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Synthesis and Cytotoxic Activity of Acetogenin Analogues

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Abstract—A set of 16 new simplified analogues of acetogenins has been designed based on: (i) the replacement of the bis THF moiety of these natural products by an ethylene glycol bis ether unit; (ii) the introduction of different lipophilic side chains (alkyl, aryl, dialkylamino, *O*-cholesteryl); (iii) the presence of the same terminal isolactone. In vitro cytotoxic activity against L1210 leukemia is reported.

Annonaceous acetogenins display various potent biological activities (cytotoxic, pesticidal, immunosuppressive, antimicrobial,...).[1] Impressive cytotoxicities as low as 10^{-13} μg/mL have been reported against various tumor cell lines,[1] including multidrug resistant ones.[2] The potent cytotoxic properties of acetogenin derivatives is mainly due to inhibition of mitochondrial NADH: ubiquinone oxido-reductase[3] and/or of an NADH oxidase[4] of the cytoplasmic membrane. The structures of the most active members of this large family of natural products are characterized by the presence of a terminal linear side chain and one to three THF rings connected via an intermediate linear chain (eventually functionnalized by hydroxyl or keto groups) to a terminal lactone moiety. Several types of lactones are known, the most active being the β-hydroxyalkyl butenolide found, for example, in bullatacin **1**.[5] However, an easy rearrangement to ketolactones (usually obtained as an unseparable thermodynamic 2:1 mixture of 2,5-*cis* and 2,5-*trans* isomers) has been observed under mild hydrolytic conditions.[6] The latter, such as bullatacinone **2**,[5] are less potently cytotoxic, and toxicity,[7] a main limitation to the therapeutic use of acetogenins, is markedly reduced compared to the former acetogenins.

Taking into account the limited availability (either by plant extraction or by total synthesis) of bis-THF aceto- and genins, it seemed worthwhile to prepare simplified analogues bearing the same key features. First, the replacement of the bis-THF moiety by an ethylene glycol bis-ether unit has been considered. This strategy retained only two stereogenic centers (instead of 6) in the central part of the target compound and both enantiomeric synthons could be prepared. These analogues have been designed to incorporate different lipophilic terminal side chains (*n*-alkyl, aryl, dialkylamino, *O*-cholesteryl) and the same ketolactone moiety. Their synthesis and preliminary results of their cytotoxic activity are now reported.

The seven-step preparation of enantiomerically pure alkynes (+)-**3a**–**i** and (−)-**3a**–**i** from solketal has been recently described.[8] After fluoride induced desilylation,[9] Sonogashira coupling with 1 equiv of lactone synthon **5**[10] afforded in 18–81% yield the desired enynes **6a**–**g** and **7a**–**g**. Hydrogenation (H_2, Pd/C or PtO_2) gave the target acetogenin analogues **8a**–**g** and **9a**–**g** in 59–92% yield. Indeed, carbonyl reduction was observed in three cases leading to mixtures of lactone alcohols **10** and **11** (in equilibrium with the other possible butanolide through translactonization).

The panel of 16 acetogenin analogues thus obtained has been tested against L1210 leukemia cells in vitro (Table

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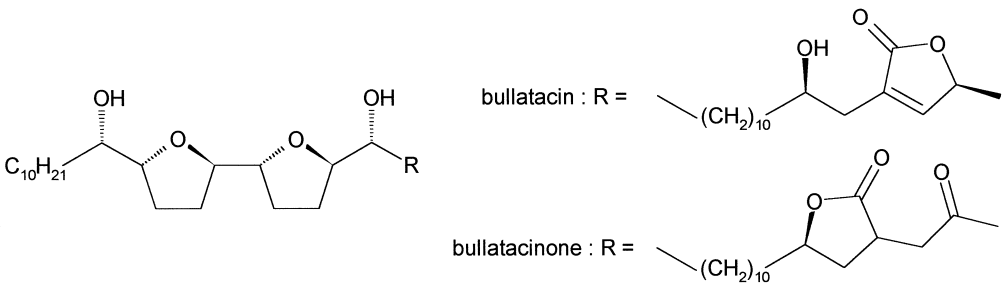


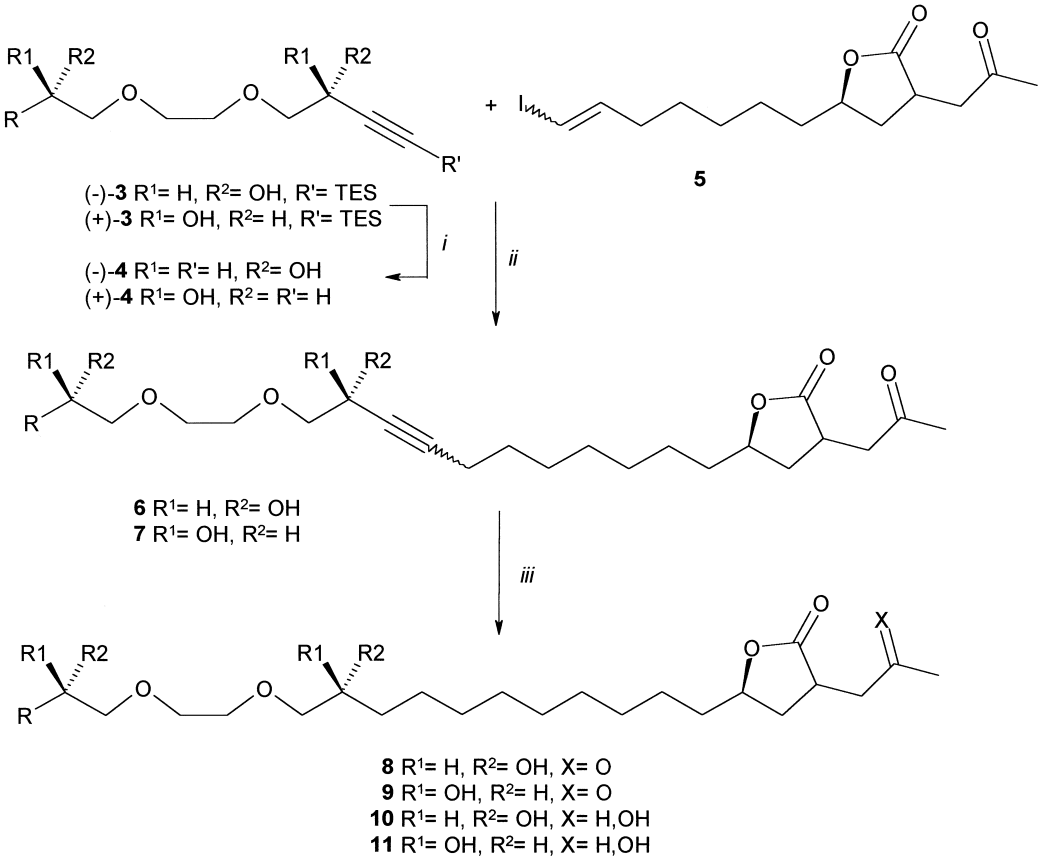
2), and the activity was compared to doxorubicin and known acetogenins (Table 1).[11]

Cytotoxicity of these simplified acetogenin analogues turns out to be lower than for bullatacinone. Indeed, several trends should be pointed out: no significant differences are observed between both series (**6** and **7**) for similar side chains; phenyl or (*para* substituted phenyl) and piperidinyl side chains lead to lower activity than more lipophilic ones such as *n*-decyl, naphthyl, *N*-dialkylamino or *O*-cholesteryl; ketone reduction seems to have little effect (see **11e** versus **7e**).

Overall, these results indicate that the terminal lactone moiety confers limited potency to annonaceous acetogenins in contrast to the THF nucleus. This may strengthen the hypothesis of required U-shaped conformation of the polyoxygenated moiety of acetogenins either for interaction with cell membranes[12] and/or with metal ions[13] since replacement of the THF rings by the ethylene glycol bis-ether leads to more conformationnally mobile compounds. Taking into account this hypothesis the synthesis and biological evaluation of conformationnally restricted, but yet simplified, analogues is underway.

Table 1. IC_{50} (μM) of doxorubicin and acetogenins (L1210)

Compound	IC_{50}
Doxorubicin	0.025
Annonacin	0.042
Bullatacin	0.0004
Bullatacinone	0.016



Scheme 1. (i) 1.3 equiv TBAF, THF, rt, 3 h, 15–84%; (ii) : 1 equiv **5**, 0.1 equiv $Pd(PPh_3)_2Cl_2$, 0.38 equiv CuI, 10 eq. *i*-Pr_2NH, PhH, 2 h, rt, 16–81%; (iii) 1 atm H_2, cat. 10% Pd/C (or cat PtO_2 for amine derivatives), AcOEt, 4–6 h, rt, 58–92%.

Table 2. IC_{50} (μM) of acetogenin analogues (L1210)

R	Compound	IC_{50}	Compound	IC_{50}
n-$C_{10}H_{21}$	**6a**	3.5	**7a**	1
Ph	**6b**	19.8	**7b**	21.6
p-$MeOC_6H_4$	**6c**	>10	**7c**	32
p-$CF_3C_6H_4$	**6d**	3.3	—	—
2-Nph	**11e**	2.1	**7e**	3
Bu_2N	**6f**	3.9	**7f**	2.5
Oct_2N	**6g**	3.7	—	—
N-piperidinyl	**6h**	28.7	**11h**	23.3
3-*O*-cholesteryl	**6i**	2.8	**11i**	12.2

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9. Unoptimized isolated yields are given. All new compounds have been characterized by ^1H, ^{13}C NMR and FAB HMRS. Optical rotations have been measured for final compounds. All lactones exist as a 2:1 thermodynamic mixture of cis and *trans* isomers.

10. Synthon **5** (c.a. 2:1 E:Z ratio, ee 86%) has been prepared in 9 steps from 1,7-octadiene (Warmerdam, E.; Rodier, S.; Renoux, B.; Gesson, J.-P. unpublished results).

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