Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 17, pp. 1913-1916, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00322-3

IN VIVO POTENT ANTIMALARIAL 1,2,4-TRIOXANES: SYNTHESIS AND ACTIVITY OF 8-(α-ARYLVINYL)-6,7,10-TRIOXASPIRO[4,5]DECANES AND 3-(α-ARYLVINYL)-1,2,5-TRIOXASPIRO[5,5]UNDECANES AGAINST *PLASMODIUM BERGHEI* IN MICE+

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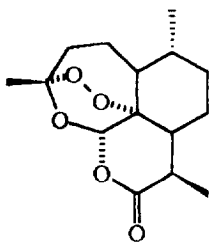
Abstract: Fourteen new trioxanes belonging to 6,7,10-trioxaspiro[4,5]decane and 1,2,5-trioxaspiro[5,5]undecane series have been synthesized and screened against *Plasmodium berghei* in mice. Several of these trioxanes show promising blood schizontocidal activity.

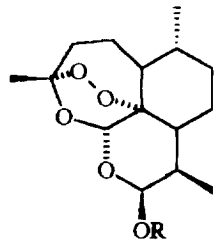
Isolation of sesquiterpene trioxane artemisinin (qinghaosu 1) as the active constituent of the Chinese traditional drug against malaria, *Artemisia annua*[1], is a milestone in malaria chemotherapy and is mainly responsible for the current interest in oxidant drugs[2]. Artemisinin and its derivatives, e.g. 2, 3 and 4 are effective against chloroquine-resistant malaria and are at various stages of drug development[3]. However, presently the focus is on the synthesis and bio-evaluation of simpler 1,2,4-trioxanes[4]. The twin objectives of these studies are (i) to develop a synthetic substitute for artemisinin and (ii) to delineate the structural requirements for the biological activity of this class of compounds. Since the publication of our first report on *in vivo* potent synthetic 1,2,4-trioxanes[5], there have been few more reports on trioxanes active in animal models[6,7,8]. Herein we report the synthesis and antimalarial activity of 8-(α-arylvinyl)-6,7,10-trioxaspiro[4,5]decanes and 3-(α-arylvinyl)-1,2,5-trioxaspiro[5,5] undecanes, two new series of 1,2,4-trioxanes. These trioxanes are structurally simpler than the active trioxanes reported so far and show promising blood schizontocidal activity against P.berghei in mice.

Synthesis of 8-(α-arylvinyl)-6,7,10-trioxaspiro[4,5]decanes (7a-g) and 3-(α-arylvinyl)-1,2,5-trioxaspiro[5,5]undecanes (8a-g)

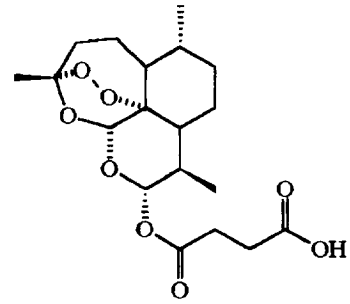
ß-Hydroxyhydroperoxides **5a-g** were prepared by photooxygenation of allylic alcohols **6a-g** according to the procedure published earlier[4e]. Acid catalysed condensation of hydroperoxides **5a-g** with cyclopentanone followed by chromatographic purification of the crude products furnished trioxoanes **7a-g** in 42-61% yields[9,10]. Similarly the reaction of **5a-g** with cyclohexanone furnished trioxanes **8a-g** in 45-73% yields[9,10].



1



2 R=Me
3 R=Et



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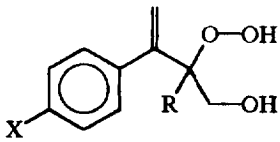
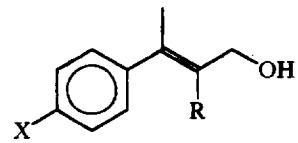
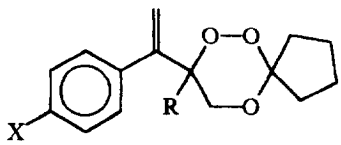


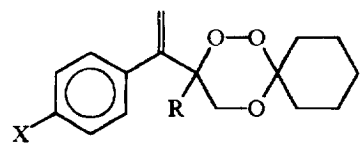
5a X=H, R=H
5b X=F, R=H
5c X=Cl, R=H
5d X=OMe, R=H
5e X=Me, R=H
5f X=H, R=Me
5g X=Cl, R=Me



6a X=H, R=H
6b X=F, R=H
6c X=Cl, R=H
6d X=OMe, R=H
6e X=Me, R=H
6f X=H, R=Me
6g X=Cl, R=Me



7a X=H, R=H
7b X=F, R=H
7c X=Cl, R=H
7d X=OMe, R=H
7e X=Me, R=H
7f X=H, R=Me
7g X=Cl, R=Me



8a X=H, R=H
8b X=F, R=H
8c X=Cl, R=H
8d X=OMe, R=H
8e X=Me, R=H
8f X=H, R=Me
8g X=Cl, R=Me

Antimalarial Activity

Trioxanes **7a-g** and **8a-g** were tested against *Plasmodium berghei* in mice model[11] using the following protocol.

Male mice (Park strain, 5 animals in each experiment) weighing 20 + 2 g were infected (*i.p.*) with an inoculum containing 10^6 parasitized erythrocytes. The test compounds were dissolved in groundnut oil and administered intraperitoneally at doses of 90 and 30 mg/kg, twice a day for 5 consecutive days commencing on day one (3 hour post infection). A group of 5 infected mice served as a negative control while a similar set treated with artimisinin (sonicated suspension in groundnut oil and given at a dose of 30 mg/kg, twice a day for 5 days) served as a positive control. Blood films of both the treated and the untreated animals were examined for malarial parasites on day 6 and thereafter every alternative day till 16th day and subsequently every 3rd day upto 30th day. A compound was considered active if it showed complete suppression of parasitaemia and extended the life span of the treated mice beyond 30 days. Untreated animals died within 10-15 days.

In this test system trioxanes **7a-e** and **8b-c** were found active at 90 mg/kg. Compounds **7f-g, 8a, 8d-g** were inactive at this dose. At 30 mg/kg dose, trioxanes **7a** and **7c** showed more than 90% suppression of parasitaemia on day 6 which eventually cleared completely and all the animals survived beyond 30 days; all other trioxanes were inactive at this dose.

From this preliminary data following trends in SAR are clear:

(i) 6,7,10-Trioxaspiro[4,5]decanes are more active than 1,2,5-trioxaspiro[5,5]undecanes,

(ii) Introduction of methyl group at carbon carrying the α-arylvinyl group leads to abolition of activity, and

(iii) Introduction of an electronegative atom in benzene ring in 1,2,5-trioxaspiro[5,5]undecane series enhances the antimalarial activity.

Considering the simplicity of the structures and easy accessibility of these trioxanes, this order of antimalarial activity is significant. We regard this an important lead and are in process of building on this lead.

Acknowledgement: We thank Mrs. Shashi Rastogi for her contribution in synthesis and A.Islam and S.Kant for their help in antimalarial screening. Partial support for this work by Indian Council of Medical Research, New Delhi is also gratefully acknowledged.

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+CDRI Communication No.5398.

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9. Yields of the trioxanes from hydroperoxide **5d** were generally poor; **7d** and **8d** were obtained only in 21% and 31% yields, respectively.
10. Selected spectral data:
    Trioxane 7a: m/e 246 (M^+), 214 (M^+-O_2); PMR (90 MHz, $CDCl_3$): δ 1.4-2.5 (m, 8H), 3.72 (d, 2H, J=7Hz), 5.18 (t, 1H, J=7Hz), 5.20, 5.37 (2s, one H each), 7.24 (s, 5H).
    Trioxane 7g: m/e 294, 296 (M^+), 262, 264 (M^+-O_2); PMR($CDCl_3$): δ 1.45 (s, 3H), 1.5-2.0 (m, 8H), 3.60 (d, 1H, J=12Hz), 3.96 (d, 1H, J=12Hz), 5.14, 5.43 (2s, one H each), 7.16 (s, 5H).
    Trioxane 8b: m/e 278 (M^+), 246 (M^+-O_2);PMR ($CDCl_3$): δ 1.0-2.2 (m, 10H), 3.61 (dd, 1H, J=11Hz, 4Hz), 3.86 (dd, 1H, J=11Hz, 10Hz), 5.07 (dd, 1H, J=10 Hz, 4Hz), 5.22, 5.33 (2s, one H each), 6.75-7.35 (m, 4H).
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(*Received in Japan* 28 *April* 1995; *accepted* 17 *July* 1995)