Sintesis kalkon dari benzaldehida dan turunan kloroasetofenon menggunakan metode microwave-asissted
organic syinthesis serta uji aktivitas antiplasmodium falciparum secara in vitro dan in silico
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INTISARI

SINTESIS KALKON DARI BENZALDEHIDA DAN TURUNAN KLOROASETOFENON MENGGUNAKAN METODE *MICROWAVE-ASSISTED ORGANIC SYNTHESIS* SERTA UJI AKTIVITAS ANTIPLASMODIUM *FALCIPARUM* SECARA *IN VITRO* DAN *IN SILICO*

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Resistensi plasmodium terhadap obat malaria secara signifikan berkontribusi terhadap penurunan angka kesembuhan penderita malaria. Salah satu senyawa yang memiliki bioaktivitas sebagai antiplasmodium yakni kalkon dapat disintesis menggunakan metode *Microwave-Assited Organic Synthesis* (MAOS**)** yang meningkatkan rendemen serta mengurangi waktu reaksi dibandingkan dengan metode konvensional. Sintesis 2-klorokalkon (senyawa **A**), 3-klorokalkon (senyawa **B**) dan 4-klorokalkon (senyawa **C**) melalui reaksi kondensasi aldol *Claisen-Schmidt* menggunakan metode MAOS**,** uji aktivitas antiplasmodium serta penambatan molekul telah dilakukan**.** Kalkon **A**, **B**, dan **C** disintesis dari benzaldehida dan turunan kloroasetofenon (2-kloroasetofenon, 3-kloroasetofenon, dan 4-kloroasetofenon) dengan katalis basa NaOH 40% (b/v). Optimasi waktu, daya dan suhu dilakukan terhadap reaksi sintesis menggunakan oven *microwave*. Hasil reaksi diidentifikasi menggunakan GC-MS, FTIR, ^{1}H-NMR dan ^{13}C-NMR. Uji aktivitas antiplasmodium dilakukan secara *in vitro* terhadap *P. falciparum strain* FCR3 dan 3D7. Penambatan molekul dilakukan secara *in silico* menggunakan perangkat lunak Autodock Vina terhadap reseptor P*f*LDH (PDB ID:1CET) dan P*f*ENR (PDB ID:1NHG) serta prediksi profil farmakokinetik melalui analisis ADMET berbasis web.

Hasil penelitian menunjukkan bahwa kalkon **A**, **B**, dan **C** telah berhasil disintesis menggunakan metode MAOS pada kondisi optimum waktu 10 menit, daya 640 Watt dan suhu 70 ^{o}C, dengan rendemen berturut-turut 98,63%; 98,63%; dan 95,89%. Hasil aktivitas antiplasmodium secara *in vitro* menunjukkan bahwa kalkon **A**, **B**, dan **C** memiliki aktivitas antiplasmodium serta nilai indeks resistensi yang baik. Kalkon **A**, **B**, dan **C** memiliki nilai IC_{50} berturut-turut 4,99; 2,71; dan 4,74 µM terhadap *P. falciparum* FCR3, serta memiliki nilai IC_{50} berturut-turut 2,55; 2,39; dan 2,48 µM terhadap *P. falciparum* 3D7. Penambatan molekul kalkon **A**, **B**, dan **C** terhadap protein P*f*LDH dan P*f*ENR menunjukkan bahwa kalkon **A**, **B**, dan **C** berinteraksi dengan residu asam amino spesifik Phe52, Val26, Ile54, Ile119, dan Ala98 pada sisi aktif protein P*f*LDH, residu asam amino Tyr267, Tyr277, Gly313, Ile323, Phe368, Ile369, Ala372, dan Lys285 pada sisi aktif protein P*f*ENR serta memiliki nilai afinitas ikatan yang rendah (negatif). Profil farmakokinetik menunjukan senyawa hasil sintesis berpotensi dikembangkan menjadi kandidat obat malaria.

Kata Kunci: 2-klorokalkon, 3-klorokalkon dan 4-klorokalkon, MAOS, aktivitas antiplasmodium, penambatan molekul

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SYNTHESIS OF CHALCONE FROM BENZALDEHYDE AND CHLOROACETOPHENONE DERIVATIVES USING THE MICROWAVE-ASSISTED ORGANIC SYNTHESIS METHOD AS WELL IN VITRO AND IN SILICO ANTIPLASMODIUM ACTIVITY TEST OF FALCIPARUM

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ABSTRACT

Plasmodium resistance to malaria drugs significantly contributes to the reduction in the cure rate for malaria sufferers. One of the compounds that has bioactivity as antiplasmodium, namely chalcone, can be synthesized using the *Microwave-Assisted Organic Synthesis* (MAOS) method which increases the yield and reduces reaction time compared to conventional methods. Synthesis of *E*-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (chalcone **A**), *E*-1-(3-chlorophenyl)-3-phenylprop-2-en-1-one (chalcone **B**), and *E*-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (chalcone **C**) by *Claisen-Schmidt* aldol condensation reaction using the MAOS method, testing antiplasmodium activity and molecular docking were carried out. Chalcones **A**, **B**, and **C** were synthesized from benzaldehyde and chloroacetophenone derivatives (2-*chloroacetophenone*, 3-*chloroacetophenone*, and 4-*chloroacetophenone*) using 40% (w/v) NaOH as base catalyst. Optimization of time, power and temperature was carried out for the synthesis reaction using a microwave oven. The reaction products were identified using GC-MS, FTIR, ^{1}H-NMR and ^{13}C-NMR. Antiplasmodium activity test was carried out *in vitro* against P. *falciparum* strains FCR3 and 3D7. Molecular docking was performed *in silico* using Autodock Vina software against P*f*LDH (PDB ID:1CET) and P*f*ENR (PDB ID:1NHG) receptors and prediction of pharmacokinetic profiles through web based ADMET analysis.

The results showed that chalcones **A**, **B**, and **C** had been successfully synthesized using the MAOS method at an optimum condition of 10 minutes, 640 Watts of power and 70^{o}C of temperature, with successive yields of 98.63%; 98.63%; and 95.89%. In vitro antiplamodium activity test showed that chalcones **A**, **B**, and **C** had good antimalarial activity and resistance index values. Chalcones **A**, **B**, and **C** have IC_{50} values of 4.99; 2.71; and 4.74 µM respectively against *P. falciparum* FCR3 and has an IC_{50} value of 2.55; 2.39; and 2.48 µM respectively against *P. falciparum* 3D7. Molecular docking of chalcones **A**, **B**, and **C** to the P*f*LDH and P*f*ENR proteins shows that the chalcones **A**, **B**, and **C** which interacted with specific amino acid residues Phe52, Val26, Ile54, Ile119, and Ala98 on the active site of P*f*LDH protein, the amino acid residues Tyr267, Tyr277, Gly313, Ile323, Phe368, Ile369, Ala372, and Lys285 on the active site of P*f*ENR protein and have a low (negative) bond affinity value. The pharmacokinetic profile shows that the synthesized compounds have the potential to be developed as malaria drug candidates.

Keywords: 2-chlorochalcone, 3-chlorochalcone and 4-chlorochalcone, MAOS, antiplasmodium activity, molecular docking