IN VIVO ANTIMALARIAL ACTIVITY OF SEMI-SYNTHETIC DERIVATIVES OF 4-NEROLIDYLCATECHOL (4-NC).

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\textbf{Introduction}: Malaria is a tropical disease caused by parasites belonging to the genus \textit{Plasmodium}. It is still one of the principal causes of morbidity and mortality worldwide despite the adoption of many control strategies that have decreased this disease \cite{1}. Resistance to available antimalarials acquired by the parasites is a source of concern and the basis for an intense search for new classes of antimalarial compounds \cite{2,3}. Natural products exhibiting significant antimalarial activity have been identified and semi-synthesis is an important strategy for improving physical and chemical properties and druggability in general \cite{3}. The phenylpropanoid 4-NC is a major, unstable component obtained from \textit{Piper peltata} (caapeba plant) that exhibits significant \textit{in vitro} and little \textit{in vivo} antimalarial activity. 4-NC derivatives exhibit greater stability and comparable \textit{in vitro} antiplasmodial activity to 4-NC \cite{4}. 

\textbf{Methods}: Diacetyl (4-NC-Ac\textsubscript{2}) and dibenzoyl (4-NC-Bz\textsubscript{2}) derivatives were obtained from 4-NC (isolated from \textit{P. peltata} roots) by standard acetylation and benzoylation procedures \cite{5}. These derivatives were tested for \textit{in vivo} antimalarial activity in groups of 3 \textit{Plasmodium berghei} NK65-infected female BALB/c mice treated orally and subcutaneously for 4 days at doses of 200, 400 and 600 mg/kg in the Peters suppression test \cite{6}. Parasitemias were evaluated by optical microscopy on the 5th and 7th days. Control animals received only vehicle. The number of the protocol Ethics Committee approval was 339265.

\textbf{Results and Discussion}: 4-NC-Ac\textsubscript{2} [600 mg/kg/day, orally and subcutaneously] exhibited the greatest suppression of parasitemia on day 5 (64 and 72%, respectively) and day 7 (56 and 70%, respectively) and was active at doses of 50 mg/kg/day. At the highest dose, 4-NC-Bz\textsubscript{2} [200 mg/kg/day, orally and subcutaneously] inhibited parasitemia by 46 and 48%, respectively, on day 5 and by 28 and 17%, respectively, on day 7. Its day 5 oral parasitemia suppression was greater than that of 4-NC. Diacetyl moieties confer greater chemical stability to 4-NC-Ac\textsubscript{2} compared to 4-NC and significantly increase \textit{in vivo} antimalarial activity. 4-NC-Bz\textsubscript{2} suppressed parasitemias less than 4-NC-Ac\textsubscript{2}. No toxicity related deaths or other signs of intoxication were observed. Was used as positive control Chloroquine [10 mg/kg] suppression of 100% and 99% by oral and subcutaneous administration, respectively on day 5 and 99% on day 7, DMSO 5% as vehicle offered no suppression. 

\textbf{Conclusion}: 4-NC derivatives exhibit antimalarial potential and more study is necessary to establish structure-antimalarial activity relations.

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