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Synthesis and Characterization of Some 5-Substituted 2-Thiol/Thione-1,3,4-Oxadiazoles

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5-(4-Aminophenyl)-2-thiol-1,3,4-oxadiazole (**1**) was synthesized *via* the reaction of carbon disulfide with 4-aminobenzoyl hydrazide. Compound **1** was converted to the corresponding diazonium salt which was introduced in coupling reaction with sodium phenoxide as coupling reagent to give azo-oxadiazole derivative containing aldehyde group **2**. The resulting aldehyde **2** was then introduced in acid-catalyzed condensation reactions with both 2-aminobenzothiazole and 2-amino-5-mercapto-1,3,4-thiadiazole to obtain the oxadiazolic-imines **3a** and **3b**, respectively. Treatment of the resulting imines **3a** and **3b** with each succinic acid, maleic acid, phthalic acid and 3-nitrophthalic anhydrides, respectively, under (2+5) cycloaddition conditions afforded eight new oxadiazoles substituted with 1,3-oxazepane and 1,3-oxazepine moieties **4a-d** and **5a-d**, respectively. The resulting imines **3a** and **3b** were also treated with sodium azide under (2+3) cycloaddition conditions to obtain two new oxadiazoles containing tetrazole moiety **4e** and **5e**, respectively. The newly synthesized oxadiazoles might have some biological, pharmaceutical and medicinal applications.

Keywords: 1,3,4-Oxadiazoles, Imines, 1,3-Oxazepanes, 1,3-Oxazepines, Tetrazoles, Azo.

INTRODUCTION

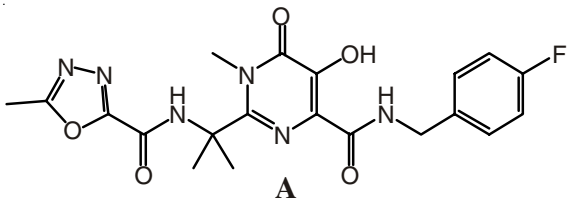
Oxadiazoles are five-membered heteroaromatic compounds including two nitrogen atoms and one oxygen atom on the ring. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important for the development of new drugs [1] and pharmacological interest [2]. For example Raltegravir [3], an antiretroviral drug **A** and Zibotentan [4], an anticancer agent **B** currently used in clinical medicine. Compounds containing 1,3,4-oxadiazole nucleus reported to be anti-inflammatory [5], anticonvulsive, anticancer [6], depressant activity [7], antibacterial [8] and antimicrobial [9] properties. One of the popular methods for the synthesis of 1,3,4-oxadiazole thione/thiol derivatives reported by Hosur *et al*. [10] to synthesize of 2-mercapto-5-aryl-1,3,4-oxadiazole **C** from the properly substituted acid hydrazides in presence of CS_2/KOH. El-Hamouly *et al*. [11] were synthesized some 1,3,4-oxadiazole derivatives and compound **D** exhibited the highest activity against breast cancer cell line (MCF7).

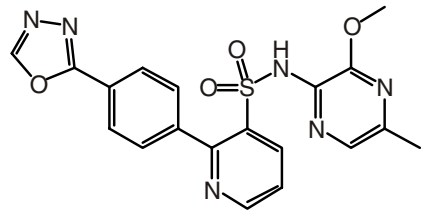
Oxazepine compounds have medical and biological importance and they have medicinal [12,13] and pharmaceutical applications [14]. Some oxazepine derivatives are considered a medical drug against the disease [15] and some of them act as inhibitors of some enzymes action [16]. Fused oxazepinone derivatives have attracted considerable attention owing to their promising biological activities [17], such as antihistaminic [18], anti-HIV [19], antidepressant [20] and antitumor activities [21]. Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antimicriobial activity [22], anti-inflammatory activity [23], antialergic [24] and anticancer [25].

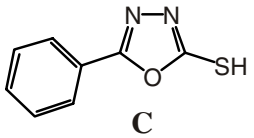
Thus, in this article, we reported here the synthesis of new 5-substituted-2-thiol-1,3,4-oxadiazole derivatives bearing biologically active heterocyclic moieties including benzothiazole, thiadiazole, oxazepane, oxazepine, tetrazole in addition of azo group, which might have some biological activity.

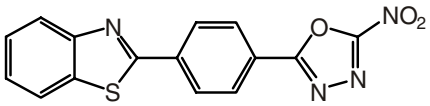
EXPERIMENTAL

The chemicals were used as purchased from Fluka, Sigma Aldrich, GCC and Merck. Benzene and THF were freshly distilled from appropriate drying agents before use. Analytical TLC was performed with silica gel 60 F_{254} plates. The reactions were monitored by TLC and visualized by development of the TLC plates with iodine vapour. Melting points were recorded on an Electro thermal Stuart SMP: 30 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on SHIMADZU FTIR-8400S infrared spectrophotometer as potassium bromide discs. ^{1}H NMR spectra was collected on NMR spectrometer 400 MHz, Avance III 400 Bruker, Germany at 400 MHz in DMSO-d_6 as solvent and TMS as an internal standard at Esfahan University, Iran. (CHNS) Elemental analysis









Structures of some bioactive 1,3,4-oxadiazole derivatives

was carried out with Perkin Elmer 300A Elemental Analyzer at Esfahan University, Iran.

5-(4-Aminophenyl)-2-thiol-1,3,4-oxadiazole (**1**) was synthesized according to Yong and Wood conditions [26] as pale yellow crystals, m.p.: 234-236 °C, yield 76 %; IR (KBr, ν_{max}, cm^{-1}): 3448 $\nu_{as.}(NH_2)$, 3352 $\nu_{s.}(NH_2)$, 3086 ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2947 and 2764 ν(N-H), intramolecularly hydrogen bonded, thione form, 2590 ν(S-H) thiol form, 1604 ν(C=N) oxadiazole and $\delta(NH_2)$ vib. coupling, 1512 ν(C=C) benzene, 1068 ν(C=S) thione form, 835, 731 and 694 $\delta_{o.o.p.}$(C-H) benzene.

(E)-2-Hydroxy-5-[{4-(5-mercapto-1,3,4-oxadiazol-2yl)phenyl}diazenyl]benzaldehyde (**2**) was synthesized following the method described by Acton [27] as red solid, m.p.: 196-198 °C, yield 78 %; IR (KBr, ν_{max}, cm^{-1}): 3402br ν(O-H), 3190 ν(N-H), thione form, 3095 ν(C-H) benzene, 2937 and 2748 ν(N-H) intramolecularly hydrogen bonded, thione form, 2885 ν(C-H) aldehyde, 2580 ν(S-H) thiol form, 1662 ν(C=O) aldehyde, 1604 ν(C=N) oxadiazole, 1477 ν(C=C) benzene, 1411 ν(N=N), 1068 ν(C=S) thione form, 842 and 721 $\delta_{o.o.p.}$(C-H) benzene.

General procedure for the synthesis of oxadiazolic-imines (3a and 3b): Azo-oxadiazolic aldehyde (**2**) (1.63 g, 5 mmol) was dissolved in 15 mL of absolute ethanol containing two drops of glacial acetic acid, then 2-aminobenzothiazole (0.75 g, 5 mmol) or 2-amino-5-mercapto-1,3,4-thiadiazole (0.665 g, 5 mmol) was dissolved in 10 mL of absolute ethanol and added drop wise. The reaction mixture was refluxed with stirring on a water bath at 70 °C for 9 to 11 h, respectively and monitored by TLC. The mixture was then allowed to cool down to room temperature, the coloured precipitate was filtered and recrystallized from ethanol.

2-[(Benzo[d]thiazol-2-ylimino)methyl]-4-[(*E*)-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl}diazenyl]phenol 3a: IR (KBr, ν_{max}, cm^{-1}): 3429br ν(O-H), 3134 ν(N-H) thione form, 3064 ν(C-H) benzene, 2928 and 2746 ν(N-H) intramolecularly hydrogen bonded, thione form, 2584 ν(S-H) thiol form, 1604s ν(C=N) oxadiazole and ν(C=N) imine, vib. coupling, 1481s ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1410 ν(N=N), 1064 ν(C=S) thione form, 839, 756 and 694 $\delta_{o.o.p.}$(C-H) benzene.

4-((E)-(4-(5-Mercapto-1,3,4-oxadiazol-2-yl)phenyl)-diazenyl)-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)-methyl)phenol 3b: IR (KBr, ν_{max}, cm^{-1}): 3259 ν(O-H), 3074 ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2928 and 2756 ν(N-H) intramolecularly hydrogen bonded, thione form, 2580 ν(S-H) thiol form, 1602s ν(C=N) oxadiazole and ν(C=N) imine, vib. coupling, 1498s ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1408 ν(N=N), 1064 ν(C=S) thione form, 840 and 702 $\delta_{o.o.p.}$(C-H) benzene.

General procedure for the synthesis of oxadiazolic-oxazepanes and oxazepines (4a-d) and (5a-d): A mixture of imine derivative (**3a**) (0.458 g, 1 mmol) or imine derivative (**3b**) (0.441 g, 1 mmol) and succinic acid or maleic acid or phthalic acid or 3-nitrophthalic anhydride (1 mmol) in dry benzene (15 mL) was refluxed on a water bath at 70 °C for 24 h. and monitored by TLC. The mixture was then allowed to cool down to room temperature, the coloured precipitate was filtered, dried and recrystallized from ethanol.

(*E*)-3-(Benzo[d]thiazol-2-yl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-1,3-oxazepane-4,7-dione (4a): IR (KBr, ν_{max}, cm^{-1}): 3163 ν(O-H) and ν(N-H) thione form, vib. coupling, 3066 ν(C-H) benzene, 2968 ν(C-H) CH_2, oxazepane, 2937 and 2764 ν(N-H) intramolecularly hydrogen bonded, thione form, 2565 ν(S-H) thiol form, 1695 ν(C=O, O=C-O and O=C-N) oxazepane, vib. coupling, 1608 ν(C=N) oxadiazole, 1539, 1510 and 1450 ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1411 ν(N=N), 1066 ν(C=S) thione form, 840 and 752 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 2.58-2.62 (t, *J* = 6.8 Hz, 2H, CH_2–CO–O, oxazepane), 2.73–2.76 (t, *J* = 6.9 Hz, 2H, CH_2–CO–N, oxazepane), 2.90 (s, 1H, S–H), 3.38 (H_2O in DMSO), 6.98–7.98 (Ar–H and C–H, oxazepane), 6.98–7.02 (t, *J* = 8.3 Hz, 1H, Ha), 7.18–7.22 (t, *J* = 8.3 Hz, 1H, Hb), 7.25 (s, 1H, Hc), 7.28–7.30 and 7.32–7.34 (dd, *J* = 7.2, 9.9 Hz, 2H, Hd; He), 7.41–7.43 and 7.45–7.48 (dd, *J* = 8.2, 11.7 Hz, 3H, 2×Hf; Hg), 7.64 (s, 1H, C–H, oxazepane), 7.73–7.75 (d, *J* = 8.1 Hz, 2H, 2×Hh). 7.96–7.98 (d, *J* = 7.8 Hz, 1H, Hi), 9.40 (s, N–H, thione form), 10.39 (s, 1H, O–H). Anal. calcd. for $C_{26}H_{18}N_6O_5S_2$: C, 55.91; H, 3.25; N, 15.05; S, 11.48 Found C, 56.18; H, 3.36; N, 15.13; S, 11.17.

(E)-3-(Benzo[d]thiazol-2-yl)-2-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (4b): IR (KBr, ν_{max}, cm^{-1}): 3068 ν(O-H), ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2935 and 2754 ν(N-H) intramolecularly hydrogen bonded, thione form, 1703 ν(C=O, O=C-O) oxazepine, 1653 ν(C=O, O=C-N) oxazepine, 1604 ν(C=N) oxadiazole, 1475br ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1411 ν(N=N), 1068 ν(C=S) thione form, 852 and 750 $\delta_{o.o.p.}$(C-H)

benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.35 (H_2O in DMSO), 6.10 (s, 2H, 2×olefinic =CH, oxazepine), 6.99–8.07 (Ar–H and C–H, oxazepine), 6.99–7.03 (t, *J* = 8.2 Hz, 1H, Ha), 7.19–7.23 (t, *J* = 8.2 Hz, 1H, Hb), 7.25 (s, 1H, Hc), 7.30–7.32 and 7.34–7.36 (dd, *J* = 9.5, 8.9 Hz, 2H, Hd; He), 7.48 (s, 1H, C–H, oxazepine), 7.62–7.64 (d, *J* = 10.4 Hz, 1H, Hf), 7.68–7.70 (d, *J* = 8.8 Hz, 2H, 2×Hg), 7.82–7.84 (d, *J* = 8.8 Hz, 2H, 2×Hh), 8.05–8.07 (d, *J* = 11.1 Hz, 1H, Hi), 9.39 (s, 1H, N–H, thione form), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{26}H_{16}N_6O_5S_2$: C, 56.11; H, 2.90; N, 15.10; S, 11.52; Found C, 56.42; H, 3.06; N, 15.01; S, 11.73.

(E)-4-(Benzo[d]thiazol-2-yl)-3-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (4c): IR (KBr, ν_{max}, cm^{-1}): 3171 ν(O-H) and ν(N-H) thione form, vib. coupling, 3061 ν(C-H) benzene, 2966 and 2806 ν(N-H) intramolecularly hydrogen bonded, thione form, 2636 ν(S-H) thiol form, 1689 ν(C=O, O=C-O) and ν(C=O, O=C-N) oxazepine, vib. coupling, 1600 ν(C=N) oxadiazole, 1554, 1487 and 1450 ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1411 ν(N=N), 1070 ν(C=S) thione form, 758 and 731 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.36 (H_2O in DMSO), 6.98–7.84 (Ar–H and C–H, oxazepine), 6.98–7.02 (t, *J* = 8.0 Hz, 1H, Ha), 7.19–7.22 (t, *J* = 7.4 Hz, 1H, Hb), 7.26 (s, 1H, Hc), 7.30–7.32 and 7.34–7.36 (dd, *J* = 9.7, 7.0 Hz, 2H, Hd; He), 7.47 (s, 1H, C–H, oxazepine), 7.52–7.60 (m, 6H, Hf; Hg; Hh; Hi; Hj; Hk), 7.68–7.70 (d, *J* = 8.8 Hz, 2H, 2×Hl), 7.81–7.84 (d, *J* = 8.6 Hz, 2H, 2×Hm), 9.60 (s,1H, N–H, thione form), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{30}H_{18}N_6O_5S_2$: C, 59.40; H, 2.99; N, 13.85; S, 10.57; Found C, 59.72; H, 3.24; N, 13.91; S, 10.33.

(E)-4-(Benzo[d]thiazol-2-yl)-3-(2-hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-6-nitro-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (4d): IR (KBr, ν_{max}, cm^{-1}): 3282 ν(O-H), 3076 ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2929 and 2760 ν(N-H) intramolecularly hydrogen bonded, thione form, 2596 ν(S-H) thiol form, 1707 ν(C=O, O=C-O) and ν(C=O, O=C-N), oxazepine, vib. coupling, 1602 ν(C=N) oxadiazole, 1533 $\nu_{as.}(NO_2)$, 1489br ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1413 ν(N=N), 1313 $\nu_{s.}(NO_2)$, 1068 ν(C=S) thione form, 840, 750 and 698 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.34 (H_2O in DMSO), 6.99–8.26 (Ar–H and C–H, oxazepine), 6.99–7.03 (t, *J* = 6.9 Hz, 1H, Ha), 7.22–7.25 (t, *J* = 3.7 Hz, 1H, Hb), 7.26 (s, 1H, Hc), 7.30–7.32 (d, *J* = 8.2 Hz, 1H, Hd), 7.43–7.45 (d, *J* = 8.5 Hz, 1H, He), 7.60–7.62 (d, *J* = 8.5 Hz, 1H, Hf), 7.68–7.70 (d, *J* = 8.4 Hz, 2H, 2×Hg), 7.76 (s, 1H, C–H, oxazepine), 7.96–8.06 (m, 3H, Hh; Hi; Hj), 8.09–8.11 (d, *J* = 8.4 Hz, 2H, 2×Hk), 8.24–8.26 (d, *J* = 7.9 Hz, 1H, Hl), 9.44 (s, 1H, N–H, thione form), 10.38 (s, 1H, O–H); Anal. calcd. for $C_{30}H_{17}N_7O_7S_2$: C, 55.30; H, 2.63; N, 15.05; S, 9.84; Found C, 55.63; H, 2.54; N, 15.14; S, 9.65.

(E)-2-(2-Hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-1,3-oxazepane-4,7-dione (5a): IR (KBr, ν_{max}, cm^{-1}): 3101 ν(O-H) and ν(N-H) thione form, vib. coupling, 3057 ν(C-H) benzene, 2933 and 2758 ν(N-H) intramolecularly hydrogen bonded, thione form, 2656 and 2551 ν(S-H) thiol forms, 1695s ν(C=O, O=C-O and O=C-N) oxazepane, vib. coupling, 1604 ν(C=N) oxadiazole, 1510 and 1487 ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1417 ν(N=N), 1064 ν(C=S) thione form, 842 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 2.57–2.60 (t, *J* = 5.0 Hz, 2H, CH_2–CO–O, oxazepane), 2.73–2.74 (d, *J* = 5.4 Hz, 2H, CH_2–CO–N, oxazepane), 2.86 and 2.90 (ss, 2H, 2×S–H), 3.35 (H_2O in DMSO), 7.12–7.84 (Ar–H and C–H, oxazepane), 7.12 (s, 1H, Ha), 7.24–7.26 (d, *J* = 8.9 Hz, 1H, Hb), 7.52–7.54 (d, *J* = 8.5 Hz, 1H, Hc), 7.68–7.70 (d, *J* = 8.8 Hz, 2H, 2×Hd), 7.81 (s, 1H, C–H, oxazepane), 7.82–7.84 (d, *J* = 8.7 Hz, 2H, 2×He), 9.54 (s, 2H, 2×N–H, thione forms), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{21}H_{15}N_7O_5S_3$: C, 46.57; H, 2.79; N, 18.10; S, 17.76; Found C, 46.88; H, 2.96; N, 17.92; S, 17.98.

(E)-2-(2-Hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione (5b): IR (KBr, ν_{max}, cm^{-1}): 3269 ν(O-H), 3169 ν(N-H) thione form, 3072 ν(C-H) benzene, 2935 and 2789 ν(N-H) intramolecularly hydrogen bonded, thione form, 2582 ν(S-H) thiol forms, 1707 ν(C=O, O=C-O and O=C-N) oxazepine, vib. coupling, 1604 ν(C=N) oxadiazole, 1537 and 1508 ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1411 ν(N=N), 1066 νν(C=S) thione form, 842 and 696 $\delta_{o.o.p.}$(C-H, benzene); ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.36 (H_2O in DMSO), 6.64–6.67 (d, *J* = 11.8 Hz, 2H, 2×olefinic =CH, oxazepine), 7.12–7.84 (Ar–H and C–H, oxazepine), 7.12 (s, 1H, Ha), 7.23–7.25 (d, *J* = 8.9 Hz, 1H, Hb), 7.51 (s, 1H, C–H, oxazepine), 7.52–7.54 (d, *J* = 7.2 Hz, 1H, Hc), 7.68–7.70 (d, *J* = 8.2 Hz, 2H, 2×Hd), 7.82–7.84 (d, *J* = 8.9 Hz, 2H, 2×He), 9.39 and 9.40 (ss, 2H, 2×N–H, thione forms), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{21}H_{13}N_7O_5S_3$: C, 46.75; H, 2.43; N, 18.17; S, 17.83; Found C, 46.93; H, 2.52; N, 18.26; S, 18.11.

(E)-3-(2-Hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-4-(5-mercapto-1,3,4-thiadiazol-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione(5c): IR (KBr, ν_{max}, cm^{-1}): 3074 ν(O-H), ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2962 and 2897 ν(N-H) intramolecularly hydrogen bonded, thione form, 2654 and 2528 ν(S-H) thiol forms, 1689 ν(C=O, O=C-O and O=C-N) oxazepine, vib. coupling, 1589 ν(C=N) oxadiazole, 1539 and 1508 ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1408 ν(N=N), 1068 ν(C=S) thione form, 839, 796 and 734 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ= 2.51 (DMSO solvent), 3.39 (H_2O in DMSO), 7.24–8.10 (Ar–H and C–H, oxazepine), 7.24–7.26 (d, *J* = 8.9 Hz, 1H, Ha), 7.53–7.55 (d, *J* = 9.1 Hz, 1H, Hb), 7.60 (s, 1H, Hc), 7.68–7.70 (d, *J* = 8.5 Hz, 2H, 2×Hd), 7.78 (s, 1H, C–H, oxazepine), 7.83–7.85 (d, *J* = 8.1 Hz, 2H, 2×He), 8.03–8.10 (m, 4H, Hf; Hg; Hh; Hi), 9.44 and 9.48 (ss, 2H, 2×N–H, thione forms), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{25}H_{15}N_7O_5S_3$: C, 50.93; H, 2.56; N, 16.63; S, 16.31; Found C, 51.15; H, 2.66; N, 16.86; S, 16.01.

(E)-3-(2-Hydroxy-5-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenyl)-4-(5-mercapto-1,3,4-thiadiazol-2-yl)-6-nitro-3,4-dihydrobenzo[e][1,3]-oxazepine-1,5-dione (5d): IR (KBr, ν_{max}, cm^{-1}): 3221 ν(O-H), 3113 ν(N-H) thione form, 3076 ν(C-H) benzene, 2924 and 2794 ν(N-H) intramolecularly hydrogen bonded, thione form,

2634 ν(S-H) thiol form, 1718 ν(C=O, O=C-O) oxazepine, 1683 ν(C=O, O=C-N) oxazepine, 1606 ν(C=N) oxadiazole, 1537 $\nu_{as.}(NO_2)$, 1568, 1510 and 1475 ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1408 ν(N=N), 1315 $\nu_{s.}(NO_2)$, 1062 ν(C=S) thione form, 750 and 690 $\delta_{o.o.p.}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.34 (H_2O in DMSO), 7.23-8.09 (Ar–H and C–H, oxazepine), 7.23–7.25 (d, *J* = 8.7 Hz, 1H, Ha), 7.53–7.55 (d, *J* = 5.8 Hz, 1H, Hb), 7.64 (s, 1H, Hc), 7.68–7.70 (d, *J* = 8.7 Hz, 2H, 2×Hd), 7.77 (s, 1H, C–H, oxazepine), 7.83–7.85 (d, *J* = 8.5 Hz, 2H, 2×He), 7.99–8.09 (m, 3H, Hf; Hg; Hh), 9.32 and 9.36 (ss, 2H, 2×N–H, thione forms), 10.39 (s, 1H, O–H); Anal. calcd. for $C_{25}H_{14}N_8O_7S_3$: C, 47.32; H, 2.22; N, 17.66; S, 15.16; Found C, 47.64; H, 2.15; N, 17.96; S, 15.07.

General procedure for the synthesis of oxadiazolic-tetrazoles 4e and 5e: A mixture of imine derivative **3a** (0.458 g, 1 mmol) or imine derivative **3b** (0.441 g, 1 mmol) and sodium azide (0.065 g, 1 mmol) in tetrahydrofuran (20 mL) was refluxed with stirring on a water bath at 70 °C for 24 h. TLC showed that the reactions were completed. The reaction mixture was then allowed to cool down to room temperature. The solvent was removed by evaporation under reduced pressure and the coloured precipitate was recrystallized from ethanol.

(E)-2-(1-(Benzo[d]thiazol-2-yl)-1H-tetrazol-5-yl)-4-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-phenol (4e): IR (KBr, ν_{max}, cm^{-1}): 3290br ν(O-H), ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2941 and 2877 ν(N-H) intramolecularly hydrogen bonded, thione form, 1597 ν(C=N) tetrazole and ν(C=N) oxadiazole, vib. coupling, 1543 ν(C=C) benzene and ν(C=N) benzothiazole, vib. coupling, 1410 ν(N=N), 1043 ν(C=S) thione form, 840 and 748 $\delta_{o.o.p}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.34 (H_2O in DMSO), 3.76 (s,1H, S-H), 6.99–7.73 (Ar–H), 6.99–7.01 (t, *J* = 5.1 Hz, 1H, Ha), 7.05–7.08 (t, *J* = 7.4 Hz, 1H, Hb), 7.19 (s, 1H, Hc), 7.23–7.24 and 7.26–7.28 (dd, *J* = 3.4, 7.7 Hz, 2H, Hd; He), 7.45–7.47 (d, *J* = 8.0 Hz, 1H, Hf), 7.52–7.54 (d, *J* = 8.4 Hz, 2H, 2×Hg), 7.64–7.66 (d, *J* = 8.2 Hz, 2H, 2×Hh), 7.71–7.73 (d, *J* = 9.7 Hz, 1H, Hi), 8.60 (s, N–H, thione form), 9.36 (s, 1H, O–H); Anal. calcd. for $C_{22}H_{13}N_9O_2S_2$: C, 52.90; H, 2.62; N, 25.24; S, 12.84; Found C, 53.23; H, 2.54; N, 25.41; S, 12.62.

(E)-4-((4-(5-Mercapto-1,3,4-oxadiazol-2-yl)phenyl)-diazenyl)-2-(1-(5-mercapto-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-yl)phenol (5e): IR (KBr, ν_{max}, cm^{-1}): 3259br ν(O-H), ν(N-H) thione form and ν(C-H) benzene, vib. coupling, 2941 and 2881 ν(N-H) intramolecularly hydrogen bonded, thione form, 1591 ν(C=N) tetrazole and ν(C=N) oxadiazole, vib. coupling, 1506 ν(C=C) benzene and ν(C=N) thiadiazole, vib. coupling, 1400ss ν(N=N), 1028 ν(C=S) thione form, 837 and 742 $\delta_{o.o.p}$(C-H) benzene; ^{1}H NMR: δ = 2.51 (DMSO solvent), 3.29 (H_2O in DMSO), 3.60 and 3.71 (ss, 2H, 2×S-H), 7.18–7.71 (Ar–H), 7.18 (s, 1H, Ha), 7.42–7.44 (d, *J* = 8.5 Hz, 1H, Hb), 7.51–7.53 (d, *J* = 8.1 Hz, 1H, Hc), 7.67–7.68 and 7.70–7.71 (dd, *J* = 3.7, 6.7 Hz, 4H, 2×Hd; 2×He), 8.45 and 8.70 (ss, 2×N–H, thione forms), 9.36 (s, 1H, O–H); Anal. calcd. for $C_{17}H_{10}N_{10}O_2S_3$: C, 42.32; H, 2.09; N, 29.03; S, 19.94; Found C, 42.55; H, 2.01; N, 29.22; S, 19.80.

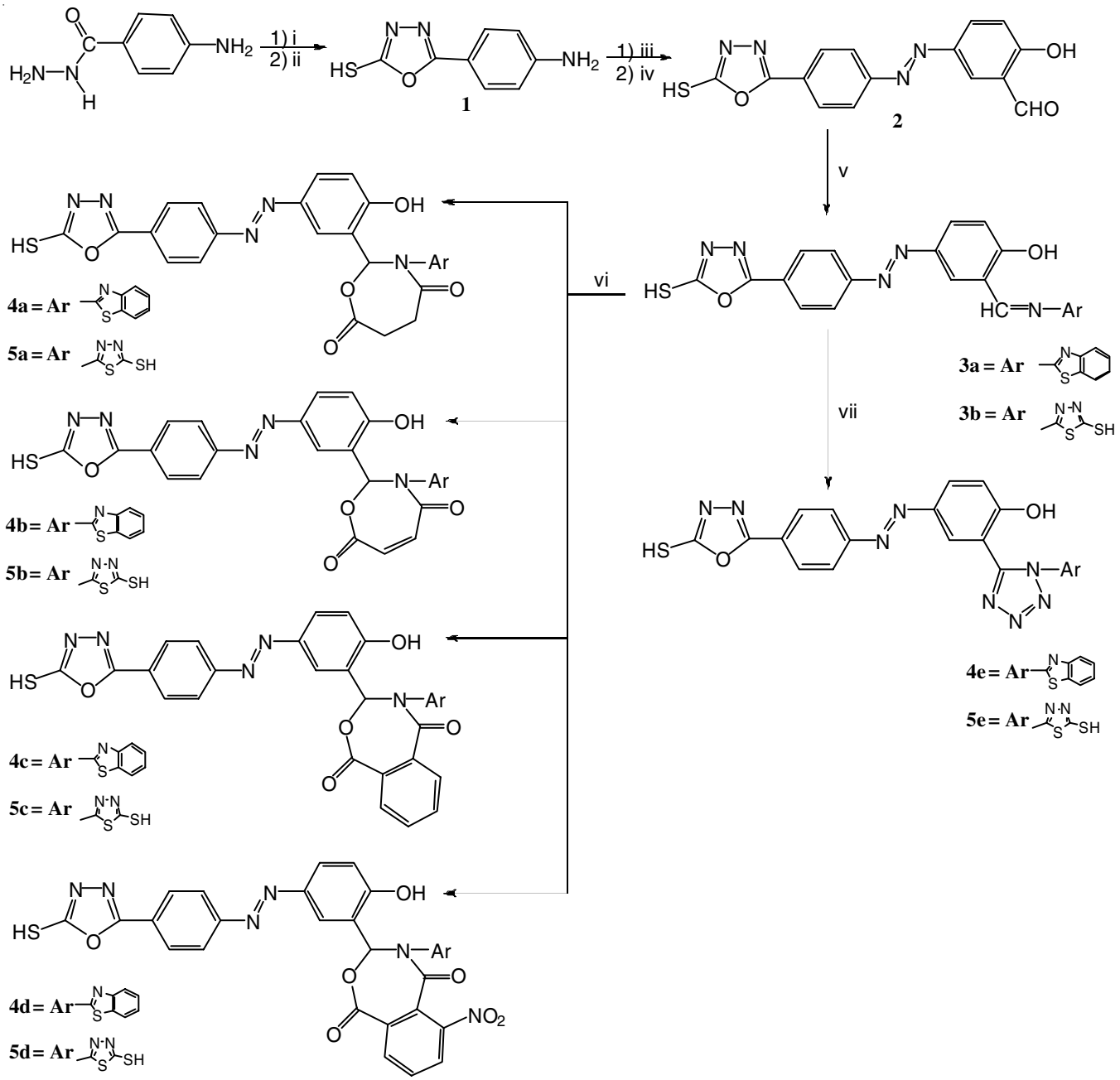
RESULTS AND DISCUSSION

4-Aminobenzoic hydrazide was converted to 5-(4-aminophenyl)-2-thiol-1,3,4-oxadiazole (**1**) by treating it with carbon disulfide in presence of potassium hydroxide as catalyst in absolute ethanol [26]. Diazotization of amino group in compound **1** using sodium nitrite and hydrochloric acid generated the corresponding diazonium salt which was directly introduced in coupling reaction with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution to give azo-oxadiazole derivative (**2**) containing aldehyde group [27]. Aldehyde group of azo-oxadiazole derivative (**2**) was condensed with two selected amines including 2-aminobenzothiazole (ABT) and 2-amino-5-mercapto-1,3,4-thiadiazole (AMT) in the presence of glacial acetic acid as catalyst in absolute ethanol to yield the azo-imine derivatives of 1,3,4-oxadiazole (**3a** and **3b**), respectively (**Schemes I** and **II**). A concerted reactions involving (2+5) cycloadditions of imine group of oxadiazolic-imines (**3a** and **3b**) with succinic acid, maleic acid, phthalic acid and 3-nitrophthalic anhydrides, as five-membered components, in dry benzene at 70 °C for 24 h gave the seven-membered 1,3-oxazepane and 1,3-oxazepine derivatives of 1,3,4-oxadiazole **4a-d** and **5a-d**, respectively in good yields (Table-1). Moreover, a concerted reactions involving the (2+3) cycloadditions of imine group of the oxadiazolic-imines (**3a** and **3b**) with sodium azide in tetrahydrofuran at 70 °C for 24 h afforded 1,5-disubstituted tetrazole derivatives of 1,3,4-oxadiazole **4e** and **5e**, respectively in good yields (Table-1).

The chemical structures of the target compounds synthesized were deduced from IR, ^{1}H NMR spectral measurements

TABLE-1
PHYSICAL PROPERTIES OF THE SYNTHESIZED COMPOUNDS

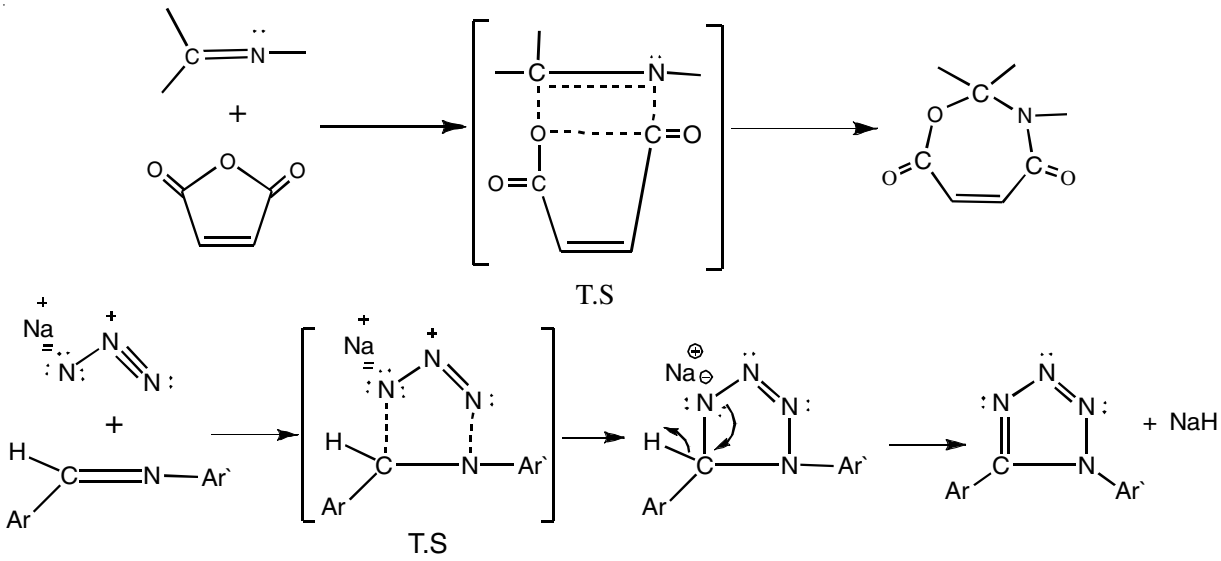
Product	Physical state	R_f (developer)	m.p. (°C)	Weight (g)/Yield (%)
3a	Orange solid	0.75 (*n*-hexane/EtOAc, 3:1)	238-240	1.626/71
3b	Red solid	0.84 (*n*-hexane/EtOAc, 2:1)	251-252	1.698/77
4a	Orange solid	0.52 (*n*-hexane/EtOAc, 1:1)	260-262	0.452/81
4b	Orange solid	0.49 (*n*-hexane/EtOAc, 1:1)	243-245	0.440/79
4c	Red solid	0.46 (*n*-hexane/EOAc, 1:1)	252-254	0.436/72
4d	Red solid	0.40 (*n*-hexane/EtOAc, 1:1)	264-266	0.508/78
4e	Light purple solid	0.50 (*n*-hexane/EtOAc, 1:1)	153-155	0.374/75
5a	Dark orange solid	0.68 (*n*-hexane/EtOAc, 1:1)	176-178	0.444/82
5b	Dark Orange solid	0.66 (*n*-hexane/EtOAc, 1:1)	183-185	0.431/80
5c	Dark orange solid	0.61 (*n*-hexane/EtOAc, 1:1)	231-233	0.418/71
5d	Red solid	0.55 (*n*-hexane/EtOAc, 1:1)	240-242	0.488/77
5e	Dark purple solid	0.60 (*n*-hexane/EtOAc, 1:1)	135-137	0.395/82



Scheme-I: Synthesis of 1,3,4-oxadiazoles, Reagents and conditions (i) CS_2, KOH, EtOH, 70 °C, 7 h; (ii) Conc. HCl; (iii) $NaNO_2$, HCl, 0-5 °C; (iv) 2-hydroxybenzaldehyde, NaOH 10 %, 5 °C; (v) ABT or AMT, EtOH, 70 °C, 11 to 9 h, respectively; (vi) succinic acid or maleic acid or phthalic acid or 3-nitrophthalic anhydrides, dry benzene, 70 °C, 24 h; (vii) NaN_3, THF, 70 °C, 24 h

and (CHNS) elemental analysis and were in good agreement with the proposed structures.

The IR and ^{1}H NMR spectra of the desired compounds **4a-e** and **5a-e** were described previously. The IR spectrum of oxadiazole derivative (**1**) showed the disappearance of the sharp doublet band for hydrazide group (-NHNH$_2$) at (3307, 3236) cm^{-1} and the strong band at 1627 cm^{-1} due to (C=O) str., additionally the appearance of the following characteristic bands: the doublet band at 3448 and 3352 cm^{-1} assigned to (-NH$_2$) str. that substituted in benzene ring, the strong band at 1604 cm^{-1} attributed to the oxadiazolic (C=N) str. and (-NH$_2$) bend. due to the vibration coupling interaction. The weak and strong bands at 2590 and 1068 cm^{-1} belong to (S-H) str. and (C=S) str. in thioenol and thioketone forms, respectively. The IR spectra of azo-oxadiazole derivative (**2**) indicated the absence of a doublet band at 3448 and 3352 cm^{-1} for (-NH$_2$) str. and appearance of the following characteristic bands: the weak band at 1411 cm^{-1} attributed to azo group (N=N) str., the broad band at 3402 cm^{-1} assigned to (O-H) str., the sharp-strong band at 1662 cm^{-1} belong to aldehydic (C=O) str., the oxadiazolic (C=N) str. appeared as weak band at 1604 cm^{-1} due to disappearance of the bending vibration of (-NH$_2$) group. IR spectra of oxadiazolic-imines (**3a** and **3b**) showed the disappearance of the sharp-strong band at 1662 cm^{-1} for aldehydic (C=O) str., also disappearing the sharp doublet band for (-NH$_2$) str. in 2-aminobenzothiazole and 2-amino-5-mercapto-1,3,4-thiadiazole at (3398, 3273) cm^{-1} and (3336, 3267) cm^{-1}, respectively and appearance of sharp-strong band



Scheme-II: Proposed mechanisms for the addition of cyclic anhydrides and sodium azide to imine

at 1604 and 1602 cm^{-1}, respectively, attributed to iminic and oxadiazolic (C=N) str. due to the vibration coupling interaction. The IR spectra of the oxadiazolic-oxazepanes and oxazepines (**4a-d** and **5a-d**) showed the appearance of one or two bands at the range 1718-1653 cm^{-1} attributed to the stretching vibrations of carbonyl groups (N-C=O and O-C=O) of the oxazepane and oxazepine rings. The spectra also showed the disappearance of the sharp-strong band at 1604 and 1602 cm^{-1} for iminic (C=N) str. and appearance of weak-medium band at the range 1608-1600 cm^{-1} assigned to oxadiazolic (C=N) str. The IR spectra of the oxadiazolic-tetrazoles **4e** and **5e** showed the absence of the sharp-strong band at 1604 and 1602 cm^{-1} for iminic (C=N) str. and appearance of medium band at 1597 cm^{-1} and 1591 cm^{-1}, respectively assigned to tetrazolic and oxadiazolic (C=N) str. due to the vibration coupling interaction.

The structures of oxazepane and oxazepine compounds **4a-d** were established by their ^{1}H NMR spectra (400 MHz, DMSO-d_6) which showed the phenolic (O-H) proton as a singlet at δ 10.39, 10.39, 10.39 and 10.38 ppm, respectively. The spectra of oxazepine compounds **4b-d** appeared (N-H) proton for thione form as a singlet at 9.39, 9.60 and 9.44 ppm, respectively, while spectrum of oxazepane compound **4a** showed both (S-H) and (N-H) protons for thiol and thione forms as a singlet signals at δ 2.90 and 9.40 ppm, respectively and two triplets at δ 2.58-2.62 (J = 6.8 Hz, 2H) and 2.73–2.76 (J = 6.9 Hz, 2H) ppm assigned to methylene groups protons (CH_2–CO–O) and (CH_2–CO–N) of the oxazepane ring, respectively. The C-H proton of oxazepane and oxazepine rings in compounds **4a-d** appeared as singlet at δ 7.64, 7.48, 7.47 and 7.76 ppm, respectively. Moreover, the olefinic (=CH) protons of the oxazepine ring in compound **4b** appeared as singlet at 6.10 ppm. The signals of aromatic protons (Ar–H) of compounds **4a-d** appeared at δ 6.98-8.26 ppm. The structures of the prepared oxazepane and oxazepine compounds **5a-d**, were confirmed by their ^{1}H NMR spectra which appeared singlet signal at δ 10.39 ppm belong to the phenolic (O-H) proton. The spectra of oxazepine compounds **5b-d** showed two singlet signals at δ (9.39, 9.40), (9.44, 9.48) and (9.32, 9.36) ppm for two (N-H) groups protons in thione forms, while spectrum of oxazepane compound **5a** showed (N-H) protons for thione forms as singlet at 9.54 ppm and (S-H) protons for thiol forms as a singlet signals at δ 2.86 and 2.90 ppm, respectively, also the triplet at δ 2.57-2.60 ppm (J = 5.0 Hz, 2H) assigned to methylene group protons (CH_2–CO–O), the doublet signal at 2.73-2.74 ppm (J = 5.4 Hz, 2H) belong to methylene group protons (CH_2–CO–N) of the oxazepane ring. The singlet signal for (C-H) proton of the oxazepane and oxazepine rings in compounds **4a-d** appeared at δ 7.81, 7.51, 7.78 and 7.77 ppm, respectively; additionally the olefinic (=CH) protons of the oxazepine ring in compound **4b** showed doublet at 6.64–6.67 (J = 11.8 Hz, 2H). The (Ar–H) protons of compounds **5a-d** appeared at **δ** 7.12-8.10 ppm and were described in details in the experimental section. It should be noted that the ^{1}H NMR spectra of compounds **4a-d** and **5a-d** showed the (C-H) proton in the oxazepane and oxazepine rings at lower field due to the high deshielding affect caused by oxygen and nitrogen atoms.

Moreover, the (CHNS) elemental analysis results were all in good agreement with the proposed chemical structures for compounds **4a-d** and **5a-d**.

^{1}H NMR spectra of the synthesized tetrazoles **4e** and **5e** showed the (O-H) proton as a singlet at **δ** 9.36 ppm. The (N-H) and (S-H) protons for thioketone and thioenol forms in compound **4e** as a singlet signals at δ 8.60 and 3.76 ppm, respectively, while in compound **5e** the two singlets at **δ** 8.45 and 8.70 ppm assigned to two (N-H) groups protons found in two thione forms, also the two singlets at **δ** 3.60 and 3.71 ppm attributed to two (S-H) groups protons present in two thiol forms. The (Ar–H) protons of compounds **4e** and **5e** appeared at **δ** 6.99-7.73 ppm.

Elemental analysis results were within ± 0.4 % of the theoretical values and in good agreement with the proposed chemical structures for compounds **4e** and **5e**.

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