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Synthesis of New 5-Aryl Tetrazoline from N-Aceto Hydrazide Cyclic Imides and Study of Biological Activity

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Abstract

The research resulted in the production of new tetrazoline derivatives. Firstly; the reaction of N-acetyl chloro cyclic imides with hydrazine hydrate to give compounds (1,2). Then, compounds (1,2) were reacted with different aromatic aldehydes to give Schiff bases (3-10). The compounds of N-(2-chloro acetyl) cyclic imides were reacted with sodium azide to give N-(azido acetyl) cyclic imides (11,12). Finally, the reaction of the prepared Schiff bases compounds with azide compounds and cyclization to give 5-aryl tetrazoline on cyclic imides (13-20). The prepared compounds were characterized by FT-IR and some of them by ^{1}H NMR, melting point, and were studied the effects of the preparing compounds on some strains of bacteria and fungi.

Keywords: cyclic imides, Schiff bases, sodium azide, tetrazoline, antibacterial.

1. Introduction

Schiff bases (imine) are one of the most commonly used families of organic compounds [1]. Also, Schiff bases have wide-ranging applications in the food industry, dye industry, analytical chemistry, catalysis, fungicide, agrochemical, and organic activities. With the increasing incidence of deep fungus, the focus is increasingly on screening for new, more effective antimicrobial drugs [2]. Heterocyclic compounds are of significant scientific importance as they are used as key feedstocks for active antimicrobial ingredients [3]. Compounds containing a five-membered heterocyclic ring have been observed to exhibit exceptional chemical behavior and a wide variety of versatile biological activities [4]. Tetrazoles are an important class of prevailing heterocycles in a myriad of natural products and biologically active compounds [5]. Moreover, tetrazoles are a unique class of heterocyclic compounds with various interesting properties. These can be used, for example, in pharmaceutical products [6], as synthetic building elements in coordinating chemistry [7], and as energetic materials with high nitrogen contents [8], anticancer agents [9], and antimicrobial activities [10]. Furthermore, 1,2,3,4-tetrazoles are a class of synthetic heterocyclic organic compounds composed of five rings composed of four nitrogen atoms and one carbon atom [11]. This general utility has led to important efforts towards the synthesis of tetrazole [12]. Tetrazoline systems, as biomolecules, have attracted scientific attention because of their particular pharmacological properties. Especially, they are widely used such as antimicrobials, anticancer, antioxidants, and antitubercular agents [13].

2. Experimental

A- Materials and instrumental

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 Gallenkamp capillary melting point apparatus. FT-IR spectra were recorded using KBr disc on Shimadzu FT-IR 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 Tahran University) with tetramethyl saline as internal standard and DMSO as a solvent.

B- Methods

Synthesis of N-(acetyl hydrazide) cyclic imides (1,2) [14]

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(0.01 mole) of N- acetyl chloro cyclic imides were dissolved in (20 ml) ethanol absolute and added 4 drops of Et_3N, then (0.01 mole) hydrazine hydrate was added drop by drop and refluxed at 4 hrs. The precipitate was collected after the solvent has volatilized, filtered, and washed with diethyl ether and purification by recrystallized from methanol, some of the physical properties and FTIR spectral data are listed in table 1.

Synthesis of Schiff bases (3-10) [15]

Equal moles of compounds (1,2) with different aromatic aldehydes (0.001 moles). Firstly, dissolved the aldehydes in (15 ml) ethanol, then 3 drops of glacial acetic acid were added to the solution, after that compounds (1,2) were added and refluxed at 6-8 hrs. The product is left until the solvent evaporated, washed with distilled water, and recrystallized from acetone, some of the physical properties and FTIR spectral data are listed in table 1.

Synthesis of N-(2-azido acetyl) cyclic imides (11,12) [16]

Sodium azide (0.005 moles) was added to a solution of N-(2-chloro acetyl) cyclic imides (0.005 moles) in (10 mL) of DMF. The reaction mixture was heated and stirred at (90 °C) for (4 hrs.) with continuous stirring. The solvent was evaporated; then the product was precipitated and filtered, washed well with diethyl ether, and recrystallized from ethanol, some of the physical properties and FTIR spectral data are listed in table 1.

Synthesis of 3-(N-acetyl cyclic imides)-4-N'-(2-cyclic imido) acetamide-5-(Schiff bases) tetrazoline (13-20) [17]

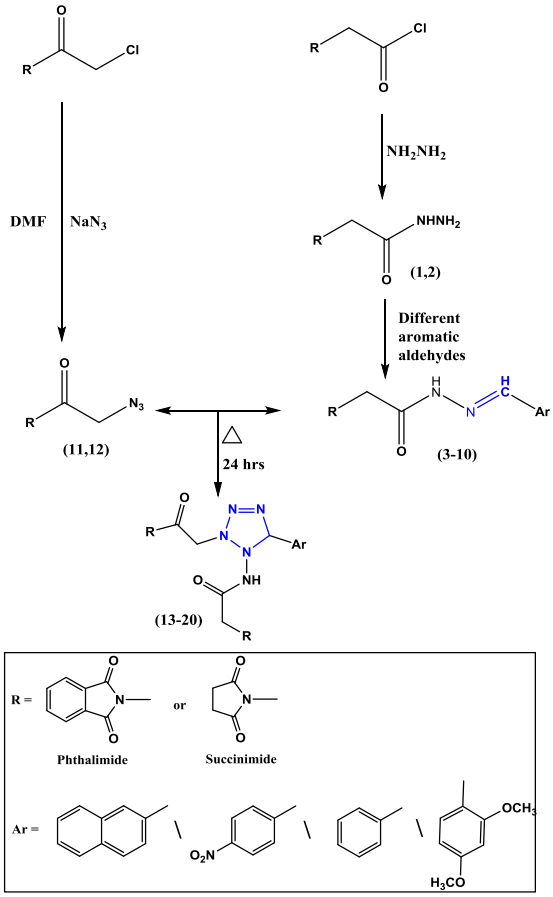
Compounds (11,12) (0.01mol) were dissolved in (50mL) of DMF and the compounds of Schiff bases (3-10) (0.01 mole) were added to the solution. The mixture was heated and stirred at 110 °C for 24 hrs. After removing the solvent, the residue was washed with diethyl ether and recrystallized from ethanol. Some of the physical properties and FTIR spectral data are listed in table 1.

3. Results and Discussions

Preparation of Schiff bases (3-10).

The compounds were synthesized from the reaction between compounds (1,2) and different aromatic aldehydes in absolute ethanol and glacial acetic acid. FT-IR spectra data of compounds (3-10) show appearance of characteristic bands at [3244-3213,

The Present work includes the reaction and synthesis of new derivatives of 5-aryl tetrazoline on cyclic imides as shown in Scheme 1.



Scheme 1

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

N-acetyl chloro cyclic imides react with hydrazine hydrate and tri-ethyl amine as a catalyst to prepare compounds (1,2). FT-IR spectra of these compounds (1,2) show appearance of the absorption bands [3319;3313, 3222;3257, 1750, 1693, 1440-1425, 1336-1301] cm^{-1} due to $\nu(NH_2)$, $\nu(NH)$, $\nu(C=O)$ imide, $\nu(C=O)$ amide, $\nu(N-N)$ and $\nu(C-N)$ respectively. These and other bands show in table (1). Also, disappearance of bands at [1800, 667] cm^{-1} due to $\nu(C=O)$ Acid chloride and $\nu(C-Cl)$.

1766-1748, 1689-1660] cm^{-1} due to ν(NH), ν(C=O) imide, ν(C=O) amide respectively, and [1660-1647, 1608-1599, 1439-1402, 1334-1301] cm^{-1} due to ν(C=N), ν(C=C), and ν(N-N), ν(C-N), respectively. These and other bands show in table (1). Also disappearance of absorption bands at (3400-3200) cm^{-1} due to ν(NH_2). ^1H NMR spectrum of compounds (3,6,7,10) showed signals at δ 2.51-4,73 ppm of (s, 2H, N-CH_2-C=O); δ 3.33-6.72 ppm of (s, 1H, N=CH-Ar); δ 8.80-8.92 ppm of (s, 1H, O=C-NH-N). Also, there is a signal at δ 2.5 ppm due to the solvent (DMSO). Others signals shown in table (2).

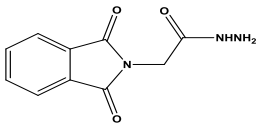
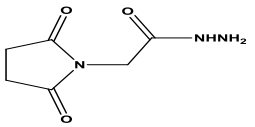
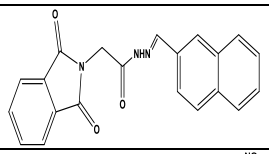
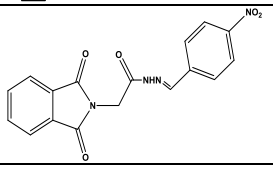
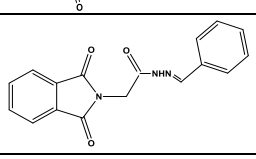
Preparation of N-(2-azido acetyl) cyclic imides (11,12).

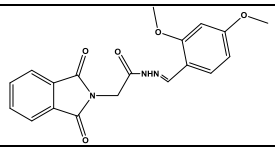
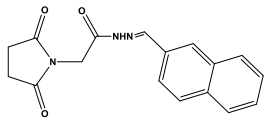
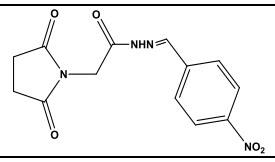
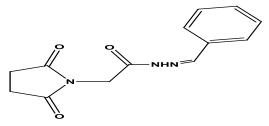
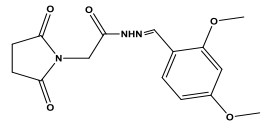
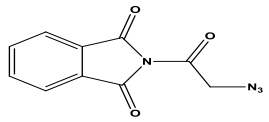
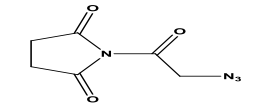
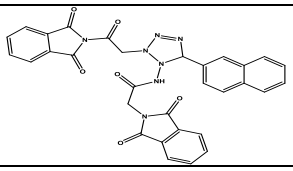
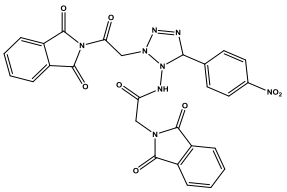
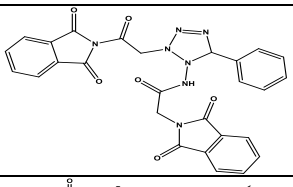
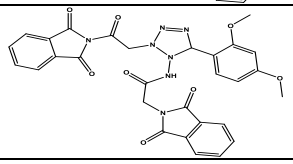
These compounds are synthesized by the reaction of N-(2-chloro acetyl) cyclic imides with sodium azide in DMF. FT-IR spectra data of compounds (11,12) shows the appearance of characteristic bands at [2947;2979, 2119;2115, 1774;1770, 1668;1688] cm^{-1} due to ν(C-H) aliphatic, ν(N_3), ν(C=O) imide and ν(C=O) amide respectively. These and other bands show in table (1). Also, the disappearance of absorption bands (715) cm^{-1} due to ν(C-Cl).

Preparation 3-(N-acetyl cyclic imides)-4-N'-(2-cyclic imido) acetamide-5-(Schiff bases) tetrazoline (13-20).

The compounds were synthesized by refluxing equimolar amounts from the compounds (3-10) with N-(azido acetyl) cyclic imides (11,12) in DMF. FT-IR spectra of this compounds (13,20) show appearance of the absorption bands [3256-3205, 3089-3010, 2980- 2931] cm^{-1} due to ν(NH), ν(C-H) aromatic, ν(C-H) aliphatic respectively, [1769-1750, 1671-1660] cm^{-1} due to ν(C=O) imide and ν(C=O) amide, and [1618-1599, 1558-1506, 1422-1414, 1330-1301] cm^{-1} due to ν(C=C), ν(N=N), ν(N-N), ν(C-N) respectively. These and other bands show in the table (1). Also, the disappearance of absorption bands [2115, 1690-1640] cm^{-1} due to ν(N_3) and ν(C=N). ^1H NMR Spectrum of compounds (16,19) showed signals at δ 3.36-3.78 ppm of (s,2H, O=C-CH_2-N); δ 4.08-4.17 ppm of (s, 1H, $(N)_2$-CH-Ar); δ 4.48-4.62 ppm of (s, 2H, $(C=O)_2$N-CH_2-C=O); δ 8.81-8.85 ppm of (s, 1H, O=C-NH-N). Also, there is a signal at δ 2.5 ppm due to the solvent (DMSO). Others signals shown in table (2).

Table (1): some physical properties and FT-IR spectral data cm^{-1} of the synthesized compounds (1-20).

NO.	Physical properties				Major FT-IR spectral data, υ, cm^{-1}				
	Structure	M.P C°	Yield %	Color	N-H	1. C-H_{arom} 2. C-H_{aliph}	1. C=O imide 2. C=O amide	1. C=N 2. C-N	Other bands
1		270 Dec.	81	white	3222	**1.** 3047 **2.** 2920 2850	**1.** 1750 **2.** 1693	**1.** – **2.** 1336	(NH_2) 3319 C=C 1602
2		135-138	64	white	3257	**1.** – **2.** 2985 2937	**1.** 1748 **2.** 1663	**1.** – **2.** 1301	(NH_2) 3313
3		252-258	70	yellow	3233	**1.** 3020 **2.** 2963 2891	**1.** 1751 **2.** 1660	**1.** 1654 **2.** 1301	-
4		> 300	72	yellow	3225	**1.** 3018 **2.** 2974 2896	**1.** 1753 **2.** 1660	**1.** 1650 **2.** 1305	(NO_2) Asym 1521 Sym 1346
5		> 300	60	Greenish yellow	3213	**1.** 3053 **2.** 2968 2891	**1.** 1748 **2.** 1660	**1.** 1648 **2.** 1328	-

6		204-210	83	Pale orange	3244	**1.** 3058 **2.** 2931 2829	**1.** 1755 **2.** 1680	**1.** 1660 **2.** 1326	(C-O-C) 1267
7		218-220	75	yellow	3244	**1.** 3006 **2.** 2975 2896	**1.** 1750 **2.** 1677	**1.** 1647 **2.** 1334	-
8		230-234	71	yellow	3234	**1.** 3089 **2.** 2977 2848	**1.** 1766 **2.** 1689	**1.** 1650 **2.** 1318	(NO_2) Asym 1519 Sym 1344
9		210-214	49	Light yellow	3217	**1.** 3058 **2.** 2931 2829	**1.** 1760 **2.** 1677	**1.** 1647 **2.** 1301	-
10		136-140	77	Greenish yellow	3230	**1.** 3006 **2.** 2947 2896	**1.** 1756 **2.** 1677	**1.** 1653 **2.** 1303	(C-O-C) 1265
11		> 300	70	brown	-	**1**. 3002 **2.** 2947 2894	**1.** 1770 **2.** 1668	**1.** – **2.** 1308	(C=C) 1614, (N_3) 2113
12		270-275	62	brown	-	**1.** – **2.** 2979 2920	**1.** 1774 **2.** 1688	**1.** – **2.** 1303	(N_3) 2115
13		210-214	78	Yellowish white	3253	**1.** 3020 **2.** 2954 2891	**1.** 1769 **2.** 1660	**1.** - **2.** 1301	(N=N) 1558
14		273-276	69	Light brown	3244	**1.** 3025 **2.** 2980 2897	**1.** 1755 **2.** 1660	**1.** - **2.** 1330	(NO_2) Asym 1521 Sym 1346 (N=N) 1556
15		212-215	55	Light brown	3250	**1.** 3020 **2.** 2954 2891	**1.** 1756 **2.** 1662	**1.** - **2.** 1301	(N=N) 1558
16		221-224	81	Yellowish brown	3256	**1.** 3010 **2.** 2975 2896	**1.** 1750 **2.** 1662	**1.** - **2.** 1303	(C-O-C) 1266 (N=N) 1558

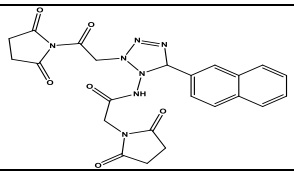
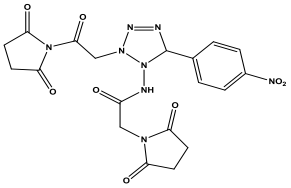
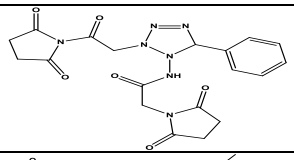
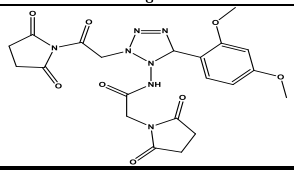
17		166-170	62	Off white	3240	**1.** 3047 **2.** 2931 2829	**1.** 1752 **2.** 1667	**1.** - **2.** 1301	(N=N) 1506
18		141-144	56	Light yellow	3205	**1.** 3089 **2.** 2977 2848	**1.** 1769 **2.** 1671	**1.** - **2.** 1310	(NO_2) Asym 1520 Sym 1344 (N=N) 1520
19		221-225	43	Off white	3229	**1.** 3047 **2.** 2931 2829	**1.** 1750 **2.** 1667	**1.** - **2.** 1302	(N=N) 1552
20		195-200	60	Light yellow	3236	**1.** 3033 **2.** 2947 2839	**1.** 1751 **2.** 1660	**1.** 1558 **2.** 1305	(C-O-C) 1269 (N=N) 1558

Table (2): 1H NMR spectral data (δ ppm) for some compounds.

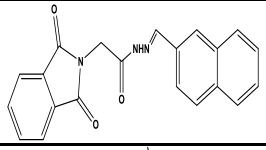
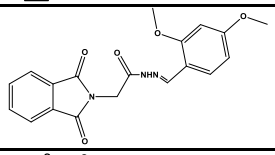
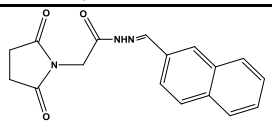
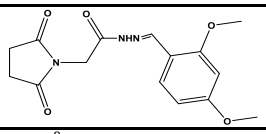
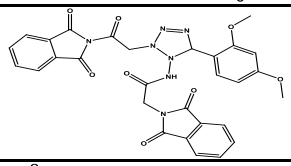
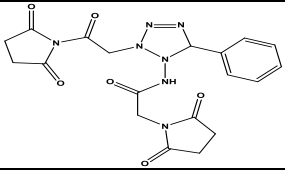
No. of Comp.	Structure	^{1}HNMR spectral data (δ ppm)
3		2.51 (s, 2H, N-CH_2-C=O); 3.33 (s, 1H, N=CH-Ar); 7.62-8.09 (m, 11H, Ar-H); 8.92 (s, 1H, O=C-NH-N)
6		3.88 (s, 6H, O-CH_3); 4.73 (s, 2H, N-CH_2-C=O); 6.66 (s, 1H, N=CH-Ar); 7.87,8.08 (d, 7H, Ar-H); 8.82 (s, 1H, O=C-NH-N)
7		2.25-2.33 (t, 4H O=C-CH_2-CH_2-C=O); 3.34 (s, 2H, N-CH_2-C=O); 6.72 (s, 1H, N=CH-Ar); 7.82 (s, 7H, Ar-H); 8.91 (s, 1H, O=C-NH-N)
10		2.62-2.65 (t, 4H O=C-CH_2-CH_2-C=O); 3.82 (s, 6H, O-CH_3); 4.61 (s, 2H, N-CH_2-C=O); 6.62 (s, 1H, N=CH-Ar); 7.85,8.10 (d, 3H, Ar-H); 8.80 (s, 1H, O=C-NH-N)
16		3.36 (s,2H, O=C-CH_2-N); 3.81 (s, 6H, O-CH_3); 4.08 (s, 1H, $(N)_2$-CH-Ar); 4.62 (s, 2H, $(C=O)_2$N-CH_2-C=O); 6.64-8.07 (d, 11H, Ar-H); 8.81 (s, 1H, O=C-NH-N)
19		2.65-2.68 (t, 8H 2(O=C-C<u>H</u>$_2$-C<u>H</u>$_2$-C=O)); 3.87 (s, 2H, O=C-CH_2-N); 4.17 (s, 1H, $(N)_2$-CH-Ar); 4.48 (s, 2H, $(C=O)_2$N-CH_2-C=O); 7.28 (s, 5H, Ar-H); 8.85 (s, 1H, O=C-NH-N)

Table (3): applications of anti-microbial for some of compounds.

No.	No. of Comp.	Antibacterial activity test		Antifungal activity test
		Staphylococus aureus (Gram-positive bacteria)	*klebsiella pneumonia* (Gram-negative bacteria)	Rhizosporium
1	Control	-	-	-
2	Phthalimide	21	14	17
3	Succinimide	13	18	18
4	1	12	12	14
5	3	16	16	18
6	7	13	20	15
7	14	14	20	22
8	16	16	21	20
9	18	18	12	15
10	20	18	14	17
11	Amoxicillin	28	30	
12	Flucanazole			14

well diameter is 6mm.
[conc.] = 0.02 g/ml; solvent: dimethylsolfoxide (DMSO).
Inhibition Zone: (-) no inhibition; (6-10) mm weak; (11-18) mm moderate; (19-30) mm strong.

4. Biological Activity [18]

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 bacteria (staphylococcus aureus) and one gram-negative bacteria (Klebsiella pneumonia). 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 (3). They also evaluated one fungal strain like pathogenic fungal (Rhizosporium), 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 (3).

5. Conclusion

The synthesized compounds were confirmed by using spectroscopic techniques (FT-IR and ^{1}H 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 (Staphylococcus aureus, Klebsiella pneumonia), and one type of fungal (Rhizosporium).

6. References

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