Synthesis of Nitro-Substituted 2-Phenylbenzofurans Derivatives as Potential Human Monoamine Oxidase Inhibitors

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Abstract:

Benzofuran (oxygen heterocycle) is a common moiety found in many biologically active natural and therapeutic products, and thus represents a very important pharmacophore. It is present in many medicinally important compounds that show biological activity, including anticancer and antiviral properties. Some benzofuran derivatives are also known as 5-lipoxygenase inhibitors, antagonists of the angiotensin II receptor, blood coagulation factor Xa inhibitors, ligands of adenosine A1 receptor and more recently as MAO inhibitors. In general, benzofurans described as MAO inhibitors have a higher selectivity to the MAO-B isoform. In our efforts to contribute to the development of novel compounds that may be useful in the treatment of neurodegenerative disorders such as PD or AD, we are focusing on 2-phenylbenzofuran derivatives. 2-Phenylbenzofurans have been selected by analogy to 3-phenylcoumarins previously described by us as potent and selective MAO-B inhibitors, and preserving the core of trans-stilbene in their structure. Based on these previous experimental results, and with the aim of finding novel and more selective MAO-B inhibitors, in the present work we continue our studies, describing the synthesis of a new series of nitro-substituted 2-phenylbenzofurans derivatives in order to compare experimental results.

Keywords: Wittig reaction, 2-phenylbenzofuran, Monoamino oxidase (MAO)

Introduction:

Monoamine oxidase (MAO) is an enzyme responsible for metabolism of monoamine neurotransmitters. This enzyme plays an important role in brain development and function, so MAO inhibitors are demonstrating great potential as therapeutic agents.[1] The MAO enzyme exists in two

isoforms, MAO-A and MAO-B. MAO-A metabolizes serotonin in the central nervous system, and inhibitors of this isoform such as phenelzine, isocarboxazid, tranylcypromine, and moclobemide are clinically used for the treatment of depression. On the other hand, the MAO-B isoform is the main isoform responsible for the central dopamine metabolism, so MAO-B inhibitors suchas selegiline and rasagiline are used for the treatment of Parkinson's disease (PD).[2]

Over the years, a large number of heterocyclic scaffolds have been exploited to design inhibitors targeting MAOs.[3,4]

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. The presence of heterocyclic structure in such different type of compounds is strongly indicative of the diverse pharmacological activities and recognition of this is reflected in efforts to find useful synthetic drugs.

Benzofuran scaffold (oxygen heterocycle) is a common moiety found in many biologically active natural and synthetic products. Therefore, it represents a very important pharmacophore in drug discovery.[5] It is present in many medicinally important compounds which show biological activity, including anticancer and anti-inflammatory properties.[6,7] Benzofuran scaffold has drawn considerable attention over the last few years due to its profound physiological and chemotherapeutic properties.[8] Some benzofuran derivatives are also known as monoamine oxidase and 5-lipoxygenase inhibitors, antagonists of the angiotensin II receptor, blood coagulation factor Xa inhibitors, ligands of adenosine A1 receptor,[5,9] and more recently as MAO inhibitors.[10–14]

In general, benzofurans described as MAO inhibitors have a higher selectivity to the MAO-B isoform. In our efforts to contribute to the development of novel compounds that may be useful in the treatment of neurodegenerative disorders such as PD or AD, we are focusing on 2-phenylbenzofuran derivatives.[14]

2-Phenylbenzofurans have been selected by analogy to 3-phenylcoumarins previously described by us as potent and selective MAO-B inhibitors, and preserving the core of trans-stilbene in their structure.[9,14]

Among the studied benzofuran series, 5-nitro-2-(4-methoxyphenyl)benzofuran has been the most active compound, presenting MAO-B selectivity and reversible inhibition (IC_{50} = 140 nM).[14]

Based on these previous experimental results, and with the aim of finding novel and more selective MAO-B inhibitors, herein we continue our studies, describing the synthesis of a new series of nitro-substituted 2-phenylbenzofuran derivatives (Figure 1).

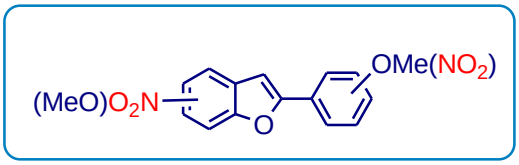
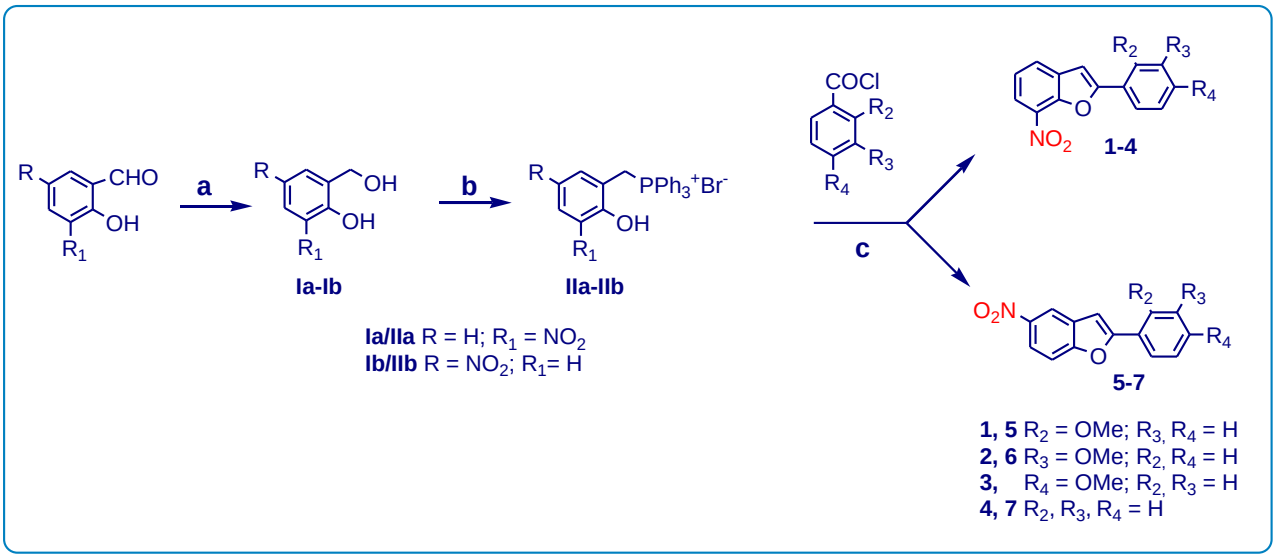


Figure 1

Results and discussion

Compounds **1–7** were efficiently synthesized according to the synthetic strategy outlined in Scheme 1. The key step for the formation of the benzofuran moiety was achieved by an intramolecular Wittig reaction between *ortho*-hydroxybenzyltriphosphonium salt and the appropriate benzoylchloride.[15]

The desired Wittig reagent **IIa-b** was readily prepared from the conveniently substituted *ortho*-hydroxybenzyl alcohol **Ia-b** and $PPh_3 \cdot HBr$.[16,17]



Scheme 1: Synthesis of 2-phenylbenzofuran derivatives via a Wittig reaction. *Reagents and conditions*: a) $NaBH_4$, EtOH, 0 °C to rt, 2 h; b) PPh_3 HBr, CH_3CN, 82 °C, 2 h; c) toluene, Et_3N, 110 °C, 2 h.

The benzofuran structures were confirmed by mass spectrometry, elemental analyses, ^{1}H-NMR and ^{13}C-NMR. In table 1 we reported yields and mp obtained for compound **1-7**.

compounds	Yeld	Mp
1	10%	167-170 °C
2	10%	115-117 °C
3	15%	104-106 °C
4	45%	152-154 °C
5	15%	174-176 °C
6	62%	148-150 °C
7	40%	164-166 °C

Table 1: Yields and Mp obtained for compound **1-7**

Materials and Methods

Starting materials, solvent and reagents were obtained from commercial suppliers (Sigma-Aldrich) and were used without further purification. All reactions were performed under N_2 atmosphere. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (0.25 mm), visualized by exposure to UV light. Column chromatography purifications were performed using. Aldrich silica gel (60-120) mesh size. Melting points were determined on a Stuart Scientific SMP 11 melting point apparatus and are uncorrected. Concentration and evaporation of the solvent after reaction or extraction were carried out on a rotary evaporator (Büchi Rotavapor) operating at reduced pressure. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian INOVA 500 spectrometer using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) using TMS (tetramethylsilane) as an internal standard. GC-MS: low resolution mass spectrometric experiments were carried out on a Saturn 2000 ion-trap coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek, CA) operating under EI conditions (electron energy 70 eV, emission current 20 mA, ion-trap temperature 200°C, manifold temperature 80°C, automatic gain control (AGC) target 21.000) with the ion trap operating in scan mode (scan range from m/z 40–400 at a scan rate of 1 scan/s).

Chemistry

General procedure for the preparation of 2-hydroxybenzylalcohols ***Ia-Ib***: Sodium borohydride (6.60 mmol) was added to a stirring solution of 2-hydroxybenzaldehyde (6.60 mmol) in ethanol (20 mL) in an ice bath. The reaction mixture was stirred at room temperature for 1 h. After that, the solvent was removed, 1N aqueous HCl (40 mL) was added to the residue and extracted with diethyl ether. The solvent was evaporated under vacuum to give the desired compounds

General procedure for the preparation of 2-hydroxybenzyltriphenylphosphonium bromide ***IIa-IIb***: A mixture of 2-hydroxybenzylalcohol (24.6 mmol) and triphenylphosphine hydrobromide (24.6 mmol) in acetonitrile (50 mL) was stirred under reflux for 2 h. The solid that formed was filtered and washed with acetonitrile to give the desired compounds.

General procedure for the preparation of 2-phenylbenzofuran ***1-7***: A mixture of 2-hydroxybenzyltriphenylphosphonium bromide (1.10 mmol) and benzoylchloride (1.11 mmol) in a mixed solvent (toluene 20 mL and triethylamine 0.5 mL) was stirred under reflux for 2 h. The precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by silica gel chromatography (hexane/ethyl acetate 9/1) to give the desired compounds **1-7**.

*7-Nitro-2-(4'-methoxyphenyl)benzofuran (**3**):* yellow solid. Yield: 15 %; mp 104-106 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = : 8.06 (d, 1H, *J* = 8.0, H6), 7.88 (d, 2H, J = 8.9, H2' and H6',), 7.82 (d, 1H, *J* = 6.8, H4,), 7.31 (t, 1H, *J* = 7.9, H5), 7.00 (d, 2H, *J* = 8.9, H3' and H5'), 6.96 (s, 1H, H3), 3.87 (s, 3H, OCH_3) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.54, 158.33, 153.25, 134.56, 130.74, 129.94, 127.76, 123.52, 123.32, 122.93, 114.25, 102.93, 56.08; Anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; found: C, 66.98; H, 4.15.

Conclusion

We have used the Wittig reaction as a key step for the efficient and general synthesis of a series of nitro-substituted 2-phenylbenzofuran derivatives. Based on previous experimental results, and with the aim of finding novel and more selective MAO-B inhibitors, the 2-phenylnbenzofuran products can be used as precursors for other molecules and for pharmacological evaluation

Acknowledgements

Giovanna Lucia Delogu gratefully acknowledge financial support from the Fondazione di Sardegna - Università degli Studi di Cagliari (Convenzione triennale per gli esercizi 2015-2017; Annualità 2015; Progetti di Ricerca di Interesse Dipartimentale (PRID).

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