Synthesis Some Novel 1,3-Thiazol-2-Amine Derivatives Containing Substituted Β-Lactam Ring and Study Their Antibacterial Activity

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Abstract
This work describes the synthesis of a family of azoles containing β-lactam ring. The 2,5-dimethyl aniline was converted into diazonium salt, which were reacted with 2-aminothiazole under acidic condition to give azo-coupling compound 1. The product was subjected to the Schiff base reaction. Imine group was prepared by the reaction of azo compound with aldehydes (4-hydroxy-3-methoxybenzaldehyde, 2-hydroxy1-1naphthaldehyde, 4-hydroxy-3,5-dimethoxybenzaldehyde, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde, 2-methylbenzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde) under acidic condition to give the products 2-6. β-lactam ring was formed by the cycloaddition reaction of compounds contains imino group with chloroacetyl chloride under basic condition to give desired products 7-11 in good yields. The antibacterial tests were carried out using disk diffusion method and activities were good for some of these compounds.
Keywords: β-Lactam ring, Diazonium salt, Antibacterial

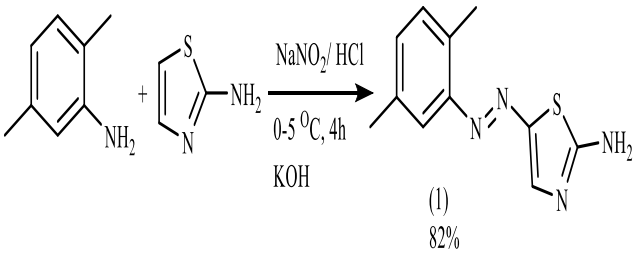
1. Introduction

Azole is an aromatic heterocyclic compound, consists of five members other than carbon atoms, at least one or more such as nitrogen, oxygen and sulfur,1 as it contains two double bonds in it structure of the compound. The thiazole ring system is present in various natural materials, and many thiazole derivatives exhibit a board range of biological activities.2 2-Aminothiazoles are one of the most important classes of heterocycles in the field of pharmaceutical and medicinal chemistry such as antifungal3 insecticidal,4 anesthetic,5,6 radioprotective,7 bactericidal and antiviral8,9 activities. Hugo Schiff reported the first compounds containing azomethine group (-HC=N-) called Schiff base and they are condensation products of ketones (or) aldehydes with primary amines.10 Schiff base with aldehydes are formed more readily than with ketone (carbonyl carbon). A wide range of Schiff base compounds and their behavior were studied because of these compounds have very flexible and diverse structure.11,12 Azo Schiff bases compounds are important intermediates for the synthesis of some application such as biological activity,13,14 catalystical,15 analytical,16 clinical,17,18 anticancer,19 Synthesis of heterocyclic compound has always drawn the attention of chemist over the years mainly because of their important biological properties. Particularly the role of β-lactam which are endowed with unique structure and potent biological activity. Recent years have seen a resurgence of interest in the development of stereo- and enantioselective methodologies. The utility of β-lactam as synthons for various biologically active compounds.20 The β-lactam ring are considered as an important contribution of science to humanity since they have been constituents of living organisms, natural products, drugs and many more substances useful to mankind and society in all walks of life.

2. Results and Discussion

2.1. The Synthesis of Compound 1

To synthesis compound 1, 1.0 equivalent of 2,5-dimethyl aniline was treated with 2-aminothiazole and sodium nitrate in the presence hydrochloric acid as shown in scheme (2-1)21

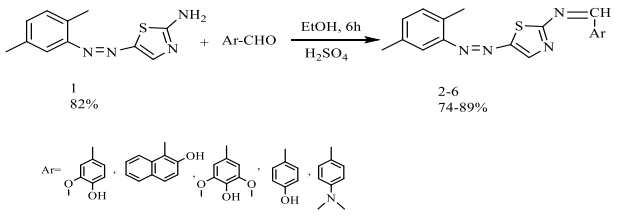


Scheme 1 Diazotization coupling step

The FT-IR spectrum of compound **1** showed the following frequencies, NH_2 stretching band for 2-aminothiazole appeared at (3410 and 3356) cm^{-1}, and two bands at (3039 and 2924) cm^{-1} related to stretching of C-H aromatic and aliphatic respectively, one band appeared at (1674 cm^{-1}) accounted to C=N group and one band at (1496 cm^{-1}) accounted to N=N and two bands at (1589 and 1435) cm^{-1} accounted for stretching of C=C aromatic.
The second step was to prepare the imine group by the reaction of the 1.0 equivalent of compound 1 with 1.0 equivalent of different derivatives of benzaldehyde (4-hydroxy-3-

doi.org/10.31838/hiv22.02.583 Received: 11.04.22, Revised:23.05.22, Accepted: 01.08.22

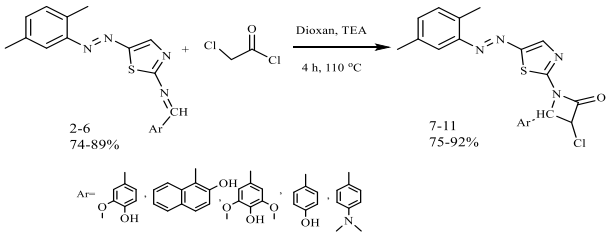
methoxybenzaldehyde,2-hydroxy1-1naphthal dehyde,4-hydroxy-3,5-dimethoxybenzaldehyde,4-hydroxybenzaldehyde) to obtain desired compound 2-6. Starting with amine 1 by dissolving it in ethanol, then aldehydes in ethanol and sulfuric acid H2SO4 were added, the mixture was heated under reflux for 6 hours the desired products was obtained in good yield see scheme 2.



Scheme 2 Condensation reaction for imine group formation

The FT-IR spectrum for compounds 2-6 shows bands in (3032-3039cm-1) related to stretching of C-H aromatic and the bands related to stretch of C=N appeared in the range of (1620-1674 cm-1).

Following the planned strategy for the synthesis of β-lactam ring22–24 compounds 2-6 that contains imine C=N group were treated with chloroacetyl chloride in the presence of TEA, compounds 7-11 were obtained in good yield, see scheme 3



Scheme 3 β-lactam ring formation

The FT-IR spectrum for compounds 7-11 shows bands in (1735-1766 cm-1) related to stretching of the carbonyl group of cyclic amides and the bands related to stretch of C=N appeared in the range of (1651-1689 cm-1). 1H-NMR spectrum for compounds 7-11 showed peaks at (3.46-4.68 ppm) related to 1H of C-Cl. 13C-NMR spectrum for compounds 7-11 showed peaks at (41.5-66.5 ppm) related to 1H of C-Cl.

3. Experimental

3.1. Synthesis of 5-((2,5-dimethylphenyl) diazenyl) thiazol-2-amine (1)

To (5 g, 20 mmol) of 2,5-Dimethyl aniline, HCl was added (2.0 mL) and heated with stirrer to dissolve the largest possible amount. Then the solution is cooled to (0-5 oC) and was added dropwise to an agitated solution of (1.32 g, 20 mmol) sodium nitrate aqueous solution. The resulted diazonium salt was slowly added to the mixture of 2-aminothiazole (20 mmol) in water at (0-5 oC). The colored mixture stirred for 2 hours and the neutralized with base KOH. The formed precipitate was filtered, and washed with ice water, recrystallized from ethanol to obtain compound 1 as a dark red solid (0.19 g, 98%) yield. Molecular formula (C11H12N4S), M.wt = 232.30 g/mol. m.p = 176-178 oC. Rf = 0.37 (Petroleum ether/EtOAc, 4:6). FT-IR (cm-1) υ: 3363, 3032, 2924, 1674, 1589, 1496, 1265 cm-1

3.2. Synthesis of compound 2-7

Compound **1** (2.0 g, 5.2 mmol) was dissolved in 5 mL of ethanol, then 3 drops of conc. sulfuric acid are added to the solution, along with (5.2 mmol) of the required aldehydes and the mixture was stirred for 6 hours, then filtered, and washed three times with cold water, and recrystallized from diethyl ether, the reaction was monitored using TLC.

4-(((5-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) imino) methyl)-2-methoxyphenol **2**

The product was obtained as a red solid (0.15 g, 74%) yield. Molecular formula ($C_{19}H_{18}O_2N_4S$), M.wt = 386 47 g/mol. m.p = 175-177 °C. R_f = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm^{-1}) υ: 3363, 3032, 2924, 1627, 1581, 1504, 1427, 1257 cm^{-1}.

1-(((5-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) imino) methyl) naphthalen-2-ol **3**

The product was obtained as a orang solid (0.18 g, 89%). Molecular formula ($C_{22}H_{18}ON_4S$), M.wt = 386.47 g / mol. m.p = 136-138 °C. R_f = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm^{-1}) υ: 3387, 3039, 2916, 1635, 1589, 1504, 1465, 1257 cm^{-1}.

4-((5-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) imino) methyl)-2,6-dimethoxyphenol **4**

The product was obtained as a brown solid (0.16 g, 82%). Molecular formula ($C_{20}H_{20}O_3N_4S$), M.wt = 396.47 g/mol. m.p = 169-171 °C. R_f = 0.36 (Petroleum ether/EtOAc, 4:6). FT-IR (cm^{-1}) υ: 3336, 3032, 2924, 1627, 1581, 1504, 1427, 1257 cm^{-1}.

4-((4-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) imino) methyl) phenol **5**

The product was obtained as a red solid (0.11 g, 55%). Molecular formula ($C_{18}H_{16}ON_4S$), M.wt = 336.41 g/mol. m.p = 173-175 oC. Rf = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm-1) υ: 3456, 3032, 2924, 1620, 1573, 1496, 1427, 1257 cm-1

4-((4-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) imino) methyl)-N, N-dimethylaniline 6

The product was obtained as a pale brown solid (0.15 g, 76%). Molecular formula ($C_{20}H_{21}N_5S$), M.wt = 363.48 g/mol. m. p = 114-116 °C. R_f = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm^{-1}) υ: 3032, 2924, 1674, 1597, 1512, 1427, 1257 cm^{-1}.

3.3. Synthesis of compound 7-11

The compounds **2-6** (2.5 mmol) was dissolved in 4 mL dioxane in an ice bath and stirred, 0.167 mL TEA was added them 0.12 mL chloroacetyl chloride over 10 minutes. Then ice to the and left for 4 h at a temperature of 100 °C, after which the precipitate is washed well with cold water and recrystallized from ethanol.

3-chloro-1-(5-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl) azetidi n-2-one 7

The product was obtained as a orang solid (0.17 g, 86%). Molecular formula (C21H19O3ClN4S), M.wt = 442.92 g / mol. m.p = 111-113 oC. Rf = 0.36 (Petroleum ether/EtOAc, 4:6). FT-IR(cm-1) υ:3410, 3101, 2924,

1759, 1689, 1597, 1519, 802 cm-1; 1H-NMR (DMSO-d6, 400MHz) δ: 2.03 and 2.21 (2s, 3H, CH3), 3.37 (s, 3H, O-CH3), 4.65 (s, 1H, C-Cl), 6.68 (s, 1H, C-H azole) 7.05–7.38 (m, 6H, Ar); 13C-NMR (DMSO-d6, 125MHz) 16.2-17.3 (CH3 aliphatic),41.5 (C-Cl),116.1-138.2 (Ar), 150.8 (azole C=N), 166.4 (C=O).

3-chloro-1-(5-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl)-4-(2-hydroxynaphthalen-1-yl) azetidin-2-one 8

The product was obtained as a brown solid (0.18 g, 90%) Molecular formula (C24H19O2ClN4S), M.wt = 462.95 g/mol. m.p = 126-128 oC. Rf = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm-1) υ: 3394, 3055, 2924, 1766, 1689, 1589, 1512, 1411, 802 cm-1; 1H-NMR (DMSO-d6, 400MHz) δ: 2.03 and 2.21 (2s, 3H, CH3), 3.27 (s, 1H, C-H), 4.65 (s, 1H, C-Cl), 6.68 (s, 1H, C-H azole) 7.07-8.08 (m, 9H, Ar), 9.98 (s, 1H, O-H); 13C-NMR (DMSO-d6, 125MHz) 16.2-17.3 (CH3 aliphatic), 112.9-138.2 (Ar), 143.90 (azole C=N), 164.42 (C-OH), 193.31 (C=O).

3-chloro-1-(4-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl)-4-(4-hydroxy-3,5-dimethoxybenzyl) azetidin-2-one 9

The product was obtained as red solid (0.16 g, 82%). Molecular formula (C22H21O4ClN4S), M.wt = 472.94 g/mol. m.p = 112-114 oC. Rf = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm-1) υ: 3410, 3101, 2924, 1759, 1689, 1597, 1519, 1411, 802 cm-1; 1H-NMR (DMSO-d6, 400MHz) δ: 2.03 and 2.21 (2s, 3H, CH3), 3.46 (s, 1H, C-H), 4.17 (s,1H, C-Cl), 4.69 (s, 6H, O-CH3), 6.68 (s, 1H, C-H azole), 7.05-8.04 (m, 5H, Ar), 9.99 (s, 1H, O-H); 13C-NMR (DMSO-d6, 125MHz) 15.8-16.2 (CH3 aliphatic), 66.5 (C-Cl), 116.1-138.2 (Ar), 143.8 (azole C=N),150.0-150.6 (O-CH3), 159.4 (C-OH), 166.4 (C=O).

3-chloro-1-(4-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl)-4-(4-hydroxybenzyl) azetidin-2-one 10

The product was obtained as a pale brown solid (0.18 g, 92%). Molecular formula (C20H17O2ClN4S), M.wt = 412.89 g/mol. m.p = 127-129 oC. Rf = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm-1) υ: 3456, 3101, 2924, 1759, 1681, 1597, 1419, 794 cm-1; 1H-NMR (DMSO- d6, 400 MHz) δ: 2.03 and 2.20 (2s, 3H, CH3), 4.19(s, 1H, C-H), 4.68 (s, 1H, C-Cl), 6.69 (s, 1H, C-H azole), 7.05-7.90 (m, 7H, Ar), 10.0 (s, 1H, O-H);13C-NMR (DMSO-d6, 125MHz) 16.2-17.3 (CH3 aliphatic), 59.9 (C-Cl), 116.1-138.2 (Ar), 143.87 (azole C=N), 159.4 (C-OH), 159.4 (C-OH), 169.0 (C=O).

3-chloro-4-(4-(dimethylamino) benzyl)-1-(4-((2,5-dimethylphenyl) diazenyl) thiazol-2-yl) aze tidin-2-one 11

The product was obtained as a red solid (0.15 g, 75%). Molecular formula (C22H22OClN5S), M.wt = 439.96 g / mol. m.p = 188-190 oC. Rf = 0.36 (Petroleum ether / EtOAc, 4:6). FT-IR (cm-1) υ: 3093, 2962, 1766, 1658, 1597, 1519, 1458, 794 cm-1 ; 1H-NMR (DMSO- d6, 400 MHz) δ: 2.06 and 2.22 (2s, 3H, CH3), 3.46 (s, 1H, C-H), 4.68 (s, 6H, 2CH3N), 6.68 (s, 1H, C-H azole), 7.11-8.09 (m, 7H, Ar); 13C-NMR (DMSO-d6, 125 MHz) 15.8-17.1 (CH3), 60.0 (C-Cl), 111.5-138.2 (Ar), 143.8 (azole C=N), 171.6 (C-N), 190.2 (C=O).

4. Antibacterial activity of synthesized compounds:

Biological activity as antibacterial agents of some synthesized compounds were tested against some identified and isolated bacteria, against two gram-positive bacterial isolates (Gr +ve) (Staphylococcus aureus and Staphylococcus epidermidis) and two gram-negative bacterial isolates (Gr -ve) (Klebsiella pneumonia and Escherichia coli), these bacteria were selected because of their importance in the medical field since it causes many diseases and its resistance to many chemical drug and antibiotic. The results in table (1) showed the study of the antibacterial activity of some synthesized compounds in two concentrations (100, 50) mg/mL, which gave moderate to good activity compared to Amoxicillin as standard, the biological activity can be explaining in the following:

For Staphylococcus Aureus: compounds (2, 4, 7, 8, 10) most active on this type of bacteria in concentration of 50 g/mL, the compounds (2, 4, 6, 7, 8, 9,10) gave moderate to good activity against the same bacteria in concentration 100 mg\mL. Staphylococcus epidermidis: compounds (2, 3, 4, 5, 7, 8, 9) most active on this type of bacteria in concentration of 100 gm\ mL. Escherichia coli: compounds (3, 7, 8, 9) most active on this type of bacteria in concentration of 100 mg/mL. Klebsiella pneumonia compounds (3, 5, 7, 8, 9) active on this type of bacteria activity in 100 mg /mL and other concentrations didn't show any activity.

Table (1): Biological values of some synthesized compounds against four bacteria

Zone of			inhibition	(In mm)	
Comp. No	Conc. (mg/mL)	Gram	positive	Gram	negative
		S. aureus	*S. epidermidis*	*K. pneumonia*	*E. coli*
2	50	11	R	R	R
	100	14	12	R	R
3	50	R	R	R	R
	100	R	11	12	15
4	50	11	R	R	R
	100	15	11	R	R
5	50	R	R	R	R
	100	R	11	12	R
6	50	R	R	R	R
	100	12	R	R	R
Amoxicillin	50	R	R	R	R
DMSO	0	0	0	0	0

3. Conclusion

The *β*-lactam ring was successfully synthesized *via* the cycloaddition reaction of imine group and chloroacetyl chloride in basic condition, the yields of the products were good.The results of antibacterial and antifungal shows good activity against selected bacteria and fungi.

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