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Synthesis, Characterization and Antimicrobial Screening of Some Bioactive 1,8-Naphthalimide Derivatives.

Ayad Kareem Khan* Suaad Mohammed Hussain Mohammed Rifat Ahmad** Fitua Manwar Aziz*** Shimaa Mutasim Abdulah*****

Department of Pharmaceutical Chemistry, College of Pharmacy, Al-Mustansiriyah University.

****Department of Chemistry, College of Science, Baghdad University.***

***** Department of Clinical Laboratory Science, College of Pharmacy, Al-Mustansiriyah University.***

E-mail: kareem_ayad@yahoo.com

Abstract:

This research include developing new heterocyclic derivatives of 1,8-naphthalimides bearing oxazoline, thiazoline, oxadiazole, thiadiazole and aminotriazole moieties as the following steps: *N*-ester-1,8-naphthalimide (1) was obtained by direct imidation of 1,8-naphthalic anhydride with ethylglycinate in dimethylsulfoxide. Compound (1) was treated with hydrazine hydrate in absolute ethanol to give *N*-acetohydrazide-1,8-naphthalimide (2). *N*-Acetophenylsemicarbazide-1,8-naphthalimide (3) and *N*-Aceto phenylthiosemicarbazide-1,8-naphthalimide (7) were synthesized via reaction of compound (2) with phenylisocyanate and phenylisothiocyanate in absolute ethanol respectively.

Cyclization of compounds (3) and (7) with *p*-substituted phenacyl bromide gives the oxazoline derivatives (4-6) and thiazoline derivatives (9-11) respectively. *N*-Methyl-[(5-(phenyl amino)-1,3,4-thiadiazol-2-yl)]-1,8-naphthalimide (8) prepared via treatment of compound (7) with phosphoric acid. Reaction of the prepared hydrazide (2) with carbon disulfide in the presence of potassium hydroxide producing *N*-Methyl-[potassium dithiocarbazate]-1,8-naphthalimide (12). Acidifying of the obtained salt (12) with 4N hydrochloric acid give *N*-Methyl-[1,3,4-oxadiazol-2-yl-5-thiol]-1,8-naphthalimide (13). The obtained salt (12) also treated with hydrazine hydrate to afford the desirable *N*-Methyl-[1,2,4-triazol-3-yl-4-amino-5-thiol]-1,8-naphthalimide (14).

All the prepared compounds in this research were characterized by recording their melting points, FTIR, ^{1}HNMR, ^{13}CNMR spectra, checked by TLC, physical properties and some specific chemical tests also. Some of the new prepared compounds were evaluated for the antimicrobial screening *in vitro* against two types of Gram positive bacteria including (*Staphylococcus aureus, Bacillus subtilis*) and two types of Gram negative bacteria including (*Escherichia coli, Pseudomonas aeuroginosa*).

More, antifungal activities of some prepared compounds performed against the yeast-like pathogenic fungus (*Candida albicans*). The antimicrobial screening carried out in three concentrations of prepared compounds. Sulfamethoxazole/Clotrimazole was used as standard drugs. The results showed that most of the tested compounds have good biological activity against the mentioned organisms compared with standard drugs above.

Keywords: *1,8-Naphthalimides, Oxazoline, Thiazoline, Oxadiazole, Thiadiazole, Aminotriazole, Synthesis, Antimicrobial screening*

تحضير، تشخيص والمسح المضاد للميكروبات لبعض مشتقات 8,1- نفثالئيميدات الفعالة حيوياً

أياد كريم خان*، سعاد محمد حسين، محمد رفعت أحمد**، فتوة منور عزيز***، شيماء معتصم عبدالله*****

*** فرع الكيمياء الصيدلانية، كلية الصيدلة، الجامعة المستنصرية**

****قسم الكيمياء، كلية العلوم، جامعة بغداد**

*****فرع العلوم المختبرية السريرية، كلية الصيدلة، الجامعة المستنصرية**

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الخلاصة :

تضمن هذا البحث تحضير مشتقات حلقية غير متجانسة جديدة لـ 8,1- نفثالئيميدات تحمل معوضات اوكسازولين، ثيازولين، اوكسادايازول، ثيادايازول وامينوترايازول كما في الخطوات الاتية:

N- **لستر**- 8,1- نفثالئيميد (1) تم الحصول عليه من التفاعل المباشر ل 8,1- حامض النفثاليك اللامائي مع كلايسينات الاثيل في ثنائي مثيل سلفوكسيد. **المركب** (1) تم معاملته مع الهيدرازين المائي في الايثانول المطلق لينتج *N* - اسيتوهيدرازايد - 8,1- **نفثالئيميد** (2) . *N* - اسيتوفنيل سيميكاربازايد - 8,1- نفثالئيميد (3) **و** *N* - اسيتوفنيل ثايوسيميكاربازايد - 8,1- نفثالئيميد (7) تم تحضيرها عبر تفاعل المركب (2) مع فنيل ايزوسيانيت وفنيل ايزوثايوسيانيت في الايثانول المطلق على التوالي . **الغلق الحلقي للمركبات** (3) **و** (7) مع بروميد الفيناسيل المعوض في الموقع بارا انتج مشتقات الاوكسازولين (4-6) ومشتقات الثيازولين (9-11) **على التوالي** . *N*- مثيل- [(5- (فنيل امينو) - 4,3,1- ثيادايازول -2- يل)]- 8,1- نفثالئيميد (8) **حضر عبرمعاملة المركب** (7) مع حامض الفسفوريك . تفاعل الهيدرازايد **المحضر** (2) مع ثنائي كبريتيد الكاربون **بوجود** هيدروكسيد البوتاسيوم انتج *N*- مثيل- [ثنائي كبريتيد كاربازيت البوتاسيوم] - 8,1- نفثالئيميد (12) . تحميض الملح الناتج (12) **مع** 4N حامض الهيدروكلوريك انتج *N*- مثيل-4,3,1 - اوكسادايازول -2- يل - 5- ثايول)]- 8,1- **نفثالئيميد** (13) . **الملح الناتج** (12) تم معاملته كذلك مع الهيدرازين المائي لينتج *N*- مثيل- [4,2,1- ترايايازول -3- يل - 4- امينو- 5- ثايول] - 8,1- نفثالئيميد (14).

جميع المركبات المحضرة في هذا البحث شخصت من خلال قياس درجات الانصهار، طيف الاشعة تحت **الحمراء** **الدقيق** ، طيف الرنين النووي المغناطيسي بنوعيه وكذلك دققت المركبات من خلال كروماتوكرافيا الطبقة الرقيقة والخواص الفيزيائية وبعض الكشوفات الكيميائية . بعض المركبات المحضرة الجديدة اختبرت فعالياتها المضادة للمايكروبات خارج جسم الكائن الحي ضد نوعين من البكتريا موجبة الصبغة ونوعين اخرين سالبة الصبغة بالاضافة الى نوع من الخمائر الشبيهة بالفطر المرضي . الكشف المضاد للمايكروبات اجري بثلاث تراكيز للمركبات المحضرة وتم استخدام سلفاميثاكسازول وكلوتريمازول كأدوية قياسية حيث اظهرت النتائج ان معظم المركبات التي تم اختبارها تمتلك فعالية جيدة تجاه الاحياء المجهرية المذكورة مقارنة بالأدوية القياسية اعلاه.

Introduction:

Naphthalimides, one type of cyclic imides [1] are being actively investigated for their spacious potential in pharmaceutical chemistry[2,3]. Naphthalimides contain desirable π-conjugated backbone with double amide moieties. This type of unique structure can easily exert non covalent forces such as π-π stacking, strong hydrophobicity and hydrogen bonds and could easily interact with various active targets in biological system, and exhibit diverse biological activities including anticancer[4], antimicrobial[5], Antitrypanosomal[6] analgesic potency[7]. Naphthalimides are well-known as broad-spectrum activity against a variety of human solid tumor cells[8].

Several derivatives have reached the phases of clinical trials. [9]. The azole moiety is an important structural feature of many biologically active compounds. [10].Various 1,3-oxazole functional group associated biological activities. [11,12]. More thiazole ring system is an important class of compounds in medicinal chemistry [13]. This structure has found applications in drug development.

A number of thiazole derivatives have been reported to possess significant and diverse biological activities [14]. Moreover, 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-aminotriazole and their derivatives have been found to be associated with diverse agricultural, industrial and pharmacological activities[15, 16, 17].

In this connection, design of 1,8-naphthalimide derivatives containing five membered ring substituent, in particular 1,3-oxazole, 1,3-thiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole fragments which could considerably affect biological properties of 1,8-naphthalimide, to develop novel and potent therapeutic agents of synthetic origin, it was decided to synthesize certain these derivatives and evaluate them for their antimicrobial properties.

Materials and Methods:

Chemicals used in this work are supplied from Merck, Sigma-Aldrich, BDH and Fluka companies and are used without further purification. Melting points were recorded using digital Stuart

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Scientific SMP30 melting point apparatus and are uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectro-photometer 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 Silica gel, and the plates were developed with iodine vapour. The antimicrobial activity was performed in clinical laboratory science department, College of Pharmacy, Al-Mustansiriyah University.

Experimental:

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

(1gm, 0.005 mol) of 1,8-Naphthalic anhydride was dissolved in (30 ml) dimethyl sulfoxide with stirring and heating. (0.837g, 0.006 mol,) 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 (16 hrs). The mixture was then poured into ice water. The yellow precipitated solid was filtered off and recrystallized from ethanol. [18]

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

To a solution of *N*-ethylglycinate-1,8-naphthalimide (1) (5 gm, 0.0176 mol) in ethanol (15 ml), hydrazine hydrate (99%) excess (10 ml) 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. [19].

Synthesis of *N*-Acetopheny-lsemicarbazide-1,8-naphthalimide (3):

To a solution of compound (2) (2.69 gm, 0.01 mol) in absolute ethanol (20 ml) phenylisocyanate (1.08 ml, 0.01 mol) was added and refluxed for (8 hrs). The reaction was cooled and the formed solid was filtered off, dried and recrystallized from chloroform-petroleum ether. [20]

Synthesis of *N*-Acetohydrazide[5-(*p*-substituted phenyl)-2-hydroxy-4,5-dihydro-1,3-oxazol-2-yl)]-1,8-naphthalimide (4-6):

A mixture of compound (3) (1 gm, 0.0025 mol) with *p*-substituted phenacylbromide (0.0025 mol) in absolute ethanol (30 ml) was refluxed for (9-12 hrs), cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washes with water, dried and recrystallized from suitable solvents [21].

Synthesis of *N*-A cetophenyl hiosemicar-bazide-1,8-naphthalimide (7):

To a solution of compound (2) (2.69 gm, 0.01 mol) in absolute ethanol (20 ml) phenylisothiocyanate (1.2 ml, 0.01 mol) was added and the reaction occur by the same method described for preparation of compound (3). The precipitate was obtained and chloroform was used for recrystallization.

Synthesis of *N*-Methyl-[(5-(phenyl amino)-1,3,4-thiadiazol-2-yl)]-1,8-naphthal- imide (8):

(1 gm, 0.0026 mol) of compound (7) in (5 ml) of phosphoric acid was refluxed at 120 ^{o}C for (30 min.). The resulted solution was cooled to room temperature, kept overnight and poured into crushed ice. The precipitate was filtered, washed with distilled water, dried and recrystallized from ethanol [22].

Synthesis of *N*-Acetohydrazono-[5-(*p*-substituted phenyl)-4,5-dihydro-1,3-thiazol -2-yl)]-1,8-naphthalimide (9-11):

A mixture of compound (7) (1 gm, 0.0026 mol) with *p*-substituted phenacylbromide (0.0025 mol) in absolute ethanol (30 ml) was prepared by the same method described for synthesis of (4-6). The precipitates were obtained and suitable solvents were used for recrystallization.

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Synthesis of *N*-Methyl-[potassium dithiocarbazate]-1,8-naphthalimide (12):

To a stirred ethanolic solution of KOH (1.68 gm, 0.03 mol) in (20 ml), hydrazide (2) (2.69 gm, 0.01 mol) was added slowly CS_2 (1.8 ml, 0.03 mol) and stirred overnight, dry ether (20 ml) was added and the precipitate was filtered, washed with ether and dried. The salt (12) was obtained in almost quantitative yield and was employed in the next step without further purification. [23].

Synthesis of *N*-Methyl-[1,3,4-oxadiazol-2-yl-5-thiol]-1,8-naphthalimide (13):

(1 gm, 0.0028 mol) of potassium salt [12] was dissolved in (100 ml) cold water then acidified with 4N hydrochloric acid to pH 2-3. The formed precipitate was filtered, dried, and then recrystallized from chloroform [24].

Synthesis of *N*-Methyl-[1,2,4-triazol-3-yl-4-amino-5-thiol]-1,8-naphthalimide (14):

A suspension of potassium salt (12) (1 gm, 0.0028 mol) in excess hydrazine hydrate (7 ml) was refluxed until the evaluation of hydrogen sulphide during reflux the color of the reaction mixture changed and a homogeneous solution resulted. After cooling, the reaction mixture was acidified with 10% HCl to yield a precipitate and ethanol-water was used for recrystallization [25].

Antimicrobial Activity Test:

The test compounds 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. 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 (24-48 hrs). Sulfamethxazole and clotri-mazole was used as a standard drug. Solvent and growth controls were kept and zones of inhibition were noted. The antimicrobial activity was evaluated by measuring the inhibition zone diameter observed are recorded [26].

Result and Discussion:

The research involved application of different synthetic methods in preparation of different new compounds containing different types of hetero rings (oxazoline, thiazoline, oxadiazole, thiadiazole and aminotriazole) linked to 1,8-naphthalimide.

These different syntheses performed in this work were summarized in Scheme (1). Naphthalic anhydride reacts with amines such as liquid ammonia [27] or alkyl amines [28] 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) were synthesized by condensation of the 1,8-naphthalic anhydride with ethyl glycinate. The reaction was carried out 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 at 16 hours. Imidation process of 1,8-naphthalic anhydride with ethyl glycinate show in the Scheme (1). Compound (1) was afforded in good yield (76%), having melting point (250-252 ^{o}C). Hydroxamic acid test give (+ve) for presence of ester [29]. Physical properties of compounds (1) are listed in Table-1, and its FTIR spectrum showed clear absorption bands at (1774) cm^{-1},due to υ(C=O) ester[30], (1701,1668) cm^{-1} due to υ(C=O) imide[31]. 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 Table-2.

^{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,

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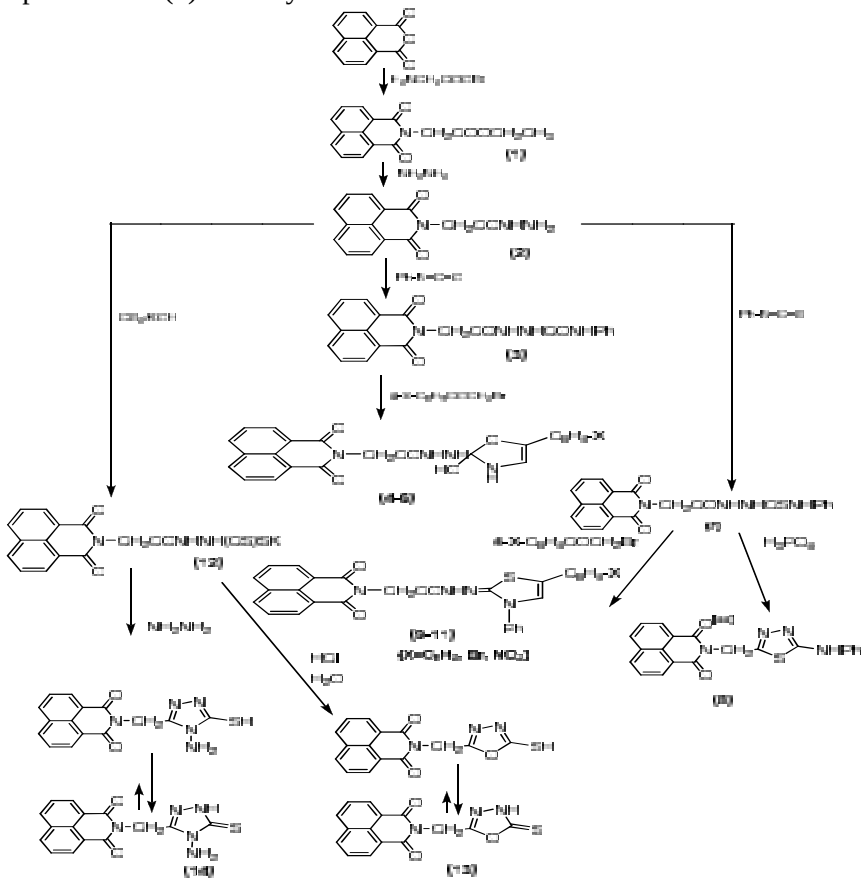
quartate signal at δ = (4.50-4.58) ppm due to (–O–$\underline{CH_2}$–) protons, and signals at δ= (7.04-7.75) ppm due to aromatic protons[32], Table-2, Figure-1.

^{13}CNMR spectrum of compound (1) showed results were listed in Table-3, Figure-2.

Compound (2) was prepared via treatment of prepared ester (1) with hydrazine hydrate in absolute ethanol. This 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.



Scheme (1)

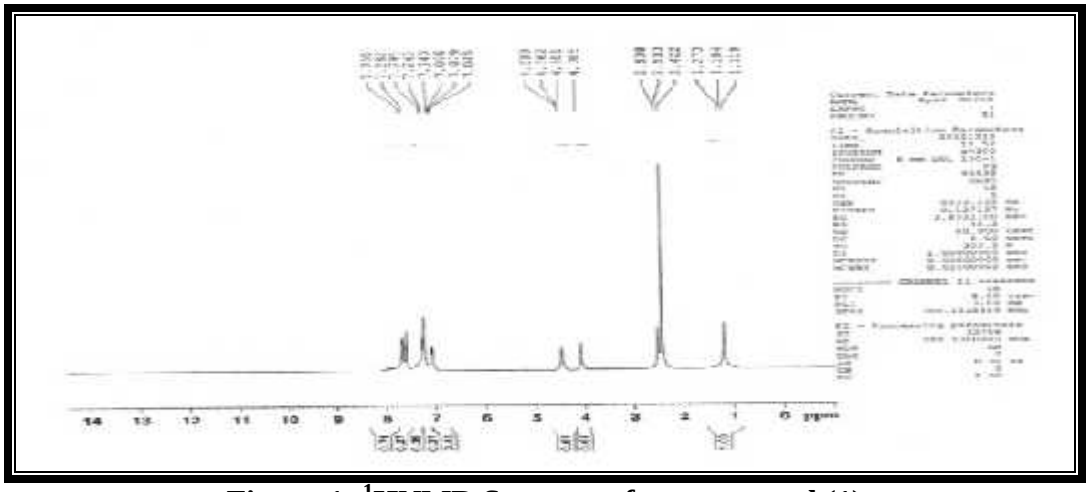


Figure-1: ^{1}HNMR Spectrum for compound (1)

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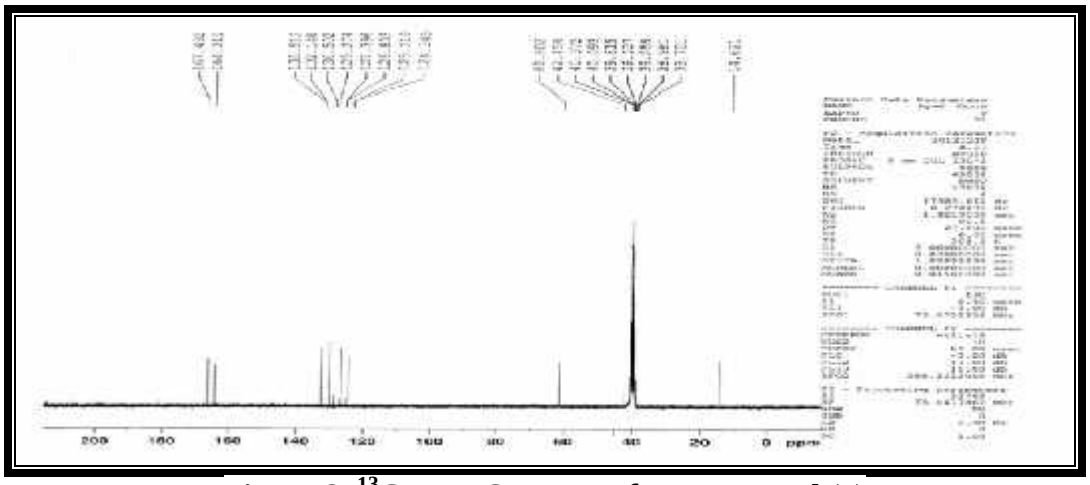

Figure-2: ^{13}CNMR Spectrum for compound (1)

Compound (2) was prepared via treatment of prepared ester (1) with hydrazine hydrate in absolute ethanol. This 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 test give (-ve) for presence 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 υ(NH_2) absorption bands at (3321)cm^{-1} asym., (3240) cm^{-1} sym, proving success of hydrazide formation .The spectrum 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, as shown in Table (3.5) and Figure (3.4). ^{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-3, Figure-4.

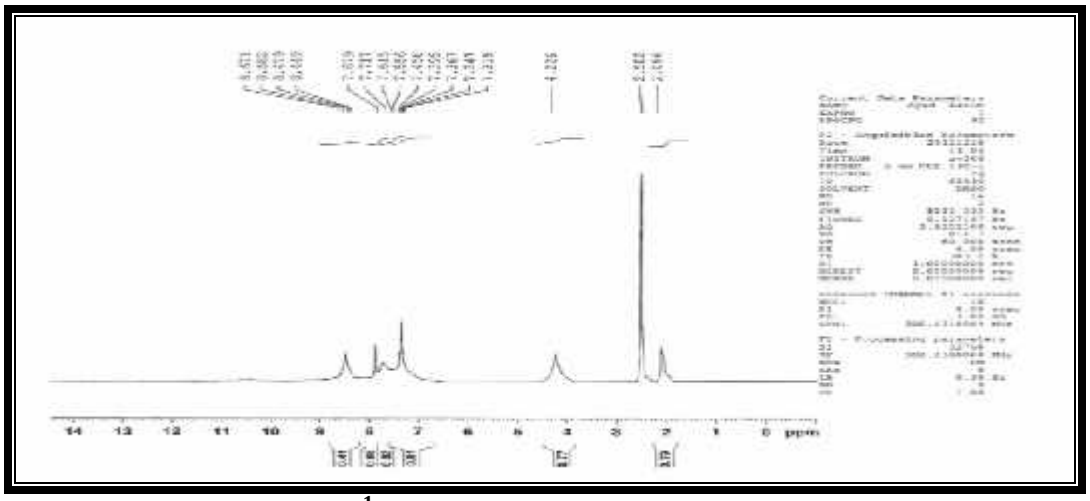

Figure-3: ^{1}HNMR Spectrum for compound (2)

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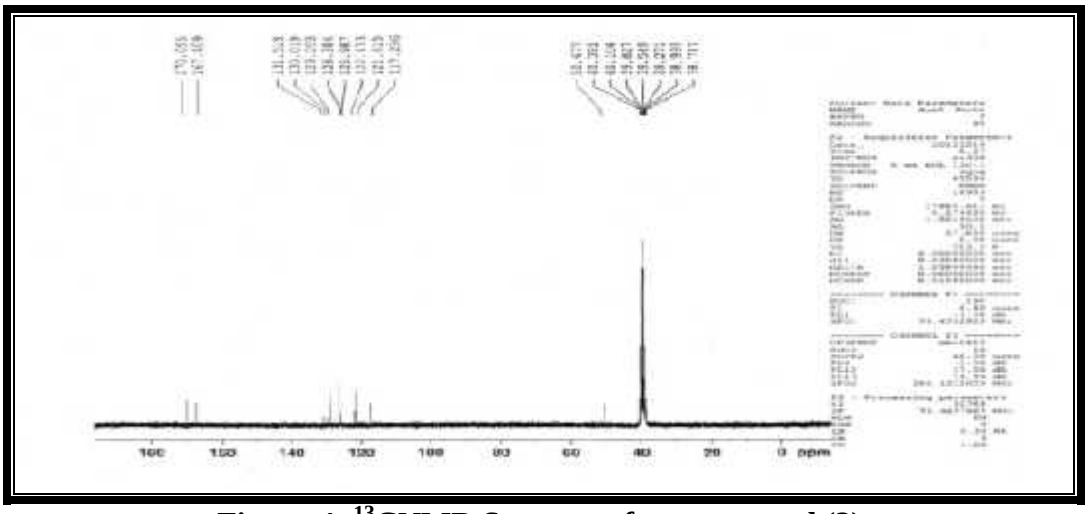

Figure-4: ^{13}CNMR Spectrum for compound (2).

The hydrazide (2) was converted to semicarbazide derivative compound (3) via reaction with phenylisocyanate in absolute ethanol as shown in Scheme (1).

FTIR spectral data showed absorption at (3288 cm^{-1}) for NH , (1742 cm^{-1}) for C=O amide in compound (3) and disappearance of ν (NH_2) at (3321 cm^{-1}) Asym., (3240 cm^{-1}), sym.

Intermolecular cyclization of compound (3) using *p*-substituted phenacylbromide gave oxazoline substituted on acetamido-*N*-naphthalimide compounds (4-6) respectively. Physical properties of these compounds are listed in Table-1. All these compounds were identified from FTIR spectra that show ν (O-H) between the range (3542-3221) cm^{-1}, ν (N-H) between the range (3414-3254) cm^{-1}. FTIR spectral data are listed in Table (1). ^{1}HNMR spectral data of compounds (4) shows signals due to (N–$\underline{CH_2}$–CO–) protons, (OH) proton, oxazole ring proton, aromatic ring protons, and (NH) protons. Results listed in Table-2 and ^{13}CNMR spectral data of compounds (4) shows results listed in Table-3. The hydrazide (2) was converted to thiosemi-carbazide derivative compound (7) by the reaction with phenyliso-thiocyanate in absolute ethanol as shown in Scheme (1). FTIR spectral data showed absorption at (3228 cm^{-1}) NH, (1747 cm^{-1}) C=O amide, and (1230 cm^{-1}) C=S for compound (7) and disappearance of ν (NH_2) at (3321 cm^{-1}) Asym. (3240 cm^{-1}) sym. Treatment of compound (7) with phosphoric acid at 120 ^{o}C affords intramolecular cyclization to give the thiadiazole substituted on -*N*-naphthalimide compound (8). Compound [8] was afforded in good yield (70%) and having melting point (213-215 ^{o}C).

FTIR spectrum of compound (8) showed clear absorption bands at (3247 cm^{-1}) due to υ(N-H), (1600 cm^{-1}) due to υ(C=N), and (678 cm^{-1}) due to υ(C-S) thiadiazole respectively. ^{1}HNMR spectral data of compound (8) shows results listed in Table-2 and ^{13}CNMR spectral data of compounds (8) shows results listed in Table-3. Also the cyclization of compound (7) using *p*-substituted phenacyl bromide gave thiazoline substituted on acetamido-N-naphthalimide compounds (9-11) respectively.Physical properties of these compounds are listed in Table-1. All these compounds were identified from FTIR spectra that show, ν(N-H) between the range (3276-3398) cm^{-1}, and (C=N) between the range (1593-1597) cm^{-1} for compounds (9-11). All details of FTIR spectral data are listed in Table-1.

^{1}HNMR spectral data of compound (10) shows signals due to (N–$\underline{CH_2}$–CO–) protons, thiazole ring proton, aromatic ring protons, and (NH) proton. Results listed in Table-2 and ^{13}CNMR spectral data of compounds (10) shows results listed in Table-3.Compound (2) has been used for the preparation of (12) via reaction of compound (2) with carbon disulfide in presence of potassium hydroxide in

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absolute ethanol.Acidifying of compound (12) with 4N hydrochloric acid give *N*-Methyl-[1,3,4-oxadiazol-2-yl-5-thiol]-1,8-naphtha-limide (13).FTIR spectrum of compound (13) showed clear absorption bands at (1712) cm^{-1} due to υ (C=O) imide, (1597) cm^{-1} due to υ (C=N), (1307) cm^{-1} due to υ (C-N), and (1122) cm^{-1} due to υ (C-O-C) oxadiazole. The appearance of absorption band at (3394) cm^{-1} due to υ (NH) indicates the presence of tautomerism. ^{1}HNMR spectral data of compounds (13) shows results listed in Table-2 and ^{13}CNMR spectral data of compounds (13) shows results listed in Table-3. Also compound (2) has been used for the preparation of *N*-Methyl-[1,2,4-triazol-3-yl-4-amino-5-thiol]-1,8-naphth-alimide(14) by the reaction of hydrazide (2) with CS_2 in ethanolic/KOH to give the dithiocarbazate salt (12) in excellent yield, which was then cyclized by refluxing with 98% hydrazine hydrate to give a moderate yield of triazole derivative (14).FTIR spectrum of compound (14) showed absorptions at (3545) cm^{-1} asym, (3471) cm^{-1} sym. due to υ (NH_2); (1603) cm^{-1} due to υ(C=N); and (1185) cm^{-1} due to υ (C=S). The appearance of absorption band at (3414) cm^{-1} due to υ (NH) indicates the presence of tautomerism. Physical properties of these compounds are listed in Table-1 and all results of FTIR spectra for compounds (12-14) are listed in Table-1.^{1}HNMR spectral data of compounds (14) shows signals due to (NH_2) protons,(N–$\underline{CH_2}$–) protons, aromatic ring protons and (NH) proton.Results listed in Table-2 and ^{13}CNMR spectral data of compounds (14) shows results listed in Table-3.

Antimicrobial Screening:

The antimicrobial activities of some synthesized compounds were determined by the agar diffusion method. Compounds (4-6, 8-11 and 13-14) were evaluated for antimicrobial activity against bacteria, i.e. *(Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeuroginosa),* and antifungal activity against the yeast-like pathogenic fungus, i.e. *(Candida albicans).* The solvent DMSO was used as a negative control and Sulfamethoxazole-Clotri-mazole were used as standard drugs. Calculated average diameters of the zone of inhibition (in mm) for tested samples with that produced by the standard drugs. Results of recorded inhibition zones are summarized in Table (4).

Observed important notification:

1- Some of the synthesized compounds exhibited potent antibacterial and antifungal bioactivity compared with standard drug used. 2- The other tested compounds were found to exhibit a moderate of low antibacterial activity.
3- When different concentrations of the compounds that exhibited a moderate antibacterial activity (8, 9, 11 and 13) were used, this compounds exhibit very good antimicrobial activity at higher concentration, while the different concentrations of compounds (14) exhibited a very good antimicrobial activity.
4- As finally result, the antimicrobial screening of some synthesized compounds showed that many of these compounds have good antimicrobial activities comparable to Sulfamethoxazole and Clotrimazole as reference drugs.

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Table-1: Physical properties and FTIR spectral data cm^{-1} of compounds (1-14).

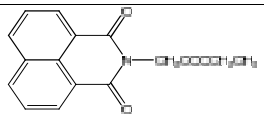
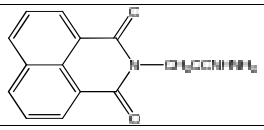
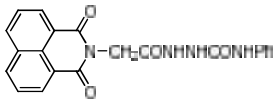
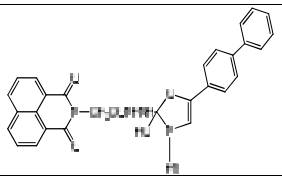
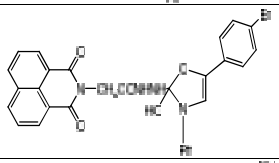
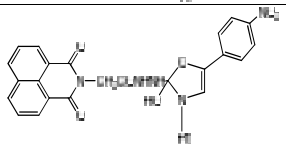
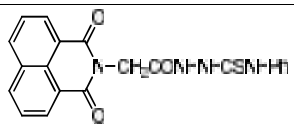
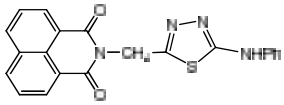
Physical properties					Major FTIR Absorption cm^{-1}				
Comp. No.	**Compound structure**	***Color***	***Yield %***	***Melting Point °C***	**¬ (NH) :**	**¬ (C=O) amide**	**¬ (C=O) imide:**	**¬ (C-N) imide**	**Others**
1		**Yellow-green**	**76**	**250-252**	**-**	**-**	**1701 1668**	**1357**	**: ¬ (C=O) ester 1774, ¬ (C-O-C) ester 1211**
2		**Off white**	**81**	**111-114**	**3414**	**1747**	**1701 1666**	**1384**	**: ¬ (NH_2) Asym.3544, sym.3498**
3		**White**	**80**	**169-172**	**3288**	**1742**	**1708 1668**	**1346**	**-**
4		**Off white**	**70**	**161-163**	**3414**	**1755**	**1701 1666**	**1348**	**¬ (OH) 3542**
5		**Off white**	**74**	**202-204**	**3254**	**1749**	**1705 1666**	**1354**	**: ¬ (OH) 3378, ¬ (C-Br) 613**
6		**Light yellow**	**66**	**177-179**	**3221**	**1742**	**1708 1666**	**1334**	**¬ (OH) 3363, ¬ (NO_2) Asym.1527, sym.1384**
7		**Pale-yellow**	**86**	**176-178**	**3228**	**1747**	**1712 1670**	**1318**	**ν (C=S) 1230**
8		**Brown**	**70**	**213-215**	**3247**	**-**	**1708 1668**	**1334**	**ν (C-S) 678 ν (C=N) 1600**

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Table-1: Continued.

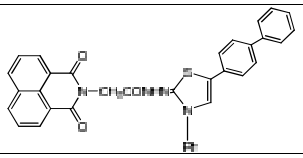
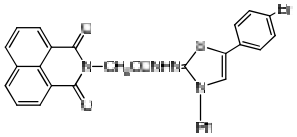
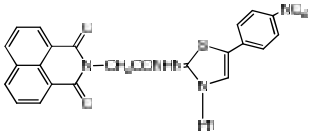
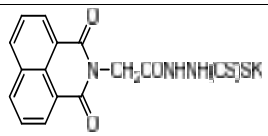
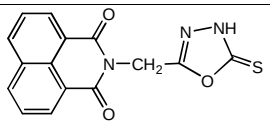
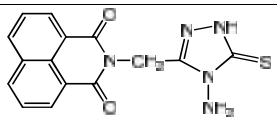
Physical properties					Major FTIR Absorption cm^{-1}				
Comp. No.	**Compound structure**	***Color***	***Yield %***	***Melting Point ^oC***	**¬ (NH) :**	**¬ (C=O) amide**	**¬ (C=O) imide:**	**¬ (C-N) imide**	**Others**
9		**Off white**	**76**	**184-186**	**3267**	**1740**	**1701 1660**	**1318**	**ν (C=N) 1595**
10		**Light brown**	**78**	**232-234**	**3398**	**1748**	**1701 1670**	**1300**	**ν (C=N) 1597, ν (C-Br) 624**
11		**Yellow-green**	**62**	**191-193**	**3291**	**1748**	**1712 1647**	**1303**	**ν (C=N) 1593, ν (NO_2) Asym.1496, Sym. 1381**
12		**White**	**90**	**181-184**	**3218**	**1748**	**1701 1656**	**1303**	**ν (C=S) 1276**
13		**Light brown**	**75**	**263-265**	**3394**	**-**	**1712 1648**	**1307**	**ν (C=N) 1597, ν (C=S) 1180, ν (C-O-C) 1122**
14		**Off white**	**78**	**228-231**	**3414**	**-**	**1703 1664**	**1353**	**ν (NH_2) asym. 3545, sym.3471, ν (C=N) 1603, ν (C=S) 1185**

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Table-2: ^{1}HNMR spectral data (δ ppm) for selected compounds.

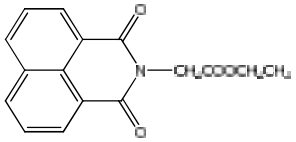
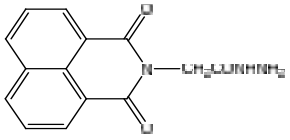
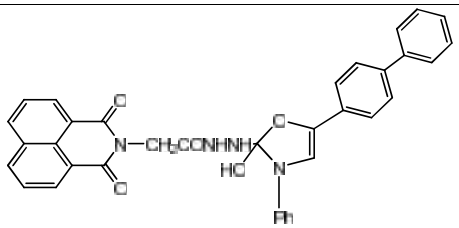
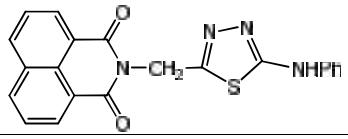
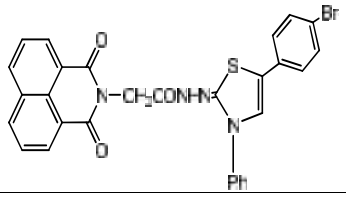
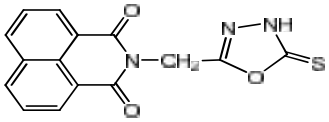
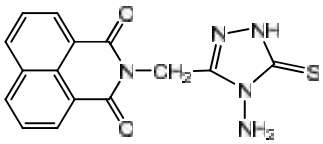
Comp. No.	Compound structure	^{1}HNMR spectral data (δ ppm)
1		1.27 (CH_3) protons, 4.08 (N–$\underline{CH_2}$–CO–) protons, 4.50 (–O–$\underline{CH_2}$–) protons, (7.04-7.75) aromatic ring protons.
2		2.09 (NH_2) protons, 4.22 (N–$\underline{CH_2}$–CO–) protons, (7.31-7.87) aromatic ring protons, 8.44 NH protons.
4		4.59 (N–$\underline{CH_2}$–CO–) protons, 5.42 (OH) proton, 5.73 oxazole ring proton, (6.78-7.80) aromatic ring protons, 8.48 (NH) protons.
8		4.01(N–$\underline{CH_2}$–) protons, (6.82-8.19) aromatic ring protons, 8.49 (NH) proton.
10		4.42(N–$\underline{CH_2}$–CO–) protons, 6.08 thiazole ring proton, (6.62-7.90) aromatic ring protons, 8.20 (NH) proton.
13		4.50 (N–$\underline{CH_2}$–) protons, (7.29-7.95) aromatic ring protons, 8.41(NH) proton.
14		3.04 (NH_2) protons, 3.82 (N–$\underline{CH_2}$–) protons, (7.30-8.09) aromatic ring protons, 8.28 (NH) proton.

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Table-3: ^{13}CNMR spectral data (δ ppm) for selected compounds.

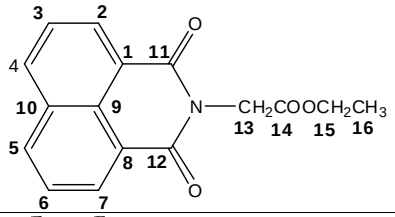
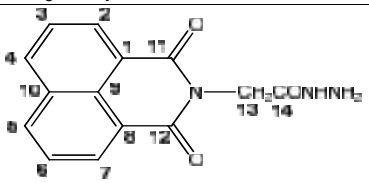
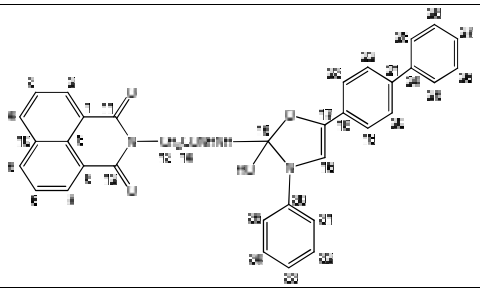
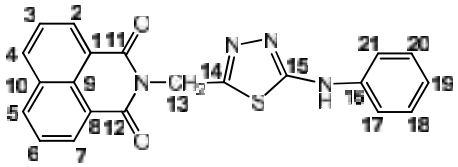
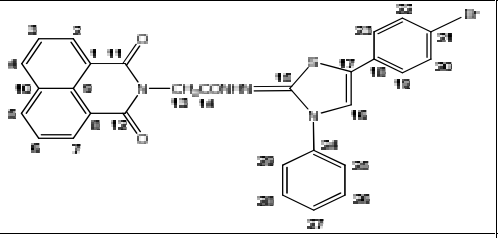
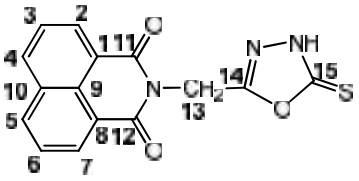
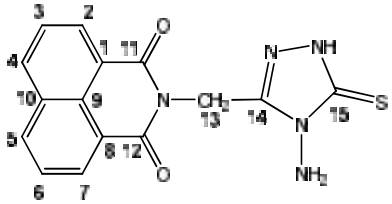
Comp. No.	Compound structure	^{13}CNMR spectral data (δ ppm)
1		14.62 (C_{16}), 42.45 (C_{15}), 61.80 (C_{13}), 124.34 (C_1, C_8), 125.11 (C_2, C_7), 126.80 (C_3, C_6), 127.39 (C_4, C_5), 132.14 (C_9), 132.51 (C_{10}), 164.31 (C_{11}, C_{12}), 167.49 (C_{14}).
2		50.67 (C_{13}), 117.28 (C_1, C_8), 121.41 (C_2, C_7), 122.17 (C_3, C_6) 125.98 (C_4, C_5), 130.01 (C_9), 131.51 (C_{10}), 167.40 (C_{11}, C_{12}), 170.09 (C_{14}).
4		49.82 (C_{13}), 119.22 (C_1, C_8), 120.01 (C_2, C_7), 122.63 (C_3, C_6), 126.41 (C_4, C_5), 129.27 (C_9, C_{10}), 131.35 (C_{18}-C_{35}), 142.33 (C_{16}), 143.67 (C_{17}), 147.42 (C_{15}), 160.24 (C_{11}, C_{12}), 169.51 (C_{14}).
8		48.72 (C_{13}), 118.60 (C_1, C_8), 121.14 (C_2, C_7), 124.02 (C_3, C_6), 125.54 (C_4, C_5), 126.34 (C_9, C_{10}), 132.52 (C_{17}-C_{21}), 142.62 (C_{16}), 146.37 (C_{15}), 150.01 (C_{14}), 161.57 (C_{11}, C_{12}).
10		50.02 (C_{13}), 120.62 (C_1, C_8), 124.84 (C_2, C_7), 125.95 (C_3, C_6), 127.41 (C_4, C_5), 130.81 (C_9, C_{10}), 134.09 (C_{18}-C_{29}), 141.36 (C_{16}), 142.44 (C_{17}), 148.73 (C_{15}), 160.71 (C_{11}, C_{12}), 169.83 (C_{14}).
13		46.02 (C_{13}), 118.17 (C_1, C_8), 119.39 (C_2, C_7), 126.66 (C_3, C_6), 128.76 (C_4, C_5), 132.69 (C_9, C_{10}), 150.06 (C_{14}), 162..47 (C_{11}, C_{12}), 175.02 (C_{15}).
14		46.55 (C_{13}), 119.92 (C_1, C_8), 122.11 (C_2, C_7), 124.57 (C_3, C_6), 127.30 (C_4, C_5), 135.94 (C_9, C_{10}), 151.30 (C_{14}), 161.23 (C_{11}, C_{12}), 178.39 (C_{15}).

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Table-4: Antimicrobial activity of selected compounds

	Staphylococcus aureus Conc. (mg/ml) Inhibition zone diameter (mm)			*Bacillus subtilis* Conc. (mg/ml) Inhibition zone diameter (mm)			*Escherichia Coli* Conc. (mg/ml) Inhibition zone diameter (mm)			*Pseudomonas aeuroginosa*. Conc. (mg/ml) Inhibition zone diameter (mm)			*Candida Albicans* Conc. (mg/ml) Inhibition zone diameter (mm)		
Comp. No.	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**
4	14	12	9	_	_	_	14	12	11	16	14	13	15	12	10
5	16	13	8	14	8	-	18	15	12	19	17	9	18	13	12
6	19	14	13	20	15	15	22	9	8	13	_	_	21	14	13
8	22	15	9	17	11	7	20	15	10	12	7	-	19	14	8
9	21	14	-	16	9	-	22	18	13	14	10	-	17	9	-
10	12	7	-	8	-	-	19	13	9	10	-	-	20	15	9
11	20	19	15	22	21	16	23	20	11	23	21	17	20	19	17
13	24	20	20	15	14	13	18	16	15	18	17	17	18	15	12
14	45	40	37	44	38	37	44	39	38	45	37	35	42	37	35
S (std.)	32	28	22	34	26	20	31	24	21	29	20	18	*	*	*
C (std.)	*	*	*	*	*	*	*	*	*	*	*	*	26	24	22

S (std.) = Sulfamethoxazole (standard antibiotic drug)
C (std.) = Clotrimazole (standard antifungal drug)
*** = not tested**
- = no inhibition zone