5th BCNP Brazilian Conference on Natural Products
XXXI RESEM
Atibaia – SP – Brazil
ISBN: 978-85-66836-10-3
Oct. 26–29th 2015

2,4-DINITROPHENYLHYDRAZONE DERIVATIVES OF NATURAL PRODUCTS AS ANTIMALARIAL AGENTS

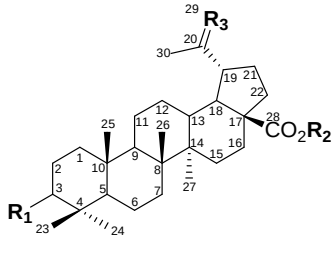
Leopoldo C. Baratto[1], Asad Ullah[2], Renata C. de Paula[3], Brás H. de Oliveira[2]

1. *Universidade Federal do Oeste do Pará, Santarém, Brazil*
2. *Universidade Federal do Paraná, Curitiba, Brazil*
3. *Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*

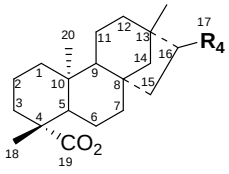
leopoldo.ufopa@gmail.com

Betulinic acid (**1a**) has been known as a moderate antiplasmodial compound. In this work a series of compounds, including the new 2,4-dinitrophenylhydrazone (2,4-DNPH) derivatives [1], was designed, synthesized and evaluated against *Plasmodium falciparum* W2 chloroquine-resistant. A 2,4-DNPH derivative of the beyerene tetracyclic-type diterpenoid isosteviol (**2a**) was also included in the test. The antimalarial activity was evaluated by [^{3}H]-hypoxanthine incorporation and lactate dehydrogenase assays in a concentration range of 1.56-50 μg/mL, using suspension of erythrocytes infected with *P. falciparum*. Results were expressed as IC_{50} values and classified with a scale from very active (IC_{50}<1 μg/mL) to inactive (IC_{50}>50 μg/mL). Cytotoxicity (CC_{50}) of the most active compounds was evaluated against HepG2 A16 cell line by MTT assay. Selectivity index (SI) was calculated by the CC_{50} value for HepG2 A16 cells divided by IC_{50} value for *P. falciparum*. The results are shown on Table 1. Most modifications in molecular structure of **1a** did not increase activity significantly. However, attachment of a 2,4-DNPH moiety at either C-3 (**1c**) or C-29 (**1j**) increased greatly the activity. Therefore, a free carboxyl at C-28, hydroxyl at C-3 and an isopropenyl at C-19 are important for the activity of 2,4-DNPH derivatives of betulinic acid. **1c** and **1j** were non-cytotoxic and SI indicated that both are at least 100 times more selective against *P. falciparum*. The 2,4-DNPH modification of C-16 of the inactive **2a** yielded a moderately active compound (**2b**). Our results showed that the antiplasmodial activity of tetracyclic diterpenes and triterpenes may be increased by addition of 2,4-DNPH moiety and these classes of terpenes, therefore, are promising models for the discovery of new antimalarial drugs.

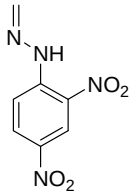
Table 1. IC_{50} values (μg/mL) of betulinic acid and isosteviol derivatives.



Betulinic acid (1a)



Isosteviol (2a)



2,4-DNPH

Compounds	R_1	R_2	R_3	R_4	IC_{50} (μg/mL)
1a	βOH	H	CH_2	-	17.7
1b	=O	H	CH_2	-	>50
1c	2,4-DNPH	H	CH_2	-	9.96
1d	2,4-DNPH	H	CHO (*R*)	-	>50
1e	2,4-DNPH	H	CHO (*S*)	-	>50
1f	2,4-DNPH	CH_3	CH_2	-	>50
1g	2,4-DNPH	Ar-CH_2-	CH_2	-	>50
1h	2,4-DNPH	H	2,4-DNPH	-	>50
1i	2,4-DNPH	H	=O	-	>50
1j	*β*-OH	H	2,4-DNPH	-	6.45
2a					>50
2b	-	-	-	2,4-DNPH	21.06
chloroquine	-	-	-	-	0.085

[1] Baratto, L.C., Porsani, M.V., Pimentel, I.C., Pereira-Netto, A.B., Paschke, R. and Oliveira, B.H. 2013. Preparation of betulinic acid derivatives by chemical and biotransformation methods and determination of cytotoxicity against selected cancer cell lines. Eur. J. Med. Chem. 68:121-131.