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Solvent free synthesis of alkyl 2-(dialkylamino)-4 phenylthiazole-5-carboxylates derivatives and *in vitro* antimycobacterial activity of these compounds against *Mycobacterium smegmatis*

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ABSTRACT

The reaction between secondary amines, benzoyl isothiocyanate, and dialkyl acetylene dicarboxylates (dialkyl but-2-ynedioates) in the presence of silica gel (SiO_2) led to alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates in fairly high yields. The structures of these products were confirmed by their IR, ^1H and $^{13}CNMR$, and mass spectra determination. All compounds have been screened for antimicrobial activity against Mycobacterium smegmatis by broth dilution and agar well diffusion methods. All the synthesized derivatives exhibited remarkable activity against this bacterium.

Keywords: Solvent free, 2-aminothiazol, Antimicrobial, *Mycobacterium smegmatis*

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by some species of genus *Mycobacterium* which are called ‘‘tuberculosis complex’’, including *Mycobacterium tuberculosis*, *Mycobacterium bovis* and *Mycobacterium africanum* [1, 2]. In the last decades, TB has re-emerged as one of the leading causes of death worldwide (nearly 3 million deaths annually) [3]. The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7,000 each day [4, 5]. These data only shows a partial depiction of global TB problem. More than 80% of TB patients are in the economically productive age of 15-49 years, which results in extensive economic and social problems. It was predicted in 2007 that near to more than one billion people will be infected with TB in the next 20 years and in about 15% of them (150 million) symptoms of the disease will be developed. Also it was predicted that 36 million individuals will die from TB if new ways for prevention and treatment are not found [6]. In 2005, the TB incidence rate was stable or in decline all over the world, and had reached a peak worldwide. However, the total number of new TB cases is still rising slowly, because there is an increase in number of cases in the African, Eastern Mediterranean and South-East Asia regions [6]. The notable increase in TB cases observed in the recent years is a result of two major factors. The first one is the increased susceptibility of people infected with HIV (Human Immunodeficiency Virus) to TB, which augments the risk of developing the disease up to 100-fold [7]. The second one is the emergence and spread of resistant strains of *M. tuberculosis* to antibiotics [8], so some strains show multi-drug resistance to even nine drugs [7]. The emergence of a better vaccine could be considered as a long term solution to the problem but in the short term, chemotherapy seems to be more effective in managing the problem [9] so developing of novel, effective and non-toxic anti-tubercular agents is a serious requirement [9-11]. The

identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of multi-drug resistant strains. To do this, biochemical pathways specific to *Mycobacteria* must be considered as goals. Many specific metabolic processes occur during the biosynthesis of mycobacterial cell wall components [12]. One of these attractive targets for designing of new anti tubercular agents is the biosynthesis of mycolic acids, the major components of the cell wall of M. tuberculosis [13]. *Mycobacterium smegmatis*, a soil dwelling saprophyte is a *Mycobacterium* model that is used to understand the pathogenesis and physiology of *M.tuberculosis*. There are many disadvantages in the direct study of the *M. tuberculosis*; *M. tuberculosis* is a Category 3 human pathogen, requiring biosafety level III laboratory and animal facilities, substantial training before handling and there is a high risk of accidental exposure during treatment of infectious samples[6]. Also, *M. tuberculosis* grows slowly and colony formation requires two to three weeks, making its utilization for experimentation, time consuming [7]. However *M. smegmatis* is avirulent and fast growing. There are many similarities in physiology and structure of *M. tuberculosis* and *M. smegmatis* According to Barry 2009 [8], 12 out of 19 *M tuberculosis* virulence genes described so far have related homologues in *M. smegmatis.* Further, to determine the usefulness of *M. smegmatis* as an anti-tubercular drug discovery model, Altaf et al. 2010 [9] quantified the efficiency of *M. smegmatis* in detecting compounds that are inhibitory towards *M. tuberculosis* in compound library screening. From their results, *M. smegmatis* clearly illustrated usefulness in tuberculosis drug discovery. The aim of this study was the Synthesis of the Solvent free Alkyl 2-(Dialkylamino)-4 phenylthiazole-5-carboxylates derivatives and the evaluation of their in vitro anti mycobacterial activities against *Mycobacterium smegmatis as* an anti-tubercular drug discovery model.

EXPERIMENTAL SECTION

Chemistry

General.

Starting materials and solvents were obtained from Merck (Germany) and Fluka(Switzerland) and were used without further purification. Flash chromatography (FC): preparation of columns with Merck silica gel (SiO_2) powder. M.p: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu-IR-460 spectrometer; ϑ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-DRX-300-Avance* spectrometer; at 300.13 (^1H) and 75.467 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT-8430* mass spectrometer; ionization potential 20 eV. Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

The title were prepared within a one step and solvent free synthesis which consists in the reaction of N-benzoylthiourea derivatives 3, which were derived from the addition of secondary amines 2 to benzoyl isothiocyanate (1), with acetylenedicarboxylates (=but-2-ynedioates) 4 proceeded in CH_2Cl_2 at room temperature to give compound 5. SiO2 Powder was found to catalyze the conversion of 5 to the alkyl 2-(dialkylamino)-4phenylthiazole-5-carboxylates: 8 under solvent-free conditions at 90^o in fairly good yields without the formation of by-products (Figure 1).

Compounds 8a – 8l: General Procedure. To a stirred soln. of benzoylisothiocyanate (1; 0.163 g,1mmol) and secondary amine 2 (1 mmol) in dry CH_2Cl_2 (5 ml) was added drop wise a mixture of dialkyl but-2-ynedioate 4 (1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. Then, after 0.5 h, SiO_2 powder (2 g) was added, and the solvent was evaporated. The dry materials were heated for 1 h at 90^o and then placed on top of a column of SiO_2 (10 g). The column was washed with AcOEt/light petroleum ether 2: 10. The solvent was then evaporated: product 8.

General method for Synthesis of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylate Derivatives:

To a stirred soln. of benzoylisothiocyanate (1; 0.163 g,1mmol) and secondary amine 2 (1 mmol) in dry CH_2Cl_2 (5 ml) was added drop wise a mixture of dialkylbut-2-ynedioate 4 (1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. Then, after 0.5 h, SiO_2 powder (2 g) was added, and the solvent was evaporated. The dry materials were heated for 1 h at 90^o and then placed on top of a column of SiO_2 (10 g). The column was washed with AcOEt/light petroleum ether 2: 10. The solvent was then evaporated: product 8.

Methyl 2-(Morpholin-4-yl-4-phenylthiazole-5-carboxylate (8a): Yield 255 mg (84%). White crystals. M.p. 130.0^o. *IR* (KBr): 3065, 2955, 2924, 1735, 1534, 1483, 1237, 1114. ^{1}*H-NMR*: 3.59 – 3.62 (*m*, (CH_2)2N);3.75 (*s*, Me); 3.82 – 3.83 (*m*, (CH_2)2O); 7.39 (br, 3 arom. H); 7.72 (br, 2 arom. H). ^{13}*C-NMR*: 51.74 (Me); 47.99 ((CH2)2N); 66.04 ($(CH_2)_2O$); 127.63, 129.15, 129.760 (5 arom. C); 133.48, 135.01, 160.74, 162.74(4 C); 170.02 (C=O). EI-MS:

304 (100,M^+), 285 (6), 273 (20), 259 (18), 247 (70), 231 (13), 215 (28), 201(8), 133 (23), 89 (28), 76 (10). Anal.calc. for C15H16N2O3S (304.36): C 59.19, H 5.30, N 9.20; found: C59.02, H 5.16, N 9.17.

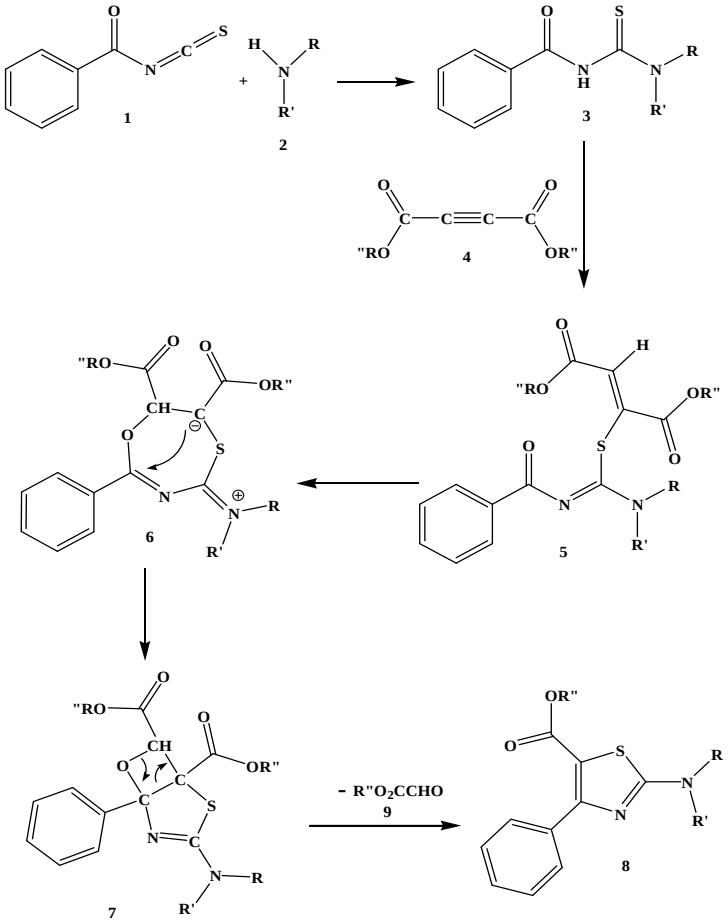


Figure1. Proposed Mechanism for the Formation of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylate Derivatives

Ethyl 2-(Morpholin-4-yl)-4-phenylthiazole-5-carboxylate (8b): Yield 254 mg (80%). White crystals.M.p.90.0 – 91.0°.*IR* (KBr): 3053, 2980, 2924, 1708, 1528, 1482, 1368, 1250. ^{1}*H-NMR*: 1.27 (t, ^{3}J=7.2,$MeCH_2$); 3.59 – 3.62 (m, $(CH_2)_2N$); 3.81 – 3.85 (m, $(CH_2)_2O$); 4.21 (*q*, ^3J=7.2, $MeCH_2$); 7.39 – 7.41 (*m*, 3arom. H); 7.72 – 7.74 (*m*, 2 arom. H). ^{13}*C-NMR*: 14.21 ($MeCH_2$); 47.98 ($(CH_2)_2N$); 60.70 ($MeCH_2$); 66.05($(CH_2)_2O$); 127.56, 129.02, 129.78 (5 arom. *H*); 133.56, 135.31, 160.85, 162.90 (4 C); 170.41 (C=O). EIMS:318 (100, M^+), 304 (7), 289 (9), 273 (27), 260 (73), 246 (24), 232 (32), 215 (29), 188 (41), 133 (71),105 (52), 39 (85), 77 (29), 56 (40). Anal.calc. for C16H18N2O3S (318.39): C 60.36,H5.70, N 8.80; found: C60.27, H 5.61, N 8.73.

Methyl 2-[Methyl(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8c): Yield 270 mg (80%).White crystals. M.p. 77.2°.*IR* (KBr): 3025, 2984, 2943, 1710, 1604, 1550, 1330, 1244. ^{1}*H-NMR*: 3.11 (*s*,MeN); 3.75 (*s*, MeO); 4.79 (*s*, CH_2N); 7.33 – 7.42 (m, 8 arom. H); 7.79 – 7.80 (m, 2 arom. H). 13C-NMR: 37.88 (MeN); 51.61 (MeO); 55.97 (CH_2N); 127.57, 127.74, 127.86, 128.81, 129.87 (10 arom. C); 129.01,134.77, 136.01, 160.41, 162.38 (5 C); 170.96 (C=O). EI-MS: 338 (85,M^+), 329 (47), 309 (37), 247 (11), 215(24), 188 (14), 146 (18), 120 (15), 103 (13), 91 (100), 77 (13), 65 (17). Anal.calc. for C19H18N2O2S (338.42): C 67.43, H 5.36, N 8.28; found: C 67.36, H 5.30, N 8.10.

Ethyl 2-[Methyl(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8d): Yield 271 mg (77%).White crystals. M.p. 73.2°.*IR* (KBr): 3059, 2983, 2926, 1702, 1605, 1550, 1331, 1242. 1H-NMR: 1.25 (*t*, ^3J=7.0, $MeCH_2$,EtO); 3.10 (*s*, MeN); 4.211 (*q*, ^3J=7.0, $MeCH_2$); 7.32 – 7.39 (*m*, 8 arom. H); 7.78 – 7.79 (*m*, 2arom. H). ^{13}*C-NMR*: 14.29 ($MeCH_2$); 37.89 (MeN); 55.93 (CH_2N); 60.55 ($MeCH_2$); 127.52, 127.73,127.83, 128.79, 129.90 (10 arom. C);

128.93, 134.89, 136.07, 160.07, 162.17 (5 C); 170.90 (C¼O). EI-MS:352 (27,Mþ), 327 (13), 323 (14), 279 (8), 215 (10), 167 (26), 149 (86), 104 (100), 91 (58), 70 (54), 57 (34),43 (48). Anal.calc. for C20H20N2O2S (352.45): C 68.16, H 5.72, N 7.95; found: C 68.02, H 5.64, N 7.81.

Methyl 4-Phenyl-2-(piperidin-1-yl)thiazole-5-carboxylate (8e): Yield 244 mg (81%). White crystals.M.p. 90.7°. IR (KBr): 3065, 2997, 2962, 2946, 1715, 1531, 1482, 1340, 1303, 1245, 1145. ^{1}*H-NMR*: 1.67 –1.72 (*m*, 3CH2 (pip)); 3.57 – 3.59 (*m*, 2CH_2 (pip)); 3.74 (*s*, Me); 7.39 – 7.41 (*m*, 3 arom. H); 7.74 – 7.77(*m*, 2 arom. H). ^{13}*C-NMR*: 23.99, 25.12, 49.17 (5 CH_2); 51.53 (MeO); 127.54, 128.90, 129.76 (5 arom. C);130.86, 134.91, 160.38, 162.44 (5 C); 170.90 (C=O). EI-MS: 302 (25, M^+), 273 (14), 246 (17), 167 (17),149 (39), 84 (21), 58 (41), 43(100). Anal.calc. for C16H18N2O2S (302.39): C 63.55, H 6.00, N 9.26; found:C 62.10, H 5.82, N 9.00.

Ethyl 4-Phenyl-2-(piperidin-4-yl)thiazole-5-carboxylate (8f): Yield 249 mg (79%). Viscous oil.*IR*(KBr): 3056, 2936, 2855, 1708, 1677, 1532, 1243. ^{1}*H-NMR*: 1.25 (*t*, ^{3}*J*=7.0, $MeCH_2$); 1.66 – 1.71 (*m*, 3 CH2(pip)); 3.58 – 3.57 (m, 2 CH2 (pip)); 4.20 (*q*, ^{3}*J*=7.0, $MeCH_2$); 7.38 – 7.40 (*m*, 3 arom. H); 7.73 – 7.76 (*m*, 2arom. H). ^{13}*C-NMR*: 14.25 ($MeCH_2$); 23.76, 25.13, 49.17 (5 CH_2 (pip)); 60.46 ($MeCH_2$); 127.49, 128.82,129.79 (5 arom. C); 130.86, 134.10, 159.99, 162.05 (4 C); 170.84 (C=O). EI-MS: 318 (60,M^+), 275 (100) ,261 (96) , 299 (20) , 201 (13) , 174 (15), 129 (15), 104 (13), 89 (18) , 43 (32). Anal.calc. for C17H20N2O2S (316.42): C 64.53, H 6.37, N 8.85; found: C 64.26, H 6.21, N 8.73.

Methyl 2-[Bis(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8g): Yield 322 mg (77%).White crystals. M.p. 107.6°. IR (KBr): 3061, 32029, 2936, 1677, 1604, 1528, 1310, 1263. ^{1}*H-NMR*: 3.73(*s*, Me); 4.72(s, 2 CH_2); 7.29 – 7.40 (*m*, 12 arom.H); 7.80 – 7.3 (*m*, 3 arom.H). ^{13}*C-NMR*: 51.59 (Me); 53.40(2 CH2); 127.55, 127.89, 128.81, 129.94 (15 arom. C); 129.05, 134.68, 135.75, 160.10, 162.31 (6 C); 171.12(C=O). EI-MS: 414 (20,M^+), 323 (82), 291 (8), 149 (4), 133 (7), 105 (6), 91 (100), 65 (12). Anal.calc. for C25H22N2O2S (414.52): C 72.44, H 5.35, N 6.76; found: C 68.02, H 5.64, N 7.81.

Ethyl 2-[Bis(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8h): Yield 321 mg (75%). White crystals.M.p. 73.1°.*IR* (KBr): 3060, 3028, 2978, 2912, 1708, 1534, 1481, 1331, 1237. ^{1}*H-NMR*: 1.25 (t, 3J=7.1, $MeCH_2$); 4.21 (*q*, ^{3}*J*=7.1, $MeCH_2$); 4.73 (*s*, $(CH_2)_2N$); 7.27 – 7.40 (*m*, 12 arom. H); 7.82 – 7.83 (*m*, 3arom. H). ^{13}*C-NMR*: 14.28 ($MeCH_2$); 53.32 (CH2)2N); 60.57 (MeCH2); 127.50, 127.87, 127.89, 128.80,129.98 (15 arom. C); 128.97, 134.81, 135.82, 159.78, 161.96 (6 C); 171.10 (C=O). EI-MS: 428 (3,M^+), 337(7), 279 (4), 206 (8), 191 (15), 167 (20), 149 (66), 105 (91), 91 (73), 70 (98), 59 (97), 48 (100). Anal.calc.for C26H24N2O2S (428.55): C 72.87, H 5.64, N 6.54; found: C 72.75, H 5.56, N 6.41

Methyl 2-[Bis(1-methylethyl)amino]-4-phenylthiazole-5-carboxylate (8i): Yield 271 mg (85%).White crystals. M.p. 105.4°. IR (KBr): 3020, 2965, 2929, 1706, 1600, 1526, 13331, 1258. ^{1}*H-NMR*: 1.42(*d*, ^{3}J=6.9, 2 $MeCH_2$); 3.74 (*s*, MeO); 3.91 – 3.96 (*m*, 2 $(Me)_2CH$); 7.37 – 7.45 (*m*, 3 arom. H); 7.81 – 7.84 (*m*, 2 arom. H). ^{13}*C-NMR*: 20.02 (Me_2CH); 51.15 (MeO); 51.44 (2 Me_2CH); 127.38, 128.78, 129.95 (5arom. C); 130.86, 135.13, 160.05, 162.62 (4 C); 168.01 (C=O). EI-MS: 318 (44, M^+), 261 (28), 234 (100),57 (38), 41 (55). Anal.calc. for C17H22N2O2S (318.43): C 64.12, H 6.96, N 8.80; found: C 63.87, H 6.71, N 8.65.

Ethyl 2-[Bis(1-methylethyl)amino]-4-phenylthiazole-5-carboxylate (8j): Yield 278 mg (83%).White crystals. M.p. 90.5°. IR (KBr): 3080, 3047, 2966, 2930, 1700, 1603, 1529, 1260. ^{1}*H-NMR*: 1.27 (*t*, 3J=7.1,$MeCH_2$); 1.42 (*d*, ^{3}*J*=6.9, Me_2CH); 3.91 – 3.95 (*m*, 2Me_2CH); 4.21 (*q*, ^{3}*J*=7.1, $MeCH_2$); 7.38 – 7.41 (m, 3arom.H); 7.81 – 7.84 (*m*, 2 arom.H). ^{13}*C-NMR*: 14.34 ($MeCH_2$); 20.04 (2 Me_2CH); 51.14 ($MeCH_2$); 60.31(2 Me_2CH); 127.32, 128.68, 129.99 (5 arom. C); 130.87, 135.28, 159.76, 162.25 (4 C); 167.98 (C=O). EIMS:332 (58,M^+), 289 (100), 275 (86), 261 (18), 247 (21), 229 (15), 174 (15), 148 (35), 129 (17), 103 (28),39 (21), 43 (24). Anal.calc. for C18H24N2O2S (332.46): C 65.03, H 7.28, N 8.43; found: C 64.21, H 6.46, N8.01.

Methyl 2-(Diethylamino)-4-phenylthiazole-5-carboxylate (8k): Yield 250 mg (86%). White crystals.M.p. 81.4°. *IR* (KBr): 3054, 3025, 2974, 2934, 1710, 1600, 1511, 1481, 1331, 1263. ^{1}*H-NMR*: 1.26 (*t*, 3J=6.9,2 $MeCH_2$); 3.54 – 3.57 (*m*, 2 $MeCH_2$); 3.73 (*s*, MeO); 7.39 (br., 3 arom. H); 7.75 (br., 2 arom. H).^{13}*C-NMR*: 12.49 (2 $MeCH_2$); 45.46 (2 $MeCH_2$); 51.61 (MeO); 127.51, 128.88, 129.80 (5 arom. C); 133.15,134.99, 160.56, 162.47 (4 C); 169.45 (C=O). EI-MS: 290 (50, M^+), 275 (12), 261 (39), 247 (77), 229 (15),215 (23), 201 (13), 149 (21), 133 (32), 103 (28), 89 (39), 57 (42), 42 (100). Anal.calc. for $C_{15}H_{18}N_2O_2S$(290.38): C 62.04, H 6.25, N 9.65; found: C 61.24, H 6.14, N 8.86.

Ethyl 2-(Diethylamino)-4-phenylthiazole-5-carboxylate (8l): Yield 259 mg (85%). White crystals.M.p. 90.1°. *IR* (KBr): 3051, 2975, 2929, 1698, 1551, 1330, 1258. ^{1}*H-NMR*: 1.23 – 1.31 (*m*, 3 $MeCH_2$); 3.56(*q*, ^{3}*J*=7.2, 2 $MeCH_2N$); 4.20 (*q*, ^{3}*J*=7.2, $MeCH_2O$); 7.38 – 7.40 (*m*, 3 arom.H); 7.75 – 7.76 (*m*, 2 arom.H). ^{13}*C-NMR*: 12.49 (2 $MeCH_2N$); 14.28 ($MeCH_2O$); 45.41 (2 MeCH2N); 60.38 ($MeCH_2O$); 127.44, 128.77,129.84 (5 arom. C); 133.44, 135.14, 160.19, 162.10 (4 C); 169.41 (C=O). EI-MS: 304 (100, M^+), 289 (12),275 (35), 261 (80), 247 (17), 232 (27), 215 (17), 202 (12), 188 (14), 133 (23), 103 (18), 89 (33), 71 (14).Anal. calc. for C16H20N2O2S (304.41): C 63.13, H 6.62, N 9.20; found: C 63.4, H 6.56, N 8.93.

2.3. Agar well Diffusion Method:

Compounds was assayed in respect of their antibacterial activity by the method that was described before (Paekh et al, 2005) with some modifications. In brief, solutions with 1mg/ml concentrations of each compounds in DMSO (Merck) was prepared. Middelbrock Agar (Merck) was prepared according to the manufactures instructions. The stabilized agar was aseptically seeded with 100 µl inoculum, containing 1.5×10^6 C.F.U/ml of *M.smegmatis* PTCC 1420 and the mixture was transferred into a sterile Petri dish. Five wells were made in agar using a sterile glass tube with 4-6 mm in diameter and 50µl of compounds was transferred to each well. 50 µl of DMSO was inoculated into another well as negative control. The antibacterial activities of compounds were determined by measuring the zones around each well after 3 days of incubation. Ceftizoxime and Ciprofloxacin were used as positive controls.

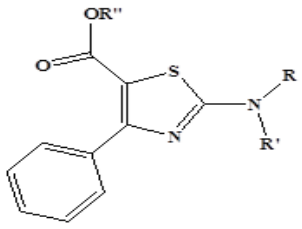
Macrodilution Method

Macro dilution method was used for determining of anti mycobacterial activity of compounds on *M. smegmatis* PTCC 1420 in nutrient broth medium. Broth medium was prepared according to manufacturer's instructions (Merck). After autoclaving a stock solution of the compound was prepared (10mg/ml). Then serial dilutions of each compound in the range of 200-0.19 µg/ml were made in nutrient broth. 10 µl of *M. smegmatis* PTCC 1420 (1.5×10^6 cells/ml which was adjusted by McFarland's turbidity standard) was transferred to each tube and incubated for three days at 37^0C. A tube containing growth medium without any compounds or antibiotics and an un-inoculated tube were used as a positive and negative growth control respectively. Ceftizoxime and Ciprofloxacin (Merck) were used as standard drugs by the concentration of 1 µg/µL. All standards treated under described conditions for comparison.

RESULTS AND DISCUSSION

The structures of products 8 were confirmed by their *IR* and ^{1}*H- and* ^{13}*C-NMR* Spectra, (Table 1) . The mass spectra of these compounds displayed molecular-ion peaks at the appropriate m/z values. The ^{1}*H-NMR* spectrum ($CDCl_3$) of 8c consisted of a *d* for the two Me_2CH groups (δ (H) 1.42, ^{3}*J*(H,H)= 6.9 Hz), a *s* for the MeO group (δ (H) 3.74), a *m* for the two Me_2CH groups (δ (H) 3.92 – 3.96), and two m for the aromatic H-atoms (δ (H) 7.39 – 7.42 and 7.81 – 7.84). The ^{1}*H*-decoupled ^{13}*C-NMR* spectrum of 8c showed 11 distinct resonances; a partial assignment of these resonances is given in the Exper. Part. The ^{1}*H*- and^{13}*C-NMR* spectra of compounds 8a – 8l were similar to those of 8c, except for the resonances of the R, R′, R″groups which exhibited characteristic signals with appropriate chemical shifts.

TABLE 1: Physical characteristics of Alkyl 2-(Dialkylamino)-4 phenylthiazole-5-carboxylates



8a-8l

code	R	R′	R″	M.P.(^{0}C)	Yield	Molecular formula
8a	-$(CH_2)_2$-O-$(CH_2)_2$-		Me	130.0	84	$C_{15}H_{16}N_2O_3S$
8b	-$(CH_2)_2$-O-$(CH_2)_2$-		Et	90.0	80	$C_{16}H_{18}N_2O_3S$
8c	$PhCH_2$	Me	Me	77.2	80	$C_{19}H_{18}N_2O_2S$
8d	$PhCH_2$	Me	Et	73.2	77	$C_{20}H_{20}N_2O_2S$
8e	-$(CH_2)_5$-		Me	90.7	81	$C_{16}H_{18}N_2O_2S$
8f	-$(CH_2)_5$-		Et	79	79	$C_{17}H_{20}N_20_2S$
8j	$PhCH_2$		Me	107.6	78	$C_{25}H_{22}N_2O_2S$
8h	$PhCH_2$		Et	73.1	75	$C_{26}H_{24}N_2O_2S$
8i	*i*-Pr		Me	105.4	85	$C_{17}H_{22}N_2O_2S$
8j	*i*-Pr		Et	90.5	83	$C_{18}H_{24}N_2O_2S$
8k	Et		Me	81.4	86	$C_{15}H_{18}N_2O_2S$
8l	Et		Et	90.1	85	$C_{16}H_{20}N_2O_2S$

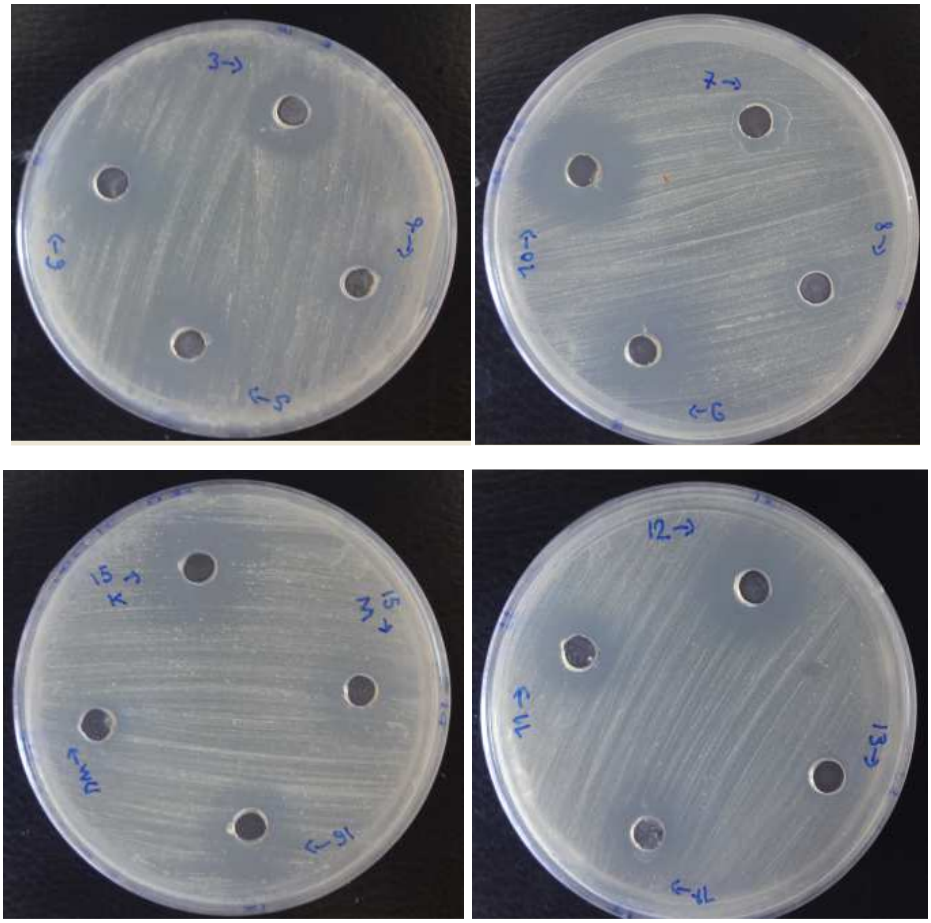
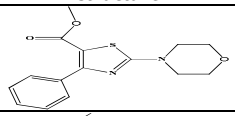
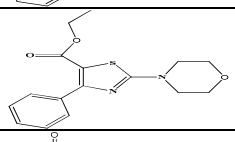
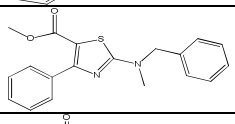
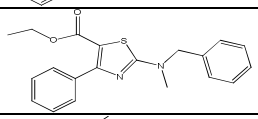
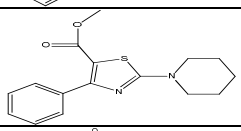
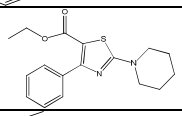
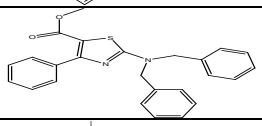
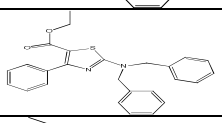
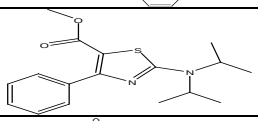
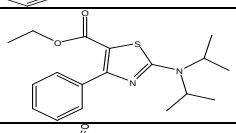
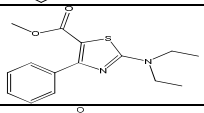
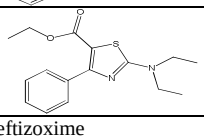


Figure 1: Inhibition zones for tested compounds

Anti mycobacterial activity

Figure 1 shows the inhibition zones for some of tested compounds. No inhibition zone were seen for DMSO, however the diameter of inhibition zones (mm)for synthesized compounds were shown in table 1 The results depicted that most of the prepared 2-aminothiazole derivatives, especially 8c, 8e, 8f, 8j and 8k and 8l had comparable activity, with tested antibiotics.

Table 1: Anti mycobacterial activities of 8a-8l synthesized compounds by determining minimum inhibitory and bactericidal concentrations and inhibitory zone diameter

code	structure	MIC(µg/ml)	MBC(µg/ml)	IZ(mm)
8a		0.19	0.78	11
8b		25	100	13
8c		0.19	0.19	15
8d		3.12	3.12	12
8e		6.26	25	15
8f		0.19	0.39	16
8g		0.19	0.19	10
8h		1.56	3.125	10
8i		0.19	3.125	13
8j		0.19	1.56	17
8k		50	12.5	15
8l		12.5	25	16
Ceftizoxime		12.5	12.5	15
ciprofloxacin		0.19	0.19	16

All 12, 2-amino thiazol derivatives were highly active against *M.smegmatis*. Some of them (8a, 8c, 8g, 8f, 8i, 8j) were even effective at concentrations as low as 0.19µg/mL. This concentration was comparable with the minimum inhibitory and minimum bactericidal concentration of ciprofloxacin (Table 1). All the compounds (except 8b, 8e, 8k and 8l) were more effective than ceftizoxime in respect of their anti mycobacterial effects by comparing MICs and MBCs. Such level of anti mycobacterial activity is comparable to other standard drugs such as isoniazid and rifampicin, which have MICs at 0.01-1.25 and 0.06-0.25 µg/mL, respectively [38]. Lipophilicity of the drug

molecules may make them more capable of penetrating various bio membranes, consequently improving their permeation properties towards microbial cell membranes (31)and correlation between lipophilicity and anti TB effects has been reported elsewhere(32).

CONCLUSION

The high anti-mycobacterial activity of compounds 8a, 8c, 8g, 8f, 8i and 8j makes them suitable hits for additional *In vitro* and *In vivo* evaluations, in order to develop new anti mycobacterial drugs or pro drugs with potential use in the tuberculosis treatment. Further studies in this area are in progress in our laboratory. Furthermore the easy workup, high yield, and short reaction times make our method of synthesis a useful addition to modern ways for synthesis of pharmaceutically active products.

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