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THE BENZOYLSALICYLAMIDE AND THE 4-FLUOROBENZOYLSALICYLAMIDE, THE NOVEL SALICYLAMIDE DERIVATIVES AND THE ANALGESIC ACTIVITIES COMPARATIVE

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ABSTRACT

The benzoylsalicylamide and the 4-fluorobenzoylsalicylamide as the novel salicylamide derivatives had been synthesized. The novel compound benzoylsalicylamide and the 4-fluorobenzoylsalicylamide were synthesized by The Schotten Baumann method, where the reaction were between salicylamide and benzoyl chloride also 4-fluorobenzoyl chloride. The analgesic activity test was done for the benzoylsalicylamide and the 4-fluorobenzoylsalicylamide compound by writhing test and compared with salicylamide as the standard compound. The benzoylsalicylamide compound yield was 58%, had a crystal shiny white needles and gave one spot in Thin Layer Chromatography with three different eluents. The compound melting point was different from the salicylamide and showed greater. The structure identification from the new compound was analysed by UV, IR, ^{1}-H-NMR, the result showed that the novel compound was benzoylsalicylamide. The analgesic activity test from benzoylsalicylamide had a greater activity if compare with the standard compound salicylamide. The 4-fluorobenzoylsalicylamide compound yield was 64% had a white powder and gave one spot in Thin Layer Chromatography with three different eluents. The compound melting point was different from the salicylamide and showed greater. The structure identification from the new compound was analysed by UV, IR, ^{1}-H-NMR, the result showed that the novel compound was 4-fluorobenzoylsalicylamide. The analgesic activity test from 4-fluorobenzoylsalicylamide had a greater activity if compare with the standard compound salicylamide also from the benzoylsalicylamide. The benzoylsalicylamide and 4-fluorobenzoylsalicylamide had been synthesized as the novel salicylamide derivatives and the

4-fluorobenzoylsalicylamide had a higher analgesic activity if compare with salicylamide as the standard compound also from the benzoylsalicylamide.

KEYWORDS: Benzoylsalicylamide; 4-fluorobenzoylsalicylamide; Synthesis; analgesic activity test.

INTRODUCTION

In this periode the existing of the new compound which will be use as a drug is a challenges. The develop the structure of the existing drug molecules were made by the scientific researches or searching and finding the new drug candidate compounds that have potent pharmacological activity.[2]

To obtain a new compound that has the potential as a new drug candidate, the modification of the drug molecul (by chemical synthesis process) is needed, with the consideration that new compounds which will be obtained had a relatively pure compounds and has higher pharmacological activity than the parent compound.[7]

The analgesics are the drugs which be use as a relieve pains and were always required by the hospitals, the clinicians and the individuals. The circulation of the analgesic drugs were used in the hospital is 43% while 32% in the pharmacies and 27% in the drug store, so these indicate that the analgesic drugs are needed and has great opportunities for further development.

Salicylamide is one of the analgesic compounds of the salicylic acid derivatives which was used by the publics. Pharmacological activity as pain relievers like aspirin, but salicylamide not have the pharmacological activity as the anti-inflammatory and the anti-rheumatic.[1]
To enhance the analgesic potency owned by salicylamide it is necessary to modify the structure so that it will be obtained the novel salicylamide derivatives which be predicted would have a higher analgesic potency than salicylamide.[15]

Salicylamide pharmacological activity is highly dependent on the physical chemical properties, an increase in the value of the log P from the novel compounds salicylamide derivatives is expected to increase the potential for the pharmacological activity as an analgesic.[1]

To produce a novel compound, the synthesis reactions carried salicylamide derivative with Schotten-Baumann method, whereas for the analgesic activity test was conducted by the writhing test method.[4, 8, 14]

In the novel compounds salicylamide derivatives which have been synthesized, looks have the same chromophore moities with salicylamide as the parent compound, but an increase in the value of the liphophylic parameter, so the novel compounds salicylamide derivatives expected will have a higher analgesic potency than the salicylamide.

METHOD

1. Synthesis benzoylsalicylamide and 4-fluorobenzoylsalicylamide

Siswandono[11] has been synthesized the new derivatives benzoylurea which had the central nervous system acitivties by the Schotten Baumann method.

Bambang Tri Purwanto[2] has been successfully used the Schotten Baumann method to synthesized the N-bromobenzoylampicillin.

Bambang Tri Purwanto[3] also used the Schotten Baumann method to synthesized the benzoylphenylurea derivatives.

Hardjono[6] has been successfully by using the method Schotten Baumann to modified urea structure became benzoyloxyurea derivatives.

Synthesis reaction to obtain the novel salicylamide derivatives performed by reacting the salicylamide (0.015 mol) with some derivative benzoyl chloride, among others, benzoyl chloride, 4-fluorobenzoyl chloride (0.0125 mol) were dissolved in acetone. The reaction was performed at a temperature of 5°C for 2 hours slowly while stirring, to maintain stability and the need to accelerate the reaction was added a solution of pyridine as a catalyst. After the reaction was finished the sodium bicarbonate solution is added to the reaction until a neutral reaction. The crystals that occur was filtered, then was made recrystallization with hot methanol solvent.[4, 8, 13]

2. The purity test and the structure characterization

a. The purity test of the compounds which were synthesized performed by thin layer chromatography (stationary phase silica gel GF_{254}) using three kinds of the solvents

(ethyl acetate: n-hexane = 7: 3; chloroform: ethyl acetate = 7: 3 and n-hexane: ethyl acetate: methanol = 8: 3: 1)

b. Characterization of the structure of the new compounds synthesized were done by using an infrared spectrophotometer (KBR pellet) and spectrometer ^{1}-HNMR (solvent DMSO-d_6).[9, 10]

3. The analgesic activity test

The analgesic activity test from the O-benzoylsalicilic acid by the writhing test method was done by Dyah *et.al*.[5]

The analgesic activity test using writhing test method with the experimental animals *(Mus musculus*) aged 2-3 months, Blab C strain, weighing 20-30 grams and physically showed no disability. Doses used in trials of analgesic activity of the novel derivatives salicylamide was 10, 25, 50, 100 and 200 mg / kg BW and administered by intra-peritoneal, the preparations were made in the form of a suspension in a solution of sodium carboxy methyl cellulose. Salicylamide used as a comparison agent with the same dose.

RESULT AND DISCUSSION

1. The compound benzoyl salicylamide ($C_{14}H_{11}NO_3$)

These compounds form is crystal shiny white needles, odorless and has a yield of 58%. Melting point 119^{o}C. Characterization of the structure, IR (KBr pellet): 3546 cm^{-1} (OH), 3232 cm^{-1} (NH), 1712 cm^{-1}, 1671 cm^{-1} (CO amide), 1480 cm^{-1} (C = C aromatic); ^{1}H-NMR (DMSO-d_6) 12.02, s (OH); 6.4, s, (NH); 6.8-8.2 m, (C_6H_5).

2. The compound 4-fluorobenzoyl salicylamide ($C_{14}H_{10}FNO_3$)

This compound is in the form of white powder, odorless and has a yield of 64%. The melting point was 216^{o}C. Characterization of the structure, IR (KBr pellet): 3218 cm^{-1} (NH secondary), 1717 cm^{-1} (CO amide), 1484 cm^{-1} (C = C aromatic), 1273 cm^{-1} (CF); ^{1}H-NMR (DMSO-d_6): 12.98, s (OH); 6.92-8.30, m (C_6H_5).

All of the compounds synthesized showed only 1 different spot and the Rf value for each compound different with the Rf of the salicylamide as the parent compound, using thin layer chromatography for the purity analysis with 3 different eluent solvent. Besides that, this result is reinforced by differences in melting point the compounds synthesized by the parent compound salicylamide, so this suggests that the compounds which were synthesized has

been formed and were different from the parent compound salicylamide, also means all the compounds synthesized can be said to be pure and not contaminated by other materials. Based on the results the yield of each compound synthesized was seen that the results of the yield above 50%, indicating that the Schotten Baumann method was the chosen method to carry out the synthesis of derivatives salicylamide by means of molecular modifications from the parent compound salicylamide by substitution with a moety of benzoyl (benzoylation).

The characterization of the structure which were analysed by the spectrophotometer IR shown that the compounds synthesized have been different with a parent compound salicylamide particularly evident from the specific carbonamide bond (CO amide) and reinforced by the results of spectra ^{1}H-NMR, which showed the number of the hydrogen atoms of each compound derivatives of salicylamide has different from the salicylamide compound.

So based on the data above, it can be concluded that the compounds synthesized were benzoylsalicylamide and 4-fluorobenzoylsalicylamide.

The analgesic activity test from the novel derivatives salicylamide can be seen in the figure below.

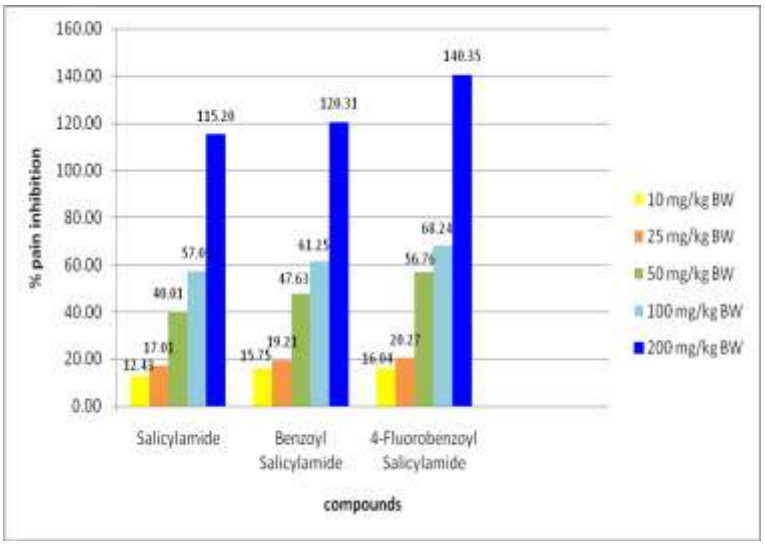

Fig 1: % effect inhibitory analgesic activity from the novel salicylamide derivatives.

Based on the analgesic activity which was shown by the percentage of inhibition of the pain in the figure 1 above, showed the curve that all new salicylamide derivative compounds have analgesic activity higher than the salicylamide compound at each dose was used.

The addition of benzoyl group at salicylamide derivates will increase the liphophylic parameter value so the novel salicylamide derivative compounds have the capability of penetration into larger biological membrane and harmony in binding with the receptor molecule will be higher. The highest analgesic activity was shown by the novel 4-fluorobenzoylsalicylamide compound at the dose 200mg/kg BW. The fluoro moeity at para position showed that the 4-fluorobenzoylsalicylamide more lipophylic than benzoylsalicylamide or salicylamide, so the 4-fluorobenzoylsalicylamide had a higher analgesic activity than both.

CONCLUSION

The novel salicylamide derivatives, benzoyl salicylamide and 4-fluorobenzoyl salicylamide, has been succeesfully synthesized and all have higher analgesic activities than the salicylamide compound. The 4-fluorobenzoylsalicylamide had a highest analgesic activity.

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