Synthesis, Evaluation Antimicrobial Activity of Some New *N*-substituted Naphthalimides Containing Different Heterocyclic Rings

Mohammed R. Ahmad[1], Suaad M. H. Al-Majidi [1] and Ayad Kareem Khan[2*]
[1]Department of Chemistry, College of Science, University of Baghdad,
[2] Department of pharmaceutical Chemistry,College of Pharmacy, University of Mustansiriyah, Baghdad, Iraq.

Abstract:
A series of new 1,8-naphthalimides linked to azetidinone, thiazolidinone or tetrazole moieties were synthesized. *N*-ester-1,8-naphthalimide (1) was obtained by direct imidation of 1,8-naphthalic anhydride with ethylglycinate. Compound (1) was treated with hydrazine hydrate in absolute ethanol to give *N*-acetohydrazide-1,8-naphthalimide (2). The hydrazine derivative (2) was used to obtain new Schiff bases (3-7). Three routes with different reagents were used for the cyclization of the prepared Schiff bases. Fifteen cyclic Schiff bases (8-22) with four- and five-membered rings were obtained.
The structures of the newly synthesized compounds were identified by their FTIR, ^{1}H-NMR, ^{13}C-NMR spectral data and some physical properties. Furthermore, these compounds were screened in three concentration for their *in vitro* antimicrobial activity measurements against both Gram (+ve) such as *Staphylococcus aureus, Bacillus* and Gram (-ve) *Escherichia Coli, pseudomonas aeuroginosa* bacteria and against *Candida albicans* fungal and they were found to exhibit good to moderate antimicrobial activities.

Keywords: 1,8-naphthalimides, azetidine-2-one, thiazolidine-4-one, 1,2,3,4-tetrazole, synthesis ,antimicrobial activity.

تحضير وتقييم الفعالية المضادة للميكروبات لبعض N–معوضات نفثالئيميدات الجديدة الحاوية حلقات غير متجانسة مختلفة

محمد رفعت احمد[1]، سعاد محمد حسين[1] و اياد كريم خان[2*]
[1]قسم الكيمياء، كلية العلوم، جامعة بغداد، [2] قسم الكيمياء الصيدلانية، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.

الخلاصة:
حضرت سلسلة جديدة من 8,1– نفثالئميدات المرتبطة بمعوضات ازيتيدينون، ثايازولدين او تترازول. N– استر–8,1– نفثالئيميد (1) حضر بالتفاعل المباشر ل 8,1– حامض النفثالك اللامائي مع كلايسينات الاثيل. المركب (1) عومل مع الهيدرازين المائي في الايثانول المطلق ليعطي N– اسيتو هيدرازايد–8,1–نفثالئيميد (2)ومن ثم مشتق الهايدرازين استخدم للحصول على قواعد شف جديدة (3 –7).ثلاثة طرق بكواشف مختلفة استخدمت للغلق الحلقي لقواعد شف المحضرة. اذ تم الحصول على خمسة عشر من قواعد شف الحلقية (8–22) بحلقات رباعية وخماسية. تراكيب المركبات المحضرة الجديدة شخصت من خلال الطرق الطيفية FTIR، ^{1}H–NMR و ^{13}C–NMR وبعض الخواص الفيزيائية حيث كانت النتائج المستحصلة مطابقة للتراكيب المقترحة . هذه المركبات المحضرة اختبرت فعاليتها المضادة للميكروبات بثلاث تراكيز مختلفة خارج جسم الكائن الحي ضد نوعين البكتريا المرضية موجبة الصبغة ونوعين اخرين سالبة الصبغة ونوع من الفطريات وقد اظهرت النتائج فعالية جيدة الى متوسطة ضد انواع الاحياء المجهرية قيد الدراسة.

*Email: kareem_ayad@yahoo.com

1. Introduction:

Cyclic imide moiety is an integral part of structures of various important molecules such as succinimide [1], maleimide [2], and phthalimide [3] possess structural features, which confer potential biological activity [4] and pharmaceutical use [5].

Naphthalimides, one type of cyclic imides [6] with strong hydrophobicity and desirable large π-conjugated backbone, could easily interact with various active targets in biological system via non-covalent forces such as π–π stacking, and exhibit diverse biological activities including anticancer [7], antibacterial[8], antitrypanosomal [9], analgesic potency [10].

Naphthalimides are well-known as broad-spectrum activity against a variety of human solid tumor cells [11]. Several derivatives have reached the phases of clinical trials [12].

1,8-Naphthalimides are generally fluorescent compounds for which a series of biological local anesthetics[13], DNA cleaving agents [14], and non-biological optical brighteners [15]. Sulfonated naphthalimides derivatives are good antiviral agents with selective in vitro activity against the human immunity deficiency virus, HIV-1 [16].

Further four or five membered heterocyclic like azetidine-2-one, thiazolidine-4-one, and 1,2,3,4-tetrazole, constitute a potential class of compounds which posses a broad field of biological activities and clinical applications [17-19].

Consideration of all these factors leads to condense the newer N-substituted naphthalimide derivatives by the combination of naphthalimide ring followed by four or five membered heterocyclic moieties in one frame may lead to synthesis compounds with interesting antimicrobial profile.

2. Experimental Materials and Instruments

Chemicals used in this work are supplied from Merck, Sigma-Aldrich, BDH and Fluka companies and are used without further purification.

Melting points were determined on digital STUART melting point apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer using KBr discs in the (500-4000) cm^{-1} spectral range.^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300MHz instrument using DMSO-d^{6} as a solvent and TMS as internal reference. Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type Polygram Silg, and the plates were developed with iodine vapour. The antimicrobial activity was performed in clinical laboratory department, college of pharmacy, Al-Mustansiriyah University.

Synthesis of N-Ethylglycinate-1,8-naphthalimide(1):

(0.005mol, 1g) of 1,8-Naphthalic anhydride was dissolved in (30ml) dimethyl sulfoxide with stirring and heating. (0.006mol, 0.837g) ethyl glycinate hydrochloride after neutralized with dilute solution of sodium bicarbonate was added and the mixture was refluxed until TLC showed no 1,8-naphthalic anhydride remained. This reaction was completed in (16hrs). The mixture was then poured into ice water. The yellow precipitated solid was filtered off and recrystallized from ethanol [20].

Synthesis of N-acetohydrizde-1,8-naphthalimide (2):

To a solution of *N*-ethylglycinate-1,8-naphthalimide (1) (0.0035mol, 1g) in ethanol (15ml), hydrazine hydrate (99%) (10ml) was added and the reaction mixture was heated under reflux for (4 hrs). After cooling, the product was filtered off and recrystallized by using ethanol [21].

Synthesis of N-acetamido-[1-imino (substituted phenyl)]-1,8-naphthalimide(3-7):

To a suspension of compound (2) (0.0038 mol, 1g) in ethanol and dioxane mixture (2:1), substituted aromatic aldehydes (0.0038mol) and 4-5 drops glacial acetic acid were added. The reaction mixture was heated under reflux about (12-15hrs). After completion of reaction, the reaction mixture was allowed to cool and poured over crushed ice. The precipitated solid thus obtained was filtered, washed with ice-cold water and recrystallized from ethanol [22].

Synthesis of N-acetamido-[4-(substituted phenyl)-3-chloroazetidine-2-one-1-yl]-1,8-naphthalimide (8-12):

A solution of compounds (3-7) (0.003mol) in dioxane (10ml) was added to a well-stirred mixture of monochloroacetyl chloride (0.006mol, 0.46ml) and triethyl amine (0.006mol, 0.83ml) in dioxane (5ml) at 0-5^{o}C. The mixture was refluxed for (10-15 hrs) and kept for 2 days at room temperature. The reaction mixture was then poured into crushed ice, filtered and washed with water. The solid product was dried and recrystallized from ethanol and water [23].

Synthesis of N-acetamido-[2-(substituted phenyl) thiazolidin-4-one-3-yl]-1,8-naphthalimide. (13-17):

A mixture of Schiff-bases (3-7) (0.003mol) in tetrahydrofuran (15ml) and mercaptoacetic acid (0.003mol, 0.2ml) with a pinch of anhydrous zinc chloride was refluxed on water bath about (14-16 hrs). The separated solid was filtered, dried and crystallized from ethyl acetate to yield products [24].

Synthesis of N-acetamido-[5-(Substituted phenyl) tetrazol-1-yl]-1,8-naphthalimide (18-22):

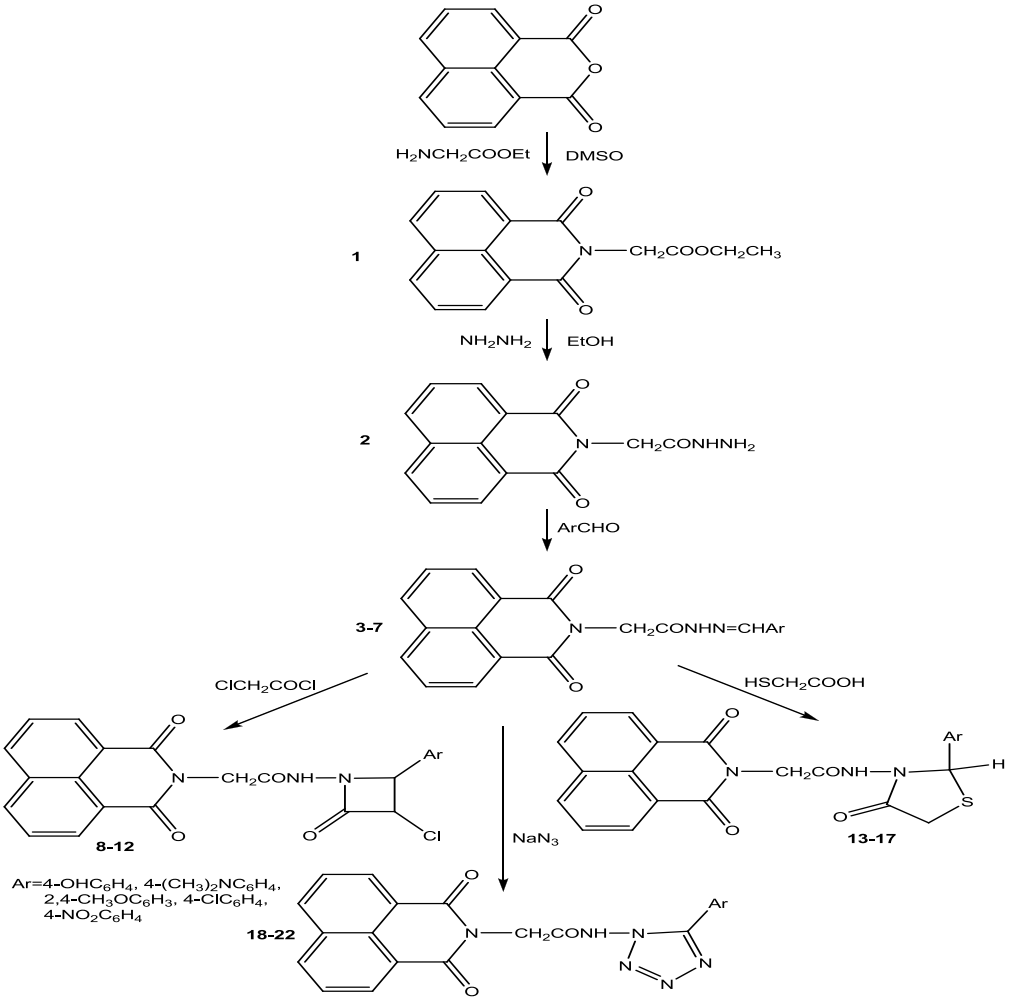
To a stirring solution of Schiff-bases (3-7) (0.003mol) in (10ml) of tetrahydrofuran, sodium azide (0.003 mol, 0.195g) in 10 ml of tetrahydrofuran was added. The mixture was refluxed for (10-14hrs), The end of reaction was checked by TLC which showed the disappearance of the starting materials. Then cooled the mixture at room temperature and the precipitate was filtered, washed with cold water, recrystallized with benzene-petroleum spirit (1:1) [25].

Antimicrobial Activity test

The tested compounds (8-22) were prepared with different concentrations (100, 50, and 25) mg/ml using dimethyl sulfoxide (DMSO) as solvent. The agar well diffusion method was used to determine antimicrobial activity [26]. The culture medium was inoculated with one of tested bacteria or fungi suspended in nutrient broth. Six millimeter diameter wells punched into the agar with fresh bacteria or fungi separately and filled with 100µl of each concentration. DMSO was used as control. The incubation was carried out at 37^{o}C for 4hr. Sulfamethxazole was used as a standard drug. Solvent and growth controls were kept and zones of inhibition were noted. The antibacterial activity was evaluated by measuring the inhibition zone diameter observed.

3. Result and Discussion

The synthetic sequences for preparation of series of new 1,8-naphthalimides , azetidine-2-one, thiazolidine-4-one, 1,2,3,4-tetrazole show in Scheme(1).



Scheme 1

Naphthalic anhydride reacts with amines such as liquid ammonia or alkyl amines to form the corresponding naphthalimides. Therefore, 1,8-naphthalic anhydride have been used as conventional starting material for preparation of 1,8-naphthalimides. Compound (1) which was synthesized by condensation of 1,8- naphthalic anhydride was reacted with ethyl glycinate in dimethyl sulfoxide media under reflux condition, and the end point of the reaction was examined by thin layer chromatography(TLC). TLC showed the imidation of 1,8-naphthalic anhydride with ethyl glycinate completed after 16 hours. The time required for completion of the imidation reaction for 1,8-naphthalic anhydride with ethyl glycinate is more than for the imidation of 1,8-naphthalic anhydride with alkyl amines. This can be attributed to the alkyl amines being more active than the ethyl glycinates in the nucleophilic displacement reaction in which the attacking group is amine. Imidation process of 1,8-naphthalic anhydride with ethyl glycinate as show in scheme (1). Compound (1) was afforded in good yield (76%), having melting point (250-252) ^{o}C. Hydroxamic acid gave (+ve) test indicating the presence of ester. Physical properties of compound (1) are listed in Table.1. FTIR spectrum showed clear absorption bands at (1774) cm^{-1}, due to υ(C=O) ester, (1701,1668) cm^{-1} due to υ(C=O) imide. Other absorption bands appeared at (1581) cm^{-1}, (1357) cm^{-1}, and (1211) cm^{-1} due to υ(C=C) aromatic, υ(C–N) imide and υ(C–O–C) ester respectively.

^{1}HNMR spectrum of compound (1) showed triplet signal at δ= (1.19-1.27) ppm due to (CH_3) protons, singlet signal at δ= (4.08) ppm belong to (N–$\underline{CH_2}$–CO–) protons, quartate signal at δ= (4.50-4.58) ppm due to (–O–$\underline{CH_2}$–) protons, and signals at δ= (7.04-7.75) ppm due to aromatic protons, Figure-1.

^{13}CNMR spectrum of compound (1) showed results were listed in Table.6, Figure-2.

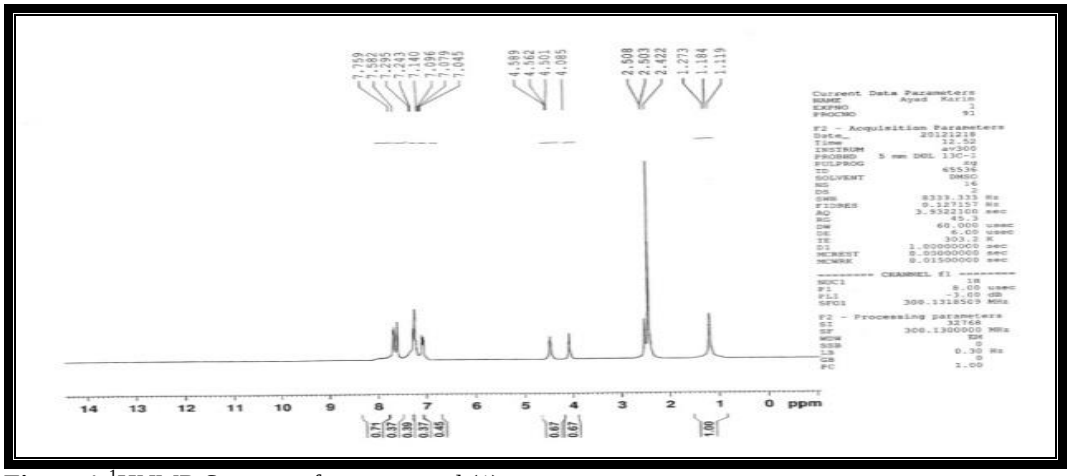


Figure 1-^{1}HNMR Spectrum for compound (1)

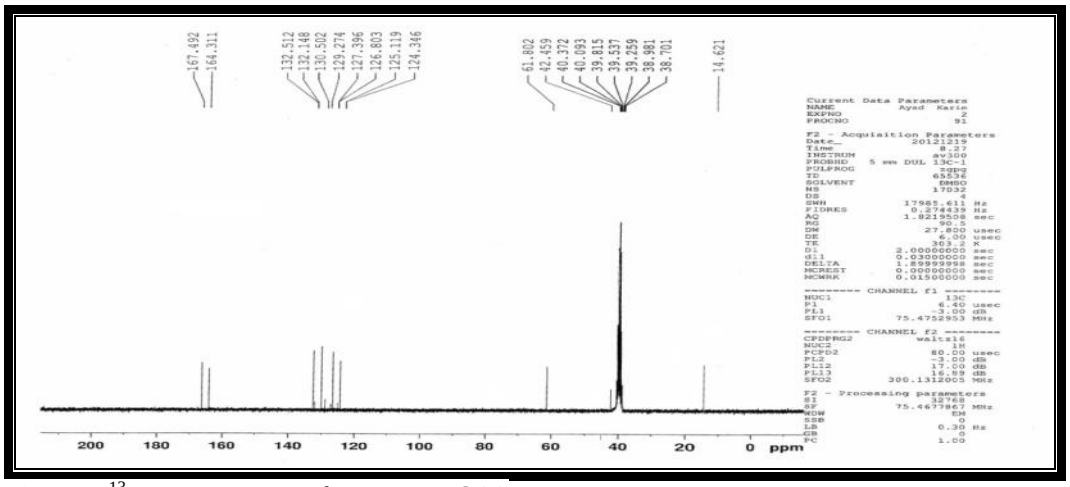


Figure 2-^{13}CNMR Spectrum for compound (1)

Compound (2) was prepared via treatment of prepared ester [1] with hydrazine hydrate in absolute ethanol. The reaction represents nucleophilic substitution reaction and its mechanism involved nucleophilic attack of amino group in hydrazine on carbonyl group in ester followed by elimination of ethanol molecule.

Compound (2) was obtained in (81%) yield having melting point (112-114)^{o} C. Hydroxamic acid gave (-ve) test indicating the absence of any traces from pervious ester.

FTIR spectrum of compound (2) showed disappearance of absorptions due to υ(C=O) and υ(C-O-C) ester at (1774) cm^{-1} and (1211) cm^{-1} and appearance of asym. υ (NH_2) absorption bands at (3321) cm^{-1}, and sym. υ (NH_2) at (3240) cm^{-1}, proving success of hydrazide formation .The spectra showed other bands at (1747) cm^{-1} (1705) cm^{-1},(1647) cm^{-1},(1585) cm^{-1} and,(1384) cm^{-1} due to υ(C=O) amide, υ(C=O) imide, υ(C=O) imide, υ(C=C) aromatic and υ(C-N) imide respectively .

^{1}HNMR spectrum of compound (2) showed signal at δ=(2.09) ppm due to (NH_2) protons, singlet signal at δ=(4.22) ppm due to (N–$\underline{CH_2}$–CO–) protons, signals at δ=(7.31-7.87) ppm due to aromatic protons and signal at δ=(8.44) ppm belong to (NH) protons, Figure-3.

^{13}CNMR spectrum of compound (2) showed results; were listed in Table.6, Figure-4.

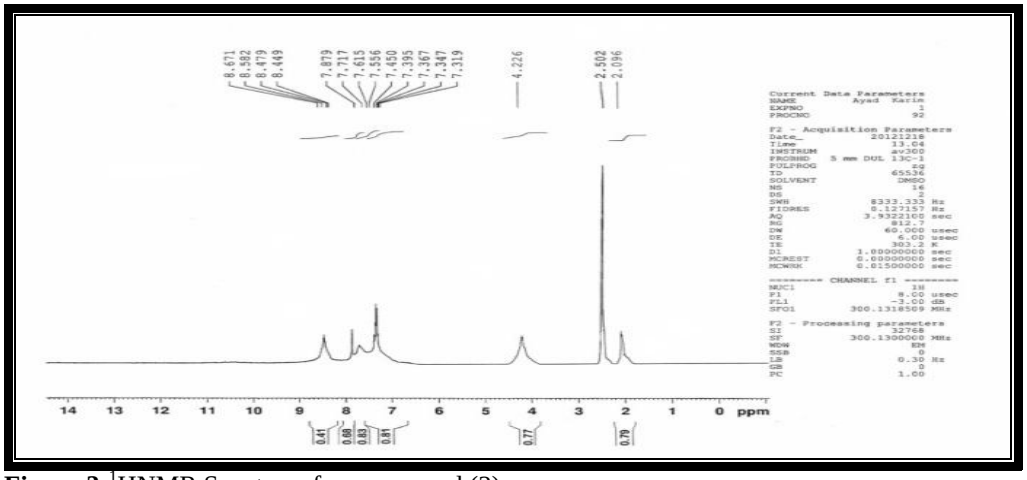


Figure 3-^{1}HNMR Spectrum for compound (2)

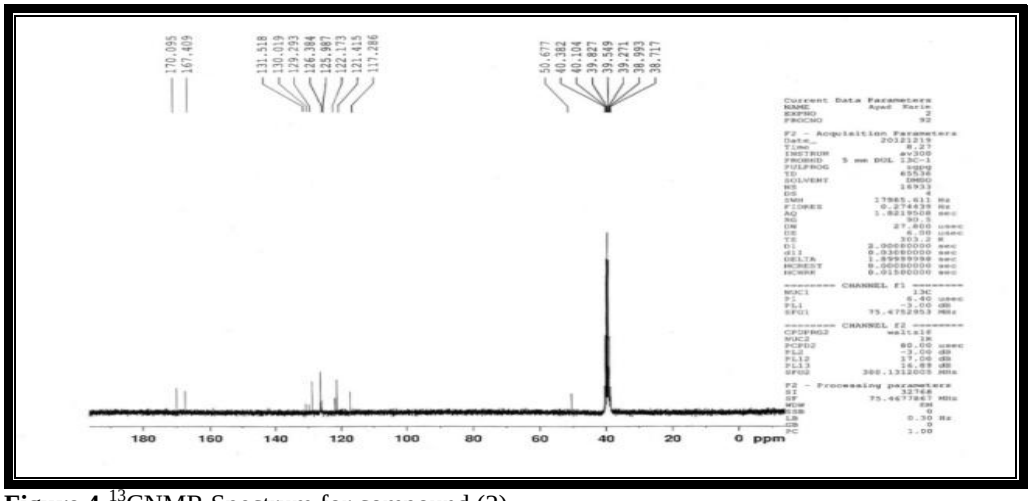
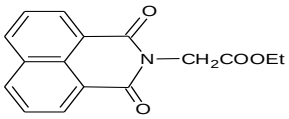
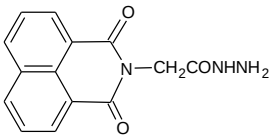
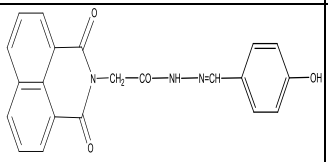
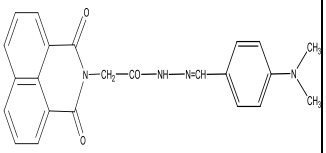
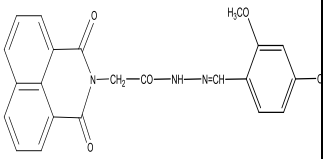
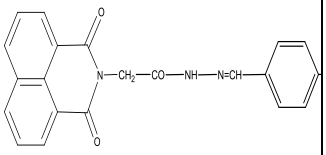
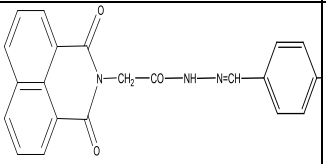


Figure 4-^{13}CNMR Spectrum for compound (2)

Synthesized hydrazide (2) treated with different substituted aromatic aldehydes resulted in the formation of Schiff's bases (3-7) according to the representative scheme (1). The yields of all the synthesized compounds were found to be in the range of 60-73%. Physical properties of compounds (3-7) are listed in Table.1. FTIR spectrum of compounds (3-7) showed

disappearance of absorptions bands due to $\upsilon(NH_2)$ at (3321,3240)cm^{-1} and appearance of υ(NH) absorption bands at (3468-3198) cm^{-1}.
The spectra shows other bands at(1732-1751) cm^{-1},(1701-1705)cm^{-1},(1662-1670) cm^{-1}, (1598-1604) cm^{-1}, (1512-1550) cm^{-1} and,(1334-1384) cm^{-1} due to υ(C=O) amide, υ(C=O) imide, υ(C=O) imide, υ(C=N) imine, υ(C=C) aromatic and υ(C-N) imide respectively .
^{1}HNMR spectral data of compounds (3 and 4) shows results listed in Table.5 and ^{13}CNMR spectral data of compounds (3 and 4) shows results listed in Table.6.

Table 1-Physical properties and FTIR spectral data of compounds (1-7)

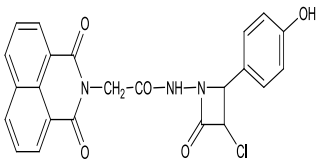
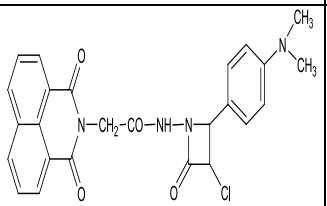
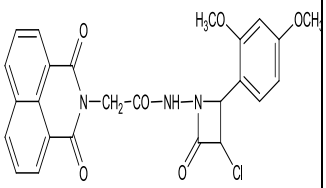
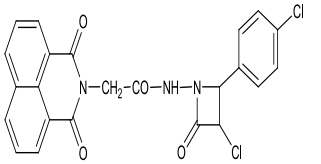
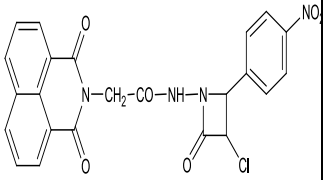
Physical properties					Major FTIR Absorption cm^{-1}				
Comp. No.	**Compound structure**	**Color**	**Yield %**	**Melting Point °C**	**ν (NH)**	**ν (C=O) amide**	**ν (C=O) imide**	**ν (C-N) imide**	**Others**
1		Yellow-green	76	250-252	-	-	1701 1668	1357	ν (C=O) ester1774, ν (C-O-C) ester 1211
2		White	81	112-114	Overlap with ν (NH_2)	1747	1705 1647	1384	ν (NH_2) Asym. 3321, sym. 3240
3		White	71	260-262	3266	1742	1701 1670	1384	υ(C=N) imine1598 ,ν (O-H) 3195
4		Off white	60	244-246	3284	1748	1701 1662	1369	υ(C=N) imine1598
5		Brown	73	288-290	3298	1751	1701 1670	1334	υ(C=N) imine 1600 ν(C-O-C) 1265,1172
6		Light brown	65	305-307	3198	1732	1701	1350	υ(C=N) imine 1600 ν (C-Cl) 879
7		Light yellow	70	244-246	3468	1748	1708	1350	υ(C=N) imine 1604 ν (NO_2) 1453, 1315

The cyclization of the prepared Schiff bases (3-7) were performed using three methods with different reagents. The first method includes treatment with chloro acetyl chloride followed by the addition of triethyl amine as catalyst. The synthetic route leaded to compounds (8-12) as show in scheme (1).

Physical properties of compounds (8-12) are listed in Table.2. FTIR spectra of compounds (8-12) showed disappearance of absorption bands at (1598-1604) cm^{-1} due to υ(C=N) imine. Also all spectra showed clear absorption bands at (1738-1753) cm^{-1}, (1701-1703) cm^{-1}, (1635-1662) cm^{-1}, (1549-1591) cm^{-1} and,(1311-1354) cm^{-1} due to υ(C=O) amide, υ(C=O) imide, υ(C=O) imide, υ(C=C) aromatic and υ(C-N) imide respectively.

^{1}HNMR spectral data of compounds (8 and 9) shows results listed in Table.5 and ^{13}CNMR spectral data of compounds (8 and 9) shows results listed in Table 6.

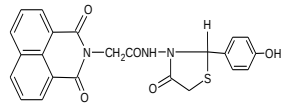
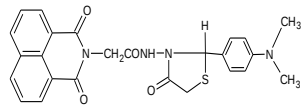
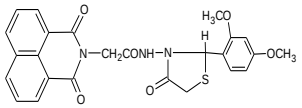
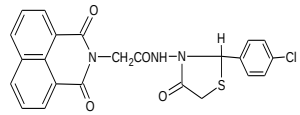
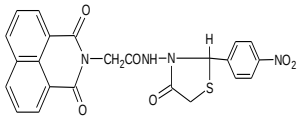
Table 2-Physical properties and FTIR spectral data of compounds (8-12)

Physical properties					Major FTIR Absorption cm^{-1}				
Comp. No.	**Compound structure**	**Color**	**Yield %**	**Melting Point ºC**	**ν (N-H)**	**ν (C=O) amide**	**ν (C=O) imide**	**ν (C-N) imide**	**Others**
8		Light brown	55	105-107	3292	1752	1701 1635	1311	ν (C-Cl) 840, ν (O-H) 3203
9		Brown	68	140-142	3267	1748	1703 1652	1354	ν (C-Cl) 833
10		White	64	121dec.	3352	1753	1701 1624	1330	ν (C-Cl) 844 ν (C-O-C) 1230;1149
11		Off white	65	130-132	3334	1738	1701 1658	1350	ν (C-Cl) 806
12		Pale yellow	72	155-157	3200	1749	1701 1662	1354	ν (C-Cl) 808 ν (NO_2) 1501,1327

The second cyclization method of Schiff bases (3-7) was done with mercaptoacetic acid in dry benzene to give thiazolidinone derivatives (13-17). The sequence of synthesis these compounds show in scheme (1). Physical properties of compounds (13-17) are listed in Table.3. FTIR spectrum of compounds (13-17) shows disappearance of absorption bands at

(1598-1604) cm^{-1} due to υ(C=N) imine. Also all spectra showed clear absorption bands at (1751-1762) cm^{-1}, (1712) cm^{-1}, (1643-1670) cm^{-1}, (1520-1593) cm^{-1} and, (1311-1354) cm^{-1} due to υ(C=O) amide, υ(C=O) imide, υ(C=O) imide, υ(C=C) aromatic and υ(C-N) imide respectively. ^{1}HNMR spectral data of compounds (13 and 14) shows results listed in Table.5 and ^{13}CNMR spectral data of compounds (13 and 14) shows results listed in Table 6

Table 3-Physical properties and FTIR spectral data of compounds (13-17)

Physical properties					Major FTIR Absorption cm^{-1}				
Comp. No.	**Compound structure**	**Color**	**Yield %**	**Melting Point °C**	**ν (N-H)**	**ν (C=O) amide**	**ν (C=O) imide**	**ν (C-N) imide**	**Others**
13		Deep brown	73	152-154	3421	1759	1712 1643	1312	ν (C-S) 667, ν (O-H) 3240
14		White	63	169-171	3412	1758	1712 1668	1342	ν (C-S) 624
15		Off white	80	142-144	3414	1762	1712 1670	1344	ν (C-S) 678. ν (C-O-C) 1261,1195
16		Off white	71	146-148	3417	1751	1712 1644	1350	ν (C-S) 609, ν (C-Cl) 822
17		Deep yellow	61	170-172	3417	1750	1712 1647	1323	ν (C-S) 659, ν (NO_2) 1500,1384

The third cyclization method of Schiff bases (3-7), with sodium azide, to give titled tetrazole derivatives (18-22) according to scheme (1).

The mechanism of the reaction systematically investigated as [3+2] cyclo additions which christened as a 1,3 -dipolar cyclo additions. It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results five membered rings [17].

Physical properties of compounds (18-22) are listed in Table.4

FTIR spectra of compounds (18-22) showed bands at (1543-1500) cm^{-1} were due to the cyclic (N=N) stretching of tetrazole ring. It also , the FTIR for these compounds appear the other absorptions bands at (1746-1756) cm^{-1},(1701-1708) cm^{-1}, (1631-1670) cm^{-1}, (1600-1616) cm^{-1}, (1539-1589) cm^{-1} and,(1342-1396) cm^{-1} due to υ(C=O) amide, υ(C=O) imide, υ(C=O) imide, υ(C=N) stretching of tetrazole ring, υ(C=C) aromatic and υ(C-N) imide respectively.

The ^{1}HNMR spectral data of compounds (18 and 19) shows results listed in Table.5 and ^{13}CNMR spectral data of compounds (18 and 19) shows result listed in Table.6

Table 4-Physical properties and FTIR spectral data cm^{-1} of compounds (18-22)

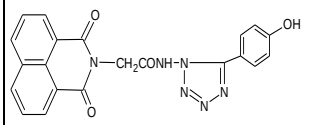
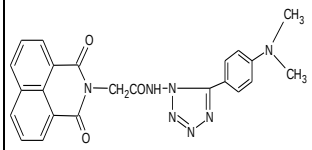
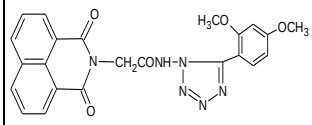
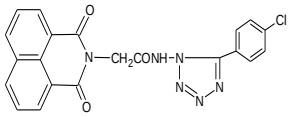
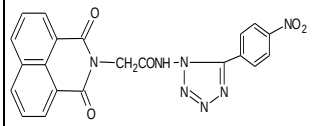
Physical properties					Major FTIR Absorption cm^{-1}				
Comp No.	**Compound structure**	**Color**	**Yield %**	**Melting Point °C**	**ν (N-H)**	**ν (C=O) amide**	**ν (C=O) imide**	**ν (C-N) imide**	**Others**
18		Off white	72	203-205	3414	1751	1705 1643	1396	ν (C=N) Cyclic1600, ν (N=N) 1539, ν (OH) 3236
19		milky	66	252-254	3394	1746	1705 1631	1350	ν (C=N) Cyclic 1603, ν (N=N) 1516
20		Light brown	83	293-295	3460	1756	1703 1670	1342	ν (C=N) Cyclic 1616, ν (N=N) 1512, ν (C-O-C) 1211,1165
21		Brown	78	261-263	3414	1754	1705 1647	1346	ν (C=N) Cyclic 1600, ν (N=N) 1500, ν (C-Cl) 813
22		green	75	277-279	3470	1756	1708 1643	1392	ν (C=N) Cyclic1610, ν (N=N) 1543, ν (NO_2) 1500,1458

Table 5-[1]HNMR spectral data (ppm) for selected compounds

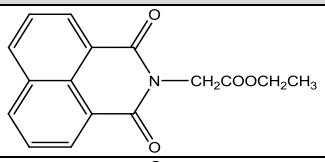
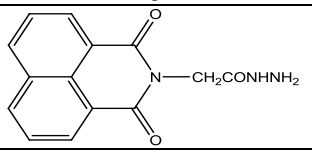
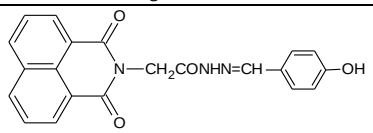
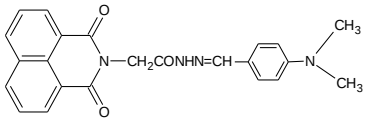
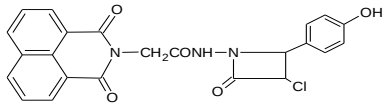
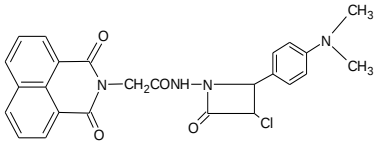
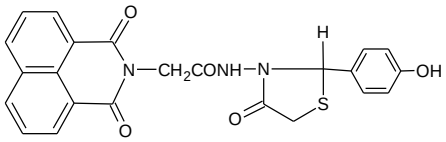
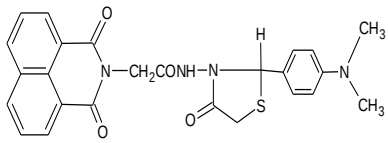
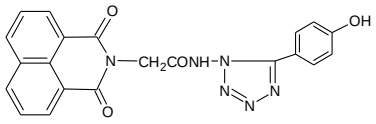
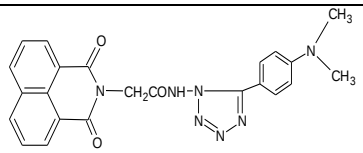
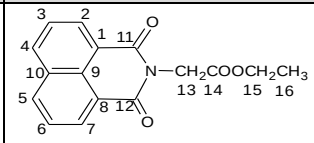
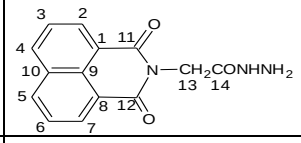
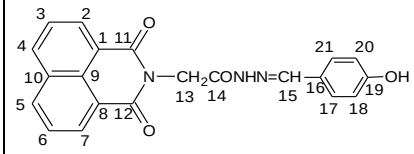
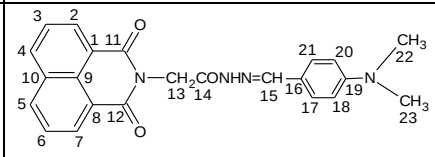
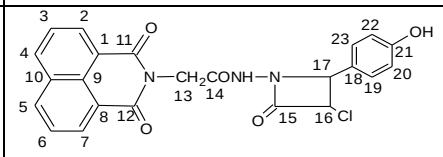
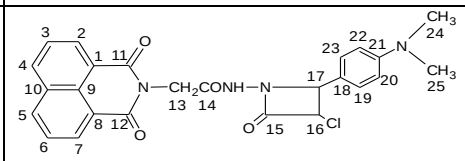
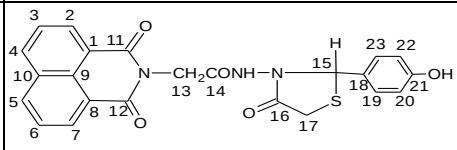
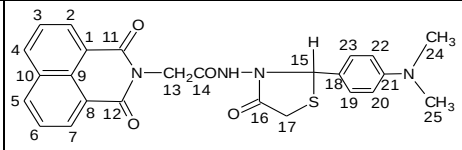
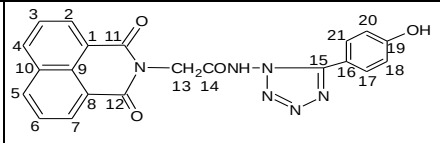
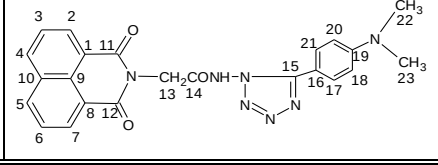
Comp. No.	Compound structure	[1]HNMR spectral data (ppm)
1		δ= 1.27 CH_3protons, δ= 4.08 (N–$\underline{CH_2}$–CO–) protons, δ= 4.50 (–O–$\underline{CH_2}$–) protons, δ= (7.04-7.75) aromatic ring protons.
2		δ= 2.09 NH_2 protons, δ= 4.22 (N–$\underline{CH_2}$–CO–) protons, δ= (7.31-7.87) aromatic ring protons, δ= 8.44 NH protons.
3		δ= 4.41 (N–$\underline{CH_2}$–CO–) protons, δ= 5.33 OH protons, δ= (6.49-7.66) aromatic ring protons, δ= 8.03 NH proton, δ= 8.60(N=CH) proton.
4		δ= 3.30 CH_3 protons, δ= 4.16 (N–$\underline{CH_2}$–CO–) protons, δ= (6.54-7.03) aromatic ring protons, δ= 8.28 NH proton, δ= 8.52(N=CH) proton.
8		δ= 4.16 (N–$\underline{CH_2}$–CO–) protons, δ=4.81 CH azetidine ring proton C_4,δ= 5.20 OH proton, δ= 5.51 CH azetidine ring proton C_3, δ= (6.46-7.87) aromatic ring protons, δ= 8.23 NH proton.
9		δ= 3.29 CH_3 protons, δ=4.14 (N–$\underline{CH_2}$–CO–) protons, δ=4.82 CH azetidine ring proton C_4, δ= 5.37 CH azetidine ring proton C_3, δ= (6.53-7.92) aromatic ring protons, δ= 8.20 NH proton.
13		δ= 3.28 CH thiazolidine ring proton C_2, δ= 3.52 CH_2 thiazolidine ring protons C_5, δ= 4.18 (N–$\underline{CH_2}$–CO–) protons, δ= 5.01 OH proton, δ= (6.91-7.98) aromatic ring protons, δ= 8.22 NH proton.
14		δ= 3.17 CH_3 protons, δ= 3.39 CH thiazolidine ring proton C_2, δ= 3.88 CH_2 thiazolidine ring protons C_5, δ= 4.14 (N–$\underline{CH_2}$–CO–) protons, δ= (6.92-7.91) aromatic ring protons, δ= 8.02 NH proton.
18		δ= 4.50 (N–$\underline{CH_2}$–CO–) protons, δ= 5.32 OH proton, δ= (6.86-7.96) aromatic ring protons, δ= 8.05 NH proton.
19		δ= 3.34 CH_3 protons, δ= 4.02 (N–$\underline{CH_2}$–CO–) protons, δ= (7.22-7.89) aromatic ring protons, δ= 8.09 NH proton.

Table 6-^{13}CNMR spectral data (ppm) for selected compounds

Comp. No.	Compound structure	^{13}CNMR spectral data (ppm)
1		δ=14.62(C_{16}), δ=42.45(C_{15}), δ=61.6 (C_{13}), δ=124.34-132.51(C_1-C_{10}), δ=164.31(C_{11}, C_{12}), δ=167.49(C_{14}).
2		δ=50.67(C_{13}), δ=117.28-131.51(C_1-C_{10}), δ=167.40 (C_{11}, C_{12}), δ= 170.09 (C_{14}).
3		δ=52.54 (C_{13}), δ=112.87-132.86 (C_1-C_{10},C_{16},C_{17},C_{18},$C_{20,}C_{21}$), δ=146.65 (C_{15}), δ=163.22 (C_{19}), δ=164.71 (C_{11}, C_{12}), δ=171.94 (C_{14}).
4		δ=41.62 (C_{22},C_{23}), δ=51.26 (C_{13}), δ=115.12-135.85 (C_1-C_{10},C_{16},C_{17},C_{18},$C_{20,}C_{21}$), δ=145.37(C_{15}), δ=156.80 (C_{19}), δ=161.79 (C_{11}, C_{12}), δ=170.30(C_{14}) .
8		δ=51.10 (C_{13}), δ=61.57 (C_{16}), δ=66.72 (C_{17}), δ=118.72-135.40(C_1-C_{10},C_{18},C_{19},C_{20},C_{22},C_{23}), δ=156.02 (C_{21}), δ=160.95 ($C_{11,}C_{12}$), δ=163.53 (C_{15}), δ=171.46 (C_{14}).
9		δ=45.62 (C_{24},C_{25}), δ=49.09 (C_{13}), δ=61.57 (C_{16}), δ= 66.53(C_{17}), δ= 117.10-135.41 (C_1-C_{10},C_{18},C_{19},C_{20},C_{22},C_{23}), δ=152.86 (C_{21}), δ=160.19 ($C_{11,}C_{12}$), δ=163.54 (C_{15}), δ=168.45 (C_{14}).
13		δ=50.25 (C_{13}), δ=61.56 (C_{15}), δ=63.35 (C_{17}), δ= 116.24-135.23 (C_1-C_{10},C_{18},C_{19},C_{20},C_{22},C_{23}), δ=156.37 (C_{21}), δ=163.52 ($C_{11,}C_{12}$), δ=168.43 (C_{16}), δ=171.28 (C_{14}).
14		δ=41.13 (C_{24},C_{25}), δ=51.71 (C_{13}), δ=61.07 (C_{15}), δ=62.15 (C_{17}), δ=118.43-135.34 (C_1-C_{10},C_{18},C_{19},C_{20},C_{22},C_{23}), δ=152.61 (C_{21}), δ=163.01 ($C_{11,}C_{12}$), δ=167.94 (C_{16}), δ=170.61 (C_{14}).
18		δ=51.27 (C_{13}), δ=117.22-133.78 (C_1-C_{10},C_{16},C_{17}, C_{18},C_{20},C_{21}), δ=143.24 (C_{15}), δ=154.58 (C_{19}), δ=162.23($C_{11,}C_{12}$), δ=171.30 (C_{14}).
19		δ=42.40 (C_{22},C_{23}), δ=51.92 (C_{13}), δ=119.31-131.04 (C_1-C_{10},C_{16},C_{17}, C_{18},C_{20},C_{21}) , δ=144.27(C_{15}), δ=150.89 (C_{19}), δ=164.51 ($C_{11,}C_{12}$), δ=170.64 (C_{14})

4. Antimicrobial study

Antibacterial activities of some newly synthesized naphthalimides linked to four or five membered heterocyclic rings against four types of pathogenic bacteria and one type of fungi were evaluated and the results are listed in Table.7

Table 7-Antimicrobial activity of compounds (8-22)

	Staphylococcus aureus **Concentrations (mg/ml) Inhibition zone diameter (mm)**			***Bacillus*** **Concentrations (mg/ml) Inhibition zone diameter (mm)**			***E. Coli*** **Concentrations (mg/ml) Inhibition zone diameter (mm)**			***Pseudomonas aeuroginosa*.** **Concentrations (mg/ml) Inhibition zone diameter (mm)**			***Candida Albicans*** **Concentrations (mg/ml) Inhibition zone diameter (mm)**		
Comp. No.	100	50	25	100	50	25	100	50	25	100	50	25	100	50	25
8	17	14	8	19	14	10	20	19	10	18	14	8	-	-	-
9	21	18	12	18	16	8	21	16	14	16	7	-	24	18	14
10	32	22	10	24	17	12	18	16	12	20	16	11	16	-	-
11	19	17	12	22	19	15	20	19	12	22	18	12	19	8	-
12	35	26	19	36	18	12	32	30	24	28	20	18	21	17	15
13	25	17	10	21	17	9	30	28	22	17	8	-	-	-	-
14	18	16	12	16	15	8	19	15	7	-	-	-	19	12	8
15	21	18	9	20	13	7	21	17	9	16	8	-	16	15	9
16	22	17	14	24	19	11	20	13	9	17	12	7	20	12	7
17	28	18	16	25	16	12	28	22	21	20	13	9	18	7	-
18	20	16	12	21	17	10	24	18	8	-	-	-	-	-	-
19	28	20	18	30	17	11	29	24	22	28	21	14	22	16	12
20	22	19	14	20	18	12	27	20	15	19	16	11	25	24	18
21	25	23	17	21	20	13	26	21	17	26	18	12	21	20	14
22	29	26	20	30	22	18	25	19	16	27	19	16	23	21	16
Sulfamethxazole (std.)	32	28	22	34	26	20	31	24	21	29	20	18	*	*	*
Clotrimazole (std.)	*	*	*	*	*	*	*	*	*	*	*	*	26	24	22

*** = not tested**

- = no inhibition zone

From the data of inhibition zone of all compounds (8-12) in Table.7, observed some important results:

The first result that the compound (12) showed high activity more than Sulfamethxazole (std.) in some cases such as against *Staphylococcus aureus, Bacillus and E.coli.* also compounds

(10,13,17,19,20,21,22) shows high activity against *Staphylococcus aureus*, while only the compounds (12,17,19,22) shows high activity against *Bacillus*. Also compounds (12,13,17,19,20,21,22) shows high activity against *E.coli.*, while only the compounds (12,19,21,22) shows high activity against *Pseudomonas aeuroginosa*. Compounds (9,12,19,20,21,22) against *Candida Albicans*. On the other hand the remaining compounds shows good to moderate activity. Some compounds such as (9,13,15) shows slow activity at concentration (25mg/ml) against *Pseudomonas aeuroginosa.* Others such as compounds (10,11,17) showed slow activity(25mg/ml) against *Candida Albicans*. Compounds (14,18) did not show any antibacterial activity against *Pseudomonas aeuroginosa*. Compounds (8,13,18) did not shows any antifungal activity against *Candida Albicans*.

References

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