SYNTHESIS OF 6-TERT-OCTYL AND 6,8-DITERT-BUTYL COUMARINS, TWO COUMARINS OF BIOLOGICAL INTEREST

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ABSTRACT

In this study, the synthesis of new coumarins with aliphatic chains is discussed. The incorporation of the 6-tert-octyl and 6,8-diter-t-butyl chains into a coumarin structure from alkylphenols, allows obtaining hydrophobic coumarins with good yields. These coumarins can be potential modulators of TRPV1 receptors. Synthesis and spectroscopic data of these new coumarins are analyzed.

Keywords: Coumarins, Alkylcoumarins, TRPV1.

INTRODUCTION

The past ten years have seen the emergence of specific small molecule antagonists targeting receptors on sensory neurons that detect painful stimuli.1 Among these new therapeutic targets, TRPV1 has attracted the most attention.2 TRPV1 (formerly known as the vanilloid receptor VR1) is probably still best recognized as the receptor for capsaicin (Figure 1, I), which is responsible for the piquancy of hot chili peppers.3 The search of new modulating ligands of TRPV1 receptors, agonists or antagonists, constitutes a strategy in the development of new drugs for the pain treatment.4

Coumarins constitute a group of natural compounds, widely distributed in the plant kingdom.5 Some coumarin derivatives are also known to act beneficially on human health due to their therapeutic effects such as inhibitory activities against various tumor cells, mycobacteria, antioxidant, antihyperglycemic, antifungal, and anti-asthmatic, which have been extensively studied in the medical and pharmaceutical fields for the treatment of human diseases.5

Previous studies have demonstrated that some coumarins exert an antinociceptive action. Scopoletin (Figure 1, I) isolated from the Polygala sabulosa plant has shown a high nociceptive activity in mice, that have been induced visceral pain.6 Muralatin R (Figure 1, II) was found to be capable of activating the transient receptor potential vanilloid 1 (TRPV1) channel through desensitization mechanism.7

The incorporation of hydrophobic chains in the coumarin structure allows to observe the conformational effect of both chains in the modulation with the TRPV1 receptor. The amide function will be linked by derivatization of the methyl ester group at R3 position, by direct substitution with primary amines or through an acid chloride and subsequent substitution. In addition, the dipole moment has been increased and new hydrogen receptors region have been incorporated on the molecule.

Compounds analogous to Capsaicin have been designed and synthesized by several research groups for studies with the TRPV1 receptor.4 Our working group has designed and synthesized structures analogous to capsaicin, which incorporate an increasing the conformational restriction on the amide bond. (Figure 2, III, region: A) with the incorporation of the heterocyclic, such as the azoles8 or a chalcone9 (Figure 2; IV and V respectively) and the action of these molecules in transfected mouse cells have been studied to evidence the efficiency of the chemical structure on the TRPV1 receptor.9,10

In this work the synthesis of new coumarins is reported, which incorporate both greater conformational restriction in B region of Capsaicin (Figure 2, VI) and hydrophobic units in the coumarin structure.

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Figure 1. Chemical structures modulating the TRPV1 receptor.

Figure 2. Compounds with conformational restrictions.

EXPERIMENTAL

All solvents and reagents were purchased from Merck and Aldrich Companies. Experiments 1H-NMR and 13C-NMR were carried out in a Bruker Ascend T 400 MHz multicore equipment, at room temperature with deuterated solvents of CDCl3 and DMSO. The chemical displacements are informed in delta units in parts per million (δ ppm), relative to the internal TMS standard. Fusion points were determined in a hot plate capillary fusion equipment. IR spectra were recorded on a Nicolet Nexus 470 FTIR instrument.
Synthesis of 2-hydroxy-3,5-diter-butylbenzaldehyde.

Formylation of diert-butylphenol with hexamethylenetetramine in acid medium were implemented according to Duff formylation method.11

A mixture of 10.42 g (5.02 x 10–3 mol) of 2,4-diter-butylphenol and 14.02 g (100 mmol) of hexamethylenetetramine in 50 ml of glacial acetic acid was stirred at 118°C for 3 h. Then, reaction mixture was cooled to room temperature, and a solution of 12.4 ml HCl 5 M is added slowly. The resulting solution was again heated to the same temperature (118°C) for half an hour. After cooling, the mixture was extracted with 100 ml of hexane (2x 50 ml).

The organic phase (n-hexane) was washed with 20 ml of water and 10 ml of a saturated solution of sodium chloride. Then, this organic phase was filtered by a thick silica gel column chromatography, which was successively washed with hexane (4x50 ml). The combined organic phase was concentrated in a rotary evaporator to afford 8.25 g of 2-hydroxy-3,5-diter-butylbenzaldehyde (yield: 73.2%); Pt: 42°C, Rf = 0.85 (20% ethylacetate/n-hexane); FTIR (KBr, v cm–1): 2958.5; 2872.1; 2743.0; 1650.4 (CO), 1470.0; 1375.3; 1260.7; 1212.6; 1169.4; 1137.3; 1084.4 (CO), 1006.0, 1150.4;1H-NMR (400 MHz, CDCl3); δ = 10.90 (1H, s, -OMe), 9.91 (1H, s, -CHO), 7.58 (1H, d, J = 12 Hz, 9H, s), 7.50 (1H, d, J = 4 Hz), 6.94 (1H, d, J = 8 Hz), 1.75 (2H, d, J = 4 Hz), 0.75 (9H, s, t-Bu), 13C-NMR (100MHz, CDCl3); δ = 196.86, 159.43, 141.80, 135.48, 130.51, 119.98, 116.98, 56.65, 37.96, 32.95, 31.84, 31.47.

Synthesis of 2-hydroxy-5-tert-octylbenzaldehyde.

Formylation of tert-octylphenol was carried out according to the Levin’s formylation method.12

Solid magnesium wires (2.0 g, 80 mmol) are added to a mixture of methanol (37.3 ml) and toluene (16.0 ml), then magnesium methoxide drops are added. The mixture is stirred at reflux temperature until the disappearance of solid magnesium. Then, 4-tert-octylphenol (26.8 g, 0.13 mol) is added to the reaction flask and is kept under stirring for an approximate 65%.

The mixture is cooled to room temperature and sulfuric acid (20%, 80 ml) is added to a round-bottomed flask containing 20 ml of water and extracting with ethyl acetate (2x20 ml), and the organic phases are concentrated. The reaction products are separated on a chromatographic column using Silicagel G and as eluent a solution of increasing concentration of ethyl acetate in n-hexane. After purification 210 mg of the compound is obtained (yield 64%); Rf = 0.57 (20% Ethylacetate/n-hexane); IR (KBr, v cm–1) 2964.5, 1706.2, 1742.8, 1621.3, 1581.5, 1469.8, 1342.1, 1246.4, 1206.0, 1150.4;1H-NMR (400 MHz, CDCl3); δ = 8.58 (1H, s), 7.72 (1H, d, J = 0 Hz), 7.43 (1H, d, J = 0 Hz), 3.97 (3H, s, O-CH3), 1.53 (9H, s, t-Bu), 1.38 (9H, s, t-Bu);13C-NMR (100 MHz, CDCl3, ppm): δ = 164.05, 156.63, 152.15, 150.54, 147.23, 137.49, 129.92, 124.01, 117.85, 116.64, 57.65, 35.16, 34.71, 31.29, 29.78.

RESULTS AND DISCUSSION

The synthesis of hydrophobic coumarins was performed according to the retrosynthetic methodology shown in Scheme I. The corresponding alkyl aldehydes were obtained by the Levin and Duff synthesis methodology.

Scheme I. Retrosynthesis of coumarins.

The Levin formylation method uses a magnesium salt to obtain an ortho formyl group.12 The salt is formed by dissolving magnesium in the phenol. According to the proposed mechanism (Scheme II), the magnesium salt formed (bisphenoxy) subsequently reacts with formaldehyde dissolved in toluene. Methanol is extracted in a toluene/methanol azeotropic mixture. The product is obtained by an acid work-up to generate the corresponding alkyl salicylaldehyde by approximately 65%.

Scheme II. Proposed mechanism for the Levin formylation.

The Levin methodology applied in the formylation of 2,4-diter-butylphenol gives a low yield, probably because of increasing the steric factors around the hydroxyl group in the formation of the magnesium salt, so the synthesis route was modified by applying the Duff formylation methodology. This synthetic way11 considers obtaining aldehydes from a phenol (or alkylphenol) (Scheme III), by reacting 2,4-diter-butylphenol with hexamethylenetetramine in acetic acid medium. The reaction in these conditions provides aldehyde with a yield of 75%.
CONCLUSIONS

An attractive synthesis route has been designed in order to prepare hydrophobic coumarins using alkylphenols. The intermediate aldehydes and the coumarins were obtained with good yields and high purity under smooth reaction conditions. 6-alkyl and 6,8-dialkyl coumarins such as their corresponding aldehydes were completely characterized by spectroscopic techniques, allowing to identify the characteristic signals. Thanks to this route, the access to a wide set of alkyl coumarins is very important to study their conformational restrictions and evaluate their biologic properties. In addition, it is important to underline that their biological activities are under study and their data will be subsequently informed.

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