

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) ANALYSIS,  
SYNTHESIS AND HEME POLYMERIZATION INHIBITION ACTIVITY (HPIA) ASSAY  
OF XANTHONE DERIVATIVES AS ANTIMALARIA

Dhina Fitriastuti  
12/339308/PPA/03907

ABSTRACT

Research on Quantitative Structure Activity Relationship (QSAR) analysis and synthesis of xanthone derivatives had been conducted to obtain new antimalaria active compounds. The HPIA assay of the synthesized xanthenes was also conducted.

The QSAR analysis was carried out using the semi empirical method of AM1 with the descriptors of atomic net charge, log P, dipole moment, polarizability, mass and volume. Statistical analysis was performed using the multilinear regression analysis. Then, the xanthone was designed using the validated best QSAR equation. 2,3,4-Trihydroxy-5-methylxanthone and 1,3,6-trihydroxy xanthone had the IC<sub>50</sub> prediction of 3.79 and 6.96 µg/mL, respectively, and were decided to be synthesized. Synthesis of xanthone was conducted from the raw material of hydroxybenzoic acid and phenol derivatives using Eaton's reagent. The synthesized xanthone in this research was 1,3,6-trihydroxyxanthone and 2,3,4-trihydroxy-5-methyl xanthone. The initial step of synthesis of 1,3,6-trihydroxyxanthone was carboxylation of resorcinol using KHCO<sub>3</sub> and CO<sub>2</sub> gas. The mixture of resorcinol and KHCO<sub>3</sub> in water was refluxed for 4 h and was passed a rapid stream of CO<sub>2</sub> for 1 h to afford 2,4-dihydroxybenzoic acid as white solid in 53% (m.p. 213.7-217.6 °C). Carboxylation product was then mixed with phloroglucinol and Eaton's reagent. The mixture was heated for 3 h at 80 °C to yield 1,3,6-trihydroxyxanthone in the form of yellowish solid (56%), 322-323 °C (dec.). The synthesis of 2,3,4-trihydroxy-5-methyl xanthone was carried out using gallic acid, *o*-cresol and Eaton's reagent with the same procedure as the first xanthone. This reaction produced 2,3,4-trihydroxy-5-methyl xanthone in 43% yield as dark red viscous liquid.

The QSAR equation describing the relationship between antimalarial activity and parameter of lipophilicity, electronic and steric properties of xanthone was:  $\text{Log}(1/\text{IC}_{50}) = (2.726)qC_1 + (1.783)qC_{10} + (0.2387)\log P + 5.282$  ( $n = 17$ ,  $r^2 = 0.683$ ,  $F_{\text{calc}}/F_{\text{table}} = 4.309$ ,  $\text{PRESS} = 0.652$ ). The results of HPIA assay of xanthone derivatives showed that the compound 1,3,6-trihydroxy xanthone, 2,3,4-trihydroxy-5-methyl xanthone and chloroquine has IC<sub>50</sub> values of 1.985, 0.755 and 1.462 mg/mL or 8.13, 2.92 and 4.57 mM, respectively. 2,3,4-Trihydroxy-5-methyl xanthone displayed better antimalarial activity than chloroquine and 1,3,6-trihydroxy xanthone.

**Keywords:** QSAR, xanthone, synthesis, HPIA assay

## ANALISIS HUBUNGAN KUANTITATIF STRUKTUR AKTIVITAS (HKSA), SINTESIS, DAN UJI PENGHAMBATAN POLIMERISASI HEM TURUNAN XANTON SEBAGAI ANTIMALARIA

Dhina Fitriastuti  
12/339308/PPA/03907

### INTISARI

Telah dilakukan penelitian analisis HKSA dan sintesis dari turunan xanton untuk menemukan senyawa aktif baru antimalaria. Uji HPIA dari xanton hasil sintesis juga telah dilakukan.

Analisis HKSA dilakukan menggunakan metode semi empirik AM1 dengan deskriptor muatan atom, log P, momen dipol, polarisabilitas, massa dan volume. Analisis statistik dilakukan menggunakan analisis regresi multilinear dan xanton di desain menggunakan persamaan HKSA terbaik yang tervalidasi. Senyawa 2,3,4-trihidroksi-5-metil xanton dan 1,3,6-trihidroksi xanton memiliki  $IC_{50}$  prediksi 3,76 dan 6,96  $\mu\text{g/mL}$  dan disintesis dalam penelitian ini. Tahap awal sintesis dari 1,3,6-trihidroksi xanton adalah karboksilasi resorsinol menggunakan  $\text{KHCO}_3$  dan  $\text{CO}_2$  gas menghasilkan asam 2,4-dihidroksi benzoat dengan persen hasil 53% (t.l. 213,7-217,6 °C). Hasil karboksilasi kemudian direaksikan dengan phloroglusinol dan reagen Eaton untuk menghasilkan padatan kuning 1,3,6-trihidroksi xanton dengan persen hasil 56% (dek. 322-323 °C). Sintesis 2,3,4-trihidroksi-5-metil xanton dilakukan menggunakan asam galat, o-kresol dan reagen Eaton dengan persen hasil 43% sebagai cairan kental merah kehitaman.

Persamaan HKSA yang dihasilkan adalah  $\text{Log}(1/IC_{50}) = (2.726)qC_1 + (1.783)qC_{10} + (0.2387)\log P + 5.282$ ; ( $n = 17$ ,  $r^2 = 0.683$ ,  $F_{\text{calc}}/F_{\text{table}} = 4.309$ ,  $\text{PRESS} = 0.652$ ). Hasil dari uji HPIA menunjukkan bahwa senyawa 1,3,6-trihidroksi xanton; 2,3,4-trihidroksi-5-metil xanton dan klorokuin memiliki nilai  $IC_{50}$  1,985; 0,755 dan 1,462  $\text{mg/mL}$  atau 8,13; 2,92 dan 4,57 mM. Senyawa 2,3,4-trihidroksi-5-metil xanton menunjukkan aktivitas antimalaria yang lebih baik dibandingkan klorokuin dan 1,3,6-trihidroksi xanton.

**Kata kunci:** HKSA, xanton, sintesis, uji HPIA