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RESEARCH ARTICLE

Synthesis and Preliminary Antibacterial Activities of New 2, 3-Disubstituted-1, 3-Oxazepane-4, 7-Diones of Benzothiazole

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Abstract

2-aminobenzothiazole **1** was converted to analogues diazonium salt which reacted with alkaline solution of 2-hydroxybenzaldehyde to yield azo-benzothiazole derivative **2** bearing aldehyde group. The resulting aldehyde **2** was then condensed with some aromatic amines including (4-nitroaniline, 3-nitroaniline, 4-aminophenol, 4-methoxyaniline, 4-bromoaniline, 4-chloroaniline and 2, 4-dichloroaniline) using microwave irradiation technique in absolute ethanol to produce seven imine derivatives of benzothiazole **3a-g**, respectively**.** Treatment of the resulting imines **3a-g** with succinic anhydride using microwave irradiation in dry benzene afforded seven new 1, 3-oxazepane-4, 7-diones **4a-g** bearing the benzothiazole moiety, respectively. Preliminary *in vitro* antibacterial activity of the target compounds were investigated using two types of bacteria, *Staphylococcus aurous* (Gram-positive) and *Escherichia coli* (Gram-negative). The results indicated that all oxazepane compounds exhibited better activity to gentamycin against Gram-positive bacteria. On the other hand, the oxazepane compounds **(4a**, **4e** and **4g)** showed greater activity against Gram-negative bacteria when compared with that of the control drug.

Keywords: *Benzothiazoles; Oxazepanes; Imines; Azo; Antibacterial activity.*

Introduction

Heterocyclic seven-membered ring constitutes the core or a key fragment of a number of bioactive compounds including isolated from natural products [1], oxazepines are a well-known class of seven-membered heterocycles with two heteroatoms (oxygen and nitrogen) [2]. Oxazepine compounds have medical and biological importance and they have medicinal [3, 4] and pharmaceutical applications [5].

Some oxazepine derivatives are considered a medical drug against the disease [6] and some of them act as inhibitors of some enzymes action [7].Fused oxazepinone derivatives have attracted considerable attention owing to their promising biological activities [8], such as antihistaminic [9], anti-HIV [10], antidepressant [11], and antitumor activities [12]. Asendin (Amoxapine) drug is used as antidepressant [13] and active drug for schizophrenia [14]. Benzothiazoles have been studied and found to have various chemical reactivity, biological and pharmacological activities such as anti-bacterial [15] and anti-fungal [16]. Benzothiazole nucleus containing molecules are also reported as anti-diabetic [17], anti-tumor [18], and anti-inflammatory [19]. Thus, in this article, we reported here the synthesis of new 2, 3-disubstituted-1, 3-oxazepine-4, 7-dione derivatives bearing the biologically active benzothiazole moiety which might have some biological activities.

Experimental

General

The chemicals were used as provided from Fluka, sigma Aldrich and Merck. 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 vapor. 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 INOVA 500 MHz varian, USA NMR spectrometer in DMSO-d_6 as solvent and TMS as an internal standard at University of Tehran, Iran. (CHNS) Analyses were deduced with Perkin Elmer 300A at University of Tehran, Iran.

Chemical Methods

***(E)*-5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxy benzaldehyde (2)** was prepared following the method described by Acton [20] as a dark brown solid, mp 141-143 ^{o}C, yield 53 %; IR (cm^{-1}): 3217 (vO-H), 3119 (vC-H, benzene), 2912 and 2739 (vC-H, aldehyde), 1656 (vC=O, aldehyde), 1608 (vC=N, benzothiazole), 1577, 1523 and 1464 (vC=C, benzene), 1433(vN=N), 758 (δo.o.p.C-H, benzene).

General Procedure for the Preparation of Imines 3a-g:

The aldehyde derivative **2** (0.283 g, 1 mmol), suitable aromatic amines (1 mmol) and absolute ethanol (1 mL) were placed in crucible. The reaction mixture was irradiated in a domestic microwave oven at (300-350W) for (30-35 min). TLC (*n*-hexane: EtOAc, 1:2) showed end of reactions. Recrystallization of crude yields was carried out using ethanol.

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E)-)((4-nitrophenyl)imino)methyl)phenol (3a):

IR **(**cm^{-1}): **(**cm^{-1}): 3352 and 3215 (vO-H), 3070 (vC-H, benzene), 1624 (vC=N, imine), 1595 (vC=N, benzothiazole), 1527 (vC=C, benzene), 1494 (vas.NO_2), 1442 (vN=N), 1305 (vs.NO_2), 752 (δo.o.p.C-H, benzene).

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E) ((3-nitrophenyl) imino) methyl) phenol (3b):

IR **(**cm^{-1}): 3321 (vO-H), 3082 (vC-H, benzene), 1614 (vC=N, imine and vC=N, benzothiazole, vib. coupling), 1525 (vas.NO_2), 1473 (vC=C, benzene), 1442 (vN=N), 1346 (vs.NO_2), 748 (δo. o.p. C-H, benzene).

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E) ((4-hydroxyphenyl) imino) methyl) phenol (3c):

IR **(**cm^{-1}): 3396 (vO-H), 3068 (vC-H, benzene), 1614 (vC=N, imine and vC=N, benzothiazole, vib. coupling), 1512 and 1454 (vC=C, benzene), 827 (δo.o.p.C-H, benzene).

4-((E)- benzo[d] thiazol- 2- yldiazenyl)-2-((E) ((4-methoxyphenyl) imino) methyl) phenol (3d)

IR **(**cm^{-1}): 3294 (vO-H), 3061 (vC-H, benzene), 2949 (vasC-H, OCH_3), 2837 (vsC-H, OCH_3), 1614 (vC=N, imine and vC=N, benzothiazole, vib. coupling), 1512 and 1448 (vC=C, benzene), 1402 (vN=N), 821 (δo.o.p.C-H, benzene).

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E) ((4-bromophenyl) imino) methyl) phenol 3e:

IR **(**cm^{-1}): 3402 (vO-H), 3051 (vC-H, benzene), 1604 (vC=N, imine and vC=N, benzothiazole, vib. coupling), 1550 and 1504 (vC=C, benzene), 1427 (vN=N), 746 (δo.o.p.C-H, benzene).

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E) ((4-chlorophenyl) imino) methyl) phenol (3f):

IR **(**cm^{-1}): 3427 (vO-H), 3059 (vC-H, benzene), 1612 (vC=N, imine and vC=N, benzothiazole, vib. coupling), 1541 and 1491 (vC=C, benzene), 1421 (vN=N), 748 (δo.o.p.C-H, benzene).

4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E) ((2, 4-dichlorophenyl) imino) methyl) phenol (3g)

IR **(**cm^{-1}): 3394 (vO-H), 3063 (vC-H, benzene), 1616 (vC=N, imine), 1589 (vC=N, benzothiazole), 1529 and 1477 (vC=C, benzene), 1438 (vN=N), 756 (δo.o.p.C-H, benzene).

General Procedure for the Preparation of 1, 3-oxazepane-4, 7-diones 4a-g:

Compounds **4a**–**g** (1 mmol), succinicic anhydride (0.1 g, 1 mmol) and benzene (1 mL) were mixed and irradiated in microwave oven at (300-460W) for (60-70 min). TLC (*n*-hexane: EtOAc, 1:1) showed end of reactions. The crude yield was recrystallized from ethanol.

2-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-(4-nitrophenyl)-1,3-oxazepane-4, 7-dione (4a):

IR **(**cm^{-1}): 3207 (vO-H), 3076 (vC-H, benzene), 1714 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1595 (vC=N, benzothiazole), 1516 (vas.NO_2 and vC=C, benzene, vib. coupling), 1444 (vN=N), 1336 (vs.NO_2), 752 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm)

=□2.49 (DMSO), 2.81 (s, 4H, CH_2-CH_2, oxazepane), 3.45 (HOD), 7.20–8.36 (m, 12H, Ar–H and C–H, oxazepane), 8.56 (s, 1H, O–H); Anal. Calcd. For $C_{24}H_{17}N_5O_6S$: C, 57.25; H, 3.40; N, 13.91; S, 6.37 Found C, 57.62; H, 3.37; N, 13.53; S, 6.6 9.

2-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-(3-nitrophenyl)-1,3-oxazepane-4,7-dione (4b)

IR (cm^{-1}): 3263 (vO-H), 3080 (vC-H, benzene), 1714 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1597 (vC=N, benzothiazole), 1527 (vas.NO_2), 1477 (vC=C, benzene), 1438 (vN=N), 1346 (vs.NO_2), 746 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.50 (DMSO), 2.81 (s, 4H, CH_2–CH_2, oxazepane), 3.44 (HOD), 7.76–8.28 (m, 12H, Ar–H and C–H, oxazepane), 8.85 (s, 1H, O–H); Anal. Cal. cd. For $C_{24}H_{17}N_5O_6S$: C, 57.25; H, 3.40; N, 13.91; S, 6.37 Found C, 56.97; H, 3.66; N, 13.53; S, 6.76.

2-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-(4-hydroxyphenyl)-1,3-oxazepane-4,7-dione (4c):

IR (cm^{-1}): 3261 (vO-H), 3068 (vC-H, benzene), 1699 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1604 (vC=N, benzothiazole), 1512 and 1477 (vC=C, benzene), 829 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.49 (DMSO), 2.73 (s, 4H, CH_2–CH_2, oxazepane), 3.45 (HOD), 6.82–7.95 (m, 12H, Ar–H and C–H, oxazepane), 8.04 and 8.11 (s, 2H, 2×O–H); Anal. Calcd. for $C_{24}H_{18}N_4O_5S$: C, 60.75; H, 3.82; N, 11.81; S, 6.76 Found C, 60.37; H, 3.45; N, 11.42; S, 7.16.

2- (5-(benzo[d]thiazol- 2-yldiazenyl)- 2-hydroxyphenyl)- 3- (4-methoxyphenyl)-1,3-oxazepane-4, 7-dione (4d):

IR (cm^{-1}): 3462 (vO-H), 3072 (vC-H, benzene), 2941 (vasC-H, OCH_3), 2837 (vsC-H, OCH_3), 1707 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1608 (vC=N, benzothiazole), 1510 and 1462 (vC=C, benzene), 1437 (vN=N), 831 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.50 (DMSO), 2.75 (s, 4H, CH_2–CH_2, oxazepane), 3.45 (HOD), 3.77 (s, 3H, O–CH_3), 7.00–8.13 (m, 12H, Ar–H and C–H, oxazepane), 8.20 (s, 1H, O–H); Anal. Calcd. for $C_{25}H_{20}N_4O_5S$: C, 61.47; H, 4.13; N, 11.47; S, 6.56 Found C, 61.08; H, 3.75; N, 11.09; S, 6.17.

2-(5-(benzo[d] thiazol- 2- yldiazenyl)- 2-hydroxyphenyl)-3- (4-bromophenyl)-1,3-oxazepane-4,7-dione (4e):

IR (cm^{-1}): 3255 (vO-H), 3063 (vC-H, benzene), 1710 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1599 (vC=N, benzothiazole), 1533 and 1485 (vC=C, benzene), 1440 (vN=N), 821 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.49 (DMSO), 2.77 (s, 4H, CH_2–CH_2, oxazepane), 3.43 (HOD), 7.23–8.18 (m, 12H, Ar–H and C–H, oxazepane), 8.20 (s, 1H, O–H); Anal. Calcd. for $C_{24}H_{17}N_4O_4SBr$: C, 53.64; H, 3.19; N, 10.43; S, 5.97 Found C, 54.03; H, 3.04; N, 10.03; S, 6.31.

2-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-(4-chlorophenyl)-1,3-oxazepane-4,7-dione (4f):

IR (cm^{-1}): 3257 (vO-H), 3066 (vC-H, benzene), 1712 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1533 and 1492 (vC=C, benzene), 1438 (vN=N), 750 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.49 (DMSO), 2.77 (s, 4H, CH_2–CH_2, oxazepane), 3.44 (HOD), 7.29–8.13 (m, 12H, Ar–H and C–H, oxazepane), 8.24 (s, 1H, O–H); Anal. Calcd. for $C_{24}H_{17}N_4O_4SCl$: C, 58.48; H, 3.48; N, 11.37; S, 6.50 Found C, 58.10; H, 3.12 N, 10.97; S, 6.88.

2- (5- (benzo[d]thiazol- 2- yldiazenyl)- 2-hydroxyphenyl)- 3- (2, 4-dichlorophenyl)-1, 3- oxazepane- 4, 7-dione (4g):

IR (cm^{-1}): 3406 and 3215 (vO-H), 3068 (vC-H, benzene), 1716 (vC=O, O=C-O and O=C-N, oxazepane, vib. coupling), 1587 (vC=N, benzothiazole), 1537 and 1473 (vC=C, benzene), 1446 (vN=N), 754 (δo.o.p.C-H, benzene); ^{1}H NMR: □□(ppm) =□2.49 (DMSO), 2.82-2.92 (m, 4H, CH_2–CH_2, oxazepane), 3.56 (HOD), 7.24–8.09 (m, 11H, Ar–H and C–H, oxazepane), 8.10 (s, 1H, O–H); Anal. Calcd. for $C_{24}H_{16}N_4O_4SCl_2$: C, 54.66; H, 3.06; N, 10.62; S, 6.08 Found C, 55.03; H, 2.82; N, 11.01; S, 6.39.

Preliminary Antibacterial Assay

The antibacterial activities of the newly synthesized oxazepane-4, 7-diones **4a-g** were determined by the agar diffusion method [21] using representative Gram (+) and Gram (–) bacteria on tryptic soya agar media. The test microorganisms to evaluate the potential antibacterial activity of the newly synthesized oxazepan-4,7-diones were

Staphylococcus aurous (Gram-positive) and *Escherichia coli* (Gram-negative).

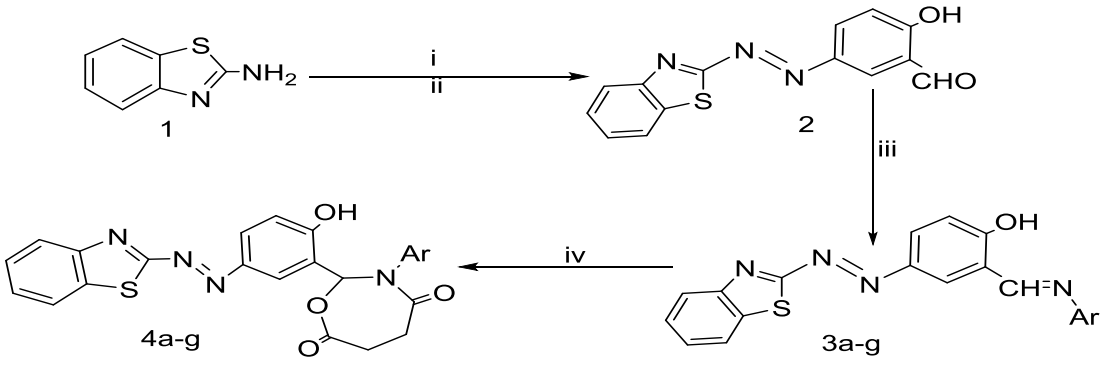
The compounds were dissolved in dimethylsulfoxide to prepare the test solutions of 10 mg/mL concentration. Gentamycin was used as a reference and the activities were presented as zones of inhibition for each compound (Table-2).

Results and Discussion

Chemistry

Diazotization of amino group in 2-aminobenzothiazole **1** using sodium nitrite and sulfuric acid generated the analogues diazonium salt which was reacted with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution to yield azo-benzothiazole derivative **2** bearing aldehyde group [20]. Aldehyde group of benzothiazole derivative **2** was condensed with aromatic amines including (4-nitroaniline, 3-nitroaniline, 4-aminophenol, 4-methoxyaniline, 4-bromoaniline, 4-chloroaniline and 2, 4-dichloroaniline) using microwave irradiation in absolute ethanol to produce seven imine derivatives of benzothiazole **3a-g** respectively, as the platforms for this work (**Scheme-I**).

The (2+5) cycloadditions of imines **3a-g** with succinic anhydride using microwave irradiation in dry benzene afforded the seven-membered 1, 3-oxazepane-4, 7-diones derivatives of benzothiazole **4a-g**, respectively in medium-good yields (Table-1). The chemical structures of the target compounds synthesized were deduced from IR, ^{1}H NMR spectral means and (CHNS) elemental analysis and were in good agreement with the proposed structures.



Ar = 4-$NO_2C_6H_4$-; 3-$NO_2C_6H_4$-; 4-OHC_6H_4-; 4-$OCH_3C_6H_4$-; 4-BrC_6H_4-; 4-ClC_6H_4-; 2,4-$(Cl)_2C_6H_4$-

Scheme-I: Synthesis of 1,3-oxazepane-4,7-diones, Reagents and conditions (i) Conc. H_2SO_4, $NaNO_2$, 0-5 °C; (ii) 2-hydroxybenzaldehyde, NaOH 10% , 5°C; (iii) Ar-NH_2, EtOH, MW (300-350W), (30-35 min); (iv) succinic anhydride, dry benzene, MW (300-460W), (60-70 min)

The IR spectrum of azo-benzothiazole derivative **2** indicated the absence of a doublet band at 3375 cm^{-1} and 3306 cm^{-1} for (NH_2)str and appearance of band at 3217 cm^{-1} assigned to (O-H)str, the strong band at 1656 cm^{-1} belong to (C=O)str, the band at 1433 cm^{-1} attributed to azo group (N=N)str, the band of benzothiazolic (C=N)str. appeared at 1604 cm^{-1}. IR spectra of the benzothiazolic-imines **3a-f** showed disappearing the strong band at 1656 cm^{-1} for aldehydic (C=O)str, also disappearing the doublet band for (-NH_2)str in the starting amines at the general range (3400-3250) cm^{-1} and appearing a band at the range (1604-1624) cm^{-1} assigned to the iminic (C=N)str. The IR spectra of 1,3-oxazepan-4,7-diones **4a-g** showed the absence of the band at the range (1604-1624) cm^{-1} which attributed to the iminic (C=N)str and appearance of strong band at the range 1699-1716 cm^{-1} attributed to the stretching vibrations of carbonyl groups (O=C-N and O=C-O) of the oxazepane ring, also the appearance of a weak band at the range 1587-1608 cm^{-1} assigned to benzothiazolic (C=N)str. The structures of oxazepane compounds **4a-g** were proven by their ^{1}H NMR spectra (500 MHz, DMSO-d_6) which showed the peak for the methylenic (CH_2–CH_2) protons of oxazepane ring as a singlet at δ 2.81, 2.81, 2.73, 2.75, 2.77, 2.77, and 2.88 ppm, respectively. The (Ar-H) protons and (C-H) proton of oxazepane ring around δ 6.82–8.36 ppm. The (O-H) proton as a singlet at 8.56, 8.85,(8.04 and 8.11), 8.20, 8.20, 8.24, and 8.10 ppm, respectively. The methoxy protons (O-CH_3) in compound **4d** appeared as a singlet at δ 3.77 ppm. Moreover, the

(CHNS) elemental analysis results were within ± 0.4% of the theoretical values and in good agreement with the proposed chemical structures for compounds **4a-h** and given in the experimental section.

Antibacterial Activities

The antibacterial activities of the newly synthesized oxazepanes **4a-g** were evaluated by the agar diffusion method [21] using representative standard strains of Gram (+) and Gram (–) bacteria on tryptic soya agar media, as listed in Table-2.

Dimethylsulfoxide was used as solvent for the test compounds. All 1,3-oxazepan-4,7-dione compounds showed better activity than the control drug against Gram- positive bacteria, while compounds **(4a**, **4e** and **4g)** were found to be greater activity than gentamycin against Gram-negative bacteria.

Table 1 :**Physical Properties of the Synthesized Compounds (3a-g) and (4a-g)**

Product	Physical state	R_f (developer)	Mp (°C)	MW (W)	Time (min)	Yield (%)
3a	Brown solid	0.77 (*n*-hexane/ EtOAc, 1:2)	175-177	350	35	66
3b	Dark brown solid	0.68 (*n*-hexane/ EtOAc, 1:2)	145-147	320	30	55
3c	Dark brown solid	0.74 (*n*-hexane/ EtOAc, 1:2)	188-190	350	30	67
3d	Brown solid	0.63 (*n*-hexane/ EtOAc, 1:2)	133-135	300	35	71
3e	Dark brown solid	0.80 (*n*-hexane/ EtOAc, 1:2)	171-173	320	30	70
3f	Brown solid	0.89 (*n*-hexane/ EtOAc, 1:2)	162-164	320	30	76
3g	Brown solid	0.81 (*n*-hexane/ EtOAc, 1:2)	125-127	310	30	60
4a	Brown solid	0.70 (*n*-hexane/ EtOAc, 1: 1)	209-211	400	60	70
4b	Dark brown solid	0.64 (*n*-hexane/ EtOAc, 1: 1)	179-181	400	60	61
4c	Dark brown solid	0.71 (*n*-hexane/ EtOAc, 1: 1)	217-219	460	70	69
4d	Dark brown solid	0.90 (*n*-hexane/ EtOAc, 1: 1)	169-171	400	65	63
4e	Brown solid	0.90 (*n*-hexane/ EtOAc, 1: 1)	189-191	400	70	73
4f	Brown solid	0.72 (*n*-hexane/ EtOAc, 1: 1)	219-221	350	65	80
4g	Dark brown solid	0.93 (*n*-hexane/ EtOAc, 1: 1)	179-181	300	60	71

Table 2 :**The Antibacterial Activity of Compounds 4a-G and Gentamycin as Control Drug**

Product	*Staphylococcus aurous* (Gram-positive)	*Escherichia coli* (Gram-negative)
4a	19	20
4b	16	15
4c	17	14
4d	23	15
4e	27	17
4f	18	13
4g	21	28
DMSO	0	0
Gentamycin	15	15

Conclusions

All synthesized 1,3-Oxazepane-4,7-diones showed greater effect against positive bacteria and some of them (compounds **4a**, **4e** and **4g**) exhibited better activity against negative bacteria than that of control drug.

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