Bioorganic & Medicinal Chemistry xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and evaluation of the antimalarial, anticancer, and caspase 3 activities of tetraoxane dimers

Richard K. Amewu [a,*], James Chadwick [a], Afthab Hussain [b], Somnath Panda [b], Rinki Rinki [b], Omar Janneh [e], Stephen A. Ward [c], Candel Miguel [d], Hollie Burrell-Saward [d], Livia Vivas [d], Paul M. O'Neill [a]

[a] Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK
[b] Department of Biomolecular & Sport Sciences, Coventry University, Priory Street, Coventry CV1 5FB, UK
[c] Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK
[d] Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
[e] Division of Biomedical Sciences, St George's University of London, Cranmer Terrace, Tooting, London SW17 0RE, UK

ARTICLE INFO

Article history:
Received 16 August 2013
Revised 18 September 2013
Accepted 19 September 2013
Available online xxxx

Keywords:
Malaria
Leukaemia
Apoptosis

ABSTRACT

The synthesis of a range of mono spiro and dispiro 1,2,4,5-tetraoxane dimers is described. Selected molecules were examined in in vitro assays to determine their antimalarial and anticancer potential. Our studies reveal that several molecules possess potent nanomolar antimalarial and single digit micromolar antiproliferative IC_{50}s versus colon (HT29-AK and leukemia (HL60) cell lines.

© 2013 Elsevier Ltd. All rights reserved.

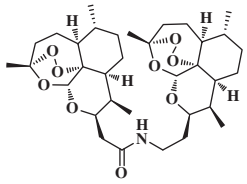
1. Introduction

It is now well established that the artemisinins possess potent antimalarial and anticancer properties. Clinically used artemisinin derivatives, such as artesunate and artemether are administered in combination with longer lasting drugs such as lumefantrine, amodiaquine, mefloquine and primaquine.[1,2]

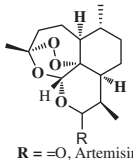
Woerdenbag et al. were the first to observe that artemisinin dimers posses both antimalarial and anticancer activity.[3] Since then a number of groups have prepared artemisnin dimers.[4–7] Chadwick et al. have prepared a variety of dimers, including **1**, using different linkers most of which have potent activity towards plasmodia and cancer cell lines.[8] Posner et al. have also reported the synthesis of various dimers of artemisinin that are capable of eliminating rodent parasite (*Plasmodium berghei*) infected mice following a 3×30 mg/kg dose.[9] Further, Galal et al. have reported the activity of dihydroartemisinin acetal dimers and their activity against solid tumour derived cell lines as well as low nanomolar antimalarial activity.[10]

Studies conducted by Mercer et al. show that the endoperoxide functionality of the artemisinis is both the pharmacophore and toxicophore and the chemical and molecular mechanisms of endoperoxide-induced cell death is mediated by heme or a heme-containing protein.[11,12]

There is a growing interest in the use of 1,2,4,5-tetraoxanes as potential antimalarial agents.[13–15] The tetraoxanes may have a similar mode of action to the artemisinins, but have the benefit that they are purely synthetic and made from readily available, cheap starting materials.[16] There have been a limited number of reports on the cytotoxicity[17,18] and the antiproliferative[19] activity of synthetic tetraoxanes. Zizak et al. observed that steroidal tetraoxanes exert dose-dependent antiproliferative activity toward tumor cell lines through induction of apoptosis.[20]



1

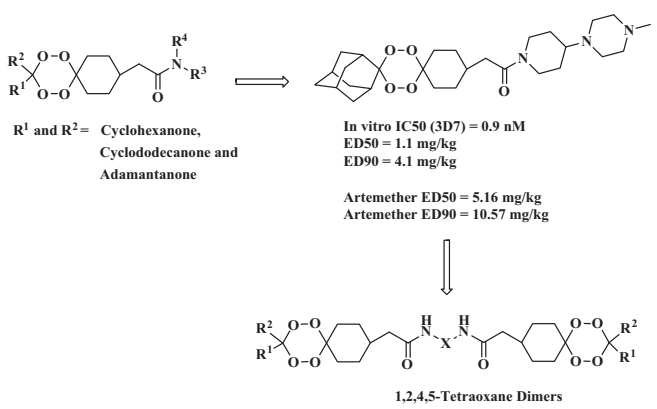


R = =O, Artemisinin (**2**)
R = α–OC(O)$(CH_2)_2CO_2Na$ (**3**)

Earlier we reported the synthesis of potent orally active dispiro 1,2,4,5-tetraoxanes.[21,22]

* Corresponding author. Tel.: +44 151 794 1133; fax: +44 151 794 3588.
E-mail address: amewu@liverpool.ac.uk (R.K. Amewu).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.09.047

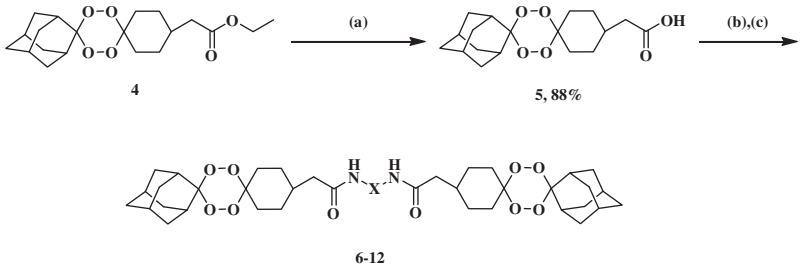


The aim of the current study was to explore the antimalarial and antiproliferative properties of a series of tetraoxane dimers with varying linker groups to include rigid and flexible diamine, diamides and piperazinyl groups.

2. Chemistry

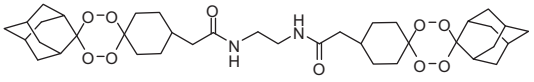
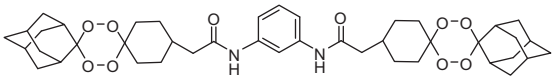
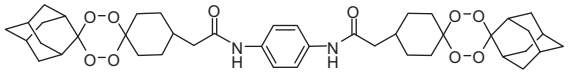
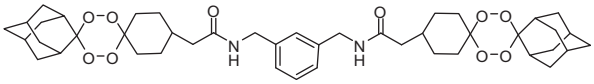
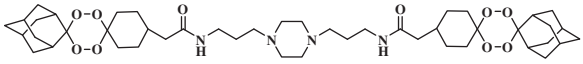
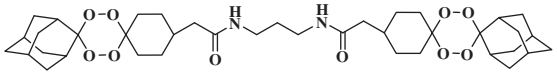
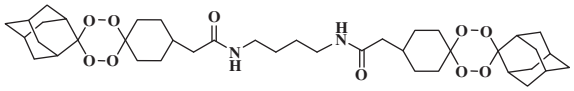
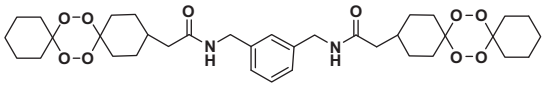
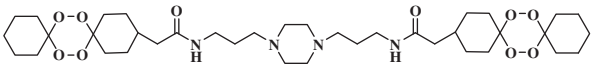
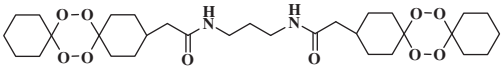
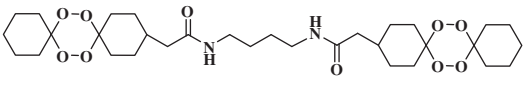
The first series of dimers was based on the key intermediate **4** previously used in the synthesis of orally active tetraoxane derivatives.[21] The ester was hydrolysed to the acid **5** followed by mixed anhydride coupling with various diamines to give **6–12** (Scheme 1, Table 1).[23,24] The yields for the preparations were generally very good (42–90%).

Previous SAR studies on tetraoxane monomers demonstrated that fusion of a cyclohexyl ring provided analogues with lower potency than their adamantine counterparts. In order to see if the



Scheme 1. Reagents and conditions: (a) KOH, MeOH, H_2O, 70 °C, 1 h; (b) $ClCO_2CH_3$, NEt_3, CH_2Cl_2, 0 °C, 1 h; (C) H_2NXNH_2, CH_2Cl_2, 0 °C, 30 min then rt, 90 min.

Table 1
Tetraoxane dimers prepared

	Structure		Yield (%)
6	6		63
7	7		90
8	8		42
9	9		88
10	10		76
11	11		51
12	12		60
13	13		66
14	14		72
15	15		68
16	16		70

Download English Version:

https://daneshyari.com/en/article/10584374

Download Persian Version:

https://daneshyari.com/article/10584374

Daneshyari.com