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Title:	Synthesis, in vitro anti-plasmodial potency, in-silico-cum-SPR binding with inhibition of PfPyridoxal synthase and rapid parasiticidal action by 3,5-bis{(E) arylidene}-N-methyl-4-piperidones
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Keywords:	Synthesis in vitro anti-plasmodial potency PfPyridoxal
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Abstract:	Twenty-five (Ia–Iu, IIa–IIb, IIIa, and IVa) diarylidene-N-methyl-4-piperidones (DANMPs) were synthesized and characterized via UV, FT-IR, NMR, and MS while Id was characterized also by single crystal XRD. Twenty-one compounds shortlisted after initial in vitro anti-plasmodial activity successive screenings at 100 μM and 10 μM were evaluated for their IC50s against chloroquine-sensitive Pf3D7, chloroquine-resistant PfINDO, and artemisinin-resistant PfMRA-1240 strains. The four most promising compounds were Ie (IC50s μM 0.35MRA, 1.39INDO, 1.923D7), If (IC50s μM 1.07MRA, 1.36INDO, 3.393D7), Ir (IC50s μM 0.74MRA, 2.45INDO, 1.443D7), and In (IC50s μM 1.27MRA, 1.8INDO, 1.73D7). Resistance indices as low as 0.2 to 0.5 for these potent compounds and <1 for most other compounds suggest their greater potency against drug resistant strains than the drug sensitive strain. The parasiticidal action of Ir was seen within 4 h against the trophozoite stage of the parasite, which is known to express the highest levels of PLP synthase. In silico docking scores of −7.0 to −8.0 kcal mol−1 between potent DANMPs and PfPLP synthase, the direct binding of Ir studied by SPR to recombinantly expressed and purified PfPdx-1 and inhibition of Pdx1 enzymatic activity by Ir suggest this vital enzyme to be a probable target for the DANMPs. The non-hemolytic nature of Ir and conformity of most DANMPs to Lipinski's parameters indicate their potential as new anti-plasmodial leads with PfPLP synthase as one of their targets.
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