ejpmr, 2022, 9(8), 402-405

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

NOVEL SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF 6-SUBSTITUTED 2-MERCAPTO BENZOTHIAZOLES

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Article Received on 09/06/2022 **Article Revised on 30/06/2022** **Article Accepted on 21/07/2022**

ABSTRACT

The synthesis of 6-substituted 2-mercapto benzothiazoles was carried out by action of ammonium thiocyanate and bromine on *p*-substituted anilines (1) to afford 6-substituted 2-aminobenzothiazoles (2) as reported in the literature. This upon treatment with aqueous potassium hydroxide under reflux conditions gave potassium salt of 2-amino thiophenol (3). This mixture was then diluted with water, filtered and 5N acetic acid was added with vigorous stirring and until it becomes acidic. Yellow crystals of substituted 2-amino thiophenols (4) were filtered off, washed with cold water and dried. These thiophenols (4) were further treated with CS_2 and potassium hydroxide in ethanol under reflux condition to provide the potassium salt of 2-mercapto benzothiazoles (5), which upon acidification with 1M HCl affords the 6-substituted 2-mercapto benzothiazoles (6a-c). The structures for the synthesized compounds are assigned on the basis of IR, ^{1}HNMR and Mass spectral studies.

KEYWORDS: Ammonium thiocyanate, 2-amino thiophenol, potassium hydroxide, 2-mercapto benzothiazoles.

INTRODUCTION

The main objective of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents. During the past decade, heterocyclic structures received special attention as they belong to a class of compounds with proven utility in medicinal chemistry. Active bicyclic molecules containing two hetero atoms. 2-mercapto benzothiazole (MBT) is an important scaffold known to be associated with several biological activities, and its derivatives are manufactured worldwide for a wide variety of applications. S-acethydrazide hydrazone[1] and S-acyl[2] derivatives of MBT were reported to possess antifungal and antibacterial activities, and were also found to be useful in the leather industry.[3] 2-(Thiocyano methylthio) benzothiazole[4] is a potential contact fungicide for several economically important crops such as barley, cotton, corn, and wheat. 2,2′-Dithiobisbenzothiazole is used as a fungicide, insecticide, sensitizer, and ant scorching agent in the vulcanization of rubber.[5]

A number of methods for the synthesis of 2-mercaptobenzothiazoles (MBTs) have been reported. Among these, classical approaches involve the reaction of thio carbanilide with sulfur or the interaction of o-amino thiophenol with carbon disulfide under high pressure.[6–13] Several groups reported synthesis of MBTs by the nucleophilic aromatic substitution reaction of a potassium/sodium *o*-ethyl dithiocarbonate with *o*-haloanilines followed by a subsequent cyclization.[14–19] Recently, two efficient approaches from 2-haloaniline precursors were applied for the synthesis of MBTs. The first approach[20] involves a copper-catalyzed condensation reaction of the 2-iodoaniline with thiols in the presence of potassium carbonate. The second[21] involves the reaction of the *o*-haloanilines with carbon disulfide in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

The last systematic review on the biodegradation and toxicity of MBT was published in 1997[22], although subsequent surveys have appeared in articles[23,24] covering the cancer risk from repeated exposure to MBT. Aspects of the chemistry of MBTs have been covered.[25–30] The discovery that MBTs are accelerators of the vulcanization of rubber has stimulated many workers to synthesize and extensively evaluate their derivatives. In this review, we present the most significant examples of compounds belonging to this class that exhibit various biological activities reported in literature. The relationship between MBT metal complexes and their pharmacological activities are not included in this review.

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.

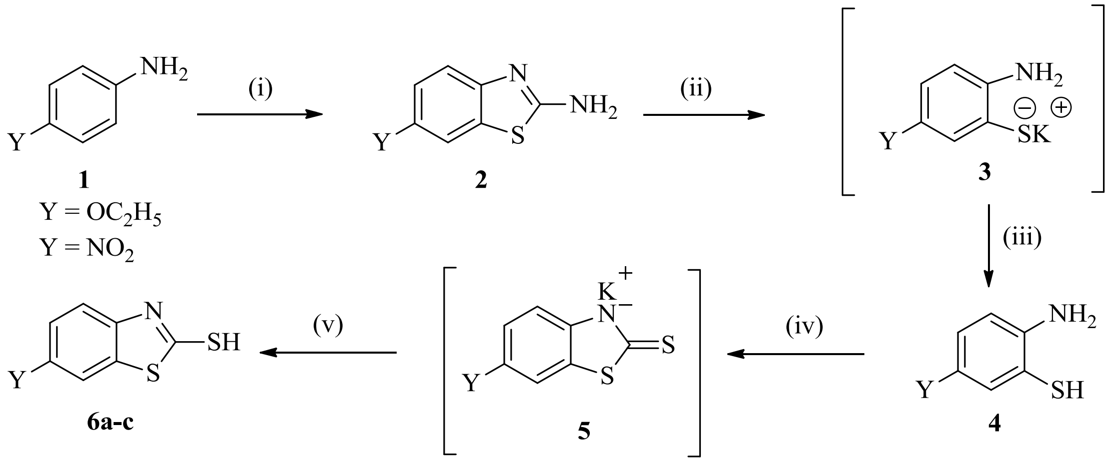
MATERIAL AND METHODS

Synthesis of 2-mercapto benzothiazole, 6-ethoxy 2-mercapto benzothiazole & 6-nitro 2-mercapto benzothiazole

In the present work, we report synthesis of 6-substituted 2-mercapto benzothiazoles was carried out by action of ammonium thiocyanate and bromine on *p*-substituted anilines (1) to afford 6-substituted 2-aminobenzothiazoles (2) as reported in the literature. This upon treatment with aqueous potassium hydroxide under reflux conditions gave potassium salt of 2-amino thiophenol (3). This mixture was then diluted with water, filtered and 5N acetic acid was added with vigorous stirring and until it becomes acidic. Yellow crystals of substituted 2-amino thiophenols (4) were filtered off, washed with cold water and dried. These thiophenols (4) were further treated with CS_2 and potassium hydroxide in ethanol under reflux condition to provide the potassium salt of 2-mercapto benzothiazoles (5), which upon acidification with 1M HCl affords the 6-substituted 2-mercapto benzothiazoles (6a-c).

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.

REACTION



6a: Y = H
6b: Y = OC_2H_5
6c: Y = NO_2

Reagents and conditions:
(i) NH_4SCN, Br_2, DCM, rt, 6-8h;
(ii) aq. KOH, reflux, 6-8 h;
(iii) 5N AcOH, 3-5 h;
(iv) CS_2, KOH, EtOH, reflux, 12 h;
(v) dil. HCl.

Chemical analysis

1. (6a) : 2-mercaptobenzothiazole

IR:(KBr/cm^{-1}) : 2551 (S-H), 1622 (C=N), 1611-1592 (C=C), EI-MS: (m/z:RA%) : 167 (M+1), **Elemental analysis:** $C_7H_5NS_2$ Calculated: (%) C, 50.27; H, 3.01; N, 8.37; S, 38.34 Found (%) : C, 50.25; H, 3.00; N, 8.32; S, 38.31

2. (6b) : 6-ethoxy 2-mercapto benzothiazole

IR:(KBr/cm^{-1}) : 2550 (S-H), 1620 (C=N), 1610-1590 (C=C), 1160 (C-O), EI-MS: (m/z:RA%) : 211 (M+1), **Elemental analysis:** $C_9H_9NOS_2$ Calculated: (%) C, 51.16; H, 4.29; N, 6.63; O, 7.57; S, 30.35 Found (%) : C, 51.11; H, 4.25; N, 6.60; O, 7.55; S, 30.32

3. (6c) : 6-nitro 2-mercapto benzothiazole

IR:(KBr/cm^{-1}): 2552 (S-H), 1622 (C=N), 1611-1590 (C=C), 1550 ($-NO_2$), EI-MS: (m/z:RA%) : 212 (M+1), **Elemental analysis:** $C_7H_4N_2O_2S_2$ Calculated: (%) C, 39.61; H, 1.90; N, 13.20; O, 15.08; S, 30.21 Found (%) : C, 39.60; H, 1.88; N, 13.18; O, 15.06; S, 30.20

RESULTS AND DISCUSSION

2-Mercapto benzothiazoles exert adverse effects on viruses and also act on yeasts and fungi. The antiviral screening results of MBT showed significant activity against two out of three viruses tested. The anti-*Candida* activity of MBT was studied against *Candida* strains and the results showed 50% growth inhibition at concentrations varying biological activities of 2-mercapto benzothiazole derivatives. The antifungal effects of MBT were also tested against *Aspergillus* *niger* with a suspension of spore-free mycelium homogenate as inoculum, and a 33 mg L−1 MBT concentration was the lower limit for 100% growth inhibition after five days of cultivation. Similar results, although obtained under other conditions, are described for the fungus *Trichophyton rubrum*. It was observed that for complete growth inhibition of *Microsporum gypseum* and *Epidermophyton floccosum*, MBT concentration had to exceed 50 mg L−1. The results of a study suggested that the thiol group of MBT is essential for its toxicity, since benzothiazole (BT) was not an active fungicide. However, in another experiment the presence of zinc destroyed the fungicidal activity of MBT, and this contradicts what was suggested above.

The antifungal activity of 6-ethoxy 2-mercapto benzothiazole, a significant inhibitory activity against *Aspergillus niger*, *Penicillium roquefortl*, and *Chaetomium globosum* (MIC 75, 50, and 50 ppm, respectively) was observed. On the other hand, 6-nitro 2-mercapto benzothiazole exhibited potent inhibitory activity against *Aspergillus niger* and *Chaetomium globosum* (MIC 5 and 7 ppm, respectively).

CONCLUSION

2-Mercapto benzothiazoles have been widely explored for industrial applications since their discovery. However, the biological activity of this class of compounds deserves further investigation. This becomes clear when microbial infections are considered. Although the research on this subject is incipient, the number of reports disclosing the effects of MBTs on pathogens of clinical interest has recently been increasing. 2-Mercapto benzothiazole compounds have been shown to be promising, which calls for the design of more efficient antimicrobial, anthelmintic, anti-inflammatory, and anti-allergic agents. Future studies will undoubtedly uncover unexpected properties and applications. Advances in this field will require analyses of the structure-activity relationships of MBTs, as well as the mechanisms of action of these compounds.

ACKNOWLEDGEMENTS

The authors are thankful to the Principal, Degloor College, Degloor for providing laboratory facilities and the Director, Indian Institute of Chemical Technology, Hyderabad for providing spectra.

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