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NOVEL SYNTHESIS AND EVALUATION OF ANTIMICROBEAL ACTIVITY OF SUBSTITUTED N-(PYRIDIN-4-YL METHYLENE)-2-AMINO BENZOTHIAZOLE

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ABSTRACT

The synthesis of N-(pyridin-4-ylmethylene)-2-amino benzothiazole (3) by reaction of 2-amino benzenethiol (1) and isonicotinaldehyde (2) stirring in presence of methyl alcohol as a solvent. This reaction mixture is kept for overnight, the crystals of N-(pyridin-4-ylmethylene)-2-amino benzothiazole (3) obtained. Filtered and dried. The synthesis of 5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole (5) by reaction of 5-nitro-2-amino benzothiazole (4) and isonicotinaldehyde (2) stirring in presence of methyl alcohol as a solvent. This reaction mixture is kept for overnight, the crystals of 5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole (5) obtained. Filtered and dried. The Purity of compound was checked by TLC. The compound observed on TLC as single spot in benzene. The structures for the synthesized compounds are assigned on the basis of IR, ^{1}HNMR and Mass spectral studies.

KEYWORDS: 2-amino benzenethiazole, 5-nitro-2-amino benzenethiazole, isonicotinaldehyde, methyl alcohol, N-(pyridin-4-yl methylene)-2-amino benzothiazole**.**

INTRODUCTION

Heterocyclic compounds, such as benzothiazole, are of great significance in organic chemistry and drug discovery due to their diverse range of physiological functions.[1] Benzothiazole and its derivatives have been extensively studied for their potential biological activities. In the 1950s, derivatives of benzothiazole, particularly 2-aminobenzothiazoles were investigated for their muscle relaxant properties. Since then, benzothiazole analogues have been found to exhibit a wide range of pharmacological actions including antibacterial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anthelmintic, anti-oxidant and anticancer properties.[2,3] There are several methods for synthesizing benzothiazole analogues. One common approach involves the condensation process where acyl chlorides, carboxylic acids, esters, nitriles and o-aminothiophenols containing substituted aldehydes are reacted to form benzothiazole derivatives. Another widely employed method is Pd/Cu/Mn/chloranil catalyzed cyclization of o-halothioformanilide. These synthetic methods have enabled the synthesis of numerous benzothiazole derivatives with diverse structural modifications and pharmacological effects. Ongoing research continues to explore the potential applications and properties of benzothiazole compounds and their derivatives.[4]

In recent decades, the problem of bacterial resistance is increasing throughout the world, leading to higher mortality and increased healthcare costs. In fact, the World Health Organization has ranked antibiotic resistance as one of the three most important public health threats of the 21st century. Undoubtedly, there is a persistent need to develop novel antibacterial compounds with novel structures and mechanisms of action to address this problem.[5-8]

DNA gyrase and topoisomerase IV are type II topoisomerases that catalyse changes in DNA topology, a function vital to DNA replication and repair.[9] Therefore, these enzymes are crucial for cell viability and offer the possibility of the discovery and development of novel antibacterial agents that can circumvent the existing bacterial resistance. DNA gyrase and topoisomerase IV are ATP-fueled heterotetrametric proteins, with DNA gyrase made up of two GyrA and two GyrB subunits, however topoisomerase IV is composed of two ParC and two ParE subunits, which are homologs of GyrA and GyrB, respectively. Type II topoisomerase enzymes are also found in eukaryotic

cells, but unlike the prokaryotic enzymes, eukaryotic topoisomerases II act as homodimer enzymes.[10] Additionally, the binding pocket is significantly more occluded in human topo II, making binding of bacterial topoisomerase inhibitors less favourable. Actually, more than three times of magnitude selectivity for the bacterial isozymes *versus* human was seen in programs at AstraZeneca.[11] Possessing similar and well-known structures from different bacterial strains in addition to the selectivity of targeting prokaryotic topoisomerase II render both DNA gyrase and topoisomerase IV attractive targets for the development of dual inhibitors with broad-spectrum antibacterial activity.[12-13]

Benzothiazole is a common scaffold in a variety of natural products and pharmaceutical agents showing broad spectrum of biological activities. Benzothiazole derivatives attracted considerable attention towards antimicrobial research, and several attempts were made for modifying the benzothiazole nucleus to improve their antimicrobial activities. Besides, hybrids of benzothiazole scaffold with other heterocycles such as thiazolidinone and thiazole are well established to have antimicrobial activity**.** Additionally, a series of benzothiazole-based compounds, represented by compound**,** displayed significant antibacterial activities against resistant bacterial strains. From SAR study of this series, it was concluded that a three-atoms-linkage between 2-aminobenzothiazole and benzylamine moieties is preferable for the antibacterial activity of these compounds.[14-15]

Benzothiazole derivatives are an important class of heterocyclic compounds that exhibit a wide range of biological properties in medicinal and agricultural chemistry.[16-20] Further industrial applications as antioxidants[21-22], vulcanization accelerators[23], and a do pant in a light emitting organic electroluminescent devices[25] have also been reported. Many reports have appeared in the literature describing the formation of benzothiazoles via one of the two major routes. However, these methodologies suffer from one or more disadvantages, such as tedious workup, high temperature, prolonged reaction time, and toxic organic solvents such as DMF and DMSO.

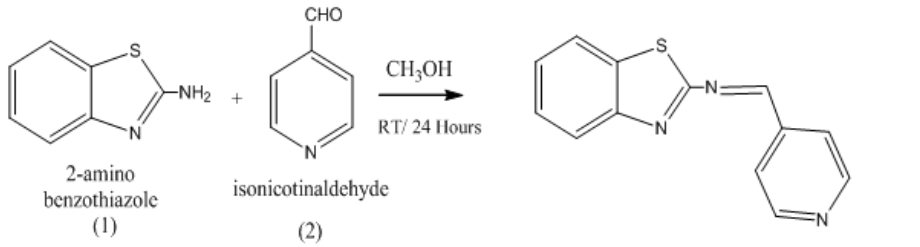
EXPERIMENTAL SECTION

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by thin layer chromatography.

MATERIAL AND METHODS

1. Synthesis of N-(pyridin-4-ylmethylene)-2-amino benzothiazole

In the present work, we report synthesis of N-(pyridin-4-ylmethylene)-2-amino benzothiazole (3) by reaction of 2-amino benzothiazole (1) and isonicotinaldehyde (2) stirring in presence of methyl alcohol as a solvent. This reaction mixture is kept for overnight, the crystals of N-(pyridin-4-ylmethylene)-2-amino benzothiazole (3) obtained. Filtered and dried. The Purity of compound was checked by TLC. The compound observed on TLC as single spot in benzene. Structures to these compounds are assigned on the basis of elemental analysis and spectral data.



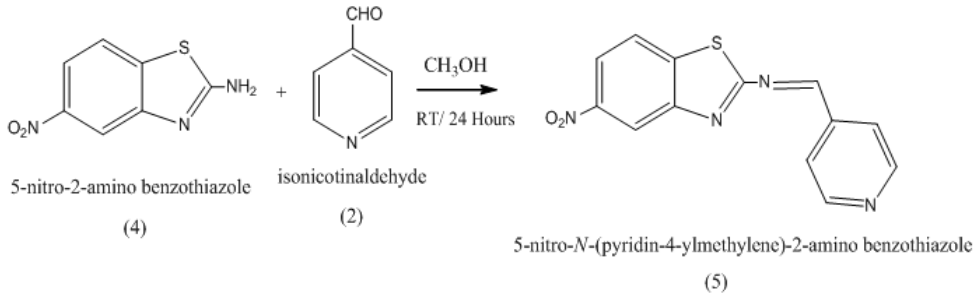
2-amino benzothiazole (1) + isonicotinaldehyde (2) → *N*-(pyridin-4-ylmethylene)-2-amino benzothiazole (3)

Chemical analysis

N-(pyridin-4-ylmethylene)-2-amino benzothiazole (3): IR:(KBr/cm^{-1}): 1621 (C=N), 1610-1591 (C=C), 780 (C-S), **EI-MS:** (m/z:RA%): 239 (M+1), **Elemental analysis:** $C_{13}H_9N_3S$ Calculated: (%) C, 65.25; H, 3.79; N, 17.56; S, 13.40 Found (%): C, 65.20; H, 3.75; N, 17.51; S, 13.36

2. Synthesis of 5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole

In the present work, we report synthesis of 5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole (5) by reaction of 5-nitro-2-amino benzothiazole (4) and isonicotinaldehyde (2) stirring in presence of methyl alcohol as a solvent. This reaction mixture is kept for overnight, the crystals of 5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole (5) obtained. Filtered and dried. The Purity of compound was checked by TLC. The compound observed on TLC as single spot in benzene. Structures to these compounds are assigned on the basis of elemental analysis and spectral data.



5-nitro-2-amino benzothiazole (4) + isonicotinaldehyde (2) → 5-nitro-*N*-(pyridin-4-ylmethylene)-2-amino benzothiazole (5)

Chemical analysis

5-nitro-N-(pyridin-4-ylmethylene)-2-amino benzothiazole (5)

IR:(KBr/cm^{-1}): 1320 & 1510 (NO_2), 1620 (C=N), 1610-1590 (C=C), 782 (C-S), **EI-MS:** (m/z:RA%): 285 (M+1), **Elemental analysis:** $C_{13}H_8N_4O_2S$ Calculated: (%) C, 54.92; H, 2.84; N, 19.71; O, 11.26; S, 11.28 Found (%) : C, 54.90; H, 2.80; N, 19.65; O, 11.22; S, 11.25

RESULTS AND DISCUSSION

The objectives of the present work are to synthesize certain substituted benzothiazole derivatives and study their antibacterial and anti-inflammatory activity in particular. Thus, an attempt has been made in this direction. As expected, substituted benzothiazoles exhibited antimicrobial activity some are equipotent to that of standard employed for comparison. Therefore, a detailed study of toxicity is necessary. There is no such a thing as completely safe drug. Drugs are powerful tools which alter physiological processes for the better or for the worse. A society which wishes to benefit from them will not achieve all the benefits are for the biological testing do not always turn out as potential new drugs, but may be intended to serve as models for evaluation of hypothesis.

CONCLUSION

In conclusion we have developed a simple methodology for the preparation of substituted Benzothiazole derivatives. The advantage of this method are extremely mild reaction conditions, short reaction time, high yield, simple experimental technique and compliance with green chemistry protocols.

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