Synthesis of new possible monoamine oxidase inhibitors.

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Abstract:

We have generated different resveratrol-coumarin hybrids with the aim of evaluate their biological applications and their pharmacological properties, particularly the inhibitory activity of monoamine oxidase enzyme. According to that, a first series of 3-aryl-4-hydroxycoumarins has been synthesized starting from aryl boronic acids and phenyliodonium zwitterions precursors by a palladium-catalyzed coupling reaction.

Keywords: coumarin, MAO, Suzuki reaction.

Introduction:

Coumarins are an important group of organic compounds from natural and synthetic origins which have different pharmacological activities as for example antibacterial,[1,2] cardioprotector, vasodilator,[3] anti-inflammator,[4] anti-HIV,[5] monoamine oxidase (MAO) inhibitor.[6,7]

MAO exists in two isoforms MAO-A and MAO-B, which differ according to the substrate specificity, MAO-A preferentially deaminates serotonin and norepinephrine. MAO-B acts preferentially on fenilethylamine. Because of the vital role that MAO plays in the inactivation of neurotransmitters, the regulation of MAO-A and MAO-B activity has been an important target for the treatment of the pathologies. In particularly MAO-B inhibitors are used in the therapy of Alzheimer's and Parkinson's diseases, while MAO-A inhibitors are used as antidepressants and anti-anxiety agents.

So far, among several MAO inhibitors, some coumarin derivatives have been described as good inhibitory MAO activity[8-12]. Related to that, in the last years our research group first investigated the MAO inhibitory activity 7-substituted coumarin derivatives (**A**) in which the activity and selectivity can be modulated depending of the substituents in the pyrone ring. (Figure 1)

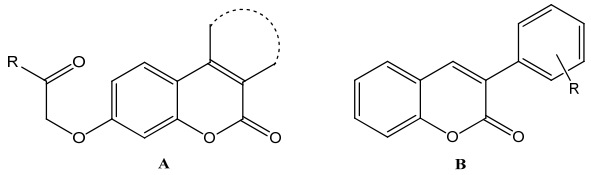


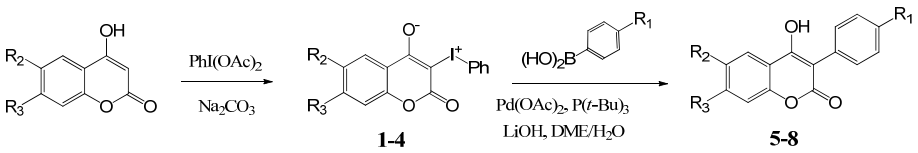
Figure 1: coumarins with MAO inhibitory activity.

Starting from these studies, in the last years our research group has carried out the synthesis of different 3-arylcoumarins (**B**) with an interesting MAO-B inhibitor activity.[13-16] On basis of that, we can conclude that substituents in the 7-position are not essentials for the MAO-B inhibition, if in the 3-position of the coumarin an aryl group is present. This results encouraged us to produce a series of 3-arylcoumarin where a hydroxyl group have been incorporated at the 4 position of the coumarin scaffold. We also pretend to introduce substituents in one or two aromatic rings with different electronic, steric and/or lipophilic properties in order to study the effects on the possible activity and/or selective MAO-A/B.

These compounds can be synthesized by construction of the substituted coumarin moiety or alternatively, by arylation of the coumarin scaffold. In our case, 3-substituted coumarins have been obtained using the last methodology introducing the aryl group by palladium-catalyzed Suzuki-Type coupling strategy.[17]

Result and discussion:

Coumarins have been obtained synthesizing initially the electrophilic specie, the pheniliodonium coumarinate. This is a molecule with a positive charge at iodine compensated by a internal charge that is localized formally at the α-carbon. We have used 4 differents type of commercial coumarins to produce 4 coumarin-based phenyliodonium zwitterions (**1-4**). Then we introduce the aryl group at the 3 position of coumarin scaffold using a palladium-catalyzed Suzuki-Type coupling reaction with 4-methoxyphenyl boronic acid under conditions indicated in scheme 1.[17] The mild reaction condictions and the commercial availability of both 4-hydroxycoumarin and boronic acids make this method a valuable tool for generating diversified 3-aryl-4-hydroxy-coumarins in order to essay as vasodilatadors, antioxidants and monoamino oxidase inhibitors.



Scheme 1: synthetic strategy for the prepared compounds

We have prepared derivatives containing different substituents in positions 3', 6 and 7.

Aryl coumarins	R1	R2	R3
5	OCH_3	H	H
6	OCH_3	Cl	H
7	OCH_3	CH_3	H
8	OCH_3	CH_3	CH_3

General experimental procedure :

All reactions were carried out under dry and deoxygenated argon atmosphere. Identification of the compounds and course of the reactions were visualized using TLC plates (Merck, silica gel 60F254) under UV light (254-366 nm).

Melting points were determined using a Reichert Kofler thermopan or in capillary tubeson a Buchi 510 apparatus and are uncorrected. 1H-NMR spectra were recorded on a Bruker WM-250 at 250 MHz using TMS as internal standard (chemical shifts in δ values, *J* in Hz).

General procedure for the preparation of 3-phenyliodonium coumarinates (1-4): Iodobenzene diacetate (1 mmol) was suspended in a solution of Na_2CO_3 (1mmol) in water (10 mL) and stirred for 2 hours at room temperature. To this solution was added a mixture of 4-hydroxycoumarin (1mmol) in water (10 mL). After the mixture was stirred at room temperature for 14 hours, the precipitate was collected by filtration, washed with water (10 mL) and dried under vacuum. The resulting white solid was used without further purification.

Following this conditions we have synthesized:

4-Hydroxy-3-(4-metoxiphenyl)iodonium coumarinate (1).

6-Chloro-4-hydroxy-3-(4-metoxiphenyl)iodonium coumarinate (2).

4-Hydroxy-6-methyl-3-(4-metoxiphenyl)iodonium coumarinate (3).

4-Hydroxy-6,7-dimethyl-3-(4-metoxiphenyl)iodonium coumarinate (4).

General procedure for cross coupling reaction: A degassed solution of boronic acid (2.2 equiv) and P(*t*-But)$_3$ (27 μL) in DME and water (4:1, 12.5 mL) was added to a mixture of iodonium ylide (0,55 mmol) LiOH/H_2O (3.0 equiv) and $Pd(OAc)_2$ (6.2 mg) under argon at room temperature. After being stirred at the same temperature for 24-48 hours the mixture was purified on column (exane:ethylacetate 8:2)**.**

Following this conditions we have synthesized:

4-Hydroxy-3-(4-metoxiphenyl)coumarin (5). Yield 65%, MP: 255-257 °C

6-Chloro-4-hydroxy-3-(4-metoxiphenyl)coumarin (6). Yield 56%, MP: 258-260 °C

4-Hydroxy-6-methyl-3-(4-metoxiphenyl)coumarin (7). Yield 50%, MP: 228-230 °C

4-Hydroxy-6,7-dimethyl-3-(4-metoxiphenyl)coumarin (8). Yield 42%, MP:221-223 °C

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