www.shd.org.rs

Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.yu • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. 73 (11) 1021–1025 (2008)
JSCS–3783

UDC **P. falciparum*:546.174+547.567:615.281
Original scientific paper

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

IGOR M. OPSENICA[1#], KIRSTEN K. SMITH[2], LUCIA GERENA[2], SANDRA GAICA[3] and BOGDAN A. ŠOLAJA[1*#]

[1]*Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158,11001 Belgrade, Serbia,* [2]*Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA and* [3]*Institute of Chemistry, Technology and Metallurgy, Njegoševa 12, 11000 Belgrade, Serbia*

(Received 13 February 2008)

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.[1] 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,[2] 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-

* Corresponding author. E-mail: bsolaja@chem.bg.ac.yu
# Serbian Chemical Society member.
doi: 10.2298/JSC0811021O

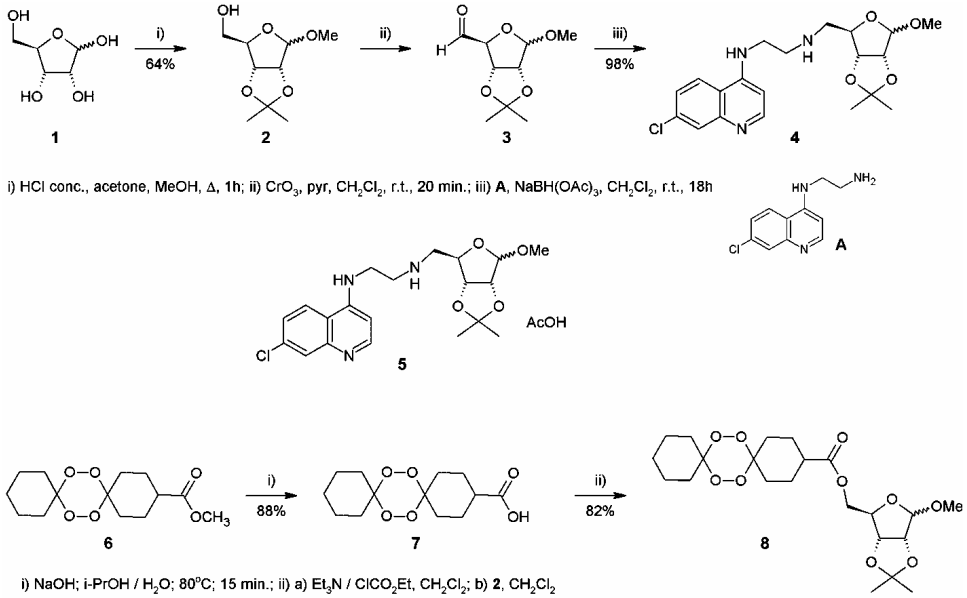
quine-susceptible), W2 (chloroquine-resistant), and TM91C235, a multidrug-resistant strain.

RESULTS AND DISCUSSION

Chemistry

Methyl 2,3-*O*-isopropylidene-D-ribofuranoside **2** was prepared from D-ribose using a mixture of acetone/methanol and HCl (Scheme 1). Compound **2** was isolated in 64 % yield as a mixture of α- and β-anomers, and was pure enough to be used directly in the subsequent step. Oxidation using pyridinium chlorochromate (PCC) afforded the aldehyde **3**, which was further transformed into amine **4** by reductive amination. Amine **4** was isolated as the salt **5** and after treatment with 1.0 % NaOH, the free amine was obtained.

The synthesis of the tetraoxane derivative was accomplished starting from ester **6**, which was hydrolyzed into acid **7** in 88 % yield, followed by further transformation *via* a mixed anhydride procedure into the corresponding ester **8** in 82 % yield.



Scheme 1.

Antimalarial activity

The synthesized compounds were screened *in vitro* against three *P. falciparum* strains: D6 (chloroquine and mefloquine (MFQ) susceptible strain), W2 (chloroquine-resistant, MFQ susceptible), and TM91C235 (multidrug-resistant strain) following the protocol given in the literature (Table I).[2b]

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

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

[a]*P. falciparum* African D6 clone; [b]*P. falciparum* Indochina W2 clone; [c]*P. falciparum* multidrug resistant TM91C23 strain (Thailand); [d]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_3CN/H_2O = 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^{-1}; nebulizer pressure 45 atm; fragmentator voltage: 70 V.

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

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

Anhydrous CrO_3 (1.02 g) was suspended in dry CH_2Cl_2 (25 mL) and pyridine (1.65 mL). The alcohol **2** (170 mg, 0.830 mmol) in anhydrous CH_2Cl_2 (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 $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were

dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by dry-flash chromatography, eluent CH_2Cl_2, to afford the known[6] aldehyde **3** (160 mg, 95.0 %).

Sodium triacetoxyborohydride (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 CH_2Cl_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 CH_2Cl_2 (2×50 mL). The combined organic layers were dried over anh. Na_2SO_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, cm^{-1}): 3302*w*, 2936*w*, 2361*w*, 1611*w*, 1580*s*, 1535*w*, 1451*m*, 1371*m*, 1331*w*, 1274*w*, 1239*w*, 1209*m*, 1158*m*, 1105*s*, 962*m*; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / 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}C-NMR (50 MHz, $CDCl_3$, δ / 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 ([M+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 CH_2Cl_2 (15 mL) was stirred for 90 min at room temperature upon adding Et_3N (61.4 μL, 0.440 mmol) and $ClCO_2Et$ (42.1 μL, 0.440 mmol). Then a solution of alcohol **2** (90 mg, 0.44 mmol) in dry CH_2Cl_2 (5.0 mL) and a catalytic amount of DMAP (5.0 mg) were added. After 120 min, the reaction mixture was diluted with H_2O, the layers were separated and the organic layer was washed with brine, dried over anh. Na_2SO_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, cm^{-1}): 3441*w*, 2986*m*, 2939*s*, 2866*m*, 1737*s*, 1449*m*, 1381*m*, 1318*s*, 1259*m*, 1194*m*, 1159*m*, 1094*s*, 1060*s*, 1016*s*, 944*m,* 926*m*. ^{1}H-NMR (200 MHz, $CDCl_3$, δ / 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}C-NMR (50 MHz, $CDCl_3$, δ / 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 ([M+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.*,[7] with modifications developed by Milhous *et al.*,[8] and the details are given elsewhere.[2a]

Acknowledgements. This work was supported by the Ministry of Science of the Republic of Serbia (Grant No. 142022) and the Serbian Academy of Sciences and Arts. The material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation or publication. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the true views of the Department of the Army or the Department of Defense.

И З В О Д

РИБОФУРАНОЗА КАО НОСАЧ ТЕТРАОКСАНСКЕ И 4-АМИНОХИНОЛИНСКЕ АНТИМАЛАРИЈСКЕ ФАРМАКОФОРЕ

ИГОР М. ОПСЕНИЦА[1], KIRSTEN K. SMITH[2], LUCIA GERENA[2], САНДРА ГАИЦА[3] и БОГДАН А. ШОЛАЈА[1]

[1]Хемијски факултет Универзитета у Београду, п. пр. 158, 11000 Београд, [2]Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA и [3]Институт за хемију, технологију и металургију, Његошева 12, 11000 Београд

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

(Примљено 13. фебруара 2008)

REFERENCES

1. Malaria Foundation International, http://www.malaria.org (October 14, 2008), and the sites for which the links are given therein
2. (a) D. Opsenica, G. Pocsfalvi, Z. Juranić, B. Tinant, J.-P. Declercq, D. E. Kyle, W. K. Milhous, B. A. Šolaja, *J. Med. Chem.* **43** (2000) 3274; (b) B. A. Šolaja, N. Terzić, G. Pocsfalvi, L. Gerena, B. Tinant, D. Opsenica, W. K. Milhous, *J. Med. Chem.* **45** (2002) 3331; (c) D. Opsenica, D. E. Kyle, W. K. Milhous, B. A. Šolaja, *J. Serb. Chem. Soc.* **68** (2003) 291; (d) I. Opsenica, N. Terzić, D. Opsenica, D. Angelovski, M. Lehnig, P. Eilbracht, B. Tinant, Z. Juranić, K. S. Smith, Y. S. Yang, D. S. Diaz, P. L. Smith, W. K. Milhous, D. Doković, B. A. Šolaja, *J. Med. Chem.* **49** (2006) 3790; (e) I. Opsenica, D. Opsenica, M. Jadranin, K. S. Smith, W. K. Milhous, M. Stratakis, B. Šolaja, *J. Serb. Chem. Soc.* **71** (2007) 1181; (f) N. Terzić, D. Opsenica, D. Milić, B. Tinant, K. S. Smith, W. K. Milhous, B. A. Šolaja, *J. Med. Chem.* **50** (2007) 5118; (g) I. Opsenica, D Opsenica, K. S. Smith, W. K. Milhous, B. A. Šolaja, *J. Med. Chem.* **51** (2008) 2261
3. L. A. Paquette, S. Bailey, *J. Org. Chem.* **60** (1995) 7849
4. I. Opsenica, N. Terzić, D. Opsenica, W. K. Milhous, B. Šolaja, *J. Serb. Chem. Soc.* **69** (2004) 919
5. C. C. Musonda, J. Gut, P. J. Rosenthal, V. Yardley, R. C. Carvalho de Souza, K. Chibale, *Bioorg. Med. Chem.* **14** (2006) 5605
6. R. F. Butterworth, S. Hannesian, *Can. J. Chem.* **49** (1971) 2755
7. R. E. Desjardins, C. J. Canfield, D. E. Haynes, J. D. Chulay, *Antimicrob. Agents Chemother.* **16** (1979) 710
8. W. K. Milhous, N. F. Weatherly, J. H. Bowdre, R. E. Desjardins, *Antimicrob. Agents Chemother.* **27** (1985) 525.