

Synthesis Characterization and Antimicrobial Studies of New Novel Derivatives of 2-Amino-6-Methylbenzothiazole

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ABSTRACT: Benzothiazole derivatives are known to have wide spectrum of therapeutic activities such as antitumor activity, antimicrobial activity, anti-inflammatory activity, anthelmintic activity, anticonvulsant activity, antileishmanial activity. Benzothiazoles consist of a 5-membered 1,3-thiazole ring fused to a benzene ring. The nine atoms of the bicycle and the attached substituents are coplanar. Heterocyclic compounds containing nitrogen and sulfur such as benzothiazole has received considerable attention in recent years due to their biological and pharmaceutical activities. The benzothiazole ring system has phenyl ring fused with thiazole ring. This ring is a potential component in nonlinear optics (NLO). The compound is used also used as an insecticide and food flavoring agent.

KEYWORDS: Heterocyclic compounds , anti-inflammatory activity, antitumor activity , antimicrobial activity , anthelmintic activity , anticonvulsant activity, antileishmanial activity , benzothiazole

I. INTRODUCTION

The heterocyclic compounds are very widely distributed in nature and are very essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant specially those containing oxygen or sulphur [1] due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals.

Heterocyclic compounds possess great applicability in industry as well as in our life in various ways. For example most of the sugars and their derivatives, including vitamin C [2], exist largely in the form of five membered (Furanosied structure) or six membered (Pyranosied structure) ring containing one oxygen atom. Further, most members of the vitamin B group possess heterocyclic rings containing nitrogen. e.g., vitamin B6 (Pyridoxine) [3], which is a derivative of the pyridine essential in amino acid metabolism.

II. RELATED WORK

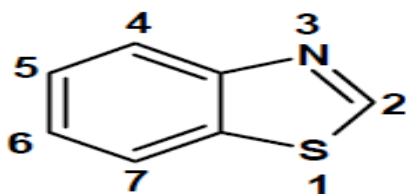
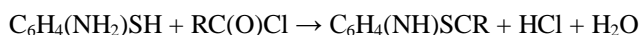
The study of benzothiazole derivatives is of considerable current interest due to their important biological and biophysical properties. Different methods used for the synthesis of benzthiazole and its derivatives have been reported. The Benzothiazole ring system bears phenyl ring fused with thiazole ring. Thiazole is a five membered heterocyclic ring system having sulfur and nitrogen as heteroatom. Benzothiazole are prepared by treatment of 2-mercaptoaniline with acid chlorides[4].

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1,3-benzothiazole

One of the earliest and most valuable methods for the synthesis of benzothiazole is the reaction of an o-aminothiaphenol, with a carboxylic acid [5-7] or its derivatives or an aldehyde. The reaction of aldehyde with o-aminophenols yields either 2, 3- dihydrobenzothiazole, depending on the aldehyde and the thiophenol employed. The reaction of various aldehydes and ketones has been reported [8-10]. 2-aminobenzothiazole and some of its derivatives have been synthesized by cyclization of the corresponding arylthioureas with SO_2Cl_2 , Br_2 and H_2SO_4 [11-13]. synthesized some novel benzothiazole derivatives by thiourea with excess 1,4-benzoquinones and 1,4-naphthoquinones in the presence of con. HCl offers a convenient route for the synthesis of a variety of 2-amino-6-hydroxybenzothiazoles and 2-amino-5- hydroxynaphtho [1,2-d] thiazoles. Livio *et. al.* [14] synthesized series of novel 2- (substituted-phenyl)-6-aminobenzothiazole as analogous of 2-(4- aminophenyl)benzothiazole prepared as hydrochloride or dihydrochloride salts. o-thiocyanato arylamines undergo spontaneous cyclization to produce 2-aminobenzothiazole in good yields. The required thiocyanatoamines are produced directly by treatment of a p-substituted arylamine with thiocyanogen which is generated in the reaction mixture containing the arylamine [15-16]. In recent years, environmentally benign synthetic methods have received considerable attention and some solvent-free, catalyst-free and microwave promoted reactions have been developed [17-20].

III. SCOPE OF THE RESEARCH

Benzthiazole derivatives are known to have wide spectrum of therapeutic activities. A well known drug such as "Riluzole" (Rilutek) [21] having benzothiazole nucleus. Biological significance includes:

• Antitumor activity

Some of potent and selective antitumor agents mostly from substituted 2-(4- aminophenyl) benzothiazoles were developed and examined, *in vitro*, their antitumor activity in ovarian, breast, lung, renal and colon carcino human cell lines [22-25]. Benzothiazole show antitumor activity, especially the phenyl substituted benzothiazole [26-27]. Hutchinson *et al.* [28] have been synthesized fluorinated analogues of 2-(4- aminophenyl) benzothiazole which possessing enhanced efficacy *in vitro* and superior potencies against human breast and ovarian tumor.

• Antimicrobial activity

Benzothiazole show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial [29-31] and antifungal [32] benzothiazole. Bhusari *et al* [33], prepared some 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles and screened them for their antibacterial activity against *Bacillus subtilis*, *Salmonella typhi*, and *S. dysentery*. Sreenivasa *et al* [34] prepared benzothiazolo triazole derivatives and found to possess good activity against *S. aureus*, *E. Coli* and *C. ablicans*.

• Anti-inflammatory activity

In the last 30 years a number of Benzothiazole derivatives have been synthesized and found to display anti-inflammatory activity [35]. Singh *et al.* [36] prepared some new 2-(4-butyl-3, 5-dimethyl pyrazol-1-yl)-6-substituted benzothiazole and 4-butyl-1- (6-substituted-2-benzothiazolyl)-3-methylpyrazol-5-ones and were found to display

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significant anti-inflammatory activity. Dogruer *et al.* [37] synthesized sixteen (2-benzothiazolone-3-yl and 2-benzoxazolone-3-yl) acetic acid derivatives and found to possess good anti-inflammatory activity.

• Anthelmintic activity

In the search of new anthelmintic agents of benzothiazole series, Nargund, [38,39] synthesized few novel 8-fluoro-9-substituted (1, 3) benzothiazole (5,1-b)-1,3,4-triazole. All these compounds were studied for their anthelmintic activity against earthworm, *perituma posthuma*. The compound with R= onitroaniline substituent was found to possess markedly higher anthelmintic activity. Some substituted imidazobenzothiazole were tested for *in vivo* anthelmintic activity against *H. nana* infection and were found to show good to moderate activity [40].

• Anticonvulsant activity

A large number of benzothiazole derivatives were evaluated for anticonvulsant activity and found to possess significant activity against various types of seizures [41-43]. Singh *et al.* [44] synthesized some 2-(4-arylthiosemicarbazidocarbonylthio) benzothiazoles were screened and found to moderate anticonvulsant activity. In the search of new anticonvulsant agents having benzothiazole nucleus, Jimonet *et al.* [45] have synthesized a lot of substituted-2-benzothiazolamines. All these compounds were found to possess significant activity.

• Antileishmanial activity

2-[(2-Chlorobenzothiazol- 6-yl) amino] benzoic acid, demonstrated an interesting antiproliferative activity towards parasites of the species *Trichomonas vaginalis*. Delmas *et al.* [46] has synthesized position 2 substitution-bearing 6-nitro and 6-amino benzothiazoles and their corresponding anthranilic acids and assessed the *in vitro* antiparasitic activity of each derivative against the parasites of the genus *leishmania infantum* and *Trichomonas vaginalis* compared to their toxicity towards human monocytes. The antiprotozoal properties depended greatly on the chemical structure of the position 2 substitution-bearing group.

Thus, the important role displayed by benzothiazole and its derivatives for various therapeutic and biological activities encouraged to synthesize some Schiff bases, 4-Thiazolidinones and 5-methyl 4-Thiazolidinones derivatives bearing benzothiazole nucleus in order to achieve compounds having better drug potential.

IV. PROPOSED METHODOLOGY

All the reactions were performed in oven-dried glassware's and under nitrogen atmosphere. Column chromatography was performed using silica gel (60–120 mesh). All melting points are uncorrected and were recorded on open capillary method. ¹H spectra were recorded at NMR Bruker 500 MHz. IR spectra were recorded on a Agilent technology FTIR spectrophotometer, using potassium bromide pellets; the frequencies are expressed in cm⁻¹. Thin-layer Chromatography was performed using commercially prepared 60 F₂₅₄ silica gel plates and visualization was effected with short wavelength UV light (254 nm) and staining over an Iodine chamber. Liquid chromatography mass spectra were recorded on Waters Acquity UPLC system.

V. EXPERIMENTAL RESULTS

Synthesis of N-(6-methyl benzothiazole-2-yl)-4-(methylsulphonyl) -2-nitrobenzamide

[A] Synthesis of 2-amino-6-methyl benzothiazole (48):

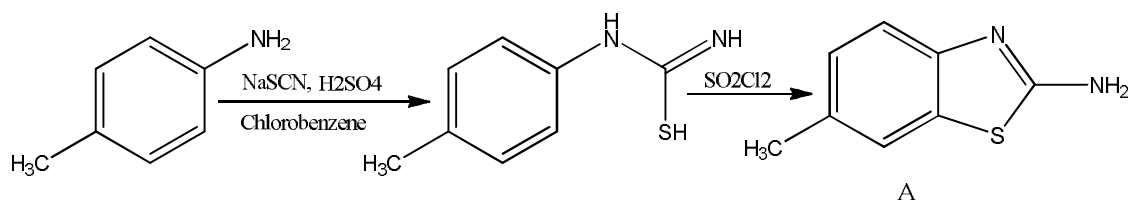
A solution of 5 g. (0.0466 mole) of *p*-toluidine in 30 ml. of chlorobenzene is prepared in a three-necked, round-bottom flask fitted with a stirrer, reflux condenser, thermometer, and dropping funnel. Over a period of 5 minutes, 2.5 g. (0.0225 mole) of concentrated sulfuric acid is added dropwise. To the finely divided suspension of *p*-toluidine sulfate is added 4.2 g. (0.0518 moles) of sodium thiocyanate, and the mixture is heated for 3 hours at 100° (inside temperature) in an oil bath. The solution, which now contains the thiourea, is cooled to 30°, and 8.45 g. (0.0626 moles) of sulfonyl chloride is added over a period of 15 minutes, with care that the temperature does not exceed 50°. The mixture is kept at 50° for 2 hours (no further evolution of hydrogen chloride), after which the chlorobenzene is removed by filtration.

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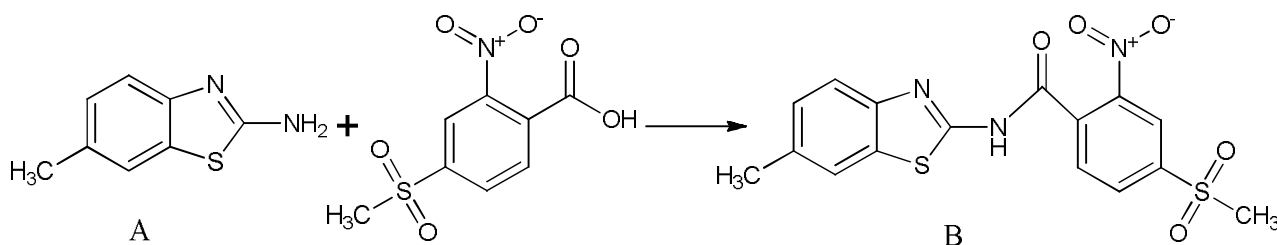
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The solid residue is then dissolved in 100 mL of hot water, alkaline the solution with concentrated ammonium hydroxide, the precipitated 2-amino-6-methyl benzothiazole is filtered and washed with water. Solid product was washed with water, the crude product was isolated and crystallized from absolute ethanol. After drying to constant weight, the product weight 110 g, yield 67%, Melting point 135–136°C. ¹H NMR (500 MHz, DMSO-d₆) δ 7.43(s, 1H), 7.38 (s, 2H), 7.23-7.21 (d, 1H), 7.02-7.00(d,1H), 2.33-2.30(s,3H), IR (KBr / cm-1) 3393, 3265, 3121, 1624, 1540, 1281, 1099, 907, 808, LC-MS (AP+): m/z=164.23, calculated for C₈H₈N₂S (M+H⁺): 165.2.

[B] Synthesis of N-(6-methyl benzothiazole-2-yl)-4-(methylsulphonyl) -2-nitrobenzamide.

A solution of 2-Amino-6-methylbenzothiazole (0.5 g, 3.048 mmole) in DMF (2 mL) was added slowly to a stirred solution of 4-Methylsulfonyl-2-nitrobenzoic acid (0.97g, 3.955 mmol), *N,N*-Diisopropylethylamine (1.178 g, 9.317mmol) and HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (1.5 g, 3.947mmol) in DMF (5mL) at 10 °C.



The reaction mixture was stirred at room temperature for 30 minutes. TLC shows the reaction completion (ethyl acetate: Hexane – 30:70 R_f 0.55). The reaction mixture was diluted with water (100 mL). Product was crystallized in aqueous solution, filtered under vacuum and crystallized with methanol 100% dried product at 50°C to give a light yellow solid (0.7 g, 1.7879 mmol, 58.8% yield). A sample was again crystallised from MeOH for melting point analysis, mp- 257-261°C, ¹H NMR (500 MHz, DMSO-d₆) δ 13.23(1H, brs), 8.66 (s, 1H), 8.45-8.44 (d,1H), 8.20-8.18(d,1H), 7.852(s,1H), 7.69-7.67(d,1H), 7.32-7.30(d, 1H), 3.45(s,3H), 2.44(s,3H), IR (KBr / cm-1) 1680, 1362, 1324, 1309, 1188, 1145, 972, 877, 821, 788, LC-MS (ESI-): m/z=391.03, calculated for C₁₆H₁₃N₃O₅S₂ (M-H⁺): 390.03.

VI. CONCLUSION

As a result, N-(6-methyl benzothiazole-2-yl)-4-(methylsulphonyl) -2-nitrobenzamide (B) is formed smoothly with the reaction of 2-amino-6-methyl benzothiazole (A), and 4-Methylsulfonyl-2-nitrobenzoic acid. Amide synthesis reaction is in the presence of HATU reactions proceeded in acceptable yields. These derivatives present a class of compounds that can be used as procedures for the synthesis of new derivatives with useful biological activities. In addition, our method has significant advantages, such as minimum time of reaction process.

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