Bioorganic & Medicinal Chemistry Letters 23 (2013) 1322–1325

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Syntheses of lipophilic chalcones and their conformationally restricted analogues as antitubercular agents

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ARTICLE INFO

Article history:
Received 1 October 2012
Revised 18 December 2012
Accepted 28 December 2012
Available online 9 January 2013

Keywords:
Antitubercular agent
Mycobacterium tuberculosis
Chalcone
Benzopyranone
Coumarin
HEK-293

ABSTRACT

Lipophilic chalcones and their conformationally restricted analogues were synthesized and evaluated for their antitubercular efficacy against *Mycobacterium tuberculosis* H37Rv strain. Compounds **16**, **24**, **25a** and **25c** were found to be active MIC at 60, 30, 3.5 and 7.5 μg-mL^{-1}. In vitro cytotoxicity of compounds **16**, **24**, **25**a, **25c** and **26** in non-cancerous human epithelial kidney cell line (HEK-293) showed that most active compound **25a** was approximately 2.85 times selective towards tubercular versus healthy cells whereas compound **24** was found to be 16 times selective.

Tuberculosis (TB) is a global health priority not only due to its morbidity and mortality but also due to its high contagious nature.[1–4] In 2010, 8.8 million people fell ill with TB and 1.4 million were died of it.[5] Thus, it is second largest killer worldwide by a single infectious disease. TB becomes fiercer in combination with HIV or cancer. Even our combination therapy of PRISE is not sufficient to tackle the situation.[6–8] Poor management of chemotherapy has emerged drug resistance. The highly lipophilic cell wall of Mycobacterium is responsible for its virulence to some extent.[9] Streptomycin (**1**), rifampicin (**2**), rifapentine (**3**), isoniazide (**4**), ethionamide (**5**) and ethambutol (**6**) are some potential drugs which are being used for tuberculosis treatment (Fig. 1). However, drug resistance is a major drawback of these agents.

Therefore, there is an urgent need to explore new antitubercular agents. Ironically, the low number of potential new chemical entities is a worrying situation at present. Considering the severity of the problem, WHO has prepared a strategic plan in Berlin declaration 2007 to stop TB globally.

In the recent past, several coumarin derivatives have been reported to exhibit antimycobacterial activity. Isoimperatorin (**7**), Osthol (**8a**) and suberosin (**8b**) were isolated from *Arracacia tolucensis* exihibiting antitubercular activity MIC at 64.0 μg-mL^{-1}, 32.0 μg-mL^{-1} and 16 μg-mL^{-1} respectively (Fig. 1).[10] Other coumarin derivatives such as ferulenol (**9**) have also been reported to exhibit potent antitubercular activity (MIC = 2.0 μg-mL^{-1}) against other species of *Mycobacterium*.[11,12] Similarly, chalcones such as licochalcone A (**10**), present in *Glycyrrhiza inflata* exhibited potent antitubercular activity (MIC = 7.1 μg-mL^{-1}).[13] Furthermore, pyranones such as **11** and **12** present in *Piper sanctum* have been reported to have potent antitubercular activity in *Mycobacterium tuberculosis* (MIC = 32 μg-mL^{-1} and 4.0 μg-mL^{-1}, respectively) (Fig. 1).[14] It is known that a moderate to high level of lipophilicity of the compounds often attributes better antitubercular activity.

In the present study, taking structural learning from natural coumarins, chalcones and pyranones, we synthesized some lipophilic chalcones of prototype **I** and their conformationally restricted analogues (styrenylchromanone) based on prototype **II** which may be considered as hybrid of coumarin and chalcone nucleus. Further, for activity modulation, we planned to have a nitrogen moiety as it is essentially present in all the frontline antitubercular drugs (Fig. 2).

The synthesized compounds were investigated for their antitubercular potential in *Mycobacterium tuberculosis* $H_{37}R_V$ strain radiometrically. Further, **16**, **24**, **25a**, **25c** and **26**, which showed significant antitubercular activity were evaluated for their toxicity

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http://dx.doi.org/10.1016/j.bmcl.2012.12.096

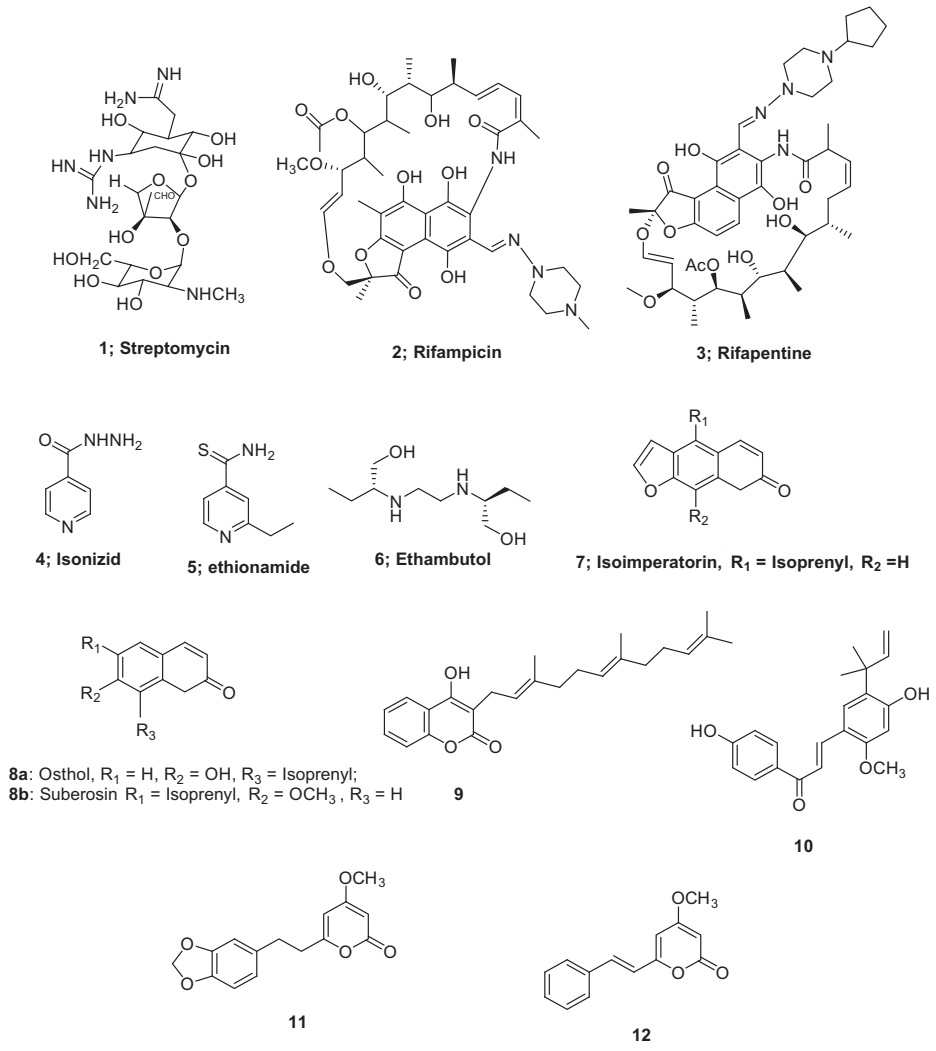

Figure 1. Some synthetic and natural anti-tubercular agents.

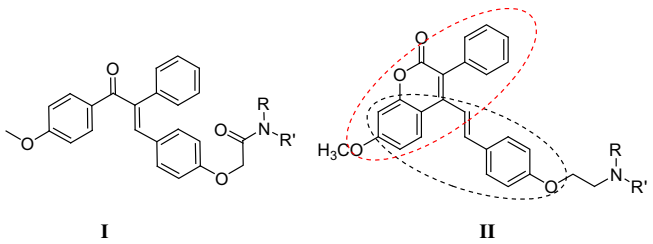

Figure 2. Prototype **I** and **II**.

in in vitro MTT assay using non-cancerous human epithelial kidney cell line (HEK-293) derived from human embryonic kidney cells.

The synthesis of chalcone derivatives of type (**I**) was started from Friedel–Crafts acylation of anisol (**13**) with phenylacetic acid (**14**) using polyphosphoric acid (PPA) at 100 °C as reported earlier which yielded deoxybenzoin **15** in good yield as single product (scheme 1).[15] Compound **15** was reacted with 4-hydroxybenzaldehyde in presence of piperidine and dry benzene at reflux yielding compound **16** as single product with trans geometry confirmed by X-Ray analysis.[15] Compound **16** on condensation with ethyl bromoacetate gave corresponding ester derivative **17**. On hydrolysis under basic reaction condition compound **17** gave corresponding carboxylic acid derivative **18** in quantitative yield. The subsequent treatment of acid **18** with different amines in presence of 1-hydroxy benzotriazole (HOBt) and dicyclohexylcarbodiimde (DCC) in dichloromethane (DCM) under basic reaction conditions at reflux afforded amide derivative of chalcone **19a** and **19b** in 68 and 75% yields, respectively.

The synthesis of target compounds of prototype (**II**) was started with 2-hydroxy-4-methoxy-acetophenone (**20a**) as reported earlier (scheme 2).[16] Briefly, compound **20a** was condensed with 4-hydroxybenzaldehyde (**21a)** in presence of piperidine and dry benzene under reflux to afford 1-(2-hydroxy-4-methoxy-phenyl)-3-(4-hydroxy-phenyl)-propenone (**22a**). Compound **22a** on reaction with phenyl acetic acid in acetic anhydride and triethyl amine at reflux gave 7-methoxy-3-phenyl-4{2-[4-acetoxy-phenyl]-vinyl}-benzopyran-2-one (**23a)** in 86% yield. Compound **23a** on hydrolysis in 2% methanolic NaOH gave 7-methoxy-3-phenyl-4{2-[4-hydroxy-phenyl]-vinyl}-benzopyran-2-one **24** in 80% yield. Similarly, compound **26** was synthesized by reaction of **20b** and **21b** using same sequence of reactions. Condensation of compound **24** with 2-chloroethyl alkylamine hydrochloride in acetone in presence of K_2CO_3 under reflux gave the desired products **25**(**a–c**) in 78–86% yields. The synthesized compounds were characterized by the use of different spectroscopy techniques.[17]

To evaluate the potential of basic pharmacophore of chalcone, **16** (hydroxyl derivative) was evaluated for its antitubercular efficacy in *Mycobacterium tuberculosis* $H_{37}R_V$ strain which showed