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Synthesis and antimycobacterial activity of pyridinium compounds with sulfonylacetamide substituent in *N*-alkyl chain

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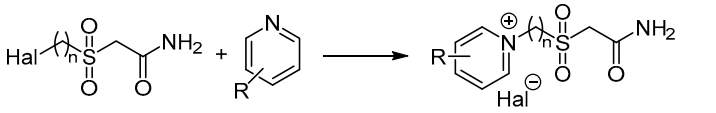


Pyridines containing amine, amide, or hydrazide substituent were quaternized with (ω-haloalkyl)sulfonylacetamides, resulting in new pyridinium compounds that exhibited tuberculostatic activity against the strain H37Rv of *Mycobacterium tuberculosis*.

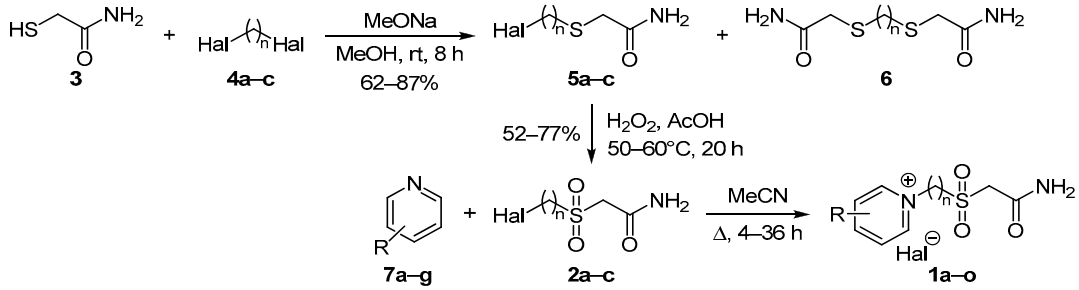
Keywords: carbamoylmethylsulfonyl group, pyridinium compounds, sulfonylacetamides, quaternization, antituberculosis activity.

Pyridinium salts are known for a great variety of useful properties that provide reasons for widespread use of such compounds. In the role of cationic surfactants they find applications as corrosion inhibitors, emulgators, detergents, antistatic additives, and phase-transfer catalysts. Pyridinium salts are also used as electrolytes, additives during extraction, polymerization, water treatment, and flotation processes.[1] *N*-Alkylpyridinium salts are used as organic synthesis reagents for the preparation of compounds belonging to various classes, for example, phenacylides, which can be further used in 1,3-dipolar cycloaddition and some types of condensation reactions.[2,3] The ability of *N*-alkylpyridinium salts to affect the permeability of biological membranes show promise in the development of new drugs, biosensors, and gene transfection agents[4] in the field of genetic engineering.

N-Alkylpyridinium salts show a broad spectrum of biological activity, primarily strong antibacterial activity against a range of microorganisms, including tuberculosis mycobacteria.[5–10] Pyridinium compounds containing steroid structures have been characterized with strong antimycobacterial activity, reaching the minimum inhibitory concentration (MIC) of 0.4 μl/ml.[5] It is essential to continue the efforts directed toward the discovery of new antituberculosis compounds, especially because of the emergence of highly resistant strains of mycobacteria.[11] Thus, it is worthwhile to synthesize new pyridine derivatives, including pyridinium salts, and to study their antimycobacterial activity.

It is known that compounds containing a carbamoylmethylsulfonyl moiety, in particular *n*-octylsulfonylacetamide, exhibit antimycobacterial properties that are not accompanied by antimicrobial action on other microorganisms.[12–14] Such compounds have been synthesized as potential inhibitors of β-ketoacyl synthase – an enzyme involved in the biosynthesis of fatty acids in mycobacteria. We have previously reported the synthesis of isocyanurate derivatives with tuberculostatic activity, containing terminal carbamoylmethylsulfonyl groups in their *N*-alkyl chains.[15,16] We assumed that the replacement of isocyanurate moiety with a pyridine ring can lead to new compounds with a broad spectrum of antimicrobial activity, including activity against *Mycobacterium tuberculosis.* During the current study we synthesized a series of pyridinium salts **1** containing carbamoylmethylsulfonyl group in the *N*-alkyl chain, while the length of methylene chain in the *N*-substituent and the type of other pyridine ring substituents were varied.

Scheme 1



2, **5 a** n = 2, Hal = Cl; **b** n = 3, Hal = Cl; **c** n = 5, Hal = Br; **4**, **6** n = 2, 3, 5
7 a R = H, **b** R = 4-NH_2, **c** R = 2-NH_2, **d** R = 3-COOMe, **e** R=3-$CONH_2$, **f** R = 3-$CONHNH_2$, **g** R = 4-$CONHNH_2$

The key starting materials for the synthesis of compounds **1** were (ω-haloalkyl)sulfonylacetamides **2**, which were obtained during this work by the reaction of thioglycolamide (**3**) with α,ω-dihaloalkanes **4a**–**c**, followed by oxidation of the obtained ω-haloalkyl sulfides **5a**–**c** (Scheme 1). The alkylation reactions of thioglycolamide (**3**) produced significant amounts of α,ω-bis(carbamoylmethylsulfanyl)alkanes **6**,[17] but their formation could be minimized by employing a large excess of α,ω-dihaloalkanes **4a**–**c**. It should be also noted that exceeding the optimal reaction temperature during the oxidation of ω-halo sulfides **5a**–**c** substantially decreased the yields of sulfones **2a**–**c**.

Sulfonylacetamides **2a**–**c** were used in reactions with various pyridine derivatives **7a**–**g**, giving a series of pyridinium salts **1a**–**o** (Table 1). As it was expected, the alkylating activity of ω-chloroalkyl sulfones **2a**–**c** in reactions with pyridines dropped sharply with an increase in the number of methylene groups from 2 to 3 and improved when the chlorine atom was replaced with bromine. For example, refluxing pyridine (**7a**) and 3-chloropropyl sulfone **2b** in acetonitrile for 39 h gave only 8% yield of pyridinium salt **1b**, while the analogous reaction with 2-chloroethyl sulfone **2a** produced pyridinium salt **1a** in 45% yield already after 4 h, and the reaction with 5-bromopentyl sulfone **2c** resulted in the formation of compound **1c** in 59% yield after 11 h.

Aminopyridines **7b**,**c** were alkylated at the ring nitrogen atom, forming crystalline salts in good yields (Table 1). The reaction of 4-aminomethylpyridine (**7h**) with 2-chloroethyl sulfone **2a** did not yield the respective pyridinium salt. Instead, HCl was eliminated already at room temperature and 2-(vinylsulfonyl)acetamide (**8**) was obtained (Scheme 2).

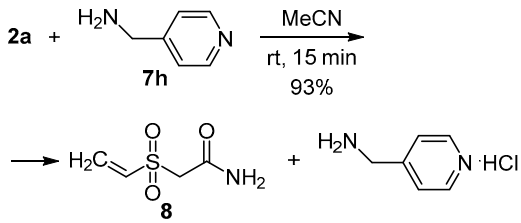
The presence of electron-withdrawing carbonyl substituents in the pyridine ring hindered the quaternization of ring nitrogen atom, for example, the refluxing of isoniazid (**7g**) with 2-chloroethyl sulfone **2a** for 22 h gave salt **1n** in merely 32% yield (Table 1).

Compound **1n** was also obtained by an alternative method, through the reaction of vinyl sulfone **8** with isoniazid (**7g**) in the presence of hydrochloric acid[18] (Scheme 3). These conditions allowed to significantly shorten the reaction duration (to 5 h) and to obtain pyridinium salt **1n** in 56% yield.

Table 1. The structures, yields, and tuberculostatic activity of pyridinium salts **1a**–**o**

Compound	R	n	Hal	Reaction duration, h	Yield, %	MIC, μg/ml
1a	H	2	Cl	4	45	6.2
1b	H	3	Cl	39	8	12.5
1c	H	5	Br	11	59	12.5
1d	4-NH_2	2	Cl	4	96	12.5
1e	4-NH_2	3	Cl	10	16	12.5
1f	4-NH_2	5	Br	10	81	12.5
1g	2-NH_2	2	Cl	5	89	12.5
1h	2-NH_2	5	Br	12	67	Not determined
1i	3-COOMe	5	Br	18	39	Not determined
1j	3-$C(O)NH_2$	2	Cl	17	37	3.1
1k	3-$C(O)NH_2$	5	Br	18	42	12.5
1l	3-$C(O)NHNH_2$	2	Cl	22	50	12.5
1m	3-$C(O)NHNH_2$	5	Br	22	52	1.5
1n	4-$C(O)NHNH_2$	2	Cl	22	32	1.5
1o	4-$C(O)NHNH_2$	5	Br	21	43	12.5
Isoniazid (**7g**)	4-$CONHNH_2$	–	–			0.1

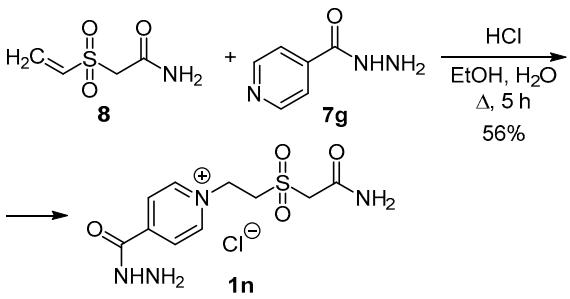
Scheme 2



All of the obtained pyridinium salts **1**, except for the salt **1i**, were isolated as crystalline products that were readily soluble in water.

The synthesized compounds **1a**–**g**,**j**–**o** were screened *in vitro* for antituberculosis activity against the laboratory strain H37Rv of *M. tuberculosis* (Table 1). All of the investigated pyridinium salts showed tuberculostatic activity with MIC values ranging from 1.5 to 12.5 μl/ml. First of all, we should note the lower tuberculostatic

Scheme 3



activity of pyridinium salts **1n**,**o** compared to isoniazid (**7g**). With β-carbamoylmethylsulfonyl group present in the *N*-alkyl chain, pyridinium salts **1a**,**j**,**n** showed tuberculostatic activity with MIC values of 6.2, 3.1, and 1.5 μl/ml, respectively. The presence of longer methylene chains resulted in a decrease of the MIC value to 12.5 μl/ml (compounds **1b**,**c**,**k**,**o**, Table 1). However, when a hydrazide substituent was introduced at the *meta* position of pyridinium ring, the opposite trend was observed, namely, the activity increased for compounds containing longer methylene spacer chains in their molecules: the MIC value for salt **1l** with two methylene groups was 12.5 μl/ml, whereas salt **1m** containing a chain of five methylene groups had the MIC value of 1.5 μl/ml. The presence of an amino group in the pyridinium ring was accompanied by an increase in the MIC value to 12.5 μl/ml for compounds **1d**,**g**, compared to compound **1a** containing an unsubstituted pyridinium ring (MIC 6.2 μl/ml). The presence of an amide or hydrazide substituent in the pyridinium ring generally helped to improve the tuberculostatic activity of the respective compounds (Table 1). The highest activity with MIC 1.5 μl/ml was shown by compounds **1m**,**n** containing hydrazide substituents in the pyridinium ring.

Thus, we have prepared new pyridinium compounds containing carbamoylmethylsulfonyl group in the *N*-alkyl chain as pharmacophoric structural motif. Such compounds exhibited tuberculostatic activity against *M. tuberculosis* strain H37Rv with MIC values in the range of 1.5–12.5 μl/ml. The activity of the obtained compounds depended both on the number of methylene groups in the spacer chain and on the pyridinium ring substituents.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance 600 (600 and 150 MHz, respectively) or Bruker MSL-400 spectrometers (400 and 100 MHz, respectively) in DMSO-d_6, internal standard TMS. The signals in ^{13}C NMR spectrum were assigned by relying on the reference spectra of related compounds.[19] MALDI-TOF mass spectra were recorded on a Bruker Ultraflex III instrument, using metallic target and *p*-nitroaniline matrix; conditions for recording of the mass spectrum: Nd:YAG, λ 355 nm, linear mode without adding of mass spectra. The elemental composition (C, H, and N) was determined on a CHN-3 analyzer, halogens were determined by Shöniger method, sulfur – by pyrolysis in oxygen stream. Melting points were determined on a Boetius hot stage.

Preparation of 2-[(ω-haloalkyl)sulfanyl]acetamides 5a–c (General method). Sodium methoxide solution was prepared by dissolving metallic sodium (2.3 g, 0.1 mol) in MeOH (100 ml), and a solution of mercaptoacetamide (**3**) (9 g, 0.1 mol) in MeOH (100 ml) was added dropwise. The obtained thiolate solution was slowly dropwise added into a flask with α,ω-dihaloalkane **4a**–**c** (0.2 mol), while maintaining 15–20°C temperature. The reaction mixture was stirred for 8 h, the precipitate was removed by filtration and the filtrate was evaporated at reduced pressure. The residue was taken up in EtOAc (100 ml), filtered after 1 day and the filtrate was evaporated.

2-[(Chloroethyl)sulfanyl]acetamide (5a)[20] was obtained from 1-bromo-2-chloroethane (**4a**). Yield 9.5 g (62%), thick transparent oil that crystallized upon storage, mp 60–61°C (Et_2O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.94 (2H, t, *J* = 7.6, CH_2S); 3.13 (2H, s, CH_2CO); 3.78 (2H, t, *J* = 7.6, CH_2Cl); 7.03 (1H, s) and 7.46 (1H, s, NH_2). Found, %: C 31.22; H 5.18; Cl 23.06; N 9.08; S 20.83. C_4H_8ClNOS. Calculated, %: C 31.27; H 5.25; Cl 23.08; N 9.12; S 20.87.

2-[(3-Chloropropyl)sulfanyl]acetamide (5b) was obtained from 1-bromo-3-chloropropane (**4b**). Yield 11.7 g (70%), thick transparent oil that crystallized upon storage, mp 68–69°C (Et_2O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.97–2.01 (2H, m, CH_2); 2.68 (2H, t, *J* = 7.1, CH_2S); 3.07 (2H, s, CH_2CO); 3.71 (2H, t, *J* = 6.4, CH_2Cl); 6.98 (1H, s) and 7.42 (1H, s, NH_2). Found, %: C 35.78; H 5.97; Cl 21.08; N 8.32; S 19.10. $C_5H_{10}ClNOS$. Calculated, %: C 35.82; H 6.01; Cl 21.15; N 8.35; S 19.13.

2-[(5-Bromopentyl)sulfanyl]acetamide (5c) was obtained from 1,5-dibromopentane (**4c**). Yield 20.9 g (87%), thick transparent oil that crystallized upon storage, mp 83–84°C (Et_2O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.43–1.49 (2H, m, CH_2); 1.53–1.60 (2H, m, CH_2); 1.77–1.84 (2H, m, CH_2); 2.56 (2H, t, *J* = 7.2, CH_2S); 3.05 (2H, s, CH_2CO); 3.53 (2H, t, *J* = 6.7, CH_2Br); 6.97 (1H, s) and 7.39 (1H, s, NH_2). Found, %: C 34.98; H 5.82; Br 33.21; N 5.79; S 13.30. $C_7H_{14}BrNOS$. Calculated, %: C 35.01; H 5.88; Br 33.27; N 5.83; S 13.35.

Preparation of 2-[(ω-haloalkyl)sulfonyl]acetamides 2a–c (General method). A solution of 2-[(ω-haloalkyl)-sulfanyl]acetamide **5a**–**c** (0.05 mol) in glacial acetic acid (100 ml) was treated by dropwise addition of 35% H_2O_2 (12.3 ml, 0.12 mol) in a way that the temperature did not exceed 60°C. The reaction mixture was further stirred at 55–60°C for 20 h. The mixture was cooled, filtered, and concentrated at reduced pressure, while avoiding evaporation to dryness. The residue was diluted with 10:1 Et_2O–MeOH mixture (100 ml), the precipitate was triturated and filtered off.

2-[(2-Chloroethyl)sulfonyl]acetamide (2a)[21] was obtained from 2-[(2-chloroethyl)sulfanyl]acetamide (**5a**) (9.27 g, 0.06 mol). Yield 8.17 g (73%), white crystals, mp 126–127°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 3.81 (2H, t, *J* = 7.1, CH_2SO_2); 3.97 (2H, t, *J* = 7.1, CH_2Cl); 4.12 (2H, s, CH_2CO); 7.50 (1H, s) and 7.77 (1H, s, NH_2). ^{13}C NMR spectrum (150 MHz), δ, ppm: 36.6 ($ClCH_2$); 55.2 (CH_2SO_2); 59.1 ($SO_2\underline{C}H_2CO$); 164.1 (C=O).

Found, %: C 25.83; H 4.31; Cl 19.06; N 7.52; S 17.28. $C_4H_8ClNO_3S$. Calculated, %: C 25.88; H 4.34; Cl 19.10; N 7.55; S 17.27.

2-[(3-Chloropropyl)sulfonyl]acetamide (2b) was obtained from 2-[(3-chloropropyl)sulfanyl]acetamide (**5b**) (8.38 g, 0.05 mol). Yield 5.14 g (52%), white crystals, mp 114–115°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.15–2.22 (2H, m, CH_2); 3.42 (2H, t, *J* = 7.7, CH_2SO_2); 3.77 (2H, t, *J* = 6.5, CH_2Cl); 4.07 (2H, s, CH_2CO); 7.45 (1H, s) and 7.74 (1H, s, NH_2). ^{13}C NMR spectrum (100 MHz), δ, ppm: 21.2 (CH_2); 35.7 ($ClCH_2$); 52.5 (CH_2SO_2); 58.2 ($SO_2\underline{C}H_2CO$); 163.8 (C=O). Found, %: C 30.02; H 4.98; Cl 17.67; N 6.92; S 16.02. $C_5H_{10}ClNO_3S$. Calculated, %: C 30.08; H 5.05; Cl 17.76; N 7.02; S 16.06.

2-[(5-Bromopentyl)sulfonyl]acetamide (2c) was obtained from 2-[(5-bromopentyl)sulfanyl]acetamide (**5c**) (8.14 g, 0.033 mol). Yield 7.11 g (77%), white crystals, mp 112–113°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.48–1.55 (2H, m, CH_2); 1.70–1.78 (2H, m, CH_2); 1.81–1.88 (2H, m, CH_2); 3.28 (2H, t, *J* = 7.9, CH_2SO_2); 3.54 (2H, t, *J* = 6.7, CH_2Br); 4.00 (2H, s, CH_2CO); 7.43 (1H, s) and 7.72 (1H, s, NH_2). ^{13}C NMR spectrum (100 MHz), δ, ppm: 20.8 (CH_2); 26.8 (CH_2); 32.1 (CH_2); 35.1 (CH_2); 52.8 (CH_2SO_2); 58.2 ($SO_2\underline{C}H_2CO$); 164.2 (C=O). Found, %: C 30.82; H 5.14; Br 29.28; N 5.09; S 11.73. $C_7H_{14}BrNO_3S$. Calculated, %: C 30.89; H 5.18; Br 29.36; N 5.15; S 11.78.

Preparation of 1-[ω-(carbamoylmethylsulfonyl)alkyl]-pyridinium halides 1a–o (General method). Equimolar amounts of 2-[(ω-haloethyl)sulfonyl]acetamide **2a**–**c** and pyridine (**7a**) or substituted pyridine derivative **7b**–**g** were refluxed in anhydrous MeCN (40–50 ml) for 4–36 h. The precipitate that formed was filtered off and washed with anhydrous MeCN.

1-[2-(Carbamoylmethylsulfonyl)ethyl]pyridinium chloride (1a) was obtained by starting from pyridine (**7a**) (0.43 g, 5.5 mmol) and 2-[(2-chloroethyl)sulfonyl]acetamide (**2a**) (1.02 g, 5.5 mmol), the refluxing duration was 4 h. Yield 0.65 g (45%), white crystals, mp 197–199°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 4.19 (2H, t, *J* = 6.4, CH_2SO_2); 4.32 (2H, s, CH_2CO); 5.21 (2H, t, *J* = 6.4, CH_2N^+); 7.56 (1H, s) and 7.98 (1H, s, NH_2); 8.20 (2H, t, *J* = 7.2, H-3,5 Py); 8.65 (1H, t, *J* = 7.7, H-4 Py); 9.21 (2H, d, *J* = 5.6, H-2,6 Py). ^{13}C NMR spectrum (100 MHz), δ, ppm: 53.0 (CH_2SO_2); 54.2 ($SO_2\underline{C}H_2CO$); 58.9 (CH_2N^+); 128.3 (C-3,5 Py); 146.0 (C-4 Py); 146.8 (C-2,6 Py); 163.9 (C=O). Mass spectrum, *m*/*z*: 229 $[M–Cl]^+$. Found, %: C 40.72; H 4.89; Cl 13.32; N 10.54; S 12.01. $C_9H_{13}ClN_2O_3S$. Calculated, %: C 40.83; H 4.95; Cl 13.39; N 10.58; S 12.11.

1-[3-(Carbamoylmethylsulfonyl)propyl]pyridinium chloride (1b) was obtained by starting from pyridine (**7a**) (0.4 g, 5.0 mmol) and 2-[(3-chloropropyl)sulfonyl]acetamide (**2b**) (1.0 g, 5.0 mmol), the refluxing duration was 40 h. Yield 0.11 g (8%), light-brown crystals, mp 200–201°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.43–2.47 (2H, m, CH_2); 3.40 (2H, t, *J* = 7.3, CH_2SO_2); 4.12 (2H, s, CH_2CO); 4.78 (2H, t, *J* = 7.3, CH_2N^+); 7.46 (1H, s) and 7.95 (1H, s, NH_2); 8.18 (2H, t, *J* = 7.1, H-3,5 Py); 8.63 (1H, t, *J* = 7.9, H-4 Py); 9.15 (2H, d, *J* = 5.9, H-2,6 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 23.5 (CH_2); 50.4 (CH_2SO_2); 53.4 ($SO_2\underline{C}H_2CO$); 59.7 (CH_2N^+); 128.4 (C-3,5 Py); 145.5 (C-4 Py); 146.3 (C-2,6 Py); 164.1 (C=O). Mass spectrum, *m*/*z*: 243 $[M–Cl]^+$. Found, %: C 42.93; H 5.38; Cl 12.65; N 10.02; S 11.41. $C_{10}H_{15}ClN_2O_3S$. Calculated, %: C 43.09; H 5.42; Cl 12.72; N 10.05; S 11.50.

1-[5-(Carbamoylmethylsulfonyl)pentyl]pyridinium bromide (1c) was obtained from pyridine (**7a**) (0.4 g, 5.0 mmol) and 2-[(5-bromopentyl)sulfonyl]acetamide (**2c**) (1.36 g, 5.0 mmol), the refluxing duration was 11 h. Yield 1.04 g (59%), white crystals, mp 129–130°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.39–1.46 (2H, m, CH_2); 1.74–1.81 (2H, m, CH_2); 1.94–2.01 (2H, m, CH_2); 3.27 (2H, t, *J* = 7.9, CH_2SO_2); 4.02 (2H, s, CH_2CO); 4.65 (2H, t, *J* = 7.4, CH_2N^+); 7.44 (1H) and 7.78 (1H, s, NH_2); 8.18 (2H, t, *J* = 7.1, H-3,5 Py); 8.62 (1H, t, *J* = 7.8, H-4 Py); 9.13 (2H, d, *J* = 5.7, H-2,6 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 21.1 (CH_2); 24.6 (CH_2); 30.6 (CH_2); 52.8 (CH_2SO_2); 58.3 ($SO_2\underline{C}H_2CO$); 60.8 (CH_2N^+); 128.6 (C-3,5 Py); 145.3 (C-4 Py); 146.0 (C-2,6 Py); 164.3 (C=O). Mass spectrum, *m*/*z*: 271 $[M–Br]^+$. Found, %: C 40.97; H 5.42; Br 22.68; N 7.94; S 9.11. $C_{12}H_{19}BrN_2O_3S$. Calculated, %: C 41.03; H 5.45; Br 22.75; N 7.98; S 9.13.

4-Amino-1-[2-(carbamoylmethylsulfonyl)ethyl]pyridinium chloride (1d) was obtained from 4-aminopyridine (**7b**) (0.47 g, 5.0 mmol) and 2-[(2-chloroethyl)sulfonyl]acetamide (**2a**) (0.93 g, 5.0 mmol), the refluxing duration was 4 h. Yield 1.32 g (95%), white crystals, mp 208–209°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 3.94 (2H, t, *J* = 6.2, CH_2SO_2); 4.22 (2H, s, CH_2CO); 4.66 (2H, t, *J* = 6.2, CH_2N^+); 6.85 (2H, d, *J* = 7.1, H-3,5 Py); 7.53 (1H, s) and 7.92 (1H, s, NH_2); 8.22 (2H, d, *J* = 7.1, H-2,6 Py); 8.29 (2H, s, 4-NH_2 Py). ^{13}C NMR spectrum (100 MHz), δ, ppm: 50.4 (CH_2SO_2); 53.0 ($SO_2\underline{C}H_2CO$); 58.9 (CH_2N^+); 109.7 (C-3,5 Py); 143.7 (C-2,6 Py); 159.4 (C-1 Py); 164.0 (C=O). Mass spectrum, *m*/*z*: 244 $[M–Cl]^+$. Found, %: C 38.61; H 4.98; Cl 12.63; N 14.97; S 11.41. $C_9H_{14}ClN_3O_3S$. Calculated, %: C 38.64; H 5.04; Cl 12.67; N 15.02; S 11.46.

4-Amino-1-[3-(carbamoylmethylsulfonyl)propyl]pyridinium chloride (1e) was obtained from 4-aminopyridine (**7b**) (0.47 g, 5.0 mmol) and 2-[(3-chloropropyl)sulfonyl]acetamide (**2b**) (1.0 g, 5.0 mmol), the refluxing duration was 10 h. Yield 0.24 g (16%), white crystals, mp 213–214°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.22–2.26 (2H, m, CH_2); 3.33 (2H, t, *J* = 7.9, CH_2SO_2); 4.11 (2H, s, CH_2CO); 4.26 (2H, t, *J* = 7.1, CH_2N^+); 6.89 (2H, d, *J* = 6.5, H-3,5 Py); 7.46 (1H, s) and 7.92 (1H, s, NH_2); 8.20 (2H, d, *J* = 6.5, H-2,6 Py); 8.34 (2H, br. s, 4-NH_2 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 23.4 (CH_2); 49.9 (CH_2SO_2); 55.6 ($SO_2\underline{C}H_2CO$); 58.3 (CH_2N^+); 110.0 (C-3,5 Py); 143.3 (C-2,6 Py); 159.3 (C-1 Py); 164.2 (C=O). Mass spectrum, *m*/*z*: 258 $[M–Cl]^+$. Found, %: C 40.85; H 5.47; Cl 12.04; N 14.24; S 10.88. $C_{10}H_{16}ClN_3O_3S$. Calculated, %: C 40.88; H 5.49; Cl 12.07; N 14.30; S 10.92.

4-Amino-1-[5-(carbamoylmethylsulfonyl)pentyl]pyridinium bromide (1f) was obtained from 4-aminopyridine (**7b**) (0.47 g, 5.0 mmol) and 2-[(5-bromopentyl)sulfonyl]acetamide (**2c**) (1.36 g, 5.0 mmol), the refluxing duration was

10 h. Yield 1.48 g (81%), beige crystals, mp 180–182°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.33–1.40 (2H, m, CH_2); 1.71–1.82 (4H, m, CH_2); 3.28 (2H, t, *J* = 7.8, CH_2SO_2); 4.01 (2H, s, CH_2CO); 4.14 (2H, t, *J* = 7.2, CH_2N^+); 6.85 (2H, d, *J* = 7.4, H-3,5 Py); 7.43 (1H, s) and 7.77 (1H, s, NH_2); 8.10 (2H, s, 4-NH_2 Py); 8.21 (2H, d, *J* = 7.4, H-2,6 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 21.1 (CH_2); 24.6 (CH_2); 30.0 (CH_2); 52.8 (CH_2SO_2); 57.2 ($SO_2\underline{C}H_2CO$); 58.3 (CH_2N^+); 109.9 (C-3,5 Py); 143.3 (C-2,6 Py); 159.1 (C-1 Py); 164.3 (C=O). Mass spectrum, *m/z*: 286 $[M–Br]^+$. Found, %: C 39.30; H 5.48; Br 21.77; N 11.42; S 8.73. $C_{12}H_{20}BrN_3O_3S$. Calculated, %: C 39.35; H 5.50; Br 21.81; N 11.47; S 8.75.

2-Amino-1-[2-(carbamoylmethylsulfonyl)ethyl]pyridinium chloride (1g) was obtained from 2-aminopyridine (**7c**) (0.44 g, 4.6 mmol) and 2-[(2-chloroethyl)sulfonyl]-acetamide (**2a**) (0.86 g, 4.6 mmol), the refluxing duration was 5 h. Yield 1.12 g (89%), white crystals, mp 212–213°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 3.90 (2H, t, *J* = 6.2, CH_2SO_2); 4.28 (2H, s, CH_2CO); 4.71 (2H, t, *J* = 6.2, CH_2N^+); 6.90 (1H, t, *J* = 6.7, H-5 Py); 7.12 (1H, d, *J* = 9.0, H-3 Py); 7.61 (1H, s, NH_2); 7.96 (1H, s) and 7.88 (1H, t, *J* = 7.8, H-4 Py); 8.06 (1H, d, *J* = 5.7, H-2 Py); 8.73 (2H, br. s, 2-NH_2 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 47.1 (CH_2SO_2); 50.1 ($SO_2\underline{C}H_2CO$); 59.0 (CH_2N^+); 113.0 (C-3 Py); 115.4 (C-5 Py); 141.2 (C-4 Py); 143.1 (C-6 Py); 154.5 (C-2 Py); 164.4 (C=O). Mass spectrum, *m/z*: 244 $[M–Cl]^+$. Found, %: C 38.60; H 5.02; Cl 12.64; N 14.98; S 11.41. $C_9H_{14}ClN_3O_3S$. Calculated, %: C 38.64; H 5.04; Cl 12.67; N 15.02; S 11.46.

2-Amino-1-[5-(carbamoylmethylsulfonyl)pentyl]pyridinium bromide (1h) was obtained from 2-aminopyridine (**7c**) (0.37 g, 4.0 mmol) and 2-[(5-bromopentyl)sulfonyl]-acetamide (**2c**) (1.09 g, 5.0 mmol), the refluxing duration was 12 h. Yield 1.46 g (67%), beige crystals, mp 169–170°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.44–1.49 (2H, m, CH_2); 1.71–1.79 (4H, m, CH_2); 3.29 (2H, t, *J* = 7.8, CH_2SO_2); 4.01 (2H, s, CH_2CO); 4.16 (2H, t, *J* = 7.4, CH_2N^+); 6.92 (1H, t, *J* = 6.2, H-5 Py); 7.07 (1H, d, *J* = 8.2, H-3 Py); 7.43 (1H, s) and 7.75 (1H, s, NH_2); 7.87 (1H, t, *J* = 7.4, H-4 Py); 8.08 (1H, d, *J* = 6.7, H-2 Py); 8.45 (2H, br. s, 2-NH_2 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 21.3 (CH_2); 24.8 (CH_2); 27.3 (CH_2); 52.8 (CH_2SO_2); 53.2 ($SO_2\underline{C}H_2CO$); 58.3 (CH_2N^+); 113.5 (C-3 Py); 115.4 (C-5 Py); 140.5 (C-4 Py); 142.7 (C-6 Py); 154.1 (C-2 Py); 164.3 (C=O). Mass spectrum, *m/z*: 286 $[M–Br]^+$. Found, %: C 39.32; H 5.44; Br 21.78; N 11.45; S 8.72. $C_{12}H_{20}BrN_3O_3S$. Calculated, %: C 39.35; H 5.50; Br 21.81; N 11.47; S 8.75.

1-[5-(Carbamoylmethylsulfonyl)pentyl]-3-(methoxycarbonyl)pyridinium bromide (1i) was obtained from methyl nicotinate (**7d**) (0.55 g, 4.0 mmol) and 2-[(5-bromopentyl)sulfonyl]acetamide (**2c**) (1.09 g, 4.0 mmol), the refluxing duration was 18 h. The reaction mixture was filtered, the filtrate was evaporated, the residue was washed with acetone (20 ml) and MeOH (20 ml), then dried at reduced pressure. Yield 0.64 g (39%), yellow transparent thick oil. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.43–1.46 (2H, m, CH_2); 1.76–1.79 (2H, m, CH_2); 1.97–2.01 (2H, m, CH_2); 3.29 (2H, t, *J* = 7.8, CH_2SO_2); 4.00 (3H, s, OCH_3); 4.02 (2H, s, CH_2CO); 4.74 (2H, t, *J* = 7.6, CH_2N^+); 7.42 (1H, s) and 7.76 (1H, s, NH_2); 8.30 (1H, t, *J* = 6.9, H-5 Py); 8.99 (1H, d, *J* = 8.1, H-4 Py); 9.33 (1H, d, *J* = 5.7, H-6 Py); 9.66 (1H, s, H-2 Py). ^{13}C NMR spectrum (150 MHz), δ, ppm: 21.1 (CH_2); 24.6 (CH_2); 30.7 (CH_2); 52.8 (OCH_3); 54.0 (CH_2SO_2); 58.3 ($SO_2\underline{C}H_2CO$); 61.3 (CH_2N^+); 128.9 (C-5 Py); 130.4 (C-3 Py); 145.6 (C-4 Py); 146.5 (C-2 Py); 148.5 (C-6 Py); 162.7 (COOMe); 164.3 ($C(O)NH_2$). Mass spectrum, *m/z*: 329 $[M–Br]^+$. Found, %: C 40.96; H 5.14; Br 19.48; N 6.80; S 7.77. $C_{14}H_{21}BrN_2O_5S$. Calculated, %: C 41.08; H 5.17; Br 19.52; N 6.84; S 7.83.

3-Carbamoyl-1-[2-(carbamoylmethylsulfonyl)ethyl]-pyridinium chloride (1j) was obtained from nicotinamide (**7e**) (0.64 g, 5.2 mmol) and 2-[(2-chloroethyl)sulfonyl]-acetamide (**2a**) (0.97 g, 5.2 mmol), the refluxing duration was 17 h. Yield 0.60 g (37%), white crystals, mp 188–189°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.24 (2H, t, *J* = 6.4, CH_2SO_2); 4.32 (2H, s, CH_2CO); 5.24 (2H, t, *J* = 6.4, CH_2N^+); 7.57 (1H, s) and 7.95 (1H, s, $CH_2C(O)N\underline{H}_2$); 8.16 (1H, s) and 8.69 (1H, s, $C(O)NH_2$); 8.30 (1H, dd, *J* = 8.1, *J* = 7.8, H-5 Py); 9.03 (1H, d, *J* = 8.2, H-4 Py); 9.31 (1H, d, *J* = 6.0, H-6 Py); 9.68 (1H, s, H-2 Py). ^{13}C NMR spectrum (100 MHz), δ, ppm: 52.9 (CH_2SO_2); 54.6 ($SO_2\underline{C}H_2CO$); 58.8 (CH_2N^+); 128.0 (C-5 Py); 134.0 (C-3 Py); 144.7 (C-4 Py); 146.1 (C-2 Py); 147.7 (C-6 Py); 163.2 ($C(O)NH_2$); 163.9 ($CH_2\underline{C}(O)NH_2$). Mass spectrum, *m/z*: 272 $[M–Cl]^+$. Found, %: C 38.97; H 4.52; Cl 11.46; N 13.63; S 10.39. $C_{10}H_{14}ClN_3O_4S$. Calculated, %: C 39.03; H 4.59; Cl 11.52; N 13.65; S 10.42.

3-Carbamoyl-1-[5-(carbamoylmethylsulfonyl)pentyl]-pyridinium bromide (1k) was obtained from nicotinamide (**7e**) (0.61 g, 5.0 mmol) and 2-[(5-bromopentyl)sulfonyl]-acetamide (**2c**) (1.36 g, 5.0 mmol), the refluxing duration was 18 h. Yield 0.83 g (42%), white crystals, mp 140–141°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.43–1.47 (2H, m, CH_2); 1.76–1.80 (2H, m, CH_2); 1.99–2.03 (2H, m, CH_2); 3.30 (2H, t, *J* = 7.8, CH_2SO_2); 4.02 (2H, s, CH_2CO); 4.69 (2H, t, *J* = 7.4, CH_2N^+); 7.42 (1H, s) and 7.77 (1H, s, $CH_2C(O)N\underline{H}_2$); 8.14 (1H, s) and 8.57 (1H, s, $C(O)NH_2$); 8.28 (1H, t, *J* = 7.1, H-5 Py); 8.97 (1H, d, *J* = 8.0, H-4 Py); 9.25 (1H, d, *J* = 6.2, H-6 Py); 9.55 (1H, s, H-2 Py). ^{13}C NMR spectrum (100 MHz), δ, ppm: 21.1 (CH_2); 24.6 (CH_2); 30.5 (CH_2); 52.7 (CH_2SO_2); 58.3 ($SO_2\underline{C}H_2CO$); 61.2 (CH_2N^+); 128.3 (C-5 Py); 134.3 (C-3 Py); 143.9 (C-4 Py); 145.2 (C-2 Py); 146.8 (C-6 Py); 163.3 ($C(O)NH_2$); 164.3 ($CH_2\underline{C}(O)NH_2$). Mass spectrum, *m/z*: 314 $[M–Br]^+$. Found, %: C 39.57; H 5.08; Br 20.21; N 10.62; S 8.11. $C_{13}H_{20}BrN_3O_4S$. Calculated, %: C 39.60; H 5.11; Br 20.27; N 10.66; S 8.13.

1-[2-(Carbamoylmethylsulfonyl)ethyl]-3-hydrazinocarbonylpyridinium chloride (1l) was obtained from nicotinyl hydrazide (**7f**) (0.60 g, 4.4 mmol) and 2-[(2-chloroethyl)sulfonyl]acetamide (**2a**) (0.81 g, 4.4 mmol), the refluxing duration was 22 h. Yield 0.70 g (50%), yellowish powder, mp 227–228°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 3.78 (2H, t, *J* = 5.9, CH_2SO_2); 3.97 (2H, t, *J* = 6.0, CH_2N^+); 4.50 (2H, s, CH_2CO); 7.52 (1H, s, $C(O)NH_2$); 7.56–7.58 (1H, m, H-5 Py); 7.89 (1H, s, $C(O)NH_2$); 8.23 (1H, d, *J* = 8.1, H-4 Py); 8.79 (1H, d, *J* = 6.2, H-6 Py); 9.05 (1H, s, H-2 Py); 11.16 (1H, s, $N\underline{H}NH_2$). ^{13}C NMR spectrum

(150 MHz), δ, ppm (*J*, Hz): 47.2 (CH_2SO_2); 49.3 ($SO_2\underline{C}H_2CO$); 56.9 (CH_2N^+); 124.2 (C-5 Py); 128.1 (C-3 Py); 135.9 (C-4 Py); 149.1 (C-2 Py); 153.3 (C-6 Py); 161.2 ($C(O)NHNH_2$); 164.2 ($C(O)NH_2$). Mass spectrum, *m*/*z*: 287 $[M–Cl]^+$. Found, %: C 37.18; H 4.67; Cl 10.93; N 17.31; S 9.90. $C_{10}H_{15}ClN_4O_4S$. Calculated, %: C 37.21; H 4.68; Cl 10.98; N 17.36; S 9.93.

1-[5-(Carbamoylmethylsulfonyl)pentyl]-3-hydrazinocarbonylpyridinium bromide (1m) was obtained from nicotinyl hydrazide (**7f**) (0.32 g, 2.4 mmol) and 2-[(5-bromopentyl)sulfonyl]acetamide (**2c**) (0.64 g, 2.4 mmol), the refluxing duration was 22 h. Yield 0.50 g (52%), light-yellow hygroscopic powder. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.47–1.49 (2H, m, CH_2); 1.76–1.78 (2H, m, CH_2); 1.99–2.02 (2H, m, CH_2); 3.29 (2H, t, *J* = 6.7, CH_2SO_2); 4.02 (2H, s, CH_2CO); 4.71 (2H, t, *J* = 6.7, CH_2N^+); 7.42 (1H, s) and 7.78 (1H, s, $C(O)NH_2$); 7.60–7.62 (1H, m, H-5 Py); 8.27 (1H, d, *J* = 8.0, H-4 Py); 8.81 (1H, d, *J* = 6.2, H-6 Py); 9.04 (1H, s, H-2 Py); 11.10 (1H, s, $N\underline{H}NH_2$). ^{13}C NMR spectrum (100 MHz), δ, ppm: 21.1 (CH_2); 24.7 (CH_2); 30.5 (CH_2); 52.8 (CH_2SO_2); 58.4 ($SO_2\underline{C}H_2CO$); 61.4 (CH_2N^+); 118.5 (C-5 Py); 124.4 (C-3 Py); 136.3 (C-4 Py); 148.8 (C-2 Py); 153.4 (C-6 Py); 164.3 ($C(O)NHNH_2$); 165.0 ($C(O)NH_2$). Mass spectrum, *m*/*z*: 329 $[M–Br]^+$. Found, %: C 38.13; H 5.15; Br 19.47; N 13.66; S 7.80. $C_{13}H_{21}BrN_4O_4S$. Calculated, %: C 38.15; H 5.17; Br 19.52; N 13.69; S 7.83.

1-[2-(Carbamoylmethylsulfonyl)ethyl]-4-hydrazinocarbonylpyridinium chloride (1n). Method I. Compound **1n** was prepared according to the general method from isonicotinyl hydrazide (**7g**) (0.55 g, 4.0 mmol) and 2-[(2-chloroethyl)sulfonyl]acetamide (**2a**) (0.74 g, 4.0 mmol), the refluxing duration was 22 h. Yield 0.41 g (32%), yellow hygroscopic powder.

Method II. A solution of 2-vinylsulfonylacetamide (**8**) (1.1 g, 7.3 mmol) in EtOH (15 ml) was added to a solution of isonicotinyl hydrazide (**7g**) (1.0 g, 7.3 mmol) in a mixture of EtOH (20 ml), water (6 ml), and concd HCl (0.7 ml). The mixture was refluxed for 5 h, filtered, and evaporated. The residue was dissolved in MeOH, filtered, evaporated, and dried at reduced pressure. Yield 1.32 g (56%), light-brown powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 3.80 (2H, t, *J* = 5.7, CH_2SO_2); 3.98 (2H, t, *J* = 5.7, CH_2N^+); 4.53 (2H, s, CH_2CO); 7.56–7.58 (1H, m, H-5 Py); 8.15 (1H, s, $C(O)NH_2$); 8.22–8.24 (2H, m, H Py); 8.94 (1H, s, $C(O)NH_2$); 8.99–9.04 (1H, m, H-6 Py); 11.81 (1H, s, $N\underline{H}NH_2$). ^{13}C NMR spectrum (100 MHz); δ, ppm (*J*, Hz): 47.0 (CH_2SO_2); 49.2 ($SO_2\underline{C}H_2CO$); 56.9 (CH_2N^+); 124.5 (C-3,5 Py); 129.8 (C-4 Py); 146.1 (C-2,6 Py); 161.0 ($C(O)NHNH_2$); 163.4 ($C(O)NH_2$). Mass spectrum, *m*/*z*: 287 $[M–Cl]^+$. Found, %: C 37.16; H 4.65; Cl 10.94; N 17.32; S 9.89. $C_{10}H_{15}ClN_4O_4S$. Calculated, %: C 37.21; H 4.68; Cl 10.98; N 17.36; S 9.93.

1-[5-(Carbamoylmethylsulfonyl)pentyl]-4-hydrazinocarbonylpyridinium bromide (1o) was obtained from isonicotinyl hydrazide (**7g**) (0.37 g, 2.7 mmol) and 2-[(5-bromopentyl)sulfonyl]acetamide (**2c**) (0.74 g, 2.7 mmol), the refluxing duration was 21 h. Yield 0.48 g (43%), light-yellow resin. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.45–1.47 (2H, m, CH_2); 1.74–1.78 (2H, m, CH_2); 1.98–2.00 (2H, m, CH_2); 3.29 (2H, t, *J* = 6.9, CH_2SO_2); 4.02 (2H, s, CH_2CO); 4.68 (2H, t, *J* = 6.9, CH_2N^+); 7.42 (1H, s) and 7.78 (1H, s, $C(O)NH_2$); 7.82–7.84 (2H, m, H Py); 8.81–8.83 (2H, m, *J* = 6.2, H-6 Py); 10.90 (1H, s, $N\underline{H}NH_2$). ^{13}C NMR spectrum (100 MHz), δ, ppm (*J*, Hz): 21.0 (CH_2); 24.38 (CH_2); 30.4 (CH_2); 52.7 (CH_2SO_2); 58.4 ($SO_2\underline{C}H_2CO$); 58.6 (CH_2N^+); 124.2 (C-3,5 Py); 128.8 (C-4 Py); 146.1 (C-2,6 Py); 161.5 ($C(O)NHNH_2$); 162.4 ($C(O)NH_2$). Mass spectrum, *m*/*z*: 329 $[M–Br]^+$. Found, %: C 38.11; H 5.15; Br 19.48; N 13.67; S 7.81. $C_{13}H_{21}BrN_4O_4S$. Calculated, %: C 38.15; H 5.17; Br 19.52; N 13.69; S 7.83.

2-(Vinylsulfonyl)acetamide (8). 4-Aminomethylpyridine (**7h**) (0.4 g, 3.8 mmol) was added to a solution of 2-[(2-chloroethyl)sulfonyl]acetamide (**2a**) (0.7 g, 3.8 mmol) in MeCN (40 ml), the reaction mixture was stirred for 15 min, filtered, evaporated, and the residue was washed with diethyl ether. Yield 0.52 g (93%), light-green thick oil that crystallized during storage, mp 78°C ($CHCl_3$) (mp 81°C[22]). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 4.06 (2H, s, CH_2CO); 6.22–6.26 (2H, m, $C\underline{H}_2$= CH); 7.00–7.04 (1H, m, CH_2=C$\underline{H}$); 7.40 (1H, s) and 7.66 (1H, s, NH_2). Found, %: C 32.18; H 4.69; N 9.37; S 21.43. $C_4H_7NO_3S$. Calculated, %: C 32.21; H 4.73; N 9.39; S 21.50.

Tuberculostatic activity studies of compounds **1a**–**o**, **7g** were performed according to the vertical diffusion method using laboratory strain H37Rv of *M. tuberculosis* on "New" brand dense nutrient medium. The nutrient medium (5 ml portions) was poured into test tubes rolling so that part of the bottom of each test tube remained free. The rolled nutrient medium was inoculated with 0.1 ml of suspension containing the strain H37Rv of *M. tuberculosis*, diluted to 10 units according to L. A. Tarasevich State Control Institute turbidity standards, and placed in thermostat in inclined position for 24 h to enable the growth of *M. tuberculosis*. The next day, the test tubes were turned to vertical position and solutions of the study compounds (0.3 ml) with concentrations of 12.5, 6.2, 3.1, 1.2, 0.6, and 0.3 μl/ml were added along the free side of each test tube. The test tubes were then placed in thermostat at 37°C temperature and incubated for 10 days. The growth of *M. tuberculosis* was evaluated according to standard method, where the presence of growth inhibition zones (larger than 10 mm) served as evidence of tuberculostatic properties of the compounds at the applied concentrations. The size of growth inhibition zone for *M. tuberculosis* (in mm) was proportional to the degree of tuberculostatic activity of the compounds. Growth inhibition zones of 100 mm or larger were interpreted as complete inhibition of *M. tuberculosis* growth.[22]

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