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FULL PAPER

Synthesis of new compounds with seven rings (oxazepine) through the ring closure of Schiff bases with study of biological activity

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In this study, Schiff base derivatives were reacted with different cyclic anhydrides to prepare some oxazepine ring derivatives. The Schiff base derivatives containing the 2-mercabto benzothiazole moiety were obtained via the reaction of different aromatic aldehyde with 2-(benzothiazol-2-ylthio) acetohydrazide. Furthermore, 2-(benzothiazol-2-ylthio) acetohydrazide was obtained via the reaction of 2-mercabto benzothiazole with ethyl chloroacetate, and then with hydrazine hydrate. The new synthesized compounds were characterized via spectral data (IR and NMR). The antibacterial activity was studied against the examples of Gram-positive (***E. coli***) and Gram-negative (***Staphylococcus aureus***) bacteria, and antifungal against ***Candida*** fungal.

KEYWORDS

Schiff base; oxazepine ring; 2-mercabto benzothiazole; antibacterial activity.

Introduction

Chemists have long faced with the unique challenges in the field of heterocyclic chemistry [1] due to its vast amount of knowledge and variety. Despite this, heterocyclic chemistry and synthesis techniques are at the heart of the current medical chemical and pharmaceutical research [2]. It is critical for medicinal chemists to have a thorough understanding of heterocyclic chemistry [3].

The ubiquitous usage of nitrogen-containing heterocycles in medicine, industry, and agriculture has attracted attention related to them [4]. 2-mercapto-1,3-benzoxazole MBO as well as its derivatives are employed to shield the metals from the environmental corrosion [5-9] as chelating agents in analytical chemistry for the discovery of metal ions and complexes for the selective flotation of sulfide minerals in metallurgy. The rubber vulcanization accelerators like 2-Mercapto-1,3-benzothiazole (MBT) and its derivatives are quite common [10-13].

Any seven-membered ring with oxygen in the first position and nitrogen in the third position, plus five carbon atoms, is called oxazepine[14]. Many kinds of heterocyclic oxazepine include 1,3-oxazepine [3, 15-19], as depicted in Figure 1, Structure (1-1) [20].

FIGURE 1 The structure of 1,3-oxazepine

The basic structure consists of seven-membered rings of 1, 3-oxazepine-4, 7-diones as well as two carbonyl groups [15,21]. The synthesis of oxazepine has been studied and reported through the periods of time [22]. It is synthesized by pre-cyclic cyclo-addition of Schiff base or hydrazone with maleic, phthalic, and succinic anhydrides [23,24] as well as by using green chemistry [18,25,26]. Various oxazepine derivatives have been found to have a wide range of biological actions, including antibacterial, antifungal, hypnotic muscle relaxant, antagonistic, inflammatory, antiepileptic, and antimicrobial properties [18,23,25,27].

Experimental

Materials and methods

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

General procedures

Synthesis of ethyl 2-(benzo[d]thiazol-2-ylthio)acetate (1) [28]

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

Synthesis of 2-(benzo[d]thiazol-2-ylthio) acetohydrazide (2) [29]

A mixture of 2-(benzo[d]thiazol-2-ylthio) ethyl acetate was stirred in (25 mL) of methanol and 10 mL of 99% hydrazine hydride for (24 hours) at room temperature. The mixture was poured into a porcelain lid to evaporate the excess methanol and hydrazine. Pale Yellow Oil, 82%.

Synthesis of new Schiff bases from 2-(benzo[d]thiazol-2-ylthio) acetohydrazide (3-7) [29]

A mixture of compound (**2**) (0.01 mol) was added to the aromatic aldehydes (0.01 mol) in absolute ethanol (25 mL) and (3-5 drops) of glacial acetic acid (G.A.A.) which was stirred for approximately (4-8 hours). Under the reduced pressure, the excess solvent was evaporated. The raw material was dried, and then it was recrystallized from chloroform. All the physical and performance properties of the vehicles are presented in Table 1.

Synthesis of oxazepine derivatives (8-22) [27]

A mixture of Schiff bases (4-7) (0.01 mol) and (0.02 mol) of (succinic anhydride, phthalic anhydride, and maleic anhydride) were re-condensed in THF (30 mL) as a solvent for (14-16 hours). The solvent is evaporated under the reduced pressure. The appropriate product has been recrystallized from chloroform. Some of the physical properties and performance of the compounds (8-12) are listed in Table 1.

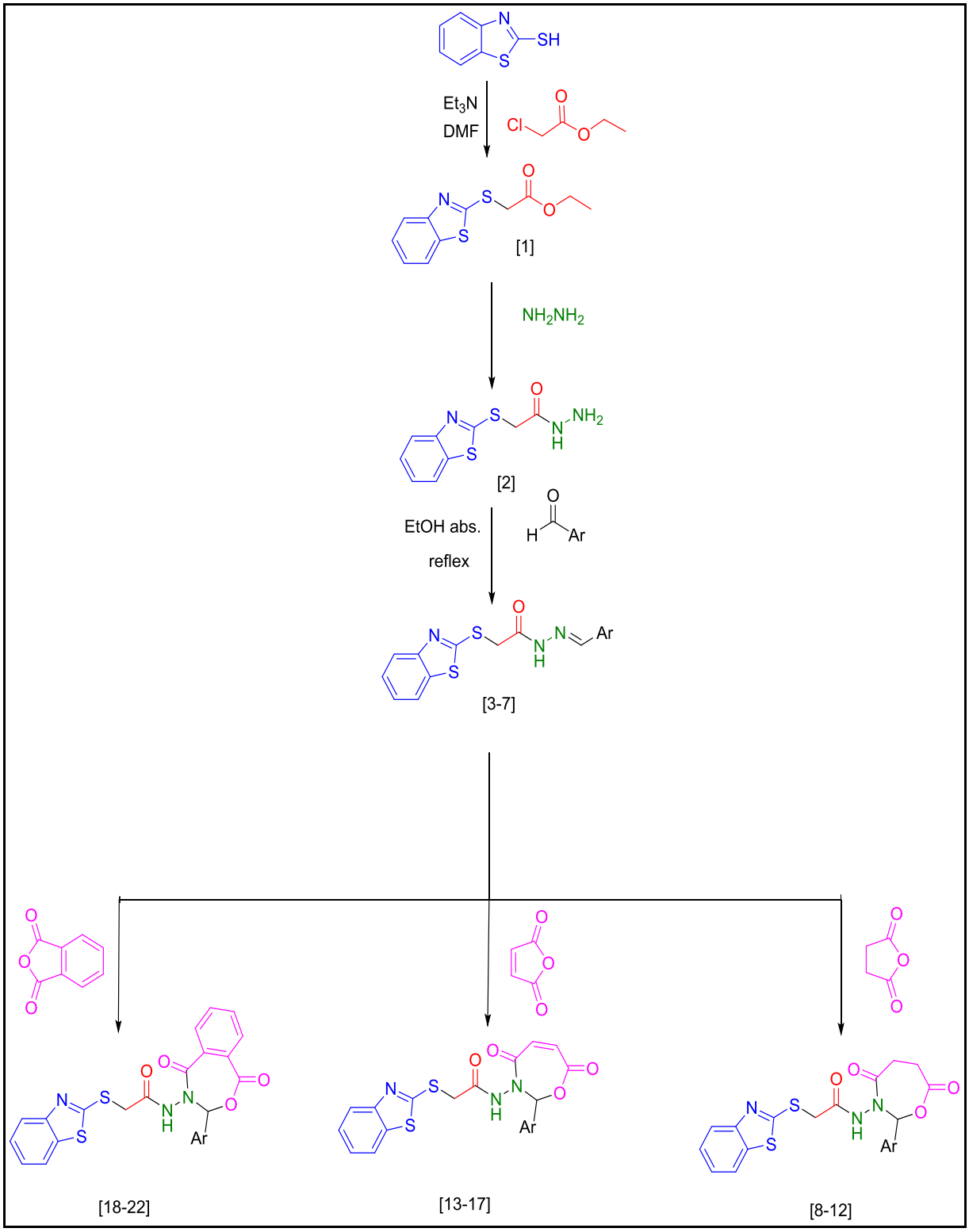
TABLE 1 Some of the physical properties of the synthesis compounds (3-17)

Comp. No.	Molecular formula	M.wt g\mol.	Yeald %	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	Pale yellow
6	$C_{16}H_{12}ClN_3OS_2$	361	80	169-172	Pale yellow
7	$C_{17}H_{15}N_3O_2S_2$	357	79	176-177	Yellow
8	$C_{20}H_{16}N_4O_6S_2$	472.49	67	Oily	Brown
9	$C_{20}H_{16}N_4O_6S_2$	472.49	65	Oily	Greenish yellow
10	$C_{21}H_{19}N_3O_5S_2$	457.52	70	170-172	Yellow
11	$C_{20}H_{16}BrN_3O_4S_2$	506.39	63	Oily	Brown
12	$C_{20}H_{16}ClN_3O_4S_2$	461.94	67	Oily	Brown
13	$C_{20}H_{14}N_4O_6S_2$	470.47	72	Oily	Dark brown
14	$C_{20}H_{14}N_4O_6S_2$	470.47	69	175-177	Brown
15	$C_{21}H_{17}N_3O_5S_2$	455.50	67	182-184	Orange
16	$C_{20}H_{14}BrN_3O_4S_2$	504.37	60	Oily	Brown
17	$C_{20}H_{14}ClN_3O_4S_2$	459.92	62	Oily	Brown
18	$C_{24}H_{16}N_4O_6S_2$	520.53	55	Oily	Dark brown
19	$C_{24}H_{16}N_4O_6S_2$	520.53	60	Oily	Brown
20	$C_{25}H_{19}N_3O_5S_2$	505.56	68	178-180	Greenish yellow
21	$C_{24}H_{16}BrN_3O_4S_2$	554.43	73	Oily	Brown
22	$C_{24}H_{16}ClN_3O_4S_2$	509.98	65	Oily	Brown

Result and discussion

Ethyl 2-(benzo[d]thiazol-2-ylthio) acetate (1) was prepared by the reaction of 2-mercaptobenzothiazole with ethyl chloroacetate in the presence of triethylamine as a catalyst, by the nucleophilic attack of the thiol group in 2-mercaptobenzothiazole on carbon in ethyl chloroacetate because the halo group is a good leaving group and the sulfur compound is a good nucleophile, the reaction is a nucleophilic substitution reaction (SN_2) which removes proton from the thiol group followed by the removal of the HCl molecule. The halo assembly can be easily replaced to obtain a compound which produces a desired harvest [1], as indicated in scheme 1. Compound 1 was characterized by FTIR spectroscopic data demonstrating a strong band at 1737 cm^{-1} due to the ester carbonyl group and bands at 1737 cm^{-1} and 2927.74 cm^{-1} for the aliphatic (CH). Group. S-H absorption bands at 2567 cm^{-1} disappeared from compound 1 were introduced in the nucleophilic substitution reaction with hydrazine hydrate, and an ethoxy group was replaced by a hydrazine group ($NH\text{-}NH_2$) to produce the corresponding acetohydrazide. FTIR spectral data of compound 2 illustrated the disappearance of C=O ester band and the appearance of clear absorption bands at 3109 cm^{-1} for N-H as well as (3286- 3199) cm^{-1} due to the asymmetrical and symmetrical stretching vibrations of (NH_2) indicating the formation of acetohydrazide. The compound acetohydrazide (2) was converted into a Schaff base derivative (3-7) by reacting with various aromatic aldehydes in absolute EtOH as a solvent and GAA as a catalyst. FTIR spectral data of compounds (3-7) depicted the disappearance of the (NH_2) absorption band at (3286-3199) cm^{-1}, and the appearance of clear absorption bands at (1591-1623) cm^{-1} for (C=N) imine. Full details of FTIR spectroscopy data of compound (3-7) are indicated in Table 2. The synthesis of diazetidine derivatives was carried out by treatment of compound (3-7) with cyclic anhydride (succinic, malic, and phthalic) via nucleophilic substitution, and then cyclization reaction was done, as well. These compounds were identified from FTIR spectra demonstrating the new and clear

absorption bands of (C=O) for oxazepine ring at (1693-1780) cm^{-1} with the disappearance of the absorption bands for (C=N) group at (1591-1623). Full details of FTIR spectroscopy data of compounds (8-22) were listed in Table 2.

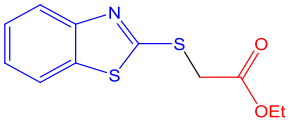
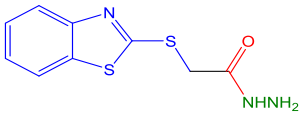
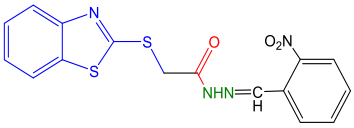
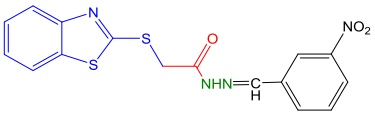
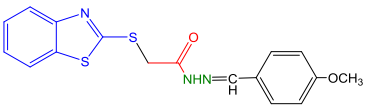
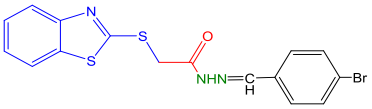
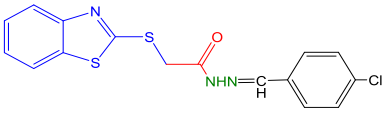


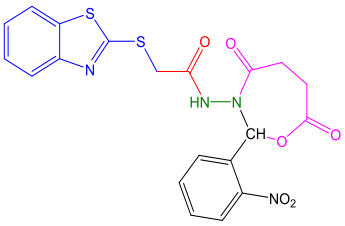
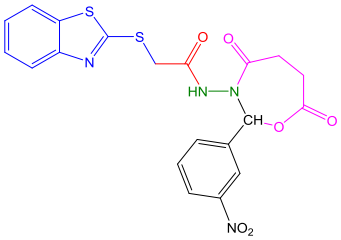
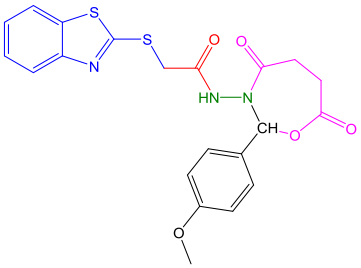
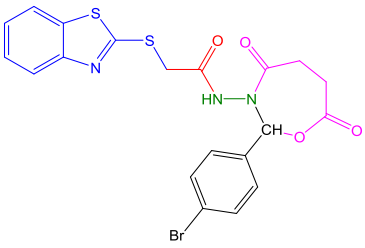
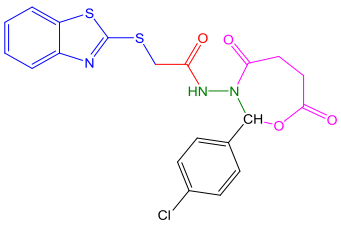
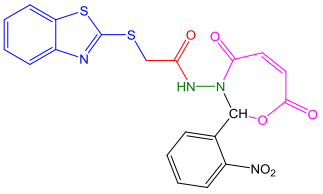
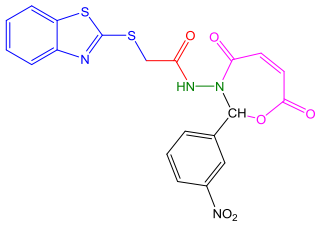
SCHEME 1 All steps to prepare oxazepine rings

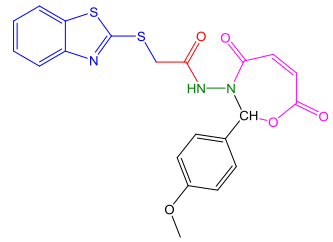
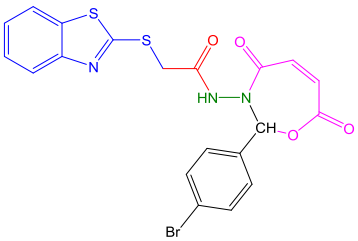
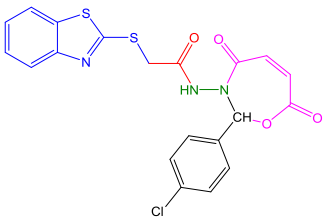
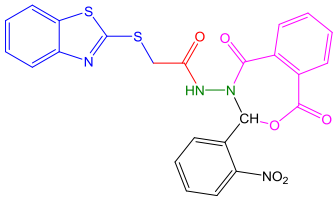
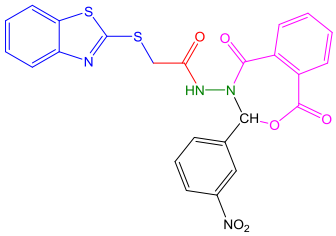
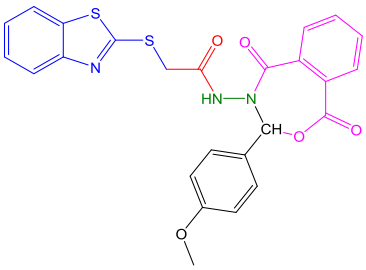
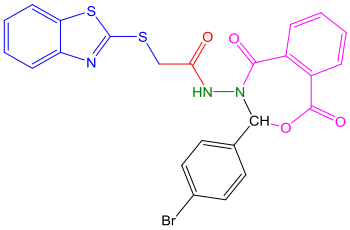
^{1}H-NMR spectra for compound 9 illustrates the singlet signal at 4.27 ppm for two protons for S-CH_2-CO, the triplet signal at 2.44 and 2.5 ppm for four protons for CH_2-CH_2 in oxazepine ring, the singlet signal at 7.85 for N-CH-O for oxazepine ring, and the singlet signal at 11.50 ppm for one proton amidic NH-CO as well as multiple signals at 7.1- 8.31 ppm for eight aromatic protons.

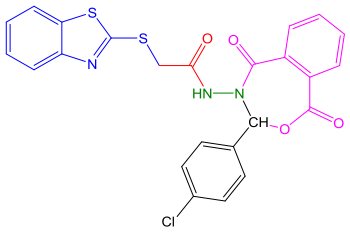
^{1}H-NMR spectra for compound 11 demonstrates the singlet signal at 3.92 ppm for two protons S-CH_2-CO, the triplet signal at 7.61, and 7.96 ppm for two protons for CH=CH in oxazepine ring, the singlet signal at 7.86 for N-CH-O for oxazepine ring, the singlet signal at 11.33 ppm for one proton amidic NH-CO, and multiple signals at 7.65- 8.31 ppm for eight aromatic protons.

TABLE 2 FTIR spectral data of compounds (1-22)

Com. No.	Structures	FTIR (KBr), spectral data cm^{-1} (N-H)	(C-H) Arom.	(C-H) alp.	(C=O) amid	(C=N)	C=O Oxazepine Ring	Others
1		-	3066	2927	-	-		(C=O) ester 1737
2		3286	3051	2987	1645	-		(NH_2) Sym.3436 Asym.3421
3		3213	3078	2977	1676	1618		(NO_2) Sym.1342 Asym.1525
4		3190	3080	2954	1979	1620		(NO_2) Sym.1352 Asym.1523
5		3247	3012	2939	1654	1604		(C-O) 1253
6		3188	3068	2974	1677	1623		(C-Br) 821
7		3284	3049	2987	1647	1591		(C-Cl) 757

8	 Molecular Weight: 472.49	3232	3037	2987	Over lapping	1610	1695	(NO_2) Sym.1373 Asym.1525
9		3207	3089	2923	1681	1622	1731	(NO_2) Sym.1348 Asym.1525
10		3193	3041	2931	1695	1600	1784	(C-O) 1201
11		3201		2956	1679	1593	1731	(C-Br) 823
12		3199		2974	1650	1604	1695	(C-Cl) 756
13		3234	3010	2923	1637	Over lapping	1718	(NO_2) Sym.1346 Asym.1525
14		3423	3011	2956	1637	1606	1700	(NO_2) Sym.1352 Asym.1523

15		3396	3004	2979	Over lap	1575	1718	(C-O) 1249
16		3218	3082	2923	1676	1593	1730	(C-Br) 821
17		3271	3009	2956	1643	1568	Over lap	(C-Cl) 757
18		3402	3080	2966	Over lap	1587	1685	(NO_2) Sym.1342 Asym.1523
19		3174	3091	2956	1681	1643	1697	(NO_2) Sym.1348 Asym.1525
20		3373	3080	2979	1691	1581	1733	(C-O) 1265
21		3222	3080	2954	1683	1631	1735	(C-Br) 823

22		3197	3070	2956	1687	1604	1737	(C-Cl) 757

Biological activities

The agar diffusion method was used for evaluating the biological activity of new synthesized compounds, the 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 for 24 hours at 37 °C. Then, the fresh prepared bacterial cells were scattered into the "Nutrient Agar".

Some of new synthesized compounds depicted the antimicrobial activity against *Staphylococcus aureus, E. coli* bacteria and *Candida.* Some of 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 *Candida.*

Anti-bacterial screening for some selected compounds

Some of the selected compounds showed an acceptable efficacy against the bacteria as follows:

1- Compound 10 is highly effective against both types of bacteria and is close to the strength of the two drugs used for comparison.
2- Compounds 13 and 14 indicated the high activity against E. coli as being stronger than both drugs.
3- As for compound 20, it gave a high activity against Candida fungi which was stronger than the drug used for comparison.
4- As for the rest of the prepared compounds, they gave varying activities from weak ones to the medium activities and close to the activity of amoxicillin. 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**,** as depicted in Figures (2-5).

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

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

TABLE 3 biological activity for some compounds

No. of Compounds	***Staphylococcus aureus* Conc.100(mg/mL) Inhibition zone diameter (mm)**	***E. coli Conc.100(mg/mL) Inhibition zone diameter (mm)***	**Candida *Conc.100 (mg/mL) Inhibition zone diameter (mm)***
2-mercapto benzothiazole	12	12	18
8	14	16	15
10	23	22	30
11	15	16	25
12	16	13	20
13	12	25	30

14	13	23	20
15	13	13	28
17	12	14	20
18	14	14	20
19	13	14	22
20	19	17	35
21	18	12	25
22	16	13	25
Amoxicillin 500 mg	10	10	--
Ciprofloxacin 500 mg	23	23	-
Metronidazole 500 mg	-	-	30
DMSO	-ev	-ev	5

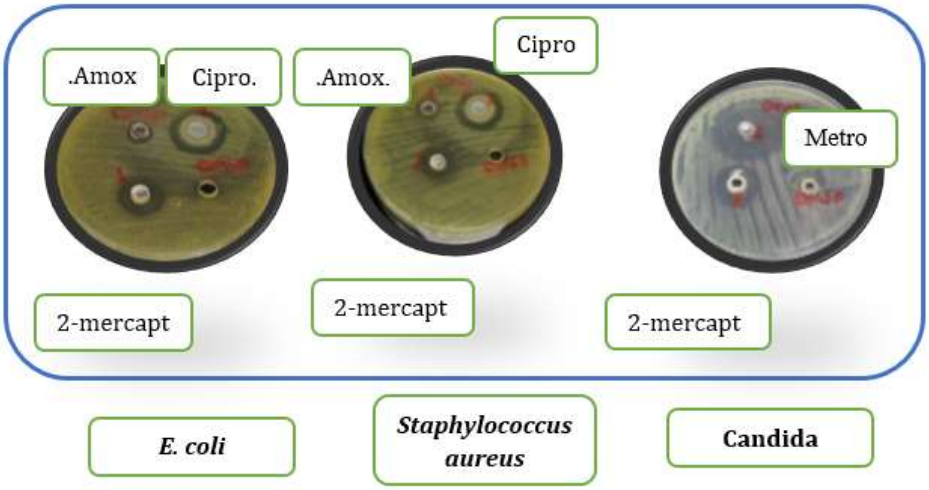


FIGURE 2 The biological activities for drugs and 2-mercaptobenzothazol

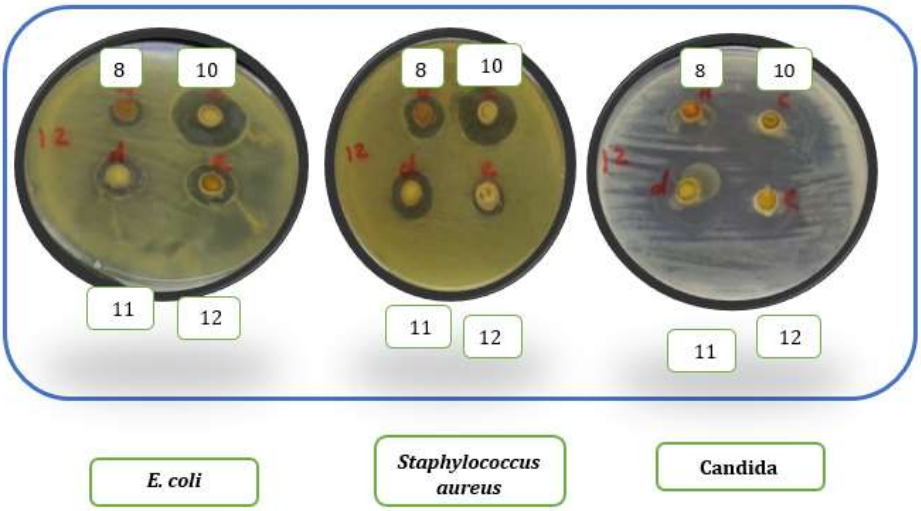


FIGURE 3 The biological activities for seven-membered ring derivatives from sccinic acid

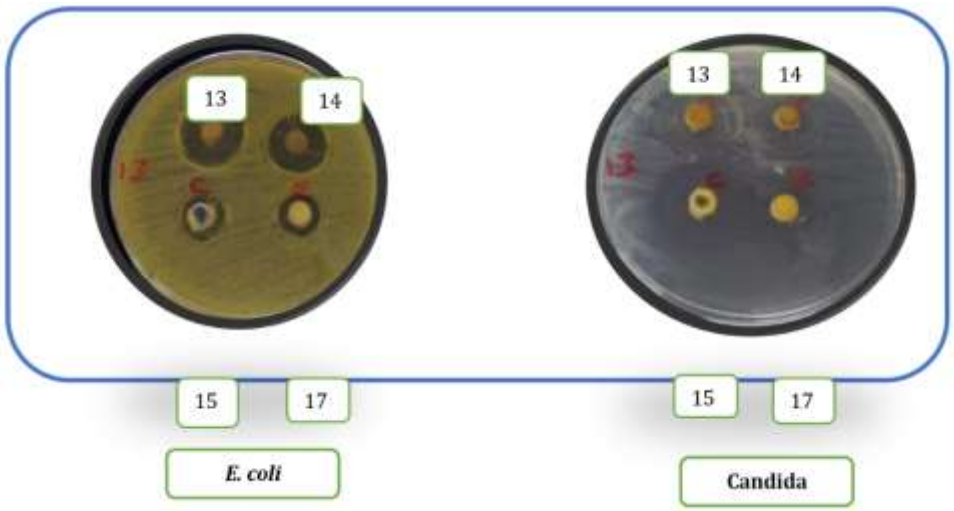


FIGURE 4 The biological activities for seven-membered ring derivatives from malic acid

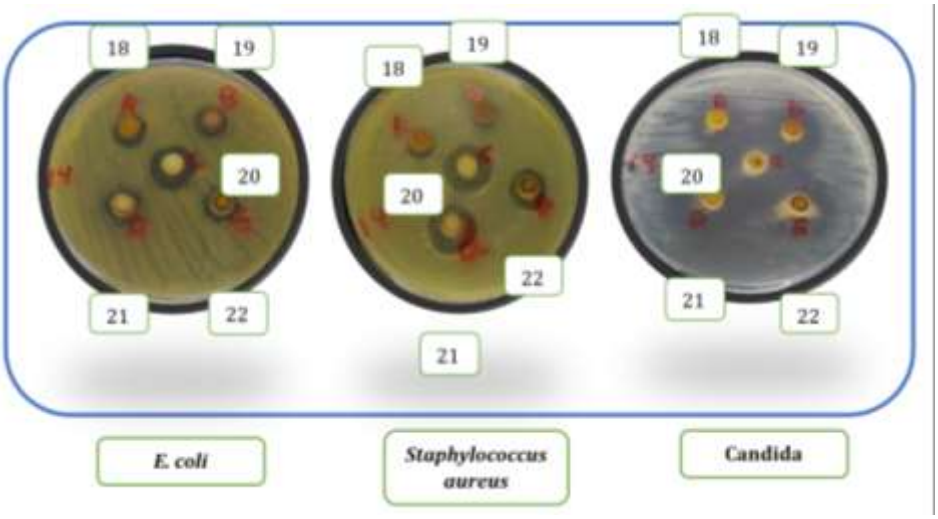


FIGURE 5 The biological activities for seven-membered ring derivatives from phathalic acid

Conclusion

The compounds (1-22) were prepared, the reactions were controlled by using the TLC test, and all prepered compounds were identified using FT-IR, some of which were identified using ^{1}HNMR and the anti-bacteria and anti-fungi activities were among the biological activities tested on them. When compared to the standard medications, several synthesized compounds were demonstrated to have the substantial antifungal efficacy, while others demonstrated the anti-bacterial efficacy.

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