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SYNTHESIS OF IN VIVO POTENT ANTIMALARIAL 1,2,4-TRIOXANES+

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Abstract : β-Hydroxyhydroperoxides (5a-h) derived from 3-aryl-2-butenol (6a-h) by dye-sensitized photooxygenation undergo a facile acid-catalysed condensation with 2-adamantanone to yield 1,2,4-trioxanes (8a-h). These trioxanes are stable at room temperature, can be stored in refrigerator for a year and are active against Plasmodium berghei in mice.

Qinghasu (artemisinin 1), a sesquiterpene 1,2,4-trioxane from Artemisia annua[1] and some of its semisynthetic derivatives (2-4) are highly active antimalarial agents, effective against both chloroquine-sensitive and resistant malaria and are particularly suited for treatment of cerabral malaria[2-3]. The limitations such as high rate of recrudescence, poor oral absorption, short half-life, embryotoxicity and limited supply associated with qinghaosu and its derivatives[4], and the realization that biological activity of this class of compounds is due to the peroxide group has led to an intense search for more potent and structurally simpler 1,2,4-trioxanes[5,6] While this research has resulted in several new routes to 1,2,4-trioxanes and some in vitro active antimalarials[7], it has yet to yield a in vivo potent compound. Herein, we report a new class of 1,2,4-trioxanes, which are easy to synthesize and are active against Plasmodium berghei in mice.

β-Hydroxyhydroperoxides 5a-h prepared[8] by photooxygenation of allylic alcohols 6a-h underwent a facile acid-catalysed condensation with 2-adamantanone (7) to furnish spiro trioxanes 8a-h in 50-85 yields[9].

A typical procedure: To an ice-cooled solution of β-hydroxyhydroperoxide 5a (70 mg) and 2-adamantanone (160 mg) in methylenechloride (2 ml), a drop of conc. hydrochloric acid was added and the reaction mixture was left at 5°C for overnight. Usual workup followed by purification by column chromatography on silica gel (eluted with 2% ethylacetate in hexane) furnished 90 mg (75%) of trioxane 8a as a colourless oil which solidified on keeping in refrigerator for several days[9].

These trioxanes are stable at room temperature and can be stored in refrigerator for a year without any change of structure or loss of activity.

In vivo antimalarial activity : In vivo antimalarial activity of all these compounds was assessed in Plasmodium berghei mouse model[10,11].

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

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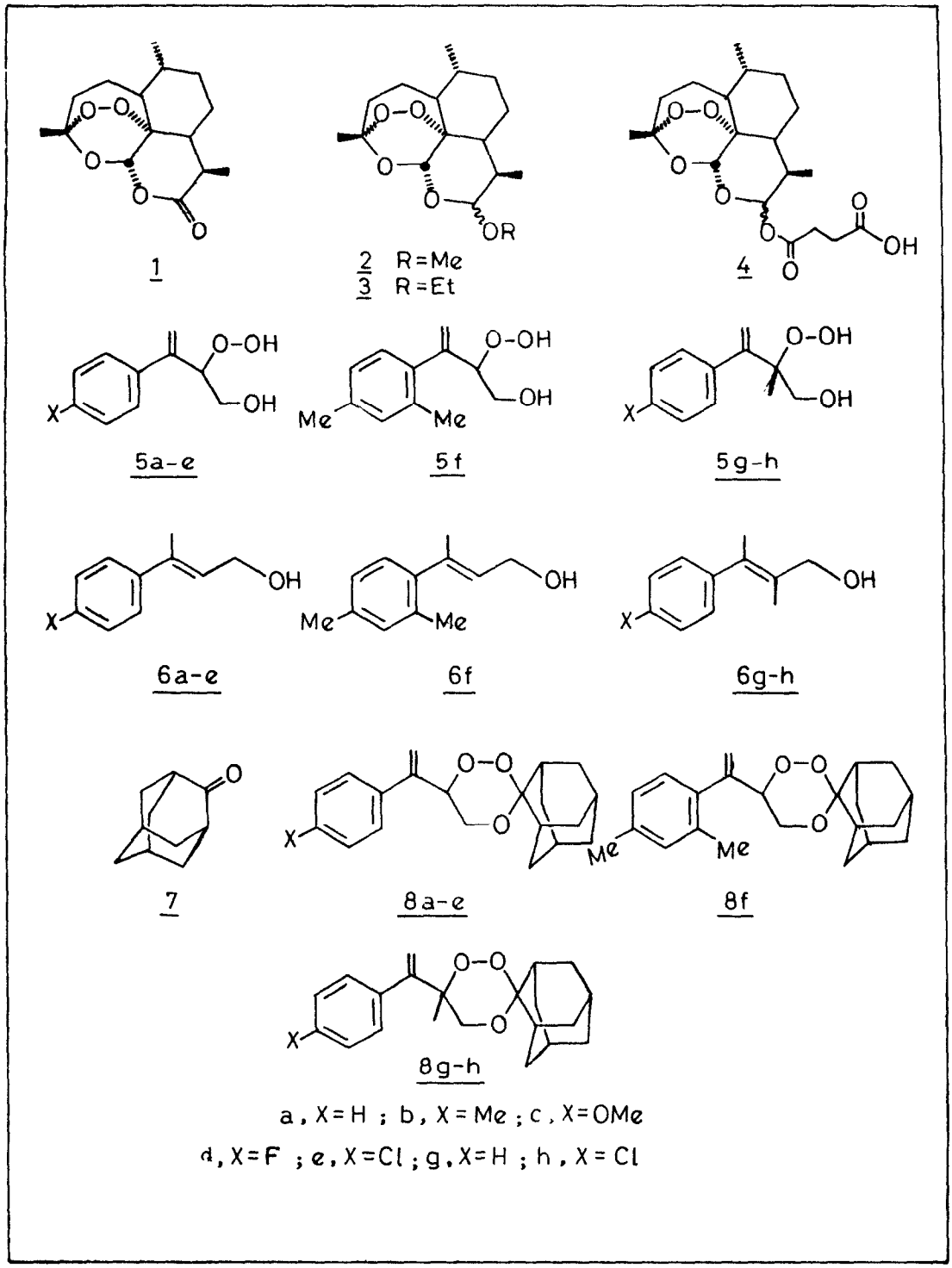
1
2 R=Me
3 R=Et
4
5a-e
5f
5g-h
6a-e
6f
6g-h
7
8a-e
8f
8g-h
a, X=H ; b, X=Me ; c, X=OMe
d, X=F ; e, X=Cl ; g, X=H ; h, X=Cl

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 chloroquine (chloroquine hydrochloride dissolved in water and given at a dose of 15 mg/kg, once a day for 4 days) served as a positive control. Blood films of both the treated and the untreated animals were examined for malarial parasite 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[12].

In this test system, trioxanes 8a-f were active at 90 mg/kg while only 8c and 8e were active at 30 mg/kg.

In summary, we have prepared a new class of 1,24-trioxane which are easy to synthesize and show in vivo antimalarial activity.

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7. See ref 5b-d, 5g, and 5e.

8. For a preliminary report on the preparation of B-hydroxyhydroperoxides and their elaboration into 1,2,4-trioxanes see ref. 5g.

9. Trioxane 8a: oil, m/e 312 (M^+), 280 (M^+-O_2), 130 (M^+-adamantanone-O_2), NMR (CCL_4, 90 MHz) : δ 1.4-2 2(m, 14H, adamantanyl moiety), 3.57 (dd, 1H, J=12Hz, 4Hz, 5-He), 3.78 (dd, 1H, J=12Hz, 10Hz, 5-Ha), 5 08 (dd, 1H, J=10Hz, 4Hz, 6-H), 5.20, 5.34 (2s, 2H, olefinic), 7.22 (m, 5H, aromatic).

Trioxane 8f : oil, m/e 340 (M^+), 308 (M^+-O_2), NMR ($CDCl_3$) : δ 2.20, 2.24 (2s, 2 x Me) 3.55 (dd, 1H, J=12Hz, 4Hz), 3.81 (dd, 1H, J=12Hz, 10Hz), 4.85 (dd, 1H, J=10Hz, 4Hz), 5.05, 5 35 (2s, 2H), 6.88 (m, 3H).

Trioxane 8g : oil, m/e 326 (M^+), 294, 144 ; NMR ($CDCl_3$) : δ 1 35 (s, 3H), 3.67 (d, 1H, J=12Hz), 4.01 (d, 1H, J=12Hz), 5.22, 5.54 (2s, 2H), 7.27 (s, 5H).

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11. This biological data is based on a primary screening at 90 and 30 mg/kg only The minimum effective doses of these compounds are being worked out and will be reported in due course

12. The life span of untreated mice as reported by other workers using a similar protocol varies from 5-7 days[3] to 7-9 days[13]. This difference could be due to difference in strain, age and general health of the mice used.

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