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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW SUCCINIMIDES BEARING DIFFERENT HETEROCYCLES

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ABSTRACT

In this work several new Succinimides linked to biologically active heterocycles namely 1,3,4-Oxadiazole,1,2,4-triazole,1,3,4-thiadiazole and phthalazine were prepared.Preparation of the new Succinimides was performed via multistep synthesis.In the first step 4-aminobenzoic acid was introduced in reaction with succinic anhydride in glacial aceticacid under reflux condition producing compound[1] N-(4-carboxyphenyl)succinimide which inturn introduced in esterification reaction in the second step producing compound [2] Ethyl-4-(N-succinimidyl) benzoate and this subssequently introduced in reacation with hydrazine hydrate affording compound[3] 4-(N-succinimidyl)phneyl hydrazide.Compound[3] reprsent the parent synthone from which all the target succinimides were synthesized via following different synthetic paths. Antimicrobial activities of the prepared imides were evaluated and the results indicated that moset of them possess high antimicrobial activity.

Keywords: Succinimides, succinimidyl benzoate, succinimidylhydrazide,phthalazine.

1- INTRODUCTION

In the past decades , the problem of multidrug resistant microorganisms has reached on alarming level around the world and the synthesis of new anti-infective compounds has became an urgent need for the tretment of microbial infections.The 1,2,4-triazole nucleus has been incorporated into a wide variety of the rapeutically important agents mainly dispalaying antimicrobial[1-4],antiviral,analgesic and anti-inflammatory activites[5,6].In addition both 1,3,4-Oxadiazole and 1,3,4-thiadiazole derivatives were reported to exhibit broad spectrum of biological activities suchasHIV activity,antimicrobial,anti-inflammatory and anticonvulsant activities[7-11].Besides heterocycles containing phthalazine moiety have been reported to possess different pharmacological properties and vasorelaxant activities.More over cyclicimides represent important functionality which have been found to maintion significant biological activity and much attention has been paid to various classes of cyclic imides due to their biological properties[12-16].

In view of these findings and in continuation to our interest the synthesis of cyclic imides linked to biologically important heterocycles the present investigation describes the synthesis of new succinimides bearing 1,2,4-triazole or 1,3,4-oxadiazole or 1,3,4-thiadiazole or phthalazine cycles and their 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 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][17]
A mixture of 4-amino benzoic acid (0.01mol,1.37g) and succinic anhydride (0.01mol,1.0 g) in (12mL) of glacial acetiv 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][4]
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][18]
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.

2-4- Preparation of N-[4\-(5-mercapto-1,3,4-Oxadiazole-2-yl)phenyl]Succinimide[4][19]
To a solution of compound[3](0.01mol,2.33g) in ethanol(25mL) at zero°C,potassium hydroxide(0.01mol,0.55g) and carbondisulfide(0.02mol,1.2mL)were added respectively. The mixtur was refluxed for 7hrs then the solvent was evaporated and the residue was dissolved in cold water then acidified with hydrochloric acid.The resultrd precipitate was filtered, dried and recrystallized from dioxane.

2-5- Preparation of N-[4\-(4-amino-5-mercapto-1,2,4-triazole-3-yl)phenyl]Succinimide[5][19]
Carbondisulfide(0.02mol,1.2mL) was added to the solution of (0.0mol,2.33g)of compound[3] in (25mL)ethanol containing(0.01mol,0.55g)of potassium hydroxide with stirring.The mixture was refluxed for one hr.and the obtained precipitate was filtered and ddried. The crude product was refluxed withasolution of (10mL)distilled water and (0.01mol)of hydrazine hydrate on a waterbath for 4 hrs. The resulted mixture was cooled then neutralized with diluted hydrochloric acid and the formed precipitate was filtered,washed with distilled water,dried and recrystallized from n-hexane.

2-6-Preparation of N-[4-(N-succinimidyl benzoyl)]-N\-phenyl thiosemicarbazide[6][19]
To a mixture of compound [3] (0.01mol,2.33g) dissolved in (20mL) of absolute ethanol (0.01mol,1.35g) of phenylisothiocyanate was added drop wise with stirring. The mixture was refluxed for 6 hrs then cooled and the obtained solid was filtered, dried and recrystallized from Acetone.

2-7-Preparation of N-[4\-(4-phenyl-5-mercapto-1,2,4-triazole-3-yl)phenyl]Succinimide[7][20]
A mixture of(0.01mol,3.7g)of compound[6] in (30mL) of 5% sodium hydroxide solution was refluxed on water bath for 2 hrs. The result solution was cooled to room temperature,filtered then the filtrate was acidified with diluted hydrochloric acid. The formed precipitate was filtered,washed with distilled water, dried and recrystallized from dioxane.

2-8-Preparation of N-[4\-(5-phenylamino)-1,3,4-thiadizole-2yl)phenyl Succinimide[8][20]
A mixture of(0.001mol,0.37g) of compound[6] in(3mL) of phosphoric acid was refluxed at 120°C for 30 minutes. The result solution was cooled to room temperature,kept over night then poured into crushed ice with stirring. the obtained precipitate was filtered, washed with distilled water, dried and recrystallized from Acetone.

2-9-Preparation of N-[4-(N-succinimidyl)benzoyl]-N\-phenylsemicarbazide[9][19]
Compound [9] was preperd by following the same method used for preparation of compound [6] except using of phenylisocyanate instead of phenylisothiocyanate.The formed precipitate was filtered, dried and recrystallized from methanol.

2-10-Preparation of N-[4\-(4-phenyl-5-oxo-4,5-dihydro-1,2,4-triazole-3-yl)phenyl]Succinimide[10][19]
Compound [10] was preperd by following the same method used for preparation of compound [7] except using of compound [9] instead of compound [6]. The resulted precipitate was filtered, dried and recrystallized from Acetone.

2-11- Preparation of N-[4-(N-succinimidyl)benzamido]phthalamic acid[11][21]

A solution of (0.01mol,2.33g)of compound[3]dissolved in (25mL) of acetone was added dropwise to the solution of(0.01mol,1.48g)of phthalic anhydride dissolved in (25mL)of acetone with stirring and cooling stirring was continued for 4 hrs then the formed amic acid was filtered,washed with diethylether, dried and recrystallized from methanol.

2-12- Preparation of1-(4-(N-succinimidyl)-1,2-dihydrophthalazine-3,6-dione[12][21]

A mixture of(0.01mol,3.79g) of compound[11] in(25mL) of acetic anhydride and (0.005mol,0.41g)of anhydrous sodium acetone was refluxed for two hrs. The resulted homogenous solution wascooled to room temperture then poured into excess cold water with stirring.The formed precipitate was filtered, washed with water, dried then recrystallized from ethanol.

Physical properties of compounds[1-12]are listed in Table(1).

2-13- 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 the petridishes 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(3).

3- RESULT AND DISCUSSION

3-1- Chemistry

The target of the present work has been directed towards building of new succinimides containing biologically active heterocycles namely 1,3,4-oxadiazole,1,3,4-thadiazole,1,2,4-triazole and phthalazine.

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 step producing compound [2] and this inturn introduced in reaction with hydrazine hydrate producing compound[3],which repesents the parent synthone from which all the target succinimdes were prepared by following different synthetic paths. The synthetic route of the new succinimides is out lined in scheme (1)and physical properties of the prepared compounds are listed in Table(1). As indicated in scheme(1)the firset stepin this work involved reaction of 4-aminobenzoic acid with succinic anhydride in glacial acetic acid under reflux condition,the reactionin this step is proceed through nucleophilic attack of amino group on one carbonyl group in succinic anhydride producing N-(4-carboxyphenyl)succinamic acid which under the in fluence of glacial acetic acidand heat didn't sparated and instead introduced directly in dehydration reaction companiand with ring-closure producing compound[1] N-(4-carboxyphenyl)succinimide.

FTIR spectrum of compound [1] showed absorption bands at3307,1693and 1666cm^{-1}due toν(C=O) carboxylic, ν(C=O)imide andν(C=O)amide respectively while absorpation bands due to ν(C=C) aromatic andν(C-N)imide appeared at 1596 and 1377 cm^{-1}. ^{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, aromatic protons 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 ofν(O-H) carboxyl absorption band and appearance of new absorption band at(1730) cm^{-1}due toν(C=O)ester these two points are good proofs for success of esterification reaction.Other absorption bands appeaerd at (1710,1674,1600and 1369) cm^{-1}due to asym .and sym ν(C=O)imide, ν(C=C) aromatic andν(C-N)imide respectively[22].^{1}HNMR spectrum of compound [2] showed triplet signals at (δ=1.32-1.33)ppm and quartet signals at (δ=2.55-2.59)ppm belong to(CH_3) protons and (OCH_2) protons. Appearance of these signals and disappearance(OH) protonsignal give another clear evidance for the success of ester[2] formation.Other signals appeared at(δ=2.89-2.99)and(7.38-7.91)ppm belong to(CH_2-CH_2) protons and aromatic protons respectively.

^{13}CNMR spectrum ofcompound[2] showed signals at (δ=14.45,28.86,62,(127-136.8),165.2 and177.5) ppm belong toCH_3, (CH_2-CH_2), (OCH_2), aromatic carbons, (C=O)ester and(C=O)imide carbons.

In the third step compound[2]was introduced in nucleophlic substitution reaction with hydrazine hydrate leading to replace ethoxy group with hydrazine(NH-NH_2)group producing the corresponding succinimidyl-phenylhydrazine[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. Other absorption 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)imide respectively. ^{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 and aromatic protons and (NH)proton respectively,while^{13}CNMR spectrum of showed signals at (δ=29.6,(125.2-129.6),127 and 177.1)ppm belong to(CH_2-CH_2)carbons, aromatic carbons, (C=O)amide and(C=O)imide carbons.In the present work compound[3] represents the parent intermediate from which all the target succinimides were prepared via following different synthetic paths. In the first path compound[3] was interoduced in reaction with CS_2 in basic medium and the resulted intermediate was treatd either with diluted HCl producing imide [4]or with hydrazine hydrate producing imide[5].

FTIR spectra of succinimides[4]and[5] showed absorpation bands at (1666-1718)cm^{-1},(1600-1672) cm^{-1},(1575-1596) cm^{-1},(1311-1360) and (669-673) cm^{-1}due toν(C=O)imide, ν(C=N), ν(C=C) aromatic,ν(C-N)imide andν(C-S) respectively. FTIR spectrum of compound [4] showed band at (1253) cm^{-1} due toν(C-O-C) oxadiazole while FTIR spectrum of compound [5] showed bands at (3461-3363) cm^{-1} due toν(NH_2). ^{1}HNMR spectrum of compound [5] showed signals at (δ=3.3,592,(7.3-814)and(13.7)ppm which belong to (CH_2-CH_2) protons,(NH_2), aromatic protons and (SH)proton respectively. While^{13}CNMR spectrum of the same compound showed signals at (δ=28.3,(125.3-134.4),150.58,169.3 and 176.1ppm which belong to (CH_2-CH_2)carbons, aromatic carbons, (C=N)triazole, (C=N)thiazole and(C=O)imide carbons.

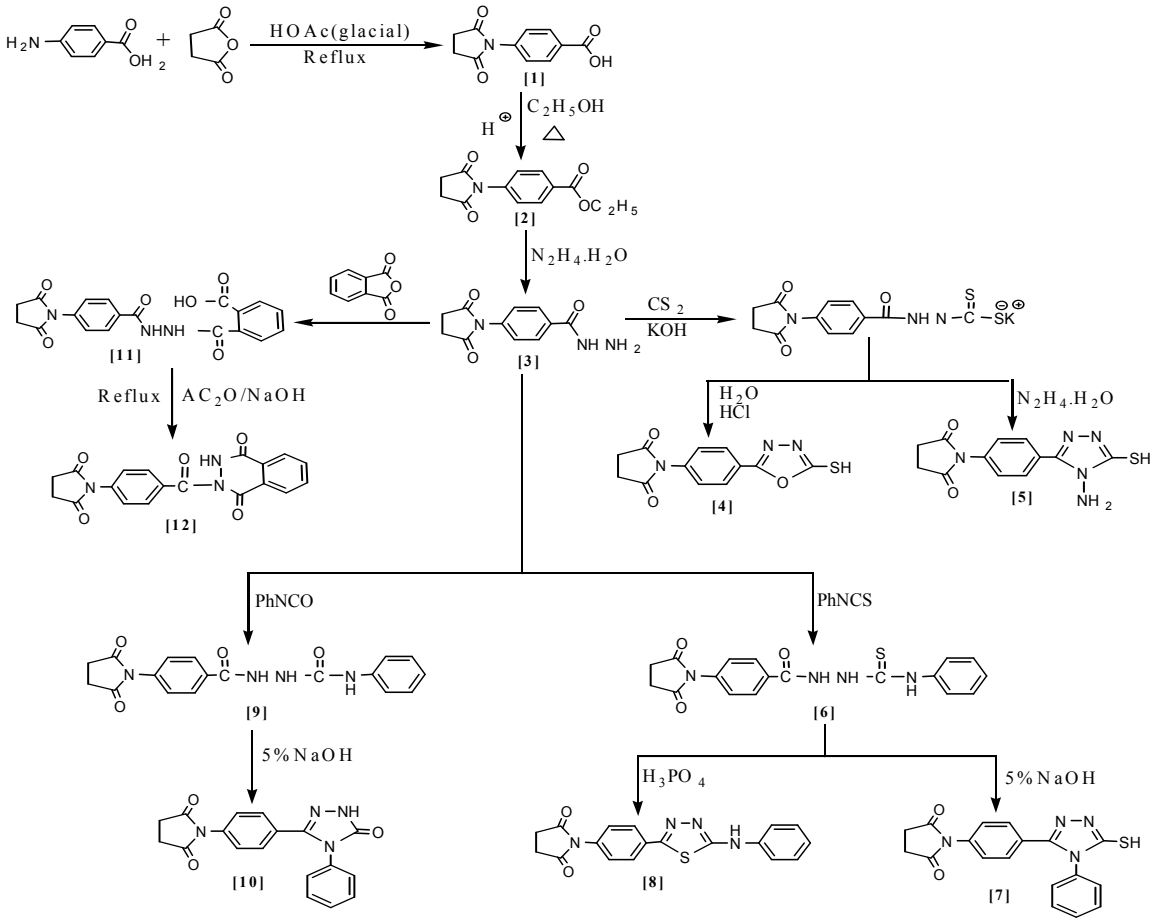
In the second synthetic path in this work compound[3] was introduced in reaction with phenyl isothiocyanate and the resulted intermediate [6] on treatment with NaOH solution afforeded succinmide[7],while on treatment with H_3PO_4 afforded succinimide[8]. FTIR spectra of compounds [6,7,8] showedabsorption bands at (1697-1720)cm^{-1},(1596-1606) $cm^{-1}$and(1330-1377) cm^{-1}due toν(C=O)imide, ν(C=C) aromatic andν(C-N)imide.Imides[7]and[8] showed bands at(3307-3282) cm^{-1}(1627-1666) $cm^{-1}$and(661-671)cm^{-1} due toν(N-H)amine, ν(C=N)andν(C-S)while compound[6] spectrum showed bands at (3209-3357) $cm^{-1}$and 1677cm^{-1} due toν(N-H)amide andν(C=O)amide respectively. ^{1}HNMR spectrum of compound [8] showed signals at (δ=2.9,(4.25,4.7),(6.72-7.32)and (7.83-7.88)ppmwhich belong to (CH_2-CH_2) protons and aromatic protons of two aromatic rings. While^{13}CNMR spectrum of the same compound showed signals at (δ=29.68,(113.7-131.8),134.8 and178.1ppm which belong to (CH_2-CH_2)carbons, aromatic carbons, (C=N) and(C=O) carbons.

In the third synthetic path in this work compound[3] was introduced in reaction with phenyl isocyanate and the resulted intermediate [9] on treatment with NaOH solution introduced in nucleophilic attack lead to intramolecular cyclization producing succinimide[10]. FTIR spectra of compounds [9,10] showed absorpation bands at (3211-3298)cm^{-1},(1700-1703) cm^{-1},(1668-1670)cm^{-1},(1544-1596) and (1313-1334) cm^{-1} due toν(N-H)amide, ν(C=O)imide,ν(C=O)amide, ν(C=C) aromatic andν(C-N)imide respectively. FTIR spectrum of compound [10] showed absorption bands at (1598)cm^{-1}due toν(C=N)triazole. ^{1}HNMR spectrum of compound [10] showed signals at (δ=2.96,(7.4-7.8)and(8.19)ppm belong to (CH_2-CH_2) protons, aromatic protons and(NH) proton. ^{13}CNMR spectrum of the compound[10] showed signals at (δ=29.4,(125.7-132),148.4 and 177.3ppm belong to (CH_2-CH_2)carbons, aromatic carbons, (C=N) and(C=O) carbons respectively.Finally the fourth synthetic line in this work involved introducing of compound[3]in reaction with phthalic anhydride producing succinimidyl phthalamic acid [11]. The reaction is proceed through nucleophilic attack of amino group in compound[3] on one carbonyl groupin phthalic anhydride to afford phthalamic acid [11] which inturn in troduced subsequently in dehydration reaction via treatment with acetic anhydride and anhydrous sodium acetate under reflux condtion affording compound [12]. FTIR spectrum of compound [11] showed absorption bands at (3454)cm^{-1},(3384,3282),(1730,1706),1664,1564 and1377 cm^{-1} due toν(O-H) carboxylic, ν(N-

H)amide, ν(C=O)imide, ν(C=O)carboxyl and amide, ν(C=C) aromatic andν(C-N)imide respectively. FTIR spectrum of compound [12] showed disappearance ofν(O-H) carboxylic band indicating success of dehydration reaction and showed absorption bands at (1730,1716)cm^{-1},1660,1602 and 1377 cm^{-1}due toν(C=O)imide, ν(C=O)amide, ν(C=C) aromatic andν(C-N)imide respectively.
All details of FTIR spectral data of the prepared compounds are listed in Table(2).

3-2- Biological Study

The newly synthesized succinimides [4,5,7,8,10,12] were tested for their in vitro antimicrobial activity against four types of bacteria including *Staphlococcus aureous,Streptococcus pyogenes,Escherrichia coli and Pseudomonas aureginosa* 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(3). The results that the majoring of the synthesized imide showed varying degrees of inhibition against the tested microorganisms. Compound[12] showed high brood-spectrum inhibitory activity against all the tested organisms,while compound[5] is highly active against *S.aureous*,compound[7] is highly active against *S.pyogenes.* Compound[10] is highly active against *E.coli* and compound [8] is highly active against *candida albicans fungi*, compound[4] was in active against *P. aureginosa*and *E.coli*while compound[5] was inactiveagainst *P. aureginosa* the rest of imides were found to be moderately or weak active against the tested organisms.



Scheme (1)

Table 1: Physical properties of the prepared compounds [1-12]

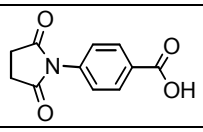
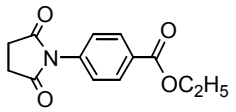
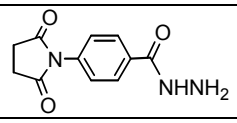
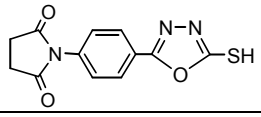
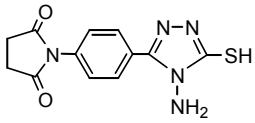
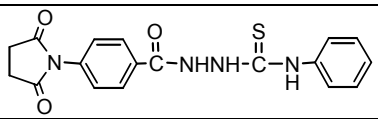
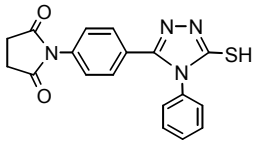
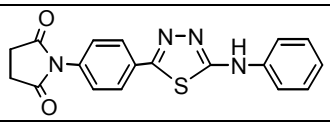
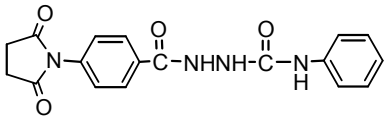
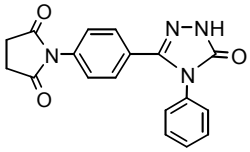
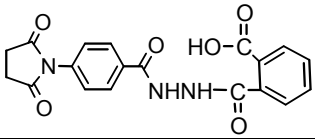
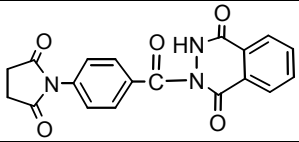
Comp. No.	Compound structure	Color	Melting Points °C	Yield %	Recrystallization Solvent
1		white	206-208	92	Ethanol
2		Faint Yellow	88-90	65	Methanol
3		Crystal white	102-104	57	n-hexane
4		black	162-164	92	Dioxane
5		Dark yellow	81-83	80	n-hexane
6		Faint Yellow	164-167	90	Acetone
7		Dark brawn	Decomp300	88	Dioxane
8		Faint Yellow	208-210	91	Acetone
9		Yellow	178-180	82	Methanol
10		Faint Yellow	228-230	87	Acetone
11		Faint brawn	109-111	77	Methanol
12		Radish brawn	194-195	84	Ethanol

Table 2: Spectral data of the prepared compounds [21-25]

Comp. No.	FTIR spectral data cm^{-1}							
	ν(C-H) aromatic ν(C-H) aliphatic	ν(C=O) imide	ν(C=N)	ν(C=C) aromatic	ν(C-N) imide	ν(C=O) amide	ν(N-H)	Others
1	3074 2927	1693	-	1596	1377	1666	-	ν(O-H) Carboxylic 3307
2	3122 2983	1710asym 1674sym	-	1600	1369	-	-	ν(C=O)Ester 1730 ν(C-O)Ester 1150
3	-	1683	-	1602	1367	1629	3240	ν(NH_2) 3430,3346
4	2921	1718asym 1697sym	1627	1596	1360	-	3355	ν(C-O-C) 1253 ν(C-S)673 ν(C=S)1330
5	3049 2981	1666	1623 1600	1575	1311	-	3205	ν(NH_2) 3461,3363 ν(C-S)669
6	3112 2937	1716asym 1699sym	-	1596	1367	1677	3357 3209	ν(C=S) 1330
7	3080 2921	1697	1666	1598	1377	-	3307	ν(C-S)661 ν(C=S) 1323
8	3047 2970	asym1720 sym1697	1627	1606	1330	-	3282	ν(C-S) 671
9	3064 2979	1703	-	1596	1313	1668	3211 3296	-
10	3091 2923	1700	1598	1544	1334	1670	3298	-
11	3001 2925	asym1730 sym1706	-	1564	1377	1664	3384 3282	ν(O-H) carboxylic 3454
12	3028 2974	asym1730 sym1716	-	1602	1377	1660	3163	-

asym=asymmetrical sym=symmetrical

Table 3: Inhibition zone of antimicrobial activity of Succinimides in mm

Comp. No.	Gram-positive bacteria		Gram-negative bacteria		Fungi
	Staphylococcus aureus	***Streptococcus pyogenes***	***Pseudomonas aureginos***	***Escherichia coli***	***Candida albicans***
4	13.4	8.2	-	-	9.2
5	18.3	7.8	-	8.4	14
7	12.5	15.3	9.9	11.1	13.7
8	13.8	9.7	10.2	11.7	19.3
10	12	8.6	7.1	15.2	10.9
12	20.7	17.5	14	18.9	22.2
Ampicillin	17	12.5	12	14	-
Fluconazole	-	-	-	-	18
DMSO	-	-	-	-	-

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