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Synthesis and antimycobacterial activity of some alkyl [5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio]propionates

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Abstract—Two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters were synthesized and screened for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system. The MIC values for the compounds showing more than 90% inhibition were determined. The result of comparison between two groups of data exhibited that among the synthesized derivatives, the compound propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio]propionate was the most active one (MIC = 1.56 μg ml^{-1}).

Tuberculosis (TB) is a respiratory transmitted disease affecting nearly 32% of the world's population; it is caused by *Mycobacterium tuberculosis*.[1,2] The exponential increase in TB cases has been greatest in areas with high prevalence of HIV infections.[2]

The emergence of multiple drug-resistant (MDR) TB has focused the attention of the scientific community throughout the world on the urgent need for new antitubercular drugs.[1] In this regard, there have been few additions of some promising new agents such as the long-acting rifamycins, fluoroquinolones, oxazolodinones, and nitroimidazopyrans to the existing mainline drugs.[1,2] In pursuit of this goal, our research efforts are directed toward the discovery of new chemical entities that are effective as antituberculosis agents and to optimize the structure to display the potent efficacy.

During recent years, there have been intense investigations of different classes of thiadiazole compounds many of which are known to possess interesting biological properties such as antimicrobial, anti-tuberculosis, and anti-inflammatory activities.[3,4]

The use of 5-nitroheterocycles as antibacterial, antiprotozoal, and anticancer agents is well established.[5,6] In our previous studies some new compounds containing 5-nitroheterocycles and 1,3,4-thiadiazole with different substituents at C_2 position of thiadiazole ring were synthesized and evaluated for activity against *M. tuberculosis*.[7,8] To get a better structure–activity relationship of these compounds, herein we would like to report the synthesis and antituberculosis activity of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters **II** and **III** (Fig. 1).

Reaction of nitroaryl aldehyde (**1**) with thiosemicarbazide in refluxing ethanol afforded compound **2**. The 2-amino-5-(nitroaryl)-1,3,4-thiadiazole (**3**) was prepared by oxidative cyclization of 5-nitroaryl carboxaldehyde thiosemicarbazone (**2**).[8] Diazotation of **3** in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(nitroaryl)-1,3,4-thiadiazole (**4**).[8,9] The reaction of **4** with thiourea in refluxing ethanol afforded the 2-mercapto-5-(5-nitroaryl)-1,3,4-thiadiazole (**5**).[9,10] Treatment of the latter with 2-bromopropionic acid ethyl ester in the presence of basic ethanol provided 2-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio] propionic acid ethyl ester (**6**).

The purity of the synthesized compounds was confirmed by thin-layer chromatography (TLC) using various

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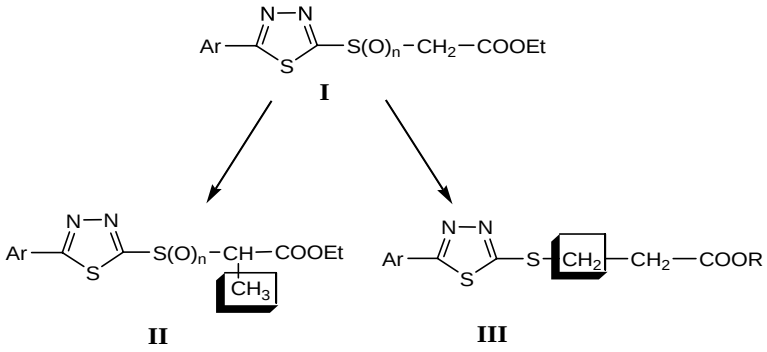


Figure 1.

solvents of different polarities. The structures of compounds were characterized using IR, NMR, mass spectra, and elemental analysis.

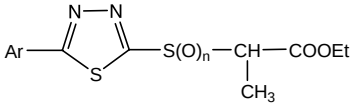
The compounds were screened for antituberculosis activity under the direction of the US National Institute of Health, NIAID Division. Primary screening was conducted at a single concentration, 6.25 μg ml^{-1} against, *M. tuberculosis* H37Rv (ATCC2729) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA). Compounds affecting <90% inhibition in the primary screening (MIC > 6.25 μg ml^{-1}) were not generally evaluated further. The active compounds were re-tested by serial dilution beginning at the concentration of 6.25 μg ml^{-1} against *M. tuberculosis* H37Rv to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460 radiometric system and BACTEC 12B medium. The MIC is defined as the lowest concentration affecting a reduction in fluorescence of 90% relative to controls.[11]

As it can be seen from the antituberculosis data reported in Table 1, among the α-propionate series (**6a–i**), all three thio analogues (**6a–c**) were active antimycobacterial agents (MIC = 3.12–6.25 μg ml^{-1}). Oxidation of S to SO in compound **6a**, containing nitroimidazole heterocycle, could largely decrease the activity of the resultant compound (**6d**) in terms of inhibition percentage and MIC value. In contrast, dioxidation of the S moiety to SO_2 in the same compound, **6a**, increased its activity (**6g**; inhibition = 100%), (MIC = 3.12 μg ml^{-1}). In nitrofuran and nitrothiophene derivatives, oxidation of S to SO has the same effect on the activity of the synthesized compounds (**6e** and **6f**). Unexpectedly, dioxidation of S to SO_2 could however decrease their activities (**6h**, inhibition = 78%; **6i**, inhibition = 82%) (Table 1).

Comparison of this series of compounds with previously synthesized derivatives lacking the methyl group at Cα position of the ester moiety[7,8] (Fig. 1, compound **I**) showed that introduction of methyl at Cα could largely increase the potency of inactive thio compound containing nitrothiophene (Fig. 1, compound **I**, $n = 0$)[8] to the corresponding active compound **6c** (inhibition = 92%; MIC = 6.25 μg ml^{-1}). The same modification at Cα in sulfonyl analogue (Fig. 1, compound **I**, $n = 2$) could also increase the inhibition percentage of the synthesized compounds (**6g–i**), among which compound **6g** showed a MIC value of 3.12 μg ml^{-1}.

To realize a better structure–activity relationship for this series of compounds, new derivatives were synthesized by introducing a methylene group to the linker attaching carbonyl and S moieties (Fig. 1; compound **III**). The target compounds (**7a–j**) were prepared by treatment

Table 1. In vitro antituberculosis activity of compounds **6a–i**



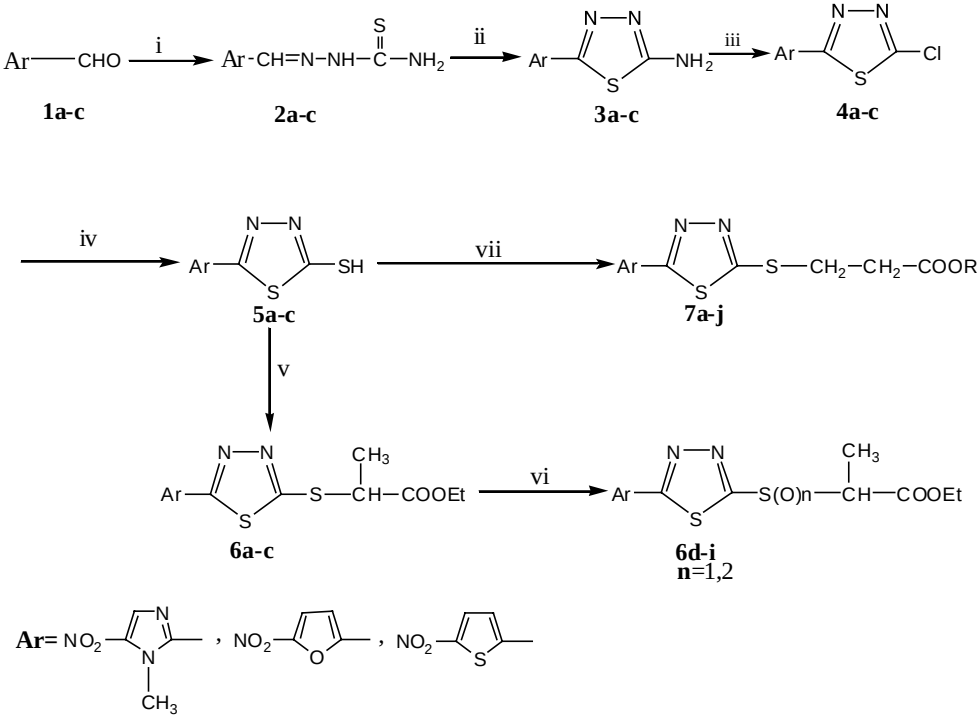
Compound	Ar	*n*	Inhibition (%)	Activity	MIC (μg/ml)
6a	1-Methyl-5-nitro-2-imidazolyl	0	90	+	6.25
6b	5-Nitro-2-furyl	0	98	+	6.25
6c	5-Nitro-2-thienyl	0	92	+	6.25
6d	1-Methyl-5-nitro-2-imidazolyl	1	11	–	>6.25
6e	5-Nitro-2-furyl	1	6	–	>6.25
6f	5-Nitro-2-thienyl	1	12	–	>6.25
6g	1-Methyl-5-nitro-2-imidazolyl	2	100	+	3.12
6h	5-Nitro-2-furyl	2	78	–	>6.25
6i	5-Nitro-2-thienyl	2	82	–	>6.25
Rifampicin					0.5–1

of 2-mercapto-5-(nitroaryl)-1,3,4-thiadiazole (**5**) with alkyl 3-bromopropionates in the presence of basic ethanol (Scheme 1). Their antituberculosis activities were evaluated with the above-described method (Table 2).

Comparison of the ethyl esters **7c**, and **7h**, with the corresponding counterparts in Table 1, showed a large decrease in the activity of the resultant compounds (inhibition = 14% and 26%, respectively).

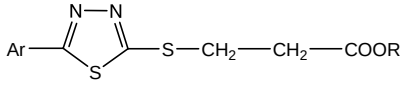
This decreasing effect could be compensated and even reversed by a proper modification of the ester moiety. Among the different groups replaced at the ester moiety in the nitrothienyl series, propyl and butyl substitution led to the active compounds **7i** (MIC = 1.56 μg ml^{-1}) and **7j** (MIC = 6.25 μg ml^{-1}), respectively. In contrast, the same modification in nitrofuryl derivatives led to totally inactive compounds **7d** and **7e** (inhibition = 0%).

Hydrolyzing the ester group had different effects in nitrothienyl and nitrofuryl series. Despite observing a large decrease in the activity of hydrolyzed nitrothienyl analogue **7f** (inhibition = 0%) the active compound **7a** (MIC = 6.25) was obtained by hydrolyzing the corresponding nitrofuryl ester.



Scheme 1. Synthesis of compounds **6** and **7**. Reagents and conditions: (i) thiosemicarbazide, EtOH, HCl, reflux; (ii) ammonium ferric sulfate, H_2O, reflux; (iii) $NaNO_2$, HCl, Cu; (iv) thiourea, EtOH, reflux; (v) ethyl 2-bromopropionate, KOH, EtOH; (vi) MCPBA, $NaHCO_3$, CH_2Cl_2, rt; (vii) alkyl 3-bromopropionate, KOH, EtOH, rt.

Table 2. In vitro antituberculosis activity of compounds **7a**–**j**



Compound	Ar	R	Inhibition (%)	Activity	MIC (μg/ml)
7a	5-Nitro-2-furyl	H	95	+	6.25
7b	5-Nitro-2-furyl	Methyl	64	–	>6.25
7c	5-Nitro-2-furyl	Ethyl	14	–	>6.25
7d	5-Nitro-2-furyl	*n*-Propyl	0	–	>6.25
7e	5-Nitro-2-furyl	*n*-Butyl	0	–	>6.25
7f	5-Nitro-2-thienyl	H	0	–	>6.25
7g	5-Nitro-2-thienyl	Methyl	76	–	>6.25
7h	5-Nitro-2-thienyl	Ethyl	26	–	>6.25
7i	5-Nitro-2-thienyl	*n*-Propyl	98	+	1.56
7j	5-Nitro-2-thienyl	*n*-Butyl	98	+	6.25
Rifampicin					0.5–1

In conclusion, among two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters, the high antimycobacterial activity of the compound **7i** makes it a suitable lead for further in vitro and in vivo evaluations.

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