

FULL PAPER

Synthesis of new 5-aryl tetrazoline from N-2-hydrazido cyclic imides and study of biological activity

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This research focused on the synthesis of some new 5-aryl tetrazoline derivatives on cyclic imides via reaction of N-(2-chloro acetyl) imides with hydrazine hydrate to give compounds (1,2). Then, compounds (1,2) reacted with different aromatic aldehydes to give Schiff bases compounds (3-10). On the other hand, compound N-(2-chloro acetyl) imides reacted with sodium azide to give compounds (11,12). And finally, react Schiff bases compounds (3-10) with compounds 11 and 12 to give the tetrazoline ring. The compounds prepared were characterized by FT-IR and some of them by ¹H-NMR. The effects of the preparing compounds on some strains of bacteria and fungi were studied.

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KEYWORDS

Cyclic imides; Schiff bases; sodium azide; tetrazoline; biological activity.

Introduction

Heterocyclic ring systems have attracted substantial attention because of their reoccurrence in numerous biologically active molecules. A short survey of the foremost active pharmacophores shows that nitrogen-based heterocycles are the foremost prevalent style of biologically relevant small molecules [1]. Still N heterocycles remain scaffolding for compounds with interesting biological activities and are used in many other pharmacological regions [2]. These ring systems have a variety of applications, from vitamins and herbicides to antifungal, antibacterial, and anti-cancer agents [3]. Schiff bases are an essential class of organic compounds, especially within the medicinal and pharmaceutical fields. Thus, the event and synthesis of new Schiff bases derivatives as potential chemotherapy continues to attract the attention of organic and medicinal

chemists [4]. Schiff bases, derived mostly from a spread of heterocyclic rings, have been reported to possess a broad spectrum and a good sort of biological activities including antiviral [5], anticancer [6], cytotoxic [7], antimicrobial [8], antibacterial [9], anticonvulsant [10], etc. Tetrazoles are compounds of increasing popularity [11] with a variety of applications. They are used in pharmaceuticals as lipophilic spacers [12] and acid replacements, in specialty explosives [13], and photography and data recording systems, [14] but they have been not been mentioned as precursors to a spread of nitrogen-containing heterocycles [15]. Moreover, tetrazole and its derivatives are present in numerous bioactive heterocyclic compounds of great interest for their various biological, pharmaceutical, and clinical applications [16]. Tetrazolin systems, as biomolecules, have attracted scientific attention due to their unique pharmacological

properties. In particular, they are widely used as antimicrobial, anticancer, antioxidant and antituberculous agents [17].

Experimental and instruments

A- Materials

All chemicals used in this study were of the highest purity available and were derived from Fluka, BDH, and Sigma-Aldrich chemicals. The melting point was registered using a Galenkamp capillary melting point apparatus. FTIR spectra were recorded utilizing KBr disc on Shimadzu FTIR 8400 Fourier Transform Infrared spectrophotometer in the department of chemistry, college of science, university of Baghdad. Some of the prepared compounds were characterized by ¹H-NMR spectra recorded on nuclear magnetic resonance in 400 MHz (Laboratory of Isfahan University) with tetramethyl saline as internal standard and DMSO as a solvent.

B- Methods

Synthesis of N-(2-hydrazido acetyl) cyclic imides (1,2) [18]

0.01 mole of N-(2-chloro acetyl) cyclic imide was dissolved in (20 mL) absolute ethanol and added 4 drops Et₃N, then 0.01 mole of hydrazine hydrate was added drop by drop and refluxed at 4 hrs. After that, the precipitate was collected. Next, the solvent was volatilized, washed with diethyl ether and purified by methanol. Some of the physical properties and FTIR spectral data are listed in Table 1.

Synthesis of Schiff bases (3-10) [19]

First, we had equal moles of compounds 1 and 2 with different aromatic aldehydes 0.001 moles. Initially, we dissolved the aldehyde in 15 mL ethanol, then 3 drops of

glacial acetic acid were added to the solution. After that compounds 1 and 2 were added and refluxed at 6-8 hrs. The product was left until the solvent was evaporated, washed with distilled water, and recrystallized from acetone. Table 1 provides some physical properties and spectral data for the FTIR.

Synthesis of N-(2-azido acetyl) cyclic imides (11,12) [20]

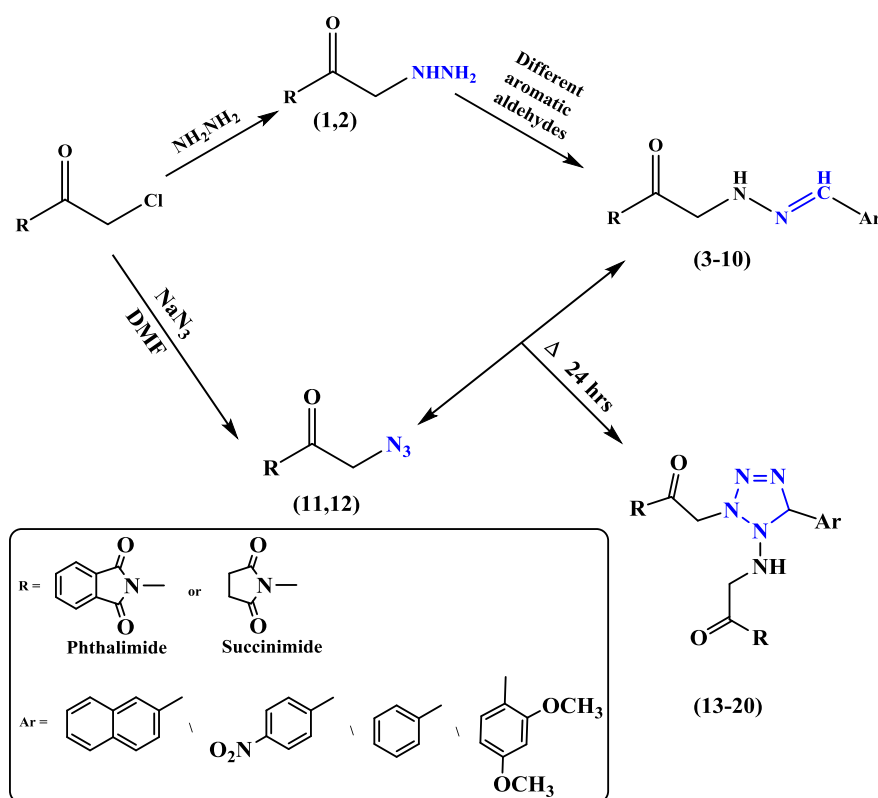
0.005 moles from Sodium azide was added to a solution of compound N-(2-chloro acetyl) cyclic imides (0.005 moles) in 10 mL of DMF. The reaction mixture was heated at 90 °C for 6 hrs. with continuous stirring. The solvent was evaporated and the products were precipitated and filtered, thoroughly washed with diethyl ether, and recrystallized from ethanol. Table 2 provides some physical properties and spectral data for the FTIR.

Synthesis of 3-(N-acetyl cyclic imides)-4-{N'-(2-amino acetyl) cyclic imides}-5-(Schiff bases) tetrazoline (13-20) [21]

Compounds 11 and 12 (0.01mol) were dissolved in DMF (30mL). Then, the compounds 3-10 (0.01 mole) were added to the solution. The mixture was heated and stirred at 110 °C for 24 hrs. After the removal of the solvent, the residue was washed with diethyl ether and re-crystallized from ethanol. Some of the physical properties of products and FTIR spectral data are shown in Table 3.

Results and discussion

This work aimed at the reaction and synthesis of novel derivatives of 5-aryl tetrazoline on cyclic imides, as shown in Scheme 1.



SCHEME 1 The chemical steps for synthesis compounds (1-20)

Preparation of N-(2-hydrazido acetyl) cyclic imides (1,2)

N-(2-chloro acetyl) cyclic imides reacted with hydrazine hydrate and tri-ethyl amine as a catalyst to prepare compounds (1,2). The FTIR spectrum of these compounds (1,2) shows the appearance of the absorption bands [3313;3310, 3253;3222, 1750, 1662, 1440, 1336-1300] cm^{-1} due to $\nu(\text{NH}_2)$, $\nu(\text{NH})$, $\nu(\text{C}=\text{O})$ imide, $\nu(\text{C}=\text{O})$ amide, $\nu(\text{N}-\text{N})$ and $\nu(\text{C}-\text{N})$ consecutively. These and other bands are shown in Table 1. Also, the disappearance of band at [667] cm^{-1} due to $\nu(\text{C}-\text{Cl})$. ^1H NMR spectrum of compound (1) showed signals at δ 3.49 ppm of (s, 2H, $\text{O}=\text{C}-\text{CH}_2-\text{N}$); δ 4.25 ppm of (s, 2H, NH_2); δ 7.87 ppm of (s, 4H, $\text{Ar}-\text{H}$); δ 8.66 ppm of (s, 1H, NH). Also, there was a signal at δ 2.5 ppm due to the solvent (DMSO).

Preparation of Schiff bases (3-10)

The compounds were synthesized from the reaction between compounds 1 and 2 and

different aromatic aldehydes in absolute ethanol and glacial acetic acid. The FTIR spectrum data of compounds 3-10 shows the appearance of characteristic bands at [3350-3200, 1770-1750, 1640-1680] cm^{-1} due to $\nu(\text{NH})$, $\nu(\text{C}=\text{O})$ imide, $\nu(\text{C}=\text{O})$ amide consecutively, and [1690-1640, 1619-1600, 1440-1400, 1336-1300] cm^{-1} due to $\nu(\text{C}=\text{N})$, $\nu(\text{C}=\text{C})$, and $\nu(\text{N}-\text{N})$, $\nu(\text{C}-\text{N})$, consecutively. These and other bands are shown in Table 1. Also, the disappearance of absorption bands at (3400-3200) cm^{-1} due to $\nu(\text{NH}_2)$. ^1H NMR spectrum of compounds (3,6) showed signals at δ 3.49, 3.38 ppm of (s, 2H, $\text{O}=\text{C}-\text{CH}_2-\text{N}$); δ 6.49, 6.66 ppm of (s, 1H, $\text{N}=\text{C}-\text{H}-\text{Ar}$); δ 7.62-8.38 ppm of (m, 11H, $\text{Ar}-\text{H}$); δ 8.82, 8.92 ppm of (s, 1H, NH). Also, there was a signal at δ 2.5 ppm due to the solvent (DMSO). Others signals are shown in Table 4.

Preparation of N-(2-azido acetyl) cyclic imides (11,12)

These compounds were synthesized by the reaction of N-(2-chloro acetyl) cyclic imides

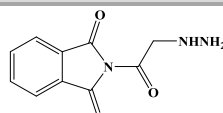
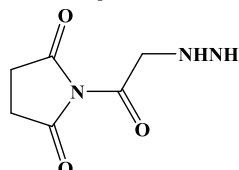
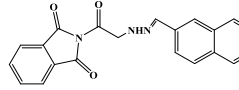
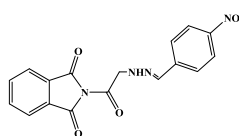
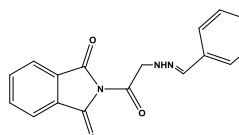
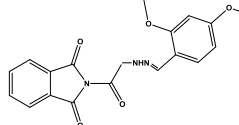
with sodium azide in DMF. The FTIR spectrum data of compounds (11,12) shows the appearance of characteristic bands at [2947;2956, 2119;2115, 1774;1772, 1671;1664] cm^{-1} due to $\nu(\text{C-H})$ aliphatic, $\nu(\text{N}_3)$, $\nu(\text{C=O})$ imide and $\nu(\text{C=O})$ amide consecutively. These and other bands are shown in Table 2. Also, there was the disappearance of absorption bands (715) cm^{-1} due to $\nu(\text{C-Cl})$.

Preparation 3-(N-acetyl cyclic imides)-4- {N'-(2-amino acetyl) cyclic imides} -5-(Schiff bases) tetrazoline (13-20)

These compounds were synthesized by refluxing equimolar amounts from the compounds 3-10 with N-(2-azido acetyl) cyclic imides (11,12) in DMF. The FTIR

spectrum of this compounds (13,20) shows the appearance of the absorption bands [3256-3222, 3053-3010, 2976-2900] cm^{-1} due to $\nu(\text{N-H})$, $\nu(\text{C-H})$ aromatic, $\nu(\text{C-H})$ aliphatic consecutively, [1770-1750, 1690-1660] cm^{-1} due to $\nu(\text{C=O})$ imide and $\nu(\text{C=O})$ amide, and [1619-1600, 1431-1420, 1422-1414, 1330-1300] cm^{-1} due to $\nu(\text{C=C})$, $\nu(\text{N=N})$, $\nu(\text{N-N})$, $\nu(\text{C-N})$ respectively. These and other bands are shown in Table 3. Also, the disappearance of absorption bands [2115, 1690-1640] cm^{-1} due to $\nu(\text{N}_3)$ and $\nu(\text{C=N})$. ^1H NMR spectrum of compounds (13,16) showed signals at δ 3.46, 3.34 ppm of (s, 4H, 2(O=C-CH₂-N)); δ 8.91, 8.81 ppm of (s, 1H, NH). In addition, there was a signal at δ 2.5 ppm due to the solvent (DMSO). Others signals are shown in Table 4.

TABLE 1 physical properties and the FTIR spectral data cm^{-1} of the synthesized compounds (1-10)

No.	Structure	Physical properties				Major FT-IR spectral data, ν , cm^{-1}					
		M.P C°	Yield %	color	N-H	1. C-H _{arom} 2. C-H _{aliph}	1. C=O imide 2. C=O amide	C=C Aro m	1. C=N 2. C-N	N-N	Other bands
1		291- 295	88	white	3253	1. 3029 2. 2964 2898	1. 1750 2. 1662	1602	1. - 2. 1333	1444	(NH ₂) 3313
2		232- 236	67	white	3222	1. - 2. 2922 2850	1. 1750 2. 1693	-	1. - 2. 1336	1440	(NH ₂) 3310
3		238- 242	75	yellow	3255	1. 3053 2. 2923 2896	1. 1758 2. 1660	1600	1. 1618 2. 1301	1438	-
4		> 300	70	yellow	3250	1. 3020 2. 2925 2897	1. 1751 2. 1664	1599	1. 1622 2. 1307	1442	(NO ₂) Asym 1519 Sym 1346
5		> 300	61	Light yellow	3248	1. 3018 2. 2981 2898	1. 1751 2. 1662	1602	1. 1622 2. 1329	1432	-
6		245- 248	87	Light orange	3245	1. 3008 2. 2945 2894	1. 1750 2. 1660	1606	1. 1631 2. 1328	1415	(C-O- C) 1267

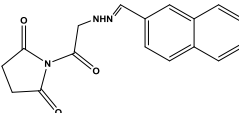
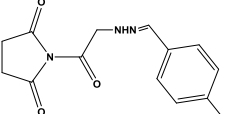
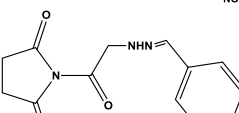
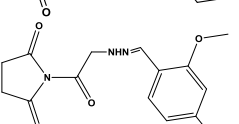
7		254-260	69	yellow	3201	1. 3064 2. 2964 2856	1. 1774 2. 1656	1606	1. 1618 2. 1307	1448	-
8		> 300	65	yellow	3244	1. 3025 2. 2954 2897	1. 1753 2. 1664	1600	1. 1628 2. 1308	1430	(NO ₂) Asym 1520 Sym 1346
9		222-226	49	Off white	3239	1. 3018 2. 2981 2899	1. 1750 2. 1662	1602	1. 1622 2. 1303	1430	-
10		198-202	72	Yellowish orange	3237	1. 3006 2. 2975 2896	1. 1752 2. 1675	1608	1. 1660 2. 1303	1417	(C-O-C) 1263

TABLE 2 physical properties and the FTIR spectral data cm⁻¹ of the synthesized compounds (11,12)

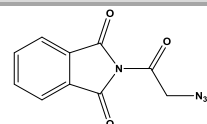
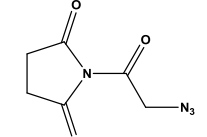
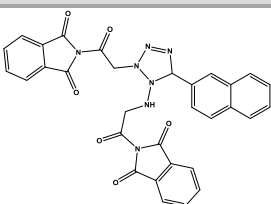
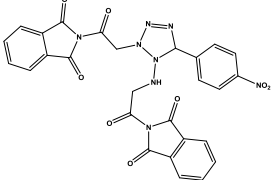
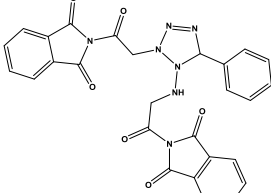
No.	Structure	Physical properties			Major FT-IR spectral data, ν , cm ⁻¹					
		M.P C°	Yield %	Color	C-H Arom.	C-H Aliph.	C=O imide	C=O amide	N ₃	Other bands
11		> 300	70	brown	3002	2947 2894	1770	1668	21 13	(C=C) 1614,
12		270-275	62	brown	-	2979 2920	1774	1688	21 15	-

TABLE 3 physical properties and the FTIR spectral data cm⁻¹ of the synthesized compounds (13-20)

No.	Structure	Physical properties				Major FT-IR spectral data, ν , cm ⁻¹					
		M.P C°	Yield %	Color	N-H	1. C-H _{arom} 2. C-H _{aliph}	1. C=O imide 2. C=O amide	C=C Arom.	1. N=N 2. C-N	N-N	Other bands
13		202-208	72	Brown	3250	1. 3053 2. 2945 2896	1. 1751 2. 1659	1618	1. 1438 2. 1302	1422	-
14		256-261	65	Light brown	3249	1. 3076 2. 2929 2899	1. 1760 2. 1665	1600	1. 1442 2. 1305	1421	(NO ₂) Asym 1519 Sym 1346
15		190-196	58	Light brown	3251	1. 3018 2. 2981 2899	1. 1750 2. 1662	1602	1. 1454 2. 1303	1420	-

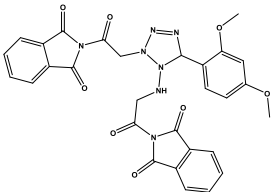
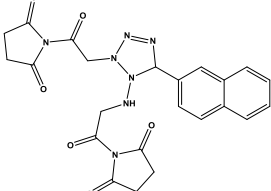
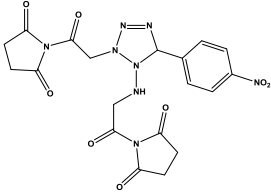
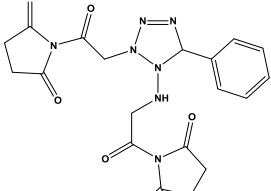
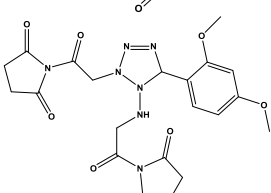
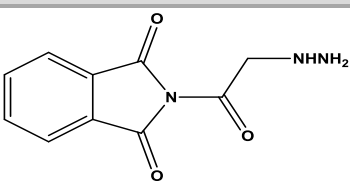
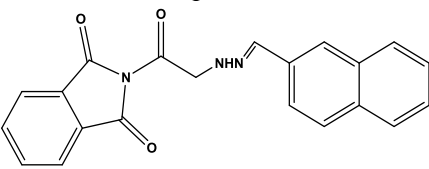
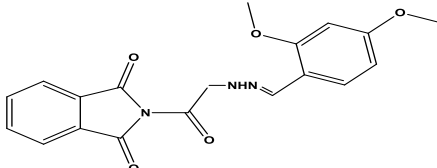
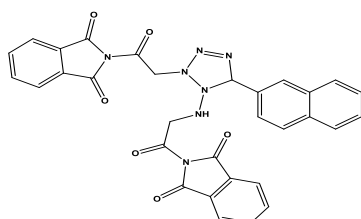
16		244-248	79	Yellowish brown	3244	1. 3010 2. 2945 2894	1. 1752 2. 1660	1606	1. 1460 2. 1328	1417	(C-O-C) 1267
17		160-166	60	Light brown	3248	1. 3053 2. 2930 2891	1. 1771 2. 1663	1600	1. 1431 2. 1301	1422	-
18		173-178	55	Light yellow	3248	1. 3029 2. 2977 2897	1. 1770 2. 1660	1599	1. 1430 2. 1305	1414	(NO ₂) Asym 1521 Sym 1346
19		151-155	42	Off white	3240	1. 3018 2. 2981 2898	1. 1754 2. 1666	1602	1. 1433 2. 1304	1420	-
20		216-220	66	Light brown	3238	1. 3011 2. 2975 2947	1. 1750 2. 1660	1608	1. 1431 2. 1304	1417	(C-O-C) 1265

TABLE 4 ¹HNMR spectral data (δ ppm) for some compounds

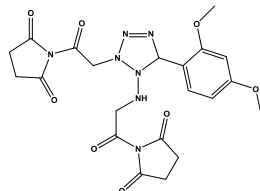
No. of Comp.	Structure	¹ HNMR spectral data (δ ppm)
1		3.49 (s, 2H, O=C-CH ₂ -N); 4.25 (s, 2H, NH ₂); 7.87 (s, 4H, Ar-H); 8.66 (s, 1H, NH)
3		3.49 (s, 2H, O=C-CH ₂ -N); 6.49 (s, 1H, N=CH-Ar); 7.62 - 8.38 (m, 11H, Ar-H); 8.92 (s, 1H, NH)
6		3.38 (s, 2H, O=C-CH ₂ -N); 3.84 (s, 6H, OCH ₃); 6.66 (s, 1H, N=CH-Ar); 7.72 - 8.22 (m, 11H, Ar-H); 8.82 (s, 1H, NH)

13



3.46 (s, 4H, 2(O=C-CH₂-N);
4.64 (s, 1H, (N)₂-CH-Ar);
7.63-8.37 (m, 15H, Ar-H); 8.91 (s, 1H, NH)

16



2.67-2.72 (t, 8H, 2(O=C-CH₂-CH₂-C=O));
3.34 (s, 4H, 2(O=C-CH₂-N);
3.79 (s, 6H, O-CH₃); 6.64 (s, 1H, (N)₂-CH-Ar);
7.25 (s, 3H, Ar-H);
8.81 (s, 1H, NH)

Biological activity [22]

Antimicrobial susceptibility tests of some synthesized compounds were performed according to the well diffusion method. A number of synthesized compounds had been evaluated on two bacterial strains, one gram-positive (*Staphylococcus aureus*) and one gram-negative (*Klebsiella pneumonia*). The samples were cultured on Muller Hinton agar

medium at a temperature of 37 °C for a period of 24 hours, and the results were good for some compounds, as shown in Table 5. Also, one fungal strain like pathogenic fungal (*Rhizosporium*) was evaluated, where samples were planted on the medium of PDA at a temperature of 28 °C for a period of (3-5) days and some results were good, as shown in the Table 5.

TABLE 5 Applications of anti-microbial for some of compounds

No.	No. of Comp.	Antibacterial activity test		Antifungal activity test
		<i>Staphylococcus aureus</i> (Gram-positive bacteria)	<i>klebsiella pneumonia</i> (Gram-negative bacteria)	<i>Rhizosporium</i>
1	Control	-	-	-
2	Phthalimide	21	14	17
3	Succinimide	13	18	18
4	\	22	35	16
5	3	15	21	14
6	7	13	20	15
7	14	21	13	14
8	18	21	14	20
9	Amoxicillin	28	30	
10	Flucanazole			14

Key to symbols:

Well diameter is 6mm.

[conc.] = 0.02 g/mL; solvent: dimethylsulfoxide (DMSO).

Inhibition Zone: (-) no inhibition; (6-10) mm weak; (11-18) mm moderate; (19-30) mm strong, (30-35) mm very strong.

Staph = *Staphylococcus aureus*; kle = *klebsiella pneumonia*; Ph = Phthalimide; Su = Succinimide

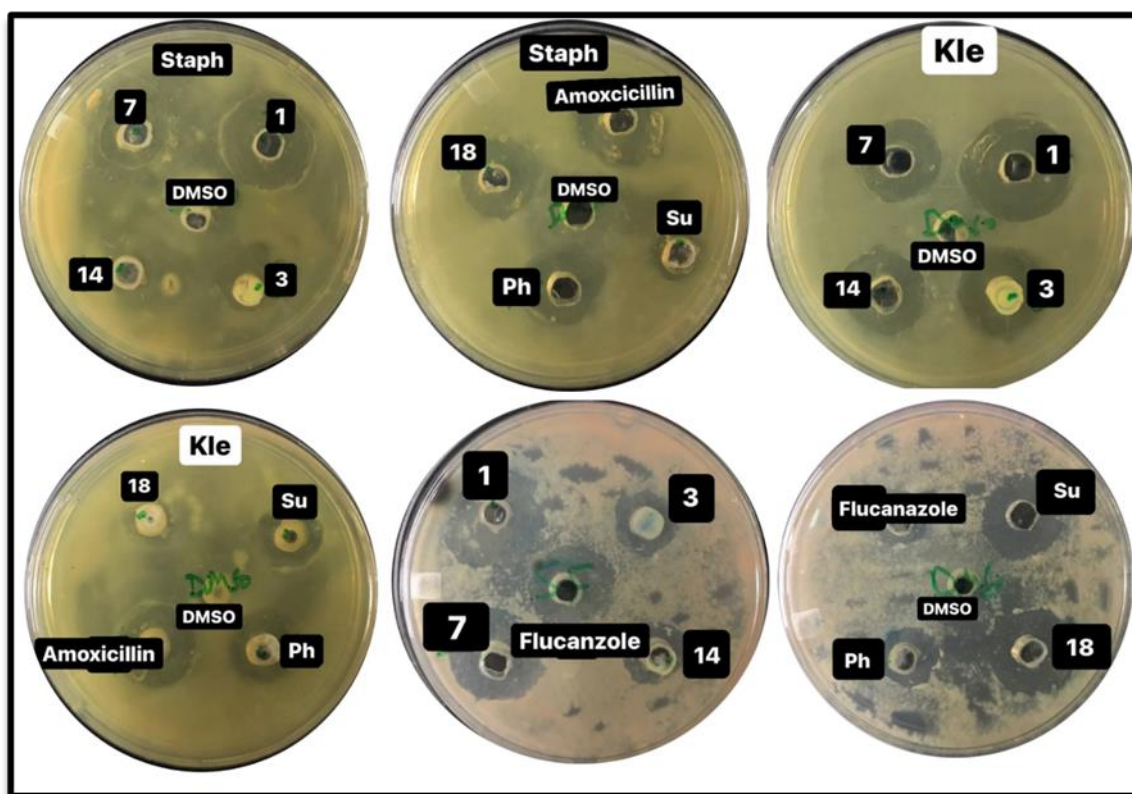


FIGURE 1 Biological activities of some prepared compounds on *Staphylococcus aureus*, *Klebsiella pneumonia* and *Rhizosporium*

Conclusion

The synthesized compounds were verified by using spectroscopic techniques (FTIR and ^1H NMR). Some of the prepared compounds gave a good efficiency. The biochemical studies revealed that the newly synthesized compounds caused activatory effects on two types of bacteria i.e. *Staphylococcus aureus*, *Klebsiella pneumonia*, and one type of fungal, i.e. *Rhizosporium*. *Staphylococcus aureus* showed moderate inhibition by the compounds 3 and 7 and high inhibition in compounds 1, 14 and 18. *Klebsiella pneumonia* showed moderate inhibition by the compounds 14 and 18, high inhibition in compounds 3 and 7, and very high inhibition in compound 1. *Rhizosporium* showed moderate inhibition in compounds 1, 3, 7, and 14, and high inhibition in compound 18. Based on what achieved, it can be said that these prepared compounds have good efficacy against bacteria and fungi.

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