Synthesis and Characterization of Some New 1,2,3-Triazole, Amic Acids, Imides, and Isoimides from Ethyl-*p*-aminobenzoate and -Study Their Biological Activity

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Abstract

This research includes the synthesis new series of hetrocyclic compounds by three routes. The first route include synthesis of N-ethylbenzoate-1,2,3-triazole derives (3,4) by diazotation of ethyl-*p*-amino benzoate and treating the resulted salt (1) with sodium azid, then ethyl acetoacetate or acetyl acetone, respectively. The second route, ethyl-*p*-aminobenzoate was allowed to react with five of acid anhydrides (maleic, phthalic, cis-1,2,3,4-tetrahydro phthalic, succinic and glutaric) produced five novel esters contain amic acids (5-9), the third route include conversion these esters contain amic acids (5-9). The third route include conversation these esters amic acids (5-9) to different isoimides (10-14) and imide (15-19) respectively, through by two different methods. The first method treatment the amic acids (5-9) was dehydrated using strong dehydrating agents. N,N-dicyclohexyl carbodiimide (DCC) or trifloroacetic anhydride-triethylamine, we obtained the isoimide (10-14). While the second method involved direct reaction of amic acids (5-9) with a mixture of acetic anhydride and anhydrous sodium acetate to give cyclic imide (15-19). The prepared compounds identified by spectral methods [FTIR, ^{1}H-NMR, ^{13}C-NMR] and measurement some of its physical properties. Furthermore antibacterial activity of some the prepared new cyclic compounds were evaluated against three types of bacteria.

Keyword: 1,2,3-triazole, amic acid, isoimide, imide.

Introduction

Cyclic imides are important in organic chemist and have different chemical and biological applications, such as antibacterial, antifungal, anitinociceptive, anticonvulsant and antitumor [1-3]. They are also applied in agriculture as herbicides, fungicides or insecticides [4,5]. Furthermore, the isoimides are crystalline, with melting points much lower than the corresponding symmetrical imides, generally cyclic isoimides are thermodynamically less stable than their corresponding imides, but high conjugation or steric factors contribute a great deal to the stability of some isoimides [6]. On the other hand 1,2,3-triazole have been widely used in synthetic intermediates and industrial application, such as dyes, anticorrosive agents, photo stabilizers, photographic materials, and agrochemicals [7]. Although the 1,2,3-triazole structural moiety does not occur in nature, it may display biological activities and there are numerous example in the literature including ant-HIV activity, anti-microbial activity against gram positive bacteria, anti-allergic, anti-convulsant, β-Iactamase in hi bitory, selective B3 adrenergic receptor Agonism, and so on [8-10].

Keeping these above fact in view it was thought worthwhile to synthesize new compounds by incorporating cyclic imide, isoimide and 1,2,3-triazole ring in a single molecular framework the resulted new molecules were expected to possess biological activity.

Experiment

- **Instrumental**

Melting points were measured with a Gallen Kamp melting point apparatus were uncorrected. The FTIR-spectra of compounds were recorded on a Shimadzu FTIR-8300 spectrophotometer as KBr disc, result are given cm^{-1}. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker spectro spin ultra shield magnets 300 MHz instrument, using DMSO-d^{6} as solvent and TMS as internal reference.

Diazonium Salt (1)

A solution of ethyl-4-amino benzoate (0.01 mole, 1.65 g) in concentration HCl (3 mL) was cooled to (0-5)°C. A cooled solution of sodium nitrite (0.01 mole, 1.5 g) in 10 mL of water was added dropwise during 10 min., and then the reaction mixture was stirred for 30 min. Physical properties of product are listed in Table (1).

Ethyl-4-azidobenzoate (2)

(2.5 mL) of an aqueous solution of sodium azid (0.012 mole, 0.78 g) was added dropwise to an aqueous solution of diazonium salt (1). The mixture was stirred for 20 minutes to give an oily compound (2). Physical properties of dry product are listed in Table (1).

1-(4-ethylbenzoate)-4-acetyl-5-methyl-1H-1,2,3-triazole (3)

To a cold solution of sodium ethoxide (7 mL) and acetyl acetone (0.01 mole, 1.3 g), ethyl-4-azidobenzoate (2) (0.01 mole, 1.92 mL) was cautiously added and the mixture was heated under reflux on a water bath for 3hrs. The resulting solid was separated and recrystallization from ethanol. Physical properties of dry product are listed in Table (1).

1-(4-ethylbenzoate)-4-carboxlyic acid-5-methyl-1H-1,2,3-triazole (4)

A mixture of ethyl-4-azidobenzoate (2) (0.01 mole, 1.3 mL) and ethyl acetoacetate (0.01 mole, 1.03 mL) in methanol (30 mL) was cooled to 0 ˚C. Sodium methoxide (0.01 mole) in (20 mL) was added gradually to the mixture and heated under reflux on a water bath for 6hrs. The crude product was recrystallized from ethanol. Physical properties of dry product are listed in Table (1).

N-substituted (4-ethyl benzoate) amic acid (5-9) [6]

In a 150 mL two- necked flask equipped with a magnetic bar stirrer, drooping funnel, and reflux condenser were placed (0.1 mole) of different acid anhydride (maleic, phthalic, 1,2,3,6-cis-tetrahydrophthalic, glutaric, and succinic) and 40 mL of a suitable solvent such as dry acetone or THF. When all the anhydride had been dissolved by stirring, a solution of (0.1 mole, 16.5 g) of ethyl-*p*-amino benzoate in 60 mL of THF was allowed to run through the dropping funnel dropwise. After about 30 min of stirring, a precipitate settled out and filtered by suction filtration. The precipitate was washed with the solvent and recrystallized from dioxane. When purification of the produced amic acid was purified by dissolving it in sodium bicarbonate solution (5%), followed by reprecipitation of the amic acid with dilute HCl. The precipitate was filtered, washed with cold water, and dried. This technique was repeated until a pure product was obtained. Physical properties of dry product are listed in Table (2).

N-substituted (4-ethyl benzoate) isoimide (10-14)[6]

To a solution of (0.01 mole) N-substituted (4-ethylbenzoate) amic acid in (30 mL) ether or dioxane, (0.01 mole, 2.51 g) of trifloro acetic anhydride (TFAA) or (0.01 mole, 2.06 g) of dicyclohexyl carbodiimide (DCC) was added, and then added 3-5 drops of triethyl amine. The reaction mixture was heated under reflux condition for 6hrs. The precipitate was filtered and recrystallized from chloroform to give isoimide derivative. Physical properties of dry product are listed in Table (3).

N-substituted (4-ethyl benzoate) imide (15-19) [6]

In 250 mL round bottom flask with magnetic bar fitted with dropping funnel and reflux condenser, was placed (0.02 mole) of either the N-substituted (4-ethylbenzoate) amic acid,of (maleic, phthalic, cis-1,2,3,4-tetrahydrophthalic, succininic and glutaric). A mixture of 22 mL acetic anhydride and 2 g of anhydrous sodium acetate was allowed to run through the dropping funnel drop wise. The additions was performed drop wise with stirring for half to 1hr. The resulting mixture was refluxed over water bath for 3hr. The reaction mixture was cooled to room temperature and the poured into a large amount of ice water. The product precipitated was collected by suction filtration and washed three times with ice water and once with petroleum ether. Recrystallization from cyclohexane. Physical properties of dry product are listed in Table (4).

Biological Activity Test

The test was performed according to the disk diffusion method [11]. The some of the prepared compounds were tested aginst two strain of Gram +ve (*Staphyloccus aureus, Staphyloccus epiderunidis*) and one strain of Gram -ve bacteria (*Escherichia coli*). Whatman No.1 filter paper disk of 5mm diameter were sterilized by autoclaving for 15 mints at 121°C. The sterile disk were impregnated with different compounds (600 µg/disk). Agar plats were surface inoculated uniformly with 100 µL from broth culture of the tested microorganism. The impregnated disk were placed on the medium suitably spaced a part and the plates incubated at 5°C for 1hr. to permit good diffution and then transferred to an incubator at 37°C for 24 hrs. The inhibition zones caused by the various compounds on the microorganisms were examined. The results are listed in Table (7).

Table (1)
Physical properties and FTIR spectral of compounds (1-4).

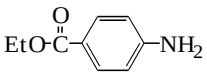
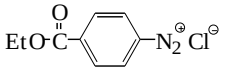
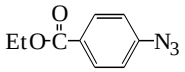
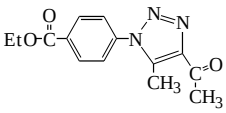
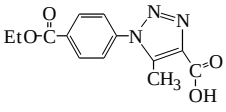
Comp. No.	*Comp. structure*	*Melting point*	*Yield %*	*color*	*Major FTIR Absorptions cm^{-1}*				
					νC-H arom.	*νC-H aliph.*	*νC=O*	*νC=C arom.*	*Other bands*
0		89-92	77	White	3070	2928-2858	1686	1597	ν(NH_2) 3422, 3342 δ1631; ν845 *p*-position
1		oil	80%	Yellow	-	-	-	-	-
2		178	85	Orange	3077	2986-2908	1719	1602	ν(N=N–N) 2120, ν (C-O) 1175, ν(*p*-position) 852
3		195-197	97	Pale yellow	3055	2935-2854	1728 (ester), 1686 (ketone)	1604	ν(N=N) 953 ν(*p*-position) 854,
4		255-257	95	yellow	3072	2989-2916	1730 ester 1724 acid	1609	ν(N=N) 980 ν(C-O) 1277, ν(*p*-position) 821, ν( ) 4362-3330

Table (2)
Physical properties and FTIR spectral amic acid compounds (5-9).

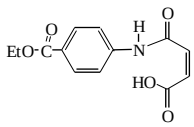
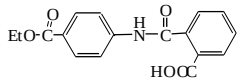
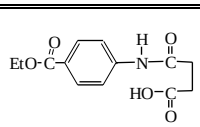
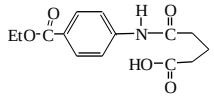
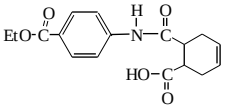
Comp. No.	Comp. structure	Melting point	Yield %	color	Major FTIR Absorptions cm^{-1}						
					ν*O-H*	ν*N-H*	ν*C-H arom.*	ν*C-H aliph.*	ν*C=O*	ν*C=C*	*Other bands*
5		278-288	99	White	3300	3211	3117	2984-2907	1711 (acid), 1583 (amid)	1620	ν(C-O) 1277, ν(*p*-position) 858, ν(C=C)1547
6		175-178	92	White	3342	3423	3092	2970-2899	1724 (ester), 1686 (amid)	1593	ν(C-O) 1280, ν(*p*-position) 844
7		131-133	97	Yellow	3223	3344	3055	2922-2899	1755 (ester), 1688 (amid)	1597	ν(C-O) 1280, ν(*p*-position) 844
8		66-68	68	Pale brown	3235	3327	3035	2925-2851	1710 (ester), 1626 (amid)	1574	ν(C-O) 1242, ν(*p*-position) 841
9		55-58	99	Yellow	3423	3344	3022	2985-2903	1690 (ester), 1633 (amid)	1597	ν(C-O) 1279, ν(*p*-position) 847

Table (3)
Physical properties and FTIR spectral isoimide compounds (10-14).

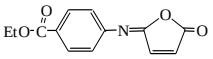
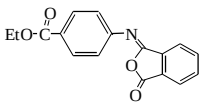
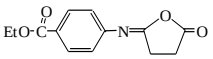
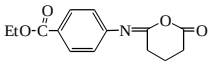
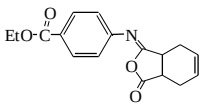
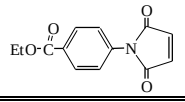
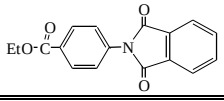
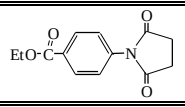
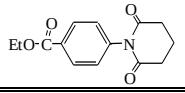
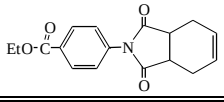
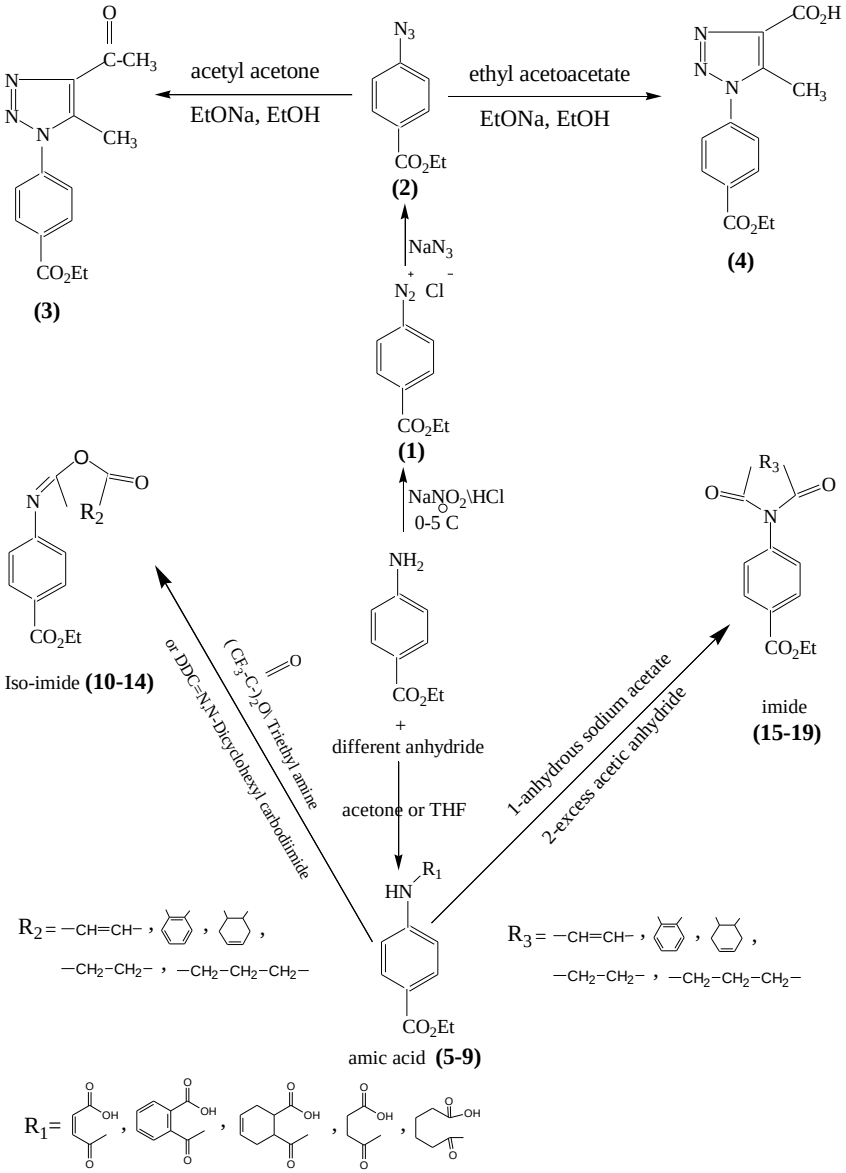
Comp. No.	Comp. structure	M.P.	Yield %	color	Major FTIR Absorptions cm^{-1}					
					ν*C-H arom*	ν*C-H aliph.*	ν*C=O*	ν*C=N*	ν*C=C*	*Other bands*
10		169-170	85	white	3110	2928-2852	1711 (ester) 1655 (anhydride)	1626	1577	ν(C-O) 1244, ν(*p*-position) 856
11		235-237	74	Pale yellow	3037	2926-2851	1750 (ester) 1709 (anhydride)	1625	1575	ν(C-O) 1244, ν(*p*-position) 850
12		72-75	68	Pale yellow	3110	2970-2903	1740 (ester) 1686 (anhydride)	1634	1599	ν (C-O) 1169, ν(*p*-position) 847
13		217-219	76	Gray	3095	2960-2908	1720 (ester) 1680 (anhydride)	1645	1605	ν(C-O) 1212, ν(*p*-position) 825
14		218-220	72	White	3124	2928-2851	1711 (ester) 1690 (anhydride)	1626	1574	ν(C-O) 1279, ν(*p*-position) 850

Table (4)

Physical properties and FTIR spectral imide compounds (15-19).

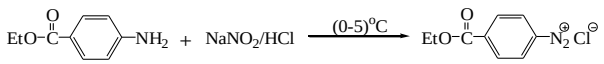
Comp. No.	*Comp. structure*	*M.P.*	*Yield %*	*color*	*Major FTIR Absorptions cm^{-1}*				
					νC-H arom.	*νC-H aliph.*	*νC=O*	*νC=C*	*Other bands*
15		108-110	78	Pale yellow	2999	2959-2903	1717 (ester)	1603	ν(C-O) 1219, ν(*p*-position) 829
16		193-195	80	White	3010	2989-2908	1784 (ester),1693 (anhydride)	1603	ν(C-O) 1169, ν(*p*-position) 833
17		93-95	69	White	3111	2989-2910	1710 (ester), 1684 (anhydride)	1599	ν(C-O) 1252, ν(*p*-position) 866
18		129-130	75	White	3002	2977-2932	1700 (ester), 1691 (anhydride)	1598	ν(C-O) 1213, ν(*p*-position) 851
19		115-118	66	Yellow	3047	2953-2905	1745 (ester), 1709 (anhydride)	1603	ν(C-O) 1277, ν(*p*-position) 857



Scheme (1)

Results and Discussion

Since all cyclic imides, isoimides and 1,2,3-triazole are very important organic compounds having wide spectrum of biological activities [12-14]. The target of this work was performed by following different strategic, the synthesis routes used in shown in Scheme (1). The first route include synthesis of N-ethylbenzoate-1,2,3-triazole derives (3,4) by prepared diazotation of ethyl-*p*-aminobenzoate to obtained diazonium chloride (1), according to the following equation [15].



The reaction must be carried out in low temperature between (0-5)°C because the high temperature decomposition of diazonium salt (1), the obtained diazonium chloride (1) was treated with calculated amount of sodium azide to afford ethyl-*p*-azidobenzoate (2). The structure of compound (2) was confirmed by physical properties which are listed in Table (1). FTIR spectra showing the absorption at ν cm^{-1} (2120 for N=N-N group).

The azide (2) were converted to 1-(4-ethylbenzoate)-4-acetyl-5-methyl-1H-1,2,3-triazole (3) and 1-(4-ethylbenzoate)-4-carboxylic acid-5-methyl-1H-1,2,3-triazole (4) by the reaction with ethylacetoacetate and acetylacetone respectively (Scheme 1). FTIR spectral showed the disappearance of the azid group (N_3) band in the starting material (2) at (2120 cm^{-1}) which is a good indication for successful condensation [16]. The spectrum also shows absorption bands at (1728 cm^{-1} for νC=O ester; 1686 cm^{-1} νC=O keton; 953 cm^{-1} for νN=N) for compound (3); 1724 cm^{-1} for νC=O ester; 1724 cm^{-1} for νC=O acid; 980 cm^{-1} for νN=N in addition appearance 4362-3330 for ν $-C(=O)-\underline{OH}$) for compound (4). While the ^{1}H-NMR spectra data of compound (3) [17] δ ppm in DMSO-d^6 solvent 1.3(t, 3H, -CH_3 ester); 1.8(s, 3H, -CH_3 triazole); 2.62(s, 3H, $-C(=O)-CH_3$); 3.92(q, 2H, -CH_2O-); 7.6-8.3(m, 4H, Ar-H). ^{13}C-NMR spectra show result were listed in Table (6). Other chemical test was carried out to characterize the prepared (3, 4) such as hydroxiamic acid test that [18] confirmed the presence of ester group.

The second route, reaction *p*-aminobenzoate with five of acid anhydride (maleic, phthalic, cis-1,2,3,4-tetrahydro-phthalic, succinic and glutaric) produced five novel ester contain amic acid (5-9) are characterized by physical properties which are listed in Table (2) and the chemical reaction with $NaHCO_3$ solution mentioned earlies. FTIR spectra of the products were showed medium intensity band at (3423-3211) cm^{-1} for νN-H. The –CO<u>OH</u> absorption was found at (3423-3223) cm^{-1} howerver it is overlap with νC-H aliphatic were observed one for carbonyl (1755-1690) cm^{-1} for carboxylic acid, the second for amide carbonyl (1688-1583) cm^{-1}. While the ^{1}H-NMR spectra data of compound (6): Fig.(1) δ ppm in DMSO-d^6 solvent: 1.28(t, 3H, -CH_3 ester); 4.15(q, 2H, -CH_2O-); 6.6(s, 1H, NH); 7.5-8.0(m, 8H, Ar-H); 10.9(s, 1H, COOH). ^{13}C-NMR spectra shows results were listed in Table (6), Fig.(2).

The third route include conversation these esters amic acid (5-9) to different isoimide (10-14) and direct to imide (15-19) respectively, through by two different methods. The first method treatment the amic acid (5-9) was dehydrated using strong dehydrating agents. N,N-dicyclohexyl carboimide (DCC) or trifloroacetic anhydride-triethylamine (TFAA-Et_3N) we obtained isoimide as a product due to withdrawing a water molecule. It was found that the dehydration using DCC was better than the used of TFAA-Et_3N as it was show from the yield and purity. (Scheme (1)).

The structures of isoimide compounds (10-14) were confirmed by physical properties which are listed in Table (3). FTIR spectra showing the absorption at ν cm^{-1} (1625-1645) for C=N; (1709-1655) for C=O isoimide (lacton) and absence of νO-H and νN-H absorption. While the ^{1}H-NMR spectra data of compound (14) δ ppm in DMSO-d^6 solvent 1.25(t, 3H, -CH_3 ester); 3.5(q,2H, -CH_2O-); 7.4-8.2(m, 4H, Ar-H). ^{13}C-NMR spectra shows result were listed in Table (6). While the second method involved direct reaction of amic acids (5-9) with a mixture of acetic anhydride and anhydrous sodium acetate to give cyclic imide (15-19) Scheme (1). The

structures of compounds (15-19) were confirmed by physical properties which are listed in Table (4) FTIR spectra showing the absorption at ν cm^{-1} (1784 for C=O asym. Imide (shoulder) and sym. Imide (sharp) at (1693-1684) also disappearance of νO-H and νN-H absorption. While the ^{1}H-NMR spectra data of compound (18) Fig.(3) δ ppm in DMSO-d^{6} solvent: 1.3(t, 3H, -CH_3 ester) 2.1(p, 2H, -CH_2-cyclic); 3.45(t, 4H, $-\overset{O}{\overset{\|}{C}}-CH_2-$ cyclic imide); 7.3-8.2(m, 4H, Ar-H). ^{13}C-NMR spectra shows result were listed in Table (6). Fig.(4).

Table (5)
^{1}H-NMR spectral data for some of the prepared compounds.

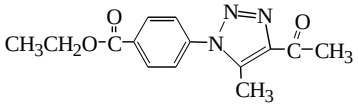
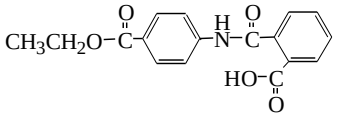
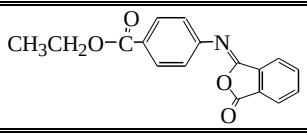
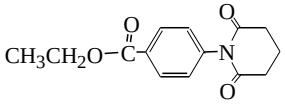
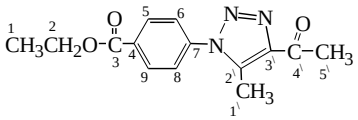
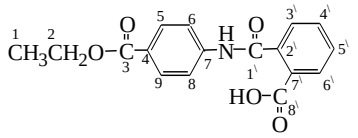
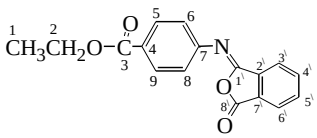
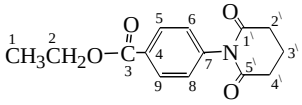
Comp. No.	***Compound structure***	***^{1}H-NMR parameters (ppm) δ-H***
3		1.3(t, 3H, -CH_3 ester); 1.8(s, 3H, -CH_3 triazole); 2.62(s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$); 3.92(q, 2H, -$CH_2O$-); 7.6-8.3(m, 4H, Ar-H)
6		1.28(t, 3H, -CH_3 ester); 4.15(q, 2H, -CH_2O-); 6.6(s, 1H, N-H); 7.5-8.0(m, 8H, Ar-H); 10.9(s, 1H, -COOH)
14		1.25(t, 3H, -CH_3 ester); 3.5(q, 2H, -CH_2O-); 7.4-8.4(m, 8H, Ar-H)
18		1.3(t, 3H, -CH_3 ester); 2.1(p, 2H, -CH_2 cyclic); 3.45(q, 2H, -CH_2O-); 4.35(t, 4H, $-\overset{O}{\overset{\|}{C}}-CH_2-$ cyclic imide); 7.3-8.2(m, 4H, Ar-H)

Table (6)
^{13}C-NMR spectral data for some of the prepared compounds.

Comp. No.	***Compound structure***	***^{13}C-NMR data (ppm)***
3		14.78C_1; 28.12 $C_{1'}$; 41.20 $C_{5'}$; 60.13C_2; 116.38C_5 and C_9; 126.05C_6 and C_8; 130.34C_4 and $C_{3'}$; 131.06C_7; 131.68 $C_{2'}$; 164C_3; 170.20 $C_{4'}$
6		14.78C_1; 60.90C_2; 113.13 $C_{5'}$; 116.61 $C_{4'}$ and $C_{6'}$; 119.29C_5 , $C_{3'}$ and C_9; 128.24C_9; 128.24C_6 and C_8; 130.63C_4 and $C_{2'}$; 139.04 $C_{7'}$; 166.36 $C_{1'}$; 168.40C_3; 169.19 $C_{8'}$
14		14.60C_1; 61.17C_2; 121.03 $C_{4'}$ and $C_{5'}$; 127.41C_6, C_8, $C_{3'}$ and $C_{6'}$; 128.22C_5; C_9; 130.21C_4 and $C_{7'}$; 130.69C_7 and $C_{2'}$; 150.07 $C_{1'}$; 169.90C_3; 172.90 $C_{8'}$
18		14.62C_1; 32.62 $C_{3'}$; 39.14 $C_{2'}$ and $C_{4'}$; 61.33C_2; 129.91C_5 and C_9; 129.99C_6 and C_8; 141.06C_4 and C_7; 165.73 $C_{1'}$ and $C_{5'}$; 173.16 C_3

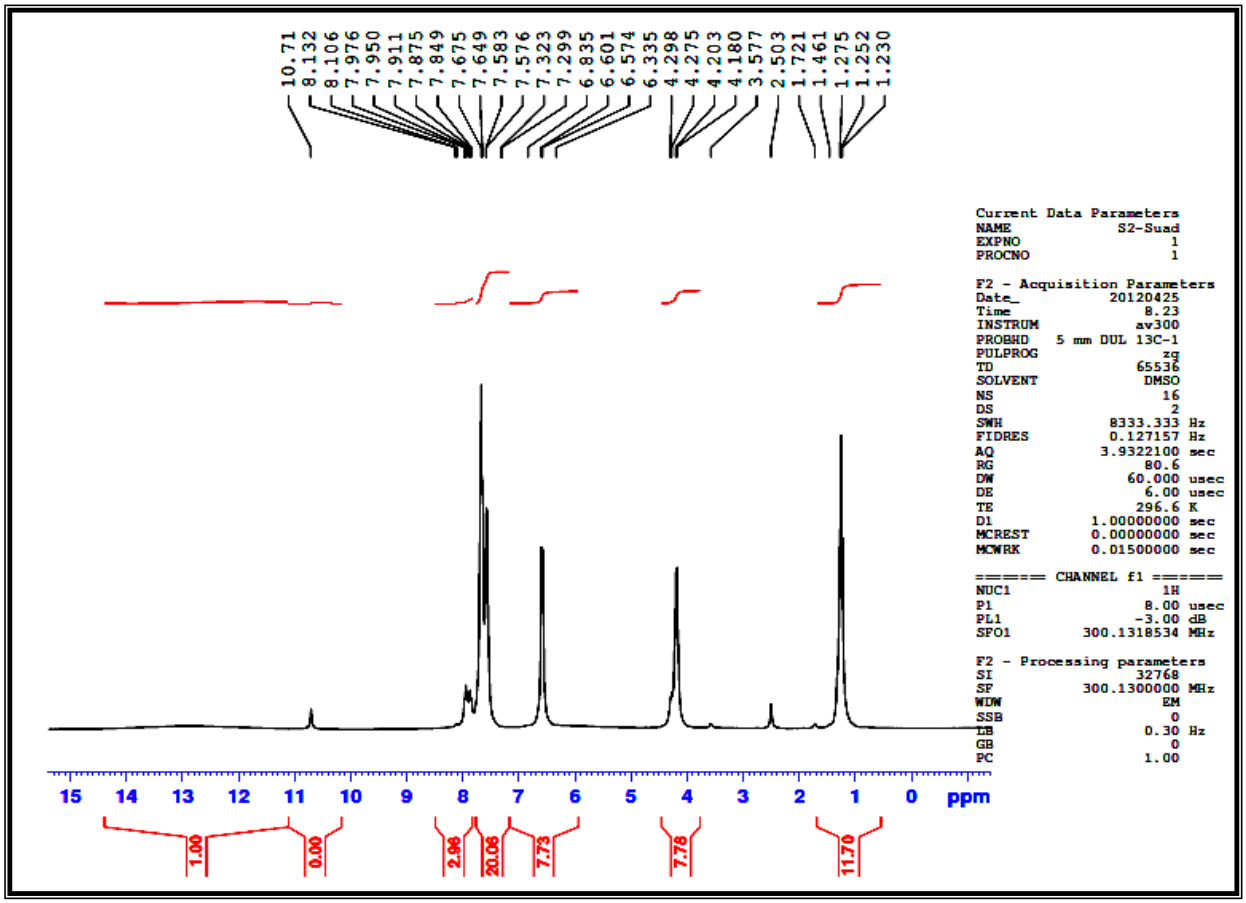


Fig.(1) ^{1}H-NMR for compound No. (6).

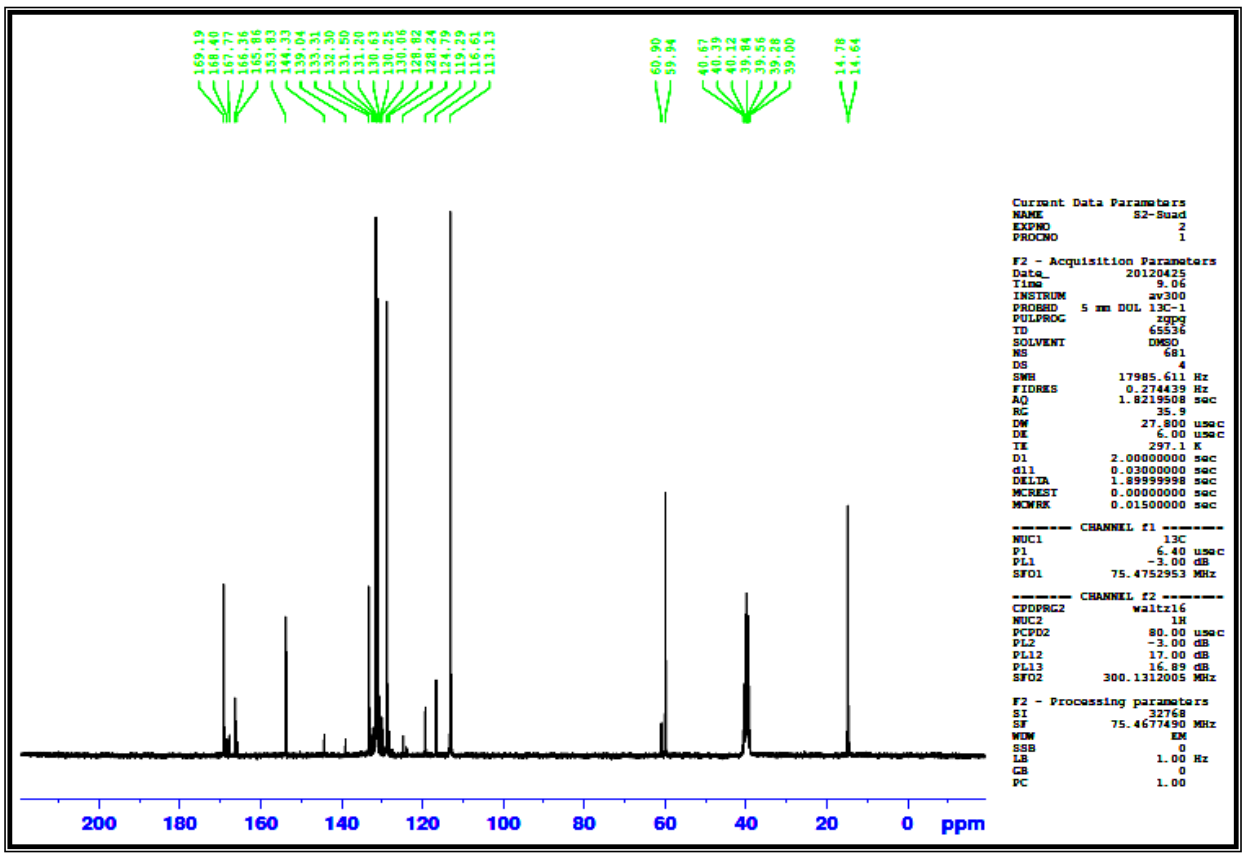


Fig.(2) ^{13}C-NMR for compound No. (6).

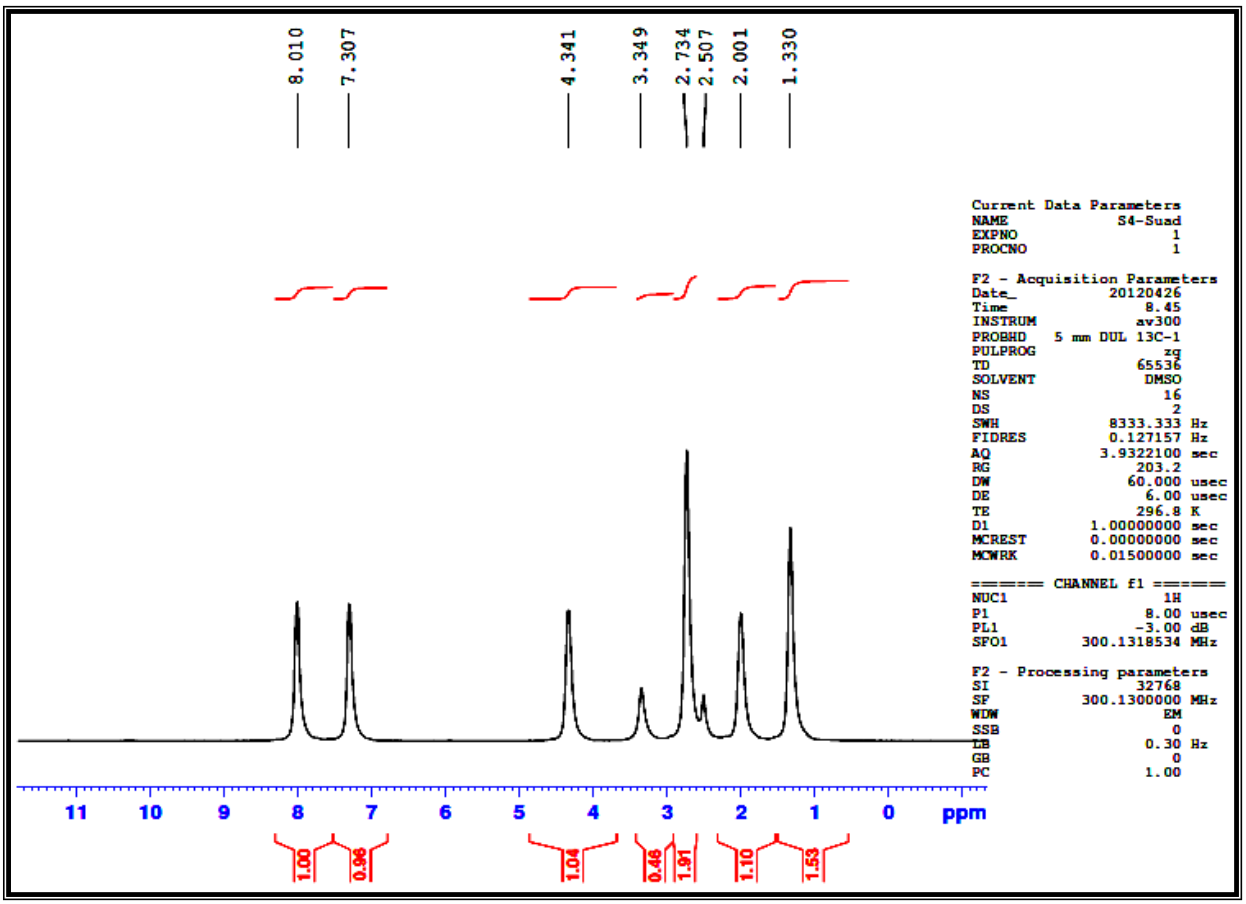


Fig.(3) ^{1}H-NMR for compound No. (18).

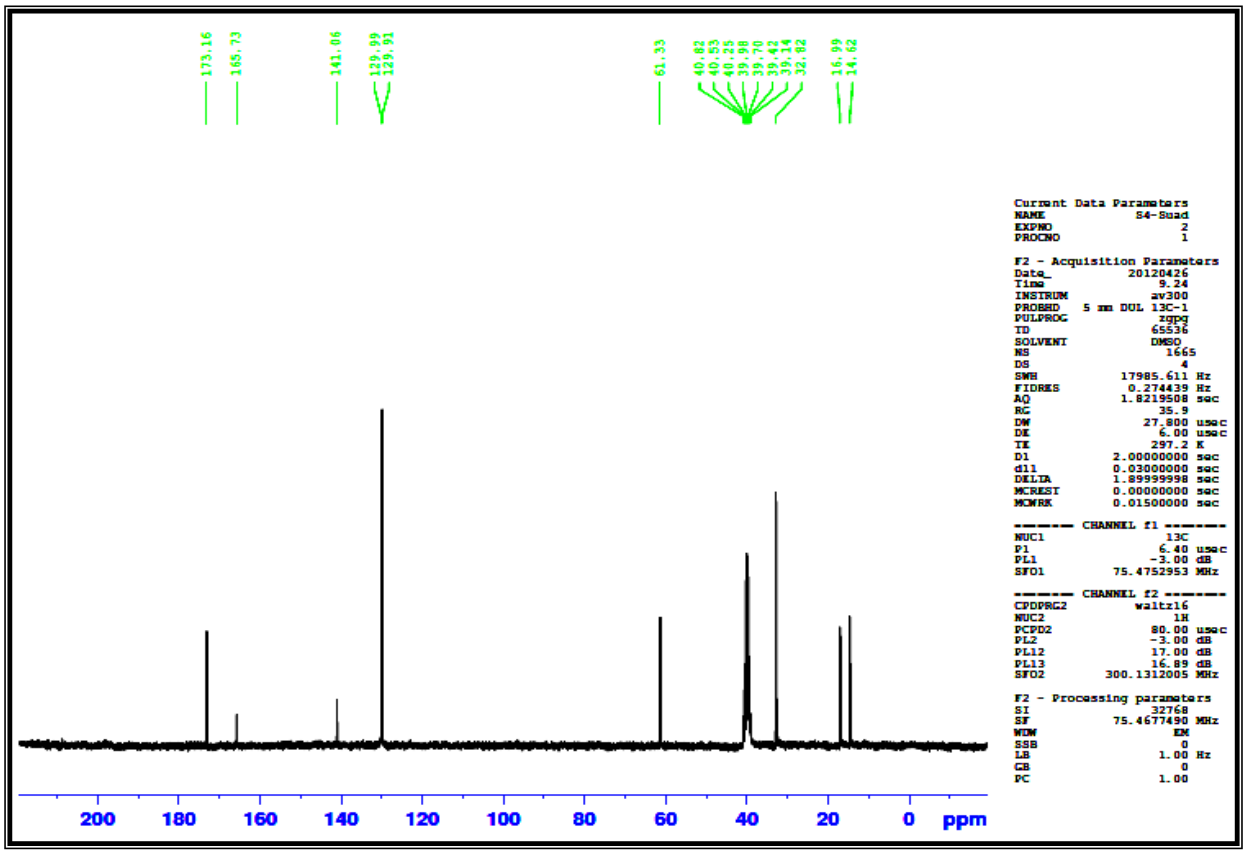


Fig.(4) ^{13}C-NMR for compound No. (18).

Antibacterial Activity

The results of antibacterial activity are listed in Table (7). The results referred that the some prepared compounds (3, 4) showed high activity against *Staphyloccus aureus*. Also compounds (7, 8) and (11, 12) show moderate and high activity against *staphyloccus aureus* respectively. While compound (14) show high specific activity against this bacteria. Isoimide compound (15-17) show high to moderate specific activity against *Staphyloccus aureus* while are inactive against (*Staphyloccus epiderunidis* and *Escherichia coli*). Compounds (3, 4, 8, 11, 12, 14) showed moderate activity against *Staphyloccus epiderunidis* while compounds (7, 12, 15, 16 and 17) showed inactivity against this bacteria. All compounds in Table (7) showed slightly or inactive against *Escherichia coli (E. coli)*.

Table (7)
Results of antibacterial activity of the tested prepared compounds.

Comp. No.	*Staph. aure*	*Staph. epide*	*E. coli*
3	+++	++	+
4	+++	++	-
7	++	-	+
8	++	++	+
11	+++	++	+
12	+++	-	+
14	++++	++	-
15	+++	-	-
16	++	-	-
17	+++	-	+

**** Solvent: DMSO; [C]: 600µg/mL***
Key to symbols:
Very highly active= ++++ (inhibition zone 21-30 mm)
Highly active= +++ (inhibition zone 15-20 mm)
Moderately active= ++ (inhibition zone 10-14 mm)
Slightly active= + (inhibition zone 6-9 mm)
Inactive = - (inhibition zone < 6 mm)

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الخلاصة

تضمن هذا البحث تحضير سلسله جديده من المركبات الحلقية غير المتجانسة من خلال ثلاث مسارات، تضمن المسار الاول تحضير مشتقات حامض البنزويك-3,2,1- ترايزول (4,3) عن طريق تحويل اثيل-٤-أمينو بنزويت الى ملح الدايازونيوم (١) ومن ثم معاملة الملح الناتج (١) مع الصوديوم ازايد وبعدها مع مثيل اسيتو أسيتت او اسيتال اسيتون على التوالي . في المسار الثاني تم مفاعلة اثيل بارا أمينو بنزويت مع خمسة من انهدريدات الحوامض (الماليك، الفثاليك، سيز-4,3,2,1-تتراهيدروفثاليك، السكسينك و الكلوتاريك) مكونا استرات جديدة حاوية على الحوامض المذكورة اعلاه (٥-٩) . المسار الثالث تضمنت تحويل استرات الحوامض الاميك (٥-٩) الى ايزواميدات (١٠-١٤) و ايميدات (١٥-١٩) على التوالي، من خلال طريقتين، تضمنت الطريقة الاولى سحب جزيئة الماء من استرات حوامض الاميك (٥-٩) باستخدام العوامل الساحبة القوية، ثنائي سايكلو هكسيل كاربوثنائي الاميد (DCC) وثلاثي فلورو حامض الخليك الامائي- ثلاثي أثيل أمين، تم الحصول على الايزوايميدات الحلقية (١٠-١٤). بينما تضمنت الطريقة الثانية التفاعل المباشر لأسترات حوامض الاميك (٥-٩) مع مزيج من خلات الصوديوم اللامائية- حامض الخليك اللامائي تكون لدينا الايميدات الحلقية (١٥-١٩). ثم تشخيص جميع المركبات المحضرة بالطرق الطيفية [FTIR,^{1}H-NMR,^{13}C-NMR] وقياس بعض الثوابت الفيزياوية، اضافة الى ذلك تضمن البحث دراسة الفعالية البايولوجية للمركبات المحضرة