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Synthesis and Antimicrobial Activity of {2-[2-(*N,N*-disubstituted thiocarbamoyl-sulfanyl)-acylamino]thiazol-4-yl}acetic Acid Ethyl Esters

{2-[2-(*N,N*-Disubstituted thiocarbamoyl-sulfanyl)acylamino]thiazol-4-yl}acetic acid ethyl esters (**3 a–x**) were synthesized by the reaction of potassium salts of *N,N*-disubstituted dithiocarbamoic acids with [2-(2-chloroalkanoyl)amino-thiazol-4-yl]acetic acid ethyl esters. The structures of the synthesized compounds were confirmed by elemental analyses, UV, IR, ^{1}H-NMR, and EI mass spectral data. The antimicrobial activities of all the compounds were investigated by microbroth dilution technique using Mueller-Hinton broth and Mueller-Hinton agar. In this study, *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi, Shigella flexneri, Proteus mirabilis* ATCC 14153 and *Candida albicans* ATCC 10231 were used as test microorganisms. Among the tested compounds **3 a, d, e, f, h, k, w** showed activity against *S. epidermidis* ATCC 12228 (MIC: 156 mg/L, 78 mg/L, 62.5 mg/L, 78 mg/L, 62.5 mg/L, 312 mg/L, 250 mg/L, respectively), compound **3 d** also had some activity against *S. aureus* ATCC 6538 (MIC: 156 mg/L) and *C. albicans* ATCC 10231(MIC: 156 mg/L). Compounds **3 l**, **3 x** were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system and BACTEC 12B medium. The preliminary results indicated that all of the tested compounds were inactive against the test organism.

Keywords: 2-[(Thiocarbamoyl-sulfanyl)acylamino]-1,3-thiazoles; Synthesis; Antibacterial; Antifungal; Antituberculosis activities

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Introduction

2-Amino-1,3-thiazoles [1–8] and *N*-substituted/*N,N*-disubstituted dithiocarbamoic acid esters [9–14] have been reported in the literature to exhibit various pharmacological activities such as antibacterial, antifungal, herbicidal, immunomodulatory, anticholinergic. In this study, potassium salts of *N,N*-disubstituted dithiocarbamoic acids were reacted with [2-(2-chloroalkanoyl)amino-thiazol-4-yl]acetic acid ethyl esters to obtain a series of new compounds which were expected to be antimicrobial agents. The antibacterial activity against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *K. pneumoniae* ATCC 4352, *P. aeruginosa* ATCC 1539, *S. typhi, Sh. flexneri, P. mirabilis* ATCC 1415 ; antifungal activity against *C. albicans* ATCC 10231 and antituberculosis activity against *Mycobacterium tuberculosis* H37Rv were investigated.

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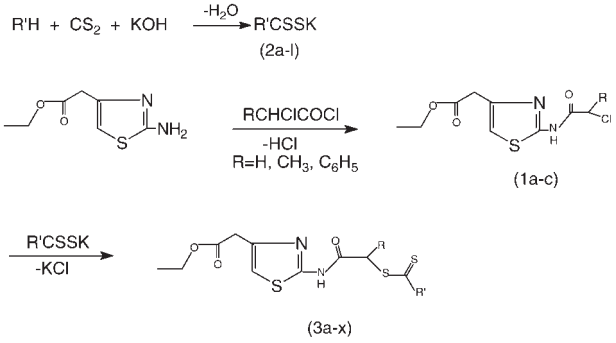

Scheme 1

Results and discussion

[2-(2-Chloroalkanoyl)amino-thiazol-4-yl]acetic acid ethyl esters (**1 a–c**), which were prepared by stirring α-haloacyl halides with (2-amino-1,3-thiazol-4-yl)acetic acid ethyl ester in dry benzene and dry pyridine for 1 h at room temperature [1, 15], were reacted with potassium salts of

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Table 1. Experimental data for compounds **3a–x**.

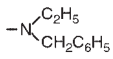
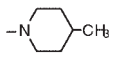
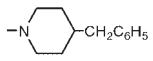
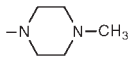
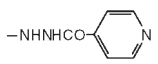
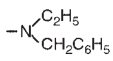
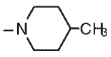
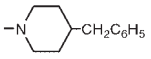
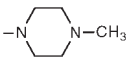
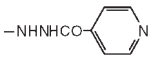
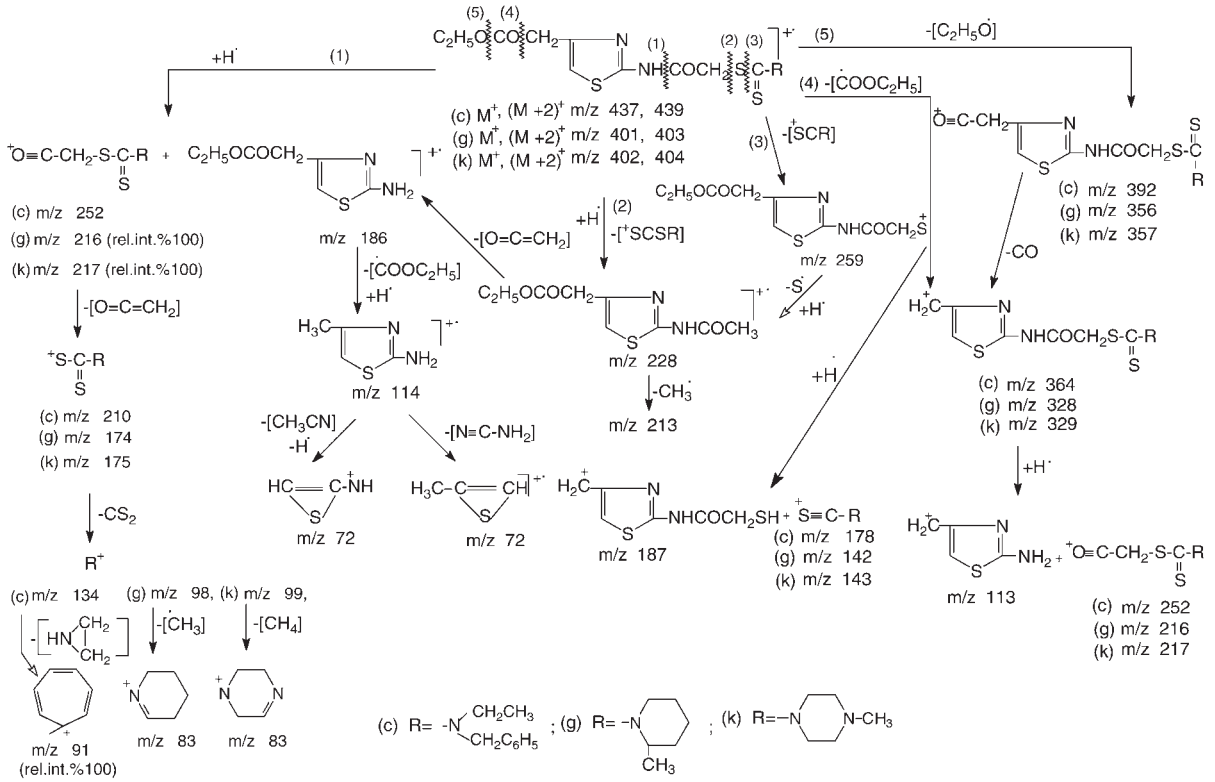
Compd.	R	R^1	Formula (MW)	Yield (%)	Mp (°C)	λ_{max}^{EtOH} (nm)
3a	H		$C_{12}H_{17}N_3O_3S_3 \cdot 1\,H_2O$ (347.47)	90	130	269
3b	H		$C_{14}H_{21}N_3O_3S_3 \cdot 0.5\,H_2O$ (375.52)	56	–	337, 271
3c	H		$C_{19}H_{23}N_3O_3S_3$ (437.58)	96	–	272
3d	H		$C_{14}H_{19}N_3O_3S_3 \cdot 0.5\,H_2O$ (373.5)	75	–	269
3e	H		$C_{14}H_{19}N_3O_4S_3$ (389.5)	92	126–8	279
3f	H		$C_{15}H_{21}N_3O_3S_3 \cdot 0.5\,H_2O$ (387.53)	90	97–100	273
3g	H		$C_{16}H_{23}N_3O_3S_3$ (401.55)	88	–	272
3h	H		$C_{16}H_{23}N_3O_3S_3 \cdot 0.5\,H_2O$ (401.55)	95	–	272
3i	H		$C_{22}H_{27}N_3O_3S_3$ (477.65)	79	–	272
3j	H		$C_{17}H_{25}N_3O_3S_3 \cdot 2.5\,H_2O$ (415.58)	87	–	251
3k	H		$C_{15}H_{22}N_4O_3S_3$ (402.55)	86	–	273, 252
3l	H		$C_{16}H_{17}N_5O_4S_3$ (439.53)	90	210–12	337, 272
3m	CH_3		$C_{15}H_{23}N_3O_3S_3 \cdot 0.5\,H_2O$ (389.57)	87	–	272
3n	C_6H_5		$C_{18}H_{21}N_3O_3S_3$ (423.56)	95	–	269, 245
3o	C_6H_5		$C_{20}H_{25}N_3O_3S_3$ (451.61)	78	131–33	274, 245
3p	C_6H_5		$C_{25}H_{27}N_3O_3S_3$ (513.68)	88	–	251
3q	C_6H_5		$C_{20}H_{23}N_3O_3S_3$ (449.59)	90	140–42	272, 244
3r	C_6H_5		$C_{20}H_{23}N_3O_4S_3$ (465.59)	82	–	246
3s	C_6H_5		$C_{21}H_{25}N_3O_3S_3$ (463.62)	94	155–56	275, 246

Table 1. (continued)

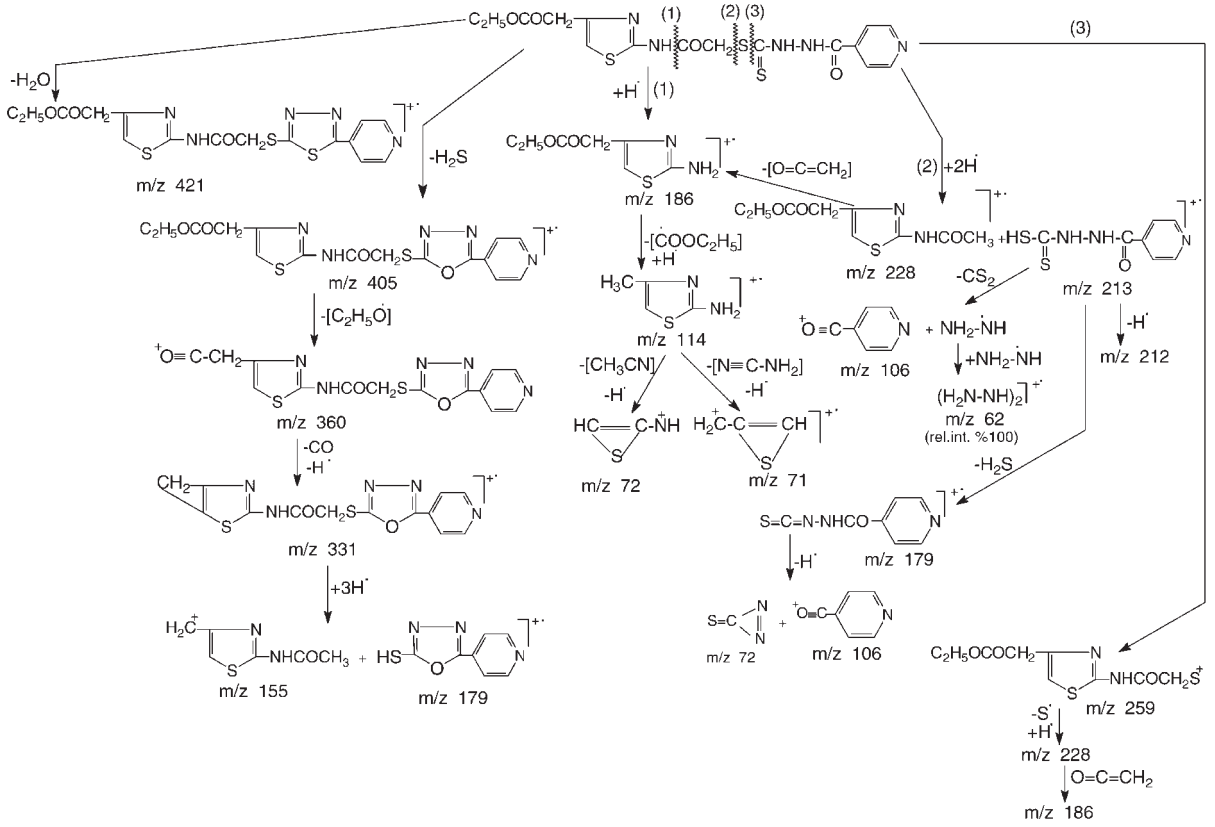
Compd.	R	R^1	Formula (MW)	Yield (%)	Mp (°C)	λ_{max}^{EtOH} (nm)
3 t	C_6H_5		$C_{22}H_{27}N_3O_3S_3$ (477.65)	90	–	251
3 u	C_6H_5		$C_{22}H_{27}N_3O_3S_3$ (477.65)	89	127–30	275, 246
3 v	C_6H_5		$C_{28}H_{31}N_3O_3S_3$ (553.74)	87	128–30	274, 251
3 w	C_6H_5		$C_{21}H_{26}N_4O_3S_3 \cdot 1.5\,H_2O$ (478.64)	79	–	273, 251
3 x	C_6H_5		$C_{22}H_{21}N_5O_4S_3 \cdot 1\,H_2O$ (515.62)	82	–	287, 251

N,N-disubstituted dithiocarbamoic acids (**2 a–l**) [16–20] to give {2-[2-(*N,N*-disubstituted thiocarbamoyl-sulfanyl)-acylamino]thiazol-4-yl}acetic acid ethyl esters (**3 a–x**) (Scheme 1, Table 1). The formulas of compounds **3 a–x** were confirmed by elemental analyses and their structures were determined by UV, IR, ^{1}H-NMR, and EI mass spectral data. The IR data were very informative and provided evidence for the formation of the expected structures. Two C=O and one C=S function absorbed strongly in the expected regions: ester C=O at 1632–1734 cm^{-1}, amide C=O at 1629–1706 cm^{-1}, thioamide C=S at 1034–1267 cm^{-1}. The ^{1}H-NMR spectral data were also consistent with the assigned structures. *CH*$_3$CH$_2$O, CH$_3$*CH*$_2$O, O=C-CH$_2$ protons, and 5-H proton of the thiazole moiety, -COCH$_2$-S-/-CO-CH-S protons and NH-CO proton appeared at 0.97–1.39, 4.04–4.11, 3.63–3.70, 6.81–7.10, 4.26–4.42/4.42–5.92, and 8.72–12.69 ppm, respectively. Aromatic protons and (CH$_3$)$_2$N, (CH$_3$CH$_2$)$_2$N, CH$_3$CH$_2$-N-CH$_2$-C$_6$H$_5$, pyrrolidine, piperidine, piperazine, and morpholine protons were observed in the expected regions. Compounds **3 r** and **3 t** were mixtures of geometric isomers as reflected by their ^{1}H-NMR spectra. The ratio of the isomers in the mixture was determined via their appropriate ^{1}H-NMR signals (1/1 for **3 r**, 1/1 for **3 t**) X-ray crystallographic studies showed that the C-N bonds of the amide and thioamide functions are shorter than single bonds [21] and restriction of rotation about these bonds can lead to different spatial arrangements [22]. In some cases stable individual rotamers of both carboxamides and thioamides could be isolated [23]. Furthermore, *cis* and *trans* conformations according to the relative positions of the C=S and S-CH$_3$ functions in *S*-methyldithiocarbamate have also been reported [24]. Restriction of rotation about C-N bonds of compounds **3 r** and **3 t** may also provide a possible explanation for the duplication of ^{1}H-NMR signals associated with the N-H, 5-H thiazole, CH-S, CH$_3$ protons. The mass spectra of the compounds **3 a–x** were recorded by EIMS. All compounds **3 a–x** (with the exception of compound **3 l**) showed molecular ions (M^+) which confirmed their molecular weights. The major fragmentation pathway involved the cleavage of the C-S bonds or bonds adjacent to the carbonyl group, which was in accordance with the literature [19, 25]. The proposed fragmentation routes of compounds **3 c**, **g**, **k**, and **3 l** are shown in Schemes 2 and 3.

The antibacterial activity of the synthesized compounds were investigated against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *K. pneumoniae* ATCC 4532, *P. aeruginosa* ATCC 1539, *S. typhi, Sh. flexneri, Pr. mirabilis* ATCC 14153 and antifungal activity against *C. albicans* ATCC 10231 using disk diffusion method and the microbroth dilution technique. Most of the compounds (**3 a**, **d**, **e**, **f**, **h**, **k** and **3 w**) were found to be weakly active against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228 and *C. albicans* ATCC 10231 when compared with cefuroxime sodium and clotrimazole. Activity increases with *N*-substituted compounds which carries nitrogen in the ring compared to the *N*-dimethyl substituted compounds. On the other hand when the ring has two nitrogens, activity decreases. That is, the activity of derivatives carrying pyrrolidine, piperidine, and morpholine is twice the activity of the derivative with piperazine moiety. The minimum inhibitory concentrations (MIC) are given in Table 2. These values indicat-



Scheme 2



Scheme 3

Table 2. MIC values mg/L of compounds **3 a**, **3 d**, **3 e**, **3 f**, **3 h**, **3 k**, and **3 w**.

Compd.	*S. aureus* ATCC 6538	*S. epidermidis* ATCC 12228	*C. albicans* ATCC 10231
3 a	–	156	–
3 d	156	78	156
3 e	–	62.5	–
3 f	–	78	–
3 h	–	62.5	–
3 k	–	312	–
3 w	–	250	–
Cefuroxime sodium	1.2	4.9	–
Clotrimazole	–	–	4.9

ed that compound **3 d** possessed significant activity against *C. albicans*, compounds **3 a**, **d**, **e** , **f**, **h**, **k** and **3 w** against *S. epidermidis* and compound **3 d** against *S. aureus.* Compounds **3 l**, **3 x** were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system and BACTEC 12B medium [26]. All of the tested compounds were inactive against the test organism.

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Experimental part

Chemistry

Melting points were measured on a Büchi 530 melting point apparatus in open capillaries and were uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. The compounds were checked for purity by TLC on silica gel HF_{254}. UV spectra were taken in ethanol on a Shimadzu Model UV 2100S UV spectrophotometer. IR spectra were recorded on KBr discs, using a Perkin-Elmer Model 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker AC 200 (^{1}H: 200 MHz, DMSO-d_6) spectrophotometer. EI/MS were determined on a VG Zab Spec (70 eV) mass spectrometer.

Synthesis of [2-(2-chloroalkanoyl)amino-thiazol-4-yl]acetic acid ethyl esters (**1 a–c**) [1]

(2-Amino-1,3-thiazol-4-yl)acetic acid ethyl ester (0.01 mol, 1.86 g) in dry benzene (4 mL) and dry pyridine (1 mL) was stirred with 2-chloroacetyl chloride (0.01 mol, 0.8 mL) or 2-chloropropionyl chloride (0.01 mol, 0.98 mL) or 2-chloro-2-phenylacetyl chloride (0.01 mol, 1.44 mL) in dry benzene (3 mL) for 1 h at room temperature. The crude product was washed with water to remove the acid and recrystallised from ethanol to obtain compound **1 a** (**1 b** and **1 c** were not recrystallised).

Synthesis of {2-[2-(N,N-disubstituted thiocarbamoyl-sulfanyl)acylamino]thiazol-4-yl}acetic acid ethyl esters (**3 a–x**)

A mixture of [2-(2-chloroalkanoyl)amino-thiazol-4-yl]acetic acid ethyl ester (0.005 mol) and the potassium salt of the appropriate *N,N*-disubstituted dithiocarbamoic acid (0.005 mol) in ethanol (40 mL) were refluxed on a water bath for 1 h. Crystals were filtered off and recrystallised from ethanol.

Spectral data of **3 a**: UV [λ_{max}, nm, EtOH]: 269. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1691 (C=O, amide), 1166 (C=S). – ^{1}H-NMR [400 MHz, δ ppm, DMSO-d_6]: 1.14 (t, J = 7.1 Hz, 3 H, CH_3CH_2O), 3.36 (s, 3 H, N-CH_3), 3.40 (s, 3 H, N-CH_3), 3.63 (s, 2 H, O=C-CH_2), 4.04 (q, J = 7.1 Hz, 2 H, CH_2O), 4.26 (s, 2 H, CH_2-S), 6.92 (s, 1 H, 5-H thiazole), 12.31 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 348 (M + 1)$^+$ (3), 347 (M$^+$) (6), 302 (2), 274 (2), 259 (4), 228 (4), 213 (1), 186 (15), 162 (28), 120 (6), 112 (3), 88 (100), 72 (12).

Spectral data of **3 b**: UV [λ_{max}, nm, EtOH]: 271, 337. – IR [ν, cm^{-1}, KBr]: 1734 (C=O, ester), 1658 (C=O, amide), 1197 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 0.97–1.39 (m, 9 H, CH_3), 2.93 (q, J = 7.2 Hz, 1 H, N-$CH_{a,b}$), 3.68 (s, 2 H, O=C-CH_2), 3.78 (q, J = 7.2 Hz, 1 H, N-$CH_{a,b}$), 3.93 (q, J = 6.3 Hz, 2 H, N-CH_2), 4.08 (q, J = 7.1 Hz, 2 H, CH_2O), 4.30 (s, 2 H, CH_2-S), 6.97 (s, 1 H, 5-H thiazole), 12.38 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 377 (M + 2)$^+$ (1), 375 (M$^+$) (4), 330 (3), 302 (4), 259 (39), 228 (31), 213 (10), 190 (100), 186 (32), 148 (8), 116 (58), 88 (32), 72 (2), 71 (3).

Spectral data of **3 c**: UV [λ_{max}, nm, EtOH]: 272. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1682 (C=O, amide), 1034 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.17 (t, J = 7.0 Hz, 6 H, CH_3), 3.67 (s, 2 H, O=C-CH_2), 3.71–3.80 (m, 1 H, N-$CH_{a,b}$-CH_3), 3.93 (t, J = 7.0 Hz, 1 H, N-$CH_{a,b}$-CH_3), 4.07 (q, J = 7.0 Hz, 2 H, CH_2O), 4.31 (s, 1 H, $CH_{a,b}$-S), 4.36 (s, 1 H, $CH_{a,b}$-S), 5.05 (s, 1 H, N-$CH_{a,b}$-Ph), 5.28 (s, 1 H, N-$CH_{a,b}$-Ph), 6.96 (s, 1 H, 5-H thiazole), 7.20–7.50 (m, 5 H, phenyl), 12.40 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 439 (M + 2)$^+$ (2), 437 (M$^+$) (12), 392 (6), 364 (6), 259 (40), 252 (73), 228 (90), 213 (18), 210 (11), 187 (16), 186 (63), 178 (14), 134 (28), 114 (6), 113 (16), 91 (100), 72 (2).

Spectral data of **3 d**: UV [λ_{max}, nm, EtOH]: 269. – IR [ν, cm^{-1}, KBr]: 1734 (C=O, ester), 1678 (C=O, amide), 1159 (C=S).- ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.17 (t, J = 7.0 Hz, 3 H, CH_3), 1.84–2.11 (m, 4 H, 3-H/4-H pyrrolidine), 3.54–3.79 (m, 4 H, 2-H/5-H pyrrolidine), 3.67 (s, 2 H, O=C-CH_2), 4.07 (q, J = 7.1 Hz, 2 H, CH_2O), 4.31 (s, 2 H, CH_2-S), 6.96 (s, 1 H, 5-H thiazole), 12.34 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 375 (M + 2)$^+$ (4), 373 (M$^+$) (23), 328 (10), 300 (12), 259 (67), 228 (22), 213 (20), 188 (100), 186 (37), 146 (32), 114 (84), 113 (16), 72 (57), 70 (29).

Spectral data of **3 e**: UV [λ_{max}, nm, EtOH]: 279. – IR [ν, cm^{-1}, KBr]: 1727 (C=O, ester), 1697 (C=O, amide), 1220 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.20 (t, J = 7.0 Hz, 3 H, CH_3), 3.68–3.72 (m, 6 H, O=C-CH_2, 3-H/5-H morpholine), 4.10

(q, J = 7.1 Hz, 6 H, CH_2O and 2-H/6-H morpholine), 4.36 (s, 2 H, CH_2-S), 6.97 (s, 1 H, 5-H thiazole), 12.32 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 391 $(M + 2)^+$ (1), 389 (M^+) (8), 344 (3), 316 (4), 259 (70), 228 (9), 213 (13), 204 (100), 186 (27), 162 (10), 130 (62), 114 (5), 113 (12), 86 (36), 72 (3).

Spectral data of **3 f**: UV [λ_{max}, nm, EtOH]: 273. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1698 (C=O, amide), 1152 (C=S). – ^{1}H-NMR [400 MHz, δ ppm, DMSO-d_6]: 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 1.61–1.67 (m, 6 H, 3-H/4-H/5-H piperidine), 3.69 (s, 2 H, O=C-CH_2), 3.93 (br. s, 2 H, 2-H piperidine), 4.10 (q, J = 7.1 Hz, 2 H, CH_2O), 4.19 (br. s, 2 H, 6-H piperidine), 4.33 (s, 2 H, CH_2-S), 6.97 (s, 1 H, 5-H thiazole), 12.38 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 388 $(M + 1)^+$ (29), 387 (M^+) (25), 259 (10), 228 (13), 213 (3), 202 (82), 186 (14), 160 (11), 128 (88), 112(18), 84 (76), 72 (51), 69 (100).

Spectral data of **3 g**: UV [λ_{max}, nm, EtOH]: 272. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1629 (C=O, amide), 1267 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.17 (t, J = 7.0 Hz, 3 H, CH_3-CH_2O), 1.20 (t, J = 7.4 Hz, 3 H, C_2-CH_3 piperidine), 1.53–1.77 (m, 6 H, 3-H/4-H/5-H piperidine), 3.67 (s, 2 H, O=C-CH_2), 3.56–3.96 (m, 3 H, 2-H/6-H piperidine), 4.07 (q, J = 7.1 Hz, 2 H, CH_2O), 4.31 (s, 2 H, CH_2-S), 6.96 (s, 1 H, 5-H thiazole), 12.36 (s, 1 H, NH). – EI/MS [*m/z* (rel.int. %)]: 403 $(M + 2)^+$ (1), 401 (M^+) (3), 356 (3), 328 (3), 259 (23), 228 (86), 216 (100), 213 (17), 187 (10), 186 (77), 174 (21), 142 (73), 114 (18), 113(7), 98 (82), 83 (21), 72(4).

Spectral data of **3 h**: UV [λ_{max}, nm, EtOH]: 272. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1666 (C=O, amide), 1151 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 0.91 (d, J = 6.1 Hz, 3 H, C_4-CH_3 piperidine), 1.17 (t, J = 7.2 Hz, 3 H, CH_3), 1.72–1.77 (m, 5 H, 3-H/4-H/5-H piperidine), 3.54–4.43 (m, 3 H, 2-H and C_6-H_{ax} piperidine), 3.67 (s, 2 H, O=C-CH_2), 4.10 (q, J = 7.1 Hz, 2 H, CH_2O), 4.30 (s, 2 H, CH_2-S), 5.14 (br. s, 1 H, C_6-H_{eq} piperidine), 6.95 (s, 1 H, 5-H thiazole), 12.36 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 403 $(M + 2)^+$ (2), 401 (M^+) (12), 328 (6), 259 (56), 228 (51), 216 (100), 213 (20), 188 (21), 186 (51), 174 (23), 142 (76), 114 (15), 98 (46), 83 (26), 72 (26).

Spectral data of **3 i**: UV [λ_{max}, nm, EtOH]: 272. – IR [ν, cm^{-1}, KBr]: 1734 (C=O, ester), 1685 (C=O, amide), 1152 (C=S).

Spectral data of **3 j**: UV [λ_{max}, nm, EtOH]: 251. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1661 (C=O, amide), 1213 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.00–1.35 (m, 3 H, CH_3-CH_2-O), 1.20 (d, J = 6.44 Hz, 6 H, C_2-CH_3 and C_6-CH_3 piperidine), 1.68–1.78 (m, 6 H, 3-H/4-H/5-H piperidine), 3.67 (s, 2 H, O=C-CH_2), 4.07 (q, J = 7.0 Hz, 2 H, CH_2O), 4.30 (s, 2 H, CH_2-S), 4.83–4.91 (m, 1 H, 2-H piperidine), 5.37–5.50 (m, 1 H, 6-H piperidine), 6.96 (s, 1 H, 5-H thiazole), 8.72 (s, 1 H, NH) (D_2O exchange). – EI/MS [*m/z* (rel. int. %)]: 417(M + 2)$^+$ (1), 415 (M^+) (1), 342 (3), 259 (4), 230 (54), 228 (100), 213 (20),188 (27), 186 (80), 156 (27), 112 (78), 97 (18), 84 (2),72(4).

Spectral data of **3 k**: UV [λ_{max}, nm, EtOH]: 252, 273. – IR [ν, cm^{-1}, KBr]: 1734 (C=O, ester), 1686 (C=O, amide), 1149 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.18 (t, J = 7.1 Hz, 3 H, C-CH_3), 2.21 (s, 3 H, N-CH_3), 2.39–2.43 (m, 4 H, 3-H/5-H piperazine), 3.68 (s, 2 H, O=C-CH_2), 3.81–4.23 (m, 4 H, 2-H/6-H piperazine), 4.08 (q, J = 7.1 Hz, 2 H, CH_2O), 4.33 (s, 2 H, CH_2-S), 6.97 (s, 1 H, 5-H thiazole), 12.38 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 404 $(M + 2)^+$ (1), 402 (M^+) (2), 357 (7), 329 (6), 259 (32), 228 (95), 217 (100), 213 (31), 187 (10), 186 (38), 175 (82), 143 (91), 114 (6), 113 (9), 99 (28), 83 (29), 72 (3).

Spectral data of **3 l**: UV [λ_{max}, nm, EtOH]: 272, 337. – IR [ν, cm^{-1}, KBr]: 1730 (C=O, ester), 1655 (C=O, amide), 1172 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 3.70 (s, 2 H, O=C-CH_2), 4.08 (q, J = 7.1 Hz, 2 H, CH_2O), 4.42 (s, 2 H, CH_2-S), 7.03 (s, 1 H, 5-H thiazole), 7.87 (d, J = 5.9 Hz, 2 H, 3-H/5-H pyridine), 8.80 (d, J = 5.9 Hz, 2 H, 2-H/6-H pyridine), 12.64 (s, 3 H, NH). – EI/MS [*m/z* (rel. int. %)]: M^+ peak was not observed. 421 $(M–H_2O)^+$ (3), 405 $(M–H_2S)^+$ (4), 360 (3), 331 (6), 259 (2), 228 (9), 213 (30), 186 (45), 179 (42), 155 (7), 106 (39), 72 (4), 71 (13), 62 (100).

Spectral data of **3 m**: UV [λ_{max}, nm, EtOH]: 272. – IR [ν, cm^{-1}, KBr]: 1728 (C=O, ester), 1629 (C=O, amide), 1206 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 0.99–1.26 (m, 9 H, C-CH_3), 1.52 (d, J = 7.3 Hz, 3 H, CH-CH_3), 2.91 (q, J = 7.2 Hz, 2 H, N-CH_2), 3.67 (s, 2 H, O=C-CH_2), 3.91 (q, J = 7.7 Hz, 2 H, N-CH_2), 4.07 (q, J = 7.1 Hz, 2 H, CH_2O), 4.71 (q, J = 7.3 Hz, 1 H, CH-S), 6.98 (s, 1 H, 5-H thiazole), 8.78 (s, 1 H, NH) (D_2O exchange). – EI/MS [*m/z* (rel. int. %)]: 391 $(M + 2)^+$ (4), 389 (M^+) (4), 344 (3), 316 (3), 273 (77), 242 (8), 213 (13), 204 (100), 186 (51), 148 (15), 116 (66), 114 (20), 72 (27).

Spectral data of **3 n**: UV [λ_{max}, nm, EtOH]: 245, 269. – IR [ν, cm^{-1}, KBr]: 1733 (C=O, ester), 1687 (C=O, amide), 1154 (C=S).

Spectral data of **3 o**: UV [λ_{max}, nm, EtOH]: 245, 274. – IR [ν, cm^{-1}, KBr]: 1712 (C=O, ester), 1697 (C=O, amide), 1231 (C=S). – ^{1}H-NMR [400 MHz, δ ppm, DMSO-d_6]: 1.17 (t, J = 7.1 Hz, 6 H, N(CH_2CH_3)$_2$), 1.23 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 3.66 (s, 2 H, O=C-CH_2), 3.72–3.75 (m, 2 H, N-CH_2), 3.89–3.94 (m, 2 H, N-CH_2), 4.07 (q, J = 7.1 Hz, 2 H, CH_2O), 5.87 (s, 1 H, CH-S), 6.98 (s, 1 H, 5-H thiazole), 7.47 (d, J = 6.8 Hz, 2 H, 2-H/6-H phenyl), 7.35–7.41 (m, 3 H, 3-H/4-H/5-H phenyl), 12.67 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 453 $(M + 2)^+$ (1), 451 (M^+) (1), 406 (6), 378 (19), 335 (100), 304 (18), 213 (14), 186 (46), 148 (58), 116 (85), 113(15), 91 (32), 72 (36).

Spectral data of **3 p**: UV [λ_{max}, nm, EtOH]: 251. – IR [ν, cm^{-1}, KBr]: 1731 (C=O, ester), 1685 (C=O, amide), 1247 (C=S).

Spectral data of **3 q**: UV [λ_{max}, nm, EtOH]: 244, 272. – IR [ν, cm^{-1}, KBr]: 1706 (C=O, ester and amide), 1157 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.16 (t, J = 7.1 Hz, 3 H, CH_3), 1.87–2.06 (m, 4 H, 3-H/4-H pyrrolidine), 3.57–3.76 (m, 4 H, 2-H/5-H pyrrolidine), 3.65 (s, 2 H, O=C-CH_2), 4.06 (q, J = 7.1 Hz, 2 H, CH_2O), 5.91 (s, 1 H, CH-S), 6.97 (s, 1 H, 5-H thiazole), 7.35–7.44 (m, 5 H, phenyl), 12.65 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 451 $(M + 2)^+$ (3), 449 (M^+) (11), 404 (10), 376 (7), 335 (75), 304 (20), 213 (38), 186 (46), 146 (50), 114 (100), 91 (4), 72 (48).

Spectral data of **3 r**: UV [λ_{max}, nm, EtOH]: 246. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1629 (C=O, amide), 1230 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.14, 1.18 (dt, J = 7.5 Hz, 3 H, CH_3), 3.41–4.08 (m, 12 H, O=C-CH_2, 2-H/3-H/5-H/6-H morpholine, CH_2O), 5.87, 5.92 (ds, 1 H, CH-S), 6.81, 6.97 (ds, 1 H, 5-H thiazole), 7.32–7.92 (m, 5 H, phenyl), 9.18, 9.21 (ds, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 391 $(M + 2)^+$ (1), 389 (M^+) (4), 344 (3), 316 (3), 273 (77), 242 (8), 213 (13), 204 (100), 186 (51), 148 (15), 116 (66), 114 (20), 72 (27).

Spectral data of **3 s**: UV [λ_{max}, nm, EtOH]: 246, 275. – IR [ν, cm^{-1}, KBr]: 1714 (C=O, ester), 1690 (C=O, amide), 1228 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.16 (t, J = 7.2 Hz, 3 H, CH_3), 1.60 (br. s, 6 H, 3-H/4-H/5-H piperidine), 3.65 (s, 2 H,O=C-CH_2), 3.89 (br. s, 3 H, 2-H and C_6-$H_{ax.}$ piperidine), 4.05 (q, J = 7.1 Hz, 2 H, CH_2O), 4.37 (br. s, 1 H, C_6-$H_{eq.}$ piperidine), 5.84 (s, 1 H, CH-S), 6.98 (s, 1 H, 5-H thiazole), 7.30–7.43 (m, 5 H, phenyl), 12.69 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 464 $(M + 1)^+$ (1), 463 (M^+) (3), 418 (4), 390 (1), 335 (100), 304 (20), 278 (60), 213 (15), 186 (58), 160 (43), 128 (78), 113 (20), 91 (45), 84 (41), 72 (24), 69 (51).

Spectral data of **3 t**: UV [λ_{max}, nm, EtOH]: 251. – IR [ν, cm^{-1}, KBr]: 1732 (C=O, ester), 1630 (C=O, amide), 1159 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.17 (t, *J* = 6.0 Hz, 3 H, *CH*$_3$-CH_2-O), 1.18 (t, *J* = 6.3 Hz, 3 H, C_2-CH_3 piperidine), 1.66–1.72 (m, 6 H, 3-H/4-H/5-H piperidine), 3.15–3.34 (m, 3 H, 2-H/6-H piperidine), 3.65 (s, 2 H, O=C-CH_2), 4.11 (q, *J* = 7.1 Hz, 2 H, CH_2O), 5.89, 5.91 (ds, 1 H, CH-S), 6.81, 6.96 (ds, 1 H, 5-H thiazole), 7.22–7.55 (m, 5 H, phenyl), 9.19, 9.22 (ds, 1 H, NH) (D_2O exchange). – EI/MS [*m/z* (rel. int. %)]: 480 $(M + 2)^+$ (1), 478 (M^+) (2), 432 (3), 404 (2), 335 (100), 304 (34), 292 (44), 213 (10), 186 (82), 174 (40), 142 (93), 113 (23), 98 (65), 91 (4), 70 (11).

Spectral data of **3 u**: UV [λ_{max}, nm, EtOH]: 246, 275. – IR [ν, cm^{-1}, KBr]: 1710 (C=O, ester), 1689 (C=O, amide), 1225 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 0.91 (d, *J* = 5.6 Hz, 3 H, C_4-CH_3 piperidine), 1.16 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$-CH_2-O), 1.71–1.76 (m, 5 H, 3-H/4-H/5-H piperidine), 3.65 (s, 2 H, O=C-CH_2), 4.06 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.37 (br. s, 2 H, 2-H piperidine), 5.14 (br. s, 2 H, 6-H piperidine), 5.86 (s, 1 H, CH-S), 6.97 (s, 1 H, 5-H thiazole), 7.31–7.56 (m, 5 H, phenyl), 12.64 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 479 $(M + 2)^+$ (1), 477 (M^+) (4), 432 (6), 404 (4), 335 (100), 304 (22), 292 (71), 214 (25), 186 (37), 174 (52), 142 (76), 114 (15), 98 (31), 91 (22), 84 (3), 72 (29), 70 (4).

Spectral data of **3 v**: UV [λ_{max}, nm, EtOH]: 251, 274. – IR [ν, cm^{-1}, KBr]: 1713 (C=O, ester), 1691 (C=O, amide), 1232 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.16 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$-CH_2-O), 1.65–1.71 (m, 5 H, 3-H/4-H/5-H piperidine), 1.91 (br. s, 2 H, *CH*$_2$-C_6H_5), 3.65 (s, 2 H, O=C-CH_2), 4.06 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.39 (br. s, 2 H, 2-H piperidine), 5.17 (br. s, 2 H, 6-H piperidine), 5.86 (s, 1 H, CH-S), 6.97 (s, 1 H, 5-H thiazole), 7.15–7.55 (m, 10 H, phenyl), 12.64 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 555 $(M + 2)^+$ (1), 553 (M^+) (1), 508 (1), 480 (1), 368 (22), 335 (64), 304 (32), 250 (12), 218 (28), 186 (84), 174 (42), 146 (3), 114 (24), 91(100), 72 (9).

Spectral data of **3 w**: UV [λ_{max}, nm, EtOH]: 251, 273. – IR [ν, cm^{-1}, KBr]: 1632 (C=O, ester and C=O, amide), 1146 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.16 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$-CH_2-O), 2.33 (s, 3 H, N-CH_3), 2.37–2.49 (m, 4 H, 3-H/5-H piperazine), 3.65 (s, 2 H, O=C-CH_2), 3.88–4.30 (m, 4 H, 2-H/6-H piperazine), 4.06 (q, *J* = 7.1 Hz, 2 H, CH_2O), 5.87 (s, 1 H, CH-S), 6.98 (s, 1 H, 5-H thiazole), 7.24–7.56 (m, 5 H, phenyl), 12.67 (s, 1 H, NH). – EI/MS [*m/z* (rel. int. %)]: 478 (M^+) (1), 433 (2), 405 (1), 335 (41), 304 (55), 259 (3), 231 (20), 213 (17), 186 (100), 174 (5), 143 (38), 113 (49), 91(80), 70 (49).

Spectral data of **3 x**: UV [λ_{max}, nm, EtOH]: 251, 287. – IR [ν, cm^{-1}, KBr]: 1734 (C=O, ester), 1685 (C=O, amide), 1153 (C=S). – ^{1}H-NMR [200 MHz, δ ppm, DMSO-d_6]: 1.17 (t, *J* = 7.0 Hz, 3 H, *CH*$_3$-CH_2-O), 3.70 (s, 2 H, O=C-CH_2), 4.06 (q, *J* = 6.9 Hz, 2 H,CH_2O), 4.42–4.51 (m, 1 H, CH-S), 7.10 (s, 1 H, 5-H thiazole), 7.31–7.56 (m, 5 H, phenyl), 7.63–7.91 (m, 2 H, 3-H/5-H pyridine), 8.66–8.87 (m, 2 H, 2-H/6-H pyridine), 10.38 (s, 3 H, NH) (D_2O exchange). – EI/MS [*m/z* (rel. int. %)]: 517 $(M + 2)^+$ (1), 515 (M^+) (2), 481 $(M\text{-}H_2S)^+$ (100), 470 (1), 442 (1), 335 (2), 329 (2), 304 (15), 213 (53), 186 (42), 180 (4), 121(35), 113 (25), 91(47), 72 (3).

Microbiology

Antibacterial activity of all the compounds against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *K. pneumoniae* ATCC 4532, *P. aeruginosa* ATCC 1539, *S. typhi, S. flexneri, Pr. mirabilis* ATCC 14153 and antifungal activity against *C. albicans* ATCC 10231 were investigated. The disk diffusion method was used. Mueller-Hinton agar (DIFCO, Detroit, USA) was melted at 100 °C and after being cooled to 56 °C, was poured into Petri Plates of 9 cm diameter in quantities of 20 mL and left on a flat surface to solidify and the surface of the medium was dried at 37 °C. Then, cultures of each bacteria and yeast strain, which after being kept in Mueller-Hinton broth (DIFCO), at 37 °C for 18–24 h and diluted with Mueller-Hinton broth to 10^5 cfu/mL, were pipetted into the Mueller-Hinton agar plate prepared as described above. The surface of the medium was allowed to dry. The 10 mg/mL (in DMSO) (E. Merck) compound impregnated disks were applied to the surface of inoculated plates. The Petri Plates were incubated at 37 °C. After 18–24 h of incubation, the Petri Plates were examined and it was found that some of compounds have been effective against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, and *C. albicans* ATCC 10231.

The minimum inhibitory concentrations (MIC) of the compounds were determined by the microbroth dilution technique using Mueller-Hinton broth (Difco. Laboratories, Detroit, MI). Serial two-fold dilutions ranged from 2500 to 2.4 mg/L for the compounds. The inoculum was prepared in broth which had been kept overnight at 37 °C and which had been diluted with Mueller-Hinton broth to give a final concentration of 10^5 cfu/mL in the test tray. The trays were covered and placed in plastic bags to prevent drying. After incubation at 37 °C for 18–24 h, the MIC was defined as the lowest concentration of compound giving complete inhibition of visible growth. MIC values of the compounds are given in Table 2.

Compounds **3 l** and **3 x** were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system and BACTEC 12B medium. The preliminary results indicated that all of the tested compounds were inactive against the test organism.

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