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Research Article

SYNTHESIS AND ANTIMICROBIAL SCREENING OF NEW NAPHTHALIMIDES LINKED TO OXADIAZOLE, THIADIAZOLE AND TRIAZOLE CYCLES

Ahlam Marouf Al-Azzawi[1*] and Ahmad Solaiman Hamd[2]

[1]Baghdad University, College of Science, Department of Chemistry, Baghdad, Iraq.
[2]Al-Anbar University, College of Veterinary Medicine, Al-Anbar, Iraq.

ABSTRACT

In this work several new naphthalimides linked to selected heterocycles namely 1,3,4-oxadiazole,1,3,4-thiadiazole and 1,2,4-triazole were prepared. Preparation of the new naphthalimides was performed via multistep synthesis. In the first step unsubstituted napthalimide was converted to its potassium salt[1] which subsequently introduced in reaction with ethyl chloro acetate producing napthalimidyl ester[2] which in turn introduced in reaction with hydrazine hydrate affording the corresponding acetohydrazide[3]. Compound[3] represents the important key intermediate from which all the new target napthalimides[4, 5, 7, 8, 10, 12, 13] were synthesized via following different synthetic paths and applying different synthetic strategies. The prepared naphthalimides were screened for their antimicrobial activity and the results indicated that they possess high antimicrobial activity against the tested organisms.

Keywords: Napthalimides, Napthalimidyl ester, acetohydrazide, key intermediate, heterocycles.

1. INTRODUCTION

Cyclic imides represent a very important chemical class in drug discovery due to their wide range of biological and pharmacological properties[1-3]. Napthalimides first discovered by Brana and Coworkers have been found to exhibit diverse biological activities, some of them have shown high anticancer activity against a variety of murine and human tumor cells[4,5] while others have shown analgesic properties[6,7]. On the other hand amongst five membered heterocycles oxadiazoles, thiadiazoles and triazole have attracted significant interest in medicinal, pesticide chemistry, polymer and material science. 1,3,4-oxadiazoles are biologically versatile compounds displaying a variety of biological effects which include antifungal, antiparasitic, anti-inflammatory and antimicrobial activities[8-12]. 1,3,4-thiadiazoles also possess various biological properties such as antitumor, anticonvulsant, antihypertensive, anaesthetic, antibacterial and cardiotonic activities[13-15]. In addition triazoles have found wide use in medicinal chemistry as common structural motifs acting as peptidomimetic moieties and as hydrogen bond acceptors. They possess important pharmacological activities such as antifungal and antiviral[15-17].

In light of the interesting variety of biological activities seen in compounds containing napthalimide, oxadiazole, thiazole and triazole moieties it was thought of interest to examine the effect of having both naphthalimide and one of the mentioned heterocycles present simultaneously in one structure. Based on this notion the target of the present work was directed towards synthesis of new naphthalimides linked to oxadiazole or thiadiazole or triazole and test their antimicrobial activities.

2. Experimental

All chemicalsused in this work were purchased from Flucka and BDH and used without further purification. Melting points were determined on Thomas Hoover apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 300 MHz

instrument using tetramethylsilane (TMS) as the internal standard and DMSO-d_6 as solvent.

2.1. Preparation of 1,8-Naphthalimide Potassium Salt [1]

A solution of (0.01 mol, 2.35) 1,8-naphthalimide in (25 mL) absolute ethanol was added to alcoholic potassium hydroxide solution [(0.01 mol) KOH in (25 mL) ethanol] with stirring. The obtained precipitate was filtered and dried.

2.2. Preparation of Ethyl-2-(N-naphthalimidyl) acetate [2][18]

To a solution of compound [1] in (20 mL) of DMF, (0.01 mol, 1.25 mL) of ethylchloroacetate was added dropwise with stirring then the mixture was refluxed for six hours, then cooled to room temperature and poured into cold water with stirring. The obtained precipitate was filtered off, washed with water, dried and recrystallized from ethanol.

2.3. Preparation of 2-(N-naphthalimidyl) acetohydrazide [3][18]

A mixture of compound [2] (0.01 mol, 2.19 g) and hydrazine hydrate (0.015mol, 0.7 mL) was refluxed for four hours then (15 mL) of ethanol was added and reflux was continued for additional eight hours with stirring. The obtained precipitate was filtered, washed with cold water, dried and recrystallized from ethanol.

2.4. Preparation of N-[(5-mercapto-1,3,4-oxadiazole-2-yl)methyl]-1,8-naphthalimide [4][18]

To a solution of compound [3] (0.01 mol, 2.69 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 hours then the solvent was evaporated and the residue was dissolved in cold water then acidified with hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from ethanol.

2.5. Preparation of N-[(4-amino-5-mercapto-1,2,4-triazole-3-yl)methyl]-1,8-naphthalimide [5][19]

Carbon disulfide (0.01 mol, 0.6 mL) was added to the solution of (0.01 mol, 2.69 g) of compound [3] in (30 mL) of absolute ethanol containing (0.01 mol, 0.55 g) of potassium hydroxide with stirring, then solution of (10 mL) of disilled water and (0.01 mol) of hydrazine hydrate was added to the mixture followed by reflux on a water bath for 4 hours. 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 ethanol.

2.6. Preparation of N-(phenylacetyl thiosemicarbazide)-1,8-naphthalimide[6][18]

To a mixture of (0.01 mol, 2.69 g) of compound [3] dissolved in (20 mL) of absolute ethanol, (0.01 mol, 1.35 g) of phenylisothiocyante was added dropwise with stirring. The mixture was refluxed for 6 hours then cooled and the obtained solid was filtered, dried and recrystallized from ethanol.

2.7. Preparation of N-[(5-mercapto-4-phenyl-1,2,4-triazole-3-yl)methyl]-1,8-naphthalimide [7][20]

A mixture of (0.001 mol, 0.4 g) of compound [6] in (3 mL) of 5% sodium hydroxide solution was refluxed on water bath for 2 hours. The resulted solution was cooled to room temperature, filtered and the filtrate was acidified with dilute hydrochloric acid. The formed precipitate was filtered, washed with distilled water, dried and recrystallized from ethanol.

2.8. Preparation of N-[(5-(phenylamino)-1,3,4-thiadiazole-2-yl)methyl]-1,8-naphthalimide [8][20]

A mixture of (0.001 mol, 0.4 g) of compound [6] in (3 mL) of phosphoric acid was refluxed at 120°C for 30 minutes. The resulted solution was cooled to room temperature, kept overnight then poured into crushed ice with stirring. The obtained precipitate was filtered, washed with distilled water, dried and recrystallized from ethanol.

2.9. Preparation of N-[2-(1,8-naphthalimide)-acetyl]-N-phenyl hydrazine carboxamide [9][18]

Compound [9] was prepared by following the same method described for preparation of compound [6] except using of phenylisocyante instead of phenylisothiocyanate. The resulted solid was filtered, dried and recrystallized from ethanol.

2.10. Preparation of N-[(5-oxo-4-phenyl-4,5-dihydro-1,2,4-triazol-3-yl)methyl]-1,8-naphthalimide [10][19]

Compound [10] was prepared by following the same method described for preparation of compound [7] except using of compound [9] instead of compound [6]. The resulted solid was filtered, dried and recrystallized from ethanol.

2.11. Preparation of N-(N\-formylaceto hydrazide)-1,8-naphthalimide [11][19]

A solution of compound [3] (0.01 mol, 2.69 g) in formic acid (20 mL) was refluxed for 20 minutes. The solvent was evaporated and the residue was recrystallized from ethanol.

2.12. Preparation of N-[(1,3,4-oxadiazole-2-yl)methyl]-1,8-naphthalimide [12][19]

To a solution of compound [11] (0.001 mol, 0.3 g) in xylene (20 mL) phosphorous pentoxide (0.5 g) was added and the mixture was refluxed for one hour with stirring. The solvent was evaporated, water (10 mL) was added and mixture was extracted with chloroform. The solvent was evaporated and the residue was recrystallized from ethanol.

2.13. Preparation of N-[(1,3,4-thiadiazole-2-yl)methyl]-1,8-naphthalimide [13][19]

Compound [13] was prepared by following the same method described for preparation of compound [12] except using of phosphorous pentasulfide instead of phosorous pentoxide. The resulted solid was filtered, dried and recrystallized from ethanol.

2.14. Biological Study

The synthesized naphthalimides [4, 5, 7, 8, 10, 12, 13] were evaluated for biological activity, i.e. antibacterial and antifungal. Antibacterial activities were determined against four different strains of bacteria including (*Stapylococcu saureus, Streptococcus pyogenes, Escherichia coli and Pseudomonas aureginosa*) using ampicillin as standard drug. The new napthalimides were also tested for their antifungal activity against *Candida albicans* fungi using Fluoconazole as a standard.

The cup plate method was used in this study, 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 cork 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 cup and the petridishes were subsequently incubated at 37°C for 48 hrs. Zones of inhibition produced by each compound was measured in (mm) and the results are listed in Table (3).

3. RESULTS AND DISCUSSION

3.1. Chemistry

In continuation of our research program directed towards synthesis of new cyclic imides linked to different heterocycles the target of the present work is synthesis of new naphthalimides connected to oxadiazole, triazole, thiadiazole and screen for their antimicrobial activity.

Strategy for performing this target involved many steps in the first one unsubstituted naphthalimide was converted to the corresponding potassium salt [1]. Compound [1] was introduced in reaction with ethyl chloro acetate in the second step producing naphthalimidyl ester [2]. Reaction of compound [2] with hydrazine hydrate in the third step gave the corresponding acetohydr azide [3]. Compound [3] is the important key intermediate from which all the target naphthalimides [4, 5, 7, 8, 10, 12, 13] were synthesized via following four different synthetic lines. The synthetic route of the new naphthalimides is outlined in Scheme (1) and physical properties of the prepared compounds are listed in Table (1). As indicated in Scheme (1) the first step in this work involved conversion of unsubstituted naphthalimide to its potassium salt [1] in order to increase the nucleophilicity of imide which is necessary in performing the subsequent step. Compound [1] was introduced in reaction with ethyl chloro acetate in the second step according to Gabriel synthesis through nucleophilic attack of negative nitrogen in compound [1] on α-carbon in ethyl chloro acetate producing naphthalimidyl ester [2]. FTIR spectrum of compound [2] showed appearance of clear absorption band at 1747 cm^{-1} due to ν(C=O) ester indicating success of ester formation. Other absorption bands appeared at (1701, 1666, 1589, 1203 and 1381) cm^{-1} due to asym. and sym. ν(C=O) imide, ν(C=C) aromatic, ν(C-O) ester and ν(C-N) imide respectively[21]. ^{1}H-NMR spectrum of compound [2] showed triplet signal at δ= (1.19-1.23) ppm belong to CH_3 protons, quartet signal at δ= (4.15-4.2) ppm belong to (-OC$\underline{H}_2$-) protons, singlet signal at δ= 4.81 ppm belong to (-C$\underline{H}_2$-CO-) protons and signals at δ=(7.85-8.49) ppm belong to aromatic protons. ^{13}C-NMR spectrum of compound [2] showed signals at δ= 14.49, 41.6, 61.6, (121.7-135.3) and (163.5-168.4) ppm belong to (CH_3), (-O$\underline{C}H_2$-), ($\underline{C}H_2$CO), aromatic carbons, (C=O) imide and (C=O) ester carbons respectivrly[21]. In the third step compound [2] was introduced in nucleophilic substitution reaction with hydrazine hydrate leading to replace ethoxy group with hydrazine (NH-NH_2) group producing the corresponding acetohyrazide [3]. FTIR spectrum of compound [3] showed disappearance of ν(C=O) ester and ν(C-O) ester bands and appearance of ν($NHNH_2$) bands at (3236, 3305) cm^{-1} proving success of acetohydrazide formation. Other bands

appeared at 1705, 1662, 1585 and 1381 cm^{-1} due to ν(C=O) imide, ν(C=O) amide, ν(C=C) aromatic and ν(C-N) imide respectively.
^{1}H-NMR spectrum of compound [3] showed signals at δ= 3.9, 4.12, (7.7-8.31) and 9.12 ppm belong to (-C$\underline{H}_2$CO-), (NHN$\underline{H}_2$) aromatic protons and (N$\underline{H}$-NH_2) protons respectively. ^{13}C-NMR spectrum of compound [3] showed signals at δ= 60.3, (123.8-138.6), 165.6 and 167.4 ppm belong to ($\underline{C}H_2CO$), aromatic carbons, (C=O) amide and (C=O) imide carbons respectivrly[21]. Compound [3] is the important key intermediate from which all the desired new naphthalimides were synthesized via following four different synthetic lines. The first synthetic line involved introducing of compound [3] in reaction with CS_2in basic medium and the resulted intermediate was treated either with diluted HCl producing imide [4] or with hydrazine hydrate producing imide [5].
FTIR spectra of naphthalimides [4] and [5] showed absorption bands at (1678-1701), 1654, 1585 and (1377-1381) cm^{-1} due to ν(C=O) imid, ν(C=N), ν(C=C) aromatic and ν(C-N) imide respectively. Also FTIR spectrum of compound [4] showed bands at 1126 and 671 cm^{-1} due to ν(C-O-C) oxadiazole and ν(C-S) while FTIR spectrum of compound [5] showed bands at (3379, 3209) cm^{-1} due to ν(NH_2).
^{1}H-NMR spectrum of compound [4] showed signals at δ= (5.07-5.18), (7.87-8.48) and 12.88 ppm belong to (CH_2), aromatic protons and (SH) proton. ^{13}C-NMR spectrum of compound [4] showed signals at δ= 35.38, (122-135.2), 158.44 and 163.4 ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O) carbons respectively. ^{1}H-NMR spectrum of compound [5] showed signals at δ= 4.2, (4.88-4.9), (7.65-8.13) and 12.6 ppm belong to (NH_2), (CH_2), aromatic protons and (SH) proton. ^{13}C-NMR spectrum of compound [5] showed signals at δ= 36.3, (118.2-136.5), 163 and 165.3 ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O) carbons respectively.
The second synthetic line in this work based also on compound [3] which introduced in reaction with phenyl isothiocyanate and the resulted intermediate [6] on treatment with NaOH solution afforded naphthalimide [7], while on treatment with H_3PO_4 afforded naphthalimide [8]. FTIR spectra of compounds [6, 7, 8] showed clear absorption bands at (3240-3417), (1678-1701), (1589-1593) and (1300-1381) cm^{-1}due to ν(NH), ν(C=O) imide, ν(C=C) aromatic and ν(C-N) imide respectively.^{1}H-NMR spectrum of naphthalimide [7] showed signals at δ= 4.36, (7.32-9.22) and 13 ppm belong to (CH_2), aromatic protons and NH proton present due to tautomerism and finally (SH) proton. ^{13}C-NMR spectrum of compound [7] showed signals at δ= 35.54, (119.4-135.39), 150.2, (168.6-169.8) and 170.4 ppm belong to (CH_2), aromatic carbons, (C=N) (C=O) imide and [(C=S) formed by tautomerism] carbons respectively.^{1}H-NMR spectrum of compound [8] showed signals at δ= 4.7, 5.5 and (6.9-8.8) ppm belong to (NH), (CH_2) andaromatic protons. ^{13}C-NMR spectrum of compound [8] showed signals at δ= 39.03, (117-141), 154.7and (163.6-165.8) ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O) imide carbons respectively.
The third synthetic line in this work involved treatment of compound [3] with phenylisocyanate and the resulted intermediate [9] on treatment with NaOH solution introduced in nucleophilic attack lead to intramolecular cyclization producing naphthalimide [10]. FTIR spectra of compounds[9] and [10] showed absorption bands at (3309-3317), (1697-1712), (1554-1597) and (1311-1377) cm^{-1} due to ν(NH), ν(C=O) imide, ν(C=C) aromatic and ν(C-N) imide respectively. ^{1}H-NMR spectrum of compound [10] showed signals at δ= 4.41 and (7.4-8.31) ppm belong to CH_2 protons and aromatic protons and NH proton. ^{13}C-NMR spectrum of compound [10] showed signals at δ= 38.1, (116-138.3), 156.4 and (162-164.7) ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O) carbons respectively.
In the fourth synthetic line compound [3] was treated with formic acid and the resulted intermediate [11] on treatment with P_2O_5 afforded naphthalimide [12] while on treatment with P_2S_5 afforded naphthalimide [13]. FTIR spectra of compounds [11, 12, 13] showed absorption bands at (1693-1728), (1589-1620) and (1377-1381) cm^{-1} due to ν(C=O) imide, ν(C=C) aromatic and ν(C-N) imide respectively. Besides FTIR spectrum of compound [11] showed clear absorption bands at (3417, 3209) and (1681) cm^{-1} due to ν(N-H) and ν(C=O) aldehyde while FTIR spectra of both compounds [12] and [13] showed disappearance of these two bands indicating success of cyclization reaction and formation of these two new compounds [12, 13]. All details of FTIR spectral data of the prepared compounds [4-13] are listed in Table (2). ^{1}H-NMR spectrum of compound [12] showed signals at δ= 4.94 and (7.82-8.52) ppm belong to (CH_2) protons and aromatic protons while ^{13}C-NMR spectrum showed signals at δ= 37.5, (126.6-140), 155.1 and 167.4 ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O) imide carbons respectively. ^{1}H-NMR spectrum

of compound [13] showed signals at δ= 5.1 and (7.44-8.1) ppm belong to (CH_2) and aromatic protons while ^{13}C-NMR spectrum showed signals at δ= 38.4, (125-140.43), 159 and 169.2 ppm belong to (CH_2), aromatic carbons, (C=N) and (C=O)carbons respectively.

3.2. Biological Study

Antimicrobial activity of the synthesized naphthalimides were examined against four strains of bacteria and candida albicans fungi by applying cup plate method. Zones of inhibition caused by each naphthalimide was measured in (mm) and the results are listed in Table (3). The results indicated that naphthalimides [4, 5, 7, 8, 13] are highly active against *Stapylococcus aureus, Streptococcus pyogenes* and *Escherichia coli.* Compounds [7, 8, 13] are also highly active against *Pseudomonas aureginosa* while compound [10] is highly active against *Escherichia coli*, and compounds [4, 8, 13] showed high activity against *Candida albicans* fungi. The rest of naphthalimides were found to be moderately active against the tested organisms.

ACKNOWLEDGMENT

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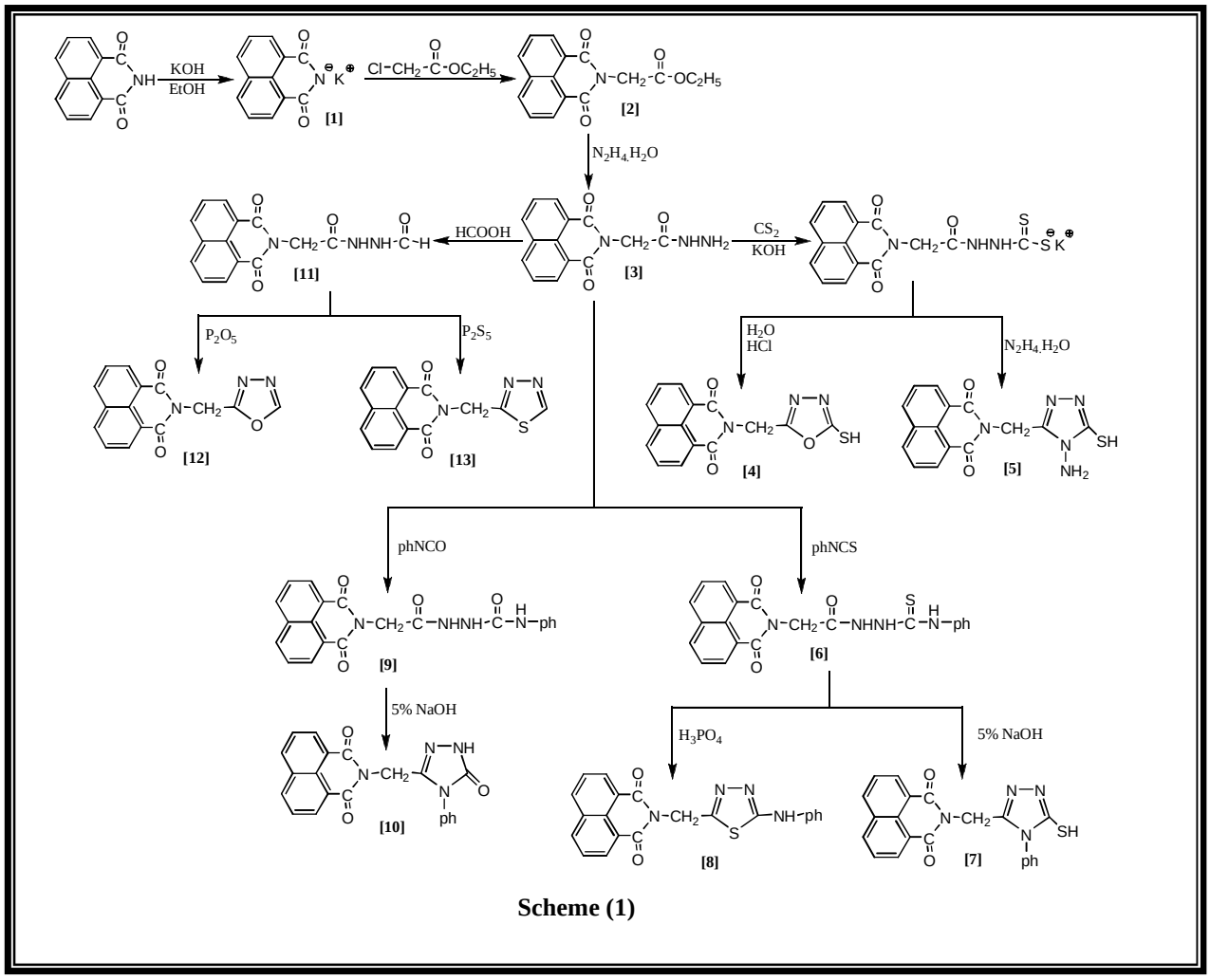


Scheme (1)

Table 1: Physical properties of prepared compounds[2-13]

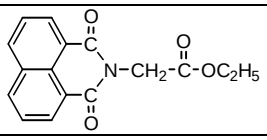
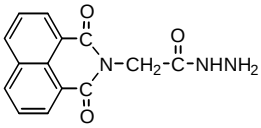
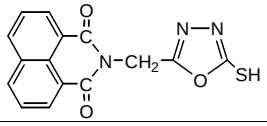
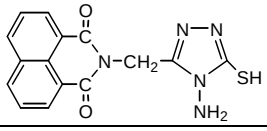
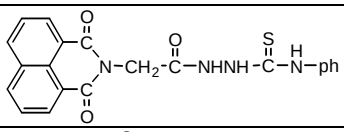
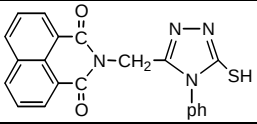
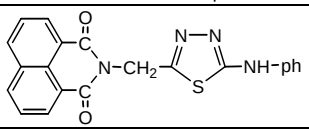
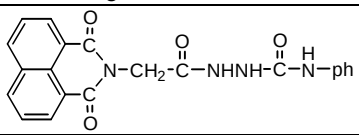
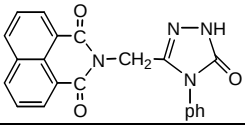
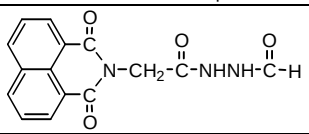
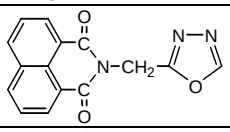
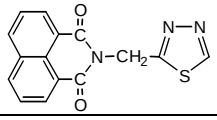
Comp. No.	Compound structure	Colour	Melting points °C	Yield %	Solvent of recrystallization
2		Brown	148-150	90	Ethanol
3		Off white	>300	85	Ethanol
4		Green	>300	73	Ethanol
5		Brown	210-212	65	Ethanol
6		Light brown	200-202	76	Ethanol
7		Yellow	156-158	73	Ethanol
8		Brown	116-118	70	Ethanol
9		Off white	>300	67	Ethanol
10		Light green	185-187	70	Ethanol
11		Light brown	>300	67	Ethanol
12		Yellow	123-125	70	Ethanol
13		Brown	Oily	60	Ethanol

Table 2: FTIR spectral data of the prepared compounds[4-13]

Comp. No.	FTIR spectral data cm^{-1}						
	ν(C=O) imide	ν(C=N)	ν(C=C) aromatic	ν(C-N) imide	ν(C=O) amide	ν(N-H)	Others
4	1701	1654	1585	1377	-	3425	ν(C-O-C) 1126 ν(C-S) 671
5	1697 1678	1654	1585	1381	-	-	ν(NH_2) 3379 3209
6	1697 1678	-	1589	1361	1662	3321 3240	ν(C=S) 1330
7	1693	1639	1593	1300	-	3417	-
8	1701	1662	1589	1381	-	3414	ν(C-S) 694
9	1710 1697	-	1597 1554	1377	1654	3309	-
10	1712	1597	1554	1311	-	3317	ν(C=O) amidetriazole 1693
11	1697	-	1620 1589	1381	1658	3417 3209	ν(C=O) aldehyde 1681
12	1728 1701	1662	1589	1381	-	-	ν(C-O-C) oxadiazole 1180
13	1693	1658	1593	1377	-	-	ν(C-S) 671

Table 3: Inhibition zones of antimicrobial activity of naphthalimides in (mm)

Comp. No.	Gram positive bacteria		Gram negative bacteria		*Candida albicans* fungi
	S. aureus	*S. pyogenes*	*P. aeruginosa*	*E. coli*	
4	18.6	14.4	11	17.1	18.3
5	17.7	12.8	11.7	15.8	14.5
7	17.1	13.5	12.5	15.3	13
8	21	16.2	14.2	20.4	21.8
10	13.5	11.1	10.8	14.7	11.4
12	14.2	12	9.6	13.2	12.5
13	20.3	15.6	13.5	19.8	20.7
Ampicillin	17	12.5	12	14	-
Fluconazole	-	-	-	-	18
DMSO	-	-	-	-	-

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