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Synthesis and Preliminary Antibacterial Study of New 2-Mercapto-1, 3-Benzothiazole Derivatives With Expected Biological Activity

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Abstract:

Benzothiazoles are bicyclic ring system which have multiple applications. as antitumor , antiviral , antibacterial , anthelmintic and some of them showed glucose level.20 lowering effect. Accordingly, research is conducted to synthesize and evaluate some new derivatives as antibacterial agents by linking 2-aminobenzothiazoles with glycine and glycine derivatives.

S-benzo[d]thiazol-2-yl2-(2-(2,4-dinitrophenyl)hydrazinyl) ethanethioate has been tested on hospital strains of E.coli and pseudomonas and found to have good activity at different concentrations.

Key words: benzothiazoles , antibacterial , chloroacetyl chloride

الخلاصة:

مجموعة البنزوثايزول هي مجموعة متكونة من حلقتين لها الكثير من الاستخدامات فقد اظهرت مركبات من هذه المجموعة فعالية ضد السرطان وكمضادات للفايروسات والبكتريا وحتى الديدان بالاضافة الى ان بعضها له قابيلية على تخفيض مستوى السكر بالدم.

ونتيجة لذلك اجري هذا البحث لتصنيع وتقييم مركبات جديدة من هذه المجموعة لها فعالية مضادة للبكتريا من خلال ربطها مع الحامض الاميني الكلايسين ومشتقاته وقد اختبر المركب الاخير من هذه المجموعة على عزلات بكتيرية من المستشفى لبكتريا ال E.coli and pseudomonas ولوحظ امتلاكه لفعالية مضادة لتلك الانواع بتراكيز مختلفة

Introduction:

Benzothiazoles are bicyclic ring system with different applications. Although they have been known from long time ago to be biologically active [1- 3], their varied biological features are still of great scientific interest. Benzothiazoles show antitumor activity, especially thephenyl-substituted benzothiazoles[4] , while condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity[5].

Recently, Racane *et al.*[6] have described the synthesis of bis-substituted amidino benzothiazoles as potential anti HIV agents. Substituted 6-nitro-and 6-aminobenzothiazoles show antimicrobial activity.[6-8]

In addition, benzothiazole derivatives were found to have anthelmintic activity [9], and some derivatives were found to have glucose lowering effect. [10]

Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole.

Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. [11]

The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole. The two rings together constitute the basic nucleus 1, 3-benzothiazle. [12]

2-Mercapto-1,3-benzothiazole Derivatives were investigated for their antibacterial activity against a range of Gram-positive and Gram-negative bacteria strains and found to have an interesting antibacterial activity with MIC values of 3.12 lg/mL against Staphylococcus aureus

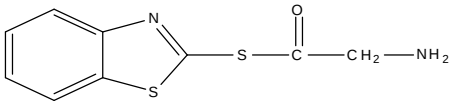
and 25 lg/mL against Escherichia coli, respectively.[13]

The 2-mercaptobenzothiazole may be prepared from the reaction of 2-aminophenol with carbon disulfide in the presence of acetic anhydride. [14]

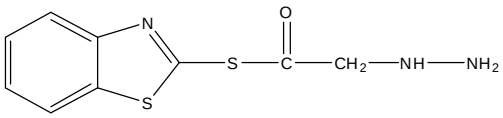
The substituents at second position of benzothiazole ring like mercapto group and hydrazine group are responsible for marked bactericidal activity and anti-inflammatory activity. [15] In addition, amino acids derivatives are used as promising antibacterial agents. [16, 17]

Accordingly, different 2-Mercapto-1, 3-benzothiazole Derivatives with glycine and substituted glycine were synthesized for their biological activity and specifically as antibacterial or anti-inflammatory agents as their structures agree with the early mentioned criteria for antibacterial benzothiazoles taking in consideration that they may have other biological actions. These compounds are as follows:

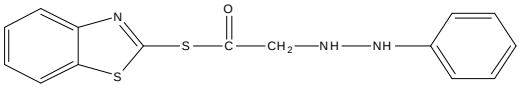
1-S-benzo[d]thiazol-2-yl 2-aminoethanethioate (linking with a glycine) comp.2



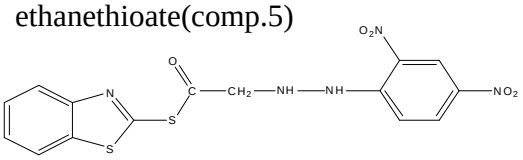
2-S-benzo[d]thiazol-2-yl 2-hydrazinylethanethioate (using glycine as a bridge)comp.3



3-S-benzo[d]thiazol-2-yl 2-(2-phenylhydrazinyl)ethanethioate (using glycine as a bridge)comp.4



4-S-benzo[d]thiazol-2-yl2-(2-(2,4-dinitrophenyl)hydrazinyl) ethanethioate(comp.5)



Materials and Methods:

Synthesis of S-benzo[d]thiazol-2-yl 2-aminoethanethioate (comp.1)

Equimolar solutions of 2-mercaptobenzothiazole (0.1mole) and chloro-acetylchloride (0.1mole) in chloroform (30ml) in the presence of K_2CO_3 was refluxed on a water bath for about 12 hrs. The solvent is removed under vacuum and the residue was recrystallized frm methanol to give compound [1].mp.97-100^oC [18]

Synthesis of S-benzo[d]thiazol-2-yl 2-aminoethanethioate (comp.2)

To 2.44 g (0.01 mole) of compound 1, add ammonia solution, heat with stirring for 1 hr. Evaporate, ammonia solution under reduced pressure, recrystallize with ethanol to get compound 2 (off-white powder, m.p. 136-138 ^oC) [CHN analysis (theroretical:practical C, 48.19; H, 3.59; N, 12.49]

Synthesis of S-benzo[d]thiazol-2-yl 2-hydrazinylethanethioate (comp.3)

To 2.4 g (0.01 mole) of compound 1 in ice-water water bath, add hydrazine solution (90 %) drop wise and product obtained during addition, leave to evaporate excess hydrazine at room temperature, then

recrystallize with ethanol to get compound 3 (m.p. 165-168^{o}C). [CHN analysis (theroretical:practical) C, 45.17; H, 3.79; N, 17.56], however this compound can also be prepared by different procedure [18].

Synthesis of S-benzo[d]thiazol-2-yl 2-(2-phenylhydrazinyl) ethanethioate (comp.4)

To 1.67 g (0.01 mole) of compound 1 add phenyl hydrazine drop wise, the product obtained during addition, decant excess phenyl hydrazine, wash with ethanol and precipitate, the product with chloroform, filter to get precipitate compound 4 (m.p. 112 ^{o}C with charring brown precipitate). [CHN analysis(theroretical:practical) C, 57.12; H, 4.15; N, 13.32]

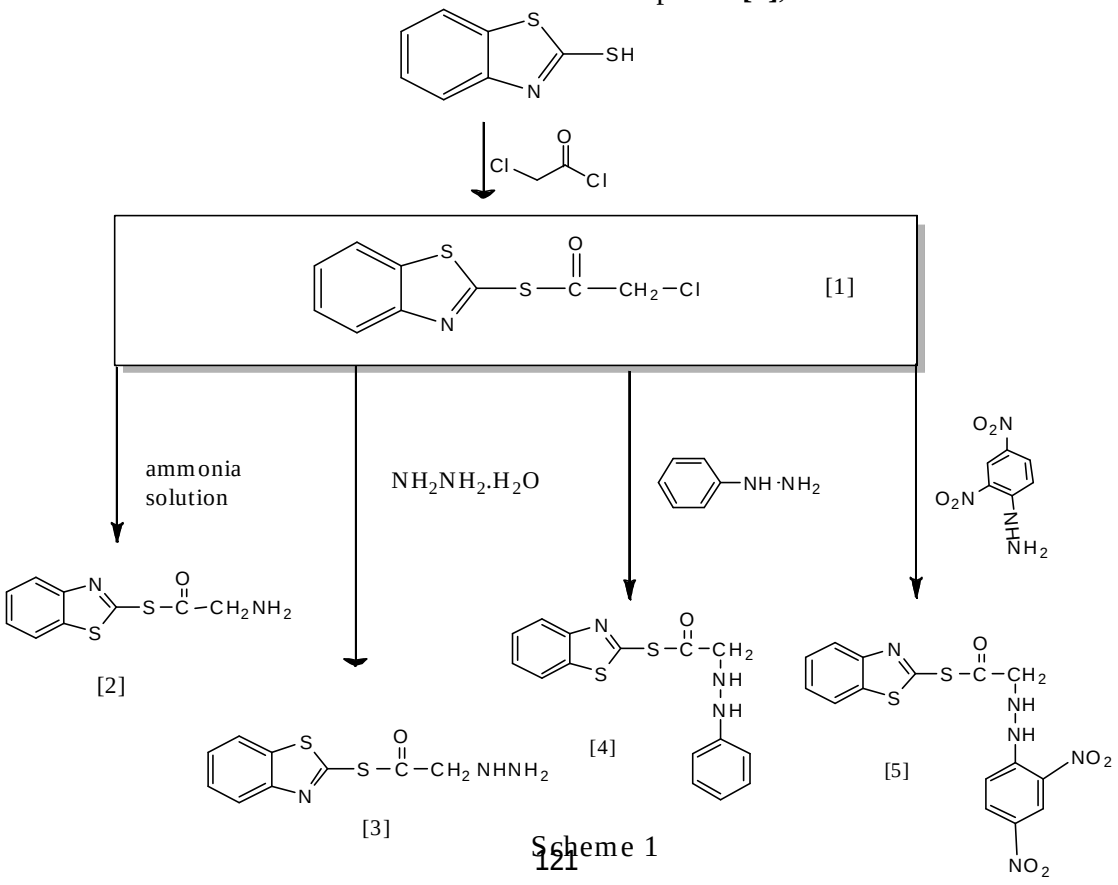
Synthesis of S-benzo[d]thiazol-2-yl2-(2-(2,4dinitrophenyl) hydrazinyl) ethanethioate (comp.5)

To 1.67 g (0.01 mole) of compound 1 add dinitro-phenyl hydrazine drop wise, a yellow precipitate is formed during addition, filter , wash with ethanol and precipitate, the product with chloroform, filter to get a clear yellow precipitate compound 4 (m.p. 124-127). [CHN analysis (theroretical:practical) C, 44.44; H, 2.73; N, 17.27]

Results and Discussion:

For the synthesis of the target benzothiazole heterocyclic derivatives, the reaction sequences are outlined as in the(scheme 1)

Accordingly reaction of 2-mercaptobenzothiazole with cloroacetyl chloride in dry acetone in resulted in compound **[1]** [18]. Compound **[1]** was treated with NH_3 solution, to afforded compound **[2].** The FTIR spectrum of compound **[2]**,



Scheme 1

showed a moderately strong band at (3389.04 cm^{-1}) due to NH_2 stretching vibration, and a band at (1674.27 cm^{-1}) for (C=O) stretching vibration. The success of the reaction has been confirmed by appearance of NH_2 stretching vibration band.

The FTIR spectrum of [3] compound shows absorption band at (1647 cm^{-1}) for (C=O) stretching vibration of amide, (3350-3284 cm^{-1}) for NH_2 stretching vibration, (3190 cm^{-1}) for NH stretching vibration.

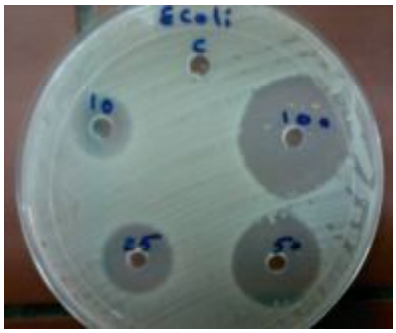
In the present investigation, the reaction of phenyl hydrazine as in compound [1] to obtain the crude product [4] that have FTIR show absorption band at (3308, 3209 cm^{-1}) due to NH stretching vibration, band at (1608 cm^{-1}) refer to (C=O) stretching vibration.

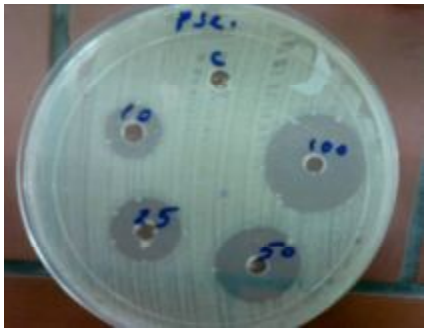
The FTIR spectrum of [5] compound showed an FTIR spectrum which exhibited bands at 3350 cm^{-1} (NH_2), 3107cm^{-1} (N-H), 1550 and 1354 cm^{-1} due to aromatic NO_2 group.

Table 1, represent the IR spectroscopy of the synthesized compound

Table 1: IR spectroscopy of the synthesized compounds Compound 5 is investigated for its antibacterial activity using laboratory strains of E.Coli and pseudomonas and showed marked zones of inhibition as shown in the following figures below.

Compound No.	ν(C=C)	ν(C=N)	ν(C=O)	ν(C-H)al. ν(C-H)ar.	Others
1	1500 1485	1607	1659	2980 3100	777 $(CH_2Cl)_{st}$
2	1425 1454	1618	1674	2950 3100	3367, 3389 $(NH_2)_{st}$
3	1458	1541	1647	2900 3100	3350-3284 $(NH_2)_{st}$ 3190 $(NH)_{st}$
4	1496	1589	1608	2835 3022	3308, 3209 $(NH)_{st}$
5	1500	1554	1612	3007 3188	3350$(NH_2)_{st}$ 3107$(NH)_{st}$ 1550,1354$(NO_2)_{st}$





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