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Antiprotozoal activities of new bicyclo[2.2.2]octan-2-imines and esters of bicyclo[2.2.2]octan-2-ols

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Abstract

Several bicyclo[2.2.2]octan-2-imines and esters of bicyclo[2.2.2]octan-2-ols were prepared. Their antitrypanosomal and antiplasmodial activities against *Trypanosoma brucei rhodesiense* (STIB 900) and the K1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine) were determined using microplate assays. Two of the synthesized bicyclo[2.2.2]octan-2-one 4′-phenylthiosemicarbazones showed the highest antitrypanosomal activity ($IC_{50} < 0.3$ μM) of the so far prepared 4-amino-6,7-diarylbicyclo[2.2.2]octane derivatives, but they are distinctly less active than suramine ($IC_{50} = 0.0075$ μM). Most of the 4′-phenylthiosemicarbazones and a single bicyclo[2.2.2]octan-2-yl benzoate exhibit attractive antimalarial activity ($IC_{50} = 0.23$–0.72 μM). Two bicyclooctanone oximes are even as active as chloroquine ($IC_{50} = 0.08$–0.15 μM, chloroquine: $IC_{50} = 0.12$ μM against sensitive strains).

Keywords: 4-Aminobicyclo[2.2.2]octane derivatives; *Trypanosoma brucei rhodesiense*; *Plasmodium falciparum*; In vitro assays; Benzoates; 4-Phenylthiosemicarbazones

1. Introduction

Human African trypanosomiasis is caused by the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. About 0.5 million people are infected with African trypanosomiasis in various countries of central Africa. The disease is fatal if untreated and therefore causes 50,000 deaths per year (Burri et al., 2000; Barrett et al., 2003). Usually, the disease proceeds from a peripheral to a CNS infection. Only four drugs are in use for treatment of trypanosomiasis. Pentamidine and suramine are not able to cross the blood–brain barrier efficiently and therefore will not cure CNS infections (Jennings et al., 2002). Melarsoprol is active against all strains of trypanosomes in all stages, however, encephalopathy, an undesired effect of this drug is usually fatal for up to 5% of the patients (WHO, 1999). D,L-α-Difluoromethylornithine (Eflornithine®) is used as an alternative to melarsoprol but unfortunately it is ineffective against *T. b. rhodesiense* (Agbo et al., 2003). Furthermore, it is also toxic and trypanosomes are showing increasing resistance to this drug (Milord et al., 1993). All of the above-mentioned drugs have to be administered parenteral and frequently cause serious side effects (Atawodi et al., 2003; Burri and Brun, 2003). A major problem is the increasing resistance of trypanosomes to these drugs (Berger et al., 1995; Barrett, 1999; Anene et al., 2001; Matovu et al., 2001). Because of this, new trypanocides with less side effects are in great demand.

Malaria kills 2–3 million people yearly (Moorthy et al., 2004). It is one of the main killers of children today (Gillespie et al., 2003). Of the several reasons that cause malaria deaths to increase, one stands out most prominently:

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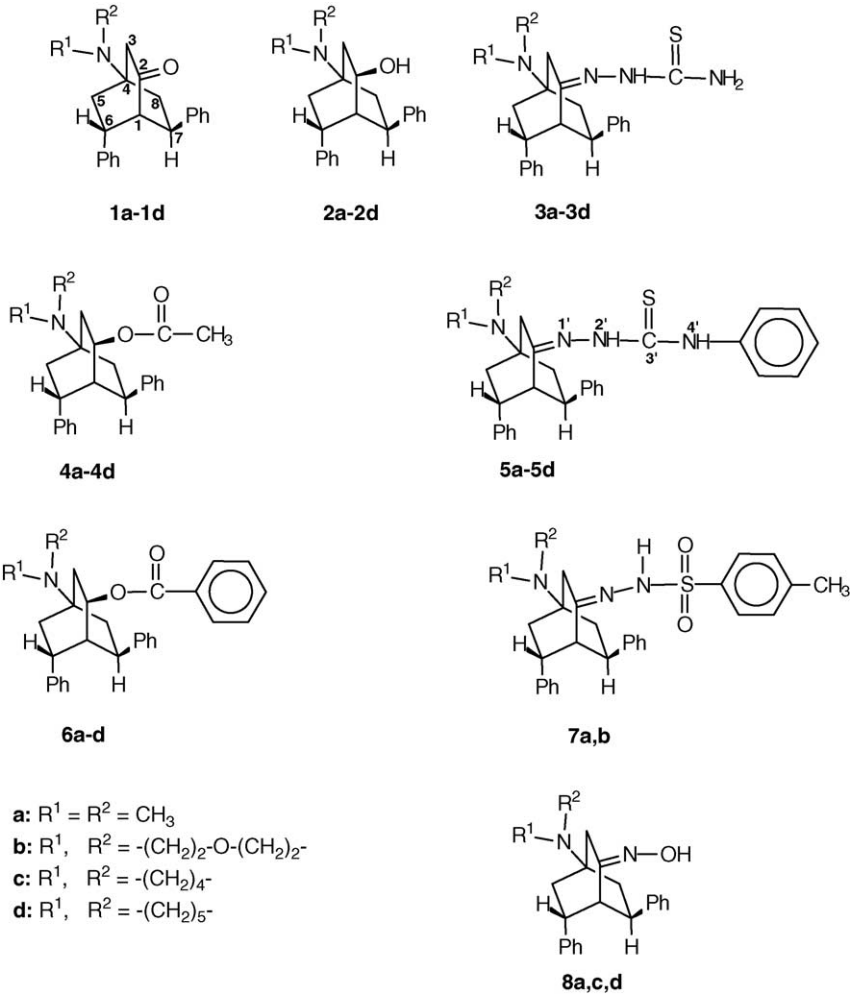
drug resistance in the deadly species of *Plasmodium falciparum* (Attaran et al., 2004). Widespread drug resistance against traditional therapeutics such as chloroquine and the combination sulfadoxine–pyrimethamine which were once highly effective, makes them almost useless in many parts of the world (Loutan, 2003; Tanser and le Suer, 2002). For the following generation of antimalarials, increasing resistance has been reported too (Bjorkman and Phillips-Howard, 1990; van Agtmael et al., 1999; White, 1992; Wiesner et al., 2003; Wongsrichanalai et al., 2002). Since loss of sensibility has been observed even for the most recently introduced artemisinine derivatives (Meshnick, 2002; Sharma et al., 2003; Turner, 1995; Wiesner et al., 2003; Yang et al., 2000), there is an urgent need for potent new antimalarial drugs.

Recently, we reported the one-pot synthesis of 4-dialkylaminobicyclo[2.2.2]octan-2-ones **1** (Weis et al., 1998) and their reduction to alcohols **2**. Compound **2a** exhibits activity against *T. b. rhodesiense* whereas compounds **1c** and **2d** show activity against the K1 strain of *P. falciparum* which is resistant to chloroquine and pyrimethamine (Weis et al., 2003). In the meantime, we prepared several derivatives of **1** and **2** such as thiosemicarbazones **3** and acetates **4** (Seebacher et al., 2003, 2004a,b). All new compounds were tested against *T. b. rhodesiense* (STIB900) and *P. falciparum* K1 using in vitro assays. The so far highest antitrypanosomal activity (IC_{50} = 0.68 μM) shows a benzenesulfonate of **2c** (Seebacher et al., 2004b). The alcohol **2d** and the thiosemicarbazones **3b**–**d** exhibit the highest antiplasmodial activity (IC_{50} = 0.84–0.99 μM) of the so far prepared derivatives.

This paper presents the syntheses of the second generations of bicyclo[2.2.2]octan-2-imines and of esters of bicyclo[2.2.2]octan-2-ols. Alcohols **2** were esterified giving benzoates **6**. Their antiprotozoal activities were compared to those of the formerly prepared acetates **4**. In order to modify the structure of thiosemicarbazones **3**, which show remarkable antiplasmodial activity, ketones **1** were converted to phenyl-substituted thiosemicarbazones **5**. Furthermore, the imino compounds **7** and **8** were prepared from **1** (Scheme 1). All synthesized compounds were tested for



Scheme 1. Structures of bicyclo[2.2.2]octane derivatives.