

**SINTESIS KALIKS[4]RESORSINARENA, KALIKS[4]PIROGALOL-
ARENA, DAN TURUNANNYA TERMODIFIKASI ALIL SEBAGAI
ANTIANKER DAN ANTIMALARIA, SERTA STUDI *IN SILICO*
PENAMBATAN DAN SIMULASI DINAMIKA MOLEKUL**

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INTISARI

Penelitian ini bertujuan untuk (1) mensintesis turunan aliloksibenzaldehida (**2a–2b**), (2) mensintesis seri kaliks[4]resorsinarena dan kaliks[4]pirogalolarena (**5a–5f**), dan turunannya termodifikasi alil (**4a–4f**), (3) mengevaluasi aktivitas antikanker payudara dan antimalaria terhadap *Plasmodium falciparum* FCR3 (resisten klorokuin) dan 3D7 (sensitif klorokuin), dan (4) mempelajari interaksi senyawa aktif melalui penambatan molekul dan simulasi dinamika molekul. Sintesis dimulai dari *O*-alkilasi 4-hidroksibenzaldehida (**1a**) dan vanilin (**1b**) menggunakan alil bromida dan K_2CO_3 untuk menghasilkan aliloksibenzaldehida (**2a–2b**) dengan hasil 99 dan 91%. Senyawa **2a–2b** dikondensasi dengan resorsinol (**3a**), pirogalol (**3b**), atau 2-metilresorsinol (**3c**) menghasilkan kaliks[4]resorsinarena dan kaliks[4]pirogalolarena termodifikasi alil (**4a–4f**) dengan hasil 56–87%. Senyawa **1a–1b** dikondensasi dengan resorsinol (**3a**), pirogalol (**3b**), atau 2-metilresorsinol (**3c**) menghasilkan kaliks[4]resorsinarena dan kaliks[4]pirogalolarena (**5a–5f**) dengan hasil 31–84%. Senyawa dikarakterisasi menggunakan spektrometer FTIR, GC–MS, LC–MS, ^1H –, dan ^{13}C NMR.

Uji bioaktivitas menunjukkan bahwa **4a** memiliki aktivitas penghambatan terhadap *cell line* payudara MCF-7 (IC_{50} 8,27 μM), melampaui kontrol positif cisplatin (22,39 μM) dan mendekati doksorubisin (1,67 μM), serta memicu kenaikan apoptosis sel seiring dengan kenaikan konsentrasi. Uji penambatan dan simulasi dinamika molekul mengonfirmasi interaksi spesifik **4a** dengan residu asam amino aktif Arg817 dan Asp831 pada reseptor faktor pertumbuhan epidermal (EGFR) melalui ikatan hidrogen pada simulasi dinamika molekul selama 100 ns. Sementara itu pada uji aktivitas antimalaria, senyawa **5d** menunjukkan potensi terbaik terhadap *Plasmodium falciparum* FCR3 dengan IC_{50} 1,48 μM , lebih aktif dibanding kontrol klorokuin (7,11 μM) dan turunan alilnya **4d** (6,38 μM). Senyawa **5d** membentuk ikatan kuat dengan residu asam amino Met30, Lys102, dan Thr101 pada dehidrogenase laktat *Plasmodium falciparum* (PfLDH) di simulasi 100 ns. Sementara itu, **4d** berinteraksi melalui ikatan hidrogen dengan residu asam amino Tyr85, Lys118, dan Ile119 pada PfLDH pada simulasi dinamika molekul selama 100 ns.

Kata kunci: Antikanker, antimalaria, kaliks[4]resorsinarena, kaliks[4]pirogalolarena, modifikasi alil, penambatan molekul

SYNTHESIS OF CALIX[4]RESORCINARENE, CALIX[4]PYROGALLOL- ARENE, AND THEIR ALLYL-MODIFIED DERIVATIVES AS ANTICANCER AND ANTIMALARIAL AGENTS, AND IN SILICO DOCKING AND MOLECULAR DYNAMICS SIMULATION

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ABSTRACT

This study aims to (1) synthesize allyloxybenzaldehyde derivatives (**2a–2b**), (2) synthesize a series of calix[4]resorcinarene and calix[4]pyrogallolarene derivatives (**5a–5f**), and their allyl-modified analogues (**4a–4f**), (3) evaluate their breast anticancer and antimalarial activities against *Plasmodium falciparum* FCR3 (chloroquine-resistant) and 3D7 (chloroquine-sensitive) strains, and (4) investigate the molecular interaction of active compounds through molecular docking and molecular dynamics simulation. The synthesis began with *O*-alkylation of 4-hydroxybenzaldehydes (**1a**) and vanillin (**1b**) using allyl bromide and K₂CO₃ to produce allyloxybenzaldehydes (**2a–2b**) with yields of 99 and 91%, respectively. Compounds **2a–2b** were subsequently condensed with resorcinol (**3a**), pyrogallol (**3b**), or 2-methylresorcinol (**3c**) to afford allyl-modified calix[4]resorcinarene and calix[4]pyrogallolarene derivatives (**4a–4f**) with yields ranging from 56–87%. Meanwhile, compounds **1a–1b** were condensed with resorcinol (**3a**), pyrogallol (**3b**), or 2-methylresorcinol (**3c**) to produce calix[4]resorcinarene and calix[4]pyrogallolarene (**5a–5f**) with 31–84% yields. Structural characterization was carried out using FTIR, GC–MS, LC–MS, ¹H–, and ¹³C NMR spectrometers.

Bioactivity assays revealed that compounds **4a** exhibited cytotoxic activity against MCF-7 breast cancer cells (IC₅₀ 8.27 μM), surpassing cisplatin (22.39 μM) and approaching doxorubicin (1.67 μM), while inducing apoptosis in a concentration-dependent manner. Molecular docking and molecular dynamics studies confirmed specific binding of **4a** to key amino acid residues Arg817 and Asp831 of epidermal growth factor receptor (EGFR) via hydrogen bonding over 100 ns molecular dynamic simulation. In the evaluation of antimalarial activity, compound **5d** demonstrated the strongest inhibition effect against *Plasmodium falciparum* FCR3 (IC₅₀ 1.48 μM), outperforming chloroquine (7.11 μM) and its allyl-modified analogue **4d** (6.38 μM). Furthermore, **5d** formed stable hydrogen-bond interactions with Met30, Lys102, and Thr101 amino acid residues of *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) in 100 ns molecular dynamic simulation, whereas **4d** interacted with Tyr85, Lys118, and Ile119 amino acid residues over the same duration.

Keywords: Allyl modification, anticancer, antimalarial, calix[4]resorcinarene, calix[4]pyrogallolarene, molecular docking