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SYNTHESIS AND ANTIBACTERIAL STUDY OF THIADIAZOLE SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

Krishnakant T. Waghmode[1]*, Vishal Jadhav[1] and Bandoba T. Nikam[2]

[1]Department of Chemistry, D. G. Ruparel College, Mahim, Mumbai, Maharashtra, India.

[2]Department of Chemistry, M. D. College, Parel, Mumbai, Maharashtra, India.

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***Corresponding Author**
Dr. Krishnakant T. Waghmode
Department of Chemistry,
D. G. Ruparel College,
Mahim, Mumbai,
Maharashtra, India.

ABSTRACT

Orthophenylene diamine was reacted with a dicarboxylic acid in acidic condition to give benzimidazole substituted carboxylic acid (3). The reaction of benzimidazole substituted carboxylic acid with thiosemicarbazide in presence of phosphorous oxychloride yielded benzimidazole substituted-2-amino thiadiazole (5). In the next step benzimidazole substituted amino benzothiazole was reacted with glyoxal to get substituted imino aldehyde (7). Imino aldehyde was reacted with different substituted aromatic amines to afford final product (9). Substituted derivatives of final product (9a-i) were synthesized in good to excellent yield. Synthesized compounds were characterized by using IR, NMR and Mass Spectroscopy. Further these compounds were subjected for their biological evaluation by studying their antibacterial activities against *Staphylococcus Aureus (S. Aureus) and Escherichia coli (E. Coli)* bacteria.

KEYWORDS: Benzimidazole, benzothiazole, o-Phenylenediamine, Antibacterial activity.

INTRODUCTION

Thiadiazole is a five-membered heterocyclic compound containing one nitrogen and two sulfur atoms at 1,3 and 4 positions respectively. Benzothiazole and their derivatives show broad spectrum of pharmacological activities,.[1] The 1,3,4-thiadiazole nucleus is one of the most important and well-known heterocyclic compounds which is common and integral part of the variety of natural products and medicinal Chemistry. Literature survey revealed that 1,3,4-thiadiazole substituted compounds show various biological activities like antibacterial activity,[2] antifungal activity,[3] antiviral activities,[4] Li et. al. have reported a detailed review on Various Biological Activities of 1,3,4- Thiadiazole Derivatives.[5]

Benzimidazole is an important pharmacophore and privileged structure in medicinal chemistry.[6] Benzimidazole is a promising organic molecule with anti-fungal, herbicidal, analgesic, antioxidant, antiallergic, antitumoral agents and various biological activities.[7]

Schiff bases are very important and significant organic compounds. They have various applications such as dyes, pigments catalysts, intermediates in organic synthesis, and polymer stabilizers.[8] Schiff bases show a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties.[8-9]

By considering the significance of benzimidazole nucleus, thiadiazole and Schiff bases, we have synthesized thiadiazole substituted benzimidazole Schiff bases and studied their antibacterial activities.

MATERIALS AND METHODS

"All the reaction was carried out in oven-dried (110 ^{0}c) or flame dried glassware, all the chemicals used were of synthetic grade from a various chemical unit like loba chemicals, SRL, Mumbai, all the melting point were taken in open capillaries and IR were recorded in KBr on FT-IR Shimadzu spectrometer, ^{1}H-NMR spectra were recorded on 600MHz spectrometer using DMSO-d^6 as a solvent and TMS internal standard, LCMS was obtained from Chemotest laboratories Mumbai".[10]

Experimental

Preparation of "3-(1*H*-benzimidazol-2-yl) propanoic acid (Compound 3)".[11]

A mixture of orthophenylene diamine (21 gm, 0.2mol),100ml of 4N HCl and succinic acid was heated together under reflux of 5hrs. "Ice cooled reaction mixture was made distinctly basic by the gradual addition of the concentrated ammonia solution, the precipitated product was collected and recrystallized from ethanol. Synthesis is given in fig.-1.

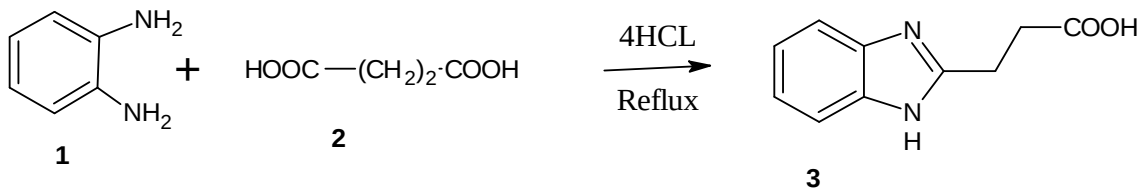

Fig. 1: Synthesis of 3-(1*H*-benzimidazol-2-yl) propanoic acid (Compound 3).

Synthesis of "5-[2-(1*H*-benzimidazol-2-yl) ethyl]-1,3,4-thiadiazol-2-amine (Compound 5)".[12]

3-(1*H*-benzimidazol-2-yl) propanoic acid was added with thiosemicarbazide in $POCl_3$. The reaction mixture was refluxed for 2 hours. Then the reaction mixture was cooled by the gradual addition of water and basified with aqueous K_2CO_3, product formed was washed with excess of water to remove unreacted base and $POCl_3$. Synthesis is given in fig.-2.

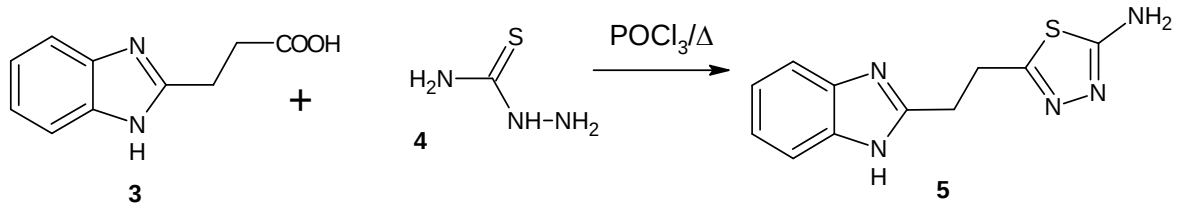

Fig.-2:-Synthesis of 5-[2-(1*H*-benzimidazol-2-yl) ethyl]-1,3,4-thiadiazol-2-amine (Compound 5).

Synthesis of "({5-[2-(1*H*-benzimidazol-2-yl)ethyl]-1,3,4-thiadiazol-2-yl}imino)acetaldehyde (Compound 7)".[13]

"In a round bottom flask, equimolar mixture of 5-[2-(1*H*-benzimidazol-2-yl)ethyl]-1,3,4-thiadiazol-2-amine and glyoxal was refluxed till the completion of reaction, progress of the reaction was checked with TLC (Hexane: Ethyl acetate- 9:1) then it was cooled with ice cold water. It was filtered and washed with cooled water and diluted HCl, the precipitate formed was filtered, washed with water and purified by crystallization with ethanol".

Synthesis is given in fig.-3.

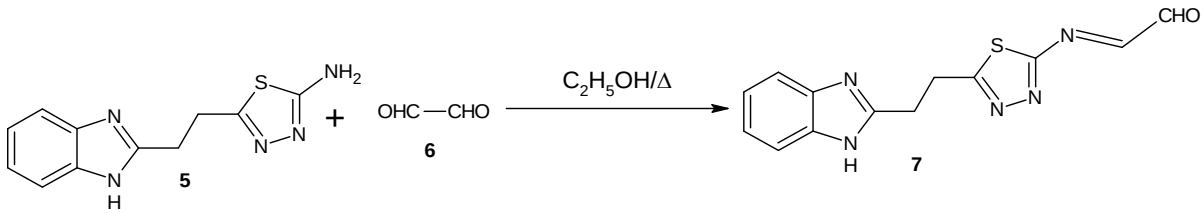

Fig. 3: Synthesis of ({5-[2-(1*H*-benzimidazol-2-yl)ethyl]-1,3,4-thiadiazol-2-yl}imino)acetaldehyde (Compound 7).

Synthesis of 5-[2-(1*H*-benzimidazol-2-yl)ethyl]-*N*-[(1*E*,2*Z*)-2-(phenylimino)ethylidene]-1,3,4-thiadiazol-2-amine (9a-i)

In a round bottom flask equimolar mixture of ({5-[2-(1*H*-benzimidazol-2-yl)ethyl]-1,3,4-thiadiazol-2-yl}imino)acetaldehyde and substituted anilines were taken in ethanol. The reaction mixture was refluxed for about 5 hours. Progress of the reaction was monitored with

TLC (n-Hexane: ethyl acetate -9:1), then it was Cooled and added with ice cold water to get precipitate, which was filtered and dried. Product was recrystallized with ethanol. All the final products 9a-i were synthesized by same procedure. Synthesis is given in fig.-4.

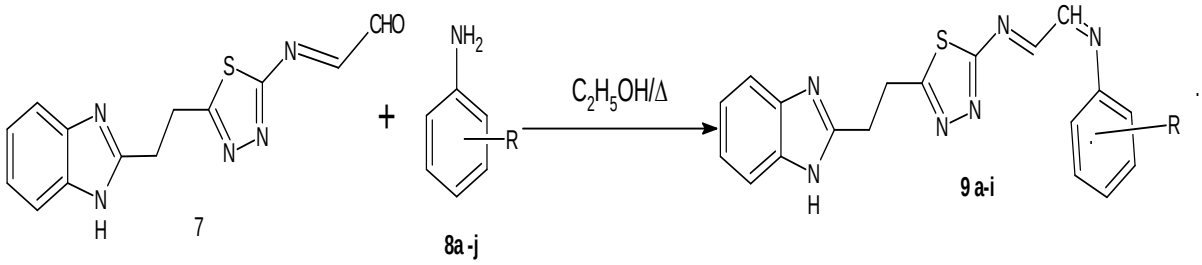

Fig.-4:-Synthesis of 5-[2-(1*H*-benzimidazol-2-yl)ethyl]-*N*-[(1*E*,2*Z*)-2-(phenylimino)ethylidene]-1,3,4-thiadiazol-2-amine (9a-i).

Reaction conditions and data of the synthesized compounds (9a-i) is given in table-1.

Table 1: Synthesis of compounds 9.a-i.

Entry	R-	Conventional Heating		mp °C
		Time in Hours	% Yield	
9a	-H	5	63	210
9b	$3NO_{2-}$	5	69	205
9c	2,4,5- $(Cl)_3$-	5	71	221
9d	3-Cl-	5	55	204
9e	4-Cl-	5	73	246
9f	2,6 di-$CH(CH_3)_2$	5	52	245
9g	2,4-di-Cl-	5	59	202
9h	3-Cl, 4-F-	5	58	230
9i	2,4-$(CH_3)_2$	5	72	209

Representative spectral data of 5-[2-(1*H*-benzimidazol-2-yl)ethyl]-*N*-[(1*E*,2*Z*)-2-(phenylimino)ethylidene]-1,3,4-thiadiazol-2-amine (9a).

mp.= 210 ^{o}C, IR(KBr) cm^{-1} : 3255-3224 broad(NH), 3116(Ar-CH), 2954(Aliphatic -CH),1680(C=C),1620(Ar-C=C), 1620(Ar-C=C), 1427(CN), 1396(CN), 1342(N=C), 1026(-CH).

^{1}H-NMR(DMSO-d^{6}) δppm:2.7-2.9(2H,t,CH2), 3.1-3.2(2H,t,CH2), 4.7(1H,s,NH), 7.4(1H,d,CH=N), 6.6-7.2(9H,m,Ar-H).

Antibacterial activity

"Synthesized compounds(9a-i) were tested for the antibacterial activity against gram -ve *Escherichia coli (E. coli)* and gram+ ve *staphylococcus Aureus(S.Aureus*), the nutrient agar medium was prepared by using bactotryptone (4g) broth (3.9g) less than 2% Nacl (2.9g) in

100 ml of water (2.9%), after 18 hours the exponentially growing culture of the 2 bacteria in nutrient broth at 37°C were diluted culture 1 cm^3 was added to 100 cm^3 sterilize and cooled nutrient agar media to give a final bacteria culture".[14] The plates were set at Room temperature and later dried at 37° for 20 hours paper discs (6mm, punched from Whatman no 41 paper) were used for the assays, discs were soaked in DMF and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that were taken triplicates, the plates were incubated at 37°C in an inverted fusion, activity has been determined by zone showing complete inhibition, Growth Inhibition was calculated with reference to positive control. Activity results of the activities are summarized in Table-2.

Table 2: Results of antibacterial activity.

	Activity index	
Compounds	**Zone if Inhibition in mm**	
	Escherichia coli gram (-)	Staphylococcus aureus gram (+)
9a	11	9
9b	10	11
9c	7	10
9d	9	8
9e	12	9
9f	9	8
9g	8	8
9h	10	7
9i	11	8
Norfloxacin std	15	18

RESULTS AND DISCUSSION

Benzimidazole derivatives processing benzothiazole and azomethine group were synthesized. Synthesized compounds gave moderate to better yields, synthesized compounds were tested for antibacterial activity against gram positive and gram-negative bacteria. From the result of antibacterial screening given in table-2, it is evident that most of the compounds are weakly active and few are moderately active against S Aureus and E coli bacteria, but compound 9e process very good against E Coli. It was observed that among all the compound which were tested, Compound 9e shows maximum zone of inhibition while compound 9c shows minimum zone of inhibition for gram (-) E Coli, Compound 9b shows maximum zone of inhibition and compound 9h shows minimum zone of inhibition for gram (+) S Aureus bacteria, all other compounds possess moderate activity against bacteria tested.

CONCLUSION

Benzimidazole induced thiadiazole Schiff bases were synthesized in good to moderate yields. All the synthesized compounds were screened for their antibacterial activities against one gram-positive and one gram-negative bacteria. All the synthesized compounds were characterized by using ^{1}H-NMR and infrared spectroscopy.

In conclusion, simple and efficient synthesis of thiadiazole substitutes Schiff bases of benzimidazole and their antibacterial activities are explained.

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