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Original Research Article

Synthesis and Characterization of Heterocyclic Compounds Derived from 2-Mercaptobenzothiozole and Study of Their Biological Activities

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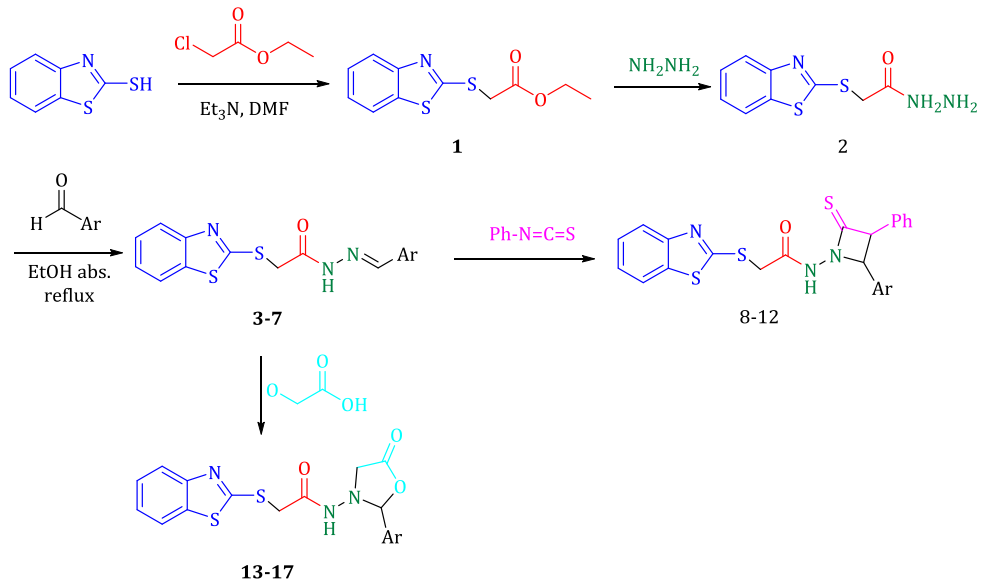
ABSTRACT

In this study, Schiff base derivatives were reacted with phenyl isothiocyanate and chloroacetic acid to give diazetidine-2-thione and oxazolidinone derivatives. The Schiff base derivatives containing the 2-mercabto benzothiazole moiety were obtained via reaction of a different aromatic aldehyde with 2-(benzothiazol-2-ylthio) acetohydrazide. Furthermore, 2-(benzothiazol-2-ylthio) acetohydrazide were obtained via reaction of 2-mercabto benzothiazole with ethyl chloroacetate, then with hydrazine hydrate. The newly synthesized compounds were characterized *via* spectral data (FT-IR and ^{1}H-NMR). The antibacterial activity was studied against examples of Gram-positive and Gram-negative bacteria.

GRAPHICAL ABSTRACT



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Introduction

The widespread use of nitrogen-containing heterocycles in agriculture, industry, and medicine has piqued researchers' curiosity. 2-mercapto-1,3-benzoxazole MBO and their derivatives, in particular, have been used to protect metals from environmental corrosive effects [1-4], as metal ion detection chelating agents in analytical chemistry and metallurgy for selective flotation of sulfide ores as collectors MBT as well as its derivatives are a common form of vulcanization accelerator for rubber [5, 6]. Metal corrosion is inhibited to a high degree by the MBT, which is applied to protect Cu, Pd, and its alloys from connecting with different media [7,8]. MBT is used to modify multilayered carbon nanotubes so that they can be used as a sorbent for simultaneous magnetic solid-phase microextraction of trace amounts of copper, cadmium, and lead ions [9]. MBT and some of their derivatives have been revealed with have anti-inflammatory, analgesic and antibacterial properties [10-15, 16]. Also, benzo[d]thiazole-2-thiol is an essential scaffold which has been associated to a variety of biological functions [6,17-19]. Furthermore, its 2-substituted sulfanyl derivatives have been demonstrated to exhibit antinociceptive, anti-inflammatory , antibacterial, anti-mycobacterial, anticonvulsant, analgesic, anti-tubercular, anti-cancer properties and inhibit human cyclooxygenase [20,21]. Microwave irradiation has proven itself as a valuable tool in chemical synthesis [22,23]. This methodology is more appropriate for numerous organic processes to enhance reaction rates, reaction times, product yields, and selectivity when compared to the traditional energy sources. However, just a few synthetic techniques for S-alkylation of benzo[d] have been documented ultrasound irradiation of thiazole-2-thiol [24]. As part of our ongoing research into the synthesis of thiazole derivatives [25,26]. We present a highly regioselective synthesis of several new physiologically active 2-substituted sulfanyl benzo[d]thiazole derivatives under extremely mild basic conditions.

Materials and Methods

Experimental

Melting points were recorded using a (Gallenkamp) melting point apparatus with a sample contained in an open capillary glass tube in an electrically heated metal block apparatus. FT-IR spectra were recorded on (SHIMADZU) FT-IR 8400 S spectrophotometer, the solid samples were run as smears. ^{1}H-NMR spectra were recorded on Ultra Shield 400 MH, with tetramethyl silane as internal standard and DMSO as solvents.

General procedures

Synthesis of ethyl 2- (benzo[d]thiazol-2-ylthio) acetate [27] (1)

A solution of (5.25 mL) of 2-mercapto benzothiazole with (45 mL) DMF and (6 mL) of trimethylamine mixed for (20 min.), thereafter (4.5 mL) of ethyl chloroacetate added gradually with mixing for half an hour at room temperature. The reaction was elevated for (14 h) at a temperature from (60 to 65 °C). The reaction mixture was poured over ice and added sodium bicarbonate, separated by the separating funnel. Brown Oil, 87%.

Synthesis of 2-(benzo[d]thiazol-2-ylthio) acetohydrazide [27] (2)

A mixture of 2 g of ethyl 2-(benzo[d]thiazol-2-ylthio) acetate in (25 mL) methanol and (10 mL) of 99% hydrazine hydride was stirred for 24 h. at r.t. The mixture was poured into a ceramic eyelid to evaporate the excess methanol and hydrazine. Pall yellow, oil, 82%.

Synthesis of new Schiff bases from 2-(benzo[d]thiazol-2-ylthio) acetohydrazide (3-7)

A mixture of equal amount of compound (2) and deferent aromatic aldehydes in EtOH absolute (20 mL) and a few drops of glacial acetic acid (G.A.A.) after that refluxed for around 4-8 h. Under reduced pressure, the remaining solvent, evaporating, thereafter the crude precipitate was dried, and then recrystallization by chloroform. Table 1 lists all of the physical properties and yields of compounds.

Synthesis of oxazolidinone derivatives (8-12)

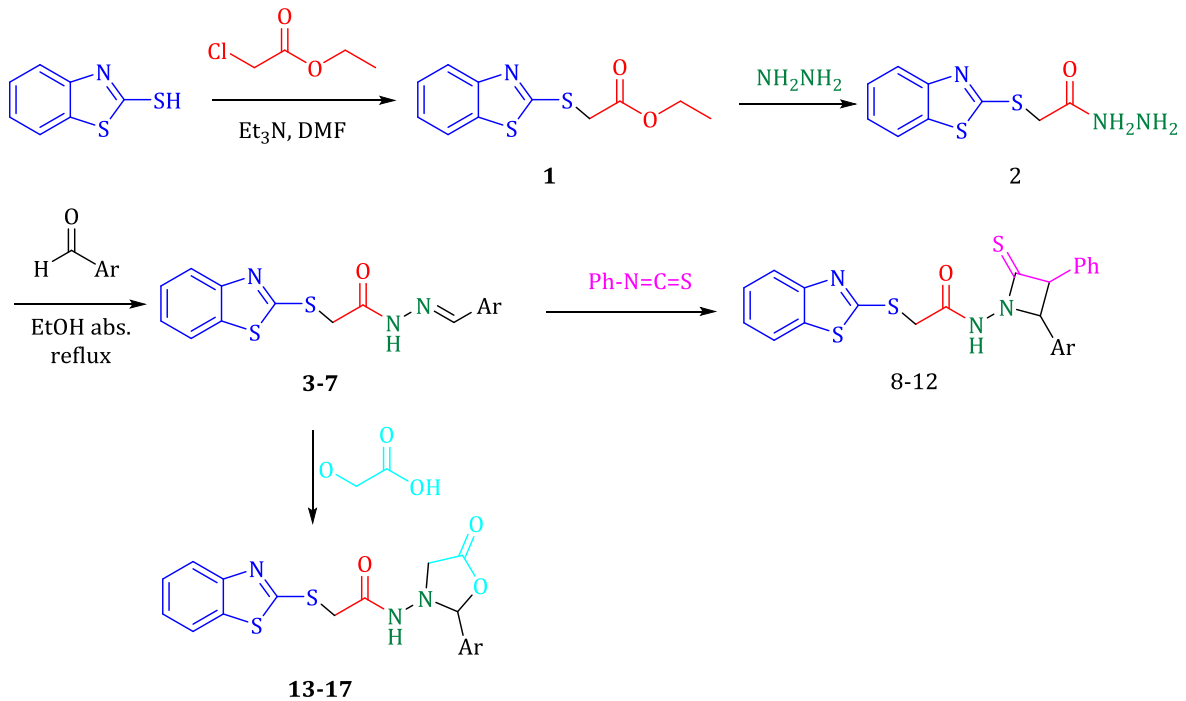
0.01 mol from a Schiff bases solution (3-7) in 25 mL THF as a solvent, was added to a mixture of chloroacetic acid (0.945 g, 0.02 mol). Next, some drops of Et_3N was added to the reaction mixture. After that, the reaction mixture was refluxed for 28-30 h, the mixture cooled. The solid product was collected, recrystallization from ethanol. Table 1 lists all of the physical properties and yields of compounds.

Synthesis of diazetidine-2-thione derivatives (13-17)

A mixture of Schiff base (3-7) (0.001 mol) in THF (25 mL) and phenyl isothiocyanate (0.02 mol) in a round bottom flask was reflux for around 9 h. Under decreased pressure, the solvent was extracted, and the residue was treated with a mixture of ethyl acetate and petroleum ether (1:1). The precipitate was filtered and dried as a consequence. Table 1 lists all of the physical properties and yields of compounds.

Table 1: Physical properties for syntheses compounds (3-17)

Compund No.	Molecular formula	M.wt (g/mol)	Yield (%)	m.p. (°C)	Color
3	$C_{16}H_{12}N_4O_3S_2$	272	87	135-136	Orange
4	$C_{16}H_{12}N_4O_3S_2$	272	77	124-125	Grow
5	$C_{16}H_{12}BrN_3OS_2$	406	81	160-162	Pall yellow
6	$C_{16}H_{12}ClN_3OS_2$	361	80	169-172	Pall yellow
7	$C_{17}H_{15}N_3O_2S_2$	357	79	176-177	Yellow
8	$C_{17}H_{13}N_5O_3S_3$	431	84	Oil	Brown
9	$C_{17}H_{13}N_5O_3S_3$	431	76	Oil	Brown
10	$C_{17}H_{13}BrN_4OS_3$	465	72	Oil	Brown
11	$C_{17}H_{13}ClN_4OS_3$	420	67	Oil	Brown
12	$C_{18}H_{16}N_4O_2S_3$	416	79	Oil	Brown
13	$C_{18}H_{14}N_4O_5S_2$	430	81	Oil	Brown
14	$C_{18}H_{14}N_4O_5S_2$	430	69	Oil	Brown
15	$C_{18}H_{14}BrN_3O_3S_2$	464	65	Oil	Brown
16	$C_{18}H_{14}ClN_3O_3S_2$	419	68	Oil	Brown
17	$C_{19}H_{17}N_3O_4S_2$	415	62	Oil	Brown



Scheme1: show all steps for syntheses of four and five membered rings

Results and Discussions

Ethyl 2-(benzo[d]thiazol-2-ylthio)acetate (1) was syntheses via reaction of 2-mercapto benzothiazole with ethyl chloroacetate in the presence of triethylamine as a catalyst, by a nucleophilic attacked of thiol group in 2-mercapto benzothiazole, the reaction is a typical substitution nucleophilic reaction (SN_2) of the thiol group followed by elimination of the HCI molecule, in which the halo group might be swapped out easily to produce a good yield producing compound due to the halo group is a good group to leave and the sulfur compound is indeed a good nucleophile (1), as indicated in scheme 1. Compound (1) was characterized FTIR spectrum data reveals a powerful absorption band at 1737 cm^{-1} due to C=O group to the ester and bands at 2842.88 cm^{-1} and 2927.74 cm^{-1} to the (CH) group aliphatic. Absorption bands at 2567 cm^{-1} for S-H was disappeared. Compound (1) was utilized to replace an ethoxy group with such a hydrazine group in a nucleophilic substitution process with hydrazine hydrate, producing the acetohydrazide. FTIR spectral data of compound (2) due to the symmetric and asymmetric stretching vibrations of amine group, the (C=O) ester band disappeared, absorption bands that become clear at 3109 cm^{-1} for NH and 3286-3199 cm^{-1} for NH_2, indicating acetohydrazide formation. The acetohydrazide compound (2) was converted to Schaff base (3-7) derivative via the reaction with deferent aromatic aldehydes in ethanol absolute as a solvent and G.A.A. as a catalyst. FTIR spectral data of compounds (3-7), band of (NH_2) at 3286- 3199 cm^{-1} was disappeared and appearance of clear absorption bands at 1591-1623 cm^{-1} for (C=N) amine. All details of FTIR spectral data of compound (3-7) were listed in Table 2. Synthesis of diazetidine derivatives by treatment of compounds (3-7) with phenyl isothiocyanate *via* (2+2) cyclization reaction. These compounds were identified from FTIR spectra indicated new clear absorption bands of (C=S) at 1292-1309 cm^{-1} (8-12), as listed in Table 2.

^{1}H-NMR spectra for compound (8) show singlet signal at 4.27 ppm for two protons S-CH_2-CO and singlet signal at 11.58 ppm for one proton amidic NH-CO, and multiplate signals at 7.3- 8.32 ppm for thirteen aromatic protons.

^{1}H-NMR spectra for compound (9) demonstrate singlet signal at 4.26 ppm for two protons S-CH_2-CO and singlet signal at 11.50 ppm for one proton amidic NH-CO and multiplate signals at 7.12- 8.49 ppm for thirteen aromatic protons.

^{1}H-NMR spectra for compound (11) depict singlet signal at 4.70 ppm for two protons S-CH_2-CO, and singlet signal at 11.36 ppm for one proton amidic NH-CO and multiplate signals at 6.81- 8.07 ppm for thirteen aromatic protons.

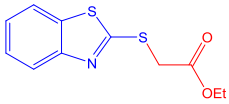
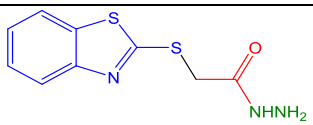
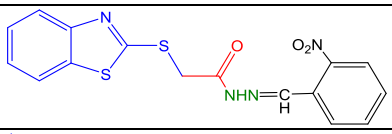
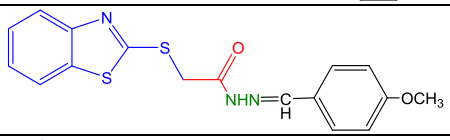
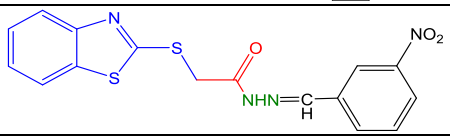
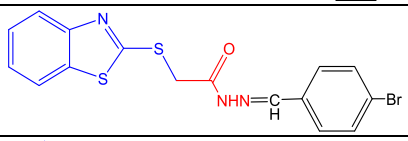
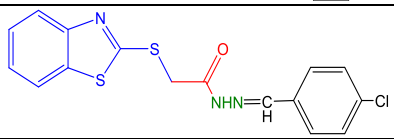
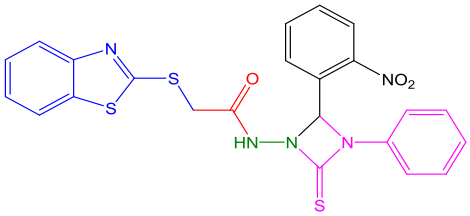
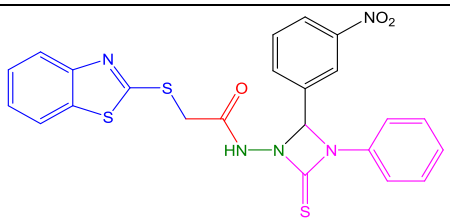
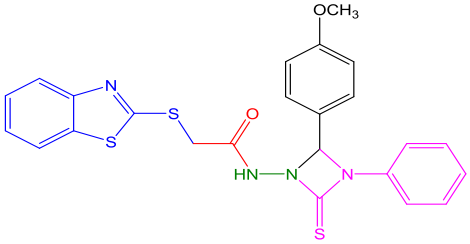
The Schiff base derivatives (3-7) react with chloro acetic acid *via* (2+3) cycloaddition reaction to give compounds (13-17). FTIR spectrum of compounds (8-12) showed disappearance of the absorption bands for (C=N) group at 1591-1623 cm^{-1} and appearance of new clear absorption bands of (C=O) ester at 1753-1795 cm^{-1}. All details of FTIR spectral data of compounds. All details of FTIR spectral data of compounds (13-17) are listed in Table 2.

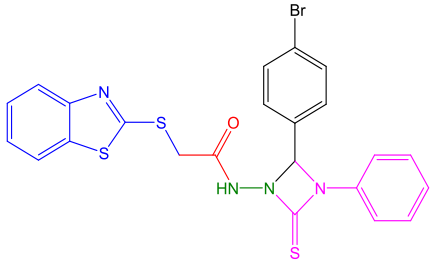
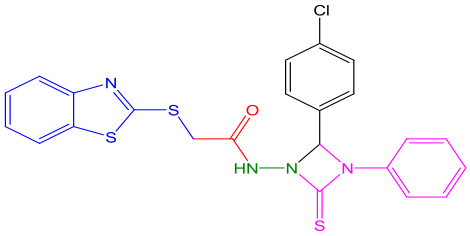
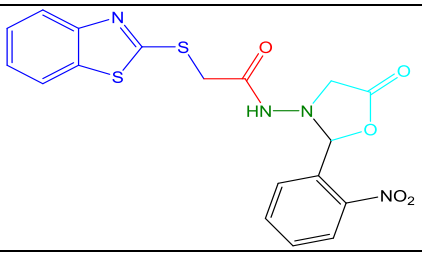
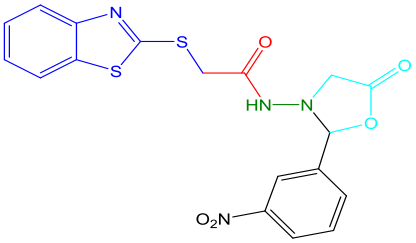
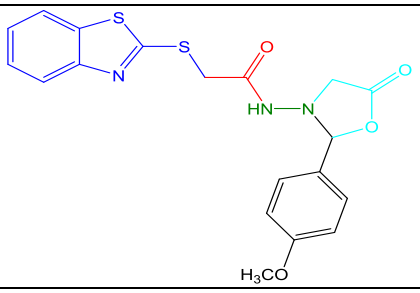
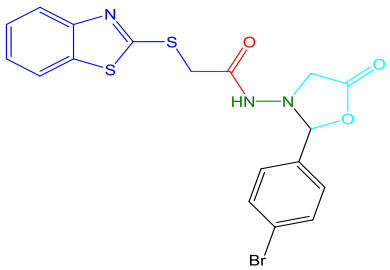
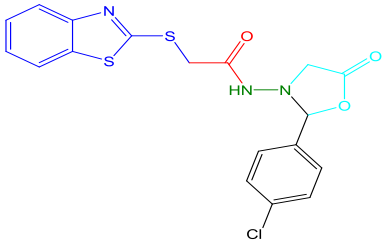
^{1}H-NMR spectra for compound (13) show singlet signal at 4.26 ppm for two protons S-CH_2-CO, singlet signal at 3.46 and 3.49 ppm for CH_2-CO in oxazolone ring and singlet signal at 10.36 ppm for one proton amidic NH-CO and multiplate signals at 6.83-8.32 ppm for eight aromatic protons.

Biological activities

The method used for evaluation was agar diffusion method, the biological activity of newly synthesized compounds and the syntheses compounds were tested against two types of bacteria +ve Gram stain (*Staphylococcus aureus),* -ve Gram stain *(E. coli)* and (Candida*)* fungi. The research species were first cultivated in the nutrient bread and incubated 24 h. at 37 °C. Then, freshly prepared bacterial cells were scattered into the "Nutrient Agar". Some of the newly synthesized compounds indicated antimicrobial activity against *Staphylococcus aureus, E. coli* bacteria, and against *Candida.* Some compounds (10,11,15,16 and 17) and campier these compounds with starting marital and some drugs, exhibited a broad spectrum of bioactivity against both *Staphylococcus aureus and E. coli* bacteria as well as against *Candida*.

Table 2: FTIR spectral data of compounds (1-17)

Compound No.	Structures	FTIR (KBr), spectral data cm^{-1}					
		ν(N-H)	ν (C-H) Arom.	ν (C-H) alp.	ν (C=O) amid	ν (C=N)	Others
1		-	3066	2927 and 2925	-	-	ν (C=O) ester 1737
2		3286	3051	2987 and 2967	1645	-	ν (NH_2) Asym.3436 Sym.3421
3		3213	3078	2977 and 2926	1676	1618	ν (NO_2) Asym.1525 Sym.1342
4		3247	3080	2939 and 2933	1654	1604	ν (C-O) 1253
5		3190	3012	2954 and 2947	1679	1620	ν (NO_2) Asym.1523 Sym.1352
6		3188	3068	2974 and 2968	1677	1623	ν (C-Br) 821
7		3284	3049	2987 and 2977	1647	1591	ν (C-Cl) 757
8		3199	3037	2956 and 2952	1685	-	ν (C=S) 1294
9		3155	3089	2954 and 2942	1681	-	ν (C=S) 1309
10		3215	3041	2977 and 2968	1674	-	ν (C-O) 1307

11		3199	3066	2958 and 2951	1679	-	ν (C=S) 1292
12		3215	3051	2985 and 2979	1683	-	ν (C=S) 1309
13		3224	3080	2972 and 2957	1641	-	ν (C=O) ester 1795
14		3174	3012	2972 and 2965	1681	-	ν (C=O) ester 1745
15		3215	3068	2975 and 2971	1674	-	ν (C=O) ester Over lap
16		3207	3064	2956 and 2951	1656	-	ν (C=O) ester 1795
17		3164	3064	2974 and 2972	1681	-	ν (C=O) ester 1743

Anti-bacterial screening for some selected compounds

Some of the selected compounds showed an acceptable efficacy against the bacteria as follows: all selected compounds gave good inhibition zone toward both types of the above-mentioned bacteria when compare them with amoxicillin, but reveal low inhibition zones compare them with ciprofloxacin, as presented in Table 3.

Compound (17) represents a good inhibition zone better than Metronidazole 500 mg drug, as listed in Table 3.

The Gram-positive bacteria are dense and have no external lipid membrane, whereas Gram negative bacteria are fine and have the external lipid membrane besides a small peptidoglycan layer. See Figure 3.

In case, the compounds have the ability to affect both the peptidoglycan of the wall as well as and the outer lipid membrane of the bacteria.

The cell membrane of fungal consist Mucoid, lip glyceride, and Sterol is the main compositions of the cell membrane of this fungus. Therefore, we can suggest that fungus inhibition is based on the ability of the tested compounds to hydrolyze mucoid, lipo-glyceride, and fungus sterol.

Table 3: Biological activity for some synthesized compounds

Assignments in d6 -DMSO	Mark	Chemical shifts δ (ppm)
CH_3-methyl group	16	(2.13-2.45),3H,s
CH_3-methyl group	3	(2.67-2.93),3H,s
CH-isoxazole	15	(6.10-6.33),H,s
CH-Benzeze	11,12	(6.57-6.98),2H,t
CH-pyridine	8	(7.09-7.29),H,t
CH-pyridine	6	(7.31-7.34),H,d
CH-thiophene	2	(7.44-7.46),H,d
CH-Benzene	13,10	(7.48–7.60),2H,t
CH-pyridine	7	(7.72-7.74),H,t
CH-thiophene	1	(7.93-7.95),H,d
CH-pyridine	9	(8.01-8.27),H,d
NH-sec amide	5	(8.32-8.33),H,s
NH-sulfonamide	14	(10.95),H,s
OH -enol	4	(13.79),H,s

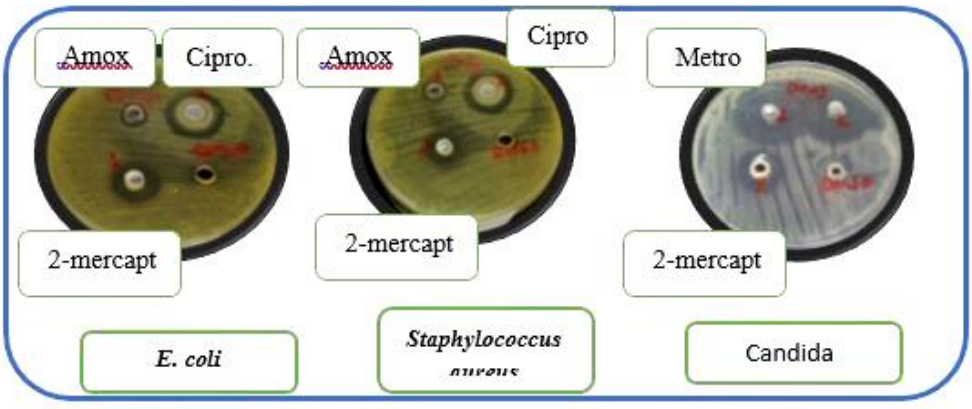


Figure 1: The biological activities for drugs and 2-mercaptobenzothazol

Figure 2: The biological activities for four membered ring derivatives

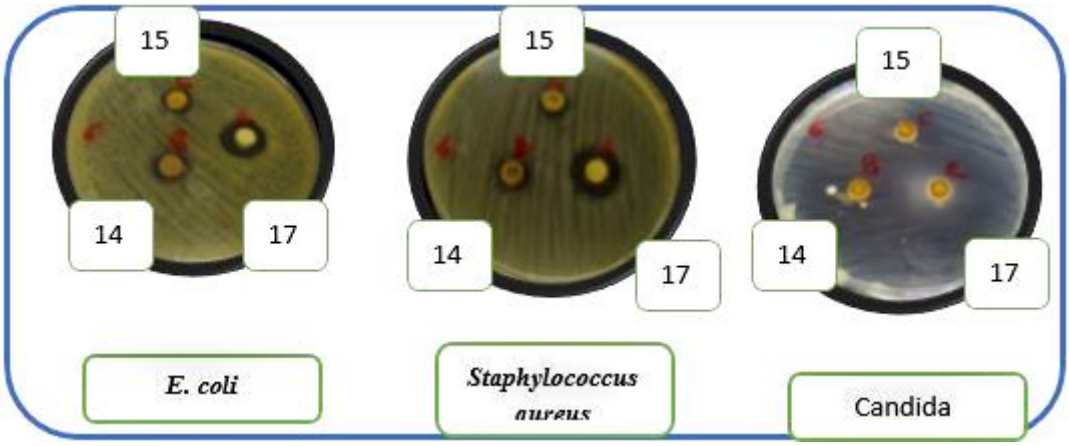


Figure 3: The biological activities for five membered ring derivatives

Conclusion

The compounds (2-17) were prepared, the reactions were controlled by using the TLC test, all prepared compounds were identified using FT-IR, some prepared compounds were identified using ^{1}HNMR, anti-bacterial, and anti-fungal were among the biological activities tested on them. When compared with the standard medications, several synthesized compounds were revealed to have substantial antifungal efficacy, while the others demonstrated antibacterial efficacy.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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