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Invited review

Benzo[*b*]acronycine derivatives: a novel class of antitumor agents

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Abstract

A hypothesis of bioactivation of the antitumor alkaloid acronycine by transformation of the 1,2-double bond into the corresponding epoxide in vivo and the suggestion that acronycine could interact with DNA, led to develop 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters (1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one diesters) as new anticancer drug candidates. Compared to acronycine these compounds were markedly more potent, both in terms of cytotoxicity and antitumor activity. The biological activity of these compounds was strongly related with their ability to give covalent adducts with purified as well as genomic DNA. Formation of those adducts involves alkylation of the exocyclic N-2 amino groups of guanines exposed in the minor groove of double helical DNA by the carbocation produced by the elimination of the acyloxy leaving group at position 1 of the drug. A transesterification process of the ester group from position 2 to position 1 accounted for the intense activity of *cis*-1-hydroxy-2-acyloxy-1,2-dihydrobenzo[*b*]acronycine derivatives. *Cis*-1,2-diacetoxy-1,2-dihydrobenzo[*b*]acronycine, which displays a particularly impressive broad antitumor spectrum, is currently developed by Servier Laboratories under the code S23906-1.

Keywords: Acronycine; Acridone; Benzo[*b*]acronycine; S-23906; DNA Alkylation; Guanine

1. Introduction

Acronycine (**1**) is a natural alkaloid, which was first isolated in 1948 from the stem bark of a small Australian Rutaceous tree, *Acronychia baueri* Schott (= *Sarcomelicope simplicifolia* (Endl.) Hartley ssp. *simplicifolia*) [1,2]. The presence of a dimethylpyran ring fused onto an acridone basic skeleton in the alkaloid was early demonstrated, but it is only in 1966 that Macdonald and Robertson [3] gave unambiguous evidence for the angular 3,12-dihydro-6-methoxy-3,3,12-trimethyl-7*H*-pyrano-[2,3-*c*]acridine-7-one structure of acronycine.

Svoboda at the Eli–Lilly Laboratories first demonstated in 1966 that acronycine displayed a large spectrum of activity against a panel of murine solid tumor models, including S-180 and AKR sarcomas, X-5563 myeloma, S-115 carcinoma and S-91 melanoma [4,5]. In contrast, the alkaloid only exhibited a marginal activity against leukemias. The activity against X5563 myeloma seemed particularly interesting, since this plasma cell tumor has several properties that relate to those of multiple myeloma in human patients. This is the reason why Scarffe [6] in 1983 performed phase I–II clinical evaluation of acronycine in patients with refractory multiple myeloma. Oral acronycine capsules produced one clear response in 16 patients. The remission was maintained 72 weeks, using daily dose of 300 mg/m^2. The limited success of this experiment was probably related to the moderate potency of acronycine and to its very low water-solubility (ca. 2–3 mg per liter of water), which did not permit an efficient parenteral formulation of the drug. However, this therapeutic trial, as well as more recent results [7,8], confirmed that acronycine exhibits interesting antitumor properties.

Despite its promising biological activities, the mechanism of action of acronycine at either cellular or molecular level has not yet been clearly established, most probably due to its moderate potency. Indeed, first observations suggested that the drug did not interact with DNA but acted primarily by alteration of subcellular organelle membranes and that its

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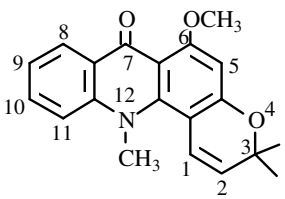
delayed effects were due to interference with the structure, function, and turnover of cell-surface components [9–12]. In contrast, more recent experiments suggested that an interaction of acronycine with DNA occurred by some non-covalent process able to stabilize the double helix against thermal denaturation [7].

The interesting antineoplastic potential of acronycine encouraged the synthesis of different series of analogues, but none of the compounds prepared during the first 25 years following the discovery of the biological properties of acronycine presented a better pharmacological profile than the parent compound [13]. Nevertheless, the examination of the structure–activity relationships in the chemical series revealed that the 1,2-double bond in the pyran ring was an essential structural requirement to observe antitumor activity [13,14]. For instance, 1,2-dihydroacronycine (**2**) and 1,2-dihydro-2-nitroacronycine (**3**) were found inactive in the course of early in vivo experiments performed at the Eli–Lilly Laboratories [4]. In this context, the isolation of the unstable acronycine epoxide (**4**) from several New-Caledonian *Sarcomelicope* species led to a hypothesis of bioactivation of acronycine by transformation of the 1,2-double bond into the corresponding oxirane in vivo [15]. Indeed, the high reactivity of this epoxide, which readily reacts with water to give the corresponding *cis* and *trans* diols, suggested that this compound could be the active metabolite of acronycine, able to alkylate some nucleophilic target within the tumor cell [15]. Consequently, there was interest in the search for new acronycine derivatives modified in the pyran ring and having a similar reactivity at the benzylic position 1 toward nucleophilic agents as acronycine epoxide, but having an improved stability [16]. Several series of analogues, including *cis*- and *trans*-1,2-dihydroxy-1,2-dihydroacronycine diesters, exhibited marked antitumor properties with a broadened spectrum and increased potency when compared with acronycine [16–18]. Among these derivatives, *cis*-1,2-diacetoxy-1,2-dihydroacronycine (**5**) was selected for further investigation, but its preclinical development was subsequently discontinued for toxicological reasons [16–18].

2. Synthesis and antitumor activity of 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one derivatives

The suggestion that acronycine could interact with DNA, by some non-covalent process stabilizing the double helix against thermal denaturation [7], led to develop structural analogues with an additional aromatic ring linearly fused onto the acronycine basic skeleton [19–21]. Indeed, interaction with DNA is known to occur mainly for compounds with sufficiently large coplanar aromatic chromophores in several related series, such as acridines, anthracene-diones and pyridocarbazoles.

The strategy used to synthesize the pentacyclic 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one (benzo[*b*]acronycine) (**6**) basic skeleton derived from that described by Hlubucek et al. [22] for the synthesis of acronycine itself. Condensation of 3-amino-2-naphthalenecarboxylic acid (**7**) with phloroglucinol (**8**) gave 1,3-dihydroxybenzo[*b*]acridin-12-(5*H*)-one (**9**). Treatment of **9** with 3-chloro-3-methylbut-1-yne afforded 6-hydroxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin7-one (**10**), through Claisen rearrangement of the corresponding intermediate dimethylpropargyl ether. Methylation of **10** with dimethyl sulfate finally furnished the desired benzo[*b*]acronycine (**6**) [23]. The corresponding racemic *cis*-diol **11** was easily obtained by catalytic osmic oxidation of benzo[*b*]acronycine (**6**) [23]. The racemic *trans* isomer **12** was prepared in two steps. Permanganate oxidation of **6** first led to 2-hydroxy-1-oxo-1,2-dihydrobenzo[*b*]acronycine (**13**). Sodium borohydride reduction of this latter compound afforded *trans*-1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine



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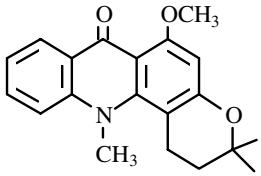

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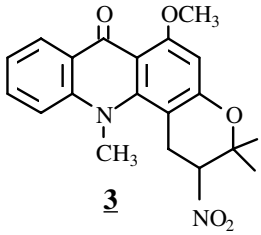

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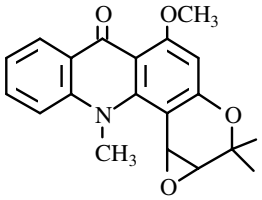

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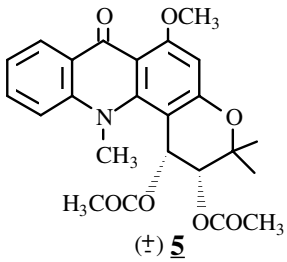
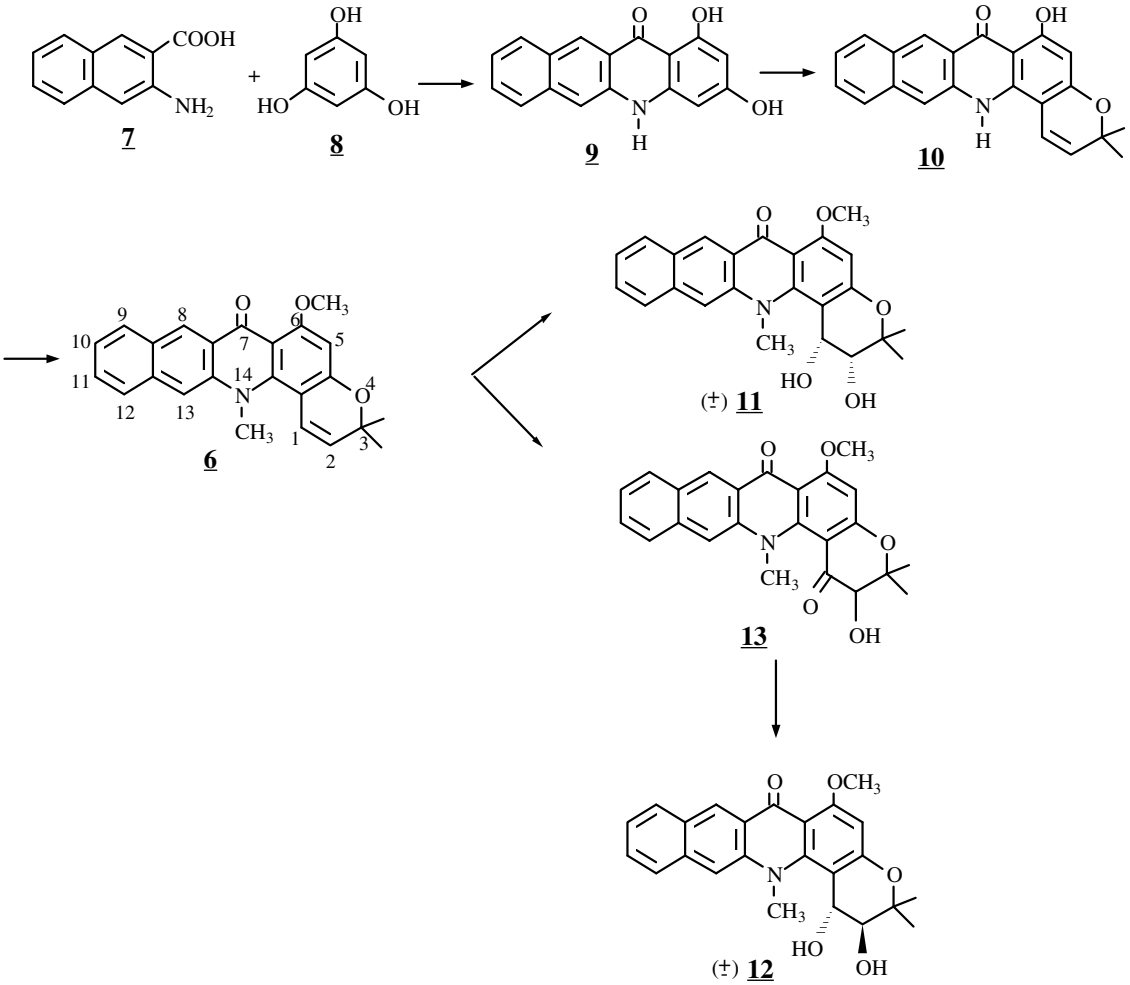


(±) **5**



(**12**) [24]. Treatment of diols **11** or **12** with an excess of acyl anhydride or acyl halide gave the corresponding diesters. When only one equivalent of acylating reagent was used, monoesters at the less hindered 2-position were obtained in good yield and with an excellent regioselectivity. A second acylation reaction performed on those monoesters gave an access to mixed diesters. Finally, reaction of the racemic *cis*-diol **11** with *N,N′*-carbonyldiimidazole afforded the corresponding cyclic carbonate **14** [23–25].

Cis- and *trans*-1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters **14–26** were first studied in vitro on L1210 leukemic cells (Table 1). Compared to acronycine and related tetracyclic diesters, compounds **14–26** were markedly more potent, the most cytotoxic derivative, compound **14**, being 1000-fold more potent than acronycine in inhibiting L1210 cell proliferation. The potency of compound **14** is noteworthy, being in the range of the most active cytotoxic drugs currently used in cancer chemotherapy, such as anthracyclines or camptothecin derivatives. The antitumor activity of the tetracyclic acronycine derivatives was revealed on the murine C38 colon adenocarcinoma [16], and induction of tumor regression in this model was subsequently shown to be

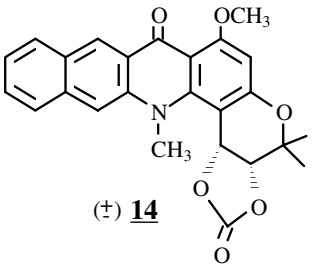
Table 1
Cytotoxicity of compounds **14–32** in comparison with acronycine (**1**)

Compound	Cytotoxicity IC_{50} (μM)/L1210
1	23
14	0.014
15	0.8
16	0.6
17	0.15
18	1.3
19	0.7
20	1.3
21	1.6
22	0.5
23	0.2
24	2.1
25	0.9
26	0.6
27	17
28	45
29	0.6
30	1.9
31	1.1
32	0.5

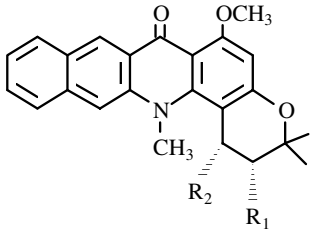
Table 2
Antitumor activity of compounds **15, 17** and **25**

Compound	Tumor growth, % (dose i.v. mg/kg) (colon 38 S.C.)
15	0 (6.25)
17	0 (12.5)
25	0 (25)

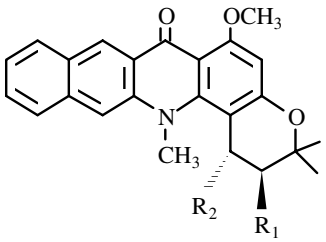
a good indicator of a marked antitumor activity of acronycine derivatives in more relevant orthotopic models of human solid tumor [26]. Consequently, 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters were evaluated in vivo on mice bearing established C38 colon adenocarcinoma. The most potent compounds (**15, 17** and **25**) were highly active, induc-



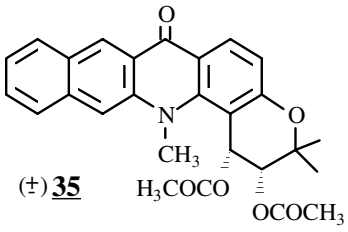
(±) **14**



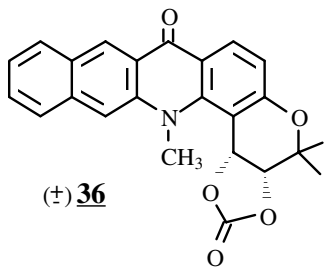
(±) **15** $R_1 = R_2 = OCOCH_3$
(±) **16** $R_1 = R_2 = OCOCH_2CH_3$
(±) **17** $R_1 = R_2 = OCOCH_2CH_2CH_3$
(±) **18** $R_1 = R_2 = OCOCH_2CH_2CH = CH_2$
(±) **19** $R_1 = R_2 = OCOCH_2CH(CH_3)_2$
(±) **20** $R_1 = R_2 = OCOCH_2CH_2COOH$
(±) **21** $R_1 = R_2 = OCOCH_2CH_2CH_2COOH$
(±) **22** $R_1 = OCOCH_2CH(CH_3)_2$ $R_2 = OCOCH_3$
(±) **23** $R_1 = OCOC_6H_5$ $R_2 = OCOCH_3$
(±) **24** $R_1 = OCOCH_2CH_2COOH$ $R_2 = OCOCH_3$
(±) **25** $R_1 = OCOCH_2CH_2CH_2COOH$ $R_2 = OCOCH_3$
(±) **27** $R_1 = OCOCH_3$ $R_2 = H$
(±) **28** $R_1 = OCOCH_3$ $R_2 = OCH_3$
(±) **29** $R_1 = OCOCH_3$ $R_2 = OH$
(±) **30** $R_1 = OCOCH_2CH(CH_3)_2$ $R_2 = OH$
(±) **31** $R_1 = OCOCH_2CH_2CH_3$ $R_2 = OH$
(±) **32** $R_1 = OCOCH_2CH_2CH = CH_2$ $R_2 = OH$
(±) **33** $R_1 = OH$ $R_2 = OCOCH_3$



(±) **26** $R_1 = R_2 = OCOCH_3$
(±) **34** $R_1 = OCOCH_3$ $R_2 = OH$



(±) **35**



(±) **36**

ing a significant rate of complete regressions (Table 2) [23–25].

From this series, the *cis*-diacetate **15** has been selected by Servier Laboratories for further development under the code S23906-1, since it displays a particularly impressive broad antitumor spectrum. Indeed, when evaluated against aggressive orthotopic models of human ovarian (IGROV1 and NIH:OVCAR-3), lung (NCI-H460 and A549) and colon (HT29 and HCT116) carcinomas, compound **15** demonstrated comparable and/or better activity than paclitaxel, vinorelbine and irinotecan, respectively [21,26]. In addition, compound **15** displayed similar antitumor activities when administred either i.v. or orally [21].

3. Mechanism of action of 1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one diesters

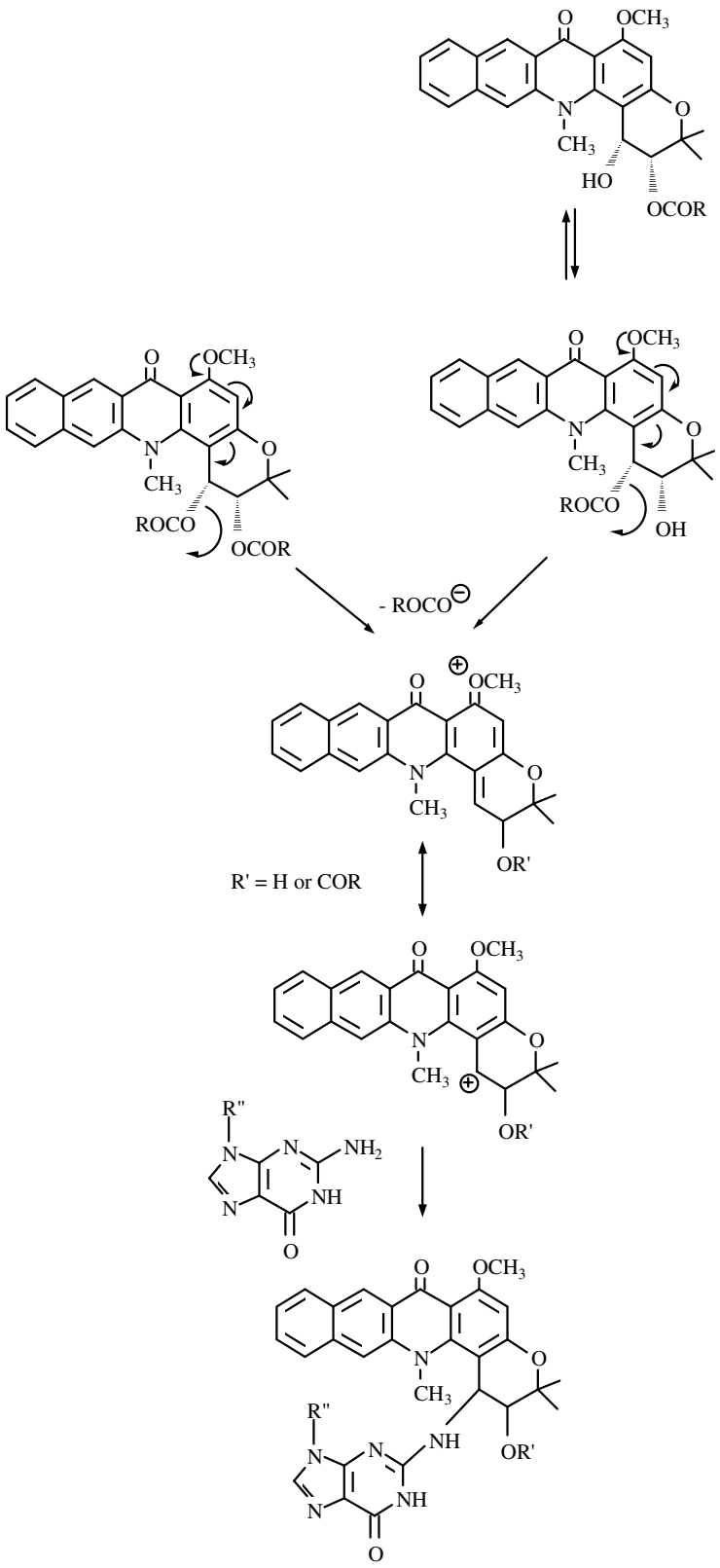
At the cellular level, S23906-1 induced an irreversible S-phase blockade of the cell cycle and efficiently triggered apoptosis in several cancer cell types [14,23,27,28]. It also caused irreversible inhibition of DNA synthesis. A short treatment with S23906-1 was sufficient to induce an increase of the cyclin E level in HT-29 cells which were arrested in S-phase and subsequently underwent apoptosis [27].

At the molecular level, diesters of 1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one were first shown to bind covalently both with purified DNA fragments and with genomic DNA extracted from treated tumor cells [24,29]. The base selectivity for alkylation was determined using synthetic duplex oligonucleotides containing a unique set of guanine–cytosine (G•C), adenine–thymine (A•T), or inosine–cytosine (I•C) base pairs [24,29]. Adducts were characterized by polyacrylamide gel shift retardation and/or fluorescence assay. This series of experiments demonstrated that 1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one diesters readily alkylated G•C base pairs, but failed to alkylate A•T and I•C base pairs. The I•C base pair only differs from the G•C base pair by the lack of the NH_2 group at position 2 of guanine, which is exposed in the minor groove of DNA. Therefore, 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters should be considered as specific alkylating agents of the exocyclic NH_2 group of the guanine [29]. In addition, the study of the structure–activity relationships indicated a strong correlation between DNA alkylation by the various 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters and their respective cytotoxic potential [24]. Additional evidence for guanine alkylation was obtained by mass spectrometry of the adducts obtained using short 7-base pairs hairpin oligonucleotides with selected diesters (i.e., **15**). The adducts of highest molecular weight observed corresponded to the addition of one molecule of drug, and to the loss of one acyloxy group when the oligonucleotide contained one guanine unit, and to the addition of three molecules of drug and to the loss of three acyloxy groups when the oligonucleotide contained three guanine units [29]. Involvement of the ester group at position 1 of the drug in the alkylation of DNA guanine units was deduced from the structure–activity relationships in the benzo[*b*]acronycine series. Indeed, all 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters prepared to date exhibited both DNA alkylating and cytotoxic properties. In contrast, structural analogues without ester leaving group at position 1, such as 2-acetoxy-1,2-dihydrobenzo[*b*]acronycine (**27**) or *cis*-2-acetoxy-1-methoxy-1,2-dihydrobenzo[*b*]acronycine (**28**) were inert towards DNA alkylation and were devoid of significant cytotoxic properties (Table 1).

1,2-Dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters were also recently shown to bind covalently with the tripeptide glutathione (GSH) acting as a nucleophile [30,31]. Formation of adducts with nucleophilic thiols had been previously described for the tetracyclic *cis*-1,2-diacetoxy-1,2-dihydroacronycine (**5**), which readily reacted with benzylmercaptan [16]. All the above data were in full agreement with the initial hypothesis, which postulated that active acronycine derivatives were able to alkylate nucleophilic targets in the tumor cell [15].

4. Activity and mechanism of action of 2-acyloxy-1-hydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one derivatives

In the course of the study of the structure–activity relationships in the benzo[*b*]acronycine series, *cis*-1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine monoesters at position 2, exemplified by acetate **29**, isovalerate **30**, butanoate **31** and pentenoate **32**, were surprisingly shown to exhibit cytotoxic activities within the same order of magnitude as the corresponding diesters, despite the lack of an ester leaving group at position 1 (Table 1) [24]. In vivo, antitumor activities similar to that of diester **15** were obtained with monoesters **29–32** [24]. The fact that compounds without a leaving group at position 1 possessed marked cytotoxic and antitumor activities could lead to the conclusion that DNA alkylation was not involved in their mechanism of action. Nevertheless, a series of gel retardation experiments performed on monoesters **29–32** demonstrated that these compounds were also able to link covalently to DNA. Mass spectral analysis revealed that the molecular weight of the adducts obtained with 7-base pairs hairpin oligonucleotides differed by one acyl group per alkylated guanine residue from those of the heaviest adducts obtained with the corresponding diesters. These results strongly suggested that *cis*-monoesters at position 2 could spontaneously lead to the corresponding more reactive *cis*-monoesters at position 1, by a transesterification process. Indeed, this reaction could explain the similar reactivity observed in both series and the difference of molecular mass of the adducts obtained with



Scheme 1

DNA. Experimental evidence for spontaneous transesterification was obtained through NMR study of *cis*-monoacetate **29**. When kept at 20 °C in DMSO containing 15% D_2O, the ^1H NMR data of **29** evolved, revealing an equilibrium between the 2-monoacetate **29** and the 1-monoacetate **33** under those conditions [24,31]. A stable 80:20 equilibrium between **29** and **33** was obtained within 48 h, and did not evolve further when the duration of the experiment was increased.

5. Conclusion

In conclusion, the mechanism of action of both diesters **14–26** and monoesters **29–32** is summarized in Scheme 1. In good agreement with this statement, the *trans* monoester **34**, in which intramolecular transesterification into the corresponding monoester at position 1 is not possible, was markedly less potent and less active in vivo than its *cis* counterpart **29**. The electron-donating methoxy group at C-6, which facilitates the formation and stabilization of a carbocation at the benzylic position 1 has a marked influence on the activity. Indeed, diesters without methoxy group at C-6, exemplified by diacetate **35** and carbonate **36**, exhibited weaker cytotoxic activities than their methoxy counterparts **14** and **15**, and showed almost no reactivity towards both purified and genomic DNA.

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