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Research paper

Design, synthesis and evaluation of diarylpiperazine derivatives as potent anti-tubercular agents

Ashok Penta [a], Scott Franzblau [b], Baojie Wan [b], Sankaranarayanan Murugesan [a, *]

[a] Medicinal Chemistry Research Laboratory, Department of Pharmacy, Birla Institute of Technology & Science, Pilani, 333031, India
[b] Institute for Tuberculosis Research, MC-964 College of Pharmacy, University of Illino's at Chicago, 833 S. Wood St, Chicago, IL, 60621-7231, USA

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ABSTRACT

Molecular hybridization is an emerging approach to design novel ligands by combination of two or more pharmacophoric subunits of known bioactive compounds. In the present study, we have designed a novel series of diarylpiperazine analogues, synthesized, characterized using FTIR, ^{1}H NMR, Mass, Elemental analysis and evaluated their *in-vitro* anti-tubercular activity. Among the reported sixteen diarylpiperazines, eleven analogues exhibited significant anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain with MIC values below 6.25 μg/mL and good selectivity index. Structure activity relationship studies concluded that, ortho-para directing group (except para chloro) substitution on ortho and para position of piperazine attached phenyl ring favored anti-tubercular activity.

1. Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis,* one of the leading causes of death worldwide [1–3]. According to the statistics from WHO, 9.0 million new infections and 1.5 million TB deaths were reported in the year 2013 [4]. It is projected that, if control measures are not strengthened further, over 125 million people will get sick with more than one billion new infections and 30 million people will die with TB by 2020 [5]. Tuberculosis has become more significant in the recent years with increased co-infection with HIV and emergence of drug resistance [multiple drug-resistant *M. tuberculosis* (MDR-TB) and extremely drug resistant *M. tuberculosis* (XDR-TB)] [6,7]. Unfortunately, first line treatment regimen of TB mainly consist of decade old drugs [8] and some of the strains have become resistant to most of the currently available anti-tubercular drugs, known as totally drug resistant *M. tuberculosis* (TDR-TB) [9]. Hence, there is an urgent need to develop novel anti-tubercular agents active against both sensitive and drug resistant strains. In the year 2012, U.S. Food and Drug Administration (US-FDA) approved new anti-tubercular drug Bedaquiline for the treatment of MDR-TB patients in combination with other drugs [10].

Nature remains one of the important source to develop anti-infective agents [11]. Identification of natural products and development of synthetic derivatives of natural products with potent activity are always promising way in drug discovery especially for anti-infective agents. β-carboline represents a tricyclic pyrido[3,4-*b*]indole ring system present in large number of natural products isolated from various sources like territorial plants [12], marine sponge [13], fast food [14] and humans [15]. Natural as well as synthetic β-carboline derivatives displayed biological activities like anti-cancer, anti-thrombotic, anti-microbial, anti-malarial, anti-leishmanial, anti-tubercular and anti-viral activity [16,17]. Manzamines are a unique group of β-carboline alkaloids with an unusual polycyclic system, present in different species of marine sponges found in the Indian and Pacific Ocean. Large number of manzamine alkaloids and their synthetic derivatives displayed significant anti-tubercular activity. Manzamine A is the first compound of this group isolated from Okinawa sponge in 1986 and exhibited potent anti-tubercular activity (MIC 1.53 μg/mL) [17,18] (Fig. 1). Nosto-carboline (Fig. 1), a new quaternary β-carboline alkaloid isolated from the freshwater cyanobacterium *Nostoc* 78-12A [19] and its synthetic derivatives exhibited significant anti-tubercular activity [20]. Along with these natural β-carboline alkaloids, semi-synthetic and synthetic β-carboline derivatives also exhibited significant to moderate anti-tubercular activity [20]. Piperazine moiety has the privileged position in the medicinal chemistry and is the second most frequent ring present in all FDA approved drugs till 2013 [21]. In addition to this, piperazine containing compounds displayed wide range of biological activities such as anti-microbial [22,23],

* Corresponding author.
E-mail address: murugesan@pilani.bits-pilani.ac.in (S. Murugesan).

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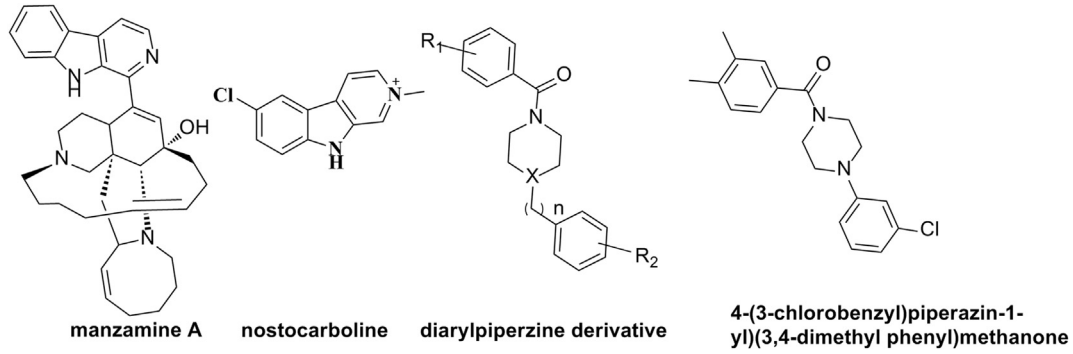


Fig. 1. Structure of some β-carboline and diarylpiperazine derivatives reported as anti-tubercular agents.

anti-protozoal [24,25], anti-leishmanial [26], anti-cancer [27], anti-tubercular [27,28] (Fig. 1) and anti-viral activity [29]. He et al., 2007, reported anti-tubercular activity of simple di-arylpiperazine derivatives as enoyl acyl carrier protein reductase InhA inhibitors. These analogues displayed significant to moderate anti-tubercular activity, among these analogues, (4-(3-chlorobenzyl)piperazin-1-yl) (3,4-dimethyl phenyl)methanone (Fig. 1) showed most potent anti-tubercular activity (IC_{50} 0.99 μM) [30].

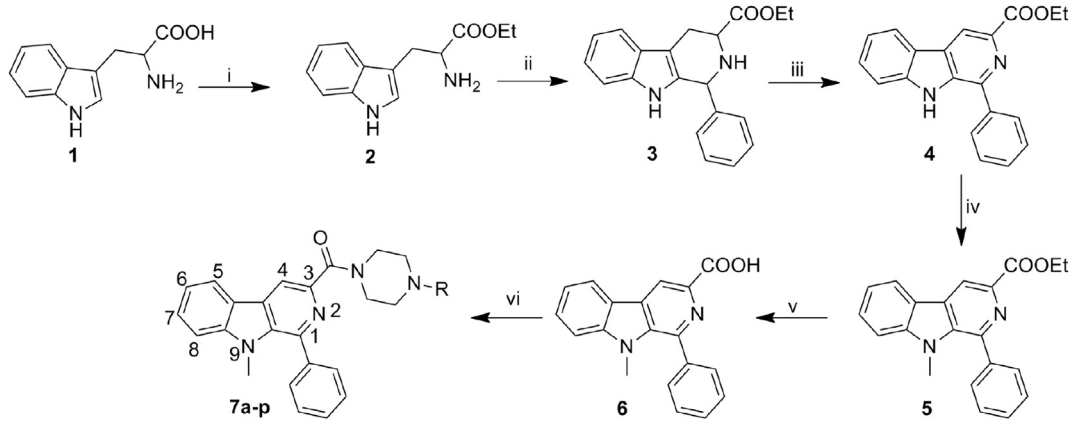
With our continuous interest to develop novel β-carboline derivatives as anti-tubercular agents, in the present study, we have designed a series of novel diarylpiperazine derivatives based on molecular hybridization technique. Molecular hybridization is a rational approach to design new ligands by combination of pharmacophoric sub-units of two or more known bioactive derivatives (β-carboline and piperazine scaffold). In the present study, we have reported design, synthesis, *in-vitro* anti-tubercular evaluation and structure activity relationship study of novel diarylpiperazine analogues.

2. Results and discussion

2.1. Chemistry

The synthetic protocol of the titled diarylpiperazine analogues is illustrated in Scheme 1. The compounds were synthesized from the starting material, DL-Tryptophan **(1)** in a sequence of reactions. Initial esterification of DL-Tryptophan **(1)** using thionylchloride to obtain the ethyl ester of tryptophan **(2)** was followed by pictet–spengler reaction in the presence of trifluoroacetic acid to afford tricyclic ethyl 2,3,4,9-tetrahydro-1-phenyl-1*H*-pyrido[3,4-*b*] indole-3-carboxylate **(3).** Upon oxidation with potassium permanganate, ethyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(4)** was obtained [31,32], continued by 9-*N* methylation with methyliodide in presence of potassium hydroxide to obtain ethyl-9-methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(5)** [33], followed by alkaline ester hydrolysis to afford 9-methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid **(6)** as key intermediate. The carboxylic acid group containing key intermediate **(6)** was further treated with appropriate amines (aryl-substituted piperazines) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and hydroxybenzotriazole (HOBt) to obtain the desired products **(7a-p)** in good to excellent yields [34].

All the synthesized compounds were characterized by IR, NMR, Mass and Elemental analysis. IR spectra of the reported compounds showed *C═O* stretching at 1652 to 1614 cm^{-1}, aromatic *C–H* stretching at 3069 to 3043 cm^{-1}, aromatic *C═C* stretching at 1597 to 1516 cm^{-1}, *C–O* stretching (methoxy) at 1253 to 1240 cm^{-1}, *N–O* asymmetric stretching at 1385 cm^{-1} and *C–Cl* absorption band at 1068 to 1054 cm^{-1}. The ^1H NMR spectrum of the compounds showed, characteristic singlet around δ ~8.50 due to position-4 proton of β-carboline ring, eight piperazine protons appeared as two multiplets around δ value 4.19 to 4.02 ($O{=}CN(CH_2)_2$) and 3.64 to 2.62 ($CN(CH_2)_2$). Piperazine protons were shifted to down field (δ ~4.19 and 3.64) on nitro substitution whereas, shifted up field in benzyl derivatives (δ ~3.91 and 2.62). Methoxy protons appeared as



Scheme 1. Reagents and conditions: i) thionylchloride, ethanol, reflux, 30 min, 76%; ii) benzaldehyde, trifluoro aceticacid, DCM, rt, 3 h, 82%; iii) $KMnO_4$, THF, rt, 24 h, 68%; iv) methyliodide, KOH, DMSO, rt, 30 min, 72%; v) 50% aq. NaOH, reflux, 30 min, 78%; vi) EDCl, HOBt, THF, piperazines, 0 °C-rt 6 h, 62–82%.