PENAMBATAN MOLEKULER, SINTESIS DAN AKTIVITAS ANTIMALARIA ANALOG KURKUMIN MONOKETON BERBAHAN DASAR 2-KLOROBENZALDEHIDA

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20/466446/PPA/06012

INTISARI

Penelitian ini bertujuan untuk mencari senyawa analog kurkumin berbahan dasar 2-klorobenzaldehida yang berpotensi sebagai kandidat obat antimalaria. Penelitian dilakukan dengan empat tahapan, yaitu 1) penambatan molekuler enam senyawa analog kurkumin yaitu senyawa (1*E*,4*E*)-1,5-*bis*(2-klorofenil)-1,4-pentadiena-3-on (A), (2*E*,5*E*)-2,5-*bis*(2-klorobenzilidin)siklopentanon (B), (2*E*,6*E*)2,6-*bis*(2-klorobenzilidin)sikloheksanon (C), (3*E*,5*E*)-3,5-*bis*-(2-klorobenzilidin)-4-piperidon (D), (3*E*,5*E*)-3,5-*bis*-(2-klorobenzilidin)-1-metil-4-piperidon (E) dan (3*E*,5*E*)-3,5-*bis*(2-klorobenzilidin)-1-benzil-4-piperidon (F) dengan tiga reseptor *Plasmodium falciparum* (P*f*ENR, P*f*LDH dan P*f*ATP6), 2) sintesis tiga senyawa analog kurkumin yang memiliki afinitas ikatan terendah dan berinteraksi pada sisi aktif ketiga reseptor target, 3) uji aktivitas antimalaria senyawa analog kurkumin secara *in vitro* terhadap *P. falciparum* FCR3 dan 3D7 untuk memperoleh nilai indeks resistensi dan 4) analisis profil farmakokinetik senyawa analog kurkumin melalui pendekatan *in silico* berbasis web.

Berdasarkan hasil analisis penambatan molekuler diketahui bahwa senyawa analog kurkumin F, C dan D memiliki prediksi aktivitas antimalaria terbaik terhadap P*f*ENR, P*f*LDH dan P*f*ATP6. Sintesis senyawa analog kurkumin F, C dan D dilakukan dengan mereaksikan 2-klorobenzaldehida dengan 1-benzil-4-piperidon, sikloheksanon dan 4-piperidon melalui reaksi kondensasi Claisen-Schmidt. Produk yang dihasilkan berupa padatan berwarna kuning dengan persen hasil berturut-turut 71; 76; dan 44%. Elusidasi struktur produk hasil sintesis dilakukan dengan analisis FTIR, MS/MS, ^{1}H-NMR dan ^{13}C-NMR. Uji aktivitas antimalaria secara *in vitro* terhadap *P. falciparum* FCR3 menunjukkan bahwa analog F memiliki aktivitas antimalaria yang sangat aktif dengan nilai IC_{50} 0,76 µM sedangkan analog C dan D memiliki aktivitas antimalaria yang dikegorikan aktif dengan nilai IC_{50} 1,07 dan 2,58 µM. Uji aktivitas antimalaria secara *in vitro* terhadap *P. falciparum* 3D7 menunjukkan bahwa analog kurkumin F, C dan D memiliki aktivitas antimalaria yang dikategorikan aktif dengan nilai IC_{50} berturut-turut 1,09; 2,41; dan 3,06 µM. Perhitungan nilai indeks resistensi menunjukkan bahwa senyawa analog kurkumin F, C dan D memiliki tingkat resistensi yang rendah sehingga berpotensi untuk dijadikan kandidat obat antimalaria. Selain itu, semua analog kurkumin hasil sintesis juga diprediksi memiliki profil farmakokinetik yang lebih baik dibandingkan kurkumin.

Kata kunci: analog kurkumin, 2-klorobenzaldehida, penambatan molekuler, uji antimalaria *in vitro*

MOLECULAR DOCKING, SYNTHESIS AND ANTIMALARIAL ACTIVITY OF MONOKETONE CURCUMIN ANALOGS FROM 2-CHLOROBENZALDEHYDE

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ABSTRACT

The objectives of this reseach was to investigate the potentials of curcumin analogs, from 2-chlorobenzaldehydes, as antimalaria drugs. This research was carried out through four main steps i.e. 1) molecular docking of six curcumin analogs, i.e., (1*E*,4*E*)-1,5-*bis*(2-chlorophenyl)-1,4-pentadiene-3-one (A), (2*E*,5*E*)-2,5-*bis*(2-chlorobenzylidene)cyclopentanone (B), (2*E*,6*E*)-2,6-*bis*(2-chlorobenzylidene)cyclohexanone (C), (3*E*,5*E*)-3,5-*bis*-(2-chlorobenzylidene)-4-piperidone (D), (3*E*,5*E*)-3,5-*bis*-(2-chlorobenzylidene)-1-methyl-4-piperidone (E), and (3*E*,5*E*)-3,5-*bis*(2-chlorobenzylidene)-1-benzyl-4-piperidone (F) with three *Plasmodium falciparum* receptors (P*f*ENR, P*f*LDH and P*f*ATP6), 2) synthesis of three curcumin analog compounds that have the lowest binding affinity and interact on the active site of the three target receptors, 3) the *in vitro* antimalarial activity assay of the synthesized curcumin analog compounds against *P. falciparum* parasites strains FCR3 and 3D7 to acquire the resistance index value, and 4) the *in silico* analysis of the pharmacokinetic profile of the synthesized curcumin analog compounds used web-based tools.

Based on the results of molecular docking, it has been revealed that curcumin analog compound F, C and D have the best predicted antimalarial activity against P*f*ENR, P*f*LDH and P*f*ATP6. The curcumin analogs of F, C and D were obtained by reacting 2-chlorobenzaldehyde with 1-benzyl-4-piperidone, cyclohexanone and 4-piperidone via the Claisen-Schmidt condensation reaction and were produced in 71; 76; and 44% yields. The structure elucidation of curcumin analogs were carried out using FTIR, MS/MS, ^{1}H-NMR and ^{13}C-NMR spectrometers. The *in vitro* antimalarial activity test to *P. falciparum* strain FCR3 showed that analog F had very active antimalarial activity with an IC_{50} value of 0.76 µM, while analog C and D had antimalarial activity which were categorized as active with IC_{50} values of 1.07 and 2.58 µM. The *in vitro* antimalarial activity assay toward *P. falciparum* strain 3D7 showed that curcumin analog F, C and D had antimalarial activity categorized as active with an IC_{50} value of 1.09; 2.41; and 3.06 µM. The calculation of the value of the resistance index shows that the analog of curcumin F, C and D have a low level of resistance so that they can be considered as the candidates for antimalarial drug. Furthermore, all synthetic curcumin analogs were also predicted to have better pharmacokinetic profiles than curcumin.

Keywords: curcumin analog, molecular docking, 2-chlorobenzaldehyde, *in vitro* antimalarial assay