ChemInform Abstract: Design, Synthesis of Some New (2-Aminothiazol-4-yl)methylester Derivatives as Possible Antimicrobial and Antitubercular Agents.

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 2012

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2012.01.008 · Source: PubMed

European Journal of Medicinal Chemistry xxx (2012) 1–11

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents

Ranjith P. Karuvalam [a], Karickal R. Haridas [a,*], Susanta K. Nayak [b], Tayur N. Guru Row [b], P. Rajeesh [a], R. Rishikesan [c], N. Suchetha Kumari [d]

[a] School of Chemical Sciences, Kannur University, Payyanur Campus, Edat P.O. 670327, Kannur, Kerala, India
[b] Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560012, India
[c] Department of Chemistry, PG and Research Centre, Sri Paramakalyani College, Alwarkurichi, Tirunelveli 627412, Tamil Nadu, India
[d] Department of Biochemistry, Justice K.S. Hegde Medical Academy, Deralakatte, India

ARTICLE INFO

Article history:
Received 12 October 2011
Received in revised form
25 December 2011
Accepted 5 January 2012
Available online xxx

Keywords:
Thiazole
Antibacterial activity
Antifungal activity
Antimycobacterial
X-ray crystallography

ABSTRACT

A series of (2-aminothiazol-4-yl)methylester (**5a**–**t**) derivatives were synthesized in good yields and characterized by ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses. The crystal structure of **5a** was evidenced by X-ray diffraction study. The compounds were evaluated for their preliminary *in vitro* antibacterial, antifungal activity and were screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The synthesized compounds displayed interesting antimicrobial activity.

1. Introduction

Tuberculosis (TB) is an infectious disease. It affects lung and other parts of body which leads to death of almost 3 million people each year and it is positioned as the leading bacterial infectious agent [1,2]. Among pharmacologically important heterocyclic compounds, thiazole and its derivatives have been well known in pharmaceutical chemistry because of their wide spectrum of biological activities [3,4] and their presence in naturally occurring compounds e.g. antibiotic like penicillin, cephalosporin, micrococcin, vitamin B1. A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of the structural complexity and biological diversity with just a minimum number of synthetic steps to assemble compounds with interesting properties. Thiazole and its derivatives are found to be associated with various biological activities such as antibacterial, antifungal and anti-inflammatory activities [5–7]. Different thiazole bearing compounds possess anti-inflammatory activities [8] and some are known to be used as pharmaceuticals. Recently many natural products containing thiazole moiety were isolated and most of them exhibit considerable cytotoxicities and anti tumor potentials [9–12] and also find applications in the drug development for the treatment of allergies [13], hypertension [14], inflammation [15], schizophrenia [16], hypnotics [17], and for the treatment of pain [18], and HIV infections [19]. And more over being investigated for the other applications such as liquid crystals [20], and molecular diodes [21], the interest in substituted thiazole with reactive functionalities resides also in their synthetic potential as building blocks for natural product synthesis [22–24]. Synthetic thiazoles offer the opportunity to increase the structural diversity of natural thiazole substrates. Thiazole core displayed a broad range of biological activities and are found in many biologically relevant molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug). Thiazole derivatives were reported to possess antidegenerative activity and coupling with other aromatic ring system forms new biological active compounds [25]. The present study highlights the recently synthesized thiazoles possessing important biological activities. In this communication, we describe the synthesis of (2-aminothiazol-4-yl)methylester (**5a**–**t**) derivatives and evaluation of their *in vitro* antibacterial activity against five strains, viz. *Staphylococcus aureus*, *Bacillus*

* Corresponding author. Tel./fax: +91 497 2806402.
E-mail address: krharidas2001@yahoo.com (K.R. Haridas).

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2012.01.008

subtilis, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli* and *in vitro* antifungal activity against five strains, viz. *Aspergillus flavus*, *Aspergillus fumigatus*, *Penicillium marneffei*, *Trichophyton mentagrophytes* and *Candida albicans*. In addition, the antituberculosis activity against *Mycobacterium tuberculosis* H37Rv ATCC 27294, and non-tubercular mycobacterial (NTM) species like *Mycobacterium smegmatis* (MC2) ATCC 19420, *Mycobacterium fortuitum* ATCC 19542 and MDR-TB strains were also carried out.

As a part of our research work on the development of useful synthetic molecules [26], it has been planned to introduce active aryl/heteroaryl methylester at the position 4 of potent 2-aminosubstituted thiazole moiety using different aryl/heteroaryl acids having active groups like fluoro, trifluoro, nitro, methoxy etc at the ring. It has been hoped that the combination of these active groups in the new molecular design would lead to better antimicrobial agents. In this communication, we report the synthesis of newly designed (2-aminothiazol-4-yl)methylester derivatives **5**(**a**–**t**) (Scheme 1) starting from thiourea and evaluated these compounds for the antimicrobial and antitubercular activities. In addition, we report here the single crystal X-ray study of **5a** to understand its conformational feature and supramolecular assembly. It helps in understanding the exact 3D structure of the molecule which would help in further understanding the mechanism of action of the drug and also in docking studies with various receptors.

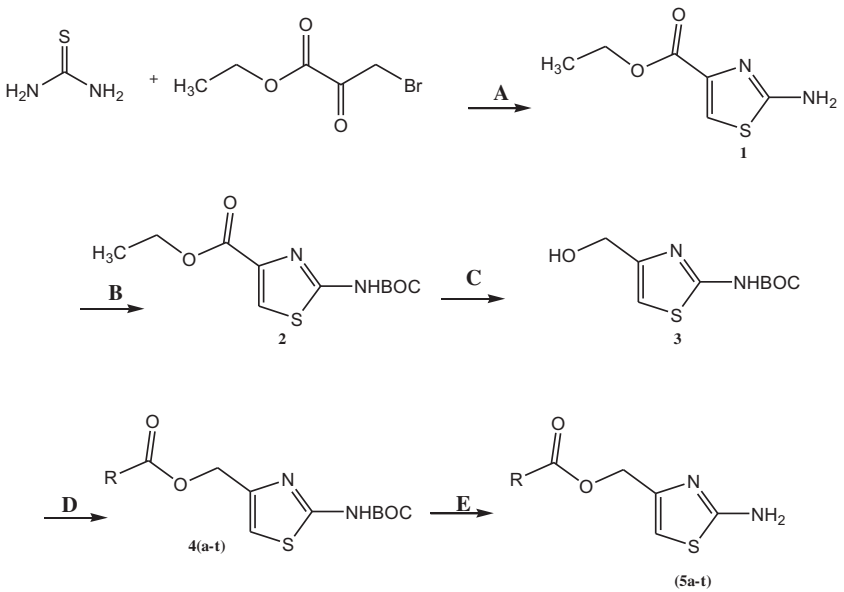
2. Results and discussion

The title compounds were synthesized by a series of reaction as shown in the Scheme 1. The intermediate ethyl-2-aminothiazole-4-carboxylate (**1**) was synthesized by cyclizing ethyl bromopyruvate and thiourea in ethanol at 90 °C [27,28]. The intermediate **1** was then converted to *tert*-butyl-4-(ethoxycarbonyl)thiazol-2-carbamate (**2**) by treating with di-*tert*-butyldicarbonate (BOC anhydride) and triethylamine in tetrahydrofuran at ambient temperature. The required key intermediate *tert*-butyl-4-(hydroxymethyl)thiazol-2-ylcarbamate (**3**) was obtained by reducing the ester to a primary alcohol using diisobutylaluminiumhydride (DIBAL-H) in dichloromethane at −78 °C for 10 h. Compound **4a**–**t** was synthesized by coupling the intermediate **3** with different substituted aryl/heteroaryl acids in presence of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide. HCl (EDC·HCl) and dimethylaminopyridine (DMAP) in dichloromethane. The title compounds **5a**–**t** synthesized by deprotecting the BOC anhydride using ethanolic HCl in ethanol at ambient temperature.

The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis. The formation of ethyl-2-aminothiazole-4-carboxylate (**1**) was confirmed by its ^{1}H NMR spectrum, where the appearance of a singlet peak at δ 7.46 ppm indicated the presence of aromatic hydrogen and the primary amine which disappeared on D_2O exchange. The formation of BOC protected derivative (**2**) was confirmed by its ^{1}H NMR spectrum. In its spectrum the disappearance of a broad peak at δ 7.23 ppm and the appearance of a singlet peak at higher δ value, i.e.; at δ 11.80 ppm and was also evidenced by LCMS spectral data. The formation of primary alcohol derivative was confirmed by its ^{1}H NMR spectrum. In its spectrum appearance of a singlet at δ 6.84 ppm (−OH) and a doublet at δ 4.4 ppm (−CH_2). The formation of (**3**) was also evidenced by LCMS spectral data. The spectral data is discussed in the Experimental section. The characterization data of **5a**–**t** are tabulated in Table 1.

2.1. Structure activity relationship

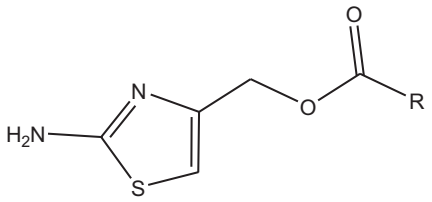
In this present study we have mainly concentrated at the region 2 of the synthesized molecules (Fig. 3). It is believed that strong lipophilic character of the molecule plays an essential role in introducing biological effect [29]. These properties are seen as an important parameter related to membrane permeation in biological system. It has been well established that the fluorinated, in particular CF_3 substituted molecules have got a significant place in modern medicinal chemistry [30]. Variety of substituted aryl groups have been attached at region 2. For example, result showed that compound **5b** displayed good activity, one of the reasons could be the presence of CF_3 group attached to the aryl ring (region 2) increases the lypophilicity of the compound there by making the molecule more cell permeable. Similarly compounds with chloro, fluoro, nitro substitution at the phenyl ring were found to be more



Scheme 1. (2-Aminothiazol-4-yl)methylester derivatives (A) Ethanol, 90 °C, 4 h. (B) Tetrahydrofuran, triethylamine, di-*tert*-butyldicarbonate, 5 h, (C) Dichloromethane, Diisobutylaluminiumhydride, −78 °C, 10 h. (D) Dichloromethane, 1-(3-dimethylaminopropyl)3-ethylcarbodiimide. HCl, dimethylaminopyridine, RCOOH, room temperature, 8 h. (E) Ethanol, ethanolic HCl, room temperature.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

Table 1
Characterization data of (2-aminothiazol-4-yl)methylester derivatives **5**(**a**–**t**)



R=Aryl, Hetroaryl

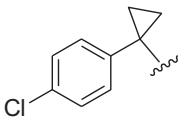
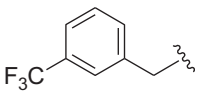
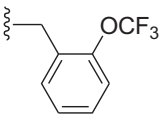
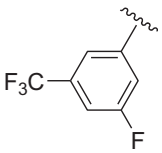
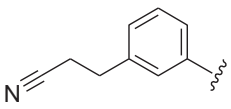
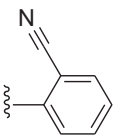
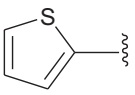
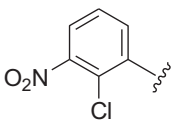
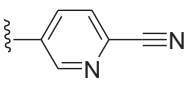
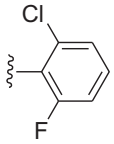
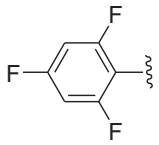
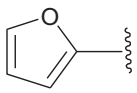
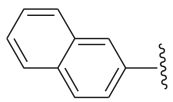
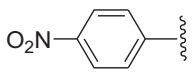
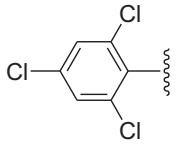
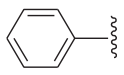
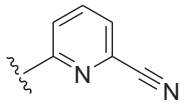
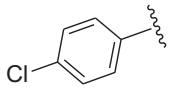
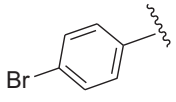
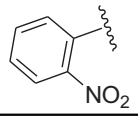
Compound	R	Mol. Formula/ Mol wt	M.p.°C	Yield * (%)
5a		$C_{14}H_{13}ClN_2O_2S$ 308.78	213–215	84
5b		$C_{13}H_{11}F_3N_2O_2S$ 316.3	ND	89
5c		$C_{13}H_{11}F_3N_2O_3S$ 332.3	178–180	85
5d		$C_{12}H_8F_4N_2O_2S$ 320.26	230–232	80
5e		$C_{14}H_{13}N_3O_2S$ 287.34	165–167	90
5f		$C_{12}H_9N_3O_2S$ 259.28	235–237	72
5g		$C_9H_8N_2O_2S_2$ 240.3	192–194	63
5h		$C_{11}H_8ClN_3O_4S$ 313.72	150–152	68
5i		$C_{11}H_8N_4O_2S$ 260.27	178–180	62

Table 1 (*continued*)

Compound	R	Mol. Formula/ Mol wt	M.p.°C	Yield * (%)
5j		$C_{11}H_8ClFN_2O_2S$ 286.71	110–112	81
5k		$C_{11}H_7F_3N_2O_2S$ 288.25	ND	68
5l		$C_9H_8N_2O_3S$ 224.24	183–185	78
5m		$C_{15}H_{12}N_2O_2S$ 284.33	157–159	68
5n		$C_{11}H_9N_2O_2S$ 279.27	160–162	85
5o		$C_{11}H_7Cl_3N_2O_2S$ 337.61	ND	62
5p		$C_{11}H_{10}N_2O_2S$ 234.27	174–176	84
5q		$C_{11}H_{10}N_2O_2S$ 260.27	185–187	80
5r		$C_{11}H_9ClN_2O_2S$ 268.72	171–173	76
5s		$C_{11}H_9BrN_2O_2S$ 313.17	163–165	72
5t		$C_{11}H_9N_3O_4S$ 279.27	166–168	82

ND-Not detected, * Isolated yield after column purification.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

active (**5d**, **5h**, **5j**, **5n**, **5r**, **5t**) than the compound with no substitution at the phenyl ring (**5p**) at the region 2 of the molecule. Further we have tried with different carboxylic acids with mono, di, tri substituted electron withdrawing substituent at the phenyl ring. The biological results indicated that the compound with electron withdrawing group at the phenyl ring at the region 2 of the molecule were more active. Furthermore some of the heterocyclic substitutions (**5i**, **5l**, **5g**) at R of the region 2 were found to be active. The weak activity of some of our compounds may be attributed to the presence of certain functional groups in the molecule.

2.2. Biological activity

All the title compounds were subjected to *in vitro* antibacterial, antifungal and antitubercular properties following standard methods.

2.2.1. Antibacterial activity

Antibacterial activity of the title compounds was investigated against five different bacterial strains, *S. aureus*, *B. subtilis*, *P. aeruginosa*, *K. pneumoniae* and *E. coli* using ciprofloxacin as reference, by serial dilution method. Table 2 depicts the antibacterial screening results (MIC μg/mL) of final compounds, **5a**–**t**.

2.2.2. Antifungal activity

Antifungal activity of the title compounds were investigated against five different strains, *A. flavus*, *A. fumigatus*, *P. marneffei* (recultured), *T. mentagrophytes* (recultured) and *C. albicans* using Ciclopiroxolamine as reference, by serial dilution method. Table 3 depicts the antifungal screening results (MIC μg/mL) of final compounds, **5a**–**t**.

2.2.3. Antitubercular study

Based on the encouraging results from the antibacterial screening, title compounds were further tested for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv, *M. smegmatis* (ATCC 19420), *M. fortuitum* (ATCC 19542) and MDR-TB strains using isoniazid and rifampicin as standards. The screening results of *in vitro* antimycobacterial activity of the final compounds are tabulated in Table 4.

2.3. X-ray crystallographic study of compound *5a*

Single crystal X-ray diffraction study has carried out on the intermediate **5a** to understand the nature of its conformational and molecular assembly. **5a** forms colorless block shaped crystal from ethanol solvents by slow evaporation method at room temperature. Single crystal data of **5a** were recollected on CrysAlis CCD Xcalibur, Eos (Nova), Oxford Diffraction with X-ray generator operating at 50 kV and 1 mA, using MoK_{α} radiation ($\lambda = 0.7107$ Å). The structures were solved and refined by using SHELXL97 [31], using the program suite WinGX. Thermal ellipsoid plot and packing diagram were generated using ORTEP-3 [32] and Mercury respectively. All the non hydrogen atoms were located in difference Fourier maps and were refined anisotropically, and hydrogen atoms were fixed geometrically and refined isotropically. The crystal structure of **5a** is $P\ 2_1/n$ space group in monoclinic space group. Crystallographic information file (CIF) is provided as supporting information file for the details crystallographic information. Fig. 1 provides the thermal ellipsoid plot with atom numbering which shows the keto group preferred the conformation *anti* to 4-chlorophenyl group and *cis* to cyclopropane ring. The molecular assembly form dimer through N–H···N (2.09 Å, 174°) hydrogen bonds and N–H···O (2.03 Å, 171°) hydrogen bond chain links the dimer (Fig. 2).

2.4. Biological results

The investigation of antibacterial screening (Table 2) revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **5b**, **5e**, **5f**, **5g**, **5i**, **5k**, **5l**, **5m** and **5r** showed good activity against *E. coli* and *P. aeruginosa*. Compounds **5b**, **5e**, **5i**, **5j**, **5l**, **5m**, **5o**, **5p** and **5r** showed good activity against *S. aureus and B. subtilis*. Compounds **5a**, **5h**, **5i**, **5l**, **5m**, **5n**, **5p**, **5r**, **5s** and **5t** showed good activity against *K. pneumoniae*.

Table 2
Antibacterial activity data of (2-aminothiazol-4-yl)methylester derivatives **5**(**a**–**t**).

Compound	MIC in μg/mL and zone of inhibition in mm				
	E. coli	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*K. pneumoniae*
	ATCC 25922	ATCC 25923	ATCC 27853	(recultured)	(recultured)
5a	6.25(16–20)	12.5(11–15)	12.5(11–15)	12.5(11–15)	6.25(16–20)
5b	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(11–15)
5c	12.5(11–15)	12.5(11–15)	25(<10)	12.5(11–15)	25(<10)
5d	25(<10)	12.5(11–15)	12.5(11–15)	12.5(11–15)	25(<10)
5e	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(11–15)
5f	6.25(16–20)	12.5(11–15)	6.25(16–20)	25(<10)	12.5(11–15)
5g	6.25(16–20)	12.5(11–15)	6.25(16–20)	25(<10)	25(<10)
5h	12.5(11–15)	12.5(11–15)	25(<10)	12.5(11–15)	6.25(16–20)
5i	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5j	25(<10)	6.25(16–20)	12.5(11–15)	6.25(16–20)	12.5(11–15)
5k	6.25(16–20)	25(<10)	6.25(16–20)	25(<10)	25(<10)
5l	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5m	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5n	12.5(11–15)	25(<10)	12.5(10–15)	12.5(10–15)	6.25(16–20)
5o	25(<10)	6.25(16–20)	25(<10)	6.25(16–20)	12.5(11–15)
5p	25(<10)	6.25(16–20)	25(<10))	6.25(16–20)	6.25(16–20)
5q	12.5(11–15)	25(<10)	25(<10)	25(<10)	25(<10)
5r	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5s	25(<10)	25(<10)	25(<10)	25(<10))	6.25(16–20)
5t	12.5(11–15)	12.5(11–15)	25(<10)	12.5(11–15)	6.25(16–20)
Ciprofloxacin (Standard)	6.25(30–40)	6.25(22–30)	6.25(16–20)	1.56(21)	6.25(23–27)

Note: MIC values were evaluated at concentration ranging between 1.56 and 25 μg/mL. The figures in the table show the MIC values in μg/mL and corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

Table 3
Antifungal activity data of (2-aminothiazol-4-yl)methylester derivatives **5**(**a**–**t**).

Compound	MIC in ug/mL and zone of inhibition in mm				
	A. flavus	*A. fumigatus*	*P. marneffei*	*T. mentagrophytes*	*C. albicans*
	(NCIM No. 524)	(NCIM No. 902)	(recultured)	(recultured)	
5a	25(<10)	25(<10)	25(<10)	25(<10)	25(<10)
5b	12.5(11–15)	12.5(11–15)	25(<10)	12.5(11–15)	25(<10)
5c	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5d	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5e	6.25(16–20)	25(<10)	6.25(16–20)	25(<10)	12.5(11–15)
5f	12.5(11–15)	12.5(11–15)	25(<10)	25(<10)	6.25(16–20)
5g	25(<10)	6.25(16–20)	25(<10)	6.25(16–20)	12.5(11–15)
5h	25(<10)	25(<10)	12.5(11–15)	25(<10)	25(<10)
5i	25(<10)	6.25(16–20)	25(<10)	6.25(16–20)	25(<10)
5j	25(<10)	25(<10)	25(<10)	25(<10)	12.5(11–15)
5k	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5l	6.25(16–20)	25(<10)	6.25(16–20)	25(<10)	6.25(16–20)
5m	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)	6.25(16–20)
5n	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5o	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
5p	25(<10)	25(<10)	25(<10)	25(<10)	25(<10)
5q	6.25(16–20)	12.5(11–15)	6.25(16–20)	12.5(11–15)	25(<10)
5r	25(<10)	6.25(16–20)	25(<10)	6.25(16–20)	25(<10)
5s	25(<10)	25(<10)	25(<10)	12.5(11–15)	6.25(16–20)
5t	25(<10)	25(<10)	12.5(11–15)	25(<10)	25(<10)
Ciclopiroxolamine (Standard)	6.25(25–30)	6.25(25–30)	6.25(20–27)	6.25(27–33)	6.25(20)

Note: MIC values were evaluated at concentration ranging between 6.25 and 100 μg/mL. The figures in the table show the MIC values in μg/mL and corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

The investigation of antifungal screening (Table 3) revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **5c**–**e**, **5k**, **5l**, **5n**, **5o** and **5q** showed good activity against *A. flavus* and *P. marneffei*. Compounds **5c**, **5d**, **5g**, **5i**, **5k**, **5n**, **5o** and **5r** showed good activity against *T. mentagrophytes and A. fumigatus.* Compounds **5c**, **5d**, **5f**, **5k**, **5l**, **5m**, **5n**, **5o** and **5s** showed good activity against *C. albicans.* Further, the preliminary antimycobacterial screening of the title compounds were carried out at 1, 10 and 100 μg/mL concentrations against three different TB strains and also against MDR-TB strain. From the result, it was noticed that the compounds **5a**–**e**, **5g**, **5h**, **5j**, **5k**, **5m**–**o**, **5q**, **5s** and **5t** were active between 1 and 10 μg/mL concentrations against *M. tuberculosis* H37Rv strain. The active compounds from the preliminary investigation were further subjected to second level of testing. The compounds which were active at 100 μg/mL

Table 4
Antitubercular activity data of (2-aminothiazol-4-yl)methylester derivatives **5**(**a**–**t**).

Preliminary *in vitro* screening results, MIC(μg/mL)					Second level screening results, MIC(μg/mL)			
Compound	MTB[a]	MS[b]	MF[c]	%[d]	MTB	MS	MF	MDR-TB
5a	1	1	10	90	1.25	1.25	1.25	>50
5b	1	10	10	95	0.625	10	10	6.25
5c	10	>100	>100	<90	5	–	–	>50
5d	1	>100	10	90	1.25	–	10	>50
5e	1	1	10	95	0.625	1.25	10	6.25
5f	10	>100	>100	<90	5	–	–	>50
5g	10	10	10	<90	10	10	10	>50
5h	1	1	10	90	0.625	1.25	10	6.25
5i	>100	>100	>100	0	–	–	–	–
5j	1	10	10	95	0.625	10	10	6.25
5k	10	10	>100	<90	5	10	–	25
5l	>100	>100	>100	0	–	–	–	–
5m	10	10	10	<90	2.5	10	10	>50
5n	1	10	10	90	1.25	10	10	1.25
5o	10	>100	>100	<90	10	–	–	>50
5p	>100	>100	>100	0	–	–	–	–
5q	10	>100	>100	<90	10	–	–	>50
5r	>100	>100	>100	0	–	–	–	–
5s	10	10	>100	<90	2.5	2.5	–	2.5
5t	1	10	10	95	0.625	10	10	12.5
Isoniazid	0.7	50	12.5	95	0.7	50	12.5	12.5
Rifampicin	0.5	1.5	1.5	95	0.5	1.5	1.5	25

[a] *Mycobacterium tuberculosis* H37Rv.
[b] *Mycobacterium smegmatis* (ATCC 19420).
[c] *Mycobacterium fortuitum* (ATCC 19542).
[d] Percentage of inhibition against *M. tuberculosis* H37Rv; '–' Not detected.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

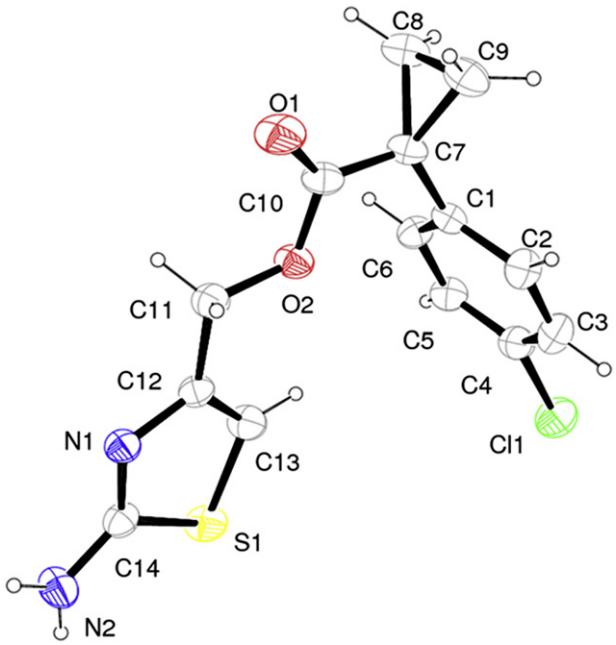


Fig. 1. ORTEP diagram of **5a** with 30% thermal ellipsoid plot for non hydrogen atoms with the atom labeling and hydrogen atoms as open circle.

concentration were not taken for further studies. The second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Amongst the tested compounds, **5b**, **5e**, **5h**, **5j** and **5t** are active at 0.625 μg/mL concentrations against *M. tuberculosis* H37Rv strain and compounds **5a**, **5d** and **5n** are active at 1.25 μg/mL concentrations. Similarly the target molecules **5a**, **5e** and **5h** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420) whereas compound **5s** is active at 2.5 μg/mL. It is interesting to note that most of the compounds showed either enhanced activity or activity in line with the reference compound isoniazid against *M. fortuitum* (ATCC 19542). Further, the compounds **5b**, **5h** displayed substantial activity against the MDR-TB strain at 12.5 μg/mL whereas **5e** exhibited promising activity at

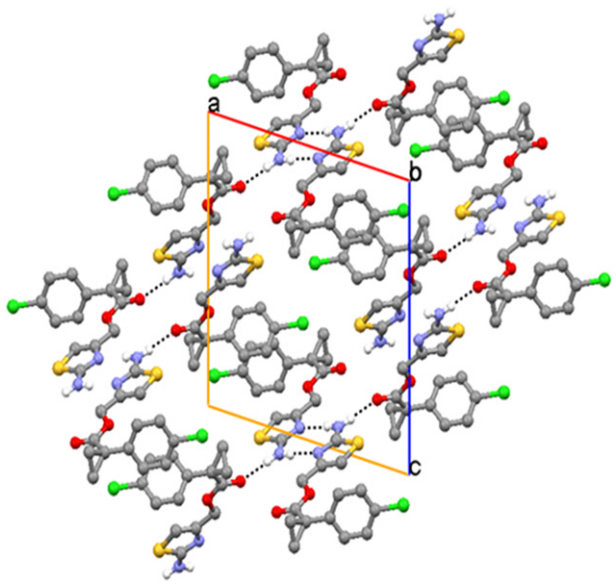


Fig. 2. Molecular assembly through hydrogen bonds of N–H···N dimer and N–H···O chains along *a*-axis.

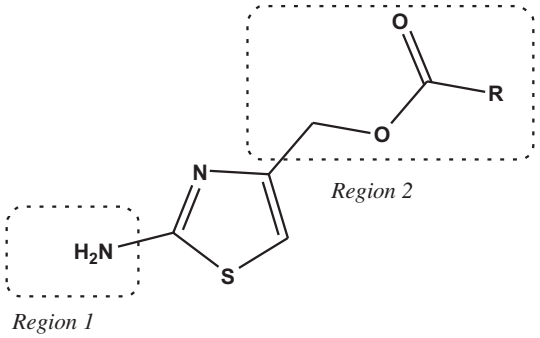


Fig. 3. Selected regions of interest for structure activity relationship.

6.25 μg/mL concentrations. Similarly the compounds **5b**, **5e**, **5h** and **5j** showed promising activity against the MDR-TB strain at 6.25 μg/mL. These are just initial screening results to check the antimicrobial potential, since this is established and further work would be done to understand their mechanism of action.

3. Conclusion

We herein report the successful synthesis of twenty newly designed derivatives of (2-aminothiazol-4-yl)methylester. They have been characterized by spectral studies. The structure of **5a** has been confirmed by X-ray crystallographic study. All the title compounds have been investigated for their antimicrobial and antimycobacterial activities, the investigation of antibacterial and antifungal screening revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **5b**, **5e**, **5i**, **5l**, **5m** and **5r** exhibited comparatively good activity against the tested bacterial strains. Compounds **5c**, **5d**, **5k**, **5n** and **5o** exhibited comparatively good activity against the five fungal strains. Further, the compounds **5b**, **5e**, **5h**, **5j** and **5t** displayed significant activity against *M. tuberculosis* H37Rv strain. Furthermore, the target molecules **5a**, **5e** and **5h** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420) whereas compound **5s** was shown to be active at 2.5 μg/mL. Similarly the compounds **5b**, **5e**, **5h** and **5j** showed substantial activity against the MDR-TB strain at 6.25 μg/mL. The halogen substituted aromatic compounds will improve the lipophilic nature of the compound at the same time methoxy substituted compound would act as an electron donors. In addition the presence of an amine group at the 2nd position of thiazole would be the essential element for hydrogen bonding with receptor. The above mentioned properties of these pharmacophores would be responsible for the promising activities of the title compounds. The scaffold synthesized in the research work can be taken for further derivatization in order to find the lead in these series.

4. Experimental

4.1. General

All reagents were purchased from Aldrich. Solvents used were extra dried. TLC experiments were performed on alumina backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and molybdic acid. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz) and AM-400 (400.13 MHz), Bruker Biospin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. Chemical shifts are reported in

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

ppm (δ) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

4.2. Procedure for the preparation of ethyl-2-aminothiazole-4-carboxylate (**1**)

Thiourea (12.93 g, 0.170 mol) was taken in a round bottom flask and charged ethanol (45 mL), stirred for 10 min, slowly added ethyl bromopyruvate (19.36 mL, 0.155 mol). The reaction mass was heated to 90 °C for 4 h. Reaction completion was monitored by TLC. Reaction was complete. The reaction mass was filtered and the ethanol layer was concentrated under reduced pressure to give a pale yellow solid. The crude product was recrystallized in ethyl-acetate/hexane to afford (**1**) (23.58 g, 90%) an off white solid. M.p. = 177–178 °C; ^{1}H NMR (DMSO) δ ppm = 1.26 (t, 3H, CH_3), 4.21 (m, 2H, CH_2), 7.23 (s, 2H, NH_2), 7.46 (s, 1H, ArH); ^{1}H NMR (DMSO–D_2O) δ ppm = 1.26 (t, 3H, CH_3), 4.21 (m, 2H, CH_2), 7.46 (s, 1H, ArH); LC/MS(ESI-MS)m/z = 173.1 (M + 1); Anal. Calcd for $C_6H_8N_2O_2S$; C, 41.85; H, 4.68; N, 16.27; Found C, 41.94; H, 4.69; N, 16.50.

4.3. Procedure for the preparation of tert-butyl-4-(ethoxycarbonyl) thiazol-2-carbamate (**2**)

The intermediate ethyl-2-aminothiazole-4-carboxylate (20 g, 0.116 mol) in tetrahydrofuran (300 mL) was stirred for 5 min, cooled the reaction mass to 0 °C and charged triethylamine (48.54 mL, 0.348 mol), the added BOC anhydride (28.26 mL, 0.123 mol) slowly to the reaction mixture, during the addition temperature was maintained at 0–10 °C, after complete addition reaction temperature was raised to ambient temperature and stirred for 5 h. Reaction completion was monitored by TLC. Reaction was complete. The reaction mass was filtered and the THF was concentrated under reduced pressure. The crude obtained was dissolved in ethylacetate (250 mL) and the organic layer was washed with water (3×100 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford (**2**) (29 g, 91.6%) as an off white solid. M.p. = 151–152 °C; ^{1}H NMR (DMSO) δ ppm = 1.26 (t, 3H, CH_3), 1.48 (s, 9H, BOC), 4.26 (m, 2H, CH_2), 8.0 (s, 1H, ArH), 11.80 (s, 1H, NH); LC/MS(ESI-MS)m/z = 273.1 (M + 1); Anal. Calcd for $C_{11}H_{16}N_2O_4S$; C, 48.52; H, 5.92; N, 10.29; Found C, 48.64; H, 5.97 N, 10.38.

4.4. Procedure for the preparation of tert-butyl-4-(hydroxymethyl) thiazol-2-ylcarbamate (**3**)

The intermediate *tert*-butyl-4-(ethoxycarbonyl)thiazol-2-ylcarbamate (**2**), (28 g, 0.102 mol) in dichloromethane (280 mL), and the reaction mixture was cooled to −78 °C, then slowly charged DIBAL-H (82.51 mL, 0.463 mol) to the reaction mixture. After the complete addition of DIBAL-H reaction temperature was raised to ambient temperature and was stirred for 10 h. Reaction completion was monitored by TLC. Reaction was complete. Then cooled the reaction mass to 0 °C, Charged MTBE (400 mL) very slowly to the reaction mass followed by 0.5 N HCl (280 mL). The reaction mass temperature was raised to ambient temperature and stirred for an hour. The reaction mixture was filtered and the organic layer was concentrated under reduced pressure. The crude obtained was dissolved in ethylacetate (300 mL) and washed the organic layer with water (3×100 mL). The organic layer was concentrated and the crude product was purified by flash chromatography on silica gel (230–400 mesh) using ethyl-acetate (20–40%) in petroleum ether as eluent to afford (**3**) (18 g, 76%) as a white solid. M.p. 101–102 °C; ^{1}H NMR (DMSO) δ ppm = 1.47 (s, 9H, BOC), 4.4 (d, 2H, CH_2), 5.17 (t, 1H, OH), 6.80 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 28.36, 60.32, 81.40, 107.57, 153.06, 153.24, 159.88; LC/MS(ESI-MS)m/z = 231.29 (M + 1); Anal. Calcd for $C_9H_{14}N_2O_3S$; C, 46.94; H, 6.13; N, 12.16; Found C, 47.01; H, 6.27; N, 12.12.

4.5. General procedure for the preparation of (**4a**–**t**)

The intermediate (**3**) (0.5 g, 0.00217 mol), EDCl (0.622 g, 0.00325 mol), DMAP (0.345 g, 0.0028 mol) were stirred in dichloromethane (6 mL) at 0 °C, and the substituted acid (0.00217 mol) were dissolved in (4 mL) of dichloromethane and charged to the reaction mixture and stirred at room temperature for 8 h. The reaction completion was monitored by TLC. Reaction was completed. The reaction mixture was diluted with (10 mL) of dichloromethane, and was washed with 10% $NaHCO_3$ (10 mL). Separated the organic layer and was washed with saturated brine solution (10 mL). The organic layer was dried over sodium sulfate and concentrated the organic layer under reduced pressure to afford compounds **4a**–**t**. The spectral data of compounds **4**(**a**–**t**) are given below.

4.5.1. tert-Butyl 4-((1-(4-chlorophenyl) cyclopropanecarboxyloyloxy)methyl)thiazol-2-ylcarbamate (**4a**)

^{1}H NMR (DMSO) δ ppm = 1.24 (t, 2H, cyclopropylCH_2), 1.48 (s, 9H, Boc), 1.53 (t, 2H, cyclopropylCH_2), 4.98 (s, 2H, CH_2), 6.93 (s, 1H, ArH), 7.39 (s, 4H, ArH), 11.46 (s, 1H, NH); LC/MS(ESI-MS)m/z = 409.62 (M + 1).

4.5.2. tert-Butyl 4-((2-(3-(trifluoromethyl)phenyl)acetoyloxy) methyl)thiazol-2-ylcarbamate (**4b**)

^{1}H NMR (DMSO) δ ppm = 1.49 (s, 9H, Boc), 3.80 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 7.12 (s, 1H, ArH), 7.51 (s, 1H, ArH), 7.65 (m, 3H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS)m/z = 317.51 (M + 1).

4.5.3. tert-Butyl 4-((2-(2-(trifluoromethoxy)phenyl)acetoyloxy) methyl)thiazol-2-ylcarbamate (**4c**)

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 3.82 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 7.16 (s, 1H, ArH), 7.65 (t, 1H, ArH), 7.95 (t, 1H, ArH), 7.98 (d, 1H, ArH), 8.07 (d, 1H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS)m/z = 433.31 (M + 1).

4.5.4. tert-Butyl 4-((3-fluoro-5-(trifluoromethyl)benzoyloxy) methyl)thiazol-2-ylcarbamate (**4d**)

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.32 (s, 2H, CH_2), 7.29 (s, 1H, ArH), 8.08 (s, 1H, ArH), 8.10 (s, 1H, ArH), 11.51 (s, 1H, ArH), 13.81 (s, 1H, NH); LC/MS(ESI-MS)m/z = 421.19 (M + 1).

4.5.5. tert-Butyl 4-((4-(2-cyanoethyl)benzoyloxy)methyl)thiazol-2-ylcarbamate (**4e**)

^{1}H NMR (DMSO) δ ppm = 1.49 (s, 9H, Boc), 2.78 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 5.28 (s, 2H, CH_2), 7.23 (s, 1H, ArH), 7.53 (t, 1H, ArH), 7.74 (t, 1H, ArH), 7.94 (d, 1H, ArH), 8.01 (d, 1H, ArH), 11.51 (s, 1H, NH); LC/MS(ESI-MS)m/z = 388.62 (M + 1).

4.5.6. tert-Butyl 4-((3-cyanobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4f**)

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.14 (s, 2H, CH_2), 7.28 (s, 1H, ArH), 7.56 (d, 1H, ArH), 7.75 (t, 1H, ArH), 8.22 (t, 1H, ArH), 8.25 (d, 1H, ArH), 11.52 (s, 1H, NH); LC/MS(ESI-MS)m/z = 360.27 (M + 1).

4.5.7. tert-Butyl 4-((thiophene-2-carboxyloyloxy)methyl)thiazol-2-ylcarbamate (**4g**)

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.24 (s, 2H, CH_2), 7.20 (s, 1H, ArH), 7.24 (d, 1H, ArH), 7.84 (t, 1H, ArH), 7.98 (d, 1H, ArH), 11.52 (s, 1H, NH); LC/MS(ESI-MS)m/z = 341.31 (M + 1).

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

*4.5.8. tert-Butyl 4-((2-chloro-3-nitrobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4h**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.22 (s, 2H, CH_2), 7.18 (s, 1H, ArH), 7.54 (t, 1H, ArH), 8.31 (d, 1H, ArH), 8.38 (d, 1H, ArH), 11.48 (s, 1H, NH).

*4.5.9. tert-Butyl 4-((6-cyanopyridine-3-carboxyloyloxy)methyl) thiazol-2-ylcarbamate (**4i**)*

^{1}H NMR (DMSO) δ ppm = 1.46 (s, 9H, Boc), 5.18 (s, 2H, CH_2), 7.20 (s, 1H, ArH), 8.52 (d, 1H, ArH), 8.82 (d, 1H, ArH), 9.64 (s, 1H, ArH), 11.52 (s, 1H, NH); LC/MS(ESI-MS)m/z = 414.62 (M + 1).

*4.5.10. tert-Butyl 4-((2-chloro-6-fluorobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4j**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.23 (s, 2H, CH_2), 6.92 (t, 1H, ArH), 7.20 (s, 1H, ArH), 7.31 (d, 1H, ArH), 7.62 (d, 1H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS)m/z = 387.89 (M + 1).

*4.5.11. tert-Butyl 4-((2,4,5-trifluorobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4k**)*

^{1}H NMR (DMSO) δ ppm = 1.47 (s, 9H, Boc), 5.23 (s, 2H, CH_2), 6.72 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.68 (s, 1H, ArH), 11.46 (s, 1H, NH); LC/MS(ESI-MS)m/z = 389.2 (M + 1).

*4.5.12. tert-Butyl 4-((furan-2-carboxyloyloxy)methyl)thiazol-2-ylcarbamate (**4l**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.24 (s, 2H, CH_2), 7.20 (s, 1H, ArH), 7.28 (t, 1H, ArH), 7.45 (d, 1H, ArH), 7.98 (d, 1H, ArH), 11.52 (s, 1H, NH); LC/MS(ESI-MS)m/z = 325.3 (M + 1).

*4.5.13. tert-Butyl 4-((2-naphthoyloxy)methyl)thiazol-2-ylcarbamate (**4m**)*

^{1}H NMR (DMSO) δ ppm = 1.46 (s, 9H, Boc), 5.22 (s, 2H, CH_2), 7.22 (s, 1H, ArH), 7.38 (m, 2H, ArH), 7.76 (m, 2H, ArH), 7.82 (d, 1H, ArH), 7.94 (t, 1H, ArH), 8.51 (d, 1H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS) m/z = 385.6 (M + 1).

*4.5.14. tert-Butyl 4-((4-nitrobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4n**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.32 (s, 2H, CH_2), 7.28 (s, 1H, ArH), 8.21 (m, 2H, ArH), 8.32 (m, 2H, ArH), 11.50 (s, 1H, NH); LC/MS(ESI-MS)m/z = 380.4 (M + 1).

*4.5.15. tert-Butyl 4-((2,4,6-trichlorobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4o**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.21 (s, 2H, CH_2), 6.70 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.67 (s, 1H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS)m/z = 438.6 (M + 1).

*4.5.16. tert-Butyl 4-((benzoyloxy)methyl)thiazol-2-ylcarbamate (**4p**)*

^{1}H NMR (DMSO) δ ppm = 1.46 (s, 9H, Boc), 5.18 (s, 2H, CH_2), 7.26 (s, 1H, ArH), 7.34 (m, 2H, ArH), 7.48 (t, 1H, ArH), 8.01 (m, 2H, ArH), 11.47 (s, 1H, NH); LC/MS(ESI-MS)m/z = 335.2 (M + 1).

*4.5.17. tert-Butyl 4-((6-cyanopyridine-2-carboxyloyloxy)methyl) thiazol-2-ylcarbamate (**4q**)*

^{1}H NMR (DMSO) δ ppm = 1.46 (s, 9H, Boc), 5.18 (d, 2H, CH_2), 7.20 (s, 1H, ArH), 8.41 (d, 1H, ArH), 8.67 (t, 1H, ArH), 9.29 (d, 1H, ArH), 11.50 (s, 1H, NH); LC/MS(ESI-MS)m/z = 361.29 (M + 1).

*4.5.18. tert-Butyl 4-((4-chlorobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4r**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.31 (s, 2H, CH_2), 7.28 (s, 1H, ArH), 8.20 (m, 2H, ArH), 8.36 (m, 2H, ArH), 11.48 (s, 1H, NH); LC/MS(ESI-MS)m/z = 369.91 (M + 1).

*4.5.19. tert-Butyl 4-((4-bromobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4s**)*

^{1}H NMR (DMSO) δ ppm = 1.46 (s, 9H, Boc), 5.30 (s, 2H, CH_2), 7.26 (s, 1H, ArH), 8.22 (m, 2H, ArH), 8.31 (m, 2H, ArH), 11.49 (s, 1H, NH); LC/MS(ESI-MS)m/z = 414.3 (M + 1).

*4.5.20. tert-Butyl 4-((4-nitrobenzoyloxy)methyl)thiazol-2-ylcarbamate (**4t**)*

^{1}H NMR (DMSO) δ ppm = 1.48 (s, 9H, Boc), 5.32 (s, 2H, CH_2), 7.28 (s, 1H, ArH), 7.59 (t, 1H, ArH), 7.67 (t, 1H, ArH), 8.28 (d, 1H, ArH), 8.43 (d, 1H, ArH), 11.50 (s, 1H, NH); LC/MS(ESI-MS)m/z = 380.2 (M + 1).

*4.6. General procedure for the preparation (2-aminothiazol-4-yl) methylester derivatives (**5a**–**t**)*

The intermediate (**4**) (1.5 mmol) was taken in ethanol (5 mL), cooled to 0 °C, slowly added ethanolic HCl (5 mL), to the reaction mixture and stirred the reaction mixture at ambient temperature for 4 h. The reaction completion was monitored by TLC. Reaction was completed. The ethanol layer was concentrated under reduced pressure. Charged 10% $NaHCO_3$ (10 mL) and extracted with ethylacetate (2×25 mL) and the organic layer was concentrated under pressure. The crude obtained was recrystalized in ethylacetate/hexane, and the solid formed was filtered to afford the title compounds **5a**–**t**. The spectral data of compounds **5**(**a**–**t**) are given below.

*4.6.1. (2-Aminothiazol-4-yl)methyl 1-(4-chlorophenyl) cyclopropanecarboxylate (**5a**)*

Appearance: white solid; m.p. 213–215 °C; ^{1}H NMR (DMSO) δ ppm = 1.22 (t, 2H, cyclopropylCH_2), 1.23 (t, 2H, cyclopropylCH_2), 4.82 (s, 2H, CH_2), 6.31 (s, 1H, ArH), 6.98 (s, 2H, NH_2), 7.38 (s, 4H, ArH); ^{13}C δ ppm (DMSO) = 16.77, 28.61, 62.78, 104.43, 128.47, 132.14, 132.62, 138.65, 146.90, 169.21, 173.26; LC/MS(ESI-MS)m/z = 309.62 (M + 1); Anal. Calcd for $C_{14}H_{13}ClN_2O_2S$; C, 54.46; H, 4.24; N, 9.07; Found C, 54.52; H, 4.32; N, 10.10.

*4.6.2. (2-Aminothiazol-4-yl)methyl 2-(3-(trifluoromethyl)phenyl) acetate (**5b**)*

Appearance: yellow oil; ^{1}H NMR (DMSO) δ ppm = 3.57 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.11 (s, 1H, ArH), 7.02 (s, 2H, NH_2), 7.06 (t, 1H, ArH), 7.07 (d, 1H, ArH), 7.25 (s, 1H, ArH), 7.29 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 46.46, 62.91, 103.28, 123.68, 124.01, 126.38, 128.74, 130.69, 132.64, 134.92, 152.91, 168.61, 171.14; LC/MS(ESI-MS)m/z = 317.42 (M + 1); $C_{13}H_{11}F_3N_2O_2S$; C, 49.36; H, 3.51; N, 8.86; Found C, 49.41; H, 3.48; N, 8.79.

*4.6.3. (2-Aminothiazol-4-yl)methyl 2-(2-(trifluoromethoxy)phenyl) acetate (**5c**)*

Appearance: off white solid; m.p. 178–180 °C; ^{1}H NMR (DMSO) δ ppm = 3.86 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.84 (s, 1H, ArH), 7.40 (d, 2H, ArH), 7.49 (m, 2H, ArH), 7.51 (s, 2H, NH_2); ^{13}C δ ppm (DMSO) = 32.19, 58.95, 107.86, 119.28, 121.83, 127.18, 127.89, 129.78, 133.07, 135.73, 147.54, 170.13, 170.40; LC/MS(ESI-MS)m/z = 333.2 (M + 1); $C_{13}H_{11}F_3N_2O_3S$; C, 46.99; H, 3.34; N, 8.43; Found C, 47.03; H, 3.39; N, 8.39.

*4.6.4. (2-Aminothiazol-4-yl)methyl 3-fluoro-5-(trifluoromethyl) benzoate (**5d**)*

Appearance: off white solid; m.p. 230–232 °C; ^{1}H NMR (DMSO) δ ppm = 5.28 (s, 2H, CH_2), 7.06 (s, 1H, ArH), 8.09 (s, 1H, ArH), 8.11 (s, 1H, ArH), 8.13 (s, 1H, ArH), 9.23 (s, 2H, NH_2); ^{13}C δ ppm

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

(DMSO) = 60.18, 108.20, 118.68, 120.92, 121.15, 122.43, 132.17, 133.35, 135.47, 161.25, 163.74, 170.54; LC/MS(ESI-MS)m/z = 321.31 (M + 1); $C_{12}H_8F_4N_2O_2S$; C, 45.00; H, 2.52; N, 8.75; Found C, 4.13; H, 2.61; N, 8.68.

*4.6.5. (2-Aminothiazol-4-yl)methyl 3-(2-cyanoethyl)benzoate (**5e**)*

Appearance: white solid; m.p. 165–167 °C; ^{1}H NMR (DMSO) δ ppm = 2.74 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 5.28 (s, 2H, CH_2), 7.17 (s, 1H, ArH), 7.23 (d, 1H, ArH), 7.28 (t, 1H, ArH), 8.17 (s, 2H, NH_2), 8.23 (d, 1H, ArH), 8.42 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 17.02, 32.84, 62.82, 104.42, 116.91, 127.41, 127.62, 127.98, 130.02, 152.74, 167.39, 169.32; LC/MS(ESI-MS)m/z = 288.31 (M + 1); $C_{14}H_{13}N_3O_2S$; C, 58.52; H, 4.56; N, 14.62; Found C, 58.63; H, 4.48; N, 14.71.

*4.6.6. (2-Aminothiazole-4-yl)methyl 2-cyanobenzoate (**5f**)*

Appearance: brown solid; m.p. 235–237 °C; ^{1}H NMR (DMSO) δ ppm = 5.17 (s, 2H, CH_2), 6.68 (s, 1H, ArH), 7.02 (s, 2H, NH_2), 7.88 (d, 2H, ArH), 8.12 (t, 1H, ArH), 8.14 (t, 1H, ArH); ^{13}C δ ppm (DMSO) = 63.55, 105.98, 112.19, 117.80, 131.39, 131.99, 133.86, 134.06, 135.75, 146.17, 163.74, 169.36; LC/MS(ESI-MS)m/z = 260.31 (M + 1); $C_{12}H_9N_3O_2S$; C, 55.59; H, 3.50; N, 16.20; Found C, 55.63; H, 3.61; N, 16.09.

*4.6.7. (2-Aminothiazole-4-yl)methyl thiophene-2-carboxylate (**5g**)*

Appearance: brown solid; m.p. 192–194 °C; ^{1}H NMR (DMSO) δ ppm = 5.08 (s, 2H, CH_2), 6.61 (s, 1H, ArH), 7.02 (s, 2H, NH_2), 7.23 (d, 1H, ArH), 7.84 (d, 1H, ArH), 7.97 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 62.69, 105.86, 128.87, 133.24, 134.36, 134.54, 146.62, 161.61, 169.35; LC/MS(ESI-MS)m/z = 241.21 (M + 1); $C_9H_8N_2O_2S_2$; C, 44.98; H, 3.36; N, 11.66; Found C, 45.13; H, 3.41; N, 11.59.

*4.6.8. (2-Aminothiazole-4-yl)methyl 2-chloro-3-nitrobenzoate (**5h**)*

Appearance: yellow solid; m.p. 150–152 °C; ^{1}H NMR (DMSO) δ ppm = 5.17 (s, 2H, CH_2), 6.72 (s, 1H, ArH), 7.16 (s, 2H, NH_2), 7.64 (t, 1H, ArH), 8.28 (d, 1H, ArH), 8.92 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 62.62, 103.78, 125.48, 126.97, 131.09, 131.82, 136.81, 148.31, 154.26, 166.41, 170.14; LC/MS(ESI-MS)m/z = 314.81 (M + 1); $C_{11}H_8ClN_3O_4S$; C, 42.11; H, 2.57; N, 13.39; Found C, 42.20; H, 2.43; N, 13.58.

*4.6.9. (2-Aminothiazole-4-yl)methyl 6-cyanopyridine-3-carboxylate (**5i**)*

Appearance: white solid; m.p. 178–180 °C; ^{1}H NMR (DMSO) δ ppm = 5.19 (s, 2H, CH_2), 6.72 (s, 1H, ArH), 7.02 (s, 2H, NH_2), 8.21 (d, 1H, ArH), 8.53 (d, 1H, ArH), 9.09 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 63.28, 116.87, 103.81, 126.32, 130.13, 134.84, 136.91, 150.98, 154.15, 166.43, 170.48; LC/MS(ESI-MS)m/z = 261.3 (M + 1); $C_{11}H_8N_4O_2S$; C, 50.76; H, 3.10; N, 21.53; Found C, 50.61; H, 3.21; N, 21.58.

*4.6.10. (2-Aminothiazole-4-yl)methyl 2-chloro-6-fluorobenzoate (**5j**)*

Appearance: off white solid; m.p. 110–112 °C; ^{1}H NMR (DMSO) δ ppm = 5.15 (s, 2H, CH_2), 6.66 (s, 1H, ArH), 7.06 (s, 2H, NH_2), 7.41 (d, 1H, ArH), 7.57 (d, 1H, ArH), 7.62 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 64.05, 106.78, 115.47, 122.21, 126.41, 131.30, 133.55, 145.67, 157.98, 160.47, 169.33; LC/MS(ESI-MS)m/z = 287.82 (M + 1); $C_{11}H_8ClFN_2O_2S$; C, 46.08; H, 2.81; N, 9.77; Found C, 46.21; H, 2.30; N, 9.62.

*4.6.11. (2-Aminothiazole-4-yl)methyl 2,4,6-trifluorobenzoate (**5k**)*

Appearance: yellow oil; ^{1}H NMR (DMSO) δ ppm = 5.14 (s, 2H, CH_2), 6.68 (s, 1H, ArH), 7.04 (s, 2H, NH_2), 7.98 (s, 1H, ArH), 8.08 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 64.18, 105.76, 132.24, 132.68, 132.94, 133.14, 134.68, 140.07, 154.17, 167.38, 170.13; LC/MS(ESI-MS)m/z = 289.32 (M + 1); $C_{11}H_7F_3N_2O_2S$; C, 45.84; H, 2.45; N, 9.72; Found C, 45.75; H, 2.53; N, 9.68.

*4.6.12. (2-Aminothiazole-4-yl)methyl furan-2-carboxylate (**5l**)*

Appearance: white solid; m.p. 183–185 °C; ^{1}H NMR (DMSO) δ ppm = 5.07 (s, 2H, CH_2), 6.69 (s, 1H, ArH), 6.71 (d, 1H, ArH), 7.01 (s, 2H, NH_2), 7.34 (d, 1H, ArH), 7.97 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 62.27, 106.01, 112.81, 119.07, 144.16, 146.48, 148.17, 158.06, 169.33; LC/MS(ESI-MS)m/z = 225.32 (M + 1); $C_9H_8N_2O_3S$; C, 48.21; H, 3.60; N, 12.49; Found C, 48.38; H, 3.69; N, 12.53.

*4.6.13. (2-Aminothiazole-4-yl)methyl 2-naphthoate (**5m**)*

Appearance: off white solid; m.p. 157–159 °C; ^{1}H NMR (DMSO) δ ppm = 5.23 (s, 2H, CH_2), 6.69 (s, 1H, ArH), 7.06 (s, 2H, NH_2), 7.67 (m, 4H, ArH), 8.05 (s, 1H, ArH), 8.21 (d, 1H, ArH), 8.78 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 62.84, 104.84, 126.09, 126.82, 128.32, 128.87, 129.82, 130.17, 131.98, 135.61, 154.70, 166.19, 170.09; LC/MS(ESI-MS) m/z = 285.3 (M + 1); $C_{15}H_{12}N_2O_2S$; C, 63.36; H, 4.25; N, 9.85; Found C, 63.42; H, 4.38; N, 9.76.

*4.6.14. (2-Aminothiazole-4-yl)methyl 4-nitrobenzoate (**5n**)*

Appearance: pale yellow solid; m.p. 160–162 °C; ^{1}H NMR (DMSO) δ ppm = 5.17 (s, 2H, NH_2), 5.24 (s, 2H, CH_2), 6.60 (s, 1H, ArH), 8.25 (m, 4H, ArH); ^{13}C δ ppm (DMSO) = 62.96, 108.34, 123.51, 130.93, 135.41, 146.25, 150.62, 164.45, 168.17; LC/MS(ESI-MS)m/z = 280.3 (M + 1); $C_{11}H_9N_2O_2S$; C, 47.31; H, 3.25; N, 15.05; Found C, 47.28; H, 3.31; N, 15.12.

*4.6.15. (2-Aminothiazole-4-yl)methyl 2,4,6-trichlorobenzoate (**5o**)*

Appearance: semi solid; ^{1}H NMR (DMSO) δ ppm = 5.12 (s, 2H, CH_2), 6.63 (s, 1H, ArH), 7.01 (s, 2H, NH_2), 7.89 (s, 1H, ArH), 7.96 (s, 1H, ArH); ^{13}C δ ppm (DMSO) = 63.21, 104.32, 131.20, 131.62, 131.79, 132.90, 134.19, 139.65, 154.09, 166.00, 168.59; LC/MS(ESI-MS)m/z = 338.6 (M + 1); $C_{11}H_7Cl_3N_2O_2S$; C, 39.13; H, 2.09; N, 8.30; Found C, 39.24; H, 2.12; N, 8.23.

*4.6.16. (2-Aminothiazole-4-yl)methyl benzoate (**5p**)*

Appearance: white solid; m.p. 174–176 °C; ^{1}H NMR (DMSO) δ ppm = 5.12 (s, 2H, CH_2), 6.62 (s, 1H, ArH), 7.11 (s, 2H, NH_2), 7.55 (d, 2H, ArH), 7.69 (t, 1H, ArH), 8.00 (d, 2H, ArH); ^{13}C δ ppm (DMSO) = 62.72, 105.59, 129.25, 129.68, 130.08, 133.86, 146.81, 165.88, 169.34; LC/MS(ESI-MS)m/z = 235.3 (M + 1); $C_{11}H_{10}N_2O_2S$; C, 56.39; H, 4.30; N, 11.96; Found C, 56.47; H, 4.21; N, 11.85.

*4.6.17. (2-Aminothiazole-4-yl)methyl 6-cyanopyridine-2-carboxylate (**5q**)*

Appearance: white solid; m.p. 185–187 °C; ^{1}H NMR (DMSO) δ ppm = 5.20 (s, 2H, CH_2), 6.83 (s, 1H, ArH), 7.14 (s, 2H, NH_2), 8.30 (d, 1H, ArH), 8.87 (t, 1H, ArH), 9.31 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 63.7, 117.96, 105.64, 128.39, 130.04, 136.78, 138.31, 152.10, 154.16, 167.12, 169.64; LC/MS(ESI-MS)m/z = 261.3 (M + 1); $C_{11}H_8N_4O_2S$; C, 50.76; H, 3.10; N, 21.53; Found C, 50.87; H, 3.21; N, 21.65.

*4.6.18. (2-Aminothiazole-4-yl)methyl 4-chlorobenzoate (**5r**)*

Appearance: off white solid; m.p. 171–173 °C; ^{1}H NMR (DMSO) δ ppm = 5.02 (s, 2H, NH_2), 5.18 (s, 2H, CH_2), 6.48 (s, 1H, ArH), 8.19 (m, 4H, ArH); ^{13}C δ ppm (DMSO) = 61.89, 107.67, 122.49, 128.67, 133.59, 146.01, 149.69, 162.34, 167.96; LC/MS(ESI-MS)m/z = 269.81 (M + 1); $C_{11}H_9ClN_2O_2S$; C, 49.17; H, 3.38; N, 10.42; Found C, 49.23; H, 3.461; N, 10.39.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008

*4.6.19. (2-Aminothiazole-4-yl)methyl 4-bromobenzoate (**5s**)*

Appearance: brown solid; m.p. 163–165 °C; ^{1}H NMR (DMSO) δ ppm = 4.98 (s, 2H, NH_2), 5.12 (s, 2H, CH_2), 6.41 (s, 1H, ArH), 8.10 (m, 4H, ArH); ^{13}C δ ppm (DMSO) = 60.96, 107.43, 121.90, 128.04, 132.91, 145.79, 148.84, 161.62, 167.21; LC/MS(ESI-MS)m/z = 314.21 (M + 1); $C_{11}H_9BrN_2O_2S$; C, 42.19; H, 2.90; N, 8.95; Found C, 42.26; H, 2.92; N, 8.92.

*4.6.20. (2-Aminothiazole-4-yl)methyl 2-nitrobenzoate (**5t**)*

Appearance: pale yellow solid; m.p. 166–168 °C; ^{1}H NMR (DMSO) δ ppm = 5.19 (s, 2H, NH_2), 5.28 (s, 2H, CH_2), 6.64 (s, 1H, ArH), 8.19 (t, 1H, ArH) 8.34 (t, 1H, ArH) 8.79 (d, 1H, ArH) 8.98 (d, 1H, ArH); ^{13}C δ ppm (DMSO) = 60.71, 107.39, 121.86, 128.19, 133.42, 148.61, 154.67, 159.18, 160.43, 163.87, 169.42; LC/MS(ESI-MS)m/z = 280.34 (M + 1); $C_{11}H_9N_3O_4S$; C, 47.31; H, 3.25; N, 15.05; Found C, 47.39; H, 3.31; N, 15.16.

4.7. Antibacterial studies

The synthesized compounds were screened for their antibacterial activity against *E. coli* (ATTC-25922), *S. aureus* (ATTC-25923), *P. aeruginosa* (ATCC-27853) and *K. pneumoniae* (recultured) and *S. pyogenes* bacterial strains by serial plate dilution method [33,34]. Serial dilutions of the drug in Mueller–Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zone of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentration of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with ciprofloxacin as standard [35,36]. MIC (μg/mL) and Zone of inhibition (mm) was determined for all the synthesized compounds and the corresponding results are summarized in Table 2.

4.8. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *A. flavus* (NCIM No. 524), *Aspergillus fumigarus* (NCIM No. 902), *P. marneffei* (recultured) and *T. mentagrophytes* (recultured) and *C. albicans* in DMSO by serial plate dilution method [37,38]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal stain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar medias was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Ciclopiroxolamine as standard. MIC (μg/mL) and Zone of inhibition (mm) were determined for all the synthesized compounds and their corresponding results are summarized in Table 3.

4.9. Antituberculosis study

The compounds were screened for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv ATCC 27294 and non-tubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420, and *M. fortuitum* ATCC 19542 by Resazurin Assay method [39] and their MIC values were determined. The standard drugs, viz. isoniazid and rifampicin were used for comparison. *M. tuberculosis* strains were grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC (Becton Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 2 standard with the same medium. From this, 50 μL of this culture was added to 150 μL of fresh medium in 96 well microtitre plates. Stock solutions (2 mg/mL) of the test compounds were prepared in dimethyl formamide (DMF). The compounds were tested at 1, 10 and 100 μg/mL concentrations. Further the second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Control tubes had the same volumes of DMF without any substrate. Rifampicin and isoniazid were used as the reference compounds. After incubation at 37 °C for 7 days, 20 μL of 0.01% Resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a color change from blue to pink after 1 h at 37 °C. Compounds which prevented the change of color of the dye were considered to be inhibitory to *M. tuberculosis*.

Acknowledgment

We thank to DST-India, for providing X-ray facility at SSCU, Indian Institute of Science, Bangalore, and Head of the Department of Biochemistry, Justice K. S. Hegde Medical Academy, to carry out biological studies. We are grateful to the Head, Chemistry Department and School of Chemical Sciences for the kind support and providing necessary laboratory facilities.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2012.01.008.

References

[1] J.P. Cegielski, D.P. Chin, M.A. Espinal, T.R. Frieden, R. Rodriquez Cruz, E.A. .Talbot, D.E. Weil, R. Zaleskis, M.C. Raviglione, Infect. Dis. Clin. North Am. 161 (2002) 1–58.
[2] M.K. Spigelman, J. Infect. Dis. 196 (2007) S28–S34.
[3] M.R. Shiradkar, K.K. Murahari, H.R. Gangadasu, T. Suresh, C.A. Kalyan, D. Panchal, R. Kaur, P. Burange, J. Ghogare, V. Mokale, M. Raut, Bioorg. Med. Chem. Lett. 15 (2007) 3997–4008.
[4] S.K. Bharti, G. Nath, R. Tilak, S.K. Singh, Eur. J. Med. Chem. 45 (2010) 651–660.
[5] N. Hans, Swiss Patent 592103, (1977), Chem. Abstract 88 (1978) 22886.
[6] K.J. Wilson, C.R. Utig, N. Subhasinghe, J.B. Hoffman, N.J. Rudolph, R. Soll, C.J. Molloy, R. Bone, D. Green, J. Randall, Bioorg. Med. Chem. Lett. 11 (2001) 915–918.
[7] K.D. Berlin, M.D. Herd, Proc. Okla. Acad. Sci. 71 (1991) 29–33.
[8] P.K. Sharma, S.N. Swonhney, A. Gupta, G.B. Sing, S. Bani, Indian J. Chem. 37B (1998) 371–375.
[9] K. Taori, V.J. Paul, H. Luesch, J. Am. Chem. Soc. 130 (2008) 1806–1807.
[10] F. Sasse, H. Steinmetz, G. Hofle, H. Reichenbach, J. Antibiot. 56 (2003) 520–525.
[11] S. Kehraus, G.M. Konig, A.D. Wright, J. Org. Chem. 67 (2002) 4989–4992.
[12] K. Gerth, N. Bedorf, G. Hofle, H. Irschik, H. Reichenbach, J. Antibiot. 49 (1996) 560–563.
[13] K.D. Hargrave, F.K. Hess, J.T. Oliver, J. Med. Chem. 26 (1983) 1158–1163.

[14] W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. Taylor, C.J.C. Connolly, A.M. Doharty, S.R. Klutchko, I. Sircar, B.A. Steinbaugh, B.L. Bately, C.A. Painchand, S.T. Rapundalo, B.M. Michniewicz, S.C.J. Olzon, J. Med. Chem. 35 (1992) 2562–2572.
[15] P.K. Sharma, S.N. Sawnhney, A. Gupta, G.B. Sing, S. Bani, Indian J. Chem. 37B (1998) 376–381.
[16] J.C. Jaen, L.D. Wise, B.W. Caprathe, H. Tecle, S. Bergmeier, C.C. Humblet, T.G. Heffner, L.T. Meltzner, T.A. Pugsley, J. Med. Chem. 33 (1990) 311–317.
[17] N. Ergenc, G. Capan, N.S. Gunay, S. Oskirimli, M. Gungor, S. Ozbey, E. Kendi, Arch. Pharm. Pharm. Med. Chem. 332 (1999) 343–347.
[18] J.S. Carter, S. Kramer, J.J. Talley, T. Penning, P. Collins, M.J. Graneto, K. Seibert, C. Koboldt, J. Masferrer, B. Zweifel, Bioorg. Med. Chem. Lett. 9 (1999) 1171–1174.
[19] F.W. Bell, A.S. Cantrell, M. Hoberg, D.R. Jaskunas, N.G. Johansson, C.L. Jordon, M.D. Kinnick, P. Lind, J.M. Morin Jr., R. Noreen, B. Oberg, J.A. Palkowitz, C.A. Parrish, J. Pranc, H. Zhang, X.X. Zhou, J. Med. Chem. 38 (1995) 4929–4936.
[20] A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. horie, K. Osakada, M. Kawamoto, T. Ikeda, J. Am. Chem. Soc. 125 (2003) 1700–1701.
[21] M. Ng, L. Yu, Angew. Chem. Int. Ed. 41 (2002) 3598–3601.
[22] K.C. Nicolaou, F. Sarabia, S. Ninkovic, M.R. Finlay, C.N.C. Boddy, Angew. Chem. Int. Ed. 37 (1998) 81–84.
[23] T.R. Kelly, F. Lang, J. Org. Chem. 61 (1996) 4623–4633.
[24] K.C. Nicolaou, N.P. King, M.R.V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, S. Sarabia, S. Ninkovic, D. Hepworth, Bioorg. Med. Chem. 7 (1999) 665–697.
[25] A.M. Panico, A. Geronikaki, R. Mgonzo, V. Cardile, B. Gentile, I. Doytchinova, Bioorg. Med. Chem. 11 (2003) 2983–2989.
[26] P.K. Ranjith, M. Siji, N. Divia, K.R. Haridas, J. Korean Chem. Soc. 54 (2010) 589–593.
[27] M. Kaspady, V.K. Narayanaswamy, M. Raju, G.K. Rao, Lett. Drug Des. Discovery 6 (2009) 21–28.
[28] W.K. George, R.M. Arjun, Tetrahedron. Lett. 47 (2006) 5171–5172.
[29] M.A. Parker, D.M. Kurrasch, D.E. Nichols, Bioorg. Med. Chem. 16 (2008) 4661–4669.
[30] H. Nakayama, K. Ishihara, S. Akiba, J. Uenishi, Chem. Pharm. Bull. 59 (2011) 1069–1072.
[31] G.M. Sheldrick, Acta Crystallogr. A64 (2008) 112–122.
[32] L.J. Farrugia, J. Appl. Crystallogr. 30 (1997) 565–566.
[33] A.L. Barry, Procedure for testing antimicrobial agents in agar media, in: V.L. Corian (Ed.), Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore, MD, 1980, pp. 1–23.
[34] D. James Mac. Lowry, J.M. Jaqua, T.S. Sally, Appl. Microbiol. 20 (1970) 46–53.
[35] C.H. Fenlon, M.H. Cynamon, Antimicrob. Agents Chemother. 29 (1986) 386–388.
[36] R. Davis, A. Markham, J.A. Balfour, Ciprofloxacin, an update review of its pharmacology, therapeutic efficiency and tolerability, Drugs 51 (1996) 1019–1074.
[37] B.A. Arthington-Skaggs, M. Molestely, D.W. Warnock, C.J. Morrison, J. Clin. Microbiol. (2000) 2254–2260.
[38] R.S. Verma, Z.K. Khan, A.P. Sing (Eds.), Antifungal Agents: Past, Present and Future Prospects, National Academy of Chemistry and Biology, Lucknow, India, 1998, pp. 55–128.
[39] K.T. Neetu, S.T. Jaya, J. Antimicrob. Chemother. 60 (2007) 288–293.

Please cite this article in press as: R.P. Karuvalam, et al., Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry (2012), doi:10.1016/j.ejmech.2012.01.008