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Synthesis of Novel B-Lactams of Benzothiazole as Antibacterial Agents

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ABSTRACT

Sodium nitrites and sulfuric acids were used to diazotize the amino function of 2-aminobenzothiazole [I]. To produce azo derivative consisting of aldehyde groups, the process of making diazonium salt was directly completed together with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution. Several substituted anilines such as (4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-chloroaniline, 2-chloroaniline, 2, 4-dichloroaniline, and 4-bromoaniline) were used to treat the compound, alongside the use of the technique of microwave irradiation in absolute ethanol so that the imine derivatives were given, correspondingly. The use of the technique of microwave irradiation in dimethylformamide, in the company of cyclization reaction of imines with α-chloroacetyl chloride separately presented new β-lactams of benzoltiazole [IV] a-g. Escherichia coli (Gram-negative) and staphylococcus aurous (Gram-positive) were used to complete the antibacterial activity of β-lactam compounds. The results of the study showed that improved activities to gentamycin against Gram-positive bacteria were displayed by the entire azetidin-2-one compounds. Alternatively, the azetidine-2-one compounds $[IV]_b$and [IV] c demonstrated larger activities against Gram-negative bacteria in comparison with that of the control drug.

Keywords: β-lactams; Benzothiazoles; Schiff bases; Azo; Antibacterial potency.

INTRODUCTION

Heterocyclic compounds are regarded as available and obtainable compounds in nature. Heterocyclic compounds are also considered substantial compounds as they are featured with various physiological activities related to this category of chemical materials(Mathur, 2019). Benzothiazole is a heterocyclic compound known for the diverse biological activities and fragile base, and the continuous scientific importance and interest among scholars and chemists(Venugopala et al., 2019). Benzolhiazoles are extensively used in medical and bioorganic areas of chemistry with various scientific uses and applications in new drug inventions and discoveries(Amnerkar et al., 2015). Several biological activities, namely: anti-diabetic(Chhabra et al., 2016), anthelmintic (Patil et al., 2015), anticancer (Osmaniye et al., 2018), and antimicrobial (Keri et al., 2015)activities.

Developing antibiotics is still one of the most noteworthy scientific improvements in contemporary medicine (Drawz & Bonomo, 2010), (Zaffiri et al., 2012), (Qin et al., 2014), (Bell & MacLean, 2018). Limitless lives are saved by antibiotics making them a constant backbone of treatment and cure from microbial infections such as bacteria (Adediran & Pratt, 2008), (Solensky, 2012),(Lingzhi et al., 2018),(Lima et al., 2020). Since the 1940s, penicillin is one of the antibiotics featured with the availability of azetidin-2-one (β-lactam) structure in the pharmaceutical chemistry arena (Kumar et al., 2013),(Solensky, 2014),(Veiga & Paiva, 2018). The β-lactam (2-azetidinone) ring, one of the highly praised and recently investigated

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heterocycles, speaks of a tale full of coincidence, curiosity, and gravity covering the fields of medicine, biology, and chemistry(Tahlan & Jensen, 2013). The β-lactam (2-azetidinone) ring is famous in the scientific field as it significantly affects the health area at the world level(Pitts & Lectka, 2014). Its fame is traced back to the penicillin discovery by Sir Alexander Fleming and its capability to destroy pathogenic bacteria in 1928 (Holikatti et al., 2014) alongside Dorothy Crowfoot-Hodgkin's use of X-ray crystallography to chemically confirm and validate its structure in 1945 (Banik, 2017).

In 1907, H. Staudinger makes efforts to firstly synthesize the chemistry of azetidin-2-one regarded as a 4-member cyclic amide (Troisi et al., 2009), (Ansari & Lal, 2009). Azetidinones consist of more common types such as β- lactam rings, namely: azetidin-2-ones, and less common types such as azetidin-3-ones (Putra, 2016). This variety in types is an outcome of the fact that they do not normally exist in nature (Haneishi et al., 2014), (Geesala et al., 2016), and (Patel & Bhasin, 2016). B-lactams' non-antibacterial properties together with cholesterol-lowering effects (Jones, 2014), antifungal (McFarland et al., 1995), anticancer (Khdur & Zimam, 2018), and antiviral (Twamley et al., 2020) have recently been of a great interest among chemical researchers. Along with their medical uses as antibacterial agents, b-lactams are used as strongly suitable synthons to prepare numerous compounds of positive biological impact (e.g., side chain of taxol) (Kidwai et al., 2000).

Experimental

General

Sigma Aldrich, Fluka, and Merck were used to provide all the required chemical materials. Silica gel 60 F_{254} plates with iodine vapor as an improver were used to conduct the analytical TLC. With the use of the melting point device of the Electro-thermal Stuart SMP 30 capillary, it was possible to measure several melting points that were found uncorrected points. Infrared spectra were noted as potassium bromide discs on SHIMADZU FTIR–8400S Infrared Spectrophotometer. ^{1}H NMR spectra were collected on INOVA 500 MHz Varian, USA NMR spectrometer in DMSO-d_6 as solvent and TMS as an internal standard at the University of Tehran, Iran. (CHNS) Analyses were also deduced with Perkin Elmer 300A at the University of Tehran in Iran.

METHODS

***(E)*-5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxy benzaldehyde [II]** [31]

The preparation process began with cooling a solution of 2-aminobenzothiazole [I] (8.1 g, 0.054 mol) in H_2SO_4 (15 mL) to 0°C. Along with continuous stirring, one drop at a time of a cold solution of ($NaNO_3$) (3.726 g, 0.054 mol) dissolved in (H_2O) (20 mL) was added as required. With the completion of the needed addition, the new reaction mixture was left in the ice-chest for 1h. Then, one drop at a time of an ice-cold solution of diazonium bisulfate was added to the cold solution of 2-hydroxy benzaldehyde (6.588 g, 0.054 mol) dissolved in (44 mL) of (10% w/v) sodium hydroxide with a continuous shake process. Having the more alkaline solution of phenol derivative led to having a more darkened dark dye. Once again, with the completion of the addition, the new reaction mixture was strongly stirred. After separating a solid out and standing it at room temperature for a period of 30 minutes, it was properly filtered off and completely washed with distilled water. Then, it was essential to collate and recrystallize the precipitated substance from ethanol to produce **[II]** a dark brown solid,

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namely: yield (7.9 g, 52%), m.p. 141-143 ºC.

General procedures to prepare imines [III] $_{a-g}$

To prepare the imines [III] $_{a-g,}$ it was essential to place the aldehyde derivative **[II**] (0.283 g, 1 mmol), suitable aromatic amines (1 mmol), and absolute ethanol (1 mL) in a pot. In a local microwave oven, the reaction mixture was irradiated at (300W) for (40 min). The end of the entire reaction was shown in TLC (*n*-hexane: EtOAc, 1:2), where ethanol was used to recrystallize crude yields.

General procedures to prepare β-lactams [IV] $_{a-g}$

To prepare the imines [III] a-g, it was essential to place the aldehyde derivative [II] (0.283 g, 1 mmol), suitable aromatic amines (1 mmol), and absolute ethanol (1 mL) in pot. In a local microwave oven, the reaction mixture was irradiated at (300W) for (40 min). The end of the entire reactions was shown in TLC (n-hexane: EtOAc, 1:2), where ethanol was used to recrystallize crude yields.

Scheme 1: Synthesis of β-lactams, Reagents and conditions (i) Conc. H_2SO_4, $NaNO_2$, 0 ^oC; (ii) 2-hydroxybenzaldehyde, NaOH 10% , 5^oC; (iii) Ar-NH_2, EtOH, MW (300W), (40 min); (iv) α-chloroacetyl chloride, DMF, MW (300W), (150 min).

Preliminary antibacterial assay

The agar diffusion technique with the use of representative Gram (+) and Gram (–) bacteria on tryptic soy agar media assisted to determine the antibacterial activities of the newly synthesized azetidin-2-one [IV] a-g. *Staphylococcus aurous* (Gram- (+) and *Escherichia coli* (Gram-(-) were the main test microorganisms to assess the possible antibacterial activity of the anew synthesized azetidine-2-one. To prepare the required test solutions of 20 mg/mL concentration, the compounds were dissolved in dimethyl sulfoxide. Table (2) showed the use of a Amoxicillin-clavulanate s a reference and the presentation of activities as zones of inhibition for each compound.

RESULTS AND DISCUSSION

Sodium nitrite and sulfuric acid were used to diazotize 2-aminobenzothiazole **[I]** to produce the analogs diazonium salt reacted with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution to provide azoaldehyde derivative **[II]**. The microwave irradiation in absolute ethanol was used to condense Aldehyde group in compound **[II]** with (4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-chloroaniline, 2-chloroaniline, 2, 4-dichloroaniline, and 4-bromoaniline) to

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produce seven imine derivatives **[III]** $_{a-g}$ correspondingly, being the required platforms for this work (**Scheme 1**). The β-lactam derivatives of benzothiazole **[IV]** $_{a-g}$, respectively in medium-good yields were produced by cyclizing imines **[III]** $_{a-g}$ with α-chloroacetyl chloride with the use of microwave irradiation in dimethylformamide as shown in (Table 1). The synthesized target compounds' chemical structures were extracted from IR, ^{1}H NMR spectral means, and (CHNS) elemental analysis and were in consistent with the suggested structures.

IR spectrum of azoaldehyde compound **[II]** showed the sharp bands' disappearance at 3402 cm^{-1} and 3273 cm^{-1} for (NH_2)str, sharp band's absence belonging to (NH_2) bending at 1643 cm^{-1}, band's appearance at 3277 cm^{-1} assigned to (O-H)str, the strong band at 1654 cm^{-1} due to (C=O)str, the weak band at 1435 cm^{-1} due to azo group (N=N)str, and the benzothiazolic (C=N)str appeared as a weak band at 1587 cm^{-1}. IR spectra of imines **[III]**$_{a-g}$ showed the strong band's disappearance at 1654 cm^{-1} for aldehydic (C=O)str, the doublet band's disappearance for (NH_2)str in the starting amines at the general range (3400-3250) $cm^{-1,}$ and the disappearance of a band at the range (1595-1620) cm^{-1} assigned to imine function (C=N)str. IR spectra of azetidinone compounds **(4a-g)** provided an obvious evidence that the reactions successfully occurred through the appearance of two bands for (C=O) stretching of β-lactam ring; the first at the range (1710-1676 cm^{-1}) while the second at the scope (1678-1643 cm^{-1}) due to the effect of the field between chlorine atom and carbonyl group oxygen atom, as the position of chlorine atom may be up or down of plane of the azetidine ring and thus the π-bond characteristic in carbonyl group (C=O) was changed. Besides, the spectra showed the benzothiazolic (C=N) str at the range (1606-1587 cm^{-1}), while (C=N) str of Schiff bases disappeared. Other bands were listed in the table (3-2).

The β-lactam compounds' structures of [IV] $_{a-g}$ were confirmed by their ^{1}H NMR spectra (500 MHz, DMSO-d_6) indicating a singlet peak for (CH-N) proton of lactam ring at δ 2.72 ppm. The peak of (CH-Cl) proton for lactam ring appeared at δ 2.88 ppm. The signals of (Ar-H) protons were around δ 6.91–8.69 ppm, where the quick exchange with acidic impurities in (DMSO) solvent, the (O-H) proton signal did not appear except in compounds [IV] $_c$ and [IV] $_e$ around δ 10 ppm.

Antibacterial activities

The agar diffusion technique with the use of representative standard strains of Gram (+) and Gram (–) bacteria on tryptic soy agar media was used to assess the antibacterial activities of the anew synthesized azetidine-2-one **[IV]**$_{a-g}$, as itemized in Table 2. Importantly, it was essential to use Dimethylsulfoxide as a solvent for the test compounds.

More importantly, the entire azetidin-2-one compounds indicated a better-quality activity than the control drug against Gram-positive bacteria, Harfard Community compounds **[IV]**$_b$and **[IV]**$_c$ showed a more improved activity Amoxicillin-clavulanate against Gram-negative bacteria**.**

Table 1: Some physical properties of compounds [III] $_{a-g}$ and **[IV]** $_{a-g}$

Product	Physical state	R_f [III](*n*-hexane/ EtOAc, 1:2) R_f [IV](*n*-hexane/ EtOAc, 1:1)	Mp (^{o}C)	Yield (%)
[III]$_a$	Roan hard	0.71	175-177	66
[III]$_b$	Dark roan hard	0.69	145-147	55
[III]$_c$	Roan hard	0.70	137-139	60
[III]$_d$	Roan hard	0.89	162-164	67

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$[III]_e$	Roan hard	0.80	151-153	70
$[III]_f$	Dark roan hard	0.79	125-127	60
$[III]_g$	Roan hard	0.81	171-173	72
$[IV]_a$	Roan hard	0.70	209-211	70
$[IV]_b$	Dark roan hard	0.64	179-181	61
$[IV]_c$	Dark roan hard	0.71	217-219	69
$[IV]_d$	Dark roan hard	0.90	169-171	63
$[IV]_e$	Roan hard	0.90	189-191	73
$[IV]_f$	Roan hard	0.72	219-221	80
$[IV]_g$	Dark roan hard	0.93	179-181	71

Table 2: The antibacterial activities of compounds $[V]_{a-g}$ and Amoxicillin-clavulanate as control drug

Product	*Staphylococcus aurous* (Gram-positive)	*Escherichia coli* (Gram-negative)
$[IV]_a$	0	15
$[IV]_b$	30	19
$[IV]_c$	28	20
$[IV]_d$	30	10
$[IV]_e$	0	0
$[IV]_f$	0	23
$[IV]_g$	0	21
DMSO	0	0
Amoxicillin-clavulanate	15	15

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Table 3: FT-IR data of compounds [III] $_{a-g}$ and [IV] $_{a-g}$ in cm^{-1}

FT-IR bands										
Com. No.	νC=O, lactam, field effect	νC=C, benzene	δo.o.p.C-H benzene	νs.NO2	νN=N	νC-H, benzene and νC-H, lactam, overlapped	νas.NO2 and νC=C, benzene, overlapped	νC=N, imine and νC=N, benzothiazole, overlapped	νC-H, benzene	νO-H
[III]$_a$			752	1303	1444		1494	1595	3064	3362 and 3219
[III]$_b$		1479	752	1348	1433		1527	1614	3072	3350
[III]$_c$		1479	756	1346	1433		1525	1620	3063	3473 , 3381
[III]$_d$		1529 and 1485	752		1446			1614	3057	3257
[III]$_e$		1529	754		1444			1616	3057	3200
[III]$_f$		1523 and 1471	758		1446			1614	3063	3282
[III]$_g$		1575, 1533 and 1479	744		1450			1612	3061	3458
[IV]$_a$	1685 and 1649	1469	756	1307			1539	1606	3063	3412
[IV]$_b$	1676 and 1645	1465	756	1309	1435		1531	1600	3061	3346
[IV]$_c$	1689 and 1649	1518 and 1464	750	1311	1431		1546	1599	3018	3018
[IV]$_d$	1710 and 1678	1525 and 1489	756		1435			1593	3059	3423
[IV]$_e$	1705 and 1643	1525 and 1475	752					1591	3053	3416
[IV]$_f$	1693 and 1656	1525 and 1471	748		1417	2978 br		1600		3387
[IV]$_g$	1685	1529 and 1475	756		1442			1587	3064	3390

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Table 4: (CHNS) Elemental analysis of compounds $[IV]_{a-g}$

Com. No.	Calculated %				Found %			
	C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
$[IV]_a$	57.25	3.40	13.91	6.37	57.62	3.37	13.53	6.6 9
$[IV]_b$	57.25	3.40	13.91	6.37	56.97	3.66	13.53	6.76
$[IV]_c$	60.75	3.82	11.81	6.76	60.37	3.45	11.42	7.16
$[IV]_d$	61.47	4.13	11.47	6.56	61.08	3.75	11.09	6.17
$[IV]_e$	53.64	3.19	10.43	5.97	54.03	3.04	10.03	6.31
$[IV]_f$	58.48	3.48	11.37	6.50	58.10	3.12	10.97	6.88
$[IV]_g$	54.66	3.06	10.62	6.08	55.03	2.82	11.01	6.39

CONCLUSIONS

In a nutshell, the entire synthesized azetidin-2-one diones indicated a better-quality effect against positive bacteria as part of them (compounds **[IV]** $_b$ and **[IV]** showed an enhanced activity against negative bacteria more than that of control drug.

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