Synthesis, Characterization and Evaluation of Antibacterial Activity of Several New 3,4-Dimethyl Maleimides and 1,8-Naphthalimides Containing 1,3,4-Oxadiazole Ring

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Abstract

A series of new cyclic imides (3,4-dimethyl maleimides) and (1,8-naphthalimides) substituted with 1,3,4-oxadiazole ring were prepared by following four different methods. The first one involved direct reaction of 5- substituted–2 -amino-1,3,4- oxadiazole with 3,4-dimethyl maleic anhydride under certain conditions while the second method involved reaction of 5-subsitiuted-2-amino-1,3,4-oxadiazole with 1,8- naphthalic anhydride in the presence of glacial acetic acid. The strategy used in performing the third method based on Gabrial synthesis involving treatment of 5-substituted-2-amino-1,3,4-oxadiazoles with chloro acetyl chloride to afford 2-(2-chloro acetyl amino)-1,3,4-oxadiazoles which in turn were used subsequently in reaction with 1,8-naphthalimide producing three new N-(2-acetyl amino-5-substituted-1,3,4- oxadiazole-2-yl)-1,8-naphthalimides. The strategy used in performing the fourth method based on Williamson reaction including reaction of the prepared 2-(2-chloro acetyl amino)-1,3,4- oxadiazoles with N-(hydroxy phenyl)- 3,4- dimethyl maleimides to afford nine new N-[2-oxyacetamido-5-substituted 1,3,4-oxadiazole-2- yl)phenyl]-3,4-dimethyl maleimides. Finally antibacterial activity of all the prepared new cyclic imides were evaluated against two types of bacteria and the results showed that most of the new imides posses high biological activity against these organisms.

Introduction

Cyclic imides are important family of organic compounds possess structural features which confer potential biological activity and pharmaceutical use[1,2]. Their molecules contain an imide ring with a general structure [-CO-N(R)-CO-], so that they are hydrophobic and neutral and can therefore cross biological membranes in vivo. A diversity of biological activities and pharmaceutical uses have been attributed to them, such as antibacterial, antifungal, anti nociceptive, anticonvulsant and antitumor [3].On the other hand 1,3,4-oxadiazoles belong to a group of heterocycles that have been attracting attention for last two decades due to their wide range of biological interactions [4,5]. Many of them exhibit antibacterial, anticonvulsant, anticancer activities and are used to fight infections involving AIDS [6-8]. They are also applied in agriculture as herbicides, fungicides or insecticides [9,10]. Keeping these above facts in view it was thought worthwhile to synthesize new compounds by incorporating cyclic imide and 1,3,4-oxadiazole ring in a single molecular framework. The resulted new molecules were expected to possess biological activity since they were built from two biologically active components.

Experimental

All chemicals employed were of analytical reagent grade and were used without further purification. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared Spectrophotometer using KBr discs. Melting points were determined in open capillaries on Thomas Hoover apparatus and were uncorrected.

^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker spectro spin ultra shield magnets 300 MHz instrument, using DMSO–d_6,$CDCl_3$ as solvents and TMS as internal reference. Elemental analysis were preformed on Perkin Elmer 240 element analyzer.

1-Preparation of 2-amino -5-substituted -1,3,4-oxadiazoles [1-6]

The titled compounds were prepared according to literature procedures [11] with minor modifications and the required semicarbazones were synthesized via direct reaction between aldehydes and hydrazine hydrate according to literatures [12].

Semicarbazone (0.01 mol) and sodium acetate (0.02 mol) were dissolved in (30-40 mL) of glacial acetic acid in a suitable round bottomed flask equipped with a dropping funnel for the addition of bromine.Bromine (0.7 mL in 5 mL glacial acetic acid) was added drop wise with stirring and cooling. Stirring was continued for 1 hr. then the resulted solution was poured on crushed ice with vigorous stirring. The resulting solid was filtered, washed thoroughly with water,dried and recrystallized from ethanol. Physical properties and FTIR spectral data of compounds [1-6] are listed in Table (1).

2-Preparation of N -(5-substituted -1,3,4-oxadiazole-2-yl)-3,4- dimethyl maleimides [7-12]

The titled imides were prepared according to literatures [13] with some modifications: A solution of (0.01 mol) of 2- amino-5-substituted -1,3,4-oxadiazole in (25 mL) of diethyl ether was added drop wise to a solution of (0.01 mol) of 3,4-dimethyl maleic anhydride dissolved in(25 mL) of diethyl ether with stirring and cooling.The resulted mixture was stirred for additional 2 hrs. at room temperature then was left over night. The obtained precipitate was filtered,washed with ether and dried then was purified by recrystallization from cyclohexane. Physical properties and FTIR spectral data of compounds [7-12]are listed in Table (2).

3-Preparation of N-(5-substituted-1,3,4-oxadiazole-2-yl)-1,8-naphthalimides [13-18]

A solution of (0.01mol) of 2-amino-5-substituted - 1,3,4-oxadiazole in (20 mL) chloroform was added drop wise to (0.01 mol) of 1,8-Naphthalic anhydride dissolved in (30 mL) of chloroform with stirring then (5mL) of glacial acetic acid was added and the mixture was refluxed for four hours [14]. The resulted mixture was cooled to room temperature before pouring into crushed ice with vigorous stirring. The obtained precipitate was filtered, washed thoroughly with water and dried then was purified by recrystallization from benzene. Table (3) lists physical properties and FTIR spectral data of the prepared imides [13-18].

4- Preparation of 5-substituted -2-(2-chloro acetyl amino) -1,3,4- oxadiazoles[19-21]

Chloro acetyl amino oxadiazoles were prepared by following literature procedures[15]. A mixture of 2- amino-5-substituted -1,3,4-oxadiazole (0.02 mol) and chloro acetyl chloride (0.02 mol) in chloroform (50 mL) was refluxed in the presence of K_2CO_3 (0.02mol) for eight hours. Excess of solvent was removed in vacuo and the residue was stirred with water before filtration. The obtained precipitate was washed with 5 % $NaHCO_3$ solution then with water and dried then was purified by recrystallization from acetone. Physical properties and FTIR spectral data of compounds [19-21] are listed in Table (4).

5-Preparation of N-(2- acetyl amino-5-substituted-1,3,4- oxadiazole –2- yl)- 1,8-naphthalimides [22-24]

Synthesis of the titled imides were performed via the following two steps:

5-1-Preparation of 1,8- Naphthalimide potassium salt

Naphthalimide (0.01 mol) was dissolved in (25mL)of absolute ethanol then was heated in a water bath. The resulted clear solution was added to alcoholic potassium hydroxide solution with stirring and cooling then the obtained precipitate was filtered and dried [16].

5-2- Preparation of compounds [22-24]

(0.01 mol) of the prepared 1,8-naphthalimide potassium salt was added gradually with stirring to (0.01 mol) of compound [19], [20] or [21] dissolved in (30 mL) of absolute alcohol [17]. The resulted mixture was refluxed for eight hours with continuous stirring then was cooled to room temperature.The obtained precipitate was filtered, washed with 5 % $NaHCO_3$ solution then with water and dried. Purification of the product was preformed by recrystallization from n-hexane. Physical properties and FTIR spectral data of compounds[22-24]are listed in Table (5).

6-Preparation of N-[4-(2-oxyacetamido-5-substituted-1,3,4-oxadiazole–2-yl)phenyl] - 3,4- dimethyl maleimides[25-27]

(0.015 mol) of 4-(hydroxy phenyl)-3,4-dimethyl maleimide was dissolved in (15 mL)

of 10 % solution of sodium hydroxide. To the resulted clear solution (0.015mol) of compound [19], [20] or [21] dissolved in (20 m L) of acetone was added gradually with stirring. The resulting mixture was refluxed for three hours then cooled to room temperature before pouring into (50 mL) of cold water with vigorous stirring. Dilute HCl solution was added drop wise with stirring and cooling until neutralization then the formed precipitate was filtered, washed with water several times, dried and finally recrystallized from cyclohexane. Physical properties and FTIR spectral data of compounds [25-27] are listed in Table (6).

7-Preparation of N - [3-(2-oxyacetamido-5-substituted-1,3,4-oxadiazole–2-yl)phenyl] -3,4-dimethyl maleimides[28-30]

The titled compounds were synthesized via reaction of equimolar amounts of 3-(hydroxy phenyl)-3,4-dimethyl maleimide and compound [19], [20] or [21] following the same procedure used in th preparation of compounds [25 – 27]. Physical properties and FTIR spectral data of compounds [28-30] are listed in Table (6).

8-Preparation of N-[2-(2-oxyacetamido-5-substituted-1,3,4-oxadiazole–2-yl) phenyl] -3,4- dimethyl maleimides[31-33]

The titled compounds were prepared by following the same procedure used in the synthesis of compounds [25-27] except using of 2-(hydroxy phenyl) -3,4- dimethyl maleimide instead of 4-(hydroxy phenyl)-3,4-dimethyl maleimide.

Physical properties and FTIR spectral data of compounds[31-33]are listed in Table(6).

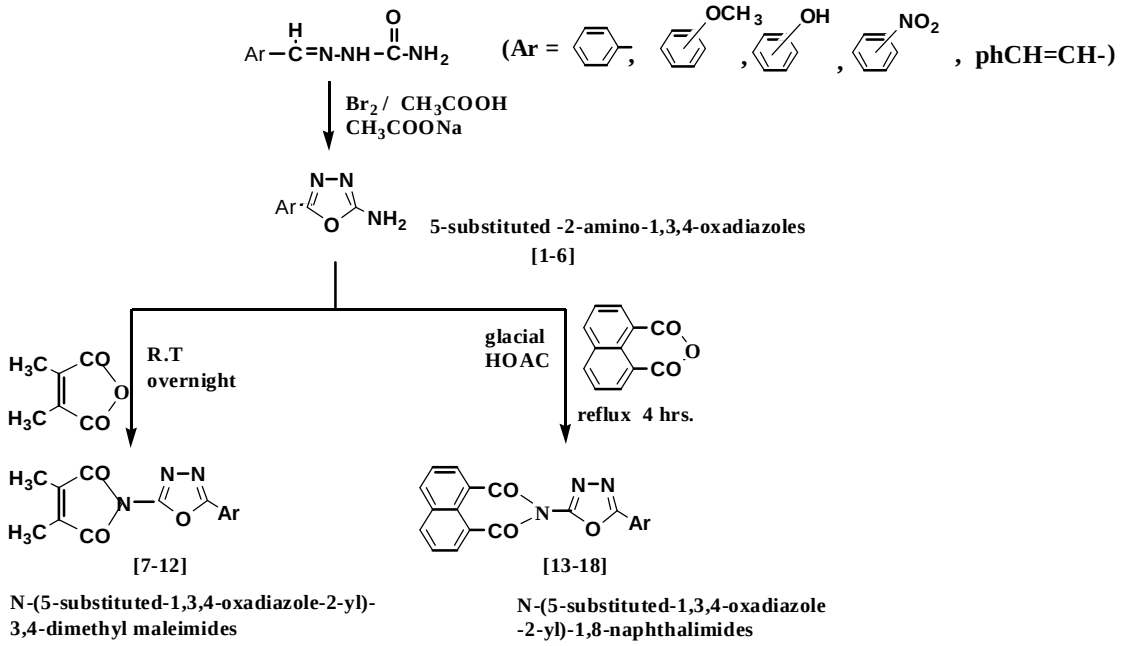
9-Biological study

The cup plate method using nutrient agar medium was employed in studying the antibacterial activity of the prepared imides against two types of bacteria, *staphylococcus aureous* (Gram positive)and *E scherichia coli* (Gram negative) respectively. DMF was used as sample solution and sample size for all the compounds was fixed at (0.1mL). Using a sterilized cork borer cups were scooped out of agar medium contained in a Petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the Petri dishes where subsequently incubated a 37 ^{0}C for 48 hours.Zones of inhibition produced by each compound was measured in mm and the results are listed in Tables (10) and (11).

Results and Discussion

Since both cyclic imides and 1,3,4-oxadiazoles are very important organic compounds having wide spectrum of biological activities [18,19] the target of the present work is to synthesize new compounds containing these two biologically active components with expected biological activity. The target of this work was performed by following different strategies, the first one involved reaction of 5-substituted-2-amino-1,3,4-oxadiazoles with selected cyclic anhydrides. Thus a series of 2-amino-1,3,4-oxadiazoles substituted with different substituents in 5-position were prepared via oxidative cyclization of the corresponding substituted semicarbazone under the influence of bromine and sodium acetate in glacial acetic acid [11].

Direct reaction of the prepared 5-substituted-2-amino-1,3,4-oxadiazoles [1-6] with 3,4- dimethyl maleic anhydride in suitable solvent under certain conditions afforded the desirable imides [7-12], while reflux of the prepared 5- substituted-2-amino-1,3,4- oxadiazoles with 1,8-naphthalic anhydride in the presence of glacial acetic acid afforded the desirable naphthalimides [13-18]. These reactions are summarized in Scheme (1).



Scheme (1).

The prepared imides [7-18] were colored solids with sharp melting points and afforded in good yields (63-87)%. Structures of the prepared imides [7-18] were confirmed by FTIR, H-NMR and ^{13}C-NMR spectroscopy and C.H.N analysis for some of them.

FTIR spectra of imides[7-12] showed clear absorption bands at (1680-1766) $cm^{-1,}$ (1643-1658) cm^{-1}, (1510-1604) cm^{-1}, (1330-1380) $cm^{-1}$and(1118-1280) cm^{-1}due to υ (C=O) imide, υ(C=N), υ(C=C) aliphatic, υ(C-N) imide and υ(C-O-C)ether respectively, while FTIR spectra of imides [13-18] showed two characteristic bands at (1758-1782) cm^{-1} and (1735-1743) cm^{-1} due to υ (C=O) imide and other absorption bands at (1581-1704) cm^{-1}, (1303-1350) cm^{-1}, (1172-1188) cm^{-1} due to υ(C=N), υ(C-N) imide and υ(C-O-C) ether respectively [20] .

On the other hand HNMR spectrum of compound [1] showed singlet signal at δ=2.5ppm belong to (NH) amine proton and multiplet signals at δ=(7.2-7.8)ppm which were assigned to aromatic protons, while ^{13}CNMR spectrum of the same compound showed two characteristic signals at 164 and157ppm belong to two carbon atoms in oxadiazole ring and signals at (100-135) ppm belong to aromatic ring carbons.

HNMR spectra of imides [9] and [10] showed clear signals involved singlet signal at δ = 2.5 ppm belong to two (CH_3) protons and multiplet signals at δ= 6.95-7.86) ppm belong to aromatic protons.

HNMR spectrum of compound [9] showed also two signals at δ= 6.88 and 7.06 ppm which were assigned to two vinylic protons while HNMR spectrum of compound [10] showed signal at δ= 3.8 ppm belong to (OCH_3) group [20].

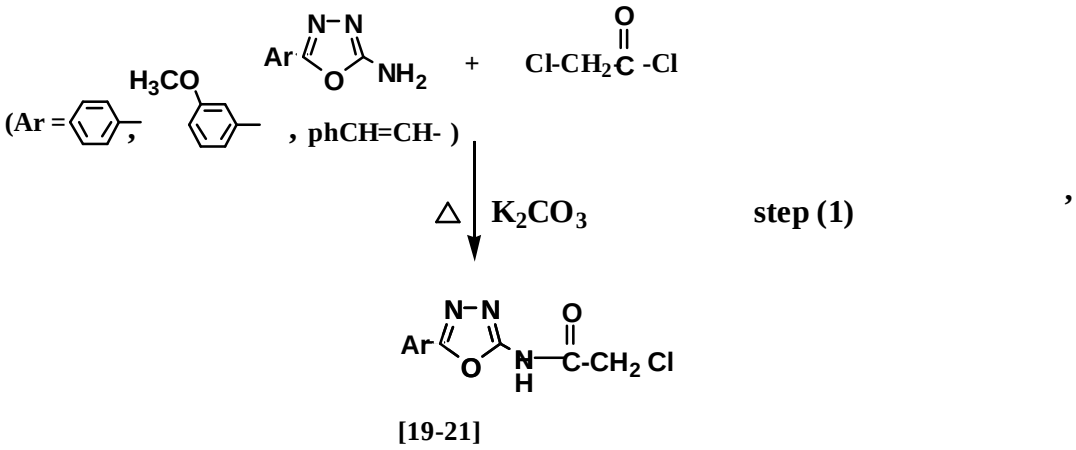
^{13}C-NMR spectrum of compound [9] showed many characteristic signals including signal at 9.3 ppm belong to two methyl groups, signals at 140 and 142 ppm belong to two vinylic carbons attached to phenyl ring .Other signals appeared at 147, (152-153) and 171.33 ppm which were attributed to vinylic carbons in imide ring, C=N carbons in oxadiazole ring and carbonyl group carbons in imide ring respectively while signals of aromatic carbons appeared at (117-125.17) ppm.

On the other hand HNMR spectra of compounds [13] and [16] showed multiplet signals δ= 7.1-7.95 ppm and at δ=8.1-8.55 ppm which belong to aromatic protons of benzene ring and naphthyl rings respectively, more over HNMR spectrum of compound [16] showed signal at δ= 3.8 ppm belong to (OCH_3) protons.

On the other hand ^{13}C-NMR spectrum of compound [13] showed many clear signals

including signals at 119.4-135.8 ppm belong to aromatic carbons of benzene and naphthyl rings, signal at 161.18 ppm belong to carbons in oxadiazole ring and signal at 164.3 belong to two carbonyl carbons in imide ring.

The second part in this work involved synthesis of new naphthalimides [22-24] connected to oxadiazole moiety through acetamido group. The strategy used in building of these compounds involved reaction of 2-amino-1,3,4-oxadiazole compounds with chloroacetyl chloride producing 2-(2-chloroacetylamino) oxadiazole derivatives [19-21] which in turn were introduced in reaction with 1,8-naphthalimide potassium salt to afford the desirable naphthalimides [22-24]. These syntheses represent a modified Gabriel synthesis and were summarized in Scheme (2).



Scheme (2).

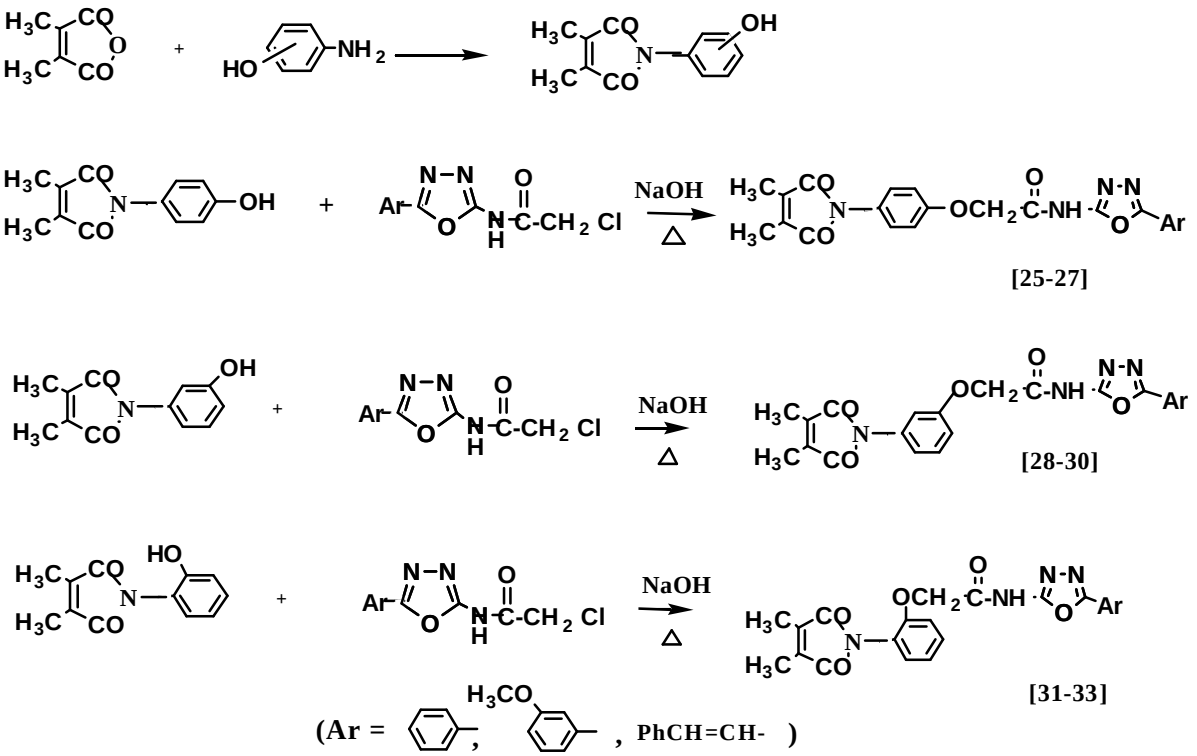
The prepared imides [22-24] are green solids having sharp high melting points.

FTIR spectra of these imides showed clear absorption bands at (3317-3402) cm^{-1} (1690-1712) cm^{-1} and (1674-1681) cm^{-1} due to υ(N-H) amide, υ(C=O) imide and υ (C=O) amide while absorption bands due to υ(C=N) and υ(C-N) were appeared at (1589-1660) cm^{-1} and(1373-1380)cm^{-1} respectively.

HNMR spectrum of compound [23] showed two clear signals at δ= 2.1and 3.66 ppm belong to (-$\underline{CH_2}$ –CO-) and (OCH_3) protons, while signals belong to benzene ring and naphthyl ring protons appeared at δ= (7-7.71) and (8-8.43)ppm respectively.

The third part of this work involved synthesis of new cyclic imides [25-33] connected to oxadiazole moiety through phenoxy acetamido group. The strategy used in building of these imides [25-33] involved reaction of the prepared 2 - chloroacetyl amino oxadiazole derivatives [19-21] with N-(hydroxy phenyl) 3,4- dimethyl maleimides in alkaline solution according to Williamson synthesis.

The three N-(hydroxyl phenyl)-3,4-dimethyl maleimides used in these syntheses were prepared according to literatures [21] via reaction of 3,4-dimethyl maleic anhydride with o, m and p-amino phenols. Synthesis of imides [25-33] can be summarized in Scheme (3).



Scheme (3).

Synthesis of imides [25-33] were preformed in alkaline medium because in alkaline solution a phenolic moiety existed as the phenoxide ion which act as a nucleophilic reagent attacked the halide 2-(2-chloro acetyl amino)-1, 3, 4- oxadiazoles and displaced halide ion affording the desirable products. Most of the prepared imides [25-28] and [32,33] are colored solids with sharp melting points while imides [29-31] are oily compounds.Structures of the prepared imides [25-33] were confirmed by FTIR, H–NMR, ^{13}C-NMR spectroscopy and C.H.N analysis for some of them.

FTIR spectra of imides [25-33] showed characteristic absorption bands at (3286-3363)cm^{-1},(1743-1680) cm^{-1} and (1640-1689)cm^{-1}which were attributed to υ(N-H) amide, υ (C=O) imide and υ(C=O) amide respectively while absorption bands due to υ(C=N) and υ(C-N) imide were appeared at (1596-1658) cm^{-1}and (1311-1396) cm^{-1}.

On the other hand HNMR spectra of compounds [26] and [32] showed singlet signals at δ= (1.95-1.97) and 2.5 ppm which were assigned to –$\underline{CH_2}$-CO- protons and two methyl protons. Signals belong to vinylic protons appeared at δ=(6.3-6.45) ppm while aromatic protons and (NH) amide proton appeared at δ=(6.8-7.8) and (8.3-9.8) ppm respectively. Finally ^{13}C-NMR spectra of compounds [26] and [32] showed characteristic signals at (9.08-9.1) and (46.11-47) ppm which were attributed to two methyl groups and –$\underline{CH_2}$-CO- respectively while signals for aromatic ring carbons appeared at (111.3-136.61) ppm. Signals belong to carbonyl carbons in imide ring appeared at (171.3-171.48) ppm while signals for C=O amide carbons, carbons in oxadiazole ring and vinylic carbons were appeared at (163.75-163.76), (156.89-158.14) and (137.66-154.47) ppm respectively.

Physical properties and FTIR spectral data of the prepared compounds in this work are

listed in Tables (1-6), HNMR and ^{13}C-NMR spectral data are listed in Tables (7) and (8) and C.H.N) analyses are listed in Table (9).

Biological activity

The prepared imides in this work were expected to posses biological activity since they were built from two biologically active moieties thus studies on the antibacterial activity of synthesized imides have been carried out against two pathogenic organisms including *staphylococcus aureous* (Gram positive) and *Escherichia Coli* (Gram negative).

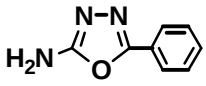
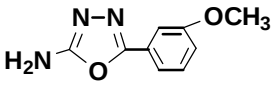
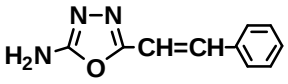
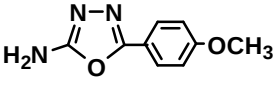
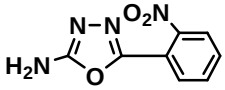
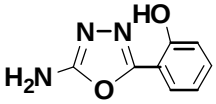
Antibacterial activity of the newly synthesized compounds in the present investigation was assessed by the cup–plate method. The results of antibacterial studies are shown in Tables (10) and (11). Among the tested imides [7-18], compounds [7], [8] and [10] showed very high activity against *Escherichia coli (E.coli)* . Also compounds [9], [11], [13], [14] and [16-18] showed high activity against *E.coli* while compounds [12] and [15] showed moderate activity against this bacteria.

On the other hand the same imides [7-18] showed less activity against *Staphylococcus aureus* (*S.aureus)* thus only compound [11] showed high activity, compounds [7],[10],[12] and [15] showed moderate to slight activity while other imides [8,9,13,14] and [16-18] were found in active against this bacteria.

Imides [22-33] showed high activity against *E.coli* except compounds [26] and [27] which showed moderate activity. Also imides [25-27], [29] and [31] showed high to moderate activity against *S. aureus* while imides [22-24] and [28, 30, 32, 33] were found in active against this bacteria.

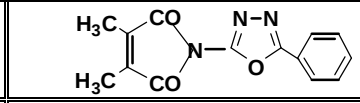
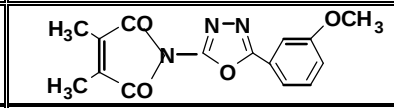
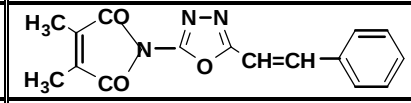
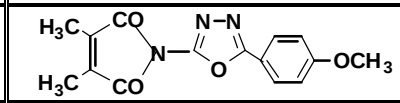
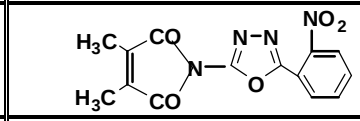
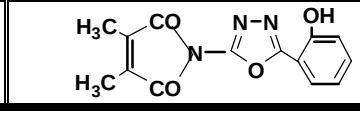
These results may be attributed to cell wall structure in the studied bacteria, thus molecules of most of the prepared imides have hydrophobic properties and this in turn made these compounds active against (Gram negative bacteria) *E.coli* which posses complex lipo poly saccharides in their cell walls and inactive against *S.aureus* due to hydrophilic properties of cell walls in (Gram positive) bacteria [22].

Table (1)
Physical properties and FTIR spectral data of 2-amino-5-substituted – 1,3,4-oxadiazoles.

Compd. No.	*Compound Structure*	*Color*	*Yield %*	*Melting Point ^{0}C*	*Major FTIR Absorptions cm^{-1} **			
					υ N-H Amine	*υ C=N*	*υ C-O-C*	*Others*
1		White	65	216-218	3301	1650	1120 1280	——
2		Pale pink	74	202-204	3310	1650	1170 1250	——
3		Yellow	82	159-160	3456	1658	1125	υ C=C Aliphatic 1525
4		Off White	70	187-188	3410	1671	1140	——
5		Brown	76	Oil	3463	1704	1134 1272	υ C-NO_2 1427 1342
6		White	88	224-225	3363	1704	1165 1290	υ O-H phenolic 3471

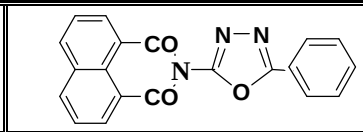
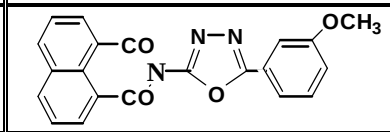
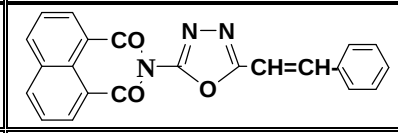
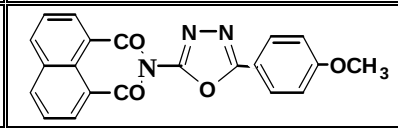
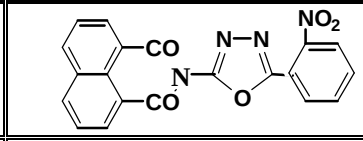
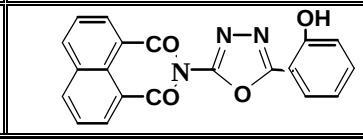
****As KBr disc.***

Table (2)
Physical properties and FTIR spectral data of Imides [7-12].

Compd. No.	Compound Structure	Color	Yield %	Melting Point ^0C	Major FTIR Absorptions cm^{-1} *				
					υ C=O Imide	υC=N	υ C-N Imide	υ C-O-C	υ C=C Aliphatic
7		White	84	124-125	1758	1650	1374	1118 1280	1596
8		Pale Yellow	70	210-212	1766	1658	1330	1180 1257	1604
9		Yellow	65	177-178	1680	1643	1342	1134	1589
10		White	87	118-120	1681	1658	1360	1180 1249	1604
11		Yellow	81	199-200	1704	1581	1380	1170	1581
12		Yellow	63	164-166	1697	1596	1342	1164 1257	1510

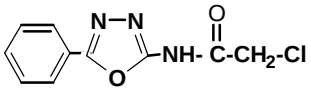
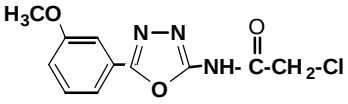
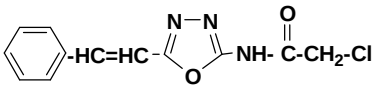
**As KBr disc.*

Table (3)
Physical properties and FTIR spectral data of Imides[13-18]

Compd. No.	Compound Structure	Color	Yield %	Melting Point ^0C	Major FTIR Absorptions cm^{-1} *				
					υ C=O Imide	υC=N	υ C-N Imide	υ C-O-C	Others
13		Off White	78	237-238	1782 1743	1666	1303	1188	___
14		Brown	81	207-208	1766 1735	1581	1303	1180	___
15		Yellow	85	198 Dec.	1758 1735	1666	1303	1188	υ C=C 1573
16		Off White	73	202-204	1761 1737	1641	1308	1176	___
17		Yellow	75	225-226	1770 1735	1596	1303	1180	υ C-NO_2 1434 1350
18		Off White	77	219-220	1766 1743	1704	1303	1172	υ O-H Phenolic 3456

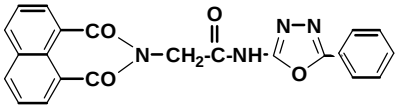
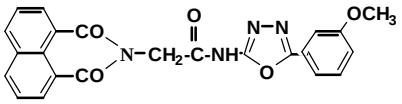
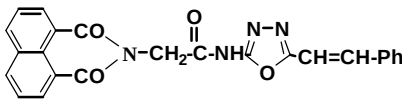
**As KBr disc.*

Table (4)
Physical properties and FTIR spectral data of compounds [19-21].

Compd. No.	Compound Structure	Color	Yield %	Melting Point ^0C	Major FTIR Absorptions cm^{-1} *				
					υ N-H Amide	υ C=O Amide	υ C=N	υ C-O-C ether	υ C-Cl Aliphatic
19		White	77	171-172	3317	1750	1650	1143	780
20		Pink	65	149-150	3325	1735	1660	1180	833
21		Yellow	72	178-180	3286	1710	1658	1134	840

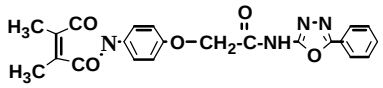
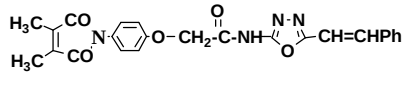
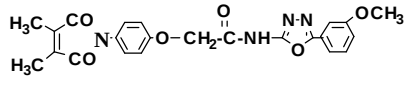
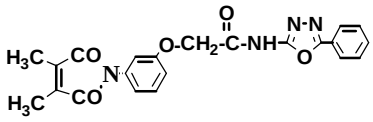
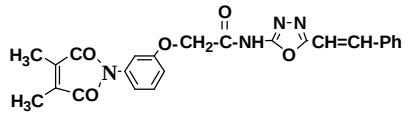
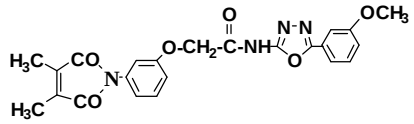
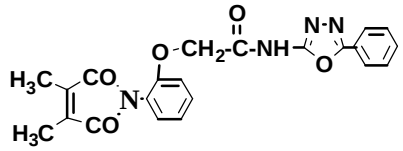
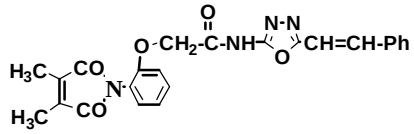
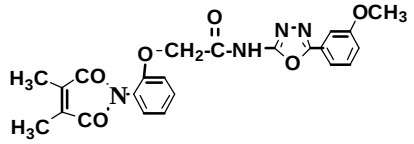
** AS KBr disc*

Table (5)
Physical properties and FTIR spectral data of Imides [22-24].

Compd. No.	Compound structure	Color	Yield %	Melting Point ^0C	Major FTIR Absorptions cm^{-1} *					
					υ N-H	υ C=O Imide	υ C=O Amide	υC=N	υ C-O-C	υ C-N
22		Green	63	241-242	3402	1690	1681	1589	1149	1380
23		Green	72	220-222	3317	1700	1674	1589	1180	1373
24		Green	80	234-235	3325	1712	1681	1660	1180	1380

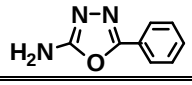
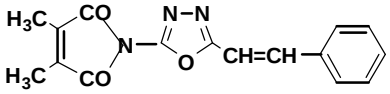
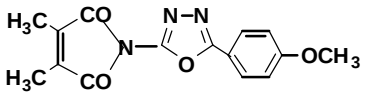
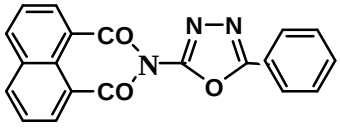
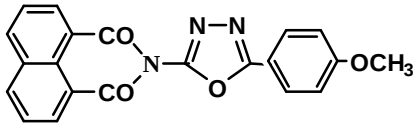
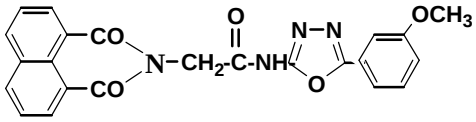
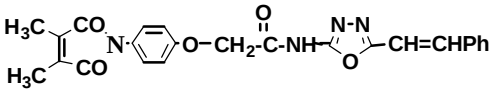
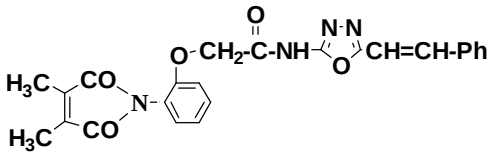
** AS KBr disc*

Table (6)
Physical properties and FTIR spectral data of Imides [25-33].

Compd. No.	*Compound structure*	*Color*	*Yield %*	*Melting Point^{0}C*	*Major FTIR Absorptions cm^{-1} **					
					υC-O-C	*υ N-H*	*υ C=O Imide*	*υ C=O Amide*	*υC=N*	*υ C-N*
25		Brown	85	136-138	1141 1234	3286	1689	1650	1596	1390
26		Deep Green	88	130-132	1141 1234	3340	1689	1660	1604	1388
27		Brown	70	185-187	1186 1257	3332	1680	1658	1604	1311
28		Off White	75	210-212	1157 1234	3300	1740	1650	1596	1330
29		Brown	90	Oily	1180 1257	3363	1712	1658	1604	1388
30		Brown	86	Oily	1180 1257	3363	1697	1660	1605	1396
31		Orange	60	Oily	1190 1280	3309	1704	1640	1596	1350
32		Yellow	72	152-153	1188 1280	3294	1697	1658	1596	1357
33		Yellow	65	147-148	1180 1257	3317	1743	1687	1658	1360

**** AS KBr disc***

Table (7)
^{1}H-NMR spectral data for some of the prepared compounds.

Compd. No.	*Compound structure*	*^{1}H-NMR spectral data*
1		**δ= 2.5 (s) ppm, NH amine, δ= 7.2-7.8 (m) ppm,5H aromatic**
9		**δ= , 2.5 (s) ppm, 6H of CH_3 δ= 6.88, 7.06 (s) ppm , 2H vinylic δ=(7.13-7.86) (m) ppm, 5H aromatic**
10		**δ= 2.5 (s) ppm, 6H of 2 CH_3,δ= 3.8(s) ppm 3H of OCH_3, δ= (6.95-7.77) (m) ppm, 4H aromatic**
13		**δ= (7.2-7.9) (m) ppm, 5H aromatic of phenyl ring, δ= (8.3-8.5) (m) ppm, 6H aromatic of naphthyl ring**
16		**δ= 3.8 (s) ppm,3H of OCH_3, δ= (7.1-7.95) (m) ppm, 4H aromatic of phenyl ring** δ= **(8.1-8.55) (m) ppm, 6H aromatic of naphthyl ring**
23		**δ= 2.1 (s) ppm, 2H of (-H_2C-C(=O)-), δ= 3.66 (s) ppm, 3H of OCH_3 , δ= (7-7.71) (m) ppm, 4H aromatic of phenyl ring, δ= (8-8.43) (m) ppm, 6H aromatic of naphthyl ring**
26		**δ= 1.97 (s) ppm, 2H of (-H_2C-C(=O)-), δ = 2.5(s) ppm, 6H of 2CH_3, δ= 6.45 ppm, 2H ,vinylic, δ= (6.8-7.7) (m) ppm,9H aromatic δ= 8.3 (s) ppm, NH amide**
32		**δ=1.95 (s) ppm, 2H of (-H_2C-C(=O)-), δ= 2.5 (s) ppm, 6H of 2 CH_3, δ= 6.3 (s) ppm, 2H ,Vinylic, δ= (6.8-7.8) (m) ppm, 9H aromatic δ= 9.8 (s) ppm, NH amide**

(S) = singlet
(m) = multiplet

Table (8)
^{13}CNMR spectral data for some of the prepared compounds.

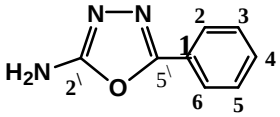
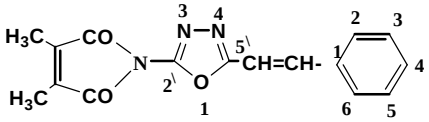
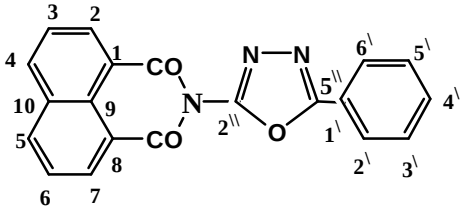
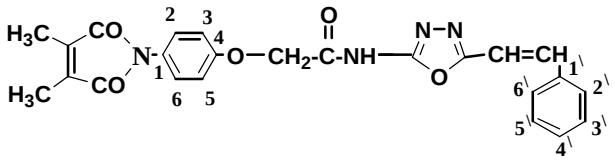
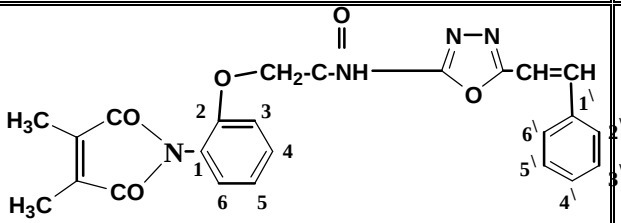
Compd. No.	*Compound structure*	*^{13}CNMR data (ppm)*
1		100 C_4, 124C_3,C_5, 128 C_2,C_6, 135 C_1, 157$C_{5\backslash}$, 164 $C_{2\backslash}$
9		9.3, 2CH_3, 117 ppmC_4, 120ppm C_3,C_5, 124 C_2,C_6, 125.17 C_1, 140, 142 two vinylic carbons, 147two vinylic carbons in imide ring, 152.1 $C_{5\backslash}$, 153 $C_{2\backslash}$, 171.33 two carbonyl carbons
13		119.4 C_4,C_{10},C_5,$C_{4\backslash}$, 125 C_3,C_6,$C_{3\backslash}$,$C_{5\backslash}$ 128 C_2, C_7, 130 $C_{6\backslash}$, $C_{2\backslash}$, 131 C_9, 132 C_1,C_8, 135.8 $C_{1\backslash}$, 161.18 $C_{2\backslash\backslash}$, $C_{5\backslash\backslash}$, 164.3 two carbonyl carbons
26		9.08 2CH_3, 47(CH_2), 111.3 $C_{4\backslash}$, 115.8 $C_{3\backslash}$, $C_{5\backslash}$, 123.5 $C_{2\backslash}$ $C_{6\backslash}$, 127.2 C_2, C_6, 129 C_3, C_5, 134.3 $C_{1\backslash}$, 135.6 C_1, 136.9 C_4, 141.13 vinylic carbon, 142.25 two vinylic carbons in imide ring, 148.65 vinylic carbon, 157.29 and 158.1 two carbons in oxadiazole ring, 163.76 (C=O) amide, 171.48 two carbonyl carbons in imide ring
32		9.1 2CH_3, 46.11 (-CH_2-), 111.35 $C_{4\backslash}$, 116.84 $C_{3\backslash}$, $C_{5\backslash}$ 119.54 C_4,C_5, 127 $C_{2\backslash}$, $C_{6\backslash}$, 129.2 C_6, 130.6 C_3, 134.35 $C_{1\backslash}$, 135.63 C_1, 136.61 C_2, 137.66 one vinylic carbon, 142.24 two vinylic carbons in imide ring, 154.47 one vinylic carbon, 156.89 and 158.14 carbons in oxadiazole ring, 163.75 (C=O) amide, 171.3 two carbonyl carbons in imide ring

Table (9)
C.H.N Analysis for some of the prepared compounds.

Compd. No.	*Calculated*			*Found*		
	C	*H*	*N*	*C*	*H*	*N*
1	59.62	4.34	26.08	59.39	4.08	26.22
4	56.54	4.71	21.98	56.77	4.50	22.14
7	62.45	4.08	15.61	62.70	4.36	15.41
10	60.20	4.34	14.04	59.91	4.58	13.89
13	70.38	3.22	12.31	70.11	3.01	12.12
16	67.92	3.50	11.32	68.12	3.33	11.59
22	66.33	3.51	14.07	66.15	3.29	13.92
26	64.86	4.50	12.61	64.62	4.70	12.82
28	63.15	4.30	13.39	63.29	4.23	13.28

Table (10)
Antibacterial activity of compounds [7-12] and [13-18].

Compd. No.	Gram negative bacteria	Gram positive bacteria
	Escherichia coli	Staphylococcus aureus
7	++++	++
8	++++	-
9	+++	-
10	++++	++
11	+++	+++
12	++	+
13	+++	-
14	+++	-
15	++	++
16	+++	-
17	+++	-
18	+++	-

Table (11)
Antibacterial activity of compounds [22-33].

Compd. No.	Gram negative bacteria	Gram positive bacteria
	Escherichia coli	Staphylococcus aureus
22	+++	-
23	+++	-
24	+++	-
25	+++	+++
26	++	++
27	++	+++
28	++++	-
29	++++	+++
30	+++	-
31	+++	++
32	++++	-
33	+++	-

Key to symbols : Inactive = - (inhibition zone < 6 mm)
Slightly active = + (inhibition zone 6-9 mm)
Moderately active = ++ (inhibition zone 9-12 mm)
Highly active = +++ (inhibition zone 13-17 mm)
Very high activity = ++++ (inhibition zone > 17 mm)

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اضافة الى ما تقدم فقد تضمن البحـــث ايضـــا دراســـة الفعالية البايولوجية للايمايدات المحضرة ضد نـــوعين مـــن البكتريا حيث اظهرت اغلب الايمايدات المحضـــرة فعاليـــة بايولوجية عالية ضد انواع البكتريا قيد الدراسة

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الخلاصة

تضمن البحث تحضير سلسلة من الايمايـــدات الحلقيـــة الجديدة وهي 4,3- ثنائي مثيل مالي ايماید و 8,1- نفثـــال ايماید الحاوية في تركيبها على حلقة 4,3,1-اوكسادايازول وذلك باتباع اربع طرائق مختلفة.

تضمنت الطريقة الاولى تحضير الايمايدات عن طريق التفاعل المباشر بين مركبـــات 5-معـــوض -2-امينـــو-4,3,1-اوكسادايازول مع 4,3-ثنائي مثيل انهيدريد الماليك تحت ظروف معينة بينما تم تحضـــير الايمايـــدات وفـــق الطريقة الثانية من خلال التفاعل بين مركبات 5-معوض-2-امينو-4,3,1- اوكسادايازول مع 8,1-انهيدريد النفثاليك بوجود حامض الخليك الثلجي .

اما الطريقة الثالثة التي اتبعت في تحضير الايمايـــدات الجديدة فقد تضمنت معاملة مركبات 5-معوض-2-امينـــو 4,3,1-اوكسادايازول مع كلوروكلوريد الاسيتيل للحصـــول علـــى مركبـــات 2-(2-كلورواســـتيل امبنـــو)-4,3,1- اوكسادايازول والتي بدورها ادخلت لاحقا في تفاعـــل مـــع 8,1- نفثال ايماید (وفق تفاعل Gabriel) منتجـــة ثـــلاث ايمايدات جديدة هي N- (2-استيل امينـــو-5-معـــوض-4,3,1-اوكسادايازول-2-يل)- 8,1-نفثال ايماید.

اما الطريقة الرابعة فقد تضـــمنت تحضـــيرعدد مـــن الايمايدات الجديدة من خلال تفاعل 2-(2-كلورواســـتيل