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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY SCREENING OF NEW SCHIFF BASES AND THEIR ACETYL OXADIAZOLE DERIVATIVESBEARING SUCCIN IMIDESMOIETY

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ABSTRACT

A series of new Schiff bases and their acetyl oxadiazole derivatives bearing succinimide moietyhave been prepared by performing multistep synthesis.In the first step 4-amino benzoic acid was introduced in reaction with succinic anhydride in glacial acetic acid under reflux producing compound [1].4-amino(N-succinimidyl) benzoic acid which inturn was introduced in esterification reaction with ethanolproducing compound [2], Ethyl-4-(N-succinimidyl)benzoate.Reaction of compound [2] with hydrazinehydrate in the thierd step gave 4-(N-succinimidyl)phenylhydrazide [3].Compound [3]represents the new amine which was introduced in the fourth step in condensation reaction with different aromatic aldehydes and ketones producing the target new Schiff bases [4-11]. In the final step the newSchiff bases were introduced in reaction with acetic anhydride under reflux affording the target acetyl oxadiazole derivatives [12-19]. Antimicrobial activities screening of the newly synthesized compounds revealed that they possess high antimicrobial activity.

Keywords: 4-amino(N-succinimidyl) benzoic acid, acetyl oxadiazole derivatives.

1.INTRODUCTION

Schiff bases are organic compounds with great utility in importont fields such as medicine, agriculture,analytical and cosmetic products[1,2] and they have been known to possess a wide variety of biological application like antimicrobial[3-5], analgesic,antioxidant and anti-inflammatory activites[6,7].

Cyclic imidesare also an important class of substrates for biological,pharmacological and chemical applications[8,9].These compounds have called the attention of scientific community mainly due to their therpeutic potentialities as hypoglycemics,analgesics besides antimicrobial[8],anti-inflammatory and anticancer activites[10-13].

Additionly,1,3,4-oxadiazole derivatives are becoing an important member in the heterocyclic family because of their wide usage as dyes,photosensitive electrial material and their broad spectrum in biological activities such as HIV-acting,antibacterial and anti fungal activites[14-17].Looking at the importance of these types of compounds it was planned to synthesize a new system incorporating these units with antimicrobial activity.

2. EXPERIMENTAL

Commercially avilable chemicals and solvent were used as received from BDH and MerK. Melting points of the new compounds were determined on Thomas Hoover apparatus and are uncorreted.FTIR spectra were recorded in KBr disc on a SHIMADZU FTIR-8400 fourier Trans form Infrared spectrophotometer. ^{1}HNMR and ^{13}CNMR spectra were registered on Bruker300MHz instrument using DMSO-$d_6$as solvent and tetramethylsilane (TMS) as the internal standerd. Heraeus D-63450 model was used for incubation samplesin biological study.

2.1. Preparation of N-(4-carboxy phenyl) Succinimide [1][18]

A mixture of 4-amino benzoic acid (0.01mol,1.37g) and succinic anhydride (0.01mol,1g) in (12mL) of glacial acetic acid was refluxed for 4 hrs with stirring. The resulted mixture was poured in cold water with stirring then the separated solid was filtered,washed twice with distilled water (30mL), dried and finally purified by recrystallization from ethanol.

2.2. Preparation of Ethyl-(4- (N-Succinimidyl)) benzoate [2][19]

A mixture of compound[1] (0.01mol,2.19g) in absolut ethanol (15mL)and(1.3mL) of conc.H_2SO_4 was refluxed for 6 hrs with stirring then excess alcohol was distilled off and the residue was cooled then poured into cold water. The separated solid was filtered,washed with distilled water,dried then recrystallized from methanol.

2.3. Preparation of4-(N-succinimidyl)phenyl hydrazide[3][20]

A mixture of compound[2] (0.01mol,2.47g)and hydrazine hydrate (0.015mol,0.7mL)was refluxed for 4 hrs then (15mL) of ethanol was added and reflux was continued for additional 8 hrs with stirring. The formed precipitate was filtered, washed with cold distilled water,dried and recrystallized from n-hexane.Physical properties of compounds[1-3]are listed in Table(1).

2.4. Preparation of Schiff bases [4 -11][21]

A mixture of(0.01mol,2.33g) compound[3] and (0.01mol) of aldehyde or ketone in absolute ethanol (20 mL) and (2-3)drops of glacial acetic acid was refluxed for 3-6 hrs with stirring. After cooling the obtained precipitate was filtered then washed with ether, dried and recrystallized from sutiable solvent.Physical properties of compounds[4-11]are listed in Table(2).

2.5. Preparation of (substituted)-3-acetyl-5-[4-(N-succinimidyl)phenyl-1,3,4-oxadiazole[12-19]

A mixture of Schiff bases [4-11] (0.003 mol) and acetic anhydride attained room temperature, excess aceticanhydride was decompsed by adding water and the mixture was stirred for further thirty minutes. The separated product was filtered,washed with water,dried and recrystallized from sutiable solvent.Physical properties of compounds[12-19]are listed in Table(3).

2.6- Biological Study

The cup plate method using nutrient agar medium was employed in studyding the antimicrobial activity of the prepared succinimides against four strains of bacteria and *candida albicans* fungi.DMSO was used as sample solution,sample size of all compounds was fixed at (0.1mL) and the used concentration for alltested compounds was (100µg/mL).

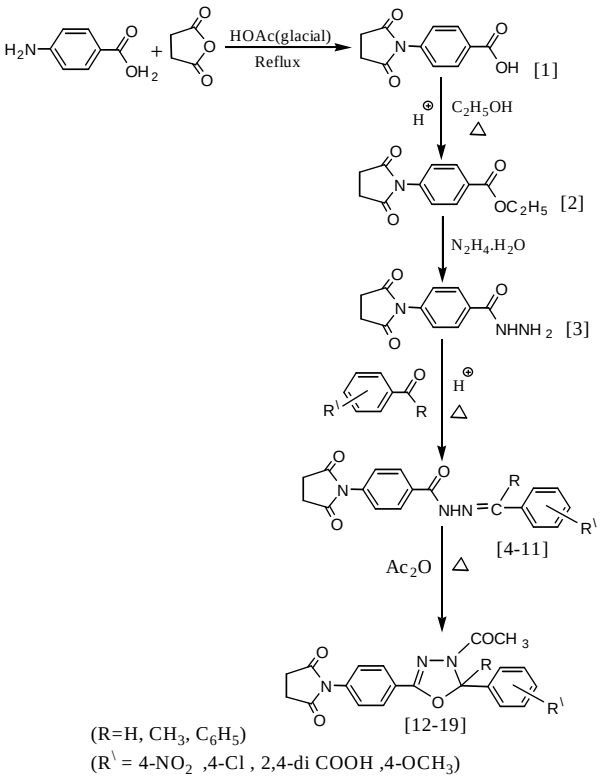
Using a sterilized cork borer cups were scooped out of agar medium contained in a petridish which was previously inoculated with the microorganisims. The tested compound solution (0.1mL) was added in the cups and thepetridishes were subsequently incubated at 37°C for 48 hrs. Ampicillin and Fluconazole were used as reference drugs and DMSO as acontrol. Zones of inhibition produced by each compound was measured in mm and results are listed in Table(7).

3. RESULT AND DISCUSSION

3.1. Chemistry

The target of the present work has been directed towards synthesis of new Schiff bases and theiroxadiazole derivatives bearing the biologically active succinimide moiety.Strategy for performing this target involved many steps in the first one 4-amino benzoic acid was introduced in reaction with succinic anhydride in glacial acetic acid producing compound [1] which introduced in esterification reaction in the second stepproducing compound [2]and this inturn introduced in reaction with hydrazine hydrate producing compound[3],which repesents the important key intermediate from which all the target schiff bases were prepared thus introducing of compound[3] in condensation reaction with different aromatic aldehydes and ketones afforded the targetschiff bases[4-11].In the final step the newly synthesizedschiff bases[4-11] were introduce in reaction with acetic anhydride producing the target acetyl oxadiazole derivatives [12-19].

The synthetic rout of the newschiff bases and theirderivatives is outlined in the scheme(1) andPhysical properties of the prepared compoundsare listed in Table(1),(2) and(3).



Scheme (1)

As indicated in scheme (1) the first step in this work involved reaction of 4-amino benzoic acid with succinic anhydride in glacial acetic acid, the reaction in this step is proceed through nucleophilic attack of amino group on one carbonyl group in succinic anhydride producing N-(4-carboxy phenyl) succinamic acid which under the influence of glacial acetic acid and heat didn't separated and instead introduced directly in dehydration reaction companiand with ring–closure producing compound [1].

FTIR spectrum of compound [1] showed absorption bands at 3307, 1693, 1666, 1596 and 1377cm^{-1}which are ottributed to ν(O-H) carboxyl,ν(C=O)imide, ν(C=O) carboxylic,ν(C=C) aromatic and ν(C-N)imiderespectively(22).

^{1}HNMR spectrum of compound [1] showed signals at (δ=2.88), (7.38-8.09) and (11.3) ppm which belong to (CH_2-CH_2) protons,aromaticprotons and (OH) proton, while ^{13}CNMR spectrum of showed signals at (δ=29.61), (124.3-137.5), (170) and at (177.6) ppm which belong to (CH_2-CH_2) carbons, aromatic carbons, (C=O) carboxyl and(C=O) imide carbons respectively [22].

In the second step compound [1] was introduced in acid-catalyzed esterification with ethanol producing compound [2]. FTIR spectrum of compound [2] showed disappearance of ν(O-H) carboxyl absorption band and appearance of new absorption band at(1730,1710, 1674, 1600 and 1369) cm^{-1}ottributed toν(C=O)ester,asym. and sym ν(C=O)imide,ν(C=C) aromaticand ν(C-N) imiderespectively[22]. ^{1}HNMR spectrum of compound [2] showed signals at (δ=1.32-1.33) (δ=2.55-2.59)ppm belong to(CH_3)protons and (OCH_2)protons. Other signals appeared at (δ=2.89-2.99) and (7.38-7.91) ppm belong to (CH_2-CH_2)protons andaromaticprotonsrespectively.

^{13}CNMR spectrum ofcompound [2] showed signals at (δ=14.45, 28.86, 62, (127-136.8), 165.2 and 177.5)ppm belong to CH_3,(CH_2-CH_2),(OCH_2),aromatic carbons, (C=O) ester and (C=O) imidecarbons.

In the third stepcompound[2]was introduced in nucleophlic substitution reaction with hydrazine hydrate leading to replace ethoxy group withhydrazine(NH-NH_2)group producing the corresponding succinimidylphenyl hydrazine[3].

FTIR spectrum of compound [3] showed disappearance ofν(C=O)ester band and appearance of ν($NHNH_2$) bands at(3430,3346,3240)cm^{-1}proving success of compound [3] formation.Otherabsorption bands appeaerd at(1683,1629,1602and 1367)cm^{-1}due toν(C=O)imide,ν(C=O)amide,ν(C=C) aromatic andν(C-N)imiderespectively.^{1}HNMR spectrum of compound [3] showed signals at

(δ=2.14,2.88,(7.25-7.77)and 8.29)ppm belong to(NH_2)protons,(CH_2-CH_2)protons andaromaticprotons and (NH)protonrespectively,while^{13}CNMR spectrum of showed signals at (δ=29.6,(125.2-129.6),127 and 177.1)ppmbelong to(CH_2-CH_2)carbons,aromatic carbons, (C=O)amide and(C=O)imidecarbons. In the present work compound[3] represents the parent amine from which all the target schiff bases were synthesized thus in the fourth step compound[3] was interoduced in condensation with different aromatic aldehydes and ketones producing the target schiff bases[4-11].

FTIR spectra of the prepared schiff bases showed disappearance of absorption bands belong toν(NH_2) and appearance of clear absorptionbands at (1666-1712)cm^{-1}belong to(1636-1701)cm^{-1}due toν(C=O)amide and bands at (1598-1658)cm^{-1}due toν(C=N) imine. Other absorpation bands appeard at (1512-1604)cm^{-1},(1311-1373)$cm^{-1}$and (3197-3356)cm^{-1} which belong toν(C=C) aromatic,ν(C-N)imide andν(N-H)amide respectively.All FTIR spectral data of schiff bases [4-11] are listed in table (5).

^{1}HNMR spectrum of compound [4] showed signals at (δ=2.9,(7.1-7.66)and (8.29)ppm whichbelong to (CH_2-CH_2)protons,aromaticprotons and (NH) amide proton.While^{13}CNMR spectrum of the same compound showed signals at (δ=29.69, (104-134.4),156.6-165.5) and 177.1ppmwhichbelong to(CH_2-CH_2)carbons,aromatic carbons, (C=N),(C=O)amide and(C=O)imidecarbons.

^{1}HNMR spectrum of compound [5] showed signals at (δ=2.1, 2.76,),(6.4-7.3) and (8.05)ppm whichbelong to(CH_3)protons,(CH_2-CH_2)protons,aromaticprotonsand (NH) amide proton.While^{13}CNMR spectrum of the same compound showed signals at (δ=19.78, 23.2(100-145.9),148.2,166.95 and 171.57) ppm whichbelong to(CH_3),(CH_2-CH_2)carbons,aromatic carbons, (C=N) and (C=O)amide and(C=O)imidecarbonsrespectively.

^{1}HNMR spectrum of compound [7] showed signals at (δ=2.46,4.8 (6.65-7.4)and(7.62)ppmbelong to(CH_2-CH_2)protons, (OCH_3)protons,aromaticprotons and(NH)amideproton. While^{13}CNMR spectrum of the compound[7] showed signals at (δ=28.46 and 43.8)belong to(CH_2-CH_2)carbons and (OCH_3)carbonssignals at (118.14-132.5) ppmaromatic carbons and signals at(δ=146.11,169.4) and(170.44)ppm belong to(C=N),(C=O) amide and(C=O) imidecarbonsrespectively.

^{1}HNMR spectrum of compound [8] showed signals at (δ=2.5belong to(CH_2-CH_2)protons,(δ=7.63-7.8)ppmbelong to aromaticprotons and signals at(δ=7.8-8.66)ppmbelong to (NH) amide proton and imineproton.While^{13}CNMR spectrum of the same compound showed signals at (δ=30.16, (123.8-135.74),147, 164.58) and 176.33)ppmwhichbelong to(CH_2-CH_2)carbons,aromatic carbons, (C=N),(C=O)amide and(C=O)imidecarbonsrespectively.

The present work involved also synthesis of new acetyl oxadiazole derivatives [12-19] based on the newly synthesized schiff bases [4-11],thusschiff bases [4-11] were introduced in reaction with acetic anhydride under reflux condition.

The reaction was proceed via nucleophilic attack of imine nitrogen on carbonyl group in acetic anhydride followed by subsequent intramolecular nucleophilic attack leading to ring–closure and producing of the targetderivatives[12-19].

FTIR spectrum of compound [12-19] showed disappearance ofabsorption bandbelong toν(NH)amide and appearance of clearabsorption bands at(1695-1733)cm^{-1}due toν(C=O)imide,(1650-1710)cm^{-1}due toν(C=O)amide and(1598-1680)cm^{-1}due toν(C=N)oxadiazole.Otherabsorption bands appeaerd at(1317-1373)cm^{-1},(1550-1602)cm^{-1} (1174-1280)cm^{-1}whichbelong toν(C-N)imide,ν(C=C) aromatic,ν(C-O-C)amiderespectively.Other details of FTIR spectral data of compounds [12-19] are listed in Table(6).

^{1}HNMR spectrum of compound [14] showed signals at (δ=1.85and2.1)ppmbelong to (CH_3) and (OCH_3)protons.signal at(δ=2.7) ppm belong to(CH_2-CH_2)protonssignals at(δ=6.8-8.3) ppmbelong toaromaticprotons. ^{13}CNMR spectrum of the same compound showed signals at (δ=20.97, 24.6,27.6and 98)ppmbelong to (CH_3),(CH_3CO),(CH_2-CH_2)carbons and carbon atom in oxadiazole ring respectively.

Other signals appeared at(δ=2.89-2.99)and(7.38-7.91)ppm belong to(CH_2-CH_2)protons andaromaticcarbonsrespectively.

Other signals appeared at(δ=105-148.5),156.5,(167.3-168.4) and (169.3-170.4)ppm belong to aromaticcarbons,(C=N),(C=O)amide and(C=O)imidecarbonsrespectively.

^{1}HNMR spectrum of compound [17] showed signals at (δ=2.3,2.6 and 6.1) ppmbelong to

(CH_3CO)protons,(CH_2-CH_2)protons and proton in oxadiazole ring.

Other signals appeared at(δ=7.0-8.1) and (9.7-9.8)ppm belong toaromaticprotons and(O-H)carboxyl protonrespectively.[13]CNMR spectrum of the same compound showed signals at (δ=20.4, 29.1and 63.1)ppmbelong to (CH_3CO)carbons,(CH_2-CH_2)carbons and carbon atom in oxadiazole ring respectively.

signalsbelong toaromaticcarbons appeared at(δ=106.9-141.2)ppm whilesignalsbelong to(C=N),(C=O)(amide and carboxyl) and(C=O) imidecarbons appeared at (δ=150,(162-163)and 184)ppm respectively.

3.2. Biological Study

The newly synthesized compounds [4-19] were tested for their in vitro antimicrobial activity against four types of bacteria including *Staphlococcus aureous,Streptococcus pyogenes,Escherrichia coli and Klebsiella pneumonia*and *candida albicans fungi* by using cup plate method.zones of inhibition caused by each compound was measured in (mm)and the results are listed in Table(7).

The results indicated that the prepared schiff bases showed different anti microbial activites against the tested microorganisms. thus compound [10] showed high activity against*S.aureous*, while compounds [4] and [8]showed high activityagainst *S.pyogenes*. Compound [9] showed very high activity against*S.pyogenes*and*Klebsiell*a and high activity against *E .Coli.* Compounds [5], [10] and [11]showed moderate activity against*Klebsiell*a and*E .Coli.* Compounds [7], [8]showed moderate activity against*S.aureous*.While compound [5] showed moderate activity against*S.pyogenes*.Compounds [7]showed moderate activity against*Klebsiell*a andCompounds [9], [10]showed moderate activity against*candida albicans fungi*. On the other hand the results of antimicrobial activities of the newly synthesized acetyl oxadiazole dervatives indicated that compound [19]possessvery high activity against*S.pyogenes*and*Klebsiell*a and high activity against *E .Coli.*while compound [18]showed high activityagainst *S.pyogenes*and*E .Coli*.compounds[12] and [17]showed high activityagainst *S.pyogenes*.Compounds[14], [15]showed moderate activity against*S.aureous*.Compounds[16], [18]showed moderate activity against*Klebsiell*a.Compounds[12], [15]showed moderate activity against*E .Coli*.Compounds [12], [18] showed moderate activity against*candida albicans fungi*.

Table 1: Physical properties of the prepared compounds [1-3]

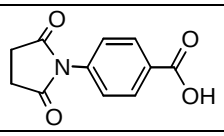
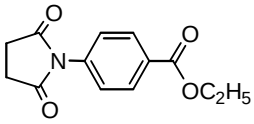
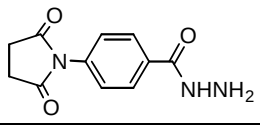
Comp. No.	Compound structure	Color	Melting Points °C	Yield %	Recrystallization Solvent
1		white	206-208	92	Ethanol
2		Faint Yellow	88-90	65	Methanol
3		Crystal white	102-104	57	n-hexane

Table 2: Physical properties of the prepared compounds [4-11]

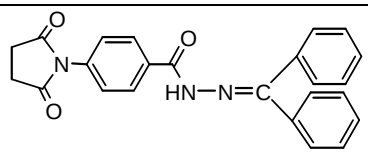
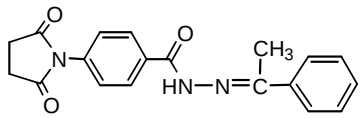
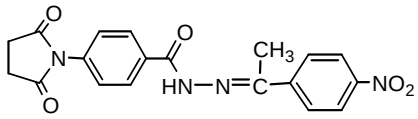
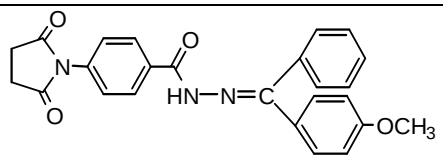
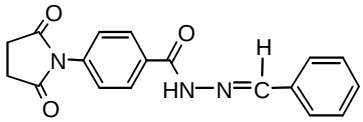
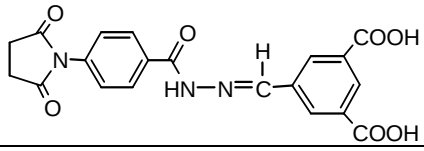
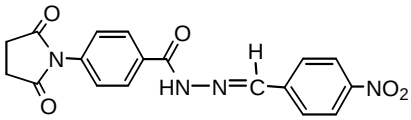
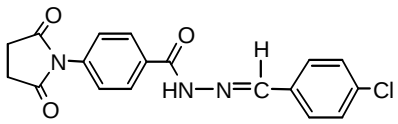
Comp. No.	Compound structure	Color	Melting Points °C	Yield %	Recrystallization Solvent
4		Pale yellow	86-88	78	Methanol
5		Yellow	108-110	95	Dioxane
6		Orange	126-128	90	n-hexane
7		Pale Orange	50-52	81	Dioxane
8		Yellow	74-76	85	Dioxane
9		Pale yellow	222-224	87	Acetone
10		yellow	134-136	93	Methanol
11		Pale yellow	90-92	85	Acetone

Table 3: Physical properties of the prepared compounds [12-19]

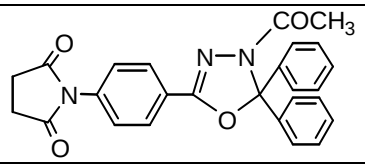
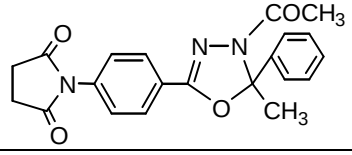
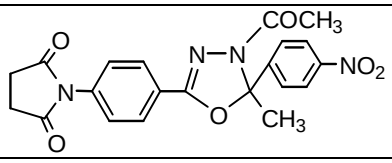
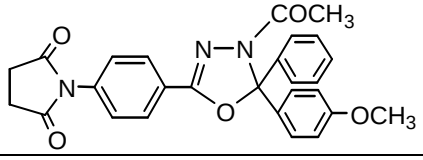
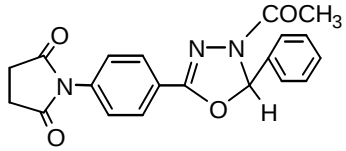
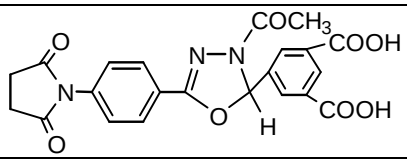
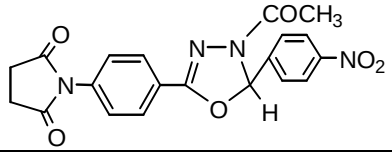
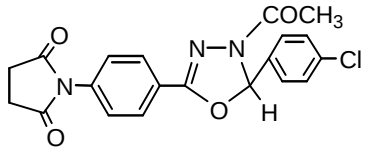
Comp. No.	Compound structure	Color	Melting Points °C	Yield %	Recrystallization Solvent
12		Pale Brown	173-174	70	Dioxane
13		Dark Brown	140-142	81	Methanol
Comp. No.	**Compound structure**	**Color**	**Melting Points °C**	**Yield %**	**Recrystallization Solvent**
14		Dark yellow	132-135	77	Ethanol
15		Pale Brown	168-170	84	Dioxane
16		Orange	223-225	83	n-hexane
17		Brown	270-272	90	Acetone
18		yellow	189-191	67	Methanol
19		Pale Brown	202-205	92	Acetone

Table 4: Spectral data Cm^{-1} of the prepared compounds [1-3]

Comp. No.	FTIR spectral data cm^{-1}						
	ν(C-H) aromatic ν(C-H) aliphatic	**ν(C=O) imide**	**ν(C=C) aromatic**	**ν(C-N) imide**	**ν(C=O) amide**	**ν(N-H)**	**Others**
1	3074 2927	1693	1596	1377	-	-	**ν(O-H) Carboxylic** 3307 **ν(C=O)carboxyl 1666**
2	3122 2983	1710asym 1674sym	1600	1369	-	-	**ν(C=O)Ester** 1730 **ν(C-O)Ester** 1150
3	3090 2970	1683	1602	1367	1629	3240	**ν(NH_2)** 3430,3346

asym.=asymmetrical sym.=symmetrical

Table 5: Spectral data Cm^{-1} of the prepared compounds [4-11]

Comp. No.	FTIR spectral data cm^{-1}							
	ν(N-H) Amide	ν(C-H) aromatic& aliphatic	ν(C=O) imide	ν(C=O) amide	ν(C=N) imine	ν(C=C) aromatic	ν(C-N) imide	Others
4	3356	3059 2924	1712	1701	1658	1597	1315	-
5	3201	3055 2935	1685	1685	1600	1566	1361	-
6	3205	3047 2943	1670	1670	1604	1512	1338	**ν(NO_2)** 1442
7	3205	3043	1666	1636	1604	1512	1373	**ν(C-O-C)** 1253,1118
8	3197	3051 2947	1693	1647	1627	1604	1311	-
9	3205	3047 2993	1666	1650	1620	1600	1373	**ν(O-H)carbo** 3460
10	3203	3043	1680	1662	1598	1521	1346	**ν(NO_2)** **1417,1330**
11	3205	3018 2925	1700	1680	1623	1595	1311	**ν(C-Cl)** 1089

Table 6: FTIR Spectral data Cm^{-1} of the prepared compounds [12-19]

Comp. No.	FTIR spectral data cm^{-1}							
	ν(C-H) aromatic ν(C-H) aliphatic	ν(C=O) imide	ν(C=O) amide	ν(C=N) oxadiazole	ν(C-N) imide	ν(C-O-C) oxadiazole	ν(C=C) aromatic	Others
12	3055 2921	1716	1703	1664	1317	1174	1598	-
13	3090 2975	1731	1699	1674	1373	1263	1598	-
14	3039 2923	1699	1650	1598	1317	1261	1550	**ν(NO_2)** 1440,1375
15	3085 2900	1733	1710	1680	1338	1280	1595	-
16	3062 2977	1695	1681	1654	1373	1263	1598	-
17	3033 2935	1697	1672	1620	1373	1265	1602	**ν(O-H)carb** 3434
18	2921	1715	1680	1630	1346	1272	1596	**ν(NO_2)** 1440,1330
19	3001 2933	1699	1681	1654	1373	1259 1174	1600	**ν(C-Cl)** 1091

Table 7: Inhibition zone of antimicrobial activity of compounds [4-19] in mm

Comp. No.	Gram-positive bacteria		Gram-negative bacteria		Fungi
	Staphylococcus aureus	***Streptococcus pyogenes***	***Klebsiellapneumonia***	***Escherichia coli***	***Candida albicans***
4	+	+++	-	++	-
5	+	++	++	++	-
6	**+**	**+**	**-**	**-**	**-**
7	**++**	**-**	**++**	**-**	**-**
8	**++**	**+++**	**-**	**-**	**-**
9	**-**	**++++**	**++++**	**+++**	**++**
10	**+++**	**+**	**++**	**++**	**++**
11	**-**	**-**	**++**	**++**	**-**
12	**+**	**+++**	**+**	**++**	**++**
13	**-**	**-**	**-**	**+**	**-**
14	**++**	**-**	**-**	**-**	**-**
15	**++**	**+**	**-**	**++**	**+**
16	**-**	**-**	**++**	**-**	**+**
17	**++**	**+++**	**-**	**+**	**+**
18	**+**	**+++**	**++**	**+++**	**++**
19	**-**	**++++**	**++++**	**+++**	**++**
Ampicillin	**+++**	**+++**	**+++**	**+++**	**-**
Fluconazole	**-**	**-**	**-**	**-**	**+++**
DMSO	**-**	**-**	**-**	**-**	**-**

Key of symbols : slightly active = + inhibition zone(6-9)mm, moderately active =+ + inhibition zone(9-12)mm, highly active = +++ inhibition zone(13-17)mm,very high active = ++++ inhibition zone(>17)mm

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