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Synthesis and mechanistic studies of PLA$_2$ inhibition by the marine alkaloid Hyrtiosulawesine

Lydia Liew$^{a}$, Marie-Lise Bourguet-Kondracki$^{a}$ and Brent Copp$^{a}$

$^{a}$Department of Chemistry, The University of Auckland, Private Bag 92019, Auckland, NZ
$^{b}$ Laboratoire de Chimie et Biochimie des Substances Naturelles, MNHN, 57 rue Cuvier, 75005 Paris, France

Background

The first isolation of Hyrtiosulawesine 1 was from an Indonesian collection of the marine sponges Hyrtios erectus and H. reticulatus. The β-carboline alkaloid has also been re-isolated from a Red Sea collection and found to display anti-phospholipase A$_2$ (PLA$_2$) activity with an IC$_{50}$ value of 14 µM.$^2$

Phospholipase A$_2$ catalyses the hydrolysis of membrane phospholipids at the sn-2 position to generate arachidonic acids (AA).$^3$ AA are precursors to a large family of compounds known as the eicosanoids associated with inflammatory reactions.$^4$ PLA$_2$ inhibition by Hyrtiosulawesine would lead to a decrease in AA and proinflammatory eicosanoids, with anti-inflammatory effect.$^5$

Aims

- Hyrtiosulawesine 1 and a series of related model compounds will be synthesised via the proposed route.
- The inhibition mechanism of PLA$_2$ will be investigated. The target analogues are chosen to examine whether the presence of the polar hydroxy groups and/or the carbonyl linkage has any effect on activity.
- The reactivity of all synthesised compounds towards biomimetic nucleophiles will be investigated to establish whether Hyrtiosulawesine can act as an electrophilic equivalent inhibitor of PLA$_2$.

Retrosynthesis of Hyrtiosulawesine

Scheme 1. Retrosynthetic Pictet-Spengler disconnection.

The proposed retrosynthesis involves a Pictet-Spengler disconnection at the carbonyl linker to give tryptamine and indole glycolic fragments or a Bischler-Napieralski disconnection to tryptamine and indole glycolic acid fragments.

Scheme 2. General route for the synthesis of aldehydes required for Pictet-Spengler coupling and the carboxylic acids required for Bischler-Napieralski cyclisation.

A flexible route allows access to aldehyde and carboxylic acid functionality

Scheme 3. Synthesis of model compound 4 with phenylacetic acid.

Reagents and conditions: (i) PyBOP TSA, DMF, rt, 24 h; (ii) DDQ, DCM/MeOH, rt, 1 h.

In the initial model reaction, the amide 2 derived from tryptamine and phenylacetic acid was subjected to the Bischler-Napieralski reaction with phosphoryl chloride as the dehydrating agent. The reaction successfully yielded the dicyclo-β-carboline 4 with the ketone linker present was achieved with DDQ in DCM with traces of water present. At the same reaction was carried out under anhydrous conditions, the β-carboline with the methylene linker was observed instead.

The amide precursors 5 and 6 were synthesised for the Bischler-Napieralski cyclisation by coupling of tryptamine with the appropriate carboxylic acids. However, under similar reactions we were unable to obtain the desired dicyclo-β-carboline.


Reagents and conditions: (i) PyBOP TSA, DMF, rt, 24 h; (ii) DDQ, DCM/MeOH, rt, 1 h.

(i) Pictet-Spengler reaction

Reduction of indole glycol chloride yielded tryptophol 8 with manipulation of protecting groups afforded the tert-butylcarbonyl protected tryptophol 9. Aldehyde 10 was obtained by oxidation with IBX.


Reagents and conditions: (i) LAH, THF, reflux, 5 h; (ii) Acetic anhydride, pyridine, 5 h; (iii) di-tert-butyl dicarbonate, DMAP, DCM, 16 h; (iv) 2 M HCl, MeOH, H$_2$O, 4 h; (v) IBX, DMF, 2 h.

The Pictet-Spengler condensation reaction is a two step process, firstly requiring formation of a Schiff base before the second acid catalysed cyclisation step to form the tetrahydro-β-carboline scaffold. Coupling of tryptamine with aldehyde 10 under standard anhydrous conditions gave the expected product 11 and as well as a second product 12 resulting from aldol condensation. Subsequent manipulations of the reaction temperature during the intermediate step, solvent system, reaction concentration and basicity were not able to completely eliminate the aldol product.

Scheme 6. Pictet-Spengler reaction under standard anhydrous conditions.

Reagents and conditions: (i) Acetic acid, H$_2$O, 6 h; (ii) DDQ, DCM/MeOH, 40 min.

However, under aqueous Pictet-Spengler condensation conditions the desired tetrahydro-β-carboline 13 was obtained with concomitant deprotection of the indolic nitrogen and with no aldol product. The tetrahydro-β-carboline was then subjected to oxidation with DDQ to yield the fully aromatised β-carboline 14 with the ketone linker B is our aim to be able to utilise the reactions as presented to complete the synthesis of hyrtiosulawesine and target analogues.

Scheme 6. Pictet-Spengler reaction under aqueous conditions.

Reagents and conditions: (i) Acetic acid, H$_2$O, 6 h; (ii) DDQ, DCM/MeOH, 40 min.

Mechanistic studies (Future steps)

A number of marine metabolites have been shown to have potent in vitro and in vivo potent anti-inflammatory activity by inhibition of specific secretory phospholipase A$_2$ including bee venom (b), Apa rapi and human synovial phospholipase A$_2$. In this study, the PLA$_2$ enzyme is the major GPCR since it has shown good correlation with the human secretory counterpart.$^1$ The study will aim to discover if there are any interactions between our target analogues and the PLA$_2$ enzyme. Biomimetic reactions would be carried out on our target analogues to determine which functional group confers anti-inflammatory activity. Subsequently, we would like to identify the nature of the interaction followed by observing where the interaction has occurred in the enzyme.

References


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