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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY EVALUATION OF NEW CYCLIC IIMIDES CONTAINING 1,3,4-THIADIAZOLE AND 1,3,4-OXADIAZOLE MOIETIES

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ABSTRACT

In the present work a variety of new cyclic imides containing two heterocycles namely 1,3,4-thiadiazole and 1,3,4-oxadiazole were synthesized. The most important step in the synthesis of these imides is the preparation of key intermediate (compound (3)) which represents the main hetrocyclic amine containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole rings and from which all the new target cyclic imides are synthesized. Synthesis of compound (3) was performed via three steps the first one involved reaction of 2-amino-5-mercapto-1,3,4-thiadiazole with ethyl chloro acetate producing 2-(5-amino-1,3,4-thiadiazole-2-yl)thioethyl acetate[1] which introduced subsequently in reaction with hydrazine hydrate producing the corresponding acetohydrazide[2] and this in turn introduced in reaction with carbon disulfide in the third step producing the mentioned amine[3]. Compound[3] was introduced successfully in reaction with different cyclic anhydrides including (maleic, citraconic, succinic, phthalic, pyridinic and pyromellitic) anhydrides producing a series of new amic acids[4-9]. In the final step dehydration of amic acids[4-9] was performed via treatment with acetic anhydride and anhydrous sodium acetate producing the desired corresponding imides[10-15]. The new imides[10-15] were screened for their antimicrobial activity against four types of bacteria and one fungi and the results indicated that they exhibit good antimicrobial activity against the tested organisms.

Keywords: Cyclic imides, acetohydrazide, pyridinic and pyromellitic anhydrides, amic acids.

1. INTRODUCTION

Cyclic imides have been attracted much more attention of organic and medicinal chemists due to their biological activities, most of them are extensively used as analgesic[1], antinociceptive agents[2] or as reactants for polymer synthesis[3].

An imide nucleus can be also found in a structure of anxiolytic, antimicrobial, anticancer and anti-inflammatory substances[4-6].

Also five membered heterocyclic compounds show various types of biological activities among them 2,5-disubstituted-1,3,4-thiadiazoles are associated with divers biological activities probably by the virtue (-N=C-S-) grouping, some of them possess antibacterial, antifungal and anticonvulsant activities[7-9]. Similarly 2,5-disubstituted-1,3,4-oxadiazoles also display wide spectrum of activities such as antibacterial, antimalarial, anti-inflammatory, antifungal and anticonvulsant[10-14].

In light of the therapeutic importance of these rings we attempted to synthesize new molecules containing the above mentioned three biologically active moieties (cyclic imide, 1,3,4-thiadiazole and 1,3,4-oxadiazole). The incorporation of these three moieties into a single molecule can change the activity of the obtained new compounds, thus the present work involved synthesis of new cyclic imides containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole moieties and investigation for their antimicrobial activity.

2. Experimental

Commercially a vailable chemicals and solvents were used as received from BDH and Merk. Melting points of the new compounds were determined on Thomas Hoover apparatus and are uncorrected. FTIR spectra were recorded on a SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer. ^{1}HNMR and ^{13}CNMR spectra were registered on Bruker 300MHz instrument using DMSO-d_6 as solvent and Tetramethylsilane (TMS) as the internal standard.

2.1. Preparation of 2-(5-amino-1,3,4-thiadiazole-2-yl-thio)ethylacetate [1][15]

ethylchloroacetate (0.01 mol, 1.25 mL) was added dropwise to a stirred solution of 2-amino-5-mercapto-1,3,4-thiadiazole (0.01 mol, 1.33 g), potassium hydroxide (0.01 mol, 0.55 g) in (20 mL) absolute ethanol with stirring.
The reaction mixture was refluxed for 8 hrs. then was filtered and the filtrate was poured on crushed ice. The resulted solid was filtered, dried then recrystallized from chloroform and collected as white crystal. Yield (80%), m.p. (78-80)°C.

2.2. Preparation of 2-(5-amino-1,3,4 thiadiazole-2-yl-thio)acetohydrazide [2][16]

A mixture of compound [1] (0.01 mol, 2.19 g) and hydrazine hydrate (0.015 mol, 0.68 mL) was refluxed for 4 hrs. then (15 mL) of ethanol was added and reflux was continued for 8 hrs. with stirring. The obtained greenish yellow precipitate was fillered, washed with cold water, dried and recrystallized from ethanol. Yield (75%), m.p. (212-215)°C.

2.3. Preparation of 5-(5-amino-1,3,4 thiadiazole-2-yl-thiomethyl)-1,3,4oxadiazole 2 thiol [3][17]

To a solution of compound [2] (0.01 mol, 2.05 g) in ethanol (25 mL) at zero°C potassium hydroxide (0.01 mol, 0.55 g) and carbon disulfide (0.02 mol, 1.2 mL) were added respectively. The mixture was refluxed for 7 hrs., then the solvent was evaporated and the residue was dissolved in cold water then acidifed with hydrochloric acid. The formed white precipitate was filtered, dried then recrystallized from ethanol. Yield (72%), m.p. (189-190)°C.

2.4. Preparation of N-[2-(2-mercapto-1,3,4 oxadiazole-5-yl-thiomethyl)-1,3,4 thiadiazole-5-yl] amic acids [4-8][18]

A solution of compound [3] (0.01 mol, 2.15 g) dissolved in (25 mL) of acetone was added dropwise to a solution of (0.01 mol) of cyclic anhydride (maleic, citraconic, phthalic, succinic or pyridinic anhydride) dissolved in (25 mL) of acetone with stirring and cooling. Stirring was continued for 4 hrs. then the precipitated amic acid was filtered off, washed with diethyl ether, dried then recrsytallized from ethanol. Physical properties of amic acids[4-8] are shown in Table (1).

2.5. Preparation of Bis-N-[2-(2-mercapto 1,3,4-oxadiazole-5-yl-thiomethyl)-1,3,4 thiadiazole-5-yl] pyromellitamic acid [9][18]

The titled bis amic acid[9] was prepared by following the same procedure used in the synthesis of amic acids[4-8] except using of (0.01 mol) of pyromellitic anhydride with (0.02 mol) of compound (3). The resulted bis amic acid was purified by recrystallization from ethanol and its physical properties are listed in Table (1).

2.6. Preparation of N-[2-(2-mercapto-1,3,4 oxadiazole-5-yl-thiomethyl)-1,3,4 thiadiazole-5-yl]imides [10-15][18]

A mixture of (0.01 mol) of one of the prepared amic acids[4-9] in (20 mL) of acetic anhydride and (0.001 mol) of anhydrous sodium acetate was refluxed with stirring for 2 hrs. The resulted homogenous solution was cooled to room temperature then poured into excess cold water with vigorous stirring. The obtained precipitate was filtered, washed with distilled water then dried and finally recrystallized from a suitable solvent. Physical properties of the prepared imides[10-15] are listed in Table (2).

2.7. Biological Study

The cup plate method using nutrient agar medium was employed in studying the antimicrobial activity of the prepared imides against four strains of bacteria including *Stapylococcus aureous, Streptococcus pyogenes, Escherichia coli* and *Pseudomonas aureginosa* respectively and *Candida albicans* fungi. DMSO was used as sample solution, sample size of all compounds was fixed at (0.1 mL) and the used concentration for all tested compounds was 100 μg/mL. Using a sterilized crok borer cups were scooped out of agar medium contained in a petridish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the petridishes were subsequently incubated at 37°C for 48 hrs.
Ampicilline and fluoconazole were used as reference drugs and DMSO as a control. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (5).

3. RESULTS AND DISCUSSION

3.1. Chemistry

The target of the present work has been directed towards synthesis of new cyclic imides containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole cycles. The key intermediate used in the synthesis of the desired imides [10-15] is compound [3] 5-(5-amino-1,3,4-thiadiazole-2-yl-thiomethyl)-1,3,4-oxadiazole-2-thiol which represents the main heterocyclic amine containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole moieties. Compound [3] was synthesized by a multi-step reaction sequence, starting from 2-amino-5-mercapto-1,3,4-thiadiazole which introduced in reaction with ethyl chloro acetate in the first step producing thiadiazolyl thioester [1]. Reaction of compound [1] with hydrazine hydrate under reflux conditions gave the corresponding acetohydrazide (2) which on treatment with carbon disulfide affording compound [3]. Subsequently compound [3] was introduced in reaction with different cyclic anhydrides including maleic, citraconic, succinic, phthalic, pyridinic and pyromellitic anhydrides affording the new amic acids [4-9] which inturn were introduced in dehydration reaction via treatment with acetic anhydride and anhydrous sodium acetate producing the new target imides [10-15]. The synthetic route of the new compounds is outlined in Scheme (1).

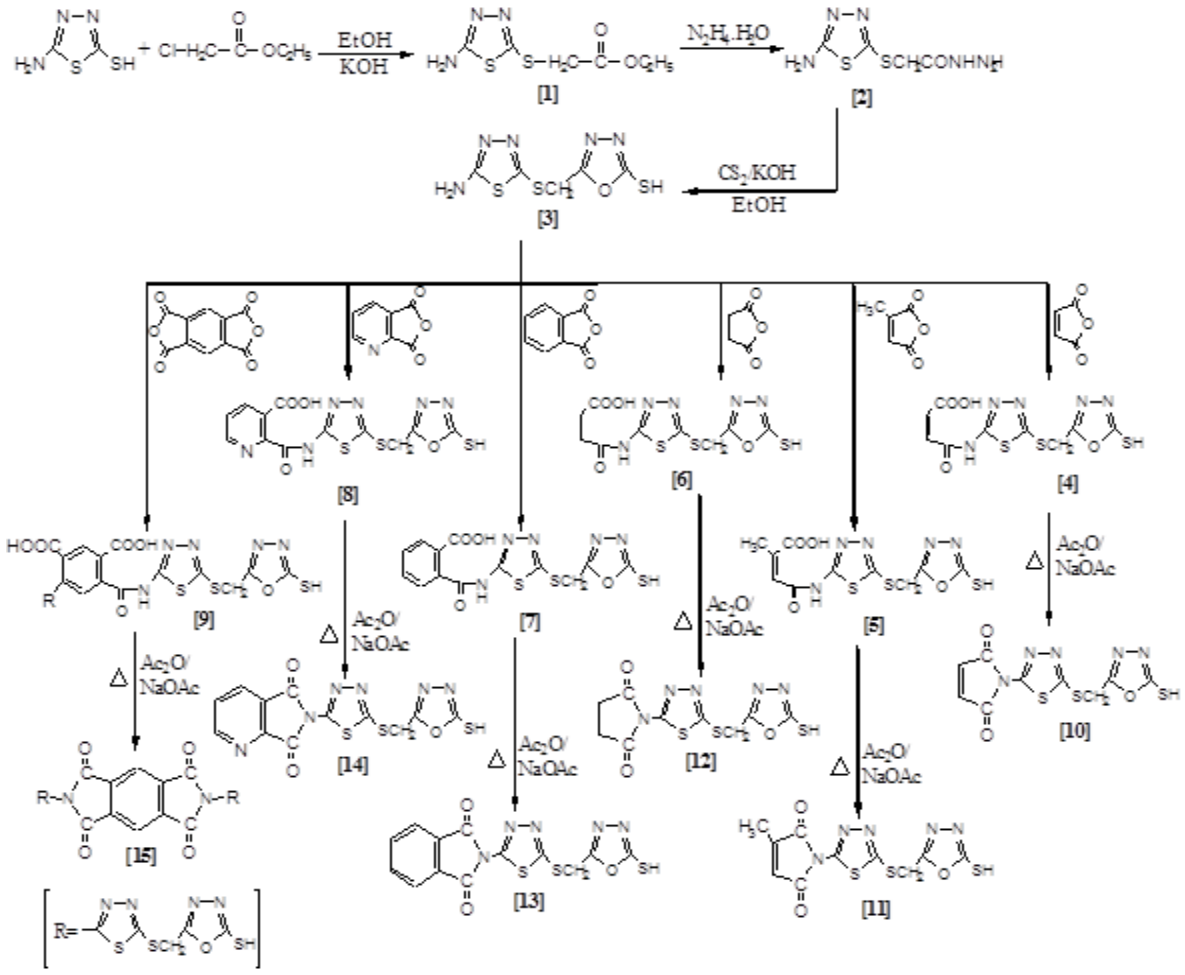
FTIR, ^{1}NMR and ^{13}CNMR spectra of the prepared compounds were recorded and found in full agreement with the proposed structures.

As indicated in Scheme (1) synthesis of conpound (3) involved three steps the first one was performed by nucleopilic attack of (SH) group in 1,3,4-thiadiazole on α-carbon in ethyle chloro acetate followed by elimination of HCl molecule producing thiadiazolyl thioester [1]. FTIR spectrum of compound [1] showed appearance of clear absorption band at 1728 cm^{-1} due to ν(C=O) ester indicating success of ester formation. The spectrum showed also bands at (3384, 3229) cm^{-1}, 1620, (1195, 1150) and 690 cm^{-1} due to $\nu(NH_2)$, ν(C=N), ν(C-O) ester and ν(C-S) respectively[19]. ^{1}HNMR spectrum of compound [1] showed triplet signal at δ=1.15-1.2) ppm belong to CH_3 protons, singlet signal at δ=(3.95) ppm belong to (SCH_2) protons, quartet signal at δ=(4.07-4.14) ppm belong to (OCH_2) protons and singlet signal at δ= 7.3 ppm belong to (NH_2) protons. ^{13}CNMR spectrum of compound [1] showed signals at δ=14.4, 36.29, 61.66, 149.27, 168.8 and 170.4 ppm belong to (CH_3), SCH_2, OCH_2, (C=N), other (C=N) and (C=O) carbons respectively.

In the second step compound [1] was introduced in nucleophilic substitution reaction with hydrazine hydrate leading to replace ethoxy group with hydrazino ($NH-NH_2$) group producing the corresponding acetohydrazide [2].

FTIR spectrum of compound [2] showed disappearance of ν(C=O) ester band and appearance of clear absorption bands at (3410-3263) cm^{-1} due to ν(NH-NH2) indicating success of acetohydrazide formation. Other bands appeared at 1685, 1643 and 667 cm^{-1} due to ν(C=O) amide, ν(C=N) and ν(C-S) respectively. ^{1}HNMR spectrum of compound [2] showed signals at δ=3.71, (3.95-4.33), 7.29 and 9.27 ppm belong to (SCH_2), ($NH-NH_2$), ($=C-NH_2$) and ($-NH-NH_2$) protons respectively. ^{13}CNMR spectrum of compound [2] showed signals at δ=39.93, 150, 168 and 170.5 ppm belong to (SCH_2), two (C=N) and (C=O) carbons respectively.

In the third step compound [2] was introduced in reaction with CS_2 in alkaline medium under reflux conditions. The reaction was proceed through nucleophilic attack of amino group in compound [2] on electron-deficient carbon in CS_2 followed by ring-closure producing compound [3].



Scheme (1)

FTIR spectrum of compound [3] showed disappearance of ν(C=O) amide band at 1685 cm^{-1} and appearance of ν(C-O-C) oxadiazole absorption band at 1134 cm^{-1} indicating success of cyclization reaction.

Other absorption bands appeared at (3402, 3248), 1608 and 671 cm^{-1} due to ν(NH_2), ν(C=N) and ν(C-S) respectively. ^{1}HNMR spectrum of compound [3] showed signals at δ= 4.38, (7.3-7.4) and 13.6 ppm belong to (SCH_2), NH_2 and SH protons while ^{13}CNMR spectrum showed signals at δ= 28.9 and (147.03-178.4) belong to (SCH_2) and four (C=N) carbons[19].

Beside the presence of 1,3,4-thiadiazole and 1,3,4-oxadiazole cycles in compound [3] molecule there is also an amino group which is ready for introducing in reaction with different cyclic anhydrides producing the corresponding amic acids. Thus a variety of amic acids including maleamic, citraconamic, succinamic, phthalamic, pyridinamic and pyromellitamic acids were synthesized via reaction of compound [3] with various cyclic anhydrides.

The reaction was proceed via nucleophilic attack of amino group in compound [3] on one carbonyl group in cyclic anhydride. Physical properties of amic acids [4-9] are listed in Table (1). FTIR spectra of amic acids [4-9] showed clear absorption bands at (3244-3452) cm^{-1} due to ν(O-H) carboxylic and ν(N-H) amide, bands at (1665-1697) cm^{-1} due to ν(C=O) carboxylic and ν(C=O) amide. Other bands appeared at (1600-1643) cm^{-1}, (1535-1566) cm^{-1}, (1145-1188) cm^{-1} and at (632-698) cm^{-1} due to ν(C=N), ν(C=C), ν(C-O) oxadiazole and ν(C-S) thiadiazole respectively. All details of FTIR spectral data of compounds [4-9] are listed in Table (3). ^{1}HNMR spectrum of compound [5] showed signals at δ= 2.03 ppm belong to CH3 protons, signal at δ= 4.6 ppm belong to (SCH_2) protons, signal at δ= (5.87-6.15) ppm belong to vinylic proton, signal at δ= 7.4 ppm belong to (NH) proton and signal at δ= 12.8 ppm belong to (OH) and (SH) protons. ^{13}CNMR spectrum of compound [5] showed signals at δ= 21.15, 27.86, 11.49, (147.8-162.75) and (170.38-

178.38) ppm belong to CH_3, SCH_2, two vinylic carbons, (C=N) and (C=O) carbons respectively[19].
^{1}HNMR spectrum of compound [6] showed signals at δ= (2.1,2.4) ppm belong to four aliphatic protons, signal at δ= 3.9 ppm belong to (SCH_2) protons and signals at δ= 12.3 and 13.2 ppm belong to SH, NH and OH protons. ^{13}CNMR spectrum of compound [6] showed signals at δ= 22.7, 22.8, 38.1, 152.4, 162, 171 and 180.9 ppm belong to aliphatic carbons, SCH_2, (C=N), (C=S) which formed by tautomerism and (C=O) carbons respectively.
^{1}HNMR spectrum of compound [7] showed signals at δ= 3.72 ppm belong to (SCH_2) protons, signals at δ= (7.9-8.04) ppm belong to aromatic protons and signals at δ= 12.3 and 14 ppm belong to OH and SH protons. ^{13}CNMR spectrum of compound [7] showed signals at δ= 35.4,(124.7-152.7), 164, 170 and 183.9 ppm belong to SCH_2, aromatic carbons, (C=N) and (C=O) carbons respectively. The final step in this work involved dehydration of amic acids [4-9] via treatment with acetic anhydride and anhydrous sodium acetate as dehydrating agent. Through this reaction dehydration and ring-closure were performed producing the desired cyclic imides [10-15]. Physical properties of imides [10-15] are listed in Table (2). FTIR spectra of the new imides showed disappearance of ν(O-H) carboxylic and ν(N-H) amide absorption bands indicating success of dehydration reaction. Besides the spectra showed characteristic absorption bands at (1681-1789) cm^{-1} due to ν(C=O) imide. Other absorptions appeared at (1620-1647) cm^{-1} due to ν(C=N), (1550-1616) cm^{-1} due to ν(C=C), (1334-1352) cm^{-1} due to ν(C-N) imide, (1153-1174) cm^{-1} due to ν(C-O) oxadiazole and at (624-690) cm^{-1} due to ν(C-S) thiadiazole. All details of FTIR spectral data of imides [10-15] are listed in Table (4).
^{1}HNMR spectrum of compound [11] showed signals at δ= (2.12-2.18) ppm belong to CH_3 protons, signal at δ= 4.59 ppm belong to (SCH_2) protons and signals at δ= 7.2 ppm and 12.78 ppm belong to vinylic proton and (SH) proton respectively. ^{13}CNMR spectrum of compound [11] showed signals at δ= 21.2, 28.06, 117.8, (147.8-163.7) and 170.8 ppm belong to CH_3, SCH_2, vinylic carbons, (C=N) and (C=O) carbons respectively.
^{1}HNMR spectrum of compound [13] showed signals at δ= 4.4, (7.3-8) and 12.7 ppm belong to SCH_2 protons, aromatic protons and SH proton respectively while ^{13}CNMR spectrum of the same compound showed signals at δ= 43, (121-132), 148, 158 and 166 ppm belong to SCH_2, aromatic carbons, (C=N) and (C=O) carbons respectively. ^{1}HNMR spectrum of compound [14] showed signals at δ= 4.36, (7.8-8) and 11 ppm belong to SCH_2 protons, aromatic protons and SH proton respectively while ^{13}CNMR spectrum of the same compound showed signals at δ= 44, (119-125), 143, 145 and 166 ppm belong to SCH_2, aromatic carbons, (C=N) and (C=O) carbons respectively.

3.2. Biological Study

Antimicrobial activity of the synthesized imides were examined against four strains of bacteria and *Candida albicans* fungi using cup plate method. Zones of inhibition caused by each compound was measured in (mm) and the results are listed in Table (5). The results indicated that compounds (12, 14 and 15) are highly active against all types of tested bacteria. Compounds (12 and 15) are also highly active against *Candida albicans* fungi. Compounds (10 and 13) are highly active against *S. pyogenes* and *E. coli* while compound (11) is highly active against *S. pyogenes* and *P. aeruginosa.* The rest of imides were found to be moderately active against the tested organisms.

ACKNOWLEDGMENT

We are very thankful to Dr.Nadum A. (Baghdad University, Biology Dep.) for performing antimicrobial study for the prepared compounds.

Table 1: Physical properties of amic acids[4-9]

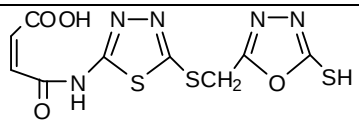
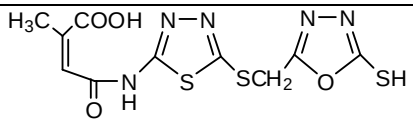
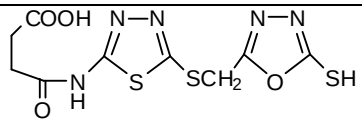
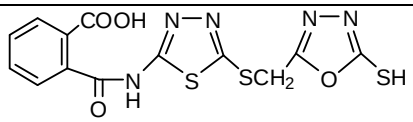
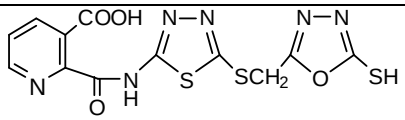
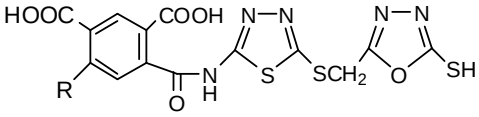
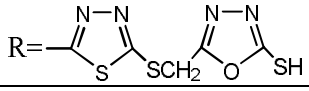
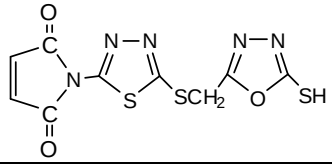
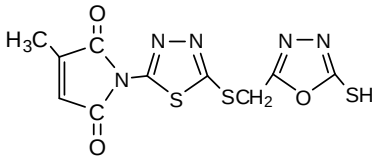
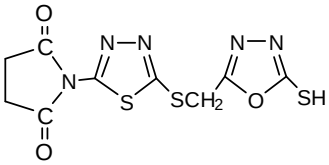
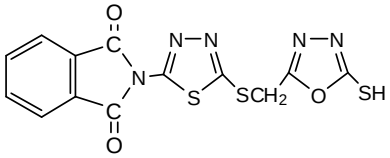
Comp. no.	Compound structure	Color	Melting points °C	Yield %	Solvent Recryst.
4		Light brown	105-107	82	Ethanol
5		Greenish yellow	118-120	85	Ethanol
6		Yellow	220-222	78	Ethanol
7		Off white	199-201	86	Ethanol
8		Deep yellow	210-212	70	Ethanol
9		Faint yellow	250 dec.	88	Ethanol
R=					

Table 2: Physical properties of prepared imides[10-15]

Comp. no.	Compound structure	Color	Melting points °C	Yield %	Solvent Recryst.
10		Brown	122-125	76	Ethanol
11		Yellow	131-133	70	Ethanol
12		Deep yellow	238-240	65	Ethanol
13		Light brown	218-220	85	cyclohexane

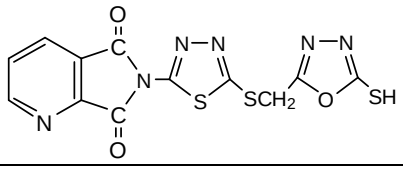
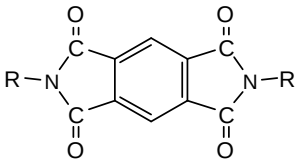
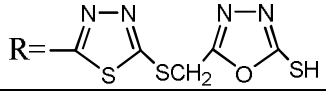
Comp. no.	Compound structure	Color	Melting points °C	Yield %	Solvent Recryst.
14		Yellow	202-204	68	Ethanol
15		Deep yellow	> 250 dec.	90	Ethanol
R=					

Table 3: FTIR spectral data of amic acids[4-9]

Comp. No.	FTIR spectral data cm^{-1}						
	ν(O-H) carboxylic ν(N-H) amide	ν(C=O) carboxylic	ν(C=O) amide	ν(C=N)	ν(C=C)	ν(C-O)	ν(C-S)
4	3404 3244	1695	1685	1614	1544	1168	671
5	3429	1697	1665	1643	1566	1172	698
6	3405	1685	1685	1618	-	1161	663
7	3437 3325	1674	1674	1624	1535	1145	632
8	3398 3275	1697	1674	1600	1566	1188	667
9	3452 3390	1670	1670	1612	1546	1153	655

Table 4: FTIR spectral data of imides[10-15]

Comp. No.	FTIR spectral data cm^{-1}					
	ν(C=O) imide	ν(C=N)	ν(C=C)	ν(C-N) imide	ν(C-O)	ν(C-S)
10	1732	1639	1620	1324	1168	667
11	1741	1640	1616	1352	1174	690
12	1733	1638	1618	1335	1158	654
13	1681	1647	1600	1350	1168	686
14	1731	1685	1610	1332	1143	630
15	1789 (sh) 1735	1620	1550	1334	1153	624

sh = shoulder

Table 5: Inhibition zones of antimicrobial activity of imides[10-15] in mm

Comp. No.	Gram positive bacteria		Gram negative bacteria		*Candida albicans* fungi
	S. aureus	*S. pyogenes*	*P. aeruginosa*	*E. coli*	
10	12.8	13.5	9.7	20.7	10.8
11	11.7	13	12.5	12	14.3
12	20.5	14.4	14	20.2	18.6
13	13.5	13.1	9.9	18.3	11.8
14	21	15	12.6	14.5	11
15	19.8	12.9	13.1	20.1	22.2
Ampicillin	17	12.5	12	14	-
Fluconazole	-	-	-	-	18
DMSO	-	-	-	-	-

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