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Original article

Synthesis and cytotoxic activity of psorospermin and acronycine analogues in the 3-propyloxy-acridin-9(10*H*)-one and -benzo[*b*]acridin-12(5*H*)-one series

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ABSTRACT

In order to explore the structure–activity relationships in the acronycine and psorospermin series, simplified analogues of the highly cytotoxic (±)-(2*R**,1′*R**)-5-methoxy-11-methyl-2-(2-methyloxiran-2-yl)-1,2-dihydro-11*H*-furo[2,3-*c*]acridin-6-one and (±)-(2*R**,1′*R**)-5-methoxy-13-methyl-2-(2-methyloxiran-2-yl)-1,2-dihydro-13*H*-benzo[*b*]furo[3,2-*h*]-acridin-6-one lacking the fused furan ring, including 3-allyloxy-1-methoxy-10-methyl-acridin-9(10*H*)-one, 3-allyloxy-1-methoxy-5-methyl-benzo[*b*]acridin-12(5*H*)-one, the corresponding epoxides, and related dihydrodiol esters and diesters were prepared. Only the simplified oxirane compounds displayed significant antiproliferative activity compared to the parent compounds. The oxirane alkylating unit appears indispensible to observe significant antiproliferative activity in both series, but the presence of the angularly fused furan ring does not appear as a crucial structural requirement to observe significant cytotoxic activity.

1. Introduction

The epoxyfuranoxanthone psorospermin (**1**) was isolated in 1980 from the roots of *Psorospermum febrifugum* Sprach. (Guttiferae), based on its significant activity *in vivo* against P388 mouse leukemia [1]. Further on, the stereochemistry and absolute configuration of this natural product were established in the group of Cassady [2,3]. Psorospermin appears as a promising agent, active against drug-resistant leukemia lines and AIDS-related lymphoma. Its mechanism of action implies interaction with DNA, through its exocyclic oxirane group, which binds covalently to the *N*-7 position of the guanine units in the major groove [4]. This activity is dramatically enhanced in the presence of topoisomerase II, since in the absence of this enzyme, alkylation is both weak and unspecific [5]. Structure–activity relationship studies have emphasized the importance of the natural (2′*R*,3′*R*) stereochemistry to observe optimum DNA alkylation and antitumor activity [6].

The pyranoacridone alkaloid acronycine (**2**), originally isolated from *Acronychia baueri* Schott (Rutaceae) [7–9], has shown antitumor properties against a large panel of experimental solid tumors models, including sarcoma, myeloma, carcinoma and melanoma [10,11]. However, its moderate potency severely hampered the subsequent clinical trials, which gave only poor results [12]. Following the isolation of the unstable acronycine epoxide (**3**) from several New-Caledonian *Sarcomelicope* species, efforts toward the design of more potent derivatives were guided by a hypothesis of bioactivation of the 1,2-double bond of acronycine into the corresponding oxirane *in vivo*. [13]. Significant improvements in terms potency were obtained with derivatives modified in the pyran ring, which had a similar reactivity toward nucleophilic agents as acronycine epoxide (**3**), but an improved chemical stability. Such compounds are exemplified by diesters of *cis*-1,2-dihydroxy-1,2-dihydroacronycine, that exhibited marked antitumor properties, with a broadened spectrum and increased potency when compared to acronycine [14]. Structural analogs in the related benzo[*a*] and [*b*]acronycine series, including an additional aromatic ring fused onto the natural alkaloid skeleton, were developed later on. Esters and diesters of 1,2-dihydro-1,2-diols in these latter series proved even more potent [15,16]: for example, diacetate **4**, which recently underwent phase I clinical trials under the code S23906-1, demonstrated comparable and/or better activity than paclitaxel, vinorelbine, and irinotecan, when evaluated against aggressive orthotopic models of human ovarian, lung, and colon cancers, respectively [17]. The mechanism of its action implies alkylation of the 2-amino group of DNA guanine residues in the minor groove, by the carbocation resulting from the elimination of the ester leaving

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group at position 1 of the drug [18–21], inducing a marked destabilization of the double helix, with the formation of single-stranded DNA [22], which finally leads to cell apoptosis [23].

Recently developed hybrid compounds associating the acridone or benzo[*b*]acridone chromophore of acronycine derivatives and the epoxyfuran alkylating unit present in psorospermin, exemplified by (±)-(2*R**,1′*R**)-5-methoxy-11-methyl-2-(2-methyloxiran-2-yl)-1,2-dihydro-11*H*-furo[2,3-*c*]acridin-6-one (**5**) and (±)-(2*R**,1′*R**)-5-methoxy-13-methyl-2-(2-methyloxiran-2-yl)-1,2-dihydro-13*H*-benzo[*b*]furo[3,2-*h*]-acridin-6-one (**6**) also displayed very potent antiproliferative activities. Interstingly, compounds of these series were shown to act through alkylation of DNA at the same guanine *N*-7 position in the major groove as natural xanthones belonging to the psorospermin series [24].

In a continuation of our studies on the structure–activity relationships in the acronycine and psorospermin series [25], we describe here the synthesis and the biological properties of simplified analogues of the latter hybrid series, including 3-allyloxy-1-methoxy-10-methyl-acridin-9(10*H*)-one (**7**), 3-allyloxy-1-methoxy-5-methyl-benzo[*b*]acridin-12(5*H*)-one (**8**), the corresponding epoxides, and related dihydrodiol esters and diesters. The choice of these target molecules was partly guided by potent cytotoxic activity toward L1210 or 9-KB cancer cells previously reported for anthraquinones (*i.e.* **9**) [26] and xanthones (*i.e.* **10** and **11**) [27] bearig epoxypropenyl subsituents.

2. Chemistry

Reaction of 1,3-dihydroxyacridone (**12**) [28,29] with allyl bromide in alkaline medium gave 3-allyloxy-1-hydroxyacridin-9(10*H*)-one (**13**). Simultaneous *N*- and O-methylation of **13** was ensured by the use of sodium hydride as base and dimethylsulfate as alkylating agent, in dimethylformamide, to give the desired 3-allyloxy-1-methoxy-10-methylacridin-9(10*H*)-one (**7**). Catalytic osmium tetroxide oxidation of **7**, using *N*-methylmorpholine *N*-oxide to regenerate the oxidizing agent [16,30], led to the corresponding racemic diol, (±)-3-(2,3-dihydroxypropyl-1-oxy)-1-methoxy-9-methylacridin-9(10*H*)-one (**14**). Selective acetylation of the primary alcohol on the side chain could be ensured by the use of acetic anhydride under controlled conditions at 0 °C, giving (±)-3-(3-acetoxy-2-hydroxypropyl-1-oxy)-1-methoxy-9-methylacridin-9(10*H*)-one (**15**) in moderate yield, whereas treatment of diol **14** with excess acetic anhydride at room temparature afforded the corresponding (±)-3-(2,3-diacetoxypropyl-1-oxy)-1-methoxy-9-methylacridin-9(10*H*)-one (**16**). Reaction of diol **14** with *N*,*N*′-carbonyldiimidazole in 2-butanone under reflux afforded the cyclic carbonate **17**. Finally, conversion of the diol **14** into the corresponding epoxide was envisioned through cyclization of an intermediate monomesylate, since this method had given previously satisfactory results with the related 2-(1,2-Dihydroxy-1-methylethyl)-5-methoxy-11-methyl-1,2-dihydro-11*H*-furo[2,3-*c*]acridin-6-ones [24]. Thus, mesylation of the primary alcohol of diol **14** with one equivalent of methanesulfonyl chloride in pyridine afforded the corresponding mesylate, which was immediately submitted without purification to alkaline treatment with potassium carbonate in the presence of 18–6 crown ether in acetone, to afford the desired epoxide **18** Charts 1.

A similar reaction sequence, starting from 1,3-dihydroxybenz[*b*]acridin-12(5*H*)-one (**19**) [15], was considered for the synthesis the corresponding analogues in the benzo[*b*]acridone series. Treatment of **19** with allyl bromide in alkaline medium afforded 3-allyloxy-1-hydroxybenz[*b*]acridin-12(5*H*)-one (**20**) in 63% yield, accompanied by smaller amounts of 4-allyl-3-allyloxy-1-hydroxybenz[*b*]acridin-12(5*H*)-one (**21**). Methylation of **20** gave 3-allyloxy-1-methoxy-5-methylbenz[*b*]acridin-12(5*H*)-one (**8**), which

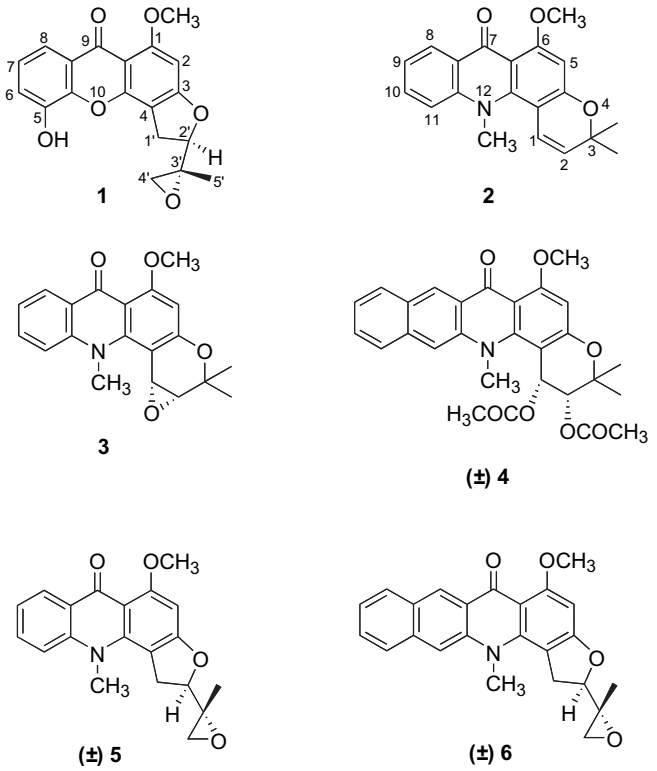

Chart 1.

was converted into the corresponding racemic diol **22** by catalytic osmic oxidation. The two esters (±)-3-(3-acetoxy-2-hydroxypropyl-1-oxy)-1-methoxy-5-methylbenz[*b*]acridin-12(5*H*)-one (**23**) and (±)-3-(2,3-diacetoxypropyl-1-oxy)-1-methoxy-5-methylbenz[*b*]acridin-12(5*H*)-one (**24**), on the one hand, and the cyclic carbonate **25**, on the other hand, could be conveniently obtained by treatment of the diol **22** with acetic anhydride and *N*,*N*′-carbonyldiimidazole, respectively. Finaly, mesylation of **22** using one

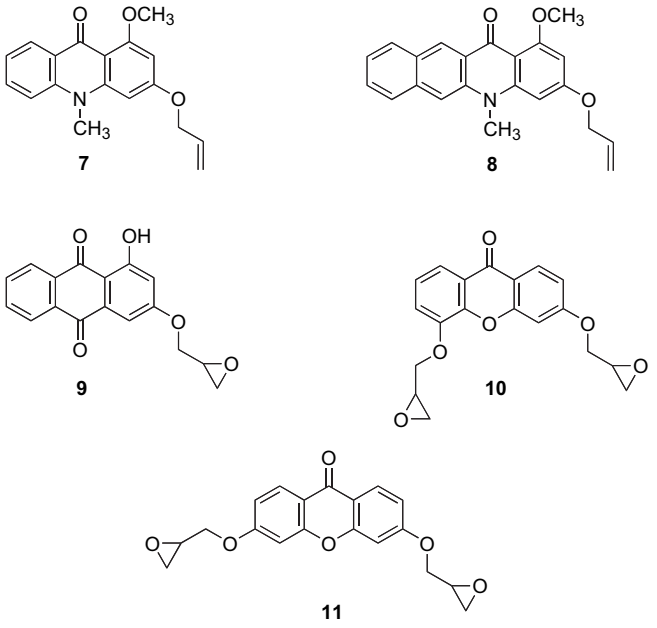

Chart 2.