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Synthesis and biological activity of polyalthenol and pentacyclindole analogues

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ABSTRACT

A series of indole sesquiterpenes analogues of polyalthenol and pentacyclindole have been synthesized starting from *ent*-halimic acid in order to test their biological activity. These analogues include diverse oxidation levels at the sesquiterpenyl moiety and different functionalization on the indole ring. All synthetic derivatives were tested against a representative panel of Gram positive and Gram negative bacterial strains, and the human solid tumour cell lines A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast) and WiDr (colon). Overall, the compounds presented activity against the cancer cell lines. The resulting lead, displaying a polyalthenol scaffold, showed GI_{50} values in the range 1.2–5.7 μM against all cell lines tested.

1. Introduction

Polyalthenol and pentacyclindole (Fig. 1) are two indole sesquiterpenes present in Nature that display significant biological activity including antimicrobial activity. Polyalthenol was isolated in 1976 from the African plant *Polyalthia oliveri* Engl. Diels (=*Greenwayodendron oliveri* Verd.) [1] and exhibits activity against clinical isolates of *Staphylococcus aureus* with a MIC_{90} of 8 μg/mL [2]. Pentacyclindole, isolated in 2010 along with polyalthenol from *Polyalthia suaveolens* (=*Greenwayodendron suaveolens*), demonstrated a MIC_{90} of 4 μg/mL [2].

In the past, our research group started diverse synthetic studies on terpene alkaloids such as (+)-agelasine C [3] and (+)-thiersindole C [4] (Fig. 2) among others. In the past few years, we have focused our attention into indole sesquiterpenes. We have reported earlier the synthesis of two polyalthenol analogues: 12-epi-*ent*-polyalthenol and 12,19-bisepi-*ent*-polyalthenol, and the pentacyclindole epimer 12-epi-*ent*-pentacyclindole [5]. Furthermore, we demonstrated the biogenetic relationship between polyalthenol and pentacyclindole that had been proposed by Williams et al. [2]

As a follow up of our previous work, herein we report on the synthesis and the biological evaluation of a series of indole sesquiterpenes analogues of polyalthenol and pentacyclindole. As a model system to study the biological activity we selected antibacterial and anticancer assays. With the results of the biological tests some structure–activity relationships (SARs) could be inferred.

2. Chemistry

For the synthesis of all indole sesquiterpenes analogues described herein we used *ent*-halimic acid as starting material [6]. The synthetic methodologies have been previously tuned up by our group in the synthesis of indole diterpenes and sesquiterpenes [3–5,7].

2.1. Analogues of polyalthenol

As it has been said before starting from *ent*-halimic acid, the synthesis of different polyalthenol analogues was achieved and the

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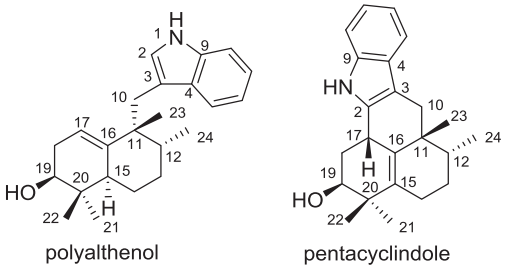


Fig. 1. Structures and stereochemistry of natural indole sesquiterpenes polyalthenol and pentacyclindole.

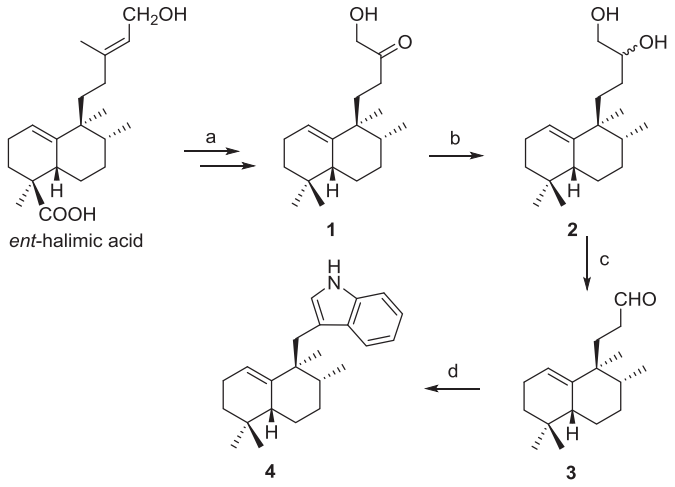
compounds were classified into: 1. C-3 desoxygenated polyalthenol analogues, 2. Analogues functionalised in the indole ring, 3. 2-methylindole analogues and 4. Polyalthenol analogues as starting materials for the synthesis of PLA2 inhibitors. Next, the synthesis of these compounds will be described in detail.

2.1.1. C-3 desoxygenated polyalthenol analogues

The first compound synthesized is a C-3 desoxygenated analogue of polyalthenol, which preparation, starting from *ent*-halimic acid, is depicted in Scheme 1. After degradation to the corresponding dinor derivative and reduction of the carboxylic group to obtain compound **1** [5,8], a further degradation to the trinor derivative aldehyde **3** is needed. This is carried out by reduction of **1** with $NaBH_4$ and reaction of the resultant diol **2** with $Pb(OAc)_4$. Then, a Fischer indolization of aldehyde **3** with phenylhydrazine in AcOH afforded the C-3 desoxygenated polyalthenol analogue **4**.

2.1.2. Analogues functionalised in the indole ring

Performing Fischer indolization reactions on aldehyde **5** using a variety of differently functionalised phenylhydrazines [9] and phenylhydrazines hydrochlorides [10] yields to the corresponding indole derivatives **6**–**15** shown in Scheme 2. Compound **5** is an important synthetic intermediate already used by our group in the synthesis of polyalthenol, pentacyclindole and a wide variety of bioactive natural products [4,5]. The synthesized polyalthenol



Scheme 1. a) See Refs. [5,8]; b) $NaBH_4$, 97%; c) $Pb(OAc)_4$, 95%; d) Phenylhydrazine, AcOH, 58%.

analogues **6**–**15** are also the synthetic precursors of the pentacyclindole analogues that we aim to obtain.

2.1.3. 2-Methylindole analogues

Analogous reactions can be performed on methylketone **16** instead of aldehyde **5** to obtain, this way, the corresponding 2-methylindoles. These compounds would permit us to obtain both a new series of polyalthenol analogues and suitable precursors for developing a series of phospholipase A_2 inhibitors ($IPLA_2$) that will be briefly commented later.

In the same manner that compound **5**, previously obtained in our group, and transformed into different bioactive natural products [4], the methylketone **16**, was treated with the adequate phenylhydrazine or phenylhydrazine hydrochloride to afford 2-methylindoles derivatives **17**–**26**.

2.1.4. Polyalthenol analogues as starting materials for the synthesis of PLA_2 inhibitors

PLA_2 inhibitors such as efipladib, giripladib and ecopladib are compounds of enormous interest due to its biological activity, so their analogues [11]. One of the most important considerations that

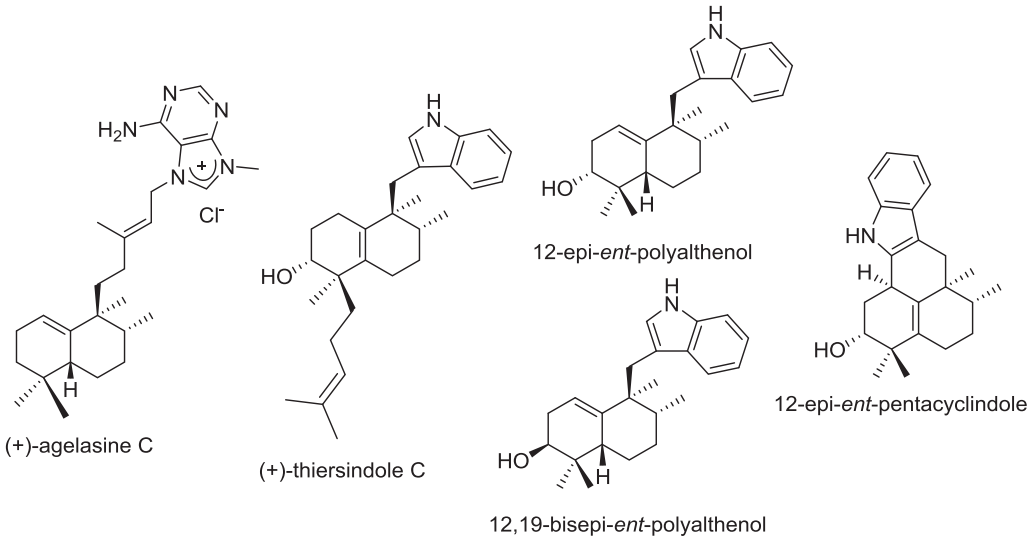


Fig. 2. Structures of (+)-agelasine C, (+)-thiersindole C and polyalthenol and pentacyclindole analogues.