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Synthesis of a New Class of Benzothiophenes Derivatives as Potential Cholinesterase Inhibitors †

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Abstract: In the present work, we have designed and prepared new 2- and 2,3-disubstituted benzo[b]thiophenes using an intramolecular Wittig reaction as it constitutes an efficient and general method for the synthesis of the benzothiophene skeleton.

Keywords: Wittig reaction; benzothiophenes; cholinesterase inhibitors

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1. Introduction

Benzothiophene and its substituted derivatives represent an important heterocyclic scaffold that have been widely found in many pharmaceuticals, natural products and material science [1].

Some benzothiophene derivatives are used as antimitotic agents, angiogenesis inhibitors, estrogen receptor antagonists and anti-inflammatory agents to name but a few [2].

Many other compounds containing the benzothiophene core are at various stages of development. For instance **CI959** an anti-inflammatory agent, **B428** a urokinase inhibitor, **PD144795** an endothelial cell activation inhibitor, **T588** a cognition enhancing agent with potential application for treating Alzheimer's dementia [3].

In particular, 3-acylbenzo[*b*]thiophenes have received considerable attention due to their presence as structural core in different bioactive compounds. For example, raloxifene (**1**) and compound (**2**) have been reported as exclusive selective estrogen receptor modulators (SERMs) and anti-tubulin agents to prevent osteoporosis in postmenopausal women (Figure 1) [2].

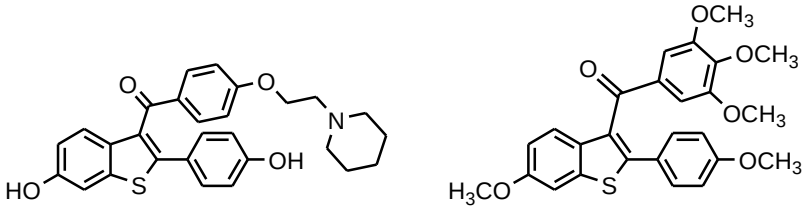


Figure 1. Representative examples of biologically active 3-acylbenzothiophene derivatives.

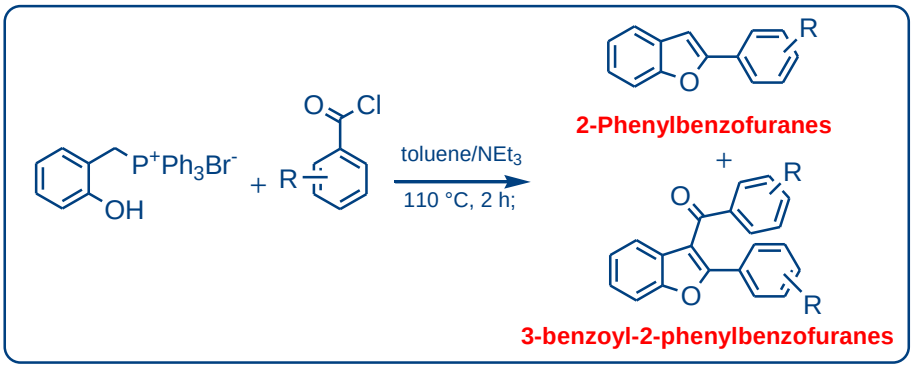
Alzheimer's disease (AD) is a progressive neurodegenerative disease most common and often associated with cognitive decline and memory fragility.

Despite the origin of this memory disorder has not yet been fully elucidated, many risk factors as oxidative stress, τ protein aggregation, inflammation, amyloid-β(Aβ) de-

posits, and low acetylcholine (ACh) levels seems to play a crucial role in developing AD [4].

In our efforts to contribute to the development of novel compounds useful in the treatment of disorders associated to the Alzheimer's disease, we evaluated the relevance of the structural features on the ChEs inhibitory activity. In the present work, we designed and prepared a new series of 2-phenylbenzothiophene and 2-benzoyl-3-phenylbenzothiphene derivatives using an intramolecular Wittig reaction as a key step [5].

This procedure has recently shown to be effective for the preparation of 2-phenylbenzofurans and 3-benzoyl-2-phenylbenzo[b]furans starting from the triphenylphosphonium salt and aroyl chlorides in toluene (Scheme 1) [6].



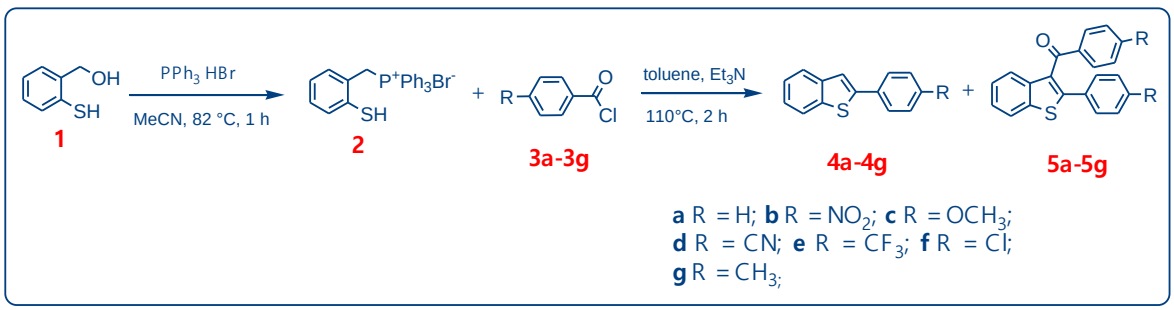
Scheme 1. Synthetic route towards 2-phenylbenzofurans and 3-benzoyl-2-phenylbenzofurans.

2. Results and Discussion

Considering the interesting pharmacological profile of 3-acylbenzothiophenes, in this work we decided to synthesize new 2,3-disubstituted benzo[b]thiophenes using the same method and conditions previously described for the synthesis of 3-benzoyl-2-phenylbenzofuranes.

2-Phenylbenzotiophenes **4a-4g** and 3-acyl-2-phenylbenzothiophenes **5a-5g** were efficiently prepared by an intramolecular Wittig reaction (Scheme 2). 2-Mercaptobenzenemethanol **1** was taken as starting material. The first step involved the formation of Wittig reagent 2-(sulphanylphenyl)methyltriphenylphosphonine bromide (**2**) by coupling reaction of **1** with triphenylphosphine hydrobromide in acetonitrile at 82 °C.

The formation of the benzotiophene ring was achieved by reaction between phosphonium salts **2** and convenient acyl chlorides **3a-3g**.



Scheme 2. Synthetic route towards 2-phenylbenzothiophenes **4a-4g** and 3-benzoyl-2-phenylbenzothiophenes **5a-5g.**

The chemical structures of all compounds synthesized were confirmed by different spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis.

3. Conclusion

With the aim to discover novel and more selective compounds useful in the treatment of Alzheimer's and neurodegenerative diseases, we have used the Wittig reaction as a key step for the efficient and general synthesis of a series of 2-phenylbenzothiophenes derivatives which can be used as precursors for more complicated molecules as well as for pharmacological evaluation.

4. 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. 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). A CIP Sil-8 CB Lowbleed/MS capillary column (30 m, 0.25 mm i.d., 0.25 mm film thickness) was used. The oven temperature was programmed from 50°C (held for 2 min) to 210°C at 20°C/min (held for 15 min). The temperature was then ramped to 350 at 20°C/min. The transfer line was maintained at 250°C and the injector port (30:1 split) at 280°C

5. Chemistry

General procedure for the preparation of 2-(sulphanylphenyl)methyltriphenylphosphonine bromide **2**: a mixture of 2-mercaptobenzenemethanol **1** (32.0 mmol) and triphenylphosphine hydrobromide (32.0 mmol) in acetonitrile (100 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-phenylbenzothiopenes ***4a-g*** *and* ***5a-g***: a mixture of 2-(sulphanylphenyl)methyltriphenylphosphonine bromide **2** (2.6 mmol) and benzoylchloride **3** (7.8 mmol) in a mixed solvent (toluene 20 mL and triethylamine 1.5 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 using hexane/ethyl acetate (9:1) as eluent to afford the desired compounds **4a-g** and **5a-g**.

2-phenylbenzothiophene ***4a***: yield 92%; mp: 172-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, 1H, *J* = 8.0 Hz), 7.76 (d, 1H, *J* = 7.5 Hz), 7.71 (d, 2H, *J* = 7.5 Hz), 7.54 (s, 1H), 7.43-7.40 (m, 2H), 7.36-7.30 (m, 3H); MS (EI, 70eV): *m*/*z* (%): 210 (100) [$M^{+\cdot}$].

2-(4-nitrophenyl)benzothiophene ***4b***: yield 74%; mp: 144-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.41 (m, 2H), 7.71 (s, 1H), 7.84–7.87 (m, 4H), 8.28 (d, 2H, *J* = 8.7 Hz); MS (EI, 70eV): *m*/*z* (%): 225 (100) [$M^{+\cdot}$].

2-(4-methoxyphenyl)benzothiophene ***4c***: yield 54%; mp: 187-1898 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85(s, 3H, O$\underline{CH_3}$), 6.96 (d, 2H, *J* = 8.7 Hz), 7.28–7.33 (m, 2H), 7.42(s 1H), 7.64 (d, 2H, *J* = 9.0 Hz), 7.74 (d, 1H, *J* = 7.5 Hz), 7.80 (d, 1H, *J* = 7.8 Hz); MS (EI, 70eV): *m*/*z* (%): 374 (100) [$M^{+\cdot}$].

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