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Ferrocenyl analogues of bisacodyl: Synthesis and antimicrobial activity

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ABSTRACT

The antibacterial activity of bisacodyl, a drug used in therapeutic as laxative is described herein for the first time. Ten original ferrocenyl analogues have been synthesized via an efficient synthetic procedure using the McMurry coupling reaction. The antibacterial activity was investigated against Gram-positive and Gram-negative foodborne pathogens including *Listeria monocytogenes*, *Escherichia coli*, *Enterococcus faecalis*, *Salmonella enterica*, *Micrococcus luteus* and *Staphylococcus aureus*. The results showed that most of these compounds exhibit an excellent antimicrobial activity, and the bisacodyl analogues seemed to be more bactericides than bacteriostatic.

1. Introduction

The global situation of bacterial diseases has become a concern in the last years due to the lack of new drugs and the antibiotic resistance. The leaving behind of the antibiotic discovery area by many pharmaceutical companies is one of the major reasons of the discovery decline. Since the year 2000, only eight antibacterial molecules have obtained a marketing authorization (AMM). Moreover, despite the discovery over the last twenty years of compounds with an interesting antibiotic activity, few of them belong to new chemical classes or have the required properties to become drugs or to circumvent resistance problems. One of the approaches to overcome drug resistance, apart from avoiding the abuse of antibiotics, is the search for new multi-target inhibitors rather than the association of several antibiotics [1–3].

At present, in order to accelerate the development of drugs with relatively low costs and reduced risks, pharmaceutical companies develop new approaches from existing drugs. This methodology known as drug repurposing allows the development of new indications for existing drugs with well-known pharmacokinetic profiles, known safety profile, already solved manufacturing issues. Concerned by the high interest in infectious disease research and considering the forgoing argues, we decided to evaluate the antimicrobial activity of bisacodyl, drug used in therapeutics as laxative [4,5].

To our delight bisacodyl showed an excellent antimicrobial activity (MIC values of 6.25–12.5 μg/mL; 3.125–12.5 μg/mL and 6.25–12.5 μg/mL against Gram-positive strains *Micrococcus*, *Staphylococcus* and *Listeria* respectively). These results encouraged us to develop a series of new analogues. In an effort to enhance the therapeutic value of bisacodyl, we developed the strategy of incorporating an organometallic ferrocenyl moiety. The use of a ferrocene group to enhance the activity of antibiotics was proposed by Edwards et al., in 1976 [6]. The advantages of the introduction of ferrocenyl moiety to increase the antimicrobial activity have been widely described in the literature [7–17]. The use of ferrocene is especially attractive because it is neutral, chemically stable, a nontoxic molecule and can be easily derivatized or functionalized. Several ferrocenyl compounds have been described for their antitumor, anthelmintic, antimalarial or antifungal properties [18–24].

To the best of our knowledge the antimicrobial activity of bisacodyl is not described in the literature. All the ferrocenyl compounds that we have synthesized were characterized and evaluated on pathogen bacteria Gram positive and Gram negative. Finally the antimicrobial effect of bisacodyl and one of its analogues was also estimated.

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2. Results and discussion

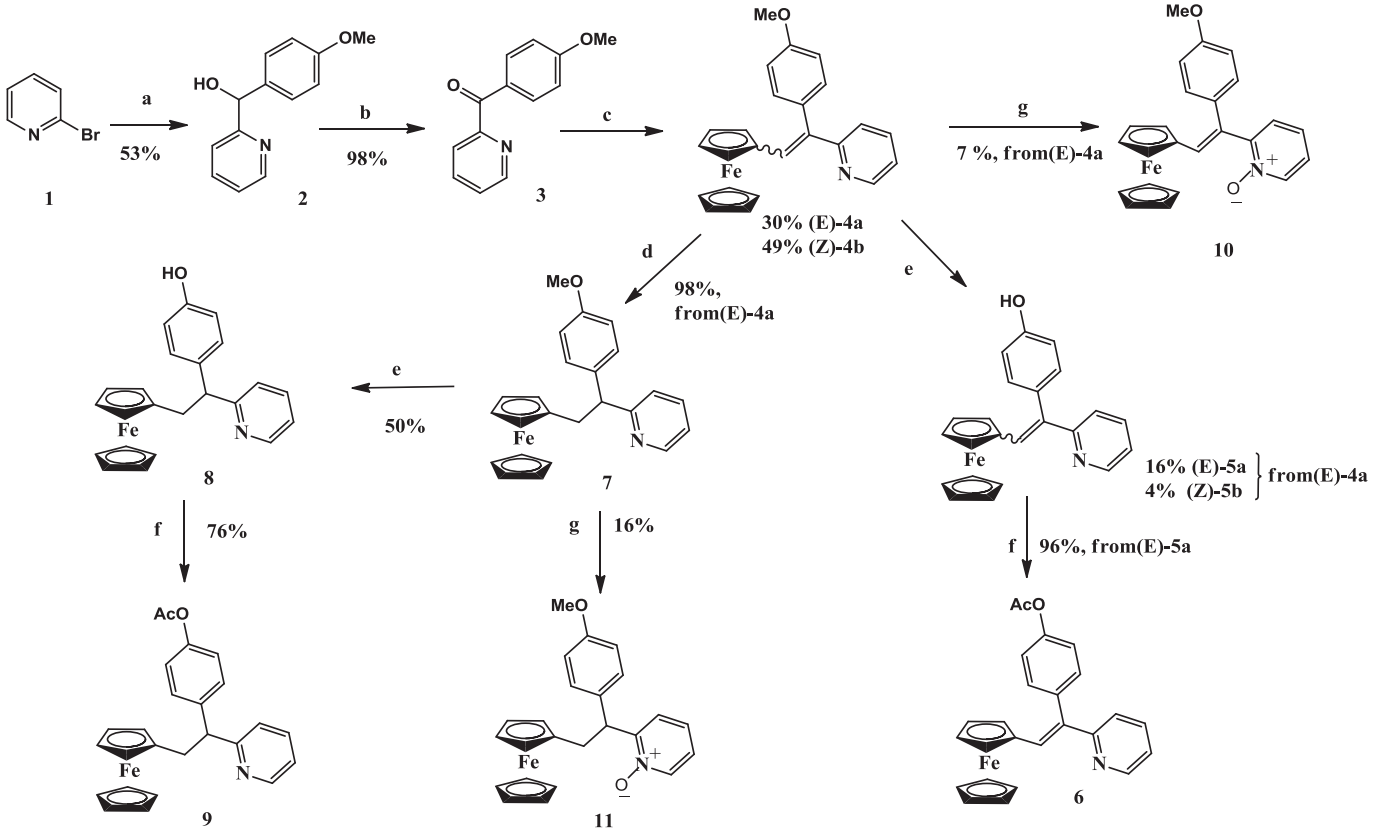
2.1. Synthesis

The synthesis reported herein implies the preparation of ferrocenyl arylethylpyridines and some corresponding *N*-oxide derivatives from commercially available reagents via a McMurry coupling reaction. General synthetic methods to obtain the target compounds are outlined in Scheme 1.

The synthesis of the ferrocenyl derivatives **4**–**11** was carried out following the synthetic pathways represented in Scheme 1. First the synthesis of the (4-methoxyphenyl) (pyridin-2-yl)methanol **2** has been performed by a lithium-bromine exchange following the procedure of Seto et al. 2004 [25], from 2-bromopyridine and *p*-anisaldehyde in anhydrous THF. The aryl ketone **3** was synthesized from the alcohol **2** in excellent yield (98%) via a base-promoted aerobic oxidation using air as a free and clean oxidant [25,26]. The key step to obtain the desired olefin intermediates involved a McMurry cross-coupling reaction between the ketone **3** and ferrocenecarboxaldehyde to afford the 2-(1-(4-methoxyphenyl)-2-ferrocenylvinyl)pyridine **4** in two separable *E* and *Z* isomers (30% and 49% yields respectively). The reaction time is very short (8 min) after preparation of $Zn/TiCl_4$ suspension. However yields can be reduced because of the possible competition between the formation of the desired cross-coupled product and the two homo-coupled compounds [27]. 2-(1-(4-methoxyphenyl)-2-ferrocenylethyl) pyridine **7** was prepared by catalytic hydrogenation of isomer **4a** in 98% yield and was obtained pure enough to be used in the next step without any purification as suggested ^1H NMR analysis.

The demethoxylated compounds **5** and **8** were synthesized by reaction with boron tribromide in dichloromethane. The reaction was conveniently carried out by mixing the reagents at 0 °C in an inert solvent and then allowing the mixture to warm up to room temperature overnight. Under these conditions the 2-(1-(4-hydroxyphenyl)-2-ferrocenylethyl)pyridine **8** was obtained in 50% yield. This result has not been optimized and could probably be improved by modifying the reaction conditions. However for the preparation of 2-(1-(4-hydroxyphenyl)-2-ferrocenylvinyl)pyridine **5**, by-products were always observed leading to lower yields. Moreover, the isomerization of the double bond was observed in this step and can be explained by the formation of a carbocation intermediate of the substrate **4a** in presence of boron tribromide in dichloromethane. It is known that organometallic complexes adjacent to a double bond advantage the stabilization of α carbenium ions by protonation of the double bond in acidic medium. A similar isomerization of analogous organometallic complexes has been described in the literature [28].

At this stage we checked the stability of such compounds. We studied the behaviour of some synthesized isomers in solution in order to evaluate a possible interconversion between Z and E isomers. Such isomerization is a well-known phenomenon that occurs in analogous organometallic compounds and it could be a serious problem to determine the exact structure of the biologically active isomer. We evaluated the isomerization of *(E)* and *(Z)* 2-(1-(4-methoxyphenyl)-2-ferrocenylvinyl)pyridine **4a** and **4b**, *(Z) 2-(1-(4-hydroxyphenyl)-2-ferrocenylvinyl)pyridine* **5b** and *(E)* 2-(1-(4-acetoxyphenyl)-2-ferrocenylvinyl)pyridine **6** by NMR spectroscopy [28]. The solutions of the corresponding isomers in chloroform or acetone were placed in an NMR tube and left at room



Scheme 1. Synthesis of ferrocenyl derivatives (a): *n*-BuLi, *p*-anisaldehyde, THF, −78 °C/r.t., 17 h; (b): NaOH, O_2, toluene, reflux, 18 h; (c): $TiCl_4$, Zn, THF, reflux, 2 h then ferrocenecarboxaldehyde, 8 min; (d): H_2, Pd/C, AcOEt, r.t., 36 h; (e): BBr_3, dichloromethane, r.t., 22 h; (f): Ac_2O, NaOH, 20 °C, 2 h for compound **6**, 48 h for compound **9**; (g): *m*-CPBA, dichloromethane, r.t., 5–12 h.