II CONGRESS OF THE BRAZILIAN
ASSOCIATION OF PHARMACEUTICAL SCIENCES

PHARMACEUTICALS OF THE FUTURE:
TECHNOLOGICAL AND TRANSLATIONAL STRATEGIES

BÚZIOS (RJ)
SEPTEMBER 24-27, 2014

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

Nogueira KL[1,2], Silva LFR[1], Pinto ACS[1], Tadei WP[1], Chaves FCM[3], Pohlit AM[1,2]
[1] Instituto Nacional de Pesquisas da Amazônia-INPA, Avenida André Araújo, 2936 - Petrópolis,69067-374 Manaus-AM, Brazil.
[2]Faculdade de Ciências Farmacêuticas da Universidade Federal do Amazonas-UFAM, Rua Alexandre Amorim, 330, Aparecida, 69010-300, Manaus-AM, Brazil.
[3]Empresa Brasileira de Pesquisa Agropecuária-EMBRAPA, Rodovia AM-010, Km 29, 69000-001, Manaus-AM, Brazil.

Introduction: Malaria is a tropical disease caused by parasites belonging to the genus *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 [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 [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 [3]. The phenylpropanoid 4-NC is a major, unstable component obtained from *Piper peltata* (caapeba plant) that exhibits significant *in vitro* and little *in vivo* antimalarial activity. 4-NC derivatives exhibit greater stability and comparable *in vitro* antiplasmodial activity to 4-NC [4]. **Methods:** Diacetyl (4-NC-Ac_2) and dibenzoyl (4-NC-Bz_2) derivatives were obtained from 4-NC (isolated from *P. peltata* roots) by standard acetylation and benzoylation procedures [5]. These derivatives were tested for *in vivo* antimalarial activity in groups of 3 *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 [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. **Results and Discussion:** 4-NC-Ac_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_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_2 compared to 4-NC and significantly increase comparative *in vivo* antimalarial activity. 4-NC-Bz_2 suppressed parasitemias less than 4-NC-Ac_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. **Conclusion:** 4-NC derivatives exhibit antimalarial potential and more study is necessary to establish structure-antimalarial activity relations.

Acknowledgements: INPA, UFAM, EMBRAPA, FAPEAM, CNPq.
References: 1. Walker. et al. Medicine, 42:100, 2014.
2. Schuck. et al. Eur. J. Med. Chem., 78: 375, 2014.
3. Cruz. et al. Malar. J., 12: 168, 2013.
4. Silva et al. Phytother. Res., 25: 1181, 2011.
5. Pinto. et al. Eur. J. Med. Chem., 44:2731, 2009.
6. Peters. Exp. Parasitol., 17:80, 1965.