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Synthesis and Evaluation of Antibacterial Activity of 1,3,4-Thiadiazol Derivatives Containing Banzimidazole Moiety

Moayed S. AL-Jawady, Shahla A.Younis

Department of Chemistry, College of Science, University of Mosul, Iraq

E-mail: algwady59@yahoo.com

Abstract **- 2-Mercaptobenzimidazole (1) was condensed with chloroacetic acid to produce (1H-benzimidazole-2-ylthio) acetic acid (2). The later compound was condensed with thiosemicarbazide to produce 5-[(1H-benzimidazole-2-ylthio) methyl]-1,3,4-thiadiazole-2-amino (3) which condensed with different aromatic aldehydes and isatin to afford Sciff bases (4a-h). The azitidin-2-ones (5a-g) were synthesized by the reaction of Schiff bases (4a-g) with chloroacetyl chloride. The structure of the synthesized compounds was confirmed on the basis of their physical and spectral data.**

Keywords **- Benzimidazole, thiadiazole, biological activity, azitidin-2-one.**

I. INTRODUCTION

The substituted benzimidazole is one of the important heterocyclic compounds which have awide spectrum of biological activity and play an important role in medical field. They are remarkably effective compounds, especially when this nucleus accompanied with thiadiazole moiety [1]. Benzimidazole derivatives were reported to possess a various biological activities such as antimicrobial [2,3], anthelmintic [4], antitumor[5], anti-inflammatory [6],antibacterial and antifungal[7]. There are numerous biological active molecules whose framework includes four and five membered containing heteroatom. Azitidin-2-one skeleton is well established as a key pharmacophore of β-lactam antibiotics. The most widely employed antibacterial agents like penicillin, cephalosporin .....etc have a β-lactam rings [8]. The present work was aimed to plane the synthesis of new 1,3,4-thiadiazole derivatives containing benzimidazole moiety. The reaction of 5-aminothiadiazole group with different aromatic aldehydes or with isatin produce a new Schiff bases as a derivatives (4a-h) led to formation of expected biologically more active compounds. Ring closer of the latest compounds (4a-g) by using chloroacetyl chloride led to produce azitidin-2-one derivatives (5a-g).The present work was aimed to plane the synthesis of new1,3,4-thiadiazole derivatives containing benzimidazole moiety. The reaction of 5-aminothiadiazole group with different aromatic aldehydes or with isatin produce a new Schiff bases as a derivatives (4a-h) led to formation of expected biologically more active compounds. Ring closure of the latest compounds(4a-g)by using chloroacetyl chloride led to produce azitidin-2-one derivatives (5a-g).

II. EXPIMENTAL SETUP

All melting points were determined on Stuard-SMP30 apparatus and are uncorrected. The FTIR spectra were recorded on FTIR.600 brot.tech engneering magement photometer using KBr disc. UV-spectra were obtained using Shiadzu-UV-Vis-160 spectrophotometer using ethanol as a solvent. The 1H-NMR spectra were measured in Gazi Osman Basa University-Turkey, recorded on 400 MHz-Brucker Avance spectrometer, by using TMS as internal standard using DMSO-d_6 as a solvent.

A. Synthesis of (1H-benzimidazole-2-ylthio) acetic acid (2). [9]:

A mixture of 2-mercapto benzimidazole (0.013 mol-2g), potassium hydroxide (0.016 mole-0.9 g) in ethanol (20 ml) was refluxed for 1 hr. After cooling chloro acetic acid (0.013 mol-1.15 g) was added in one portion. The mixture was stirred for 18 hr at room temperature, and then the

reaction mixture was poured into ice-water (100g), and stirred for further 30 min at (0-10 °C). The solid was filtered off, washed thoroughly with water to remove the chloride ion, dried with an air and recrystillized from water to give 80% of the title compound with mp 208-210 °C (Reported 206-208 °C) [9]

B. Synthesis of 5-[(1H-benzimidazole-2-ylthio)methyl]-1,3,4-thiadiazole-2-amine(3)[10]:

To a mixture of compound (2) (0.01 mol-2 g) and thiosemcarbazide (0.01 mol-0.9 g), polyphosphoric acid (25 ml) was added. The mixture was heated on an oil bath at 120 °C for 16hr. After cooling, the mixture was poured on a crushed ice-water with stirring. The mixture was neutralized to (pH-7) by adding concentrated ammonia solution. The precipitate was filtered off, washed with water, dried and recrystillized from ethanol to afforded 90% of white powder, mp (283-285 °C).

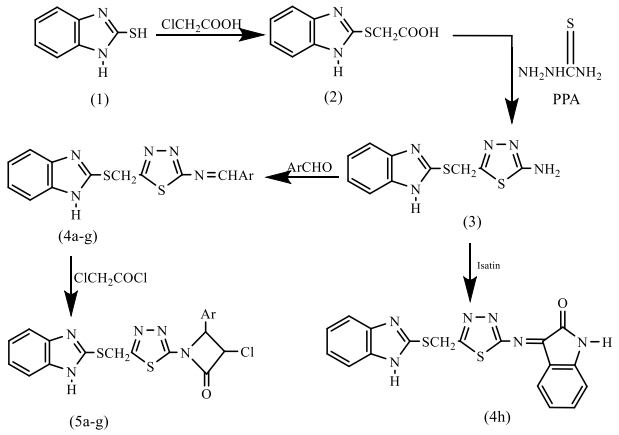
C. Synthesis of 5-[(1H-benzimidazole-2-ylthio)methyl]-N-[(1E)arylidene]-1,3,thiadiazole]-2-amine (4a-g), [11]:

To a mixture of the amino compound (3) (0.01 mol-2.6 g) and an appropriate aromatic aldehyde or isatin (0.01 mol) in methanol (50 ml), 3-4 drops of glacial acetic acid was added. The mixture was refluxed for 3 hr. After cooling, the resulted solid was filtered off, washed with small amount of methanol, dried and recrystalized from ethanol.The physical and spectral data of compounds (4a-g) are listed in tables I ,III & IV.

D.Synthesis of 1-{5-[(1H-benzimidazole-2-ylthio)methyl]-1,3,4-thiadiazole-2-yl}-3-chloro-4-arylazitidin-2-one (5a-g),[12]:To a stirred solution of compound (4a-g) (0.01 mol) in 1,4-dioxane (25 ml), triethylamine (0.01 mol-1ml) and chloroacetyl chloride (0.01 mol-2ml) were added drop wise with stirring at (0-20 °C). The stirring was continued at room temperature for 30 minutes, then refluxed for 5hr. The volatile materials were distilled off and the residue was poured on a crashed ice-water. The resulting solid separated was filtered and recrystallized from ethanol to give the corresponding compounds (5a-g). The physical and spectral data are listed in tables II and V.

III.RESULTS AND DISSCSION

The first synthon in this research is (1H-benzimidazole-2-ylthio) acetic acid (2) which is synthesized via the reaction of the 2-mercapto benzimidazole (1) with chloro acetic acid under basic conditions [13].The compound (2) was converted to 5-[(1H-benzimidazole-2-ylthio)methyl]-1,3,4-thiadiazole (3) by its reaction with thiosemicarbazide under the influence of PPA, at 120 °C for 16 hr. This method gave more than 80% yield, in contrast to the [14] methods which gave low yield.



Scheme

The structure of compound (3) was confirmed on the basis of the spectral data. The IR spectrum showed the following characteristic absorption bands: at 1626 cm^{-1} for the C=N band stretching, at 3116 cm^{-1} for the N-H band stretching and at 899 cm^{-1} related to the C-S band stretching, the ^{1}H-NMR spectrum showed the following chemical shifts (δ): a singlet band for two protons at 4.0 ppm the CH_2protons, a singlet band for two protons at 4.8 ppm for NH_2protons, a singlet band for one proton at 12.5 ppm related to NH protone and multiplet band for four protons at 6.9-7.5 ppm for the aromatic protons. The UV spectrum showed absorption band at λmax (318) nm attributed to the n→π* electronic transition.All products were characterized by physical and spectral data. The IR spectra for compounds (4a-f) showed characteristic absorption peak in the region (1643-1655 cm^{-1}) stretching for (C=O amide) group , at (1581-1616 cm^{-1}) stretching

group for (C=N) group , (3022-3077 cm^{-1}) and at (3248-3302 cm^{-1}) due to (NH)group.

The compound (3) was used to synthesize the Schiff-bases (4a-h) by its reaction with aromatic aldehydes and isatin in presence of catalytic amount of glacial acetic acid [15]. The structure of the synthesized Schiff bases was confirmed on the basis of the spectral data .

The IR spectra of compounds (4a-h) showed the following absorption bands (as KBr disk) (Table III): at (1616-1697)$cm^{-1}$of the C=N band stretching, at (740-744) cm^{-1} for the C-S band stretching, at (3153-3413) cm^{-1} for the N-H band stretching, and 1732 cm^{-1} for C=O isatin.The1H-NMR spectrum of compound (4a) as representative to identify these compounds.

It showed the following chemical shifts (δ) (Table IV): a singlet signal for three protons at 3.4 ppm for the methoxy protons, a singlet for two protons 4.1 ppm for the CH_2protons, a multiplet signal for seven protons at (6.9-7.3) related to the aromatic protons, singlet signal for one proton at 7.4 for OH proton, a singlet signal for one proton at 9.7 ppm related to N=CH proton and a singlet signal for one proton at 12.5 ppm corresponding to NH proton. The UV spectra of compounds (4a-h) showed a maximum absorption (Table III) λmax (304-314) nm related to the $n\rightarrow \pi^*$ electronic transitions.

Finally, the reaction of the imino compounds (4a-g) with chloroacetyl chloride in presence of triethylamine afforded the azitidine-2-one compounds (5a-g) . The IR spectra for these compounds showed the following absorption bands (sa KBr disk) (Table V): at (1570-1618) cm^{-1} for the C=N band stretching, at (742-752) cm^{-1} for the C-S band stretching, at (1635-1738) for the C=O band stretching at (619-868) cm^{-1} for the C-Cl band stretching and at (3116-3429) cm^{-1} for the NH stretching. The 1H-NMR spectrum of compounds (5c), was taken as a representative model to identify these compounds (Table VI): the spectrum showed the following chemical shifts (δ): a doublet signal for one proton at (1.91-2.0) ppm for the Cl-CH proton, a doublet signal for one proton at (3.1-3.4) ppm for Ar-CH proton, a singlet signal for three protons at (3.1) ppm related to methoxy protons, a singlet signal for two protons at (4.04) for CH_2protones. A multiplet signal for eight protons at (7.1-7.6) related to the aromatic protons and a singlet signal for one proton at (11.2) ppm for the NH proton. The UV spectra (Table V) of compounds (5a-g) showed a maximum absorptions at λmax (304-314) nm related to $n\rightarrow\pi^*$ electronic

IV.BIOLOGICAL ACTIVITY [16]

The synthesized compounds (Table VII) were screened for their invitro antibacterial activity against: Escherichia Coli, Pseudomonas Aeruginosa, Klebsilla Preumonia, Staphylococcus Aurens and Bacillns Subtilis, by measuring the zone of inhibition in (mm). The antibacterial activity was performed by cup plate method at concentration (100 mg/ml) and reported in table VII for antibacterial activity.McFarland agar was employed as culture medium and DMSO was used as solvent control for antibacterial activity. Cephalexin was used as standard for antibacterial activity.

The results are summarized in table VII, from the obtained data, it revident that compound (5a) possess a very good activity against staph. Bacteria.

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Table I
The physical data of compounds (4a-g)

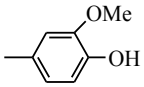
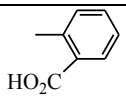
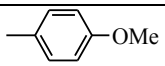
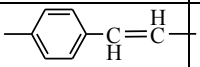
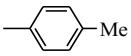
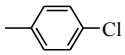
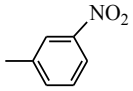
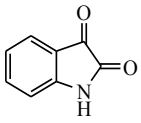
Comp. No.	Ar	m.p/°C	Yield%	color
4a		190-195	80	Brown
4b		295-297	85	Yellow
4c		150-153	79	Yellow
4d		280-282	81	Yellow
4e		295-297	60	Pale yellow
4f		298-300	66	Pale yellow
4g		296-298	58	Pale yellow
4h		235-237	54	Yellow

Table II
The physical data of compounds (5a-g)

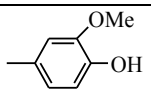
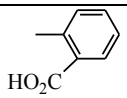
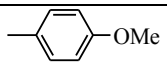
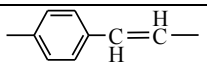
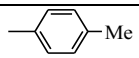
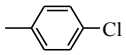
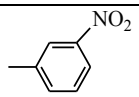
Comp. No.	Ar	m.p/°C	Yield%	color
5a		178-180	22	Brown
5b		195-197	20	Brown
5c		219-220	18	Brown
5d		150-155	21	Brown
5e		161-163	33	Brown
5f		178-180	38	Pale brown
5g		223-225	40	Brown

Table III
The spectral data of compounds (4a-h)

Comp. No.	UV(EtOH), λmax(nm)	IR (KBr) υ. (cm^{-1})				
		C=N	C=C	C-S	NH	CH
4a	314	1616	1516	742	3300	2979
4b	304	1618	1514	744	3153	2981
4c	306	1697	1558	744	3421	3116
4d	309	1655	1533	744	3155	3116
4e	306	1618	1514	744	3410	3151
4f	306	1624	1520	741	3330	2982
4g	308	1619	1525	744	3320	2984
4h	306	1616	1514	741	3413	3153

Table IV
1H-NMR data for Schiff bases (4a-h)

Comp. No.	Signals
4a	3.4 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 6.9-7.3 (m, 7H, ArH), 7.4 (s, 1H, OH), 9.7 (s, 1H, N=CH), 12.5 (s, 1H, NH).
4c	3.2 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 7.1-7.5(m, 8H, ArH), 9.8 (s, 1H, N=CH), 11.5 (s, 1H, NH).

Table V
The spectral data of azitidin-2-one derivatives (5a-g)

Comp. No.	UV(EtOH), λmax(nm)	IR (KBr) υ. (cm^{-1})						
		C=N	C=C	C-O	NH	CH	C-S	C-Cl
5a	292	1609	1509	1647	3116	3035	752	868
5b	284	1618	1508	1739	3413	2954	742	619
5c	284	1570	1508	1635	3429	3232	742	619
5d	296	1592	1509	1710	3250	3040	747	630
5e	295	1616	1507	1649	3410	2960	750	640
5f	293	1620	1510	1637	3405	2965	745	642
5g	286	1622	1510	1632	3412	2957	747	647

Table VI

^{1}H-NMR data for azitidin-2-one derivatives (5a-g)

Comp. No.	Signals
5a	1.92-2.0 (d, 1H, Cl-CH), 3.0-3.4 (d, 1H, Ar-CH), 3.0 (s,3H, OMe), 4.1 (s, 2H, CH_2), 7-7.5 (m, 7H, ArH) 7.6 (s, 1H, OH), 11.1 (s, 1H, NH)
5c	1.92-2.01 (d, 1H, Cl-CH), 3.1-3.4 (d, 1H, Ar-CH), 3.1 (s, 3H, OMe), 4.04 (s, 2H, CH_2), 7.1-7.6 (m, 8H, ArH), 11.2 (s, 1H, NH)

Table VII

Antibacterial data

Comp. No.	Antibacterial *				
3	13	12	10	11	13
4a	R	11	R	12	R
4b	11	15	12	16	R
4c	R	13	19	14	11
5a	18	12	13	26	13
5b	19	15	12	30	14
5c	25	18	19	32	16