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# Synthesis of new 2-Mercaptobenzothiazoles derivatives which contain oxothiazolidinone moiety with biological activity

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**Abstract**
An important class of chemical compounds with bioactive properties and significant industrial value is 2-Mercaptobenzothiazoles (2-MBT). In this research, oxothiazolidinone derivatives of 2-mercaptobenzothiazole have been synthesized through the reaction of Schiff base derivatives of 2-mercaptobenzothiazole with mercapto-acetic acid 5 a-d, and their antibacterial effects against four pathogenic bacteria (Staphylococcus aureus, Escherichia coli, Bacillus subtilis, and Mycobacterium tuberculosis) were assessed. These compounds' FTIR, 1HNMR, and physical property measurements were used to characterize the compounds and determine their identities.

**Keywords: 2-Mercaptobenzothiazoles, oxothiazolidinone**

## Introduction

A wide range of biological applications for benzothiazole (BT) derivatives, including analgesic, anticancer, antioxidant, anti-inflammatory, anti-diabetic, anti-convulsant, anti-tubercular, anti-malarial, anti-leishmanial, anti-histaminic, antibacterial, antiviral, and antifungal, have been discovered through research [1-3]. The important skeleton 2-Mercaptobenzothiazole (2- MBT) and its derivatives are produced all over the world for a wide range of medical uses. It is well known for its relationship with several biological activities [4,5]. The addition of the benzyl moiety to 2-MBT is notable for its antibacterial and anticancer properties. Numerous compounds with a variety of pharmacological properties can be produced by altering the benzyl moiety [6,7].

The main objective of organic and medicinal chemistry is to produce substances that may be used as human therapeutic agents. Recent interest in heterocyclic structures has increased since they are The essential scaffold 2-Mercaptobenzothiazole (MBT) is known to be involved in a number of biological processes, and its derivatives are produced all over the world for a range of uses. S-acyl derivatives of MBT[8] and S-acethydrazidehydrazone were found to have antifungal and antibacterial properties [9].

## MATERIALS AND METHODS

China's hyper-chem provided the chemicals needed in the synthesis. Using silica gel GF254 (type 60) pre-coated aluminum sheets from Merck (Germany), thin-layer chromatography (TLC) was used to evaluate the completion of reactions and the purity of the chemicals. Five solvent systems, including ethyl acetate: hexane (4:6) and ethyl acetate: hexane (6:4), were employed in the exposure to UV-254 nm radiation. The uncorrected melting points were found using the Stuart SMP3 melting point instrument in open capillary

tubes. The infrared spectra were produced using the thin film technique, (, cm-1), on a Shimadzu FTIR spectrophotometer, (Japan), at the Almustansiria University College of Science and the University of Baghdad's College of Pharmacy. On a BRUKER model Ultra shield 300 MHz spectrophotometer and a BRUKER model Ultra shield, 1HNMR spectra were acquired.

**Chemical synthesis:**

1. **Synthesis of 2-(benzo[d]thiazol-2-ylthio)acetic acid (1) [10]:**
   In 50 mL of ethanolic potassium hydroxide (1 g of KOH in 50 mL of ethanol 70%), 1.7 g (0.01 mol) of 2-mercaptobenzothiazole and 0.8 g (0.01 mol) of chloroacetic acid were added and refluxed for three hours. A precipitate was created when the ethanol evaporated from the air and it was then dissolved in water and acidified with hydrochloric acid. The precipitate was collected and crystallized from ethanol**;**mp 184$^{O}$C**;** yield 78%. FTIR: 3308 cm$^{-1}$(C-H stretching of aromatic H); 3112 cm$^{-1}$ (O-H stretching of carboxylic acid) and 1720 cm$^{-1}$ (C=O of carboxylic acid).
2. **Synthesis of 2-(benzo[d]thiazol-2-ylthio)acetyl chloride (2) :**
   A mixture of 2.25 g (0.01 mol) of the acid (1), 0.7 mL of thionyl chloride in 20 mL of dry benzene was refluxed for 7 h. The excess of thionyl chloride and benzene was distilled off, and the remaining oil.
3. **Synthesis of 2-(benzo[d]thiazol-2-ylthio)acetohydrazide(3) [11] :**
   2.4 g of the acid (2) was dissolved in 50 ml of methanol, and 1.5 ml of the 99% hydrazine hydrate were then added. The reaction was stirred continuously throughout the night after being refluxed for 9 hours at 65oC. A hot air stream was used to evaporate the solvent. After adding cold water to the residue, a white precipitate formed. This was filtered, rinsed with cold water, dried, and then washed with ether.mp 190$^{O}$C**;** yield 88%. FTIR: 3428 cm$^{-1}$(N-H stretching of Primary amine); 1678 cm$^{-1}$ (C=O of secondary amide) and 1590 cm$^{-1}$ (N-H bending of amine).

4. **Synthesis of 2-(benzo[d]thiazol-2-ylthio)acetohydrazide (4a-d)[12]:**
   A hydrazine derivative of compound (3) (2.4 g, 0.01 mol) was mixed with an equal amount of each of the corresponding aldehydes listed in Table 1 and stirred at room temperature for 0.5 to 1 hours with the addition of two to three drops of HCl as a catalyst. To determine when the reaction was finished, TLC was utilized. The crude product was then concentrated at lower pressure to isolate the hydrazones. Following this procedure, the precipitate was filtered, rinsed with 10 ml of water, and recrystallized from ethanol.
   **4 (a):**m.p.199-201$^{O}$C**;** yield 83%.FTIR: 3584 cm$^{-1}$(O-H stretching of free OH), 3317 cm$^{-1}$(N-H stretching of secondary amine); 1672 cm$^{-1}$ (C=O of secondary amide),1655 cm$^{-1}$ (N=C stretching of imine) and 1377 cm$^{-1}$(O-H bending of phenol).
   **4(b):**m.p. 197-200 $^{O}$C**;** yield 83%.FTIR: 3581 cm$^{-1}$(O-H stretching of free OH), 3312 cm$^{-1}$(N-H stretching of secondary amine); 1670 cm$^{-1}$ (C=O of secondary amide), 1654 cm$^{-1}$ (N=C stretching of imine) and 1370 cm$^{-1}$(O-H bending of phenol).
   **4(c):** m.p. 193-195 $^{O}$C**;** yield 78%. FTIR: 3310 cm$^{-1}$(N-H stretching of secondary amine); 1671 cm$^{-1}$ (C=O of secondary amide), 1652 cm$^{-1}$ (N=C stretching of imine) and 751 cm$^{-1}$ (C-Cl stretching of halo alkane).
   **4(d):** m.p. 192-194 $^{O}$C**;** yield 77%. FTIR: 3311 cm$^{-1}$(N-H stretching of secondary amine); 1672 cm$^{-1}$ (C=O of secondary amide) and 1204 cm$^{-1}$ (C-F stretching of halo alkane).

**Table 1: Name of aldehydes used**

| R | Name of aldehyde |
|---|---|
| a | 4- hydroxyl benzaldehyde |
| b | 3- hydroxyl benzaldehyde |
| c | 4-Chloro benzaldehyde |
| d | 4-Flouro benzaldehyde |

**5. Synthesis of compounds (5a-d) [13] :**

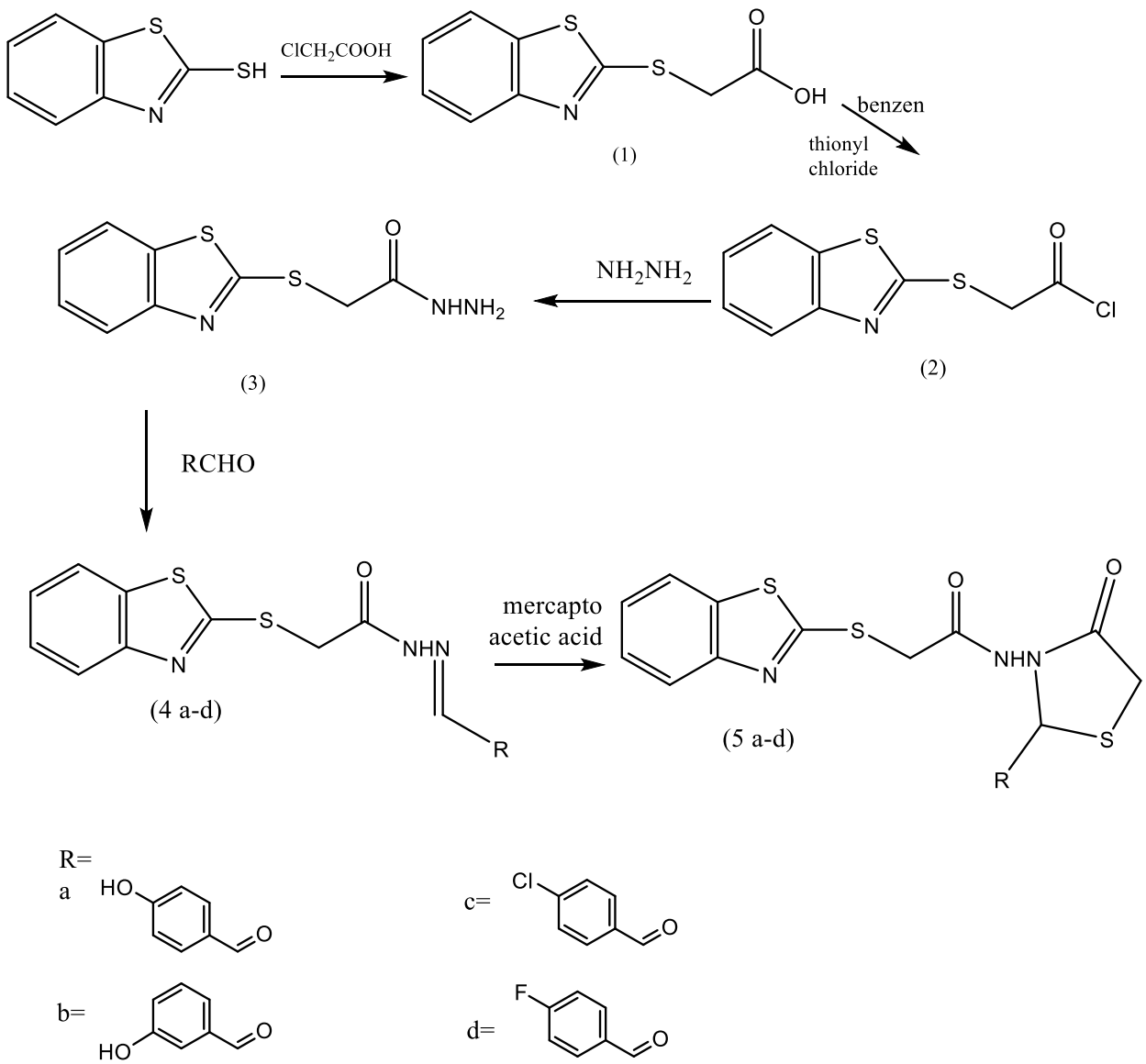
The reaction occurred out in a combination of hydrazine derivatives (4a-d) (1 mmol) and excess mercaptoacetic acid (5 ml) at 60 $^{o}$C for approximately 6 hours, as determined by TLC. Ethyl acetate (10 ml) was added, followed by the addition of water (10 ml), MgSO4, drying, and concentration to create an oily material. Petroleum ether was then used to triturate the finished product.

**5 (a):**m.p. 227-229 $^{O}$C**;** yield 79%. FTIR: 3577 cm$^{-1}$(O-H stretching of free OH), 3321 cm$^{-1}$(N-H stretching of secondary amine); 2555 cm$^{-1}$ (S-H stretching of thiol) and 1746 cm$^{-1}$ (C=O of cyclic amide).$^{1}$HNMR (300 MHz,:DMSOd6): 11.2 (1,s,NH-C=O), 9 (1,s,OH of phenol), 3.8 (1,m, S-CH-C=O of thiazolidinone ring) and 6.7-7.8 (8H,m, aromatic ring).

**5(b):**m.p. 222-223$^{O}$C**;** yield 75%. FTIR: 3571 cm$^{-1}$(O-H stretching of phenol), 3307 cm$^{-1}$(N-H stretching of secondary amine); 2553 cm$^{-1}$ (S-H stretching of thiol) and 1745 cm$^{-1}$ (C=O of cyclic amide). $^{1}$HNMR (300 MHz,:DMSOd6): 11.1 (1,s,NH-C=O), 8.9 (1,s,OH of phenol), 3.7 (1,m, S-CH-C=O of thiazolidinone ring) and 6.7-7.8 (8H,m, aromatic ring).

**5(c):** m.p. 218-219$^{O}$C**;** yield 77%. FTIR: 3309 cm$^{-1}$(N-H stretching of secondary amine); 1669 cm$^{-1}$ (C=O of secondary amide)and 750 cm$^{-1}$ (C-Cl stretching of halo alkane). $^{1}$HNMR (300 MHz,:DMSOd6): 11 (1,s,NH-C=O), 3.72 (1,m, S-CH-C=O of thiazolidinone ring) and 6.7-7.8 (8H,m, aromatic ring).

**5(d):** m.p. 215-216$^{O}$C**;** yield 74%. FTIR: 3308 cm$^{-1}$(N-H stretching of secondary amine); 1670 cm$^{-1}$ (C=O of secondary amide) and 1201 cm$^{-1}$ (C-F stretching of halo alkane). $^{1}$HNMR (300 MHz,:DMSOd6): 10.8 (1,s,NH-C=O), 3.67(1,m,S-CH-C=O of thiazolidinone ring) and 6.7-7.8 (8H,m, aromatic ring).




**Scheme (1): Synthesis of 2-Mercaptobenzothiazoles derivatives**

**Table 2: The characterization and physical parameters of the target compounds and their intermediates**

| No | Molecular formula | . Molecular weight | Melting Point °C | % yield | physical appearance |
|---|---|---|---|---|---|
| 1 | $C_9H_7NO_2S_2$ | 225.28 | 184 | 78 | Yellow powder |
| 2 | $C_9H_6ClNOS_2$ | 243.72 | - | 67 | Pale-yellow oily |
| 3 | $C_9H_9N_3OS_2$ | 239.31 | 190 | 88 | Off White powder |

| | | | | | |
|---|---|---|---|---|---|
| 4a | $C_{16}H_{13}N_3O_2S_2$ | 343.42 | 199-201 | 83 | White powder |
| 4b | $C_{16}H_{13}N_3O_2S_2$ | 343.42 | 197-200 | 83 | White powder |
| 4c | $C_{16}H_{12}ClN_3OS_2$ | 361.86 | 193-195 | 78 | White powder |
| 4d | $C_{16}H_{12}FN_3OS_2$ | 345.41 | 192-194 | 77 | White powder |
| 5a | $C_{18}H_{15}N_3O_3S_3$ | 417.52 | 227-229 | 79 | yellow oil |
| 5b | $C_{18}H_{15}N_3O_3S_3$ | 417.52 | 222-223 | 75 | yellow oil |
| 5c | $C_{18}H_{14}ClN_3O_2S_3$ | 435.96 | 218-219 | 77 | Pale yellow oil |
| 5d | $C_{18}H_{14}FN_3O_2S_3$ | 419.51 | 215-216 | 74 | Pale yellow oil |
| 2-MBT | $C_7H_5NS_2$ | 167.24 | 177–180 | - | Orange crystals |

**Result and discussion:**

All compound prepared are identified by FT-IR spectroscopy, compound 1 is prepared by reaction of 2-mercaptobenzothiazoleand chloroacetic acid in which show the 3112 $cm^{-1}$ (O-H stretching of carboxylic acid) and 1720 $cm^{-1}$ (C=O of carboxylic acid) and change in melting point to 184 $^{O}$C, while in compound 2 which is prepared by reaction of 2-(benzo[d]thiazol-2-ylthio)acetic acidwith thionyl chloride can't make FT-IR spectroscopy due to the acyl group which prepared is unstable at room temperature so kept in the solvent we use in the next step of synthesis, Compound 3 was prepared by reaction of 2-(benzo[d]thiazol-2-ylthio)acetyl chloride and hydrazine hydrateand show FTIR: 3428 $cm^{-1}$(N-H stretching of Primary amine); 1678 $cm^{-1}$ (C=O of secondary amide) and change in melting point to 190 $^{O}$C.

In Compound 4 were prepared by mixture of hydrazine derivative of compound (3) and of the corresponding aldehydes listed in above chemical synthesis, so in compound 4a show 3584 $cm^{-1}$(O-H stretching of free OH), 3317 $cm^{-1}$(N-H stretching of secondary amine); 1672 $cm^{-1}$ (C=O of secondary amide), 1655 $cm^{-1}$ (N=C stretching of imine) and 1377 $cm^{-1}$(O-H bending of phenol) and the melting point appear 199-201°C. Compound 4b show 3581 $cm^{-1}$(O-H stretching of free OH), 3312 $cm^{-1}$(N-H stretching of secondary amine); 1670 $cm^{-1}$ (C=O of secondary amide), 1654 $cm^{-1}$ (N=C stretching of imine) and 1370 $cm^{-1}$(O-H bending of phenol) and the melting point appear 197-200°C, while compound 4c show the disappearing of O-H stretching vibration and appear of 3310 $cm^{-1}$(N-H stretching of secondary amine); 1671 $cm^{-1}$ (C=O of secondary amide), 1652 $cm^{-1}$ (N=C stretching of imine) and 751 $cm^{-1}$ (C-Cl stretching of halo alkane) themelting point appear 193-195°C, while compound 4d show the disappearing of O-H stretching vibration and 3311 $cm^{-1}$(N-H stretching of secondary amine); 1672 $cm^{-1}$ (C=O of secondary amide) and 1204 $cm^{-1}$ (C-F stretching of halo alkane), the melting point appear 192-194°C. Compound 5 were prepared by mixture of hydrazine derivatives 4 a-d and excess of mercaptoacetic acid, compound 5a show 3577 $cm^{-1}$(O-H stretching of free OH), 3321 $cm^{-1}$(N-H stretching of secondary amine); 2555 $cm^{-1}$ (S-H stretching of thiol) and 1746 $cm^{-1}$ (C=O of cyclic amide) and change in melting point to 227-229 $^{O}$C. Compound 5b show 3571 $cm^{-1}$(O-H stretching of phenol), 3307 $cm^{-1}$(N-H stretching of secondary amine); 2553 $cm^{-1}$ (S-H stretching of thiol) and 1745 $cm^{-1}$ (C=O of cyclic amide) and change in melting point to 222-223$^{O}$C. Compound 5c 3309 $cm^{-1}$(N-H stretching of secondary amine); 1669 $cm^{-1}$ (C=O of secondary amide) and 750 $cm^{-1}$ (C-Cl stretching of halo alkane) and change in melting point to 218-219$^{O}$C, while compound 5d show 3308 $cm^{-1}$(N-H stretching of secondary amine); 1670 $cm^{-1}$ (C=O of secondary amide) and 1201 $cm^{-1}$ (C-F stretching of halo alkane), the melting point appear 215-216°C.

**Biological Activities**

Using the broth micro-dilution method, 5a-d's antibacterial properties were assessed against four bacteria, including Gram-positive and Gram-negative bacteria, at concentrations between 256 and 1 µg/mL. The tests were done on three harmful bacteria, including S. aureus, E. coli, and B. subtilis. Table 2 presents

the outcomes. With minimum inhibitory concentrations (MIC) of 6 and 18 µg/mL for S. aureus and B. subtilis, respectively, compound 5c significantly inhibited both bacteria. With MIC values ranging from 30 to 60 µg/mL, compounds 5a, b, and d showed a moderately effective antibacterial activity against S. aureus, E. coli, and B. subtilis. Compound 5c's antitubercular effects in M. tuberculosis were marginal (MIC: 54 µg/mL).

**Table 2. Antibacterial activities of compounds 5 a-d.**

| **Compound** | **minimum inhibitory concentration (MIC) values in µg/mL** | | | |
|---|---|---|---|---|
| | S. aureus | E. coli | B. subtilis | M. tuberculosis |
| 5 a | 61 | 30 | 120 | 122 |
| 5 b | 60 | 60 | 120 | 122 |
| 5 c | 6 | 60 | 18 | 54 |
| 5 d | 59 | 60 | 120 | 120 |
| Chloramphenicol | 8 | 4 | 2 | - |
| Ethambutol | - | - | - | 8 |

**Antibacterial Assay**

According to a previously established procedure [(14)], the antibacterial activities of compounds 5(a-d) were assessed against Gram-positive bacteria S. aureus ATCC 25923, B. subtilis ATCC 6633, and Gram-negative bacteria E. coli ATCC 25922. The test chemicals (1 mg/mL for a-d) were dissolved in DMSO. The minimum inhibitory concentration (MIC) values were established as the lowest concentration of test chemical that, when observed visually after an overnight incubation in 96-well microtiter plates, stopped the growth of more than 99% of the bacterial population. In a nutshell, 100 L of each bacterial solution (105 CFU/mL) was infected in each well before being combined in triples with 100 L of each chemical solution and control. At 37°C, the microplates were incubated for 24 hours. The ultimate amounts of each test substance in theUsing sequential 2-fold serial dilutions, wells were in the 256–1 µg/mL range. By adding the medium, the final DMSO concentration was kept at 0.5%. The positive control and the negative control utilized were Chloramphenicol and DMSO, respectively. Based on the prior findings [(15)], a detailed technique of the antitubercular activity of compounds 5 a–d against M. tuberculosis H37Rv was provided. DMSO served as the blank control. A positive control was Ethambutol.

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