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Original article

Design, synthesis and evaluation of acridine and fused-quinoline derivatives as potential *anti*-tuberculosis agents

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ABSTRACT

The synthesis of twelve acridine and polycyclic acridine derivatives prepared *via* the Friedländer reaction is described. The one-pot reactions of 2-amino-5-chloro or 5-nitro-benzophenones and a variety of cyclanones and indanones were carried out in a MW oven under TFA catalysis in good yields. The products were designed according natural antituberculosis products and were evaluated for growth inhibitory activity towards *Mycobacterium tuberculosis* $H_{37}Rv$ (Mtb) through the National Institute of Allergy and Infectious Diseases (NIAID, USA). Three of them underwent additional testings. The cyclopenta[*b*]quinoline derivative **9** and the acridine derivative **13** showed remarkable MIC values against the rifampin resistant strain. The former exhibited bactericidal activity at 50 μg/mL, its intracellular activity is similar to rifampin and it was not cytotoxic at low concentrations so it can be considered a new lead compound.

1. Introduction

Currently, one third of the world's population is infected with *Mycobacterium tuberculosis* and 8.9–9.9 million new and relapse cases of tuberculosis (TB) are reported every year. The emergence of new cases, the increased incidence of multi-drug resistant strains of *M. tuberculosis*, the adverse effects of first- and second-line *anti*-tuberculosis drugs, and the incidence of TB associated with viral infections (Human Immunodeficiency Virus, HIV) have led to renewed research interest in natural products in the hope of discovering new antitubercular leads.

Natural products and some of their derivatives have been reported to exhibit remarkable growth inhibitory activity towards *M. tuberculosis* and some of them have been selected as prototype molecules for the development of new antitubercular agents. A large group of alkaloids with complex structures and potent inhibitory activity was described [1].

Investigations of extracts from the ascidian *Lissoclinum notti* and *Diplosoma* sp. led to the isolation of reported pyridoacridone alkaloids. Among them, ascididemin (**1**) exhibited potent antitubercular activity but it also showed high toxicity against Vero cells (SI values >1), Fig. 1. For this reason, a series of simplified tetracyclic-core analogous were prepared in an effort to decouple mammalian cell toxicity from anti-TB activity. The two most interesting compounds were found to inhibit the growth of *M. tuberculosis* $H_{37}Rv$ but negligible cytotoxicity towards Vero and P388 cells [2].

Acridine derivatives, atebrin and quinacrine, have been widely used in malaria chemotherapy during World War II in the absence of quinine and this skeleton is still being explored for betters antimalarials. In 2006, a series of 9-substituted tetrahydroacridines was synthesized and evaluated against *M. tuberculosis* $H_{37}Rv$ and $H_{37}Ra$ strains and exhibited potent activities comparable to the standard drugs [3]. In 2004, Jain et al. [4] reported a series of substituted quinolones with high anti-TB activity. The most effective compound, 2,8-dicyclopentyl-4-methylquinoline exhibited activity against both drug-sensitive and drug-resistant *M. tuberculosis*. It is worthwhile to mention that many of these analogs were initially synthesized as the precursors for targeted antimalarials.

More recently, three quinoline alkaloids (**2**–**4**) isolated from the leaves of *Lunasia amara* Blanco (Rutaceae) revealed interesting activity against *M. tuberculosis* $H_{37}Rv$, Fig. 2 [5].

For the above exposed, the chemotherapeutic properties of acridone and quinoline alkaloids and their synthetic analogs continue to attract interest.

In this regard, we have prepared the acridindione derivative **5** employing a MW-assisted three-component Hantzsch-type condensation of aniline, benzaldehyde and dimedone [6] but it showed no inhibition against *M. tuberculosis* (National Institute of Allergy and Infectious Diseases, NIAID, USA). 1,2,3,4-

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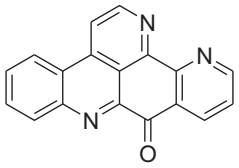

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Fig. 1. Structure of ascididemin.

Tetrahydroacridin-9-one and three fused 4-quinolone analogs were also synthesized under MW irradiation with shorter reaction time and from easily starting materials compared to the known methods in order to design potential *anti*-tuberculosis agents [7]. On the other hand, a series of novel acridine derivatives was reported as potent DNA-binding and apoptosis-inducing antitumor agents [8].

We have previously prepared a series of polysubstituted quinolines synthesized *via* the microwave-assisted Friedländer reaction and a catalytic amount of concentrated hydrochloric acid (Scheme 1). These products were obtained in good yields at short times and were tested against the parasites causing malaria, leishmaniasis and trypanosomiasis, other types of neglected diseases. Among them the tetrahydroacridine derivative **6** was also described [9], Scheme 2.

The aim of the present study was to prepare a number of analogs of **6** in order to explore preliminary aspects of the structure–antiTB activity relationship. The synthetic procedure involves the Friedländer reaction under MW irradiation and trifluoroacetic acid (TFA) catalysis and the targeted products resemble both quinoline and acridine nuclei from natural antitubercular compounds.

2. Results and discussion

2.1. Chemistry

Herein, the synthesis of twelve acridine and polyclyclic acridine derivatives (**6**–**17**) prepared *via* the Friedländer reaction is described (Table 1). The one-pot reactions of 2-amino-5-chloro or 5-nitro-benzophenones and a variety of cyclanones and indanones were carried out in a MW oven at constant power (400 W), Scheme 2. The reactions proceed to completion between 2 and 7 min in good to excellent yields, meanwhile when they were performed under conventional heating the reaction times extended to 2–3 h and the yields were lower or similar, as it was shown earlier [9]. The use of TFA as catalyst proved to be more efficient and milder than the hydrochloric acid catalysis in both experimental conditions. Cyclic ketones such as cyclohexanone, cycloheptanone, dimedone

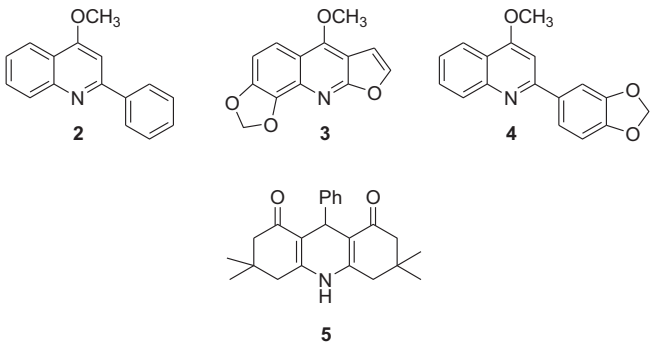
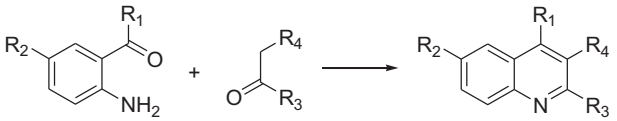


Fig. 2. Quinoline alkaloids isolated from *L. amara* B (**2**–**4**) and a synthetic acridindione derivative **5**.



Scheme 1. Synthesis of quinolines *via* the Friedländer reaction.

and cyclopentanone were used as starting materials to obtain compounds **6**–**9** and **13**–**15**, meanwhile 2-indanone produced **10**, 1-indanone **11** and **16**, and 1,3-indanodione yielded **12** and **17**. Certain substituted 1-indanones were employed in 2007 for achieving indenoquinolines also *via* Friedländer synthesis but in the presence of sodium ethoxide as catalyst at refluxing temperature of ethanol [10].

Although the features of the Friedländer reaction are generally well understood, its mechanism has not unambiguously established. Experimental reports support two different mechanistic proposals. One pathway involves the initial formation of the Schiff base from the 2-amino-substituted aromatic compound and the carbonyl partner followed by an intramolecular aldol reaction to give the hydroxyl imine adduct with subsequent loss of water to produce the quinoline. Alternatively, it has been proposed that the initial rate-limiting step is an intermolecular aldol reaction which in turns gives the quinoline [11]. However it is well established that MW-reactants interactions are increased with the polarity of the material. We could assume the formation of the Schiff base followed by cyclodehydration considering the possible MW activation effects by dipole–dipole interactions according to the literature [12].

2.2. Biological evaluation

2.2.1. In vitro activity against M. tuberculosis

The synthesized products **6**–**17** were evaluated for growth inhibitory activity towards *M. tuberculosis* $H_{37}Rv$ (Mtb) through the National Institute of Allergy and Infectious Diseases (NIAID, USA). The structure of the named compounds and their IC_{50} and IC_{90} values are shown in Table 1. Amikacin, cycloserine, ethambutol, isoniazid, pyrimethamin, primethamine and rifampim were used as reference drugs.

Compounds **9**, **13** and **14** exhibited IC_{50} values of 73.41, 44.35 and 61.93 μM, respectively and underwent additional testing. This subset was determined by an algorithm that considered primarily activity and analytical quality of the samples but also considered other aspects such as chemotype series and solubility.

This testing includes *in vitro* testing of $H_{37}Rv$ under both anaerobic and aerobic conditions as well as minimal bactericidal concentration (MBC). Single drug resistant strain testing (isoniazid, rifampin and moxifloxacin resistant Mtb strains) and intracellular inhibition of Mtb $H_{37}Rv$ growth using murine macrophage cell line and cytotoxicity in this cell-line were also determined.

2.2.2. Minimal inhibitory concentration (MIC)

The MIC for each compound was determined by testing ten, two-fold dilutions in concentration ranges. The MIC is reported as the lowest concentration (μg/mL) of drug that visually inhibited growth of the organism. In addition, the percentage of inhibition at the MIC is provided (Table 2). Rifampin and isoniazid were used as positive controls. Although MIC values of compounds **9**, **13** and **14** were higher than the MIC values for the reference drugs, the tested compounds showed good percent inhibition values (83, 69 and 72% respectively) against the rifampin resistant strain (RMP-R). Compounds **9** and **13** exhibited the best results.