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Synthesis and Structure Elucidation of 1,3 bis(*p*-Hydroxyphenyl)urea

(Sintesis dan Elusidasi Struktur 1,3 bis(*p*-Hidroksifenil)urea)

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Abstract: Paracetamol is a well known and commonly used analgesic-antipyretical agent. However, it exhibits hepatotoxic side effect if used for the long term or using exessive dose (10-15 g for single dose). A new compound of 1.3 bis (*p*-hydroxyphenyl)urea (code-name as HP2009) is an analgesic agent, and it is predicted that its hepatotoxic side effect is lower than that of paracetamol. The compound HP2009 was succesfully synthesized. The result showed that by using molar ratios of *p*-aminophenol and urea 2:9.5, pH 1 for reaction condition, refluxing for about 1 hr and evaporating time was set up for 30 minutes, the yield of HP 2009 will be 99.49%. The crystals obtained was characterized using spectroscopic methods, and showed undoubtedly that the product was 1.3 bis(p-hydroxyphenyl)urea.

Keywords: 1.3bis (*p* - hydroxyphenyl)urea, synthesis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic analysis, paracetamol.

Abstrak: Parasetamol adalah analgetika-antipiretika yang sering digunakan. Parasetamol memiliki kelemahan efek samping hepatotoksik jika dikonsumsi untuk waktu yang lama atau dosis yang berlebih (10-15 g dosis tunggal). Senyawa 1,3 bis (*p*-hidroksifenil)urea (selanjutnya senyawa diberi kode HP2009) merupakan analgesik yang diprediksi mempunyai efek samping hepatotoksisitas lebih rendah dibanding parasetamol. Senyawa HP2009 telah berhasil disintesis. Hasil penelitian menunjukkan bahwa reaksi sempurna memerlukan waktu penguapan 30 menit; rasio mol *p*-aminofenol:urea = 2:9,5; pada pH 1 dan waktu refluks 1 jam mendapatkan hasil 99,49%. Kristal yang diperoleh dikarakterisasi menggunakan metode spektroskopi dan tidak diragukan lagi menunjukkan bahwa produk adalah 1,3 bis (*p*-hidroksifenil)urea .

Kata kunci: 1,3bis (*p*-hidroksifenil) urea, sintesis, IR, ^{1}H-NMR, ^{13}C-NMR dan analisis spektroskopi massa, parasetamol.

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INTRODUCTION

PARACETAMOL or acetaminophenol is a well known analgesic-antipyretics for common cold. However, its hepatotoxic side effect has made the FDA to give a warning that paracetamol can not be administered for children under 3 years old or used for more than 10 days, unless the doctor prescribed it[1].

This side effect was due to paracetamol metabolite, NAPQI (*N*-acetyl-*p*-benzoquinon imine) which covalently bonded to negatively hepatic macromolecule cells. This irreversibly covalent bonding attached at the ortho position of quinone moeity (Figure-1)[2]. Van de Straat (1987) stated that this covalent bond between NAPQI anf hepatic cells formed at ortho position of phenolic paracetamol[1,2,3,4].

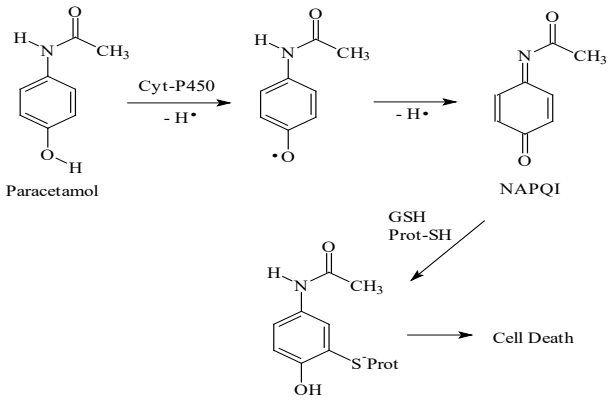

Figure 1. Hepatotoxic mechanism by NAPQI[2].

Various efforts have been carried out to improve the paracetamol's analgesic effect or to eliminate the side effects, through modification of the molecule structure of this compound. The modified structures which have already been synthesized were: anycidine, phenaldine, phenacetine, lactyl phenetidyl, phenachol, criolin, *p*-acetoxyacetanilide, phenetsal and pertonal[4]. Van de Straat *et al*. (1986) synthesized some 3-monoalkyl, 3.5-dialkyl paracetamol derivatives and 2.6-dimethyl-4-hydroxy-acetanilide[5], but so far these new derivatives failed to compete with paracetamol in the market. Some of paracetamol derivatives have

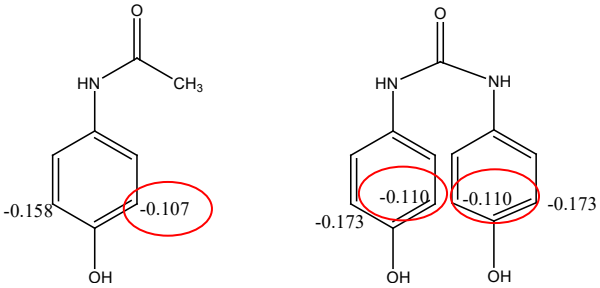

Figure 2. Net charge of *ortho*-carbon atom on paracetamol (left) and HP2009 (right).

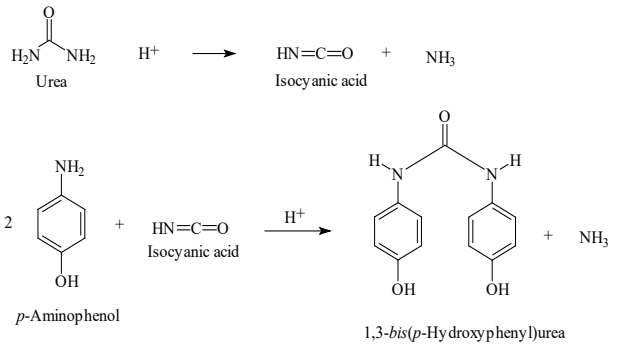

Figure 3: Synthesis reaction of HP 2009.

been made to improve the analgesic effect and reduce the side effect[5, 6, 7. 8, 9].

To reduce this side effect of paracetamol, a new molecule of 1.3-bis(*p*-hydroxyphenyl) urea was designed. This new molecule, designated as HP2009, is predicted to have less hepatotoxic side effect than that of the paracetamol, since the HP2009 has atomic charge (- 0.110) binding to hepatic cells, less positive than the paracetamol (- 0.107) (Figure-2). Synthesis of HP2009 could be carried out by reaction between *p*-aminophenol and urea, under acidic condition. Synthetic reaction was given in Figure-3.

MATERIALS AND METHODS

MATERIALS. *p*-Aminophenol p.a (E . Merck), urea (E . Merck), ethanol p.a (E . Merck), TLC plate (E . Merck), chloroform p.a (E . Merck), ethyl acetate p.a (E . Merck), hydrochloric acid (HCl).

Instruments. One set of glass-ware for synthesis: Round Bottom Flask (100 mL), Allinh Condenser, Heating Mantle, Beaker-glass (100 mL), pH indicator, Thermophan (Reichert Austria; Nr . 340,579), Infrared (IR) Spectrophotometer (Shimadzu FTIR - 8201 PC), NMR-Spectrometer 500 MHz (HITACHI FT- NMR-R 1900), Gas-Chromatography - Mass Spectroscopy (GC-MS) (Shimadzu GC- 17A / Shimadzu QP- 5000).

METHODS. Synthesis of 1,3 Bis(*p*-Hydroxyphenyl) Urea (HP2009). Synthesis of 1.3 bis (*p*-Hydroxyphenyl) urea, HP 2009, was carried out using methods developed by Davis and Blancard[10]. This methods, *p*-aminophenol and urea used as starting materials and the reaction was given in Figure-3.

The *p*-aminophenol (2.18g, 0.02mol) on a 250 mL round bottom flask was added by solution of hydrochloric acid (3 mL, 25%) which was previously diluted by aquadest (48 mL) (keep away from sun light). Urea (4.8g, 0.08mol) was then added to the reaction mixture, followed by addition several drops (~1 mL) of hydrochloric acid solution (25%), until acidic of reaction mixture reached pH 3.

Then the reaction mixture was heated for 30 minutes on a fume cupboard, followed by refluxing on gentle-boiling condition for 1 hour (using heating mantle at scale-4 max). Cooling down the reaction mixture using water at room temperature, and put on ice-bath. Then cooled it at the freezer for 2 hours. Crystalls so obtained was separated, washed with water, and dried at the oven for one day at 50 ^{0}C. The following day, the crystall was purified by recrystallization using hot ethanol and gave a product of HP2009 in 99.49% yields as a pinkly-white crystals. The structure of the product was then elucidated by using spectroscopic methods.

Structure Elucidation of The Synthetic Product: 1,3 Bis (*p*-Hydroxyphenyl)Urea (HP2009). Infrared Spectroscopic Analysis. Infrared (IR) spectroscopic analysis of the synthetic product: HP2009, was carried out on KBr pellet, and using IR-spectrophotometer (Shimadzu FTIR-8201 PC). The IR spectrum of HP2009 was recorded and wave-numbers of various vibration patterns were analyzed.

^{1}H Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis. ^{1}H NMR spectroscopic analysis of the synthetic product: HP2009 was carried out using NMR-spectrometer 500 MHz (HITACHI FT- NMR- R 1900). Solvent used in this analysis was d_6-DMSO and all proton chemical shifts (δ_H) was recorded. All of the resonance peaks at the 1H NMR spectrum was then analyzed.

^{13}C NMR Spectroscopic Analysis. ^{13}C NMR spectroscopic analysis of the synthetic product: HP2009 was carried out using NMR-Spectrometer 500 MHz (HITACHI FT- NMR- R 1900). Solvent used in this analysis was d_6-DMSO, and all carbon-13 chemical shifts (δ_C) was recorded. All of the resonance peaks at the ^{13}C NMR spectrum was then analyzed.

Gas Chromatographic-Mass Spectrometric (GC-MS) Analysis. GC-MS analysis of the synthetic Product: HP2009 was carried out using instrument GC-MS (Shimadzu GC- 17A / Shimadzu QP-5000). An Electron Impact Mass Spectrometer (EI-MS) was used to determine the molecular weight and structure of HP2009.

RESULTS AND DISCUSSION

Structure Elucidation of The Synthetic Product: 1,3 Bis(*p*-Hydroxyphenyl)Urea (HP2009). Analysis of all spectroscopic data of HP2009 was carried out based on standard literatures[11, 12, 13].

Result of IR Spectrum Analysis of HP2009. IR Spectrum of HP 2009 shown as in Figure 4. Vibration peak at wave-number (Vmax) 3310 cm^{-1} derived from stretching-vibration of phenolic hydroxyl group (phenolic-OH str); where as Vmax 1639 cm^{-1} is due to stretching vibration of carbonyl group (C=O str) of the molecule HP 2009. Vibration at Vmax 1575 cm^{-1} overlaps with that of 1509 cm^{-1}, and are due to bending vibration of two secondary amide groups: -NH bend; where as stretching vibration C=C of the aromatic ring appears at Vmax 1464 cm^{-1}.

Result of ^{1}H NMR Spectroscopic Analysis of HP2009. The ^{1}H NMR Spectrum of HP 2009 shown as in Figure 5. Based on its synthetic history, the molecule HP2009 is predicted as a kind of symmetrical urea derivative. ^{1}H NMR spectrum showed four resonance-peaks, i.e., at δ_H 0.90237 (singlet, s); 8.1689 (singlet, s); 7.1857 (doublet, d); and 6.6746 (doublet, d) ppm. Proton-integral ratios of these four peaks are respectively 1:0,98:2.003:2.009,

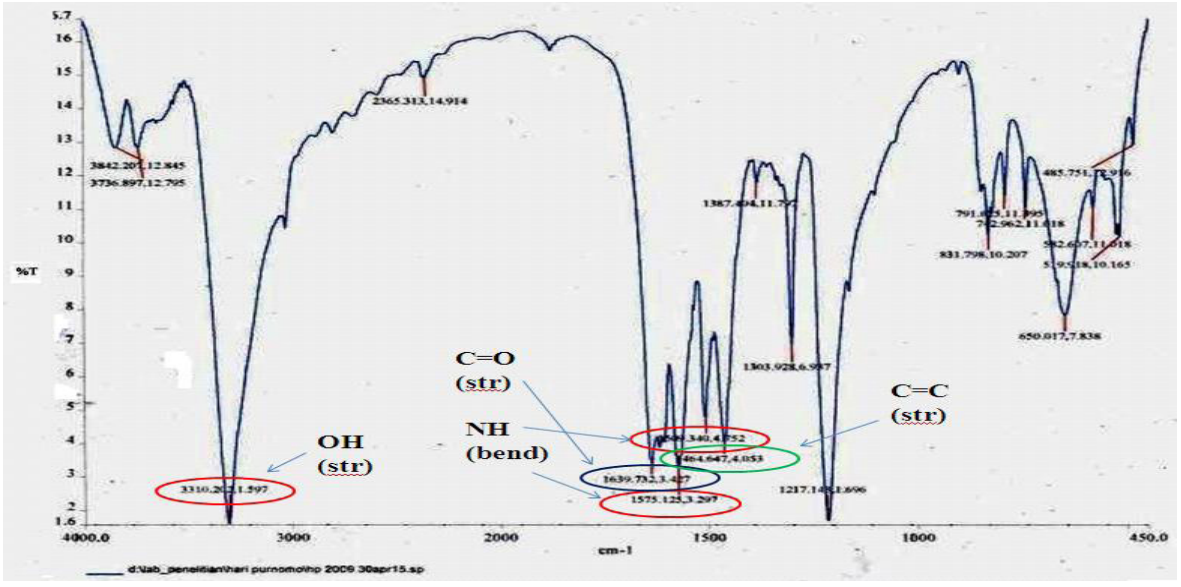

Figure-4: IR Spectrum of HP 2009.

these are equivalent with 2:2:4:4 protons. Therefore, total protons within the molecule of HP2009 is 12 and this is in accord with the predicted molecular structure of HP2009. Chemical shift (δ_H) at 9.0237 ppm is due to resonances of two amide protons. Generally, amide proton apprears at δ_H 8.5-5.0 ppm[11,12]. However, their capability for enolization, they will appears at more down-field position. The singlet peak at δ_H 8.1689 ppm with integration of 2 protons is due to two phenolic-protons. The doublet peaks at δ_H 7.1857 and 6.6746 ppm, each with integration of four protons are undoubtedly due to eight aromatic protons of H2, H2', H3, H3' and H5, H5', H6, H6' respectively.

Result of ^{13}C NMR Spectroscopic Analysis of HP2009. The ^{13}C NMR Spectrum of HP 2009 shown as in Figure-6. Two carbon chemical shifts (δ_C) at 115.1865 and 120.2990 ppm are derived from resonances of *sp2* carbon binding to protons, i.e., C2, C3, C5 and C6 (of the Ring-A), and C2', C3', C5' and C6' (of the Ring-B). Resonances of C5, C6, C5' and C6" appears at δ_C 115.1865, while C2, C3, C2' and C3' appears at δ_C more down-field than the previous cluster of carbons, i.e., at δ_C 120.2990 ppm due to anisotropic effect of the amide group. Resonances at δ_C 131.4589 and 152.3478 ppm are due *sp2* quartenary carbon, i.e., C1, C4 (of Ring A) and C1', C4' (of Ring-B). C1 and C1' appears at δ_C 152.3478 due effect of amide group, while C4 and C4' appears at δ_C 131.4589 ppm.

Result of Mass Spectroscopic Analysis of HP2009. The Mass Spectrum of HP 2009 shown as in Figure-7. Mass spectrum of HP 2009 showed a molecular ion at m/z 244 and a base peak at m/z 109. The molecular ion is in accord with molecular weight of proposed molecule of HP 2009. The base peak is due to the radical-cation of p-aminophenol which appears at m/z 109.

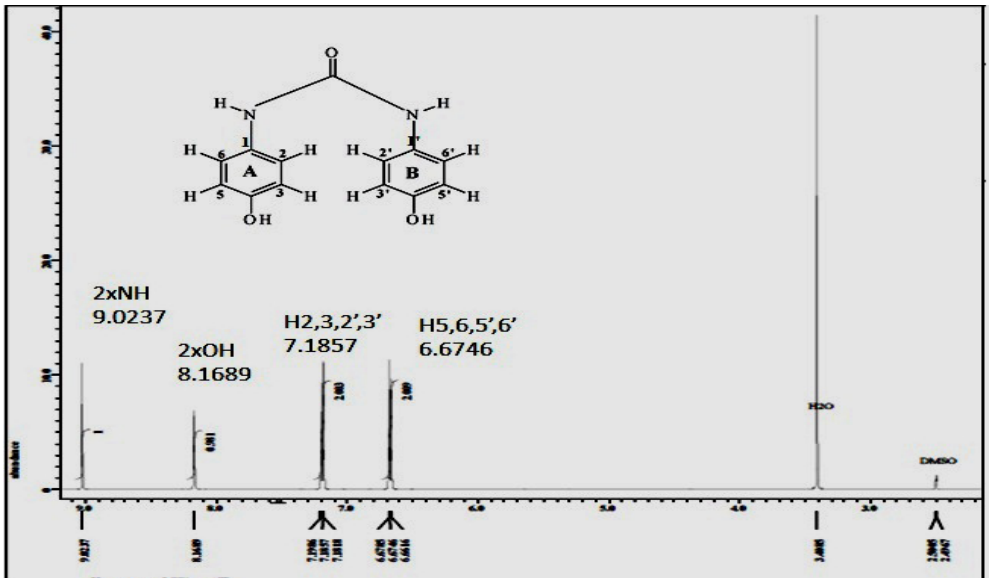

Figure 5. ^{1}H NMR spectrum of HP2009.

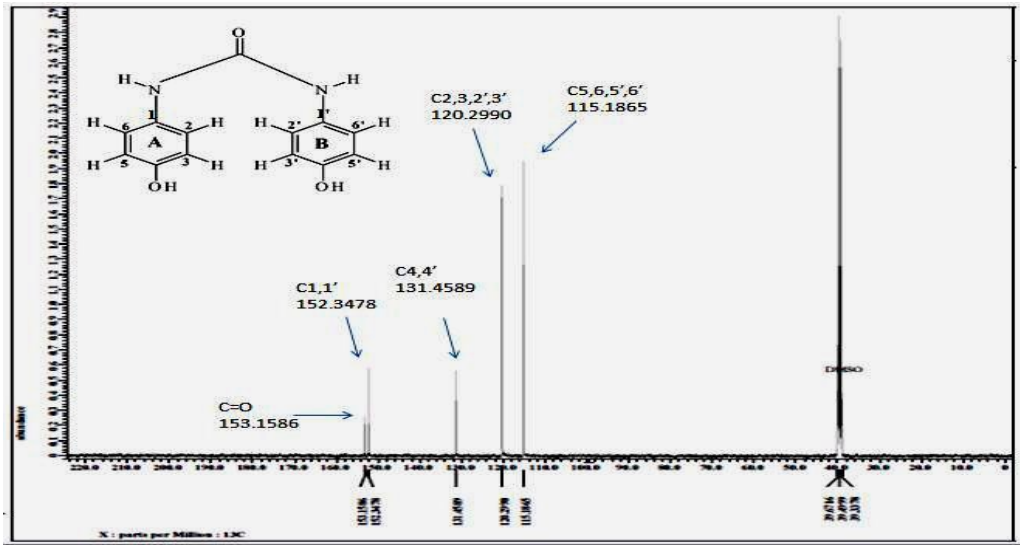

Figure 6: ^{13}C NMR spectrum of HP2009

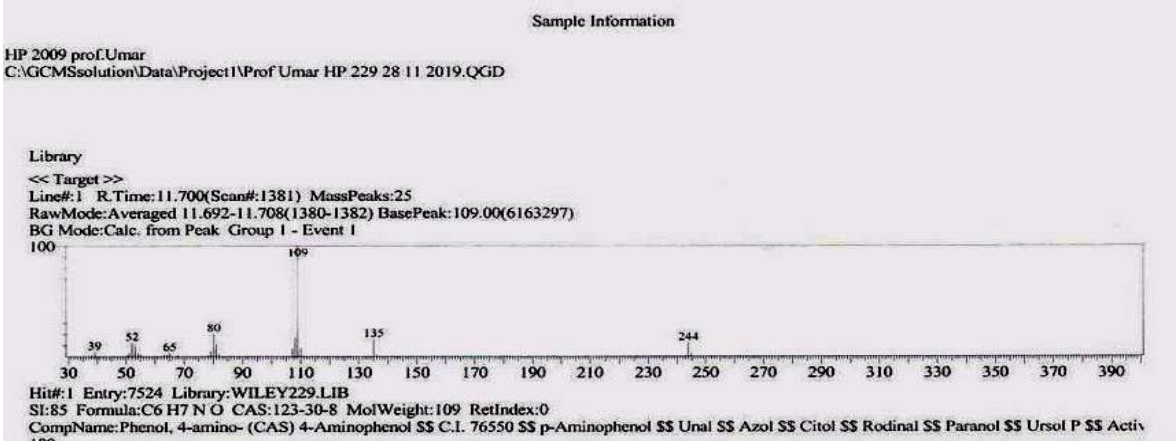

Figure 7. Mass spectrum of HP2009.

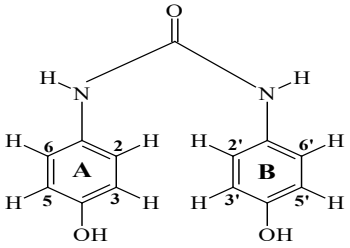

Figure 8. Chemical structure of 1,3 bis(*p*-hydroxyphenyl)urea (HP2009).

CONCLUSION

All spectroscopic data undoubtedly confirmed that the molecule of HP 2009 has chemical stucture as shown in Figure-8.

ACKNOWLEDGMENT

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