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One pot Synthesis and Antibacterial Activity of Substituted Benzothiazolyl Acetamide

Chidrawar Anil*

P.G. Department of Chemistry, A. V. Education Society's, Degloor College, Degloor Dist. Nanded. Maharashtra (India) Pin-431717. Mobile No. 9423140093
Email: anilchidrawar74@gmail.com

ABSTRACT

Substituted benzothiazoles have received considerable attention during last two decades as they are endowed with the variety of biological activities and have the wide range of therapeutic properties. A literature survey indicates that benzothiazole derivatives possess different pharmacological and biological activities; which of most potent activity is anti-bacterial activity.

2-chloroacetyl amino-6-substituted benzothiazole and pyridine was dissolved properly then added a solution of 2-hydrazino benzothiazole in pyridine and refluxed for 5 hours to give 2- [2-(1,3-benzothiazol-2-yl) hydrazino] -*N*-(6-substituted-1,3-benzothiazol-2-yl) acetamide. The newly synthesized compounds were characterized by elemental analysis and spectral data.

KEYWORDS; 2-chloroacetyl amino-6-substituted benzothiazole, pyridine, 2-hydrazino benzothiazole.

***Corresponding author**

Anil Chidrawar

P.G. Department of Chemistry, A. V. Education Society's, Degloor College, Degloor

Dist. Nanded. Maharashtra (India) Pin-431717.

Mobile No. 9423140093 *Email:* anilchidrawar74@gmail.com

INTRODUCTION

Benzothiazole derivatives are an important class of heterocyclic compounds that exhibit a wide range of biological properties in medicinal and agricultural chemistry[1-5]. Further industrial applications as antioxidants, vulcanization accelerators and a dopant in a light emitting organic electroluminescent devices[6] have also been reported. Many reports have appeared in the literature describing the formation of benzothiazoles via one of the two major routes. The most commonly used method involves the condensation of o-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters in the presence of a catalyst such as p-toluenesulfonic acid (PTSA) in an organic solvent[7-14]. Another route is based on oxidative cyclization of thiobenzanilides using various oxidants[15].

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. Carrying out organic reactions in water has become highly desirable in recent years to meet environmental considerations. The use of water as a sole medium of organic reactions would greatly contribute to the development of environmentally friendly processes. It would be even more desirable to carry out catalytic organic reactions in water, which normally require delicate reaction conditions in order for the catalyst to be stable and yet reactive.

Substituted benzothiazole is an important class of heterocyclic compounds that exhibits a wide range of biological properties such as inhibitors of stearoyl-coenzyme desaturase, antitumor[16-18], antimicrobial[19], LTD_4 receptor antagonist[20], etc. For example, the investigations of benzothiazole as a key pharmacore led to Merck investigational new drugs such as the orexin receptor antagonist and the Gram-positive selective antibacterial.

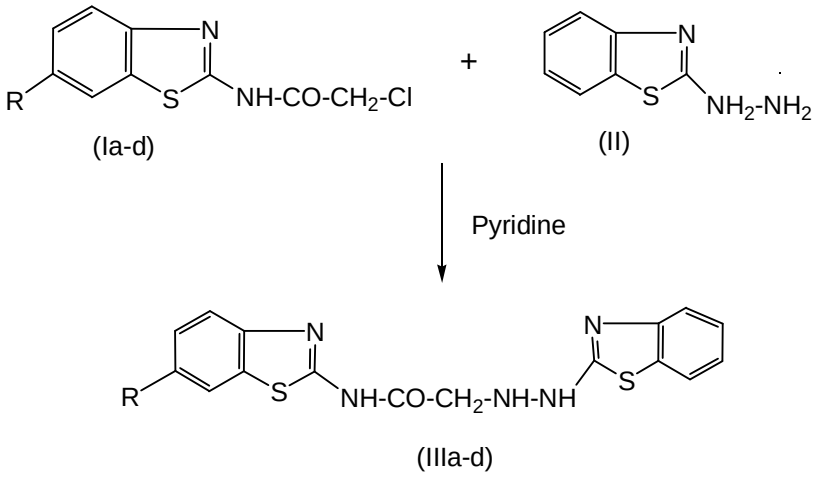
In view of these reported biological activities of this system, synthesis of such condensed system has attracted much attention in recent years. In this note, we report one pot synthesis of 2-[2-(1,3-benzothiazol-2-yl)hydrazino]-*N*-(6-substituted-1,3 -benzothiazol 2-yl)acetamide.

EXPERIMENTAL

Melting points were determined in open capillary tube and were uncorrected. IR spectra were detected by using potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO by using TMS. Mass spectra were detected by using FT VG-7070 H Mass Spectrometer. All the reactions were monitored by TLC.

The *in vitro* activities of the synthesized compound for tuberculosis inhibition against the *Mycobacterium tuberculosis* H37Rv (ATCC27294) strain were performed using the microplate Alomar blue assay (MABA) 24 method at TAACF. Compounds exhibiting fluorescence are tested in a BACTEC-460 radiometric system25, 26 and/or broth microdilution assay. The activities are expressed as minimum inhibitory concentration (MIC, µg/mL). Compounds demonstrating at least 90% inhibition were retested at lower concentrations to determine the actual MIC, a value defined as the lowest concentration inhibiting ≈ 90% of the inoculums relative to the control.

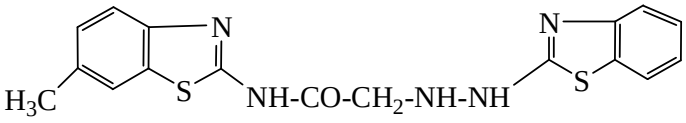
MATERIALS AND METHODS



General Procedure

1) Preparation of 2-[2-(1,3-benzothiazol-2-yl)hydrazino]-N-(6-methyl- 1,3- benzothiazol-2-yl) acetamide (IIIa):

A mixture of 2-chloroacetyl amino-6-methyl benzothiazole (0.1mole) and pyridine was dissolved properly then added to the RB flask containing a solution of 2-hydrazino benzothiazole (0.1 moles) in pyridine and refluxed for 5 hours. After completion of the reaction, it was cooled to room temperature, filtered and dried. The product was recrystallized from alcohol.



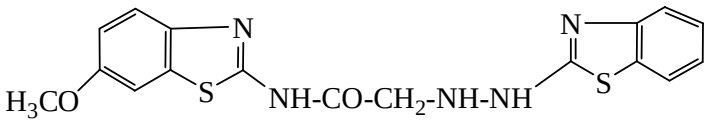
(IIIa)

Yield : 52 %, IR:(KBr/cm^{-1}) : 3410, 3280 & 3320 (-NH), 1670 (CO), ^{1}H-NMR: (DMSO): δ 2.35 (s 3H CH_3), δ 2.40 (s 2H CH_2), δ 4.05 (s 1H -NH), δ 4.10 (s 1H -NH), δ 4.15 (s 1H -NH), δ

6.95 (d 3H Ar-H), δ 8.12 (d 2H Ar-H), δ 8.22 (d 2H Ar-H), EI-MS: (m/z:RA%): 370 (M+1), Elemental analysis : $C_{17}H_{15}N_5OS_2$, Calculated: (%) C 55.26, H 4.09, N 18.96, O 4.33, S 17.36 Found (%) : C 55.20, H 4.01, N 18.88, O 4.31, S 17.32

2) Preparation of 2-[2-(1,3-benzothiazol-2-yl)hydrazino]-N-(6-methoxy-1,3-benzothiazol-2-yl) acetamide (IIIb):

A mixture of 2-chloroacetyl amino-6-methoxy benzothiazole (0.1 mole) and pyridine was dissolved properly then added to the RB flask containing a solution of 2-hydrazino benzothiazole (0.1 mole) in pyridine and refluxed for 5 hours. After completion of the reaction, it was cooled to room temperature, filtered and dried. The product was recrystallized from alcohol.

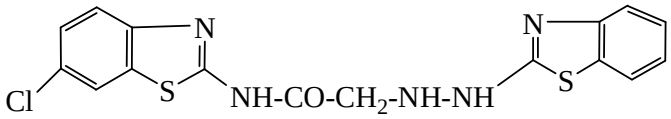


(IIIb)

Yield : 61 %, IR:(KBr/cm^{-1}) : 3400, 3410 & 3425 (-NH), 1672 (CO), ^{1}H-NMR: (DMSO): δ 3.73 (s 3H OCH_3), δ 2.45 (s 2H CH_2), δ 4.00 (s 1H -NH), δ 4.05 (s 1H -NH), δ 4.10 (s 1H -NH), δ 7.53 (d 3H Ar-H), δ 8.10 (d 2H Ar-H), δ 8.17 (d 2H Ar-H), EI-MS: (m/z:RA%): 386 (M+1), Elemental analysis : $C_{17}H_{15}N_5O_2S_2$, Calculated: (%) C 52.97, H 3.92, N 17.00, O 8.30, S 16.64 Found (%) : C 52.95, H 3.90, N 16.90, O 8.24, S 16.61

3) Preparation of 2-[2-(1,3-benzothiazol-2-yl)hydrazino]-N-(6-chloro-1,3-benzo thiazol-2-yl) acetamide (IIIc):

A mixture of 2-chloroacetyl amino-6-chloro benzothiazole (0.1 mole) and pyridine was dissolved properly then added to the RB flask containing a solution of 2-hydrazino benzothiazole (0.1 mole) in pyridine and refluxed for 5 hours. After completion of the reaction, it was cooled to room temperature, filtered and dried. The product was recrystallized from alcohol.



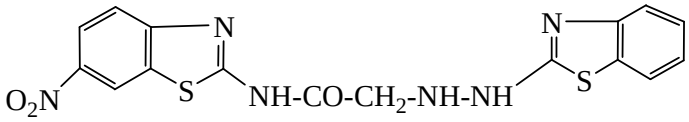
(IIIc)

Yield : 54 %, IR:(KBr/cm^{-1}) : 3390, 3415 & 3420 (-NH), 1700 (CO), ^{1}H-NMR: (DMSO): δ 2.78 (s 2H CH_2), δ 4.01 (s 1H -NH), δ 4.05 (s 1H -NH), δ 4.12 (s 1H -NH), δ 7.80 (d 3H Ar-H), δ 7.55 (d 2H Ar-H), δ 8.10 (d 2H Ar-H), EI-MS: (m/z:RA%): 390 (M+1), Elemental analysis :

$C_{16}H_{12}ClN_5OS_2$, Calculated: (%) C 49.29, H 3.10, Cl 9.09, N 17.96, O 4.10, S 16.45 Found (%) : C 49.25, H 3.07, Cl 9.06, N 17.90, O 4.08, S 16.41

4) Preparation of 2-[2-(1,3-benzothiazol-2-yl)hydrazino]-N-(6-nitro-1,3-benzo thiazol-2-yl) acetamide (IIId):

A mixture of 2-chloroacetyl amino-6-nitro benzothiazole (0.1 mole) and pyridine was dissolved properly then added to the RB flask containing a solution of 2-hydrazino benzothiazole (0.1 mole) in pyridine and refluxed for 5 hours. After completion of the reaction, it was cooled to room temperature, filtered and dried. The product was recrystallized from alcohol.



(IIId)

Yield : 51 %, IR:(KBr/cm^{-1}) : 3395, 3410 & 3417 (-NH), 1710 (CO), 1560 and 1332 (-NO_2), ^{1}H-NMR: (DMSO): δ 2.80 (s 2H CH_2), δ 4.00 (s 1H -NH), δ 4.05 (s 1H -NH), δ 4.10 (s 1H -NH), δ 8.50 (d 3H Ar-H), δ 7.60 (d 2H Ar-H), δ 8.45 (d 2H Ar-H), EI-MS: (m/z:RA%): 401 (M+1), Elemental analysis : $C_{16}H_{12}N_6O_3S_2$, Calculated: (%) C 47.99, H 3.02, N 20.99, O 11.99, S 16.02 Found (%) : C 47.95, H 3.00, N 20.96, O 11.97, S 16.00

RESULTS AND DISCUSSION

All the synthesized compounds were screened for antibacterial activity studies at a concentration of 50 µg /ml & 100 µg /ml using DMSO as a control against Aspergillus Niger and Penicillium sp species by well diffusion method on nutrient agar media, Ampicillin 50 µg /ml & 100 µg /ml used as standard against Gram positive and Gram-negative bacteria. Compounds IIIa and IIId show good antibacterial activity against Penicillium sp species and compounds IIIb and IIIc shows good antibacterial activity against Aspergillus Niger species.

CONCLUSION

Two moieties are fused and screened for antibacterial studies they showed a broad spectrum of antibacterial activity. They showed good activity against Penicillium sp and Aspergillus Niger species. Newly synthesized compounds are responsible for the antibacterial activity, but it is interesting to note that benzothiazole moieties, when fused with other moieties, showed a broad spectrum antibacterial activity. Hence in search of a new generation of antibiotics, it may be worthwhile to explore the possibility in this area by fusing different moieties and increase potency.

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