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Synthesis, crystal structure, and antioxidant properties of novel 1,2,4-triazol-5-ones containing 3,4-dimethoxyphenyl and 3,4-dihydroxyphenyl moiety

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A series of new 4-(3,4-dimethoxyphenethyl)-5-akyl/aryl-2H-1,2,4-triazol-3(4H)-ones **(3a-g)** was obtained by the reaction of ethyl 2-(ethoxy)(alkylidene/arylidene)hydrazinecarboxylate **(1)** and 2-(3,4-dimethoxyphenyl)ethanamine **(2)**. Compounds **4a-f** and **5** were synthesized from the reaction of corresponding compounds **3a-f** and **3g** with BBr_3, respectively. With elemental analysis, IR, ^{1}H-NMR, and ^{13}C-NMR spectral data, 14 newly synthesized compounds were characterized. The structure of compound **3a** was inferred through IR, ^{1}H- and ^{13}C-NMR, elemental analysis, and X-ray spectral techniques. In addition, the newly synthesized chemicals were screened for their antioxidant properties. Among the chemicals tested, **4a**, **4c**, **4d**, **4f**, and **5** exhibited the highest degree of antioxidant activity.

Key Words: Synthesis, 1,2,4-triazole-3-one, antioxidant activity, X-ray

Introduction

The synthesis of 1,2,4-triazole derivatives has been attracting widespread attention due to their diverse biological activities, such as antimicrobial, antiinflammatory, anti-TB, and antiproliferative and analgesic antitumor activities.[1−8] There are some antimicrobial drugs containing a triazole moiety. For instance, fluconazole and itraconazole are used in medical therapy.[9−10] In addition, vorozole, letrozole, fadrozole, and anastrozole are

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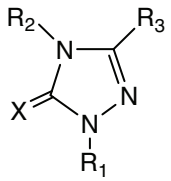
nonsteroidal drugs used for the treatment of estrogen-dependent breast cancer.[11] It is known that 1,2,4-triazole moieties strongly interact with the heme iron and aromatic substituents of the active site of aromatase.[12] 2,4-Dihydro-3*H*-1,2,4-triazol-3-one derivatives **(1)** have been found to be the basic skeleton of several biologically active compounds, such as angiotensin II antagonists, anticonvulsant agents, and the phytotoxic natural products **(3)** isolated from *Actinomadura*, and 3-thione derivatives (**2**) have also been reported to have antidepressant activity (Figure 1).[13]



1:X=O
2:X=S

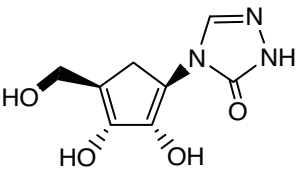


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Figure 1.

Antioxidants are widely studied for their capacity to protect organisms and cells from damage induced by oxidative stress during metabolism. Active components preventing or reducing the impact of oxidative stress on cells is a recent research field. Exogenous chemicals in food systems and endogenous metabolic processes in the human body produce highly reactive free radicals, particularly oxygen-derived free radicals. Because they are capable of oxidizing biomolecules, they cause cell death, thus leading to tissue damage. Free radical oxidative processes also play a significant pathological role in causing human diseases. Many disease manifestations, such as cancer, emphysema, cirrhosis, atherosclerosis, and arthritis, have been correlated with oxidative tissue damage. In addition, excessive generation of reactive oxygen species (ROS) induced by various stimuli leads to a variety of pathophysiological abnormalities such as inflammation, diabetes, genotoxicity, and cancer. Antioxidants are highly important for the potential treatment of these kinds of diseases, for they scavenge and prevent the formation of free radicals, and so in recent years there has been a growing interest in finding new antioxidant compounds.[14–15]

Hydroxytyrosol, or 2-(3,4-dihydroxyphenyl)ethanol, is a simple phenol extracted from olive oil and wine, which is now used in integrators and cosmetics. Studies on the consumption of antioxidants in foods and in vitro studies on cells have shown that hydroxytyrosol might contribute to the prevention of human diseases. Interestingly, at high molecular concentrations, hydroxytyrosol inhibits or delays the rate of growth of a range of bacteria and fungi. Thus, this simple phenol, like other molecules characterized by a catechol ring, shows both antioxidant and prooxidant activities.[16]

In view of these facts, the aim of the present study was to synthesize the compounds containing catechol and triazole rings that have radical scavenging properties and interact with the stable free radical DPPH.

Experimental section

All chemicals were obtained from Fluka Chemie AG (Buchs, Switzerland). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian XL-200 NMR spectrophotometer in DMSO-d_6. IR spectra were recorded on a PerkinElmer

Spectrum One FT-IR spectrometer in KBr pellets. The MS spectra were measured with a Micromass Quattro LC/ULTIMA LC-MS/MS spectrometer with EtOH as a solvent. The experiment was performed in the positive ion mode. Elemental analyses were performed on a Hewlett-Packard 185 CHN analyzer. Melting points were measured on an electrothermal apparatus and are uncorrected. Compound **(1)** was prepared as described by Ikizler and Sancak.[17]

General procedure for the preparation of 4-(3,4-dimethoxyphenethyl)-5-alkyl/aryl-2H-1,2,4-triazol-3(4H)-ones (3a-g):

Ethyl 2-(ethoxy)(alkylidene/arylidene)hydrazinecarboxylate **(1)** (10 mmol), together with 2-(3,4-dimethoxy phenyl)ethanamine **(2)** (1.25 g, 10 mmol), was heated without solvent in a sealed tube for 2 h at 160-180 °C. The mixture was then cooled to room temperature and a solid formed. The crude product was recrystallized using acetone/petroleum ether (1:2) to afford the desired compound.

4-(3,4-dimethoxyphenethyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (3a): Yield: 1.95 g (74.14%); colorless crystals, mp 108 °C. IR (KBr, ν, cm^{-1}): 3314 (NH), 1714 (C=O), 1590 (C=N), 1262 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.76 (s, 3H, CH_3), 2.92 (t, 2H, Ar–CH_2), 3.83-3.86 (m, 6H, OCH_3), 3.78 (t, 2H, N-CH_2), 6.60-6.69 (m, 2H, arom. H), 6.78-6.82 (m, 1H, arom. H), 10.28 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 11.48 (CH_3), 34.49 (Ar-CH_2), 43.29 (CH_2), 55.86 and 55.89 (OCH_3), arom. C [111.28 (CH), 111.88 (CH), 120.90 (CH), 130.18 (C), 147.91(C), 149.01(C)], 145.28 (C=N), 155.79(C=O). Anal. Calc. for $C_{13}H_{17}N_3O_3$ M^+: (264.06) C, 59.30; H, 6.51; N, 15.90. Found: C, 59.36; H, 6.48; N, 15.97%.

4-(3,4-dimethoxyphenethyl)-5-ethyl-2H-1,2,4-triazol-3(4H)-one (3b): Yield: 2.16 g (78.22%), colorless crystals, mp 120 °C. IR (KBr, ν, cm^{-1}): 3321 (NH), 1704 (C=O), 1584 (C=N), 1259 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.02 (t, 3H, CH_3), 2.40 (q, 2H, CH_2), 2.80 (t, 2H, Ar–CH_2), 3.74-3.79 (s, 6H, OCH_3), 3.65 (t, 2H, N-CH_2), 6.66-6.70 (m, 2H, arom. H), 6.85-6.87 (m, 1H, arom. H), 11.38 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 9.40 (CH_3), 18.01 (CH_2), 33.58 (Ar-CH_2), 41.65 (N-CH_2), 55.31 and 55.16 (OCH_3), arom. C [111.59 (CH), 112.29 (CH), 120.60 (CH), 130.29 (C), 148.17 (C), 148.47(C)], 147.33 (C=N), 154.92 (C=O). Anal. Calc. for $C_{14}H_{19}N_3O_3$ M^+: (277.92) C, 60.63; H, 6.91; N, 15.54. Found: C, 60.69; H, 6.96; N, 15.62%.

4-(3,4-dimethoxyphenethyl)-5-propyl-2H-1,2,4-triazol-3(4H)-one (3c): Yield: 2.23 g (76.70%), colorless crystals, mp 124 °C. IR (KBr, ν, cm^{-1}): 3329 (NH), 1698 (C=O), 1593 (C=N), 1260 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 0.88 (t, 3H, CH_3), 1.50-1.62 (m, 2H, CH_3-C$\underline{H}_2$-CH_2), 2.04 (q, 2H, CH_3-CH_2-C$\underline{H}_2$), 2.94 (t, 2H, Ar–CH_2), 3.77-3.84 (s, 6H, OCH_3), 3.84 (t, 2H, N-CH_2), 6.62-6.66 (m, 2H, arom. H), 6.77-6.81 (m, 1H, arom. H), 10.87 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 13.61 (CH_3), 19.00 (CH_3–$\underline{C}H_2$), 27.22 (CH_3–CH_2–$\underline{C}H_2$), 34.47 (Ar-CH_2), 43.03 (N-CH_2), 55.86 and 55.89 (OCH_3), arom. C [111.43 (CH), 112.03 (CH), 120.83 (CH), 130.28 (C), 148.07 (C), 149.06 (C)], 147.94 (C=N), 155.96 (C=O). Anal. Calc. for $C_{15}H_{21}N_3O_3$ M^+: (291.98) C, 61.84; H, 7.27; N, 14.42. Found: C, 61.80; H, 7.34; N, 14.48%.

4-(3,4-dimethoxyphenethyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (3d): Yield: 2.27 g (70.05%), colorless crystals, mp 148 °C. IR (KBr, ν, cm^{-1}): 3434 (NH), 1710 (C=O), 1592 (C=N), 1265 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.68 (t, 2H, Ar–CH_2), 3.59-3.69 (s, 6H, OCH_3), 3.91 (t, 2H, N-CH_2), 6.39-6.44 (m, 2H, arom. H), 6.72-6.76 (m, 1H, arom. H), 7.34-7.58 (m, 5H, arom. H), 11.88 (s, 1H, NH); ^{13}C-NMR

(DMSO-d_6, δ, ppm): 33.16 (Ar-CH_2), 42.38 (N-CH_2), 54.93 and 55.29 (OCH_3), arom. C [111.53 (CH), 111.81 (CH), 120.32 (CH), 127.30 (C), 145.30 (C), 148.40 (C), phenyl H 127.68 (CH), 128.52 (CH), 129.66 (CH), 129.78 (C)], 146.63 (C=N), 154.95 (C=O). Anal. Calc. for $C_{18}H_{19}N_3O_3$ M^{+1}: (326.20) C, 66.45; H, 5.89; N, 12.91. Found: C, 66.40; H, 5.94; N, 12.95%.

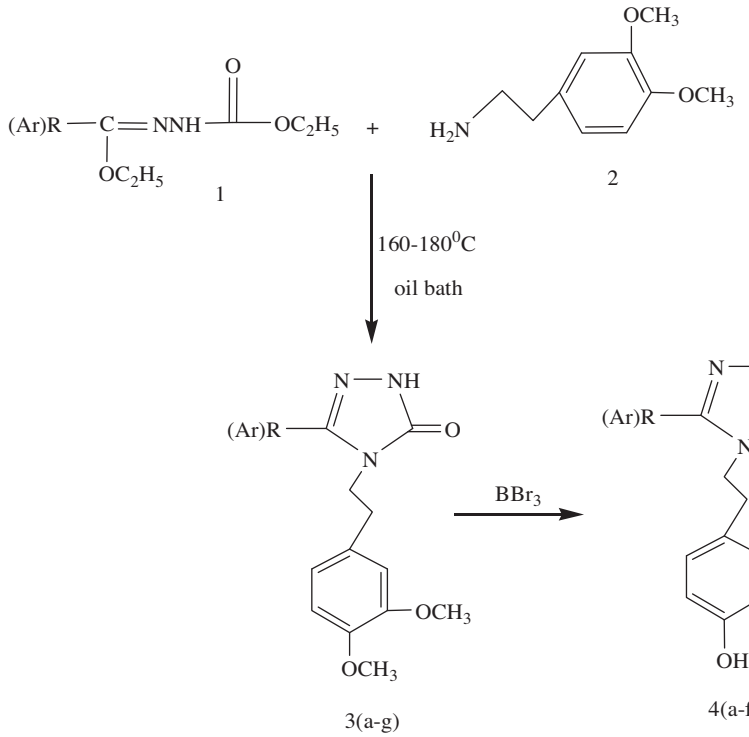
4-(3,4-dimethoxyphenethyl)-5-p-tolyl-2H-1,2,4-triazol-3(4H)-one (3e): Yield: 2.65 g (68.91%), colorless crystals, mp 135 °C. IR (KBr, ν, cm^{-1}): 3427 (NH), 1681 (C=O), 1618 (C=N), 1277 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.43 (s, 3H, CH_3), 2.86 (t, 2H, Ar–CH_2), 3.86 and 3.91 (s, 6H, OCH_3), 3.60-3.66 (t, 2H, N-CH_2), 6.71-7.75 (m, 7H, arom. H), 10.17 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 21.41 (CH_3), 36.10 (Ar-CH_2), 41.18 (N-CH_2), 55.74 and 55.87 (OCH_3), arom. C [111.26 (CH), 111.99 (CH), 120.73 (CH), 131.84 (C), 148.17(C), 148.90 (C), phenyl C [127.34 (C), 127.63 (CH), 129.30 (CH), 140.24 (C)], 147.52 (C=N), 155.80 (C=O). Anal. Calc. for $C_{19}H_{21}N_3O_3$ M^+: (339.39) C, 67.24; H, 6.24; N, 12.38. Found: C, 67.29; H, 6.18; N, 12.34%.

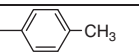
4-(3,4-dimethoxyphenethyl)-5(thiophen-2ylmethyl)-2H-1,2,4-triazol-3(4H)-one (3f): Yield: 2.25 g (65.21%), colorless crystals, mp 138 °C. IR (KBr, ν, cm^{-1}): 3329 (NH), 1715 (C=O), 1593 (C=N), 1262 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.58 (t, 2H, Ar–CH_2), 3.85 (s, 2H, thiophene CH_2), 3.73 and 3.78 (s, 6H, OCH_3), 3.65 (t, 2H, N-CH_2), 6.55-7.46 (m, 6H, arom. H), 11.59 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 26.75 (thiophene CH_2), 34.30 (Ar-CH_2), 42.87 (N-CH_2), 56.03 and 56.12 (OCH_3), arom. C [111.49 (CH), 113.03 (CH), 121.34 (CH), 130.88 (C), 148.18 (C), 149.32 (C), thiophene C [126.34 (C), 127.30 (CH), 127.76 (CH), 138.18 (C)], 146.49 (C=N), 155.60 (C=O). Anal. Calc. for $C_{17}H_{19}N_3O_3S$ M^+: (346.01) C, 59.11; H, 5.54; N, 12.17. Found: C, 59.17; H, 5.59; N, 12.11%.

5-(3,4-dimethoxybenzyl)-4(3,4-dimethoxyphenethyl)-2H-1,2,4-triazol-3(4H)-one (3g): Yield: 2.44 g (61.06%), colorless crystals, mp 130 °C. IR (KBr, ν, cm^{-1}): 3336 (NH), 1710 (C=O), 1592 (C=N), 1265 (C-O-C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.52 (t, 2H, Ar–CH_2), 3.37 (s, 2H, 3,4-dimethoxy-CH_2), 3.71 (bs, 6H, OCH_3), 3.58 (t, 2H, N-CH_2), 6.59-7.92 (m, 6H, arom. H), 11.51 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 30.84 (3,4-dimethoxy-CH_2), 33.46 (Ar-CH_2), 42.00 (N-CH_2), 55.17, 55.22, 55.32 (OCH_3), arom. C [111.69 (CH), 111.71 (CH), 112.21 (CH), 120.42 (CH), 120.53 (CH), 127.35 (C), 130.14 (C), 147.39 (C), 148.49 (C), 148.62 (C)], 146.44 (C=N), 154.94 (C=O). Anal. Calc. for $C_{21}H_{25}N_3O_5$ M^+: (400.14) C, 63.14; H, 6.31; N, 10.52. Found: C, 63.19; H, 6.26; N, 10.59%.

General procedure for the preparation of 4-(3,4-dihydroxyphenethyl)-5-alkyl/aryl-2H-1,2,4-triazol-3(4H)-ones (4a-f):

A solution of 4-(3,4-dimethoxyphenethyl)-5-akyl/aryl-2H-1,2,4-triazol-3(4H)-ones **(3a-f)** (10 mmol) in chloroform (100 mL) was added to a solution of boron tribromide (10 mmol) in chloroform (200 mL) at 0 °C. The reaction mixture was then stirred under a nitrogen atmosphere at ambient temperature for 1 h, and was poured into ice containing sufficient 50% sodium hydroxide to attain a pH of 10. The addition of concentrated sulfuric acid provided a precipitate that was extracted into ether. The combined organic extract was washed with water and brine, and then dried and concentrated in a vacuum to obtain compounds **4a-f**. The crude product was recrystallized using ethyl acetate and petroleum ether (1:4) to afford the desired compound (Scheme 1).



3,4	R/Ar
a	—CH_3
b	—CH_2CH_3
c	—$CH_2CH_2CH_3$
d	
e	
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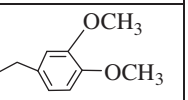
g	

Scheme 1. Synthesis of compounds **3** and **4**.

4-(3,4-dihydroxyphenethyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (4a): Yield: 1.32 g (56.32%), colorless crystals, mp 223 °C. IR (KBr, ν, cm^{-1}): 3217 (OH), 1694 (C=O), 1587 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.78 (s, 3H, CH_3), 2.64 (t, 2H, Ar-CH_2), 3.60 (t, 2H, N-CH_2), 6.33-6.52 (m, 2H, arom. H), 6.60-6.64 (m, 1H, arom. H), 8.75 (bs, 2H, OH), 11.31 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6 δ, ppm): 11.05 (CH_3), 33.64 (Ar-CH_2), 42.19 (N-CH_2), arom. C [115.51 (CH), 116.15 (CH), 119.45 (CH), 128.85 (C), 144.49 (C), 145.11 (C)], 143.78 (C=N), 154.80 (C=O). Anal. Calc. for $C_{11}H_{13}N_3O_3$ M^+: (236.00) C, 56.16; H, 5.57; N, 17.86. Found: C, 56.21; H, 5.51; N, 17.81%.

4-(3,4-dihydroxyphenethyl)-5-ethyl-2H-1,2,4-triazol-3(4H)-one (4b): Yield: 1.29 g (55.76%), colorless crystals, mp 134 °C. IR (KBr, ν, cm^{-1}): 3222 (OH), 1698 (C=O), 1593 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.36 (s, 3H, CH_3), 2.13 (s, 2H, CH_2), 2.66 (t, 2H, Ar-CH_2), 3.68 (t, 2H, N-CH_2), 6.35-6.58 (m, 2H, arom. H), 6.65-6.69 (m, 1H, arom. H), 8.78 (bs, 2H, OH), 11.36 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 16.25 (CH_3), 26.33 (CH_2), 33.71 (Ar-CH_2), 42.22 (N-CH_2), arom. C [115.53 (CH), 116.18 (CH), 119.49 (CH), 128.88 (C), 144.55 (C), 145.16 (C)], 143.80 (C=N), 154.86 (C=O). Anal. Calc. for $C_{12}H_{15}N_3O_3$ M^+: (249.27) C, 57.82; H, 6.07; N, 16.86. Found: C, 57.88; H, 6.12; N, 16.81%.

4-(3,4-dihydroxyphenethyl)-5-propyl-2H-1,2,4-triazol-3(4H)-one (4c): Yield: 1.29 g (46.0%), colorless crystals, mp 175 °C. IR (KBr, ν, cm^{-1}): 3227 (OH), 1710 (C=O), 1605 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 0.84 (t, 3H, CH_3), 1.41-1.52 (m, 2H, CH_3-C$\underline{H}_2$), 2.08 (t, 2H, CH_2-C$\underline{H}_2$), 2.66 (t, 2H, Ar-CH_2), 3.63 (t, 2H, N-CH_2), 6.35-6.58 (m, 2H, arom. H), 6.53-6.64 (m, 1H, arom. H), 8.67 (bs, 2H, OH), 11.33 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 13.39 (CH_3), 18.27 ($CH_3\underline{C}H_2$), 26.33 ($CH_2\underline{C}H_2$), 33.56 (Ar-CH_2), 42.05 (N-CH_2), arom. C [115.42 (CH), 116.04 (CH), 119.35 (CH), 128.77 (C), 143.76 (C), 147.18(C)], 143.76

(C=N), 154.89 (C=O). Anal. Calc. for $C_{13}H_{17}N_3O_3$ M^+: (264.00) C, 59.30; H, 6.51; N, 15.96. Found: C, 59.34; H, 6.57; N, 15.91%.

4-(3,4-dihydroxyphenethyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (4d): Yield: 1.36 g (46%), colorless crystals, mp 175 °C. IR (KBr, ν, cm^{-1}): 3256 (OH), 1692 (C=O), 1595 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.53 (t, 2H, Ar-CH_2), 3.76 (t, 2H, N-CH_2), 6.18-6.36 (m, 2H, arom. H), 6.37-6.57 (m, 1H, arom. H), 7.46-7.52 (m, 5H, arom. H), 8.75 (bs, 2H, OH), 11.89 (s, 1H, NH); ^{13}C-NMR (DMSO-$d_6\delta$, ppm): 33.25 (Ar-CH_2), 42.69 (N-CH_2), arom. C [115.40 (CH), 115.78 (CH), 119.04 (CH), 127.76 (CH), 128.69 (CH), 128.14 (C), 129.14 (CH), 145.30 (C), 146.51 (C)], 143.75 (C=N), 154.95 (C=O). Anal. Calc. for $C_{16}H_{15}N_3O_3$ M^+: (298.00) C, 64.64; H, 5.09; N, 14.13. Found: C, 64.69; H, 5.14; N, 14.18%.

4-(3,4-dihydroxyphenethyl)-5-p-toly-2H-1,2,4-triazol-3(4H)-one (4e): Yield: 1.41 g (46.87%), colorless crystals, mp 186 °C. IR (KBr, ν, cm^{-1}): 3258 (OH), 1699 (C=O), 1597 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.41 (s, 3H, CH_3), 2.56 (t, 2H, Ar-CH_2), 3.82 (t, 2H, N-CH_2), 6.21-6.45 (m, 2H, arom. H), 6.54-6.59 (m, 1H, arom. H), 7.61-7.67 (m, 5H, arom. H), 8.78 (bs, 2H, OH), 11.88 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 24.03 (CH_3), 33.27 (Ar-CH_2), 42.70 (N-CH_2), arom. C [115.42 (CH), 115.79 (CH), 119.10 (CH), 127.84 (CH), 128.70 (CH), 128.18 (C), 129.17 (CH), 145.33 (C), 146.55 (C)], 143.78 (C=N), 154.91 (C=O). Anal. Calc. for $C_{17}H_{17}N_3O_3$ M^+: (311.34) C, 65.58; H, 5.50; N, 13.50. Found: C, 65.62; H, 5.56; N, 13.58%.

4-(3,4-dihydroxyphenethyl)-5-(thiophen-2-ylmethyl)-2H-1,2,4-triazol-3(4H)-one (4f): Yield: 1.53 g (48.28%), colorless crystals, mp 189 °C. IR (KBr, ν, cm^{-1}): 3216 (OH), 1694 (C=O), 1583 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm) 2.55 (t, 2H, Ar-CH_2), 3.84 (t, 2H, thiophene CH_2), 3.68 (t, 2H, N-CH_2), 6.36-6.70 (m, 3H, arom. H), 6.90-7.49 (m, 3H, arom. H), 8.83 (bs, 2H, OH), 11.57 (s, 1H, NH); ^{13}C-NMR (DMSO-$d_6\delta$, ppm): 25.96 (thiophene CH_2), 33.46 (Ar-CH_2), 42.34 (N-CH_2), arom. C [115.50 (CH), 116.00 (CH), 119.28 (CH), 128.58 (C), 145.13 (C), 146.65 (C)], thiophene C [125.51 (CH), 126.50 (C), 126.97 (CH), 137.39 (C)], 143.83 (C=N), 154.77 (C=O). Anal. Calc. for $C_{15}H_{15}N_3O_3S$ M^+: (318.00) C, 56.77; H, 4.76; N, 13.24. Found: C, 56.70; H, 4.82; N, 13.28%.

The synthesis of 4-(3,4-dihydroxyphenethyl)-5-(3,4-dimethoxyphenethyl)-2H-1,2,4-triazol-3(4H)-one (5):

A solution of 4-(3,4-dimethoxyphenethyl)-5-(3,4-dimethoxyphenethyl)-2H-1,2,4-triazol-3(4H)-one **(3g)** (10 mmol) in chloroform (100 mL) was added to a solution of boron tribromide (40 mmol) in chloroform (300 mL) at 0 °C. The reaction mixture was then stirred under a nitrogen atmosphere at ambient temperature for 1 h and poured into ice containing sufficient 50% sodium hydroxide to attain a pH of 10. The addition of concentrated sulfuric acid provided a precipitate that was extracted into ether. The combined organic extract was washed with water and brine, dried, and concentrated in a vacuum to obtain compound **5**. The crude product was recrystallized using ethyl acetate and petroleum ether (1:4) to afford the desired compound.

4-(3,4-dihydroxyphenethyl)-5-(3,4-dimethoxyphenethyl)-2H-1,2,4-triazol-3(4H)-one (5): Yield: 2.44 g (61.06%), colorless crystals, mp 130 °C. IR (KBr, ν, cm^{-1}): 3293 (OH), 1693 (C=O), 1687 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.38 (t, 2H, Ar-CH_2), 3.38 (t, 2H, Ar-CH_2), 3.40 (t, 2H, N-CH_2), 6.22-6.75 (m, 6H, arom. H), 8.75-9.00 (m, 4H, OH), 11.45 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): 31.25 (Ar-CH_2), 33.98 (Ar-CH_2), 43.15 (N-CH_2), arom. C [116.25 (CH), 116.71 (CH), 120.30 (CH), 126.46 (C),

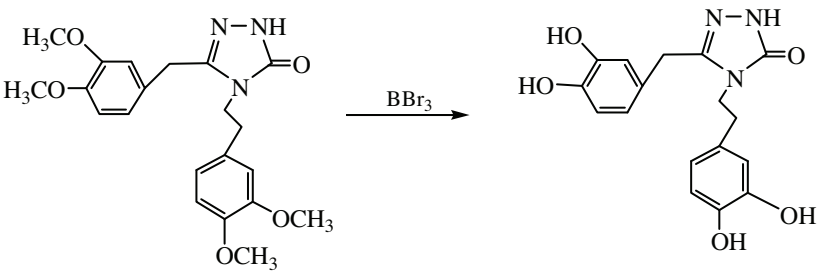
126.47 (CH), 144.18(C), 144.53 (C), 145.44 (C), 145.68 (C)], 147.99 (C=N), 155.82 (C=O). Anal. Calc. for $C_{17}H_{17}N_3O_5$ M^+: (344.00) C, 59.47; H, 4.99; N, 12.24. Found: C, 59.53; H, 4.91; N, 12.28%.

Results and discussion

In the first part of this study, compounds **3a-g** were synthesized via the reaction of compound **1** with compound **2** (Scheme 1). Analytical and spectroscopic data of **3** confirmed the success of the cyclization reaction.

The synthesis of 4-(3,4-dihydroxyphenethyl)-5-akyl/aryl-2H-1,2,4-triazol-3(4H)-ones **(4a-f)** was performed by the reaction of **3** with BBr_3 at reflux temperature in the presence of chloroform. The compounds were characterized by elemental analyses, mass spectral data, and ^{1}H- and ^{13}C-NMR and IR spectra.

Compound **5** was synthesized via the reaction of compound **3g** with BBr_3 (Scheme 2).



3g **5**

Scheme 2. Synthesis of compound **5**.

Some of synthesized compounds were investigated for antioxidant activity, and compounds **4a**, **4c**, **4d**, **4f**, and **5** were found to be active. As a result, the data obtained from our research could guide us toward the development of novel antioxidant compounds.

Antioxidant activity

DPPH assay: The radical scavenging activity of the synthesized compounds against stable free radical 2.2-diphenyl-2-picrylhydrazyl hydrate (DPPH, Sigma-Aldrich Chemie, Steinheim, Germany) was determined spectrophotometrically. When DPPH reacts with antioxidant compounds, which can donate hydrogen, it is reduced. Following the reduction, its deep violet color in methanol bleached to yellow, showing a significant absorption decrease at 517 nm (18). Then 50 μL of various concentrations of the compounds dissolved in methanol were added to 5 mL of a 0.004% methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was read against a blank at 517 nm (ATI-UnicamUV-2 UV-Vis spectrophotometer, Cambridge, UK). Free radical DPPH inhibition in percentage (I%) was calculated as follows: I% = (A_{blank} – A_{sample} /A_{blank})× 100, where A_{blank} is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound. Compound concentrations providing 50% inhibition (IC50) were calculated from a graph plotted as inhibition percentage against compound concentration. Tests were carried out in triplicate, and butylated hydroxytoluene (BHT) was used as a positive control (Figures 2 and 3).[18]

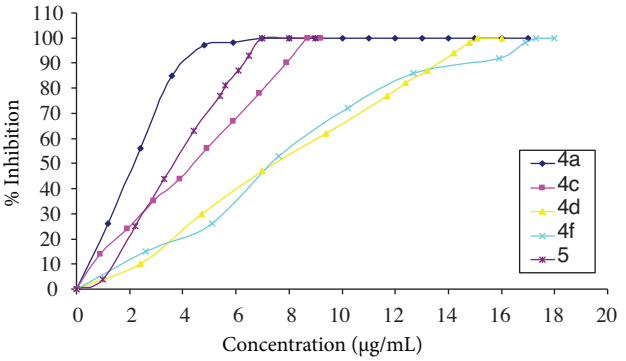


Figure 2. I% values of compounds **4a**, **4c**, **4d**, **4f**, and **5**.

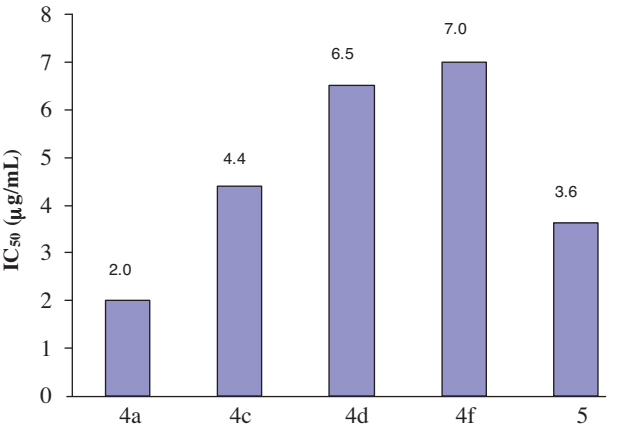


Figure 3. IC_{50} values of compounds **4a**, **4c**, **4d**, **4f**, and **5**.

Crystal structure determination of 3a

Data collection

The crystal structure of compound **3a** ($C_{13}H_{17}N_3O_3.H_2O$), with crystal dimensions of 0.49 × 0.45 × 0.43 mm, was determined by single crystal X-ray diffraction. The data collection was performed on a Bruker Smart Area-CCD diffractometer with Mo K_α radiation ($\lambda = 0.71073$ Å) at 293(2) K. The systematic absences and intensity symmetries indicated the monoclinic $P2(1)/c$ space group. A total of 9002 reflections (3430 unique) within the θ range of $[1.58° < \theta < 28°]$ were collected in the rotation mode with $R_{int} = 0.022$. The data collection method was ϕ and ω scans with κ offsets. The program used for cell refinement and data collection was Bruker SMART.[19] The structure was solved with direct methods by using SHELXS-97[20] and was refined by full-matrix least square techniques on F^2 using SHELXL-97.[20] A molecular plot was prepared with ORTEPIII for Windows.[21] WinGX software[22] was used to prepare material for publication.

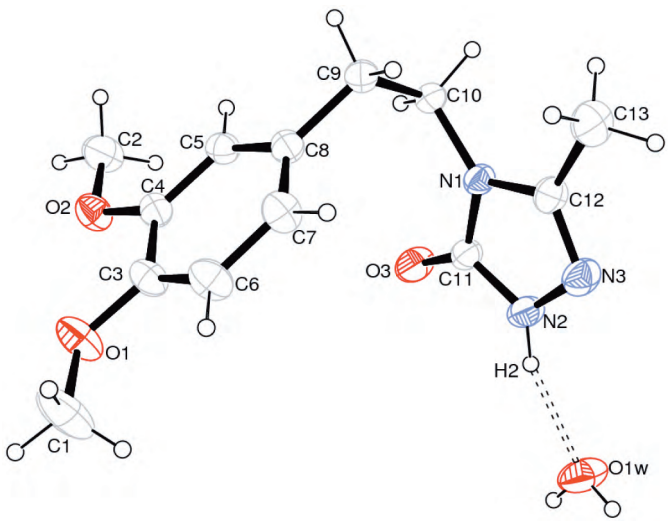


Figure 4. ORTEPIII diagram of compound **3a**.

The crystal structure of compound **3a**, $C_{13}H_{17}N_3O_3 \cdot H_2O$, was determined by single crystal X-ray diffraction technique (Figures 4 and 5). Compound **3a** crystallizes in the triclinic space group in the asymmetric unit, with the following unit-cell parameters: a = 13.302(3) Å, b = 6.8441(15) Å, c = 16.390(4) Å, β =103.611(4)°, γ =1450.2(6)°, and V = 1450.2(6) Å^3, with Z = 4; crystallographic data are shown in Table 1. The structure of compound **3a** consists of one triazole ring and one benzene ring. Nonhydrogen fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters are listed in Table 2. Hydrogen bond geometries are given in Table 3. The 1,2,4-triazole ring and the benzene ring are planar, with the maximum deviation from the least squares planes being 0.0097(16) Å for atom C11 and -0.0119(17) Å for atom C3. Atom N1 has a substituent. Therefore, the C12—N1 and C11—N1 bond distances [1.3725(18) Å] are longer

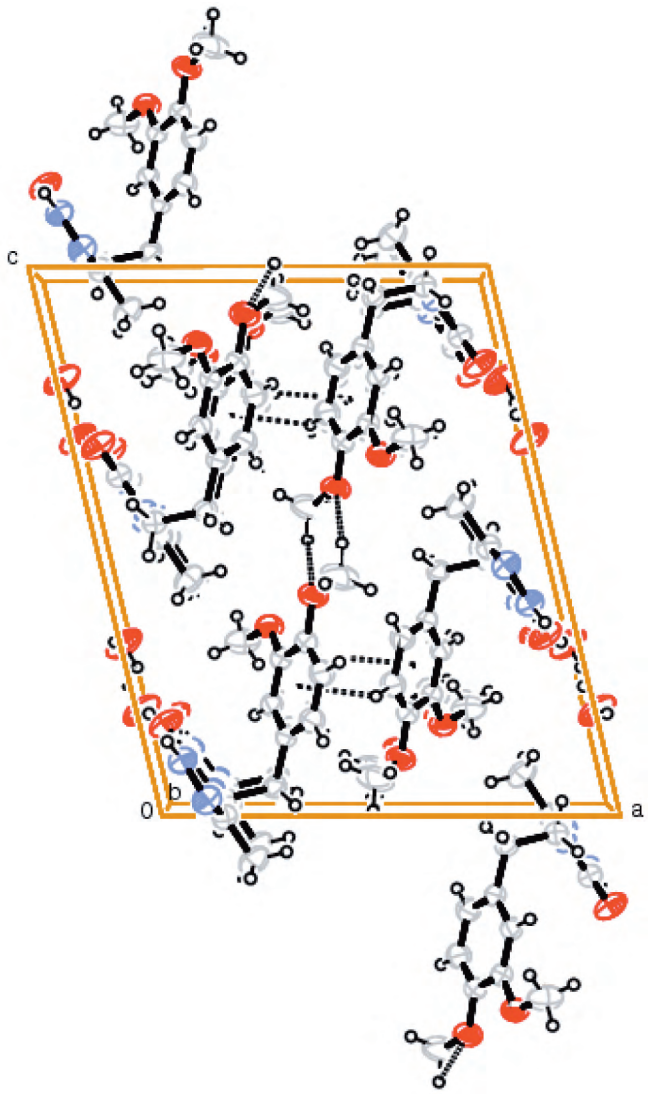


Figure 5. Packing diagram of compound **3a**.

than C11—N2 [1.3415(19) Å]. The N3-N2 bond length [1.3775(18) Å] agrees with the values reported in the literature [1.3823(17) Å,[23] 1.398(4) Å[24]]. The N3=C12 bond length [1.296(2) Å] is longer than some values reported in the literature.[25,26] However, it is close to other reported values.[27,28] In the 1-, 2-, and 4-triazole ring, atoms N2 and N3 have no substituents, and the N2—N3 bond length, 1.3776(18) Å, is close to values reported in the literature.[29] The O3—C11 bond length of 1.238(18) Å lies within the range previously reported.[30,31] The dihedral angle between the benzene and triazole rings is 55.25(5)°.

Table 1. Crystal and experimental data.

Chemical formula	$C_{13}H_{17}N_3O_3.H_2O$
M_r	281.31
Cell setting, space group	Monoclinic, $P2(1)/c$
Temperature (K)	293(2)
a, b, c (Å)	13.302 (3), 6.8441(15), 16.390(4)
V (Å^3)	1450.2(6)
Z	4
D_x (mg/cm^3)	1.288
Radiation type	Mo K
μ (mm^{-1})	0.10
Crystal form, color	Prism, colorless
Crystal size (mm^3)	0.49 × 0.45 × 0.43
Data collection	
Diffractometer	CCD area detector
No. of measured independent	9002, 3430, 2325
and observed reflections	
Criterion for observed	$I > 2\sigma$(I)
reflections	
R_{int}	0.022
$\theta_{\max}$	28.0
Refinement	
Refinement on	F^2
No. of reflections	3430
No. of parameters	191
$(\Delta/\sigma_{\max}$	< 0.0001
$(\Delta\rho)_{\max}, (\Delta\rho)_{\min}$ (e Å^{-3})	0.24, -0.20
Extinction method	SHELXL
Extinction coefficient	0.016 (2)

Table 2. Nonhydrogen fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters.

Atom	x	y	z	U^*_{iso}/U_{eq}
C1	0.5147(2)	-0.2298(4)	0.43692(13)	0.1008(9)
C2	0.26410(18)	0.3800(3)	0.31609(12)	0.0726(6)
C3	0.40713(12)	-0.0753(3)	0.31778(9)	0.0512(4)
C4	0.34313(11)	0.0842(2)	0.28652(9)	0.0447(4)
C5	0.29715(11)	0.0937(2)	0.20180(9)	0.0438(3)
C6	0.42567(14)	-0.2152(3)	0.26334(11)	0.0598(5)
C7	0.37943(13)	-0.2021(3)	0.17766(10)	0.0554(4)
C8	0.31448(11)	-0.0501(2)	0.14621(9)	0.0435(3)
C9	0.26236(11)	-0.0348(2)	0.05421(9)	0.0455(4)
C10	0.14760(11)	-0.0889(2)	0.03348(9)	0.0411(3)
C11	0.09050(12)	-0.3522(2)	0.11927(9)	0.0437(3)
C12	0.14547(12)	-0.4551(2)	0.00939(10)	0.0465(4)
C13	0.18530(17)	-0.4517(3)	-0.06812(12)	0.0679(5)
N1	0.13011(9)	-0.29154(16)	0.05338(7)	0.0397(3)
N2	0.08680(11)	-0.54737(18)	0.11189(8)	0.0513(3)
N3	0.11974(11)	-0.61303(19)	0.04310(9)	0.0552(4)
O1	0.44746(10)	-0.0743(2)	0.40274(7)	0.0698(4)
O2	0.33325(9)	0.22234(17)	0.34433(7)	0.0570(3)
O3	0.06365(11)	-0.24874(17)	0.17240(7)	0.0644(4)
O1W	0.00840(14)	-0.85485(19)	0.19067(9)	0.0798(5)

Table 3. Hydrogen-bonding geometry (Å, °) for (I).

D-H...A	D–H	H...A	D...A	D–H...A
N2-H2...O1W	0.86	1.971	2.796(2)	160
C1-H1A...O1^{i}	0.96	2.550	3.297(2)	135
O1W-H1W...O3^{ii}	0.82	1.932	2.738(2)	168
O1W-H2W...O3^{iii}	0.80	2.030	2.829(2)	178

D: donor, A: acceptor. Symmetry transformations used to generate equivalent atoms. ^{i}-x+1, -y, -z+1; ^{ii}-x, y-1/2, -z+1/2; ^{iii} x, y-1, z.

Supplementary data: CCDC, 698179.

The crystal structure is stabilized by intra- and intermolecular interactions, C-H...π, and $\pi-\pi$ stacking interactions. There are 3 intermolecular and 1 intramolecular hydrogen bonds in the structure (Table 3). In the N-H...O-type N2-H2...O1W intramolecular hydrogen bond, the N2...O1W distance is 2.796(2) Å and the intramolecular strong interaction is of the D-H... type. It has an angle of 160° (Figure 4). The intramolecular hydrogen bond supplies a leading contribution to the stabilization of the crystallographically

observed conformation of compound **3a**. In the intermolecular hydrogen bonds, 1 C-H...O-type (C1-H1A...O1) and 2 O-H...O-type (O1W-H1W...O3 and O1W-H2W...O3) C1-H1A...O1 intermolecular hydrogen bonds are weaker than others. The O-H...O-type intermolecular hydrogen bonds, O1W-H1W...O3 and O1W-H2W...O3, have short hydrogen-acceptor distances (1.932 Å and 2.030 Å, respectively). Both of these hydrogen bonds, O1W-H1W...O3 and O1W-H2W...O3, are nearly linear (168° and 178°, respectively) and fairly strong. In addition, there is one remarkable intermolecular $\pi - \pi$ stacking interaction between the triazole rings [Cg1...Cg1 = 3.3810(12) Å; symmetry code: -x, 1-y, -z]. Since the perpendicular distance between the interacting π-rings is smaller than 3.8 Å, this stacking interaction supplies a considerable contribution to the stabilization of the crystal structure. On the other hand, the crystal structure also has an intermolecular C-H...π contact involving the benzene ring of a symmetry-related molecule at (1-x, -1/2+y, 1/2-z) [C6...Cg2 = 3.680(2) Å, H6...Cg2 = 2.86 Å, and C6-H6...Cg2 = 148°].

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References

1. Unver, Y.; Dugdu, E.; Sancak, K.; Er, M.; Karaoglu, Ş. A. *Turk. J. Chem.* **2009**, *33*, 135-147.
2. Unver, Y.; Dugdu, E.; Sancak, K.; Er, M.; Karaoglu, Ş. A. *Turk. J. Chem.* **2008**, *32*, 441-455.
3. Turan-Zitouni, G.; Kaplancikli, Z.; Erol, K.; Kilic, F. S. *Il Farmaco* **1999**, *54*, 218-223.
4. Sancak, K.; Unver, Y.; Er, M. *Turk. J. Chem.* **2007**, *31*, 125-134.
5. Emilsson, H.; Salender, H.; Gaarder, J. *Eur. J. Med.* **1985**, *21*, 333-337.
6. Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Papakonstantinou-Garoufalias, C. M. *Il Farmaco* **2002**, *57*, 253-257.
7. Holla, B. S.; Poorjary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem.* **2002**, *37*, 511-517.
8. Foroumadi, A.; Soltani, F.; Moshafi, M. H.; Ashraf-Askari, R. *Il Farmaco* **2003**, *58*, 1023-1028.
9. Gürsoy, A.; Demirayak, S.; Cesur, Z. *Pharmazie* **1990**, *45*, 246-250.
10. Verreck, G. K.; Six, G.; Van den Mooter, L.; Baert, L.; Peeters, J.; Brewster, M. E. *Int. J. Pharm.* **2003**, *251*, 165-174.
11. Clemons, M.; Coleman, R. E.; Verma, S. *Cancer Treat. Rev.* **2004**, *30*, 325-332.
12. Chen, S.; Kao, Y. C.; Laughton, A. *J. Steroid Biochem.* **1997**, *61*, 107-127.
13. Kawasaki, I.; Domen, A.; Kataoka, S.; Yamauchi, K.; Yamashita, M.; Ohta, S. *Heterocycles* **2003**, *60*, 351-363.
14. Klika, K.; Saleem, A.; Sinkkonen, J.; Kähkönen, M.; Loponen, J.; Tähtinen, P.; Pihlaja, K. *Arkivoc* 2004, *8*, 83-105.
15. Balakrıshna, A.; Veera, M.; Reddy, N.; Nayak, K.; Manjunath, M.; Reddy, C. *Chem. Pharm. Bull.* **2008**, *56*, 1486-1489.

16. Ammendola, S.; Mosca, L.; Bovicellic, P. *Arkivoc* **2008**, *8*, 105-115.
17. Ikizler, A. A.; Sancak, K. *Collect. Czech. Commun.* **1995**, *60*, 903-909.
18. Yüksek, H.; Alkan, M.; Çakmak, I.; Ocak, Z.; Bahçeci, Ş.; Çalapoğlu, M.; Elmastaş, M.; Kolomuç, A.; Aksu, H. *J. Mol. Sci.* **2008**, *9*, 12-32.
19. Bruker (1997), SADABS (Version 2.10), SMART (Version 5.044), and SAINT (Version 5.01). Bruker AXS Inc., Madison, Wisconsin, USA.
20. Sheldrick, G. M. *SHELXS-97 and SHELXL-97, Programs for the Solution and Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
21. Farrugia L. J. *J. Appl. Cryst.* **1997**, *30*, 565.
22. Farrugia L. J. *J. Appl. Cryst.* **1999**, *32*, 837-838.
23. Iskeleli, N. O.; Çoruh, U.; Bekircan, O.; Ağar, A.; Şaşmaz, S.; Erdönmez, A. *Acta Cryst.* **2005**, *E61*, 1659-1661.
24. Ustabaş, R.; Çoruh, U.; Sancak, K.; Ünver, Y.; Vazquez-Lopez, E. M. *Acta Cryst.* **2006**, *E62*, 5520-5522.
25. Liu, Y. F.; Chantrapromma, S.; Rai, S.; Fun, H. K.; Zhang, Y. H.; Xie, F. X.; Tian, Y. P.; Ni, S. S. *Acta Cryst.* **1999**, *C55*, 93-94.
26. Zhu, D. R.; Xu, Y.; Liu, Y. J.; Song, Y.; Zhang, Y.; You, X. Z. *Acta Cryst.* **2000**, *C56*, 242-244.
27. Puviarasan, K.; Govindasamy, L., Shanmuga Sundara Raj, S.; Velmurugan, D.; Jayanthi, G.; Fun, H. K. *Acta Cryst.* **1999**, *C55*, 951-952.
28. Çoruh, U.; Kahveci, B.; Şaşmaz, S.; Ağar, E.; Kim, Y. A. *Acta Cryst.* **2003**, *E59*, 530-531.
29. Kalkan, H.; Ustabaş, R.; Sancak, K.; Ünver, Y.; Vazquez-Lopez, E. M. *Acta Cryst.* **2007**, *E63*, 2449-2450.
30. Ustabaş, R.; Çoruh, U.; Sancak, K.; Dügdü, E.; Vazquez-Lopez, E. M. *Acta Cryst.* **2006**, *E62*, 4265-4266.
31. Ustabaş, R.; Çoruh, U.; Sancak, K.; Ünver, Y.; Vazquez-Lopez, E. M. *Acta Cryst.* **2007**, *E63*, 2982-2983.