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N-(3-TRIFLUOROMETHYLBENZOYL)-N'PHENYLUREA, A NOVEL COMPOUND OF THE CENTRAL NERVOUS SYSTEM DEPRESSANT

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INTRODUCTION

The development of drug molecules which have a spesific activity of pharmacological effect to become the new molecul drug is a challenge in this decade. The new compound which have a spesific action is the need and very necessary. [12] The method for having the new compound is doing by the synthesis from some reactans and the very important step is the proccess. The presence of the compound which have the activity as the central nervous system (CNS) depressant needed to be developed, that is a new challenge and felt more further considering the side effects that drugs have. [4, 7] Urea is a chemical compound that is very well known in the world and in Indonesia, this compound has been able to be produced by the chemical industry. The use of urea compounds in the world and also in Indonesia was limited as a plants fertilizer; it turns out on further development of one of the urea derivative compounds that have pharmacological activity as a central nervous system depressant drug, namely bromisoval. The use of this compound as a depressant of the central nervous system when a barbiturate derivative is no longer effective as a depressant of the central nervous system. [5, 6] 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] urwanto B.T, 1991, have successfully synthesize new compounds *N*-bromobenzoylampicillin having an antibacterial activity by Shotten-Bauman method.[2] Purwanto B.T.,2011, have successfully synthesize new compounds *N*-benzoyl-*N*'phenylurea having a CNS depressant activity by Shotten-Bauman method. The development of the *N*-benzoyl-*N*'phenylurea

derivative compounds is predicted could increase the CNS activity depressant. [3] The depressant activity test of the central nervous system implemented by the Barbituric Sleeping Time (BST) method which consists of two steps, first the timing of peak activity and second is the potentiation test of the compound. [1, 16, 18]

METHOD OF THE EXPERIMENTAL

1. Synthesized N-(3-Trifluoromethylbenzoyl)-N'phenylurea

All the reagents and reactants which were used in this experiment have a pure analysis grade. *N*-(3-trifluoromethylbenzoyl)-*N*' phenylurea was prepared by reacting *N*-phenylurea (0.125 mol) with 3-trifluoromethylbenzoyl chloride (0,150 mol) with slowly stirrer by Schotten Baumann method which was modified in the used of the solution and the catalyst The reaction was done in cool temperature and after its finished, the mixture compounds was taken in room temperature for about one hour and then were refluxed for about 7-8 hours. The $NaHCO_3$ solution was added to the mixtures until the bubbles were loosed. Collected the crystal and filtrate it with Buchner. Recrystallizations was done by added the hot methanol. [8, 17]

2. Identification of The Structure

The first identification for the compound was done by chromatography method (TLC) with 3 different eluent and also by melting point. The next step was the structure identification was done by using spectrophotometric UV-VIS, Infra Red method and spectrometric ^{1}H-NMR also MS. [9, 11]

3. Cns Depressant Activity Test

The CNS depressant activity test has been done by Barbituric Sleeping Time (BST) method using the male mice (BLAB C strain, 20-30 gram weighed, 2-3 months age, healthy) as the experimental animals and bromisoval compound as the standard, also the *N*-benzoyl-*N*'phenylurea as the lead compound, the penthotal sodium injection as the sleep inducer and all the compounds was injected to the mice by intraperitoneal (ip) routes. [1, 16, 17]

RESULTS AND DISCUSSION

The compound which has been synthesized is the white like cotton crystals with a yield of 76.10%, it indicates that the method of Schotten Baumann as an elective method of the synthesis. In the next stage test thin-layer chromatography on compounds synthesized by using 2 different solvents (hexane: acetone = 4: 2 and hexane: ethyl acetate = 4: 2) gave single spots with different Rf with compound from *N*-phenylurea. The above shows that the

compound was synthesized have been formed and relatively pure.At the melting point analysis test, the compound has been synthesized has a melting point (195^{o}C) and it was different with the *N*-phenylurea compound (145^{o}C). In this test has been proven that the compound has been synthesized have been formed and has a purity because there were no other impurities in it. Identification of the structure of the compound has been synthesized performed with ultraviolet spectrophotometer, Infrared, ^{1}-HNMR and mass spectrometer.

The synthesized compound, λmaks (nm) = 230, 258; IR, 3467 cm^{-1} (NH secondary), 1697 cm^{-1} (-CO), 1603,1560 cm^{-1} (C = C arom); ^{1}-HNMR (DMSO-d_6 solvent), 7.00 to 8.40, m, (C_6H_5), 10.60, s, (NH), 11.40, s, (NH); MS (EI), 308 (M) $^{+}$, 189 (CH_3 (C_6H_5)$NCONH_2$) $^{+}$

The *N*-phenylurea compound, λmaks (nm) = 204, 238; IR, 3428 cm^{-1} (NH primary), 1655 cm^{-1} (CO), 1553 cm^{-1} (C = C aromatic); ^{1}-HNMR (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 identification of the structure the spectrophotometer with a variety of instruments, the structure of the compound has been synthesized had a different structure with the parent compound, especially on the number of hydrogen atoms (^{1}-HNMR) and the presence of 2 peaks of the carbonyl group which was existed on the compound (IR). On the identification of the structure with the mass spectrometer showed that the synthesized compound has a molecular weight of 308 and the identification of the structure was suitable as shown on the literature Pavia, 2009 and Silverstein, 2009, [9, 11], so it can be ascertained based on the characterization of the structure of the compound synthesized have formed. The structure of the compound was showed on figure 1.

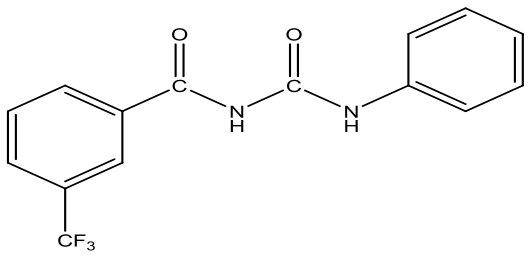

Figure 1: The structure of the compound namely *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea

Isovalerilurea is one of the urea derivatives who has successfully made by Reksohadipodjo [10]; bromasilurea made by Tjipta Surasa [15]; benzoilurea made by Siswandono [13]; benzoiltiourea made by Suzanna [14]. All of these compounds which have been synthesized

have the depressant acitivity and all these compounds have the pharmacopore moieties ureide acyclic ($OCNH_2CONH_2$). The *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea showed the depressant activity, because it has an ureide acyclic structure, the pharmacopore moeity too ($OCNH_2CONH_2$). The depressant activity test of the central nervous system divided in two stages, the early stages, and the compound which has been synthesized had a peak activity to the longest time sleeping mice at 30 minutes, while the peak activity time for bromisoval (standard compound) showed the longest time on sleep at 60 minute. The inducer compound (thiopental), which was gave the potentiation by administered intra-peritoneal and all compounds were gave to the mice with 5 different doses and the curve can be seen in Figure 2 below.

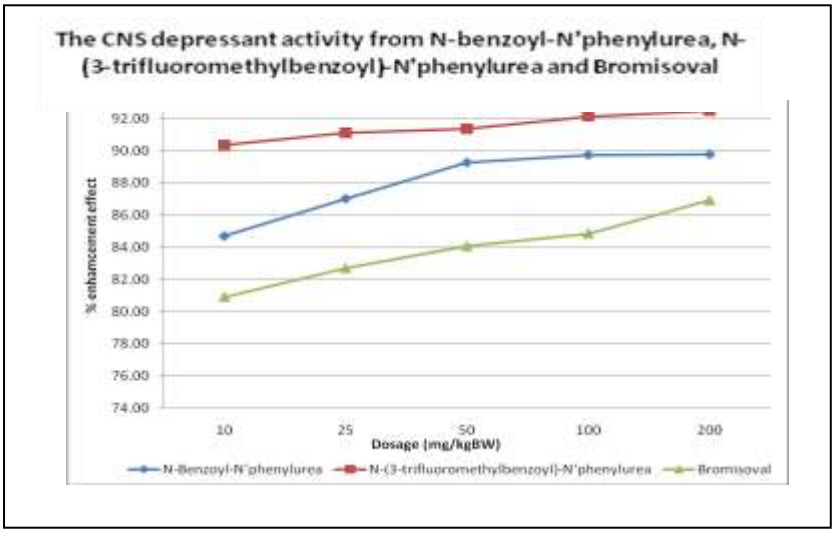

Figure 2: Comparison of the depressant activity test of the central nervous system *N*-Benzoyl-*N*'phenylurea; *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea and bromisoval.

Based on the figure 2 showed that the depressant activity of *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea as a novel cns depressant was higher than the standard compound bromisoval and the lead compound *N*-benzoyl-*N*'phenylurea at the same dose, it can be seen that the addition of benzoyl group led to the compound becomes more non-polar so it is very easy in penetration into the biological membranes. Based on these results demonstrate that the *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea can be developed into a new compound of the drug candidate with the central nervous system effect of depressant.

CONCLUSION

The *N*-(3-trifluoromethylbenzoyl)-*N*'phenylurea as a novel cns depressant had been

synthesized and had the depressant activity of the central nervous system is higher than the standard compound bromisoval, also *N*-benzoyl-*N*'phenylurea.

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