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**Studi Penambatan Molekuler, Sintesis, dan Uji Antiplasmodial In Vitro Turunan Garam (1)-N-Benzil- dan (1)-N-Heterosiklik-1,10-Fenantrolinium Bromida**
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# STUDI PENAMBATAN MOLEKULER, SINTESIS, DAN UJI ANTIPLASMODIAL IN VITRO TURUNAN GARAM (1)-N-BENZIL- DAN (1)-N-HETEROSIKLIK-1,10-FENANTROLINIUM BROMIDA

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## INTISARI

Penelitian ini bertujuan untuk mengembangkan turunan garam (1)-*N*-benzil- dan (1)-*N*-heterosiklik-1,10-fenantrolinium bromida yang berpotensi sebagai kandidat antiplasmodial. Penelitian dilakukan dengan empat tahapan, yaitu 1) penambatan molekuler tujuh turunan garam (1)-*N*-benzil- dan (1)-*N*-heterosiklik-1,10-fenantrolinium bromida dengan protein P*f*ENR, 2) sintesis turunan garam yang menghasilkan energi ikatan terendah dan interaksi spesifik dengan residu asam amino penting dari P*f*ENR, 3) uji aktivitas antiplasmodial terhadap *P. falciparum strain* FCR3 dan 3D7 serta sitotoksisitas terhadap sel normal NIH/3T3 secara *in vitro* senyawa hasil sintesis, dan 4) prediksi ADMET senyawa hasil sintesis menggunakan pkCSM.

Berdasarkan penambatan molekuler, semua ligan usulan menghasilkan energi ikatan lebih rendah daripada klorokuin dan hanya ligan **A**, **D**, **F**, dan **G** yang menghasilkan energi ikatan lebih rendah daripada ligan standar. Interaksi spesifik terjadi antara ligan usulan dan sisi aktif P*f*ENR pada residu asam amino penting TYR277 dan TYR267 melalui ikatan hidrogen ataupun interaksi hidrofobik. Ligan (1)-*N*-(3-nitrobenzil)-1,10-fenantrolinium bromida **A** dan (1)-*N*-(piridin-2-ilmetil)-1,10-fenantrolinium bromida **B** dipilih untuk disintesis karena membentuk ikatan hidrogen dengan TYR277, LYS285, ALA219 (ligan **A**) dan ALA219 (ligan **B**) serta ikatan hidrofobik terutama dengan TYR277 melalui interaksi *π-π T-shaped* (ligan **A**) dan *π*-alkil (ligan **B**), dengan energi ikatan berturut-turut sebesar -7,59 dan -6,09 kkal/mol.

Sintesis garam **A** dan **B** dilakukan melalui tiga tahap reaksi yaitu reduksi 3-nitrobenzaldehida atau 2-piridinkarboksaldehida, brominasi 3-nitrobenzil atau piridin-2-ilmetanol, dan reaksi $S_N2$ antara 1,10-fenantrolin anhidrat dan 3-nitrobenzil atau 2-(bromometil)piridina. Garam **A** dan **B** hasil sintesis berupa padatan krem dan oranye dengan persen hasil total berturut-turut 17 dan 3%. Hasil uji aktivitas antiplasmodial terhadap *P. falciparum* menunjukkan bahwa garam **A** dan **B** tergolong aktif dan selektif dengan nilai $IC_{50}$ berturut-turut 2,24 dan 3,00 µM dengan IS 573.039,2 dan 317,8 (terhadap *strain* FCR3) dan 1,19 dan 1,73 µM dengan IS 1.078.662,0 dan 551,2 (terhadap *strain* 3D7). Berdasarkan prediksi ADMET, garam **A** dan **B** memenuhi kriteria sebagai kandidat obat yang aman dan layak untuk dikembangkan terutama sebagai agen antiplasmodial oral.

Kata kunci: P*f*ENR, *P. falciparum strain* FCR3, *P. falciparum strain* 3D7, turunan garam (1)-*N*-benzil-1,10-fenantrolinium bromida, dan turunan garam (1)-*N*-heterosiklik-1,10-fenantrolinium bromida.

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# *STUDY OF MOLECULAR DOCKING, SYNTHESIS, AND IN VITRO ANTIPLASMODIAL ASSAY OF (1)-N-BENZYL- AND (1)-N-HETEROCYCLIC-1,10-PHENANTHROLINIUM BROMIDE SALTS*

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## *ABSTRACT*

This study aimed to develop (1)-*N*-benzyl-1,10-phenanthrolinium bromide salts as potential antiplasmodial candidates. The research was conducted in four stages: (1) molecular docking of seven derivatives of (1)-*N*-benzyl- and (1)-*N*-heterocyclic-1,10-phenanthrolinium bromide salts with the P*f*ENR protein, (2) synthesis of the salts possessing the lowest binding energy and specific interactions with the key amino acid residues of P*f*ENR, (3) *in vitro* assay of synthesized compounds for antiplasmodial activity against *P. falciparum* FCR3 and 3D7 strain and cytotoxicity against NIH/3T3 normal cells, and (4) ADMET prediction of the synthesized compounds using pkCSM.

Based on a molecular docking study, all proposed ligands exhibited lower binding energies than chloroquine, and only ligands **A**, **D**, **F**, and **G** showed binding energies lower than the standard ligand. Specific interactions between the proposed ligands and the active site of P*f*ENR were observed at key amino acid residues, TYR277 and TYR267, either through hydrogen bonding or hydrophobic interactions. Among these, (1)-*N*-(3-nitrobenzyl)-1,10-phenanthrolinium bromide (ligand **A**) and (1)-*N*-(pyridin-2-ylmethyl)-1,10-phenanthrolinium bromide (ligand **B**) were selected to synthesize. Hydrogen bonds were formed between ligand **A** and the amino acid residues TYR277, LYS285, and ALA219, while ligand **B** interacted with ALA219. Hydrophobic interactions, particularly with TYR277, were observed through $\pi$-$\pi$ T-shaped (ligand **A**) and $\pi$-alkyl (ligand **B**) interactions. The binding energies of **A** and **B** were -7.59 and -6.09 kcal/mol, respectively.

The synthesis of salts **A** and **B** was conducted in three steps: the reduction of 3-nitrobenzaldehyde or 2-pyridinecarboxaldehyde, the bromination of 3-nitrobenzyl or pyridin-2-ylmethanol, and the $S_N2$ reaction of anhydrous 1,10-phenanthroline with 3-benzyl bromide or 2-(bromomethyl)pyridine. The synthesized compounds **A** and **B** were obtained as cream and orange solids, with total yields of 17 and 3%, respectively. *In vitro* antiplasmodial assays against *P. falciparum* revealed that **A** and **B** salts were categorized as active and selective, with $IC_{50}$ values of 2.24 and 3.00 µM and SI of 573,039.2 and 317.8, respectively, against FCR3 strain; and $IC_{50}$ values of 1.19 and 1.73 µM with SI values of 1,078,662.0 and 551.2, respectively, against the 3D7 strain. Based on ADMET prediction, both salts met the criteria for safe drug candidates and were suitable for further development, particularly as oral antiplasmodial agents.

Keywords: P*f*ENR, *P. falciparum* FCR3 strain, *P. falciparum* 3D7 strain, (1)-*N*-benzyl-1,10-phenanthrolinium bromide salt, and (1)-*N*-heterocyclic-1,10-phenanthrolinium bromide salt.