it is due to the addition of benzoyl group with methoxy moiety led to compound becomes more non-polar nature so it is very easy in penetration into biological membranes. Beside that, the *N*-(4-methoxybenzoyl)-*N*'phenylurea compound has the same pharmacophore acyclic ureide too, so it showed an activity of the central nervous system depressant also. Based on these results demonstrate that the *N*-(4-methoxybenzoyl)-*N*'phenylurea obtained can be developed into a new drug candidate compound which has the depressant activity to the central nervous system

CONCLUSION

The *N*-(4-methoxybenzoyl)-*N*'phenylurea had been synthesized and had the depressant activity of the central nervous system is higher than the standard compound bromisoval and the parent compound *N*-benzoyl-*N*'phenylurea.

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