# Catecholthioether Derivatives: Preliminary Study of *in-Vitro* Antimicrobial and Antioxidant Activities

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**In this research, synthesis, antimicrobial and antioxidant activities of a series of catecholthioethers having benzoxazole and tetrazole moieties are described. Antimicrobial activity was evaluated by minimum inhibitory concentration (MIC) assay. The synthesized compounds were tested *in vitro* against three Gram-positive bacteria including *Staphylococcus aureus* (clinical isolated), *Staphylococcus aureus* ATCC 25922, *Enterococcus faecium* (clinical isolated), and two Gram-negative bacteria including *Klebsiella pneumoniae* (clinical isolated) and *Pseudomonas aeruginosa* 27853 and the yeast *Candida albicans* in comparison with control drugs. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 4—256 μg/ml. This shows compounds having tetrazole moiety were the most active against Gram-negative strains, whereas compounds having benzoxazole moiety were more active against Gram-positive ones. Also both of them showed significant antifungal activity against *Candida albicans* and had lower activity than the compared control drugs (Sulfamethoxazole and Fluconazole). The antioxidant activity was assessed using two methods, including, 1,1-biphenyl-2-picrylhydrazyl (DPPH) radical scavenging, and reducing power assays. Some of the catecholthioether derivatives showed antioxidant activity more than Trolox and butylated hydroxyanisole (BHA) as reference antioxidants.**

**Key words** catecholthioether; benzoxazole; tetrazole; antioxidant activity; antimicrobial activity

Growing evidence suggests that RNOS (reactive nitrogen and oxygen species) involved in the damage of biomolecules, contributes to etiology of several human diseases.[1)] Several studies reported the antioxidant activity of plant extracts and their relationship with the phenolic compound content.[2—6)] *o*- and *p*-Dihydroxybenzenes are ubiquitous in nature. Their functionalized derivatives are extensively used in chemical and pharmaceutical industries as well as synthetic intermediates in the manufacturing of food antioxidants.[7—9)]

The Catechol and its mono-substituted derivatives (with OH, $CH_3$, $OCH_3$, CHO, and COOH groups) are active in part against Pseudomonas, Bacillus, but not penicillium species.[10)] Recent observation suggests that benzoxazoles possess potential activity with lower toxicities in the chemotherapeutic approach in man,[11,12)] inhibiting activity on eukaryotic topoisomerase II enzyme in cell-free system,[13—16)] anti-tumor,[17)] anticosulavant,[18)] antifungal,[19)] antiallergic,[20)] antituberculosis,[21)] antiproliferative,[22)] and antiviral activities.[23—25)]

Tetrazolic thioethers have also found widespread use in the modern approach to the synthesis of biologically active compounds and various drugs. This interest stems from the ability of tetrazoles to mimic the carboxylic acid group, which has motivated the incorporation of tetrazoles into biological active molecules.[26—31)] For example, as it is shown in Fig. 1, the compound **I** derivatives has well-known antiviral and anti-inflammatory properties,[32,33)] 1-aryl-thiotetrazolyl acetanilides (**II**, **III**) have demonstrated activities as human immunodeficiency virus-1 (HIV-1) non-nucleoside reverse transcriptase inhibitors,[34—36)] and 1-phenyl-5-arylthiotetrazole (**IV**) is used as activating reagent in RNA synthesis.[37)]

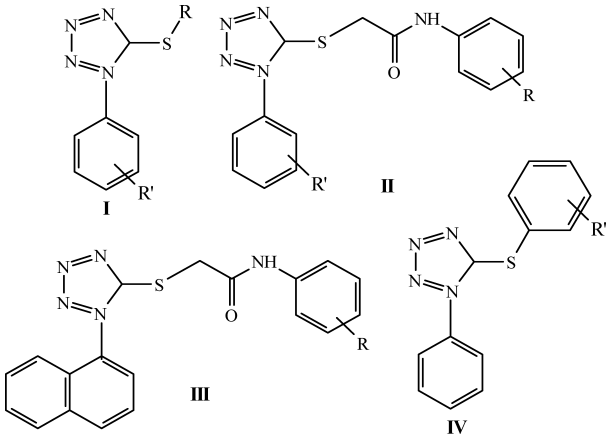


Fig. 1. Structures of Biologically Active Tetrazolic Thioethers

Due to a broad spectrum of activities reported in the literature so far, we have prepared a number of catecholthioethers having benzoxazole[38)] and tetrazole[39)] moieties for evaluating their antimicrobial and antioxidant activities (Chart 1).

## Results and Discussion

**Antimicrobial Activity** Catecholthioether derivatives **1A**—**5A** and **1B**—**3B** have been synthesized through electrooxidative-Michael type reactions of catechols with 1-phenyl-5-mercaptotetrazole or 2-mercaptobenzoxazole and characterized by spectral data as shown in Chart 1. The antimicrobial activity of the synthesized compounds **1A**—**5A** and **1B**—**3B** were tested *in vitro* against three Gram-positive bacteria (clinical isolated of *Staphylococcus aureus*, *Staphy-*

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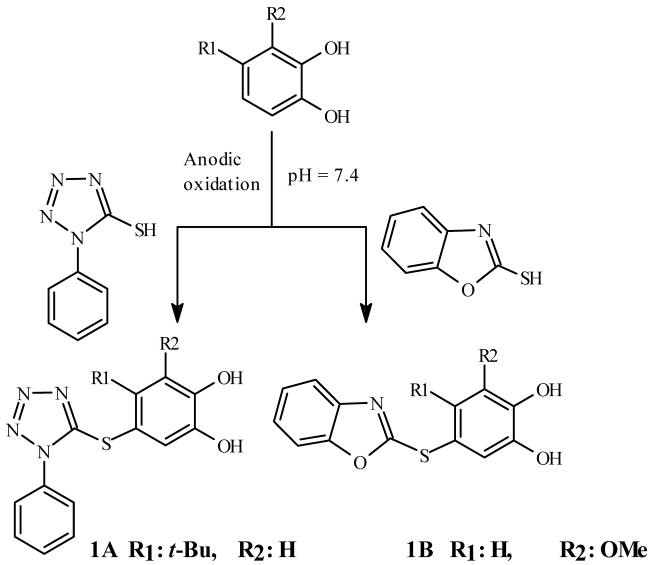
*lococcus aureus* ATCC 25922, clinical isolated of *Enterococcus faecium*), two Gram-negative bacteria (clinical isolated of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* 27853), and the yeast *Candida albicans* by using twofold serial dilution technique,[40,41] and were compared with control drugs (Sulfamethoxazole and Fluconazole). All the biological results of the compounds are given in Table 1. The synthesized compounds showing minimum inhibitory concentration (MIC) values between 8—256 $\mu$g/ml are able to inhibit *in vitro* growth of the screened microorganisms and Table 1 showed lower antibacterial activity against the screened microorganisms than the reference drugs. It could be noticed that most of the compounds were more active as antifungal than as antibacterial, which could guide us to design further new antifungal compounds. Also it may be concluded that the influence of the substitution of $R_1$ and $R_2$ on the catecholic moiety at positions C-5 and C-6 is important for having antibacterial and antifungal activities.

The results reported in Table 1 showed that both benzoxazole and tetrazole rings had the same effect to inhibit *in vitro* growth of screened microorganisms. However, among the synthesized compounds, **4A** was more potent against all the screened microorganisms showing MIC values between 16—128 $\mu$g/ml. Moreover, the compounds **2B** and **3B** (MIC value for both 64 $\mu$g/ml) are found to be the most active derivatives against Gram-negative bacteria (*P. aeruginosa*) which is often resistant to antibiotic therapy. Finally, regarding to high hydrophilicity of the synthesized tetrazolic and benzoxazolic compounds, they showed more effect on Gram-negative bacteria than Gram-positive ones. However, the comparison between **1A** and **4A** shows that the smaller the size of the substitution, the higher the potency of the compound.

The synthesized compounds were also tested against *Candida albicans* for their antifungal activity and possessed MIC values between 4—16 $\mu$g/ml. However, the compound **2A** which had methoxy substitution at position C-5 could inhibit *in vitro* growth of *Candida albicans* having the same inhibitory activity as fluconazole (MIC value 4 $\mu$g/ml). No difference was observed between all the other compounds having MIC values 16 $\mu$g/ml. Furthermore we found that electron-donating substitutions (methoxy and methyl) on the catecholic ring at positions C-5 and C-6 increased antifungal activity.

**Antioxidant Activity** The antioxidant activity was assessed using two methods, including, 1,1-biphenyl-2-picrylhydrazyl (DPPH) radical scavenging,[42] and reducing power[43] assays according to the methods described in the literature (Table 2). The results of antioxidant activity in both methods are approximately similar to each other. All the synthesized compounds except **5A** exhibited very good antioxidant properties. They were also more potent than BHA and Trolox as reference compounds. It should be noted that when electron-donating groups are added to the catecholic ring at positions C-5 and C-6, the antioxidant activity is increased. This is due to the stabilization of the generated radical during oxidation (Fig. 2). The compounds **1A**, **2A**, and **3A** have well antioxidative activity with a major activity for **2A** ($IC_{50}$ 0.17, 1.56 $\mu$M). The results of antioxidant activity indicated that in addition to catecholic moiety, tetrazolic and benzoxazolic rings were also effective and necessary in the assays. However, it is seems that benzoxazole moiety is more potent than tetrazole one due to delocalizing free electron during oxidation. For example, compounds **1B**, **2B**, and **3B** showed antioxidative activity having $IC_{50}$ values 0.15, 0.28 and 1.5 $\mu$M respectively *via* DPPH method, whereas tetrazolic similarities (**1A**, **2A**, **4A**) have $IC_{50}$ values 1.55 and 0.17, and 4.5 $\mu$M respectively *via* the same assay. Overall, the result of DPPH assay was relatively consistent with that of reducing power




**1A** $R_1$: *t*-Bu, $R_2$: H **1B** $R_1$: H, $R_2$: OMe
**2A** $R_1$: H, $R_2$: OMe **2B** $R_1$: *t*-Bu, $R_2$: H
**3A** $R_1$: H, $R_2$: Me **3B** $R_1$: Me, $R_2$: H
**4A** $R_1$: Me, $R_2$: H
**5A** $R_1$: H, $R_2$: H

Chart 1. Synthetic Routes of Catecholthioethers through Electro-Organic Pathway

Table 1. The MICs (in $\mu$g/ml) Values of Catecholthioethers against Bacteria and Fungus

| Compound | *E. faecium* (Clinical isolated) | *K. pneumoniae* (Clinical isolated) | *S. aureus* (Clinical isolated) | *S. aureus* ATCC 25922 | *P. aeruginosa* ATCC 27853 | *Candida albicans* (Clinical isolated) |
|---|---|---|---|---|---|---|
| **1A** | 128 | 64 | 256 | 256 | 128 | 16 |
| **2A** | 64 | 128 | 256 | 128 | 128 | 4 |
| **3A** | 128 | 16 | 256 | 128 | 128 | 16 |
| **4A** | 64 | 16 | 64 | 64 | 128 | 16 |
| **5A** | 256 | 16 | 256 | 128 | 128 | 16 |
| **1B** | 256 | 256 | 64 | 256 | 256 | 16 |
| **2B** | 256 | 128 | 16 | 256 | 64 | 16 |
| **3B** | 256 | 128 | 32 | 64 | 64 | 16 |
| Fluconazole | — | — | — | — | — | 4 |
| Sulfamethoxazole | 4 | 8 | 4 | 2 | 8 | — |

Table 2. The $IC_{50}$ (in $\mu$M) Values of Catecholthioethers According to DPPH Radical Scavenging, and Reducing Power Assays

| Entry | Compound | $IC_{50}$ | |
|---|---|---|---|
| | | DPPH | Reducing power |
| 1 | **1A** | 1.55 | 3.22 |
| 2 | **2A** | 0.17 | 1.56 |
| 3 | **3A** | 0.31 | 2.67 |
| 4 | **4A** | 4.5 | 3.8 |
| 5 | **5A** | 10 | 17.23 |
| 6 | **1B** | 0.15 | 1.55 |
| 7 | **2B** | 0.28 | 2.54 |
| 8 | **3B** | 1.5 | 3.28 |
| 9 | Trolox | 5 | 4.1 |
| 10 | BHA | 4.8 | 3.9 |

assay. The potencies for the antioxidative activity of the test compounds compared to the reference drugs are in the following order: **1B**>**2A**>**2B**>**3A**>**1A**≈**3B**>**4A**>BHA>Trolox>**5A**.

In summary, we have reported biological evaluation of catecholthioether derivatives, which represent antioxidant and antimicrobial activities. All of the synthesized catecholthioethers showed some antimicrobial activity. A strong antioxidant activity was obtained against reducing power and DPPH radical scavenging, showing more potent than the compared control drugs Trolox and BHA.

## Experimental

**Electro-Organic Synthesis of Catecholthioethers** In a typical procedure, a solution (*ca.* 100 ml) of water/acetonitrile (90/10), containing 0.2 M acetate sodium, 1.0 mmol of catechols and 1.0 mmol of 1-phenyl-5-mercaptotetrazole, was electrolyzed in an undivided cell equipped with a carbon anode (an assembly of four rods, 6-mm diameter, and 10-cm length), and a large platinum gauze cathode at 0.20 V *vs.* SCE, at 25 °C. The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration, washed copiously with distilled water and characterized by spectral data and were compared with those reported in the literature.[38,39] The final products (**1A**—**5A**, **1B**—**3B**) were obtained purely and no extra purification was needed.[38,39]

**4-*tert*-Butyl-5-(1-phenyl-1*H*-tetrazol-5-ylthio)benzene-1,2-diol (1A)**[39] mp 181—183 °C; yield 59%; IR (KBr) $cm^{-1}$: 560, 610, 691, 700, 725, 880, 943, 1055, 1090, 1155, 1287, 1340, 1355, 1401, 1490, 1539, 1599, 2902, 3088, 3510; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 1.12 (s, 9H), 6.80 (s, 1H), 6.91 (s, 1H), 7.63—7.80 (m, 5H), 9.08 (broad, 1H), 9.56 (broad, 1H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 31.1, 33.8, 112.1, 114.8, 120.8, 124.8, 129.7, 130.5, 133.3, 142.0, 143.8, 145.4, 153.2; MS (EI, 70 eV) 342 ($M^+$, 100), 298 (9), 283 (10), 255 (7), 197 (22), 180 (35), 164 (24), 135 (14), 118 (46), 91 (15), 77 (14), 65 (9); HR-MS (EI) Calcd for $C_{17}H_{18}O_2N_4S$ 342.1150, Found 342.1152.

**3-Methoxy-5-(1-phenyl-1*H*-tetrazol-5-ylthio)benzene-1,2-diol (2B)**[39] mp 82—83 °C; yield 58%; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 3.69 (s, 3H), 6.61—670 (m, 2H), 7.62—7.69 (m, 5H), 8.75—9.40 (broad); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 56.0, 109.7, 113.8, 115.4, 124.9, 125.1, 129.9, 130.7, 133.2, 136.5, 146.4, 148.6, 149.7, 154.3; MS (EI, 70 eV) 316 ($M^+$, 32), 256 (4), 230 (5), 171 (100), 156 (10), 118 (65), 84 (38), 77 (8), 65 (6); HR-MS (EI) Calcd for $C_{14}H_{12}O_3N_4S$ 316.0630, Found 316.0625.

**3-Methyl-5-(1-phenyl-1*H*-tetrazol-5-ylthio)benzene-1,2-diol (3A)**[39] mp 160—161 °C; yield 76%; IR (KBr) $cm^{-1}$: 653, 695, 710, 810, 847, 910, 1083, 1302, 1428, 1490, 1520, 1610, 2993, 3050, 3450; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 2.16 (s, 3H), 6.70 (d, $J$=8.34 Hz, 1H), 6.94 (d, $J$=8.34 Hz, 1H), 7.66—7.74 (m, 5H), 8.67 (broad, 1H), 9.86 (broad, 1H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 14.0, 113.2, 114.6, 124.9, 127.3, 129.2, 130.0, 130.7, 133.2, 144.4, 147.7, 154.5; MS (EI, 70 eV) 300 ($M^+$, 45), 230 (9), 213 (6), 155 (80), 118 (100), 93 (17), 77 (17), 65 (21); HR-MS (EI) Calcd for $C_{14}H_{12}O_2N_4S$ 300.0681, Found 300.0675.

**4-Methyl-5-(1-phenyl-1*H*-tetrazol-5-ylthio)benzene-1,2-diol (4A)**[39] mp 169—171 °C; yield 65%; IR (KBr) $cm^{-1}$: 690, 715, 723, 821, 874, 1050, 1098, 1130, 1198, 1250, 1450, 1490, 1529, 1601, 2902, 3075, 3480; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 2.16 (s, 3H), 6.76 (s, 1H), 6.95 (s, 1H), 7.66—7.70 (m, 5H), 9.22—9.48 (broad, 2H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 19.5, 113.1, 117.9, 122.6, 124.9, 129.9, 130.7, 133.2, 133.3, 144.0, 148.0, 154.3; MS (EI, 70 eV) 300 ($M^+$, 46), 267 (21), 155 (64), 118 (100), 93 (17), 91 (18), 77 (12), 65 (16); HRMS (EI) Calcd for $C_{14}H_{12}O_2N_4S$ 300.0681, Found 300.0686.

**4-(1-Phenyl-1*H*-tetrazol-5-ylthio)benzene-1,2-diol (5A)**[39] mp 135—136 °C; yield 92%; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 4.51 (broad, 2H), 6.79—7.01 (m, 3H), 7.58—7.69 (m, 5H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 114.3, 116.4, 121.4, 125.1, 126.1, 129.9, 130.7, 133.1, 146.2, 147.8, 154.5; MS (EI, 70 eV) 286 ($M^+$, 23), 141 (48), 118 (100), 91 (10), 77 (10), 65 (6); HR-MS (EI) Calcd for $C_{13}H_{10}O_2N_4S$ 286.0524, Found 286.0512.

**5-(Benzo[*d*]oxazol-2-ylthio)-3-methoxybenzene-1,2-diol (1B)**[38] mp 157—159 °C; IR (KBr) $cm^{-1}$: 679, 743, 810, 1000, 1095, 1109, 1132, 1203, 1217, 1237, 1298, 1332, 1356, 1452, 1511, 1605, 2841, 2940, 2995, 3040, 3510; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 3.75 (s, 3H), 5.46 (broad, 1H), 6.80 (s, 1H), 6.91 (s, 1H), 7.22 (m, 2H), 7.46 (m, 2H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 56.6, 110.7, 110.9, 113.6, 116.6, 119.0, 124.9, 125.1, 137.3, 141.9, 146.9, 149.2, 151.7, 164.1; MS (EI, 70 eV) 289 ($M^+$, 100), 202 (10.2), 171 (22.4), 152 (12.2), 128 (12.3), 85 (19.4), 63 (20.4), 39 (42.8). *Anal.* Calcd for $C_{14}H_{11}NO_4S$: C, 58.13; H, 3.80; N, 4.84; S, 11.07. Found: C, 58.08; H, 3.75; N, 4.74; S, 11.11.

**4-(Benzo[*d*]oxazol-2-ylthio)-5-*tert*-butylbenzene-1,2-diol (2B)**[38] mp 168—171 °C; IR (KBr) $cm^{-1}$: 651, 744, 811, 859, 961, 1099, 1138, 1213, 1240, 1291, 1364, 1416, 1456, 1501, 1597, 2866, 2963, 3013, 3506; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 1.24 (s, 9H), 7.06—7.52 (m, 6H), 5 (broad, 2H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 31.4, 34.0, 110.2, 112.0, 115.8, 118.6, 122.3, 124.4, 124.6, 141.9, 142.6, 144.9, 145.9, 151.5, 163.4; MS (EI, 70 eV) 315 ($M^+$, 77.5), 300 (100), 152 (55.1), 91 (28.6), 63 (12.2), 39 (20.4). *Anal.* Calcd for $C_{17}H_{17}NO_3S$: C, 64.76; H, 5.39; N, 4.44; S, 10.15. Found: C, 64.66; H, 5.45; N, 4.35; S, 10.22.

**4-(Benzo[*d*]oxazol-2-ylthio)-5-methylbenzene-1,2-diol (3B)**[38] mp 198—200 °C; IR (KBr) $cm^{-1}$: 641, 745, 815, 869, 1003, 1096, 1134, 1236, 1270, 1354, 1380, 1424, 1454, 1496, 1599, 3078, 3427, 3523; $^1$H-NMR $\delta$ ppm (200 MHz, DMSO-$d_6$): 2.23 (s, 3H), 6.85 (s, 1H), 7.2 (m, 3H), 7.5 (m, 2H), 9.3 (broad, 2H); $^{13}$C-NMR $\delta$ ppm (50 MHz, DMSO-$d_6$): 20.1, 110.7, 113.3, 118.5, 118.9, 123.6, 124.7, 125.0, 134.1, 141.9, 144.5, 148.6, 151.7, 164.0; MS (EI, 70 eV) 273 ($M^+$, 100), 240 (72.9), 222 (18.6), 194 (30.5), 166 (78), 108 (23.7), 91 (22.0), 65 (35.6), 39 (54.2). *Anal.* Calcd for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.03; N, 5.12; S, 11.72. Found: C, 61.45; H, 4.10; N, 5.20; S, 11.65.

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