SENYAWA ANALOG KURKUMIN MONOKETON BERBAHAN DASAR 4-KLOROBENZALDEHIDA SEBAGAI KANDIDAT ANTIMALARIA: PENAMBATAN MOLEKUL, SINTESIS DAN UJI AKTIVITAS ANTIMALARIA SECARA *IN VITRO*

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20/466458/PPA/06024

INTISARI

Studi penambatan molekul telah dilakukan terhadap senyawa analog kurkumin monoketon (1E,4E)-1,5-bis(4-klorofenil)-1,4-pentadien-3-on (**AK A**), (2E,5E)-2,5-bis(4-klorobenziliden)siklopentanon (**AK B**), (2E,6E)-2,6-bis(4-klorobenziliden)sikloheksanon (**AK C**), (3E,5E)-3,5-bis(4-klorobenziliden)-4-piperidon (**AK D**), (3E,5E)-3,5-bis(4-klorobenziliden)-1-metil-piperidin-4-on (**AK E**), dan (3E,5E)-3,5-bis(4-klorobenziliden)-1-benzil-piperidin-4-on (**AK F**) dengan protein *Pf*LDH, *Pf*ENR dan *Pf*ATP6. Tiga senyawa analog kurkumin terbaik berdasarkan interaksi dengan residu asam amino spesifik dan nilai afinitas ikatan terendah hasil penambatan molekul disintesis melalui reaksi kondensasi Claisen-Schmidt dari 4-klorobenzaldehida dengan variasi keton. Hasil reaksi diidentifikasi menggunakan TLC *scanner*, FTIR, MS/MS, ^{1}H-NMR dan ^{13}C-NMR, diuji aktivitasnya sebagai kandidat antimalaria secara *in vitro* terhadap *P. falciparum strain* FCR3 dan 3D7, serta dievaluasi terhadap profil ADMET.

Hasil penelitian diperoleh tiga senyawa analog kurkumin terbaik yaitu senyawa **AK C**, **E**, dan **F** yang berinteraksi dengan residu asam amino spesifik Ile54, Ala98, Ile119, Phe52, Val26 pada sisi aktif protein *Pf*LDH. Senyawa **AK C**, **E**, dan **F** juga berinteraksi dengan residu asam amino spesifik Tyr267, Pro314, Phe368, Ile369, dan Lys285 pada sisi aktif protein *Pf*ENR, serta dengan residu asam amino spesifik Leu268 pada sisi aktif protein *Pf*ATP6. Ketiga senyawa analog kurkumin memiliki interaksi dengan residu asam amino spesifik dan nilai afinitas ikatan terendah terhadap protein *Pf*LDH, *Pf*ENR dan *Pf*ATP6 dibandingkan dengan kurkumin. Sintesis senyawa **AK C**, **E**, dan **F** diperoleh rendemen masing-masing 56,51%; 56,52%; dan 30,39%. Uji aktivitas antimalaria secara *in vitro* menunjukkan senyawa **AK C**, **E**, dan **F** memiliki aktivitas antimalaria serta nilai indeks resistensi yang lebih baik dibandingkan kurkumin. Senyawa **AK C**, **E**, dan **F** memiliki nilai IC_{50} berturut-turut 0,173; 0,447; dan 0,018 μM terhadap *P. falciparum strain* FCR3, serta memiliki nilai IC_{50} berturut-turut 0,924; 2,268; dan 0,336 μM terhadap *P. falciparum strain* 3D7. Senyawa **AK C**, **E**, dan **F** memiliki nilai indeks resistensi yang lebih rendah dan memiliki profil ADMET yang lebih baik dari kurkumin sehingga berpotensi dikembangkan menjadi kandidat obat antimalaria.

Kata kunci: 4-klorobenzaldehida, analog kurkumin, penambatan molekul, aktivitas antimalaria.

MONOKETONE CURCUMIN ANALOGUES FROM 4-CHLOROBENZALDEHYDE AS ANTIMALARIAL CANDIDATE: MOLECULAR DOCKING, SYNTHESIS, AND IN VITRO ANTIMALARIAL ACTIVITY

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ABSTRACT

Molecular docking studies have been carried out by the monoketone curcumin analogues compound of (1E,4E)-1,5-bis(4-chlorophenyl)-1,4-pentadiene-3-one (**AK A**), (2E,5E)-2,5-bis(4-chlorobenzyliden)cyclopentanone (**AK B**), (2E-6E)-2,6-bis(4-chlorobenzyliden)cyclohexanone (**AK C**), (3E,5E)-3.5-bis(4-chlorobenzyliden)-4-piperidone (**AK D**), (3E,5E)-3,5-bis(4-chlorobenzyliden)-1-methyl-piperidine-4-one (**AK E**), and (3E,5E)-3,5-bis(4-chlorobenzyliden)-1-benzyl-piperidine-4-one (**AK F**) with *Pf*LDH, *Pf*ENR and *Pf*ATP6 proteins. The three best curcumin analog compounds are based on interactions with specific amino acid residues and the lowest molecular affinity value, synthesized through the condensation reaction of claisen-schmidt from 4-chlorobenzaldehyde with ketone variations. The reaction results were identified using TLC scanner, FTIR, MS/MS, ^{1}H-NMR, and ^{13}C-NMR, tested for their *in vitro* activity as antimalarial candidates against *P. falciparum* strains FCR3 and 3D7, and evaluated their ADMET profile.

The results showed that the three best curcumin analogues were compounds **AK C**, **E**, and **F** which interacted with specific amino acid residues Ile54, Ala98, Ile119, Phe52, Val26 on the active site of *Pf*LDH protein. Compounds **AK C**, **E**, and **F** also interacted with specific amino acid residues Tyr267, Pro314, Phe368, Ile369, and Lys285 on the active site of *Pf*ENR protein, as well as with specific amino acid residues of Leu268 on the active site of *Pf*ATP6 protein. The three curcumin analogue compounds have interactions with specific amino acid residues and the lowest binding affinity for *Pf*LDH, *Pf*ENR and *Pf*ATP6 proteins compared to curcumin. Synthesis of **AK C**, **E**, and **F** was obtained in yields of 56.51%; 56.62%; and 30.39%, respectively. In vitro antimalarial activity test showed that **AK C**, **E**, and **F** had better antimalarial activity than curcumin. The IC_{50} of **AK C**, **E**, and **F** was 0.173; 0.447; and 0.018 µM, respectively against *P. falciparum* strain FCR3, and 0.924, 2.268, and 0.336 µM, respectively against *P. falciparum* strain 3D7. **AK C**, **E**, and **F** compounds have lower resistance index and have a good ADMET profile than curcumin so that they have the potential to be developed as antimalarial drug candidates.

Keywords: 4-chlorobenzaldehyde, curcumin analogues, molecular docking, antimalarial activity.