

## Multicomponent Solvent-Free Synthesis, Antimicrobial and Antifungal Evaluation of Novel *N*-Amino Benzylthiolates

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Novel *N*-amino benzylthiolates were synthesized *via* multicomponent reaction of malononitrile, isothiocyanates and benzyl halides under conventional and solvent-free conditions. Various electron-donating and -withdrawing substituents within both isothiocyanates and benzyl halides were used to demonstrate the efficiency of new methodology. A broad spectrum of antibacterial and antifungal activities were observed especially within benzyl halides containing electron-withdrawing aryl substituents.

**Keywords:** Multicomponent synthesis, Solvent-free condition, *N*-Amino benzylthiolate, Antibacterial activity, Antifungal property

### INTRODUCTION

Aminothiolates are organic sulfides containing amino substituents that have been applied as starting materials in chemical reactions [1-4]. Both amino and sulphide functional groups are part of chemical structure of many biomolecules such as axitinib, ceftaroline fosamil, captodiame and ticagrelor. Axitinib is a targeted drug in the treatment of pancreatic and thyroid cancers [5] and ceftaroline fosamil is a cephalosporin antibiotic against acute skin infections [6]. Captodiame has been recommended as an antihistamine agent to prevent benzodiazepine withdrawal syndrome [7]. While ticagrelor is a preventory drug in heart attack in patients with acute coronary syndrome [8].

*N*-Amino alkylthiolates are useful synthons in organic synthesis. They showed significant antibacterial and antioxidant properties as well as nuclease activity toward the cleavage of genomic DNA [9]. Heterocycles such as thiazole, isothiazole and pyrazole derivatives were incorporated with them [10-13], synthesis usually includes formation of thiolate salt, followed by *S*-alkylation and final cyclization.

*N*-Amino thiolate salts were prepared *in situ* using reaction of active methylene compounds and alkyl or aryl isothiocyanates in the presence of bases such as KOH, K<sub>2</sub>CO<sub>3</sub>, NaOEt, Li<sub>2</sub>CO<sub>3</sub>, NaH, *n*-BuLi and NEt<sub>3</sub> [14-20]. A variety of organic solvents including *N,N*-dimethylformamide, tetrahydrofuran, toluene, ethanol and mineral oil have been applied as reaction media. These salts are alkylated with alkyl halides,  $\alpha$ -halo carbonyl or their equivalents, oxiranes, aziridines and  $\alpha$ -halo imines. Accordingly, *N*-amino alkylthiolates were often synthesized as intermediate or final products *via* multistep reactions [13,21-23], and multicomponent process was rarely used in their preparation [24].

To the best of our knowledge, we developed a multicomponent solvent-free procedure to synthesize several new *N*-amino benzylthiolates. No report has been published on the synthesis of these compounds under solvent-free conditions. The inhibitory potentials of all compounds were evaluated against a variety of pathogenic bacteria and fungi.

### EXPERIMENTAL

#### Chemicals

All chemicals, solvents, antibiotics, antifungal agents

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and bacterial and fungal media were obtained from commercial sources (Merck, Aldrich, HiMedia) and used as received. Melting points were recorded on a Kruss type KSP1N melting point apparatus without correction. The reaction progress was monitored by aluminium TLC plates pre-coated with silica gel with fluorescent indicator F254 using CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH (8:2, v/v). The IR spectra were recorded on KBr disks with a Bruker Tensor-27 FT-IR spectrometer. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were acquired on a Bruker FT-NMR Ultra Shield-400 spectrometer (400 and 100 MHz, respectively). Low-resolution mass spectra (EI, 70 eV) were measured on a Varian Mat CH-7 instrument. All CHNS/O analyses were performed by a Thermo Finnigan Flash EA microanalyzer. Initial bacterial or fungal suspensions were adjusted with a Jenway 6405 UV-Vis spectrophotometer.

### General Procedure for the Synthesis of N-Amino Benzylthiolates 4a-j

#### Conventional method using acetonitrile as solvent.

10 mmol of each malononitrile (1) (0.66 g), isothiocyanates 2, benzylhalides 3 and potassium carbonate (1.38 g) in acetonitrile (20 ml) were heated under reflux for 3-7 h. After cooling to room temperature, 20 ml water was added to the reaction mixture and the aqueous phase was extracted twice with 15 ml of diethyl ether. The extracts were combined and washed respectively with 15 ml 5% NaOH (aq) and water. The organic phase was dried over anhydrous MgSO<sub>4</sub> and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol containing various amounts of water to afford N-amino benzylthiolates 4a-j. The solvent-free condition 10 mmol of each malononitrile (1) (0.66 g), isothiocyanates 2, benzylhalides 3 and triethylamine (1.01 g) were vigorously stirred at 80 °C for 2-4 h. The resulting reaction mixture was extracted and purified according to the conventional method.

**2-((Benzylthio)(phenylamino)methylene)malononitrile (4a).** Orange crystal; m.p.: 85-87 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.90 (s, 2H, CH<sub>2</sub>), 7.11-7.38 (m, 10H, 2 Ar-H), 7.91 (s, 1H, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 38.3 (CH<sub>2</sub>), 59.1 (NC-C=C), 113.9, 114.8 (2C≡N), 124.2 (C-2",6"), 127.5 (C-4"), 128.3 (C-4'), 128.8 (C-2',6'), 128.9

(C-3',5'), 129.5 (C-3",5"), 134.3 (C1'), 137.0 (C1"), 169.3 (NC-C=C) ppm; IR (KBr) ν: 3196 (N-H), 2218 (C≡N), 1592 (C=C), 1459 (CH<sub>2</sub>), 1096 (C-S) cm<sup>-1</sup>; MS *m/z* 291 (M<sup>+</sup>, 11), 91 (100); Anal. Calcd. for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>S: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 70.13; H, 4.52; N, 14.38; S, 10.97%.

**2-(((2-Chlorobenzyl)thio)(phenylamino)methylene)malononitrile (4b).** Orange crystal; m.p.: 92-94 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.06 (s, 2H, CH<sub>2</sub>), 7.13-7.39 (m, 9H, 2Ar-H), 8.24 (br, 1H, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 36.5 (CH<sub>2</sub>), 59.1 (NC-C=C), 113.9, 114.7 (2C≡N), 124.3 (C-2",6"), 127.3 (C-4"), 127.6 (C-4'), 129.6 (C-3",5"), 129.9 (C-3'), 130.0 (C-5'), 130.9 (C-6'), 132.2 (C-2'), 134.3 (C-1'), 137.0 (C-1"), 169.8 (NC-C=C) ppm; IR (KBr) ν: 3180 (N-H), 2210 (C≡N), 1617 (C=C), 1444 (CH<sub>2</sub>), 1054 (C-S) cm<sup>-1</sup>; MS *m/z* 325 (M<sup>+</sup>, 9), 201 (100); Anal. Calcd. for C<sub>17</sub>H<sub>12</sub>ClN<sub>3</sub>S: C, 62.67; H, 3.71; N, 12.90; S, 9.84. Found: C, 62.61; H, 3.69; N, 12.94; S, 9.85%.

**2-(((2-Nitrobenzyl)thio)(phenylamino)methylene)malononitrile (4c).** Dark brown crystal; m.p.: 195-196 °C (decomp.); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 3.59 (s, 2H, CH<sub>2</sub>), 6.97 (t, *J* = 7.2 Hz, 1H, H-4"), 7.16-7.21 (m, 4H, H-2",3",5",6"), 7.45 (d, *J* = 7.4 Hz, 3H, H-4',5',6'), 7.96 (m, 1H, H-3'), 8.87 (s, 1H, NH) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 42.8 (CH<sub>2</sub>), 60.7 (NC-C=C), 114.7, 115.6 (2 C≡N), 123.7 (C-4"), 124.4 (C-2",6"), 126.1 (C-6'), 127.3 (C-4'), 128.0 (C-3",5"), 130.9 (C-5'), 131.6 (C-3'), 137.7 (C-1"), 141.6 (C-1'), 146.9 (C-2'), 162.4 (NC-C=C) ppm; IR (KBr) ν: 3194 (N-H), 2196 (C≡N), 1625 (C=C), 1397 (CH<sub>2</sub>), 1054 (C-S) cm<sup>-1</sup>; MS *m/z* 336 (M<sup>+</sup>, 4), 271 (100); Anal. Calcd. for C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S: C, 60.70; H, 3.60; N, 16.66; S, 9.53. Found: C, 60.75; H, 3.59; N, 16.63; S, 9.50%.

**2-(((Perfluorophenyl)methyl)thio)(phenylamino)methylene)malononitrile (4d).** Yellow crystal; m.p.: 99-101 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 4.19 (s, 2H, CH<sub>2</sub>), 6.69-6.90 (m, 3H, H-3",4",5"), 7.16 (m, 2H, H-2",3"), 10.87 (br, 1H, NH) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 22.7 (CH<sub>2</sub>), 43.6 (NC-C=C), 112.9, 113.2 (2 C≡N), 120.4 (C-1'), 122.0 (C-2",6"), 122.9 (C-4"), 128.7 (C-3",5"), 135.3 (C-1"), 139.2 (C-2',6'), 143.0 (C-4'), 148.2 (C-3',5'), 158.9 (NC-C=C) ppm; IR (KBr) ν: 3197 (N-H), 2192 (C≡N), 1539 (C=C), 1446 (CH<sub>2</sub>), 1128 (C-S) cm<sup>-1</sup>; MS *m/z* 381 (M<sup>+</sup>,

7), 168 (100); Anal. Calcd. for  $C_{17}H_8F_5N_3S$ : C, 53.55; H, 2.11; N, 11.02; S, 8.41. Found: C, 53.60; H, 2.10; N, 10.98; S, 8.43%.

**2-(((2,4-Dinitrobenzyl)thio)(phenylamino)methylene) malononitrile (4e).** Black crystal; m.p.: 125-127 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 5.86 (s, 2H, CH<sub>2</sub>), 7.02 (t,  $J = 6.9$  Hz, 1H, H-4"), 7.24-7.33 (m, 4H, H-2",3",5",6"), 7.69 (d,  $J = 8.8$  Hz, 1H, H-6'), 8.31 (d,  $J = 8.8$  Hz, 1H, H-5'), 8.66 (s, 1H, H-3'), 10.17 (br, 1H, NH) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 48.6 (CH<sub>2</sub>), 88.5 (NC-C=C), 114.5, 114.9 (2C≡N), 120.4 (C-2",6"), 121.6 (C-3'), 124.5 (C-4"), 129.5 (C-3",5"), 133.0 (C-6'), 133.4 (C-5'), 134.7 (C-1"), 143.9 (C-1'), 146.4 (C-4'), 148.4 (C-2'), 170.6 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3187 (N-H), 2199 (C≡N), 1627 (C=C), 1343 (CH<sub>2</sub>), 1124 (C-S)  $cm^{-1}$ ; MS  $m/z$  381 ( $M^+$ , 11), 291 (100); Anal. Calcd. for  $C_{17}H_{11}N_5O_4S$ : C, 53.54; H, 2.91; N, 18.36; S, 8.41. Found: C, 53.60; H, 2.90; N, 18.32; S, 8.38%.

**2-(((2,4-Dichlorobenzyl)thio)(phenylamino)methylene) malononitrile (4f).** Cream crystal; m.p.: 205-206 °C (decomp.);  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 4.43 (s, 2H, CH<sub>2</sub>), 7.11 (d,  $J = 7.0$  Hz, 2H, H-2",6"), 7.22 (t,  $J = 7.0$  Hz, 1H, H-4"), 7.33-7.46 (m, 4H, H-5',6',3",5"), 7.62 (s, 1H, H-3'), 11.19 (br, 1H, NH) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 35.0 (CH<sub>2</sub>), 54.9 (NC-C=C), 115.5, 116.0 (2C≡N), 123.8 (C2",6"), 126.7 (C-4"), 128.1 (C-5'), 129.5 (C3",5"), 129.6 (C-3'), 133.0 (C-1'), 133.3 (C-6'), 133.9 (C-4'), 134.7 (C-2'), 139.0 (C-1"), 167.9 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3195 (N-H), 2215 (C≡N), 1552 (C=C), 1406 (CH<sub>2</sub>), 1049 (C-S)  $cm^{-1}$ ; MS  $m/z$  360 ( $M^+$ , 13), 160 (100); Anal. Calcd. for  $C_{17}H_{11}Cl_2N_3S$ : C, 56.68; H, 3.08; N, 11.66; S, 8.90. Found: C, 56.62; H, 3.09; N, 11.64; S, 8.92%.

**2-(((4-Nitrophenyl)amino)((perfluorophenyl)methyl)thio)methylene)malononitrile (4g).** Bright yellow crystal; m.p.: 98-100 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 4.21 (s, 2H, CH<sub>2</sub>), 6.78 (d,  $J = 8.3$  Hz, 2H, H-2",6"), 8.01 (d,  $J = 8.3$  Hz, 2H, H-3",5"), 11.23 (s, 1H, NH) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 21.7 (CH<sub>2</sub>), 48.7 (NC-C=C), 113.1 (C-1'), 113.8, 117.0 (2C≡N), 121.7 (C-2",6"), 124.8 (C-3",5"), 138.1 (C-4"), 139.3 (C-2',6'), 140.8 (C-1"), 143.0 (C-4'), 146.9 (C-3',5'), 160.8 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3416 (N-H), 2177 (C≡N), 1572 (C=C), 1400 (CH<sub>2</sub>), 1125 (C-S)  $cm^{-1}$ ; MS  $m/z$  426 ( $M^+$ , 6), 181 (100); Anal. Calcd. for  $C_{17}H_7F_5N_4O_2S$ : C, 47.90; H, 1.66; N, 13.14; S, 7.52. Found:

C, 47.85; H, 1.65; N, 13.17; S, 7.54%.

**2-(((Perfluorophenyl)methyl)thio)(*p*-tolylamino)methylene)malononitrile (4h).** Orange crystal; m.p.: 97-98 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 2.26 (s, 3H, CH<sub>3</sub>), 4.42 (s, 2H, CH<sub>2</sub>), 7.01 (d,  $J = 7.8$  Hz, 2H, H-2",6"), 7.16 (d,  $J = 7.8$  Hz, 2H, H-3",5"), 10.94 (s, 1H, NH) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 20.9 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 56.3 (NC-C=C), 111.4 (C-1'), 113.6, 116.4 (2C≡N), 123.7 (C-2",6"), 129.9 (C-3",5"), 135.9 (C-1"), 136.5 (C-4"), 139.4 (C-2',6"), 143.0 (C-4'), 146.9 (C-3',5'), 186.1 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3173 (N-H), 2210 (C≡N), 1635 (C=C), 1442 (CH<sub>2</sub>), 1066 (C-S)  $cm^{-1}$ ; MS  $m/z$  395 ( $M^+$ , 12), 213 (100); Anal. Calcd. for  $C_{18}H_{10}F_5N_3S$ : C, 54.69; H, 2.55; N, 10.63; S, 8.11. Found: C, 54.73; H, 2.53; N, 10.67; S, 8.07%.

**2-(((2,4-Dinitrobenzyl)thio)(ethylamino)methylene) malononitrile (4i).** Black crystal; m.p.: 120-122 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.17 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>), 3.17 (q,  $J = 7.1$  Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.89 (s, 2H, SCH<sub>2</sub>), 7.70 (d,  $J = 8.1$  Hz, 1H, H-6'), 8.28 (d,  $J = 8.1$  Hz, 1H, H-5'), 8.43 (s, 1H, NH), 8.61 (s, 1H, H-3') ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 14.3 (CH<sub>3</sub>), 37.6 (CH<sub>2</sub>CH<sub>3</sub>), 42.0 (SCH<sub>2</sub>), 86.5 (NC-C=C), 114.6, 115.3 (2C≡N), 121.9 (C-3'), 126.8 (C-6'), 132.3 (C-5'), 142.7 (C-1'), 145.7 (C-4'), 148.1 (C-2'), 186.1 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3180 (N-H), 2216 (C≡N), 1527 (C=C), 1473 (CH<sub>2</sub>), 1058 (C-S)  $cm^{-1}$ ; MS  $m/z$  333 ( $M^+$ , 7), 239 (100); Anal. Calcd. for  $C_{13}H_{11}N_5O_4S$ : C, 46.84; H, 3.33; N, 21.01; S, 9.62. Found: C, 46.88; H, 3.32; N, 20.99; S, 9.65%.

**2-((Ethylamino)((perfluorophenyl)methyl)thio)methylene)malononitrile (4j).** Orange crystal; m.p.: 104-106 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.24 (t,  $J = 7.3$  Hz, 3H, CH<sub>3</sub>), 3.40 (q,  $J = 7.3$  Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 4.55 (s, 2H, SCH<sub>2</sub>), 7.95 (s, 1H, NH) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 14.4 (CH<sub>3</sub>), 22.8 (SCH<sub>2</sub>), 38.5 (CH<sub>2</sub>CH<sub>3</sub>), 59.4 (NC-C=C), 112.4 (C-1'), 115.7, 116.1 (2C≡N), 139.3 (C-2',6'), 142.8 (C-4'), 146.3 (C-3',5'), 165.8 (NC-C=C) ppm; IR (KBr)  $\nu$ : 3195 (N-H), 2200 (C≡N), 1618 (C=C), 1475 (CH<sub>2</sub>), 1045 (C-S)  $cm^{-1}$ ; MS  $m/z$  333 ( $M^+$ , 3), 123 (100); Anal. Calcd. for  $C_{13}H_8F_5N_3S$ : C, 46.85; H, 2.42; N, 12.61; S, 9.62. Found: C, 46.81; H, 2.41; N, 12.66; S, 9.66%.

### ***In vitro* Antimicrobial and Antifungal Activity**

Gram-negative bacterial strains including *Pseudomonas*



respectively prepared in 10% DMSO and double-distilled water at initial concentrations of 10240 and 17.6  $\mu\text{g ml}^{-1}$ . All antibiogram tests were performed at least three times independently, and the results were reported as mean values.

## RESULTS AND DISCUSSION

### Chemistry

Novel *N*-amino alkylthiolates 4a-j were efficiently synthesized *via* multicomponent reactions of malononitrile (1), alkyl or aryl isothiocyanates 2 and benzyl halides 3 under two different conditions (Scheme 1). The higher product yields were obtained in the presence of triethylamine under solvent-free condition (Table 1). Reaction times were reduced in the absence of solvent due to packing of the reacting molecules.

Chemical structure of aminothioliates 4a-j were characterized through spectral data. *S*-Methylene groups appeared in a wide range of chemical shifts in NMR spectra due to their adjacent aryl substituents. These effects were also evident in chemical shifts of two carbons of olefinic bonds. In  $^{13}\text{C}$  NMR, two signals were observed with the magnetically inequivalent carbons of the nitrile groups.

### Evaluation of Antimicrobial and Antifungal Properties

Inhibitory properties of the synthesized aminothioliates were assessed against a variety of Gram-positive and -negative bacterial pathogens as well as some fungi (Tables 2-4). Ampicillin and fluconazole were used as positive controls in antimicrobial and antifungal susceptibility tests. In General, wider and better effects were observed with derivatives on Gram-positive strains, which is due to the impermeability of the cell wall of Gram-negative bacteria. Results showed that in compounds 4a-f containing *N*-phenyl substituents, substitution of nitro groups in 2 and 4 positions on Ar rings diminished antibacterial potentials. On the other hand, we observed two chloro substituents on the ring system induced significant antibacterial effects. Introduction of electron-withdrawing nitro or electron-donating methyl groups into position 4 on R rings intensified antibacterial activities. Aminothioliolate 4h containing perfluorobenzyl and *p*-tolylamino substituents could inhibit the growth of all tested bacteria except *Streptococcus equinus*. Furthermore,

this compound had no effect on *Candida albicans*. Thioliates were more efficient in blocking *Candida albicans*, among which compound 4i showed the best results.

Totally different behavior was observed in experiments using compounds 4i,j containing *N*-ethyl substituents against fungi. They could not block an identical strain. In structurally similar compounds, 4d, g, h, j, antifungal effects of ethylamino thiolate 4j is only slightly more than thiolate 4d. However, antibacterial properties of thiolate 4e were more significant than those for 4i.

All derivatives were effective on Gram-negative *Acinetobacter baumannii*. Despite the fact that the most limited range of antibacterial activities were observed with *N*-amino alkylthiolate 4a, it showed inhibitory effects against this important nosocomial pathogen. In addition, compound 4a as well as derivatives 4d, f, g were the only effective agents on all three fungal strains. In series 4a-f, much better results were observed with *N*-amino alkylthiolate 4d according to the range of antifungal effects and MIC values. Changing phenyl substituents to 4-nitrophenyl improved antifungal activity, however, not much of improvement was observed when 4-tolyl group was introduced to the main cores. Broader antifungal effects were observed with alkylthiolate 4e compared to structurally similar derivatives 4a-f.

## CONCLUSIONS

In conclusion, two efficient multicomponent procedures were applied to prepare novel *N*-amino alkylthiolates 4a-j. Products were synthesized within higher yield and shorter reaction time under solvent-free condition. Inhibitory activity of newly made derivatives were studied on various bacterial and fungal pathogens. The results showed that electron-donating aryl substituents in isothiocyanates and electron-withdrawing aryl substituents in benzyl halides improved range of antibacterial activities and inhibitory rates. Antifungal effects increased in the presence of electron-withdrawing groups in both isothiocyanate and benzyl halide.

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**Table 2.** Inhibitory Activities of Aminothiولات 4a-j Against Gram-negative Pathogenic Bacteria

Bacteria		Products										Antibiotic
		4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	Ampicillin
<i>Acinetobacter baumannii</i>	MIC <sup>a</sup>	64	8	256	16	1024	16	16	256	1024	1024	64
	MBC <sup>b</sup>	128	16	512	64	2048	64	64	512	2048	2048	128
<i>Pseudomonas aeruginosa</i>	MIC	-	-	-	-	-	-	-	128	128	16	1024
	MBC	-	-	-	-	-	-	-	256	256	64	2048
<i>Klebsiella pneumonia</i>	MIC	-	-	-	-	-	-	-	16	512	-	32
	MBC	-	-	-	-	-	-	-	64	1024	-	64
<i>Escherichia coli</i>	MIC	-	-	8	64	8	256	16	64	-	256	32
	MBC	-	-	16	128	16	512	64	128	-	512	64
<i>Shigella flexneri</i>	MIC	-	512	16	128	8	64	16	16	128	64	8
	MBC	-	1024	64	256	16	128	64	64	256	128	32
<i>Shigella dysenteriae</i>	MIC	-	-	16	64	8	-	-	128	-	-	256
	MBC	-	-	64	128	16	-	-	256	-	-	256
<i>Proteus mirabilis</i>	MIC	-	-	-	-	16	128	-	64	512	16	8
	MBC	-	-	-	-	64	256	-	128	1024	64	32
<i>Proteus vulgaris</i>	MIC	-	-	16	64	8	-	-	128	-	-	8
	MBC	-	-	64	128	16	-	-	256	-	-	32
<i>Salmonella enterica</i>	MIC	-	-	1024	512	512	1024	128	512	-	1024	8
	MBC	-	-	2048	1024	1024	2048	256	1024	-	2048	16
<i>Salmonella typhi</i>	MIC	-	-	8	-	8	-	-	128	1024	-	2
	MBC	-	-	16	-	16	-	-	256	2048	-	8
<i>Enterococcus faecalis</i>	MIC	-	-	1024	-	512	256	512	128	512	-	8
	MBC	-	-	2048	-	1024	512	1024	256	1024	-	16

No noticeable antibacterial effect at the initial concentrations. <sup>a</sup>Values reported as  $\mu\text{g ml}^{-1}$ . <sup>b</sup>Values reported as  $\mu\text{g ml}^{-1}$ .

**Table 3.** Inhibitory Activities of Aminothiolates 4a-j Against Gram-positive Pathogenic Bacteria

Bacteria		Products										Antibiotic
		4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	Ampicillin
<i>Streptococcus agalactiae</i>	MIC <sup>a</sup>	8	8	-	64	64	256	16	256	256	1024	8
	MBC <sup>b</sup>	16	16	-	128	128	512	64	512	512	2048	16
<i>Streptococcus pyogenes</i>	MIC	1024	-	-	-	-	128	16	16	256	256	4
	MBC	2048	-	-	-	-	256	64	64	512	512	8
<i>Staphylococcus epidermidis</i>	MIC	512	128	8	128	16	64	16	8	-	512	0.25
	MBC	1024	256	16	256	64	128	64	16	-	1024	2
<i>Streptococcus pneumonia</i>	MIC	64	512	512	-	256	64	256	64	128	-	8
	MBC	128	1024	1024	-	512	128	512	128	256	-	16
<i>Rhodococcus equi</i>	MIC	128	512	8	64	64	256	128	128	1024	-	8
	MBC	256	1024	16	128	128	512	256	256	2048	-	32
<i>Staphylococcus aureus</i>	MIC	-	16	1024	-	-	16	-	512	-	1024	8
	MBC	-	64	2048	-	-	64	-	1024	-	2048	32
<i>Bacillus thuringiensis</i>	MIC	-	-	8	-	64	64	64	8	16	64	8
	MBC	-	-	16	-	128	128	128	16	64	128	32
<i>Listeria monocytogenes</i>	MIC	-	-	8	-	16	-	256	128	-	-	8
	MBC	-	-	16	-	64	-	512	256	-	-	16
<i>Bacillus cereus</i>	MIC	256	128	1024	8	512	1024	1024	8	-	512	32
	MBC	512	256	2048	16	1024	2048	2048	16	-	1024	64
<i>Streptococcus equinus</i>	MIC	-	-	16	64	-	-	-	-	-	-	8
	MBC	-	-	64	128	-	-	-	-	-	-	32
<i>Bacillus spizizenii</i>	MIC	-	64	8	16	-	-	256	256	-	512	8
	MBC	-	128	16	64	-	-	512	512	-	1024	16

No noticeable antibacterial effect at the initial concentrations. <sup>a</sup>Values reported as  $\mu\text{g ml}^{-1}$ . <sup>b</sup>Values reported as  $\mu\text{g ml}^{-1}$ .

**Table 4.** Inhibitory Activities of Aminothioliates 4a-j Against Pathogenic Fungi

Fungi		Products										Antifungal
		4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	Fluconazole
<i>Aspergillus fumigatus</i>	MIC <sup>a</sup>	16	128	-	256	-	128	64	512	256	-	32
	MFC <sup>b</sup>	64	256	-	512	-	256	128	1024	512	-	64
<i>Candida albicans</i>	MIC	128	128	64	64	16	256	16	-	8	-	256
	MFC	256	256	128	128	64	512	64	-	16	-	512
<i>Fusarium oxysporum</i>	MIC	256	-	16	16	16	512	64	128	-	64	128
	MFC	512	-	64	64	64	1024	128	256	-	128	256

No noticeable antibacterial effect at the initial concentrations. <sup>a</sup>Values reported as  $\mu\text{g ml}^{-1}$ . <sup>b</sup>Values reported as  $\mu\text{g ml}^{-1}$ .

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