PENGEMBANGAN EPOKSIDA KALKON SEBAGAI ANTIMALARIA: SINTESIS, AKTIVITAS ANTIPLASMODIUM, DAN PENAMBATAN MOLEKUL

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INTISARI

Dalam pengembangan obat antimalaria, turunan kalkon telah banyak dilaporkan sebagai kandidat antiplasmodium, sedangkan senyawa epoksida belum banyak dilaporkan. Penelitian ini bertujuan untuk mensintesis epoksida kalkon dan mempelajari potensinya sebagai antiplasmodium yang didukung dengan kajian penambatan molekul. Lima epoksida kalkon yang berhasil disintesis yakni (3-(4-klorofenil)oksiran-2-il)(fenil)metanon (E6), (3-(4-nitrofenil)oksiran-2-il)(fenil) metanon (E9), (4-metoksifenil)(3-fenilloxiran-2-il)metanon (E11), (3-(4-klorofenil)oksiran-2-il)(4-metoksifenil)metanon (E16), dan (4-metoksifenil)(3-(4-nitrofenil)oksiran-2-il)metanon (E19) dengan persen hasil berturut-turut 52,36%; 62,50%; 61,37%; 55,98%; dan 41,49%. Epoksida kalkon disintesis melalui reaksi epoksidasi terhadap senyawa kalkon menggunakan hidrogen peroksida (H_2O_2) 30% dalam penangas es dengan pengadukan selama 5 jam dan hasilnya dianalisis menggunakan FTIR, GC-MS, ^{1}H- dan ^{13}C-NMR

Epoksida kalkon diuji aktivitas antiplasmodiumnya terhadap *Plasmodium falciparum* strain 3D7 dan FCR-3. Nilai IC_{50} kelima epoksida kalkon terhadap strain 3D7 berturut-turut adalah 98,133; 48,574; 209,702; 58,868; 55,249 μM; sedangkan dengan strain FCR-3 berturut-turut 11,198; 3,784; 39,396; 5,451; 3,869 μM, dengan indeks resistensi 0,114; 0,078; 0,188; 0,093; 0,070. Hasil penambatan molekul kelima epoksida kalkon pada protein PDB ID 1J3I (*sensitive-protein*) dan 4DP3 (*resistance-protein*) menunjukkan bahwa semua epoksida kalkon mempunyai energi ikat yang lebih rendah dibandingkan *native ligand*nya, sedangkan senyawa E9 menunjukkan interaksi ikatan hidrogen paling kuat dengan residu asam amino pada situs aktif protein. Studi penambatan molekul juga dilakukan terhadap turunan neolignan yang secara teoritis merupakan hasil hidrolisis epoksida kalkon. Senyawa turunan neolignan paling baik sebagai antiplasmodium adalah senyawa N9 yang merupakan hasil hidrolisis dari senyawa E9.

Urutan nilai IC_{50} terhadap *P. falciparum* strain 3D7 maupun FCR-3 dari aktivitas plasmodium paling kuat adalah E9, E19, E16, E6, E11, sedangkan urutan indeks resistensi dari yang terbaik adalah E19, E9, E16, E6, E11. Data uji *in vitro* dan penambatan molekul menunjukkan bahwa senyawa E9 memberikan aktivitas antimalaria yang potensial terhadap *Plasmodium falciparum* 3D7 dan FCR-3 dengan nilai indeks resistensi yang cukup rendah.

Kata kunci: sintesis, epoksidasi, antiplasmodium, indeks resistensi, penambatan molekul

DEVELOPMENT OF CHALCONE EPOXIDES AS ANTIMALARIA: SYNTHESIS, ANTIPLASMODIAL ACTIVITY, AND MOLECULAR DOCKING

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ABSTRACT

In the development of antimalarial drugs, chalcone derivatives have been reported previously as antiplasmodial candidates, whereas epoxide compounds have not been extensively reported. This study aims to synthesize chalcone epoxides and investigate their potential as antiplasmodial agents, supported by molecular docking studies. Five chalcone epoxides were successfully synthesized, namely (3-(4-chlorophenyl)oxiran-2-yl)(phenyl)methanone (E6), (3-(4-nitrophenyl)oxiran-2-yl)(phenyl)methanone (E9), (4-methoxyphenyl)(3-phenyloxiran-2-yl)methanone (E11), (3-(4-chlorophenyl)oxiran-2-yl)(4-methoxyphenyl)methanone (E16), and (4-methoxyphenyl)(3-(4-nitrophenyl) oxiran-2-yl)methanone (E19), with yields of 52.36, 62.50, 61.37, 55.98, and 41.49 respectively. The chalcone epoxides were synthesized through an epoxidation reaction of chalcone compounds using 30% hydrogen peroxide (H_2O_2) in an ice bath with stirring for 5 hours, and the products were characterized using by FTIR, GC-MS, ^{1}H- and ^{13}C-NMR.

The antiplasmodial activity of the chalcone epoxides were evaluated against *Plasmodium falciparum* strains 3D7 and FCR-3. The IC_{50} values of the five chalcone epoxides against the 3D7 strain were 98.133, 48.574, 209.702, 58.868, and 55.249 μM, respectively, while against the FCR-3 strain they were 11.198, 3.784, 39.396, 5.451, and 3.869 μM, respectively, with resistance indices of 0.114, 0.078, 0.188, 0.093, and 0.070. Molecular docking studies using PDB ID: 1J3I (sensitive-protein) and PDB ID: 4DP3 (resistance-protein) revealed that all chalcone epoxides exhibited lower binding energies compared to their native ligands, with compound E9 showing the most favorable hydrogen bonding interactions with amino acid residues. Molecular docking studies were also conducted on neolignan derivatives, which theoretically are the hydrolysis products of chalcone epoxides. The best neolignan derivative as an antiplasmodial agent was compound N9, which is the hydrolysis product of compound E9.

The order of IC_{50} values against both P. falciparum strains 3D7 and FCR-3, from the strongest plasmodial activity, were E9, E19, E16, E6, E11, while the order of resistance indices from the best were E19, E9, E16, E6, E11. In vitro test data and molecular docking studies indicate that compound E9 exhibits potential antimalarial activity against *Plasmodium falciparum* 3D7 and FCR-3 with a relatively low resistance index.

Keywords: synthesis, epoxidation, antiplasmodium, resistance index, molecular docking