European Journal of Medicinal Chemistry 44 (2009) 2017–2029

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, anti-tuberculosis activity and 3D-QSAR study of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines

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ARTICLE INFO

Article history:
Received 8 April 2008
Received in revised form
19 September 2008
Accepted 2 October 2008
Available online 11 October 2008

Keywords:
Tuberculosis
Ring-substituted quinolines
CoMFA
Amino acid conjugates
Anti-tuberculosis

ABSTRACT

The synthesis, antimycobacterial activity and 3D-QSAR study of two series of 4-(adamantan-1-yl) group containing quinolines conjugated to amino acids are described. The most potent analogs displayed in vitro antimycobacterial activity ranging between 1.00 and 3.125 μg/mL. To understand the relationship between structure and activity, a 3D-QSAR analysis has been carried out by Comparative Molecular Field Analysis (CoMFA). The activities of molecules in the test sets were nicely predicted by the CoMFA model generated with field alignment. The best model was obtained using atom-fit alignment. Based on the molecular fields the relationships between structure and activity were easily rationalized.

1. Introduction

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global public health emergency. The disease has advanced, and currently causes approximately 2 million deaths annually [1]. Several interlinked factors contribute to this progression: (a) development of strains resistant to most commonly used drugs such as isoniazid and rifampicin; (b) the spread of the HIV/AIDS pandemic (one third of the approximately 40 million HIV cases worldwide are coinfected with *Mycobacterium tuberculosis*, and for these individuals, the risk of developing clinical TB is about 10% per year); (c) the difficulty of TB detection in infected individuals (less than 40% of TB cases are detected); and finally; (d) the rising incidence of multidrug-resistant (MDR) TB. To overcome shortcomings of existing regimens of anti-TB drugs, new structural classes of drugs acting via novel biochemical pathways are required [2–4]. Ideally, the new classes of anti-TB drugs must be of low molecular weight, inexpensive for easy availability to poor patients, and possess activity against drug-resistant strains of commonly used anti-TB drugs.

Previously, we had reported the discovery of ring-substituted quinolines as a new structural class of anti-TB compounds [5]. The lead compound 2,8-dicyclopentyl-4-methylquinoline (DCMQ) synthesized in one-step is a promising inhibitor and exhibited encouraging activities against drug-sensitive and several single drug-resistant strains (SDR) of *M. tuberculosis*. The promising activity against SDR strains of several of the currently used anti-TB agents suggests that ring-substituted quinolines exemplified by DCMQ possibly act by new and yet unknown biochemical pathway(s). In attempts to modify the structure of the lead compound DCMQ, we have synthesized several new series of ring-substituted quinolines [6–10]. In one such study, we have reported the synthesis and promising anti-tuberculosis activity of a series of ring-substituted quinolinecarbohydrazides/carboxamides [7]. The most active compounds 4-(adamantan-1-yl)-2-quinolinecarbohydrazide and 4-(adamantan-1-yl)-2-quinolinecarboxamide (Fig. 1) have displayed 99% and 98% inhibition at 6.25 μg/mL, respectively against drug-sensitive *M. tuberculosis H37Rv* strain. Both compounds were synthesized using a facile three-step synthetic process in high yields. Therefore, both compounds were considered ideally suited for further structural optimization. In continuation of our anti-tuberculosis drug discovery program and structural diversification of ring-substituted quinolines, herein we report synthesis of various amino acid derivatives (series 1–2, Fig. 2) of 4-

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doi:10.1016/j.ejmech.2008.10.004

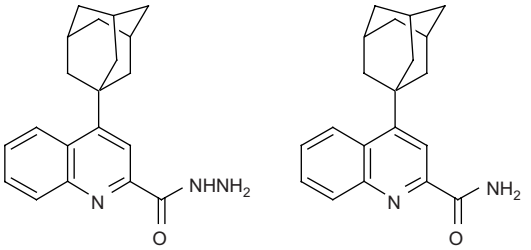

Fig. 1. Structure of promising ring-substituted quinolines.

(adamantan-1-yl)-2-quinolinecarbohydrazide and 4-(adamantan-1-yl)-2-quinolinecarboxamide. Amino acids used were chosen in a way to study the effect of various lipophilic, hydrophilic and cationic groups present on their side chain on the biological activity. As remarked earlier, the exact molecular target for the ring-substituted quinolines remains unknown. Ligand-based techniques have been employed successfully by us and other research groups in the past to help in designing newer classes of antimicrobial agents [8,11–15]. Therefore, we have used the ligand-based approach of 3D-QSAR (CoMFA) for a better understanding of the structure activity relationship of the synthesized ring-substituted quinolines.

2. Results and discussion

2.1. Chemistry

4-(Adamantan-1-yl)-2-quinolinecarbohydrazide (**4**) was synthesized in three convenient steps from commercially available quinoline-2-carboxylic acid (**1**) as described earlier [7]. The latter compound **4** upon reaction with suitably side chain protected commercially available Boc-L-amino acids in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in anhydrous dichloromethane (DCM) as solvent for 8 h at ambient temperature afforded {1-[*N*′-(4-adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]alkyl carbamic acid *tert*-butyl esters **6**–**18** (Scheme 1). Compounds **6**–**18** upon reaction with 33% hydrogen bromide (HBr) solution in acetic acid at ambient temperature for 30 min easily and cleanly produced 4-(adamantan-1-yl)-quinoline-2-carboxylic *N*′-(2-aminoalkyl)hydrazides **19–31** as hydrobromide salts (Scheme 1).

The key intermediate 4-(adamantan-1-yl)-2-quinolincarboxylic acid (**5**) required for the synthesis of compounds described in Series 2 was synthesized in three steps from commercially available quinoline-2-carboxylic acid (**1**) as described earlier [10]. We next attempted reaction of **5** with side chain protected L-amino acid methyl esters. Conventional methods using DCC or 1,3-diispropylcarbodiimide (DIC) as coupling reagents in DCM or *N*,*N*-dimethylformamide (DMF) as solvent failed. In situ generated acid chloride mediated coupling method using **5**, thionyl chloride

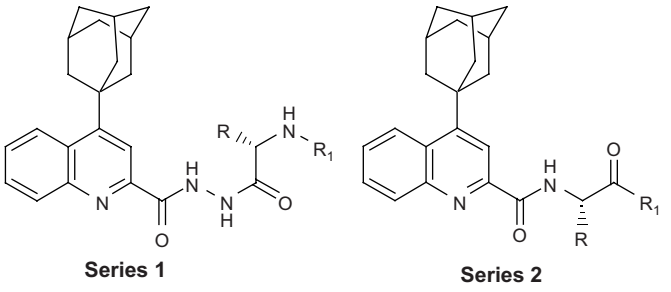

Fig. 2. General structure of newly synthesized ring-substituted quinolines.

($SOCl_2$) and triethylamine (Et_3N) in dichloroethane (DCE) as solvent at 80 °C also failed. We reasoned that $SOCl_2$ mediated reaction failed presumably due to the instability of the in situ formed acid chloride at elevated temperature. Finally, a highly efficient one-pot protocol for the reaction of **5** with amino acids was devised. In this method, compound **5** upon treatment with $SOCl_2$ in the presence of pyridine and DCM as solvent for 1 min at ambient temperature produced 4-(1-adamantyl)-2-quinolinecarbonyl chloride in situ. This intermediate upon reaction with suitably side chain protected L-amino acid methyl esters in the presence of DMAP in DCM successfully provided methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates **32**–**44** (Scheme 1). Compounds **32**–**38**, **40**–**41** and **44** upon reaction with hydrazine hydrate in the presence of abs. ethanol for 48 h at ambient temperature produced *N*2-[1-hydrazino-carbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides **45**–**51**, **53**–**54** and **57**. For, remaining compounds **39** and **42**–**43** (where the side chain functionality was protected, i.e. in cases of Orn, Lys with carbobenzyloxy and Tyr with benzyl) an additional deprotection step was performed. The deprotection at the side chain was achieved by reaction of **39** and **42**–**43** with 33% HBr in acetic acid at ambient temperature for 30 min to produce *N*2-[1-hydrazinocarbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides **52** and **55**–**56** as their hydrobromide salts (Scheme 1).

2.2. Biological activity

In vitro activities of the synthesized derivatives (Series 1–2) against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampicin and isoniazid) were initially carried out using the Microplate Alamar Blue Assay (MABA) at a concentration of 6.25 μg/mL [16]. Compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system [17] and the (%) inhibition are summarized in Tables 1 and 2. Compounds demonstrating ≥90% inhibition at 6.25 μg/mL in the primary screening were further evaluated at the lower concentration of 3.125 and 1.0 μg/mL to determine MIC value that is the minimum concentration exhibiting 99% inhibition. Isoniazid (99% inhibition, MIC = 1 μg/mL) was included, as a standard drug, for comparison.

From Series 1, analogs **7** [R = H, $R_1 = CO_2C(CH_3)_3$], **8** [$R = CH(CH_3)CH_2CH_3$, $R_1 = CO_2C(CH_3)_3$], **9** [$R = CH_2CH(CH_3)_2$, $R_1 = CO_2C(CH_3)_3$], **12** [$R = CH_2C_6H_5$, $R_1 = CO_2C(CH_3)_3$], **25** ($R = CH_2C_6H_5$, R_1 = H), **28** (R = 1*H*-imidazol-4-yl-methyl, R_1 = H), and **31** [$R = (CH_2)_3NHC(=NH)NH_2$, R_1 = H] exhibited inhibition that ranged between 81 and 92% of *M. tuberculosis H37Rv* at 6.25 μg/mL. While, analogs **14** [R = 1*H*-indol-2-yl-methyl, $R_1 = CO_2C(CH_3)_3$], **15** [R = 1*H*-imidazol-4-yl-methyl, $R_1 = CO_2C(CH_3)_3$], and **18** [$R = (CH_2)_3NHC(=NH)NH_2$, $R_1 = CO_2C(CH_3)_3$] were more potent and displayed 99% inhibition of *M. tuberculosis H37Rv* at the lower tested concentration of 3.125 μg/mL. These analogs upon evaluation at the lower dose of 1 μg/mL inhibited the growth of mycobacteria by <50%. All remaining analogs displayed inhibition that ranged between 36 and 78% against *M. tuberculosis H37Rv* at 6.25 μg/mL. A general observation of the structure activity relationship indicated that the presence of *t*-Boc [$NHCO_2C(CH_3)_3$] group produced compounds with higher potency when compared to compounds with free amino group at the side chain. For example, analog **14** containing a *t*-Boc group was active at 3.125 μg/mL (99% inhibition), while its counterpart analog **27** containing an amino group was comparatively less potent and displayed 56% inhibition at 6.25 μg/mL. Similarly, other *t*-Boc group containing analogs **7**, **8**, **9**, **12**, **14**, **15** and **18** were more potent than their amino group containing counterparts (Table 1).

From Series 2, analogs **34** [$R = CH(CH_3)CH_2CH_3$, $R_1 = OCH_3$], **35** [$R = CH_2CH(CH_3)_2$, $R_1 = OCH_3$], **36** [$R = (CH_2)_2SCH_3$, $R_1 = OCH_3$] and **54** (R = 1*H*-imidazolyl-4-ethyl, $R_1 = NHNH_2$) displayed inhibition that ranged between 83 and 99% of *M. tuberculosis H37Rv* at