

ANTIMALARIAL ACTIVITY OF TRITERPENOIDS WITH THE CUCURBITANE SKELETON

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Introduction

Malaria, caused by protozoan parasites of the genus *Plasmodium*, is a devastating infectious disease in developing countries. One of the biggest problems that have hindered the control of malaria is the emergence and spread of drug resistant *Plasmodium* strains, particularly *Plasmodium falciparum*. In order to overcome this problem, new therapeutic agents based on new mechanisms of action or with new structures are urgently needed. Plants have been an important source of medicines against malaria. Quinine and artemisinin, two of the most important antimalarials currently in use, were derived from plants [1,2].

Momordica balsamina L. (Cucurbitaceae), a vegetable used as food, has also been widely used in traditional medicine, mainly for the treatment of fever and malaria in Mozambique and South Africa [3].



Figure 1. *Momordica balsamina*.

Aim of the study

Continuing our search for biologically active compounds from *Momordica balsamina* [4,5], the aim of this work was to find out antimalarial compounds from this medicinal African plant (Fig. 1).

Results and Discussion

Bioassay-guided fractionation of the methanol extract of *Momordica balsamina* led to the isolation of three new cucurbitane-type triterpenoids, balsaminols C-E (1–3). Their structures were elucidated on the basis of spectroscopic methods including 2D NMR experiments (COSY, HMQC, HMBC and NOESY), (Figs. 3–5).

Balsaminols C-E, together with ten cucurbitacins isolated from the same plant (4–13), were evaluated for their antimalarial activity against the *Plasmodium falciparum* chloroquine-sensitive strain 3D7 and the chloroquine-resistant clone Dd2.

As it can be observed in Table 1, most of the compounds displayed antimalarial activity. Compounds 9 and 12 revealed the highest antiplasmodial effects against both strains (IC₅₀ values: 4.6, and 7.4 μM, 3D7, respectively; 4.0, and 8.2 μM, Dd2, respectively).

When comparing the results obtained for compounds 1–13, rings A and B seem to play an important role in the antiplasmodial activity.

Furthermore, the preliminary toxicity toward human cells of compounds 1–13 was investigated in breast cancer cell line (MCF-7). Compounds were inactive or showed weak toxicity (IC₅₀ values > 19.0).

We can conclude that the isolated compounds were responsible for the activity found in the extracts in a preliminary screening and may be interesting as leads for the development of new antimalarials. Our study also supports the use of *Momordica balsamina* against malaria in traditional medicine

Table 1. Antimalarial activity, cytotoxicity, and selectivity Index of compounds 1–13.

Compound	IC ₅₀ ± SD				Selectivity Index ^a		
	<i>P. falciparum</i> 3D7		<i>P. falciparum</i> Dd2		MCF7 cells		
	μM	μg/mL	μM	μg/mL	μM	MCF7/3D7	MCF7/Dd2
1	19.6 ± 1.5	9.2 ± 0.7	22.4 ± 4.0	10.5 ± 1.9	70.5 ± 2.9	3.6	3.2
2	25.9 ± 5.6	11.1 ± 2.4	45.6 ± 1.9	19.6 ± 0.8	> 133.3	> 5.1	> 2.9
3	20.4 ± 2.1	9.3 ± 1.0	19.6 ± 4.6	9.0 ± 2.1	44.2 ± 3.9	2.2	2.3
4	19.1 ± 3.4	9.0 ± 1.6	27.3 ± 6.1	12.9 ± 2.9	65.1 ± 1.6	3.4	2.4
5	18.7 ± 1.6	9.1 ± 0.8	19.2 ± 2.7	9.4 ± 1.3	34.0 ± 0.1	1.8	1.8
6	14.6 ± 1.3	7.2 ± 0.6	33.0 ± 6.3	16.2 ± 3.1	47.0 ± 0.4	3.2	1.4
7	17.1 ± 0.4	8.1 ± 0.2	23.5 ± 4.9	11.4 ± 2.4	40.0 ± 1.3	2.3	1.7
8	15.2 ± 5.4	7.4 ± 2.6	17.9 ± 3.7	8.7 ± 1.8	31.0 ± 3.7	2.0	1.7
9	4.6 ± 0.5	2.9 ± 0.3	4.0 ± 0.5	2.5 ± 0.3	19.0 ± 0.8	4.2	4.7
10	13.2 ± 0.8	6.3 ± 0.4	17.6 ± 0.7	8.3 ± 0.3	> 133.3	> 10.1	> 7.6
11	17.7 ± 1.3	8.6 ± 0.6	28.3 ± 4.6	13.8 ± 2.2	55.4 ± 2.9	3.1	2.0
12	7.4 ± 0.8	3.3 ± 0.4	8.2 ± 0.7	3.8 ± 0.3	30.7 ± 2.3	4.2	3.7
13	30.6 ± 6.4	14.0 ± 2.4	50.1 ± 0.1	23.0 ± 0.04	45.3 ± 0.7	1.5	0.9
CQ	16 nM	–	200 nM	–	–	–	–

^a Selectivity index (SI) = cytotoxic IC₅₀/antiplasmodial IC₅₀.

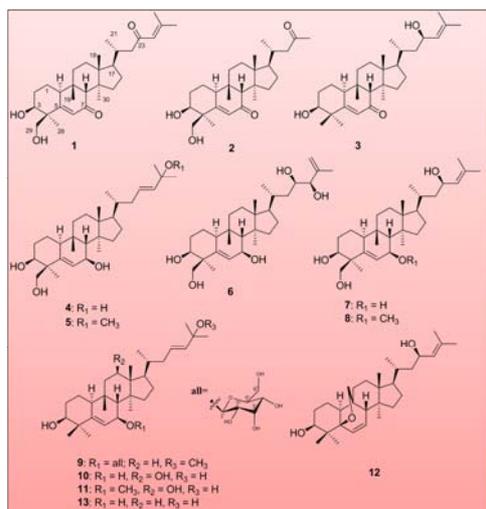


Figure 2. Structure of compounds isolated from *M. balsamina* 1–13.

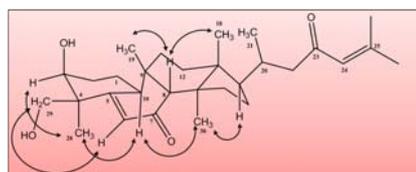


Figure 3. Key NOESY correlations of compound 1.

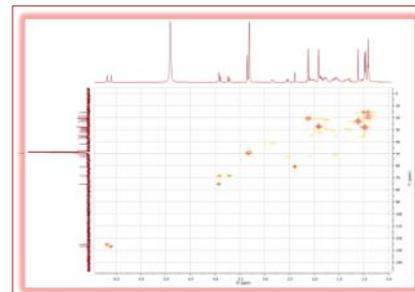


Figure 4. HMQC spectrum of compound 1.

Experimental Procedures

Isolation of Compounds: The powdered aerial parts of *Momordica balsamina* were extracted at room temperature with methanol. The methanol extract was further fractionated by liquid-liquid extraction and chromatographic methods, until the isolation of pure compounds (Fig. 2). All the structures were deduced from their physical and spectroscopic data.

Antimalarial Assay: The evaluation of the antimalarial activity of compounds was performed against chloroquine-sensitive (3D7) and resistant (Dd2) *P. falciparum* strains by using a standardized SYBR Green I-based fluorescence assay [6].

In vitro Cytotoxicity Assay: Compounds were evaluated for their *in vitro* cytotoxic activity against human breast cancer cells (MCF-7) by using the MTT assay [6].

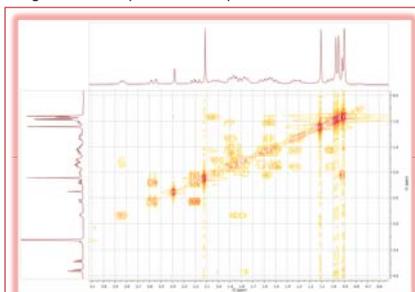


Figure 5. COSY spectrum of compound 2.