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Original scientific paper

## Ribofuranose as a carrier of tetraoxane and 4-aminoquinoline antimalarial pharmacophores

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**Abstract:** Several tetraoxane and 4-aminoquinoline molecules were prepared in order to examine the influence of ribofuranose as a carrier molecule on the antimalarial activity of test compounds. The synthesized compounds showed pronounced antimalarial activity against *Plasmodium falciparum* chloroquine susceptible D6, chloroquine resistant W2 and multidrug-resistant TM91C235 (Thailand) strains. The aminoquinoline derivative **4** was more active against W2 and TM91C235 strains than the control compounds (CQ and MFQ).

**Keywords:** tetraoxanes; 4-aminoquinolines; malaria; *P. falciparum*.

### INTRODUCTION

Malaria is an infectious disease that affects more than 500 million people per annum, causing approximately two million deaths.<sup>1</sup> It is most common in tropical and subtropical areas and 90 % of all cases are found in sub-Saharan Africa. Antimalarial drug resistance, particularly the widespread resistance of many *Plasmodium falciparum* strains to most readily available drugs, such as chloroquine (CQ), hinders malaria control and is therefore a major public health problem. Resistance to antimalarial drugs has increased the global cost of controlling the disease. So far, no resistance to artemisinin (ART) or ART derivatives has been reported. Resistance, as well as the absence of a vaccine for protection against malaria causes an urgent need for new effective, safe and affordable drugs.

Following previous results,<sup>2</sup> new tetraoxanes and 4-aminoquinoline molecules with ribofuranose as carrier molecules were synthesized. The synthesized tetraoxanes were screened *in vitro* against three *P. falciparum* strains: D6 (chloro-

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TABLE I. *In vitro* antimalarial activities of tetraoxanes **4–8** against *P. falciparum* D6,<sup>a</sup> W2,<sup>b</sup> and TM91C235<sup>c</sup> strains

Compound	<i>IC</i> <sub>50</sub> / nM			<i>IC</i> <sub>90</sub> / nM		
	D6	W2	TM91C235	D6	W2	TM91C235
<b>4</b>	40.37	141.35	58.25	72.77	232.96	134.45
<b>5</b>	40.03	176.82	61.39	76.77	282.75	127.99
<b>8</b>	115.97	599.23	701.38	405.63	1454.42	2286.79
<b>6</b>	29.20	40.41	26.96	83.92	62.48	110.22
MFQ <sup>d</sup>	7.38	4.99	51.92	16.83	11.28	102.47
CQ <sup>d</sup>	13.62	371.65	178.07	19.89	662.35	391.42

<sup>a</sup>*P. falciparum* African D6 clone; <sup>b</sup>*P. falciparum* Indochina W2 clone; <sup>c</sup>*P. falciparum* multidrug resistant TM91C235 strain (Thailand); <sup>d</sup>control compounds

The synthesized aminoquinoline derivatives **4** and **5** had similar activity; the amine **4** was less active against *P. falciparum* strain D6 in comparison to the controls CQ and MFQ. Compound **4** was 2.5–3 times more active than CQ against W2 and TM91C235 strains.

On the other hand, the tetraoxane **8** was less active than CQ and MFQ, and significantly less active than the corresponding ester **6** against the three *P. falciparum* strains. According to these results, it is suggested that increased polarity of molecule, caused by hydrolysis of the isopropylidene and/or methoxy group in the *in vitro* test may be the cause of the observed small activity. Increasing the polarity of the molecules impedes their transport through biological membranes. In addition, the presence of hydroxy groups can cause facilitated secretion as a consequence of phase II metabolism.

#### EXPERIMENTAL

For general remarks, see references 2a, 2b, and 2c.

ESI–MS spectra of the synthesized compounds were recorded on an Agilent Technologies 6210 Time-of-Flight LC/MS instrument in the positive ion mode using CH<sub>3</sub>CN/H<sub>2</sub>O = 1/1 with 0.20 % HCOOH as the carrying solvent solution. The samples were dissolved in pure acetonitrile (HPLC grade). The selected values were as follows: capillary voltage 4 kV; gas temperature 350 °C; drying gas 12 L min<sup>-1</sup>; nebulizer pressure 45 atm; fragmentator voltage: 70 V.

Methyl 2,3-*O*-isopropylidene-D-ribofuranoside,<sup>3</sup> 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane-3-carboxylic acid,<sup>4</sup> *N*<sup>1</sup>-(7-chloroquinolin-4-yl)ethane-1,2-diamine<sup>5</sup> were prepared according to known procedures.

*N*<sup>1</sup>-(7-Chloro-4-quinolinyl)-1,2-ethanediamine-*N*<sup>2</sup>-{[(3*a*S,4*R*,6*a*S)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]methyl} (**4**)

Anhydrous CrO<sub>3</sub> (1.02 g) was suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and pyridine (1.65 mL). The alcohol **2** (170 mg, 0.830 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added after 15 min into the resultant red solution and the reaction mixture was stirred for 20 min. Then the mixture was poured onto cold saturated aqueous NaHCO<sub>3</sub>. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×20 mL). The combined organic layers were

dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent evaporated. The crude product was purified by dry-flash chromatography, eluent  $\text{CH}_2\text{Cl}_2$ , to afford the known<sup>6</sup> aldehyde **3** (160 mg, 95.0 %).

Sodium triacetoxymethylborohydride (168 mg, 0.790 mmol) was added to a mixture of aldehyde (80 mg, 0.39 mmol) and amine **A** (175 mg, 0.790 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured onto 1.0 % NaOH (20 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (2×50 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to dryness. The crude product was purified by dry-flash chromatography, eluent EtOAc/MeOH = 9/1. Yield: 156 mg (98.0 %). Oil. **4**: IR (KBr,  $\text{cm}^{-1}$ ): 3302w, 2936w, 2361w, 1611w, 1580s, 1535w, 1451m, 1371m, 1331w, 1274w, 1239w, 1209m, 1158m, 1105s, 962m;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 8.52 (*m*, H-C(2')), 7.95 (*m*, H-C(5')), 7.75 (*m*, H-C(8')), 7.34 (*m*, H-C(6')), 6.38 (*m*, H-C(3')), 5.92 (1H, *bs*), 4.62 (2H, *m*), 4.33 (1H, *m*), 3.32 (5H, *m*), 3.06 (2H, *m*), 2.79 (2H, *d*), 1.97 (2H, *bs*), 1.49 (3H, *s*), 1.31 (3H, *s*);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 151.99, 149.87, 149.05, 134.83, 128.62, 125.23, 121.28, 116.23, 112.47, 109.74, 99.16, 86.05, 85.30, 82.61, 55.15, 52.15, 47.12, 41.89, 26.44, 24.87; (+)ESI-HRMS (*m/z*, %): 408.18229 ( $[\text{M}+\text{H}]^+$ , 100); calculated 408.16845.

(3*aS*,4*R*,6*aS*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane-3-carboxylate (**8**)

A solution of carboxylic acid **7** (120 mg, 0.440 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) was stirred for 90 min at room temperature upon adding  $\text{Et}_3\text{N}$  (61.4  $\mu\text{L}$ , 0.440 mmol) and  $\text{ClCO}_2\text{Et}$  (42.1  $\mu\text{L}$ , 0.440 mmol). Then a solution of alcohol **2** (90 mg, 0.44 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5.0 mL) and a catalytic amount of DMAP (5.0 mg) were added. After 120 min, the reaction mixture was diluted with  $\text{H}_2\text{O}$ , the layers were separated and the organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to dryness. The crude product was purified by dry-flash chromatography, eluent: hexane/EtOAc (9/1). Yield: 165 mg (82.0 %). Colorless foam, softening at 87–89 °C. IR (KBr,  $\text{cm}^{-1}$ ): 3441w, 2986m, 2939s, 2866m, 1737s, 1449m, 1381m, 1318s, 1259m, 1194m, 1159m, 1094s, 1060s, 1016s, 944m, 926m.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 4.62 (2H, *m*), 4.36 (1H, *m*), 4.12 (2H, *m*), 3.31 (3H, *m*), 3.00–1.40 (20H, *m*), 1.48 (3H, *s*), 1.32 (3H, *s*);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ ,  $\delta$  / ppm): 174.12, 112.58, 109.34, 108.41, 107.19, 85.14, 84.19, 81.75, 64.69, 54.88, 41.42, 29.44, 26.38, 25.27, 24.94, 21.99; (+)ESI-HRMS (*m/z*, %): 481.20359 ( $[\text{M}+\text{Na}]^+$ , 100); calculated 481.20442.

#### *In vitro antimalarial activity*

The *in vitro* antimalarial drug susceptibility screen is a modification of the procedures first published by Desjardins *et al.*,<sup>7</sup> with modifications developed by Milhous *et al.*,<sup>8</sup> and the details are given elsewhere.<sup>2a</sup>

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## ИЗВОД

РИБОФУРАНОЗА КАО НОСАЧ ТЕТРАОКСАНСКЕ И 4-АМИНОХИНОЛИНСКЕ  
АНТИМАЛАРИЈСКЕ ФАРМАКОФОРЕИГОР М. ОПСЕНИЦА<sup>1</sup>, KIRSTEN K. SMITH<sup>2</sup>, LUCIA GERENA<sup>2</sup>, САНДРА ГАИЦА<sup>3</sup> и БОГДАН А. ШОЛАЈА<sup>1</sup><sup>1</sup>Хемијски факултет Универзитета у Београду, б. бр. 158, 11000 Београд, <sup>2</sup>Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA и <sup>3</sup>Институт за хемију, технологију и металургију, Њевошева 12, 11000 Београд

У овом раду приказана је синтеза неколико рибофуранозидних тетраоксана и 4-аминохинолина у циљу сагледавања односа структура–активност ове врсте антималярија. Једињења су показала изражену антималяријску активност према хлорокин-осетљивом (D6), хлорокин-резистентном (W2) и вишеструко резистентном (TM91C235 (Thailand)) соју *Plasmodium falciparum*. Аминохинолински дериват **4** је активнији према W2 и TM91C235 сојевима од контролних једињења (хлорокин и мефлокин).

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