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Synthesis of Some 5-nitro Heteroaryl-phenylpropenones with Antituberculosis

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ABSTRACT

The treatment of tuberculosis (TB) faces several challenges, such as the emergence of drug-resistant TB, long treatment duration, management of latent TB, and toxic adverse effects leading to non-compliance with treatment. To address this, WHO encourages the search for new molecules that are more effective and better tolerated. In this context, hybrid molecules of the 5-nitro heteroaryl-phenylpropenone type have been designed as new anti-tuberculosis drugs. These compounds were developed by molecular hybridization, combining a pentagonal 5-nitro heteroaryl with a phenylpropenone functional chain. Four derivatives were synthesized by condensation of a 5-nitro heteroaryl carbaldehyde derivative and a selected ketone, with yields ranging from 20 to 74%. Their structure was confirmed by spectroscopic methods. These new compounds must now be evaluated on different strains of *Mycobacterium tuberculosis* to confirm their anti-tuberculosis potential.

Keywords: 5-nitro heteroaryl-phenylpropenone, Heteroaryl pentagonals, Chalcones, Anti-tuberculous.

INTRODUCTION

Tuberculosis remains one of the deadliest infectious diseases, particularly in regions with limited access to treatment[1]. Despite progress, challenges such as non-compliance, long treatment duration, adverse effects, latent bacilli management, and multi-drug resistance persist[2-4]. According to the WHO, drug-resistant bacilli compromise global tuberculosis control efforts, necessitating continued research into new drugs[4-6]. Nitrated pentagonal heterocycles, especially 5-nitro derivatives, have emerged as promising candidates for tackling resistant strains[7-8]. Bicyclic 5-nitro derivatives, such as delanamide, show potential for drug-resistant tuberculosis treatment[9]. These heterocycles, vital in medicinal chemistry, are present in various therapeutic agents[10-11]. Combining them with nitro groups and chalcone phenylpropenone linkages may yield novel anti-tuberculosis compounds[12-13]. This study focuses

on synthesizing 5-nitro heteroaryl-phenylpropenone hybrids as potential anti-tuberculosis drugs. The Claisen-Schmidt condensation method[14], often performed in basic media, is widely used for synthesizing chalcone hybrids due to the stability of enolate intermediates compared to carbocations in acidic conditions. However, basic conditions pose challenges for unstable compounds, such as 5-nitroheteroaryl-derived aldehydes, which are prone to ring opening. Although acidic conditions are less explored due to lower yields, they provide an alternative for such sensitive compounds[15-16]. Here, we aim to synthesize these hybrids using the acid Claisen-Schmidt method, contributing to the development of innovative anti-tuberculosis drugs.

MATERIALS AND METHODS

Identification and characterization of all the products

Proton (^{1}H, 300MHz) and carbon (^{13}C, 75 MHz) NMR spectra were recorded on a Brucker avance 300 apparatus at room temperature in appropriate solvents. Spectra were referenced to the solvent in which they were made (^{1}H:$CDCl_3$ =7.26 ppm) and (^{13}C:$CDCl_3$ = 77.16 ppm). Tetramethylsilane (TMS) is used as reference and chemical shifts are expressed in parts per million (ppm) while coupling constants (J) are expressed in Hertz (Hz). Signal multiplicity is represented by the following abbreviations: s (singlet), d (doublet), m (multiplet or massive). Solvents and reagents were purchased from Sigma Aldrich (France) and used as supplied. The melting points of the compounds were determined on a Köfler bench and are uncorrected.

Design of 5-nitro heteroaryl-phenylpropenones

Tuberculosis remains a major infectious disease worldwide, necessitating innovative strategies to overcome drug resistance. One promising approach involves hybrid molecules combining multiple chemical entities with strong anti-infective potential[17,18]. Following this concept, we designed 5-nitro heteroaryl-phenylpropenones by linking pentagonal 5-nitro heteroaryls to the phenylpropenone chain of chalcones. Pentagonal 5-nitro heterocycles are key scaffolds in therapeutic agents such as nitrofuran (nifuratel, nifuroxazide), 5-nitroimidazole (metronidazole, secnidazole), and 5-nitrothiazole derivatives (niridazole, tenonitrozole)[19]. Notably, metronidazole targets dormant *Mycobacterium tuberculosis*, a phase resistant to conventional drugs[20,21]. Metronidazole analogues, including delamanide, are used against multidrug-resistant tuberculosis (MDR-TB) by inhibiting mycolic acid synthesis, essential for bacterial cell walls[22–25]. Studies also highlight the antituberculosis potential of nitrated pentagonal heterocycles, such as 5-nitro furan derivatives, which inhibit *M. tuberculosis* growth and stimulate immune cells like macrophages[26–29]. Chalcones, phenolic compounds found in plants, exhibit diverse biological activities, including anti-tuberculosis effects[30]. They act via mechanisms such as inhibiting thiol-functional enzymes, disrupting cell wall synthesis, and modulating immune responses[31]. Chalcones also impair bacterial biofilm formation, a key virulence factor of *M. tuberculosis*. Synthetic chalcones have shown activity against *M. tuberculosis* by compromising cell wall integrity[32] and interfering with bacterial enzymes[33]. Combining the complementary properties of chalcones and 5-nitro heterocycles, we synthesized 5-nitro heteroaryl-phenylpropenones as potential anti-tuberculosis agents targeting multiple aspects of *M. tuberculosis* biology. This strategy holds promise for developing new therapies to combat drug-resistant tuberculosis.

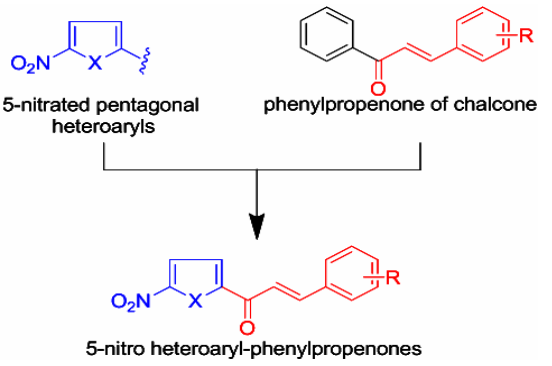

Fig. 1. Design of 5-nitro heteroaryl-phenylpropenones for anti-tuberculosis

Synthesis of 5-nitro heteroaryl-phenylpropenones

Basic Claisen-schmidt condensation test

Commercial acetophenone was reacted with 5-nitro-furan-2-carbaldehyde or 5-nitrothiophene-2-carboxaldehyde using a basic condensation method to produce 5-nitro heteroaryl-phenylpropenones (Fig. 2). This approach, based on the method described[34] by Ouattara Mahama. involves reacting a methyl ketone derivative with 1.2 equivalents of an aromatic aldehyde in a solution of ethanolic sodium hydroxide (7.5 equivalents) at room temperature for

4 to 6 hours. The reaction progress was monitored hourly by thin-layer chromatography (TLC), which showed the disappearance of starting aterials and the formation of at least four new products. However, these products were difficult to identify under our experimental conditions.

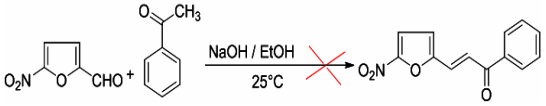

Fig. 2. Basic condensation test for 5-nitro heteroaryl-phenylpropenone derivatives

In an attempt to limit what appeared to be parasitic reactions, we carried out two further tests, adjusting the number of base (NaOH) equivalents and the reaction time, as summarized in the Table I below.

Table I: Conditions of the different condensation tests in basic medium

	Number of moles of NaOH	Reaction time	Observation
Test 1	7.5 Equivalent	6 hours	Several products
Test 2	5 Equivalent	4 hours	Several products
Test 3	2 Equivalent	4 hours	Several products

Attempts to optimize the synthesis method failed to yield the desired 5-nitro heteroaryl-phenylpropenones. This failure could be explained by the instability of 5-nitro-furan-2-carbaldehyde and 5-nitro thiophene-2-carboxaldehyde in basic media. Indeed, these compounds can undergo degradation or transformation reactions, such as hydrolysis or nucleophilic addition reactions. Such reactions can lead to the loss of the nitro function or the formation of ring-opening degradation products[35]. (Figure 3)

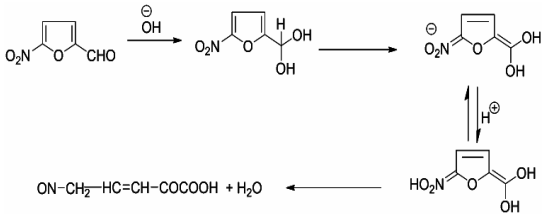

Fig. 3. Reaction diagram showing the degradation of 5-nitro-furan-2-carbaldehyde in a basic medium

Claisen-schmidt condensation in acid medium

Given the difficulties of condensation in a basic medium, we opted for condensation in an acidic medium using the method described by Tawari and colleagues[36]. This involves reacting 5-nitro-furan-2-carbaldehyde or 5-nitrothiophene-2-carboxaldehyde (1a or 1b) with acetophenone or its 4-nitro derivative (2a or 2b) in acetic acid. The reaction is carried out at reflux in the presence of sulfuric acid as catalyst (Fig. 4). The 5-nitro heteroaryl-phenylpropenones (3a-3d) are obtained in yields ranging from 20.66% to 74.31%.

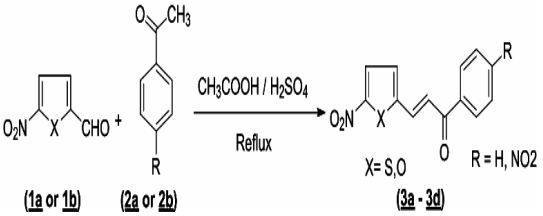

Fig. 4. Acid condensation of 5-nitroheteroaryl-phenylpropenone derivatives

The synthesis of 5-nitro heteroaryl-phenylpropenone derivatives follows this general procedure: In a round-bottom flask, 5-nitrothiophene-2-carboxaldehyde (500 mg, 3.18 mmol) or 5-nitrofuran-2-carboxaldehyde (500 mg, 3.18 mmol) is combined with acetophenone (600 mg, 3.81 mmol) or 4-nitroacetophenone (600 mg, 3.81 mmol) and 0.2 mL of concentrated sulfuric acid in 5 mL of acetic acid. The reaction mixture is heated under reflux for 3–5 hours. After completion, the mixture is cooled to room temperature for 5 hours. The resulting crystals are filtered and washed several times with cold methanol. The product is then dried in an oven at 50°C for 24 hours. The reaction mechanism involves an aldol condensation followed by crotonization in acidic conditions. Initially, the acetophenone carbonyl group is protonated, allowing tautomerization to its enol form. The enol's double bond acts as a nucleophile, attacking the aldehyde's carbonyl group to form a β-hydroxyketone. This intermediate then undergoes dehydration, yielding the desired product as shown in Figure 5.

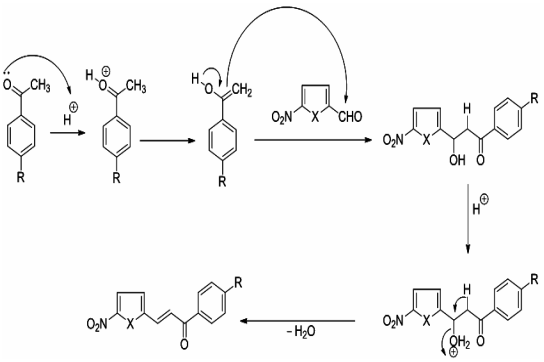

Fig. 5. Reaction mechanism in acid medium

RESULTS AND DISCUSSION

The different strategies and synthesis

methods adopted during our research allowed us to synthesize four derivatives with 5-nitro heteroaryl-phenylpropenone structures for antituberculosis applications. The proton and carbon NMR data of the different synthesized molecules are given below.

(E)-3-(5-nitrofuran-2-yl)-1-phénylprop-2-èn-1-one

Light brown powder, yield : 74.31%, m.p.: 139°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–7.98 (m, 2H), 7.90 (d, J = 4.3 Hz, 1H), 7.82 (d, J = 15.5 Hz, 1H), 7.70–7.60 (m, 1H), 7.58–7.48 (m, 3H), 7.29 (d, J = 4.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ 188.69, 146.27, 137.28, 134.86, 133.52, 129.59, 129.05, 128.87, 128.20, 127.53, 127.1, 124.96, 119.0.

(E)-3-(5-nitrofuran-2-yl)-1-(4-nitrophényl)prop-2-èn-1-one

Black brown powder, yield : 72.48%, m.p. : 220°C, ^{1}H NMR (300 MHz, $CDCl_3$) : δ 8.40 (d, J = 7.6 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 17.2 Hz, 2H), 7.46 (d, J = 15.2 Hz, 1H), 7.36 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ 186.72, 146.84, 146.82, 133.80, 130.17, 130.13, 128.54, 127.50, 127.62, 126.73, 125.64, 120.55, 119.42.

(E)-3-(5-nitrothiophen-2-yl)-1-phénylprop-2-èn-1-one

Golden green powder, yield : 42.58%, m.p. : 175°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–8.04 (m, 2H), 7.78 (d, J = 15.5 Hz, 1H), 7.68–7.61 (m, 1H), 7.59–7.51 (m, 3H), 7.39 (d, J = 3.8 Hz, 1H), 6.86 (d, J = 3.8 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) : δ 187.1, 144.20, 133.6, 130.86, 130.1, 128.6, 128,2, 127.0, 125.10, 121.38, 118.70.

(E)-3-(5-nitrofuran-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one

Yellow powder, yield : 20.66 %, m.p.: 265°C, ^{1}H NMR (300 MHz, $CDCl_3$) : δ 8.44–8.35 (m, 2H), 8.26–8.18 (m, 2H), 7.80–7.58 (m, 2H), 7.41 (d, J = 3.8 Hz, 1H), 6.93 (d, J = 3.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ 189.1, 146.20, 146.6, 131.91, 130.7, 128.1, 127,80, 126.90, 124.6, 122.0, 120.1.

The chemical structures of all 5-nitro heteroaryl-phenylpropenones were confirmed using proton and carbon NMR (Nuclear Magnetic Resonance) spectroscopy. Proton NMR (^{1}H NMR) analysis revealed consistent features across the compounds, with numerous signals in the aromatic region between 6 ppm and 10 ppm. Notably, the ^{1}H NMR spectra showed the disappearance of the methyl group (CH_3) signal from acetophenone at δ = 2.61 ppm. Instead, two doublets corresponding to ethylenic protons appeared, along with an enrichment of signals in the aromatic region. The ethylenic protons were detected at approximately δ = 7.88 ppm (Hb) and δ = 7.46 ppm (Ha), with a coupling constant of 15 Hz (Fig. 6). However, due to conjugation, these protons resonate in weaker fields and overlap with the aromatic signals, making their precise identification challenging. This phenomenon was similarly observed by Etchié Degny in his study of chalcones from quinoxaline and pyrimidine series[37]. The coupling constant of 15 Hz confirms that the 5-nitro heteroaryl-phenylpropenone derivatives adopt a trans (E) configuration[38].

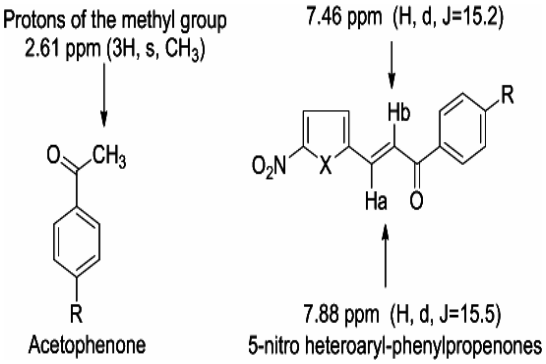

Fig. 6. Remarkable protons of acetophenone and 5-nitroheteroaryl-phenylpropenones in ^{1}H NMR

Furthermore, in carbon NMR spectroscopy, in addition to the signals from the aromatic and ethylenic carbons, we observe on the spectra of all the compounds and at approximately the same chemical shift, a signal around 188 ppm that we can attribute to the carbon of the carbonyl group deblinded by mesomeric conjugation with the ethylenic double bond.

CONCLUSION

This study focuses on the search for new anti-tuberculosis molecules. The goal is to develop more effective compounds that can overcome the drug resistance observed with many current anti-tuberculosis treatments. Using the pharmacochemical approach of molecular hybridization, we designed new compounds with a 5-nitro heteroaryl-phenylpropenone structure. The synthesis involved the condensation of acetophenone derivatives with 5-nitroheterocyclic carbaldehydes in

an acidic medium using the Claisen-Schmidt method. Four 5-nitro heteroaryl-phenylpropenone derivatives were successfully synthesized, isolated, and purified, with yields ranging from 20% to 73%. The structures of these compounds were confirmed through standard spectroscopic techniques, including ^{1}H and ^{13}C NMR. These new derivatives, combining the anti-infective properties of the 5-nitroheteroaryl pharmacophore with the phenylpropenone activity modulator of chalcones, are promising candidates for anti-tuberculosis evaluation and may exhibit strong therapeutic potential.

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Conflict of interest

The author declare that we have no conflict of interest.

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