Synthesis, Characterization and Antibacterial Screening of New 1-Aminoanthraquinone Derivatives

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Abstract

This research includes the synthesis of new heterocyclic derivatives of 1-aminoanthraquinone bearing 2-aminobenzothaizole moieties.

Substituted 2-aminobenzothiazole obtained from the reaction of 4-substituted aniline with ammonium thiocyanate in bromine and glacial acetic acid. Then these derivatives were used to prepare of 2-(2-chloroacetylamino)-6-substituted benzothiazole compounds (1-6) by treating with chloroacetyl chloride in chloroform. Refluxing these compounds with 1-aminoanthraquinoe in absolute ethanol gave *N*-[(2-(2-Acetamido)-6-substituted benzothiazole-2-yl]-1-aminoanthraqiunone compounds (7-12). The characterizations of all synthesized compounds were confirmed by their melting points, and FTIR, ^{1}HNMR, ^{13}CNMR spectroscopy.

Some of the new prepared compounds were evaluated for the antibacterial activity screening against two types of Gram positive bacteria including (*Streptococcuss pneumoniae*, *Enterococcus faecalis*) and two types of Gram negative bacteria including (*Salmonella typhi.*, *Acinetobacte sp.*) and compared with ceftriaxone was used as standard drugs. The results showed that most of the tasted compounds have well to moderate biological activity against the mentioned organisms compared with standard drug above.

Keywords**:** 1-Aminoanthraquinone, 2-Aminobenzothiazole, Synthesis, Antibacterial.

Introduction

Anthraquinones (anthracene-9,10-dione) have attracted the interest of researches due to their significant biological activities such as antitumour, [1] anti-inflammatory, [2] antimalarial, [3] antimicrobial, [4] antifungal, [5] antileukemic, [6] antiviral and anti-HIV properties. [7] Anthraquinone derivatives are also used as antioxidants. [8] Among them the anthracyclines such as doxorubicin and daunorubicin have been widely applied as chemotherapeutic drugs with broad clinical indications as anticancer compounds. [9] They are also present broad spectrum activity as anti-neoplastic agents. [10]

Many amino-substituted anthraquinones show significantly increased antiproliferative activities against human/mammalian cancer cell lines [11] and are known to have potential antitumor activity, but are less toxic to normal cells and display low cardio toxicity. [12] Some of aminoanthraquinones such as Acid Blue 25 (AB-25), Reactive Blue 2 (RB-2), and Acid Blue 129 (AB-129) also known as good nucleotide-binding proteins. [13] Additionally, an aromatic amine 1-Aminoanthraquinone (1-amino-AQ) and its derivatives are an important class of dyestuffs used for the coloring of textiles, such as synthetic and natural fibers, and there is a continuous interest in optimizing this class of compounds. [14] Moreover, a large number of papers and patents have been reported on 2-aminobenzothiazole derivatives possess significant and diverse biological activities. [15,16] In this connection based on these widely range of bioactivities, the aim of this research therefore to design of some new 1-aminoantharaquinone derivatives containing 2-aminobenzothiazole fragments which could considerably affect biological properties of 1-aminoantharaquinone, to develop novel and potent therapeutic agents of synthetic origin. It was decided to synthesize certain of derivatives and evaluate them as antibacterial agents.

Experimental

Materials and Methods

All chemicals used in this work were supplied from Fluka, Merck, BDH and Sigma-Aldrich companies and were used without further purification. Melting points were recorded by digital melting point equipment

(Stuart Scientific SMP30). FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer using KBr discs in the range (500- 4000) cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were run on Bruker 300MHz instrument using DMSO-d^6 as a solvent and all chemical shifts, δ were recorded in ppm relative to TMS signal. Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type Polygram Silica gel, and the plates were developed with iodine vapour. The antibacterial screening was performed in Biology department, College of Science, Baghdad University.

Synthesis of 2-amino-6-substituted benzothiazoles.

In a suitable round bottomed flask fitted with a dropping funnel (0.01mol) of 4-substituted aniline was dissolved in (15mL) of glacial acetic acid then (0.01mol, 0.76g) of ammonium thiocyanate was added with stirring. The dropping funnel was supplied with (0.025mol, 0.5mL) of bromine dissolved in (10mL) of glacial acetic acid, then this solution was added to the mixture drop wise with stirring and cooling for three hours. The resulting mixture was diluted with distilled water then 10% solution of sodium hydroxide with stirring until precipitation of the product. The precipitate was filtered and dried then recrystallized from a suitable solvent. [17]

Synthesis of 2-(2-Chloroacetylamino)-6-substituted benzothiazole (1-6).

Equimolar solution of 2-(6-substituted) aminobenzothiazole (0.01mol.) and chloroacetyl chloride (0.01mol.) in chloroform (30ml) in the presence of triethylamine is refluxed for about 14 h. Excess of solvent was removed and the residue stirred with water (50 ml). The residue was washed with 5% $NaHCO_3$ solution and subsequently with water. The crude product is dried and recrystallized from suitable solvents to furnish colored solid. [18]

Synthesis of *N*-[(2-(2-Acetamido)-6-substituted benzothiazole-2-yl]-1-aminoanthraqiunone (7-12).

To compounds (1-6) (0.01 mol.) dissolved in (20ml) absolute ethanol. 1-aminoanthraquinoe (0.0l mol, 2.23 gm) was added gradually. After addition, reaction mixture was refluxed for (8-12 hrs)**.** Ethanol and 1-aminoanthraquinoe were recovered through distillation. The residue was washed with sodium bicarbonate to remove the acid impurities and finally with water. The product was crystallized from a suitable solvent. [19]

Antibacterial Activity Test

All the newly synthesized compounds were evaluated for their in vitro antibacterial activity against *Streptococcuss pneumoniae*, *Enterococcus faecalis*, *Salmonella typhi.* and *Acinetobacte sp*. Disk diffusion method [20] was used for determination of the preliminary antibacterial activity. Disks measuring six millimeter in diameter were punched from filter paper. The test compounds were prepared with different concentrations using dimethyl sulfoxide (DMSO) as solvent. Different concentration have been prepared for each compound as follows: 1mg/ml, 5mg/ml,10mg/ml, 15mg/ml, 20mg/ml, 25mg/ml, 50mg/ml, 100mg/ml in DMSO 0.1ml of each solution from the prepared concentration was added to test tubs contains 5ml of the nutrient broth Tow test tubs were left one without addition and to the other tube, DMSO was added only as control, the bacterial suspension was diluted and 1ml of the diluted suspension to the tubes including the control. Disks of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37^{o}C for (24 hrs). Ceftriaxone 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 The MIC (µg/mL) values of the tested compounds against the tested bacteria strains are recorded. [21]

Results and Discussion

Series of 2-amino benzothiazoles substituted with different substituents were prepared in quantitative yield according to a known method. This depends on thiocyanogen method which involved reaction of substituted primary aromatic amine with ammoniumthiocyanate and bromine in glacial

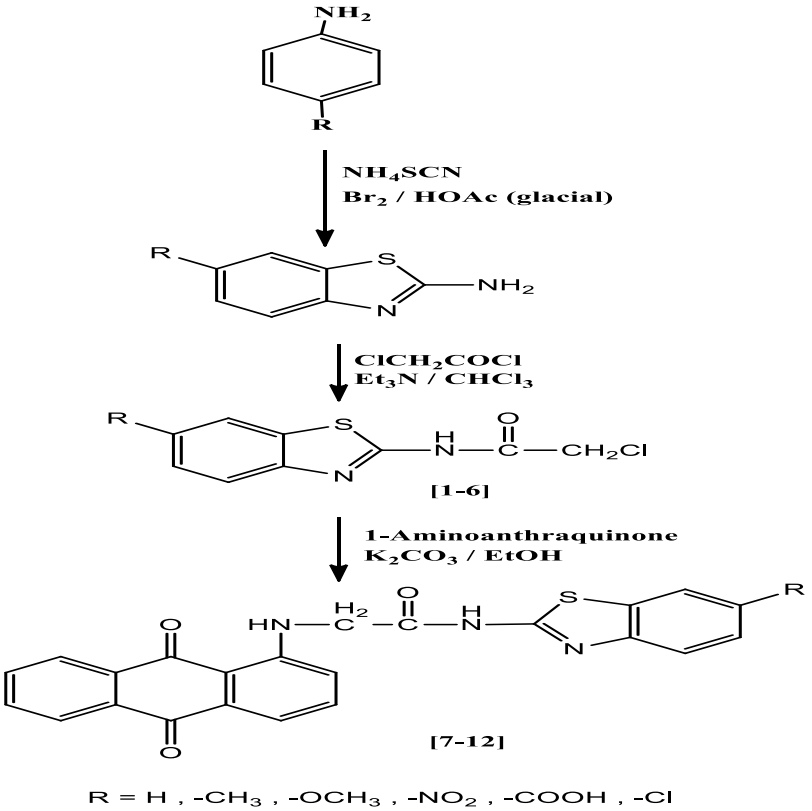
acetic acid. Melting points of the purified benzothiazoles were determined as well as their FTIR spectra were recorded. It was noticed that physical properties and spectral data of the prepared benzothiazole are fitted with those reported in the literatures. [22]

The 2-(2-chloroacetylamino)-6-substituted benzothiazoles compounds (1-6) were prepared via condensation of substituted 2-aminobenzothiazole with chloroacetylchloride in chloroform in presence of anhydrous potassium carbonate as a base. The mechanism of this reaction involved nucleophilic attack of amino group in 2-aminobenzothiazoles on carbonyl group of chloroacetylchloride followed by elimination of HCl molecule. Compounds (1-6) are colored, solids and having sharp melting points and their physical properties are listed in Table (1).

FTIR spectra of compounds (1-6) showed clear absorption bands at (3164-3373) cm^{-1}, (1666-1718) cm^{-1}, (1610-1644) cm^{-1} and (1549-1588) cm^{-1} belong to υ(NH) amide, υ(C=O) amide, υ(C=N) and υ(C=C) aromatic, respectively. Other bands appeared at (806-844) cm^{-1} and (672-709) cm^{-1} belongs to υ(C-Cl) aliphatic and υ(C-S) in thiazole ring, respectively. FTIR spectral data of compounds [1-6] are listed in Table (2).

The final way in the chemical synthesis involved direct reaction of 6-substituted-2-aminobenzothiazole with 1-aminoanthraquinone under certain conditions to give new compounds (7-12). FTIR spectra of compounds (7-12) showed clear absorption bands at (3193-3290) cm^{-1}, (1643-1703) cm^{-1}, (1610-1644) cm^{-1} and (1528-1574) cm^{-1} belong to υ(NH) amide, υ(C=O) amide, υ(C=N) and υ(C=C) aromatic, respectively. Other bands appeared at (1610-1668) cm^{-1} and (672-709) cm^{-1} belongs to υ(C=O) carbonyl and υ(C-S) in thiazole ring, respectively.

FTIR spectral data of compounds (7-12) are listed in Table (2). These steps are summarized in Scheme (1).



Scheme (1) Synthesis of compounds (1-12).

^{1}H-NMR spectrum of compound (8) displayed signals attributed to (CH_3), (CH_2), (NH) at 1-position of anthraquinone ring, and also it was found signals belong to aromatic ring protons and (NH) amide respectively. Results of ^{1}H-NMR were listed in Table (3), Fig.(1).

^{13}CNMR spectrum of compound (8) showed signals belong to (CH_3) at 6-position of benzothiazole ring, (CH_2), aromatic carbons, carbon at 2-position of benzothiazole ring, (C=O) amide and (C=O) carbonyl respectively. Results of ^{13}C-NMR were listed in Table (4), Fig.(2).

^{1}H-NMR spectrum of compound (9) showed signals belong to (OCH_3), (CH_2), (NH), at 1-position of anthraquinone ring, also aromatic ring protons and (NH) amide respectively.

Results of ^{1}HNMR were listed in Table (3). ^{13}CNMR spectrum of compound (9) showed signals belong to (OCH_3) at 6-position of benzothiazole ring, (CH_2), aromatic carbons, carbon at 2-position of benzothiazole ring, (C=O) amide and (C=O) carbonyl respectively. Results of ^{13}C-NMR were listed in Table (4).

^{1}H-NMR spectrum of compound (10) which contain signals belong to (CH_2), (NH) at 1-position of anthraquinone ring, also aromatic ring protons and (NH) amide respectively. Results of ^{1}H-NMR were listed in Table (3), Fig.(3).

^{13}CNMR spectrum of compound (10) showed signals belong to (CH_2), aromatic carbons, carbon at 2-position of benzothiazole ring, (C=O) amide and (C=O) carbonyl respectively. Results of ^{13}C-NMR were listed in Table (4), Fig.(4).

^{1}H-NMR spectrum of compound (11) showed signals belong to (COOH), (CH_2), (NH) at 1-position of anthraquinone ring, aromatic ring protons and (NH) amide respectively. Results of ^{1}HNMR were listed in Table (3).

^{13}C-NMR spectrum of compound (11) showed signals belong to (COOH) at 6-position of benzothiazole ring, (CH_2), aromatic carbons, carbon of 2-position of benzothiazole ring, (C=O) amide and (C=O) carbonyl respectively. Results of ^{13}CNMR were listed in Table (4).

Table (1)
Physical Properties of Synthesized Compounds (1-12).

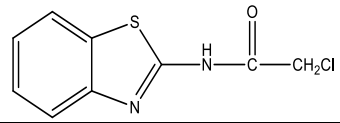
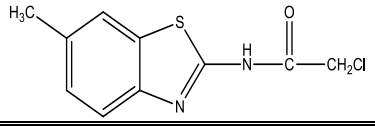
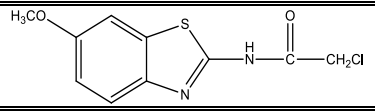
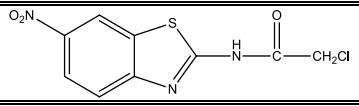
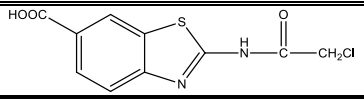
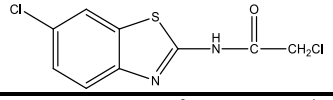
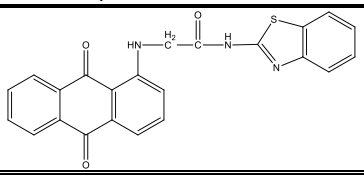
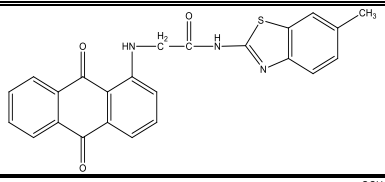
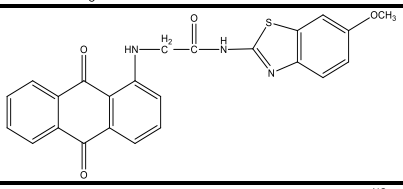
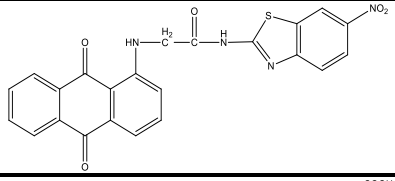
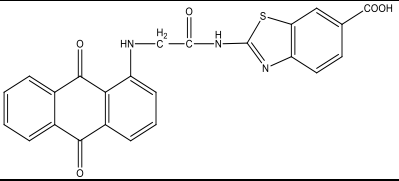
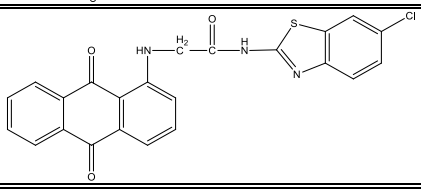
Comp. No.	*Structure*	*Color*	*Yield %*	*Melting Point °C*	*Solvent of Recryst.*	*R_f Value*
1		White	66	198-200	Ethanol	0.70
2		Green yellow	72	183-187	Ethanol -water 1:1	0.57
3		Brown	55	156-159	Ethanol -water 1:1	0.60
4		Light brown	63	177-178	Methanol -Ethanol 1:1	0.54
5		Off White	61	201-204	Dioxane -Ethanol 1:1	0.62
6		White	80	134	Ethanol	0.61
7		Red	83	245-246	Ethanol -water 1:1	0.72
8		Brown	79	223-225	Dioxane	0.77
9		White	74	284-287	Dioxane	0.69
10		Light Yellow	68	271-272	Dioxane -Ethanol 1:1	0.56
11		Dark brown	51	226	Dioxane -Ethanol 1:1	0.63
12		Dusty	69	187	Dioxane	0.68

Table (2)
FTIR Spectral Data cm^{-1} of Compounds (1-12).

Comp. No.	*V(N-H) Amide*	*V(C-H) Arom.*	*V(C-H) Aliph.*	*V(C=O) Amide*	*V(C=N) Thiazole*	*V(C=C) Arom.*	*V(C-S) Thiazole*	*Othres*
1	3217	3079	2969	1718	1610	1560	672	V(C-Cl) 807
2	3356	3068	2971	1714	1623	1579	708	V(C-Cl) 812
3	3373	3051	2949	1699	1644	1588	688	V(C-Cl) 806
4	3164	3055	2930	1680	1612	1549	676	V(C-Cl) 818, V(NO_2) 1509,1311
5	3166	3040	2937	1666	1638	1582	709	V(C-Cl) 820 V(O-H) 3203
6	3248	3022	2951	1692	1626	1580	675	V(C-Cl) 844
7	3215	3070	2966	1695	1620	1528	719	V(C=O) 1662
8	3244	3056	2945	1678	1620	1546	686	V(C=O) 1657
9	3184	3030	2938	1703	1614	1566	685	V(C=O) 1668
10	3243	3046	2960	1688	1625	1574	669	V(C=O) 1610 V(NO_2) 1502,1326
11	3193	3066	2955	1701	1598	1566	644	V(C=O) 1625 V(O-H) 3208
12	3290	3064	2978	1643	1608	1572	651	V(C-Cl) 832 V(C=O) 1628

Table (3)
^{1}HNMR Spectral Data (δ ppm) For Selected Compounds.

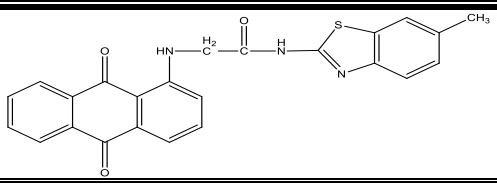
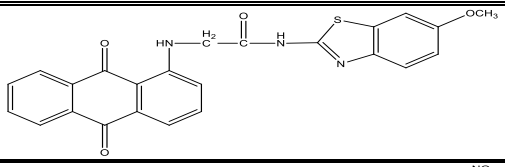
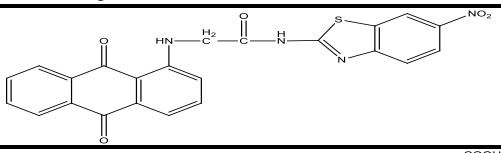
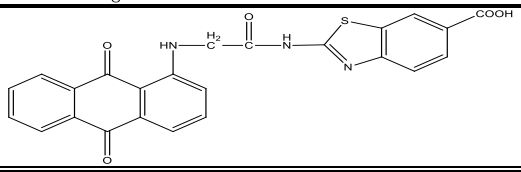
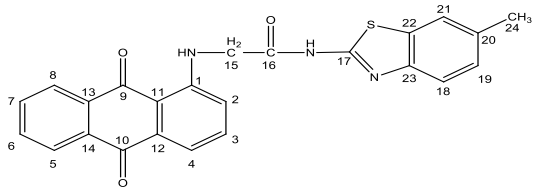
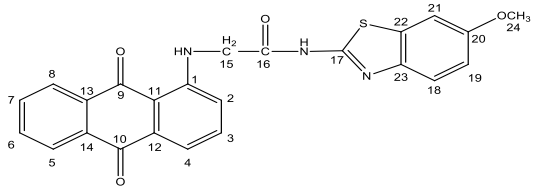
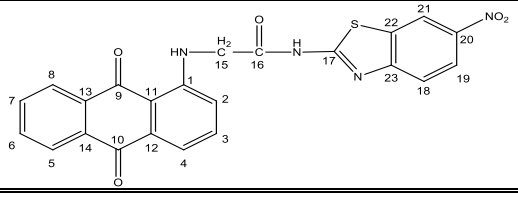
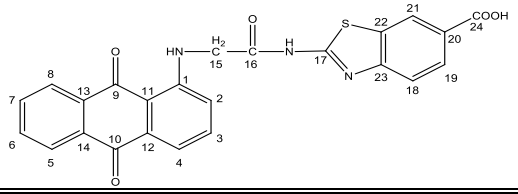
Comp. No.	*Compound Structure*	*^{1}HNMR Spectral Data (δ ppm)*
8		2.08 CH_3 protons 3.42 (N–**CH_2**–CO–) protons 4.02(C-**NH**-CH_2) proton (7.38-8.12) aromatic ring protons 8.90 (C-**NH**-CO-) proton.
9		3.36 OCH_3 protons 3.74 (N–**CH_2**–CO–) protons 4.71 (C-**NH**-CH_2) proton (7.01-8.20) aromatic ring protons 8.86 (C-**NH**-CO-) proton.
10		3.61 (N–**CH_2**–CO–) protons 4.58 (C-**NH**-CH_2) proton (7.00-7.55) aromatic ring protons 8.70 (C-**NH**-CO-) proton.
11		3.64 COOH proton 3.98 (N–**CH_2**–CO–) protons 4.45 (C-**NH**-CH_2) proton (7.29-8.12**)** aromatic ring protons 8.76 (C-**NH**-CO-) proton.

Table (4)
^{13}CNMR Spectral Data (δ ppm) For Selected Compounds.

Comp. No.	*Compound Structure*	*^{13}CNMR spectral data (δ ppm)*
8		28.24 C_{24} , 55.65 C_{15} ,109.49-145.47 (C_1-C_8), (C_{11}-C_{14}), (C_{18}-C_{23}), 166.85 C_{17} , 169.49 C_{16} , 180.16 C_9, C_{10}
9		26.15 C_{24} , 52.44 C_{15} , 118.41-141.67 (C_1-C_8), (C_{11}-C_{14}), (C_{18}-C_{23}) , 164.33 C_{17} , 170.91 C_{16} , 178.25 C_9, C_{10}
10		53.38 C_{15} , 123.74-132.57 (C_1-C_8),(C_{11}-C_{14}), (C_{18}-C_{23}), 167.75 C_{17} , 168.11 C_{16} , 179.98 C_9, C_{10}
11		51.37 C_{15} , 121.72-143.81 (C_1-C_8), (C_{11}-C_{14}), (C_{18}-C_{23}) , 152.24 C_{24} , 165.37 C_{17} , 171.50 C_{16} , 180.77 C_9, C_{10}

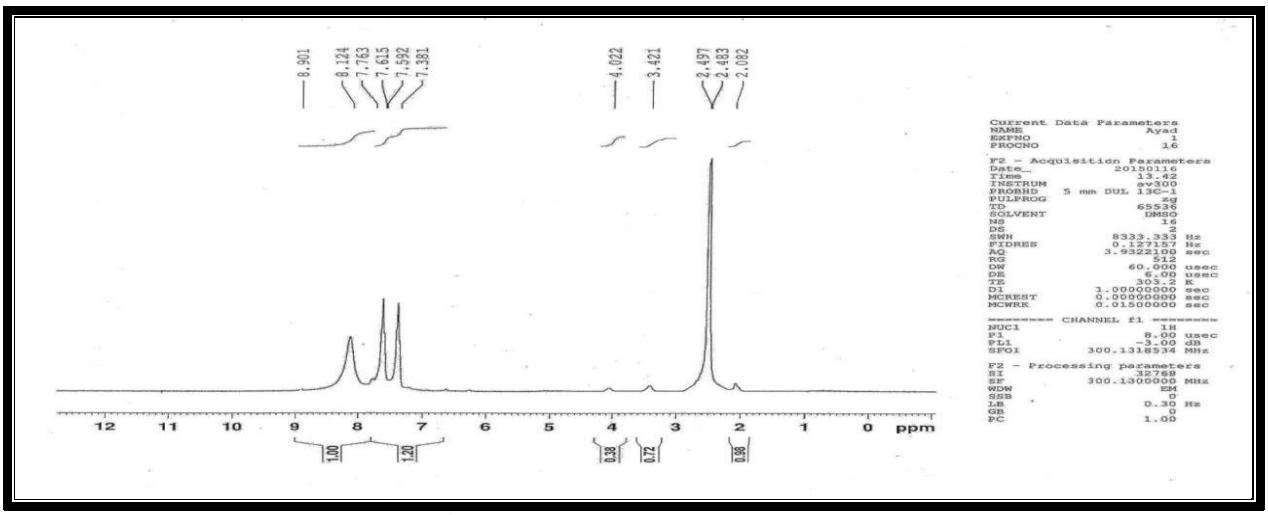


Fig.(1): ^{1}HNMR Spectrum for compound (8).

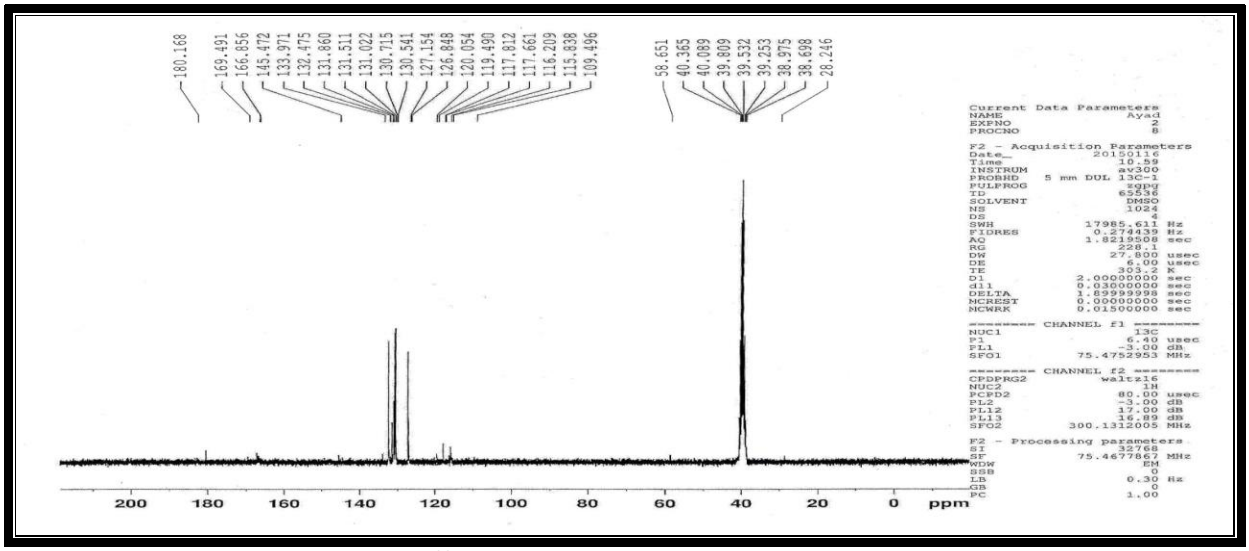


Fig.(2): ^{13}CNMR Spectrum for compound (8).

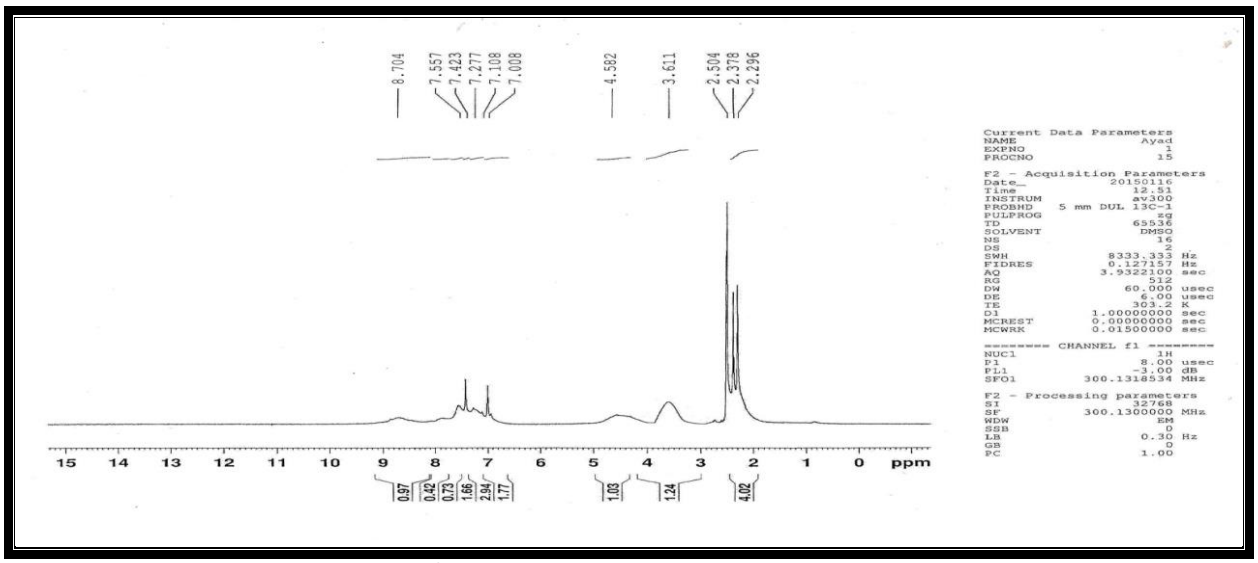


Fig.(3): ^{1}HNMR Spectrum for compound (10).

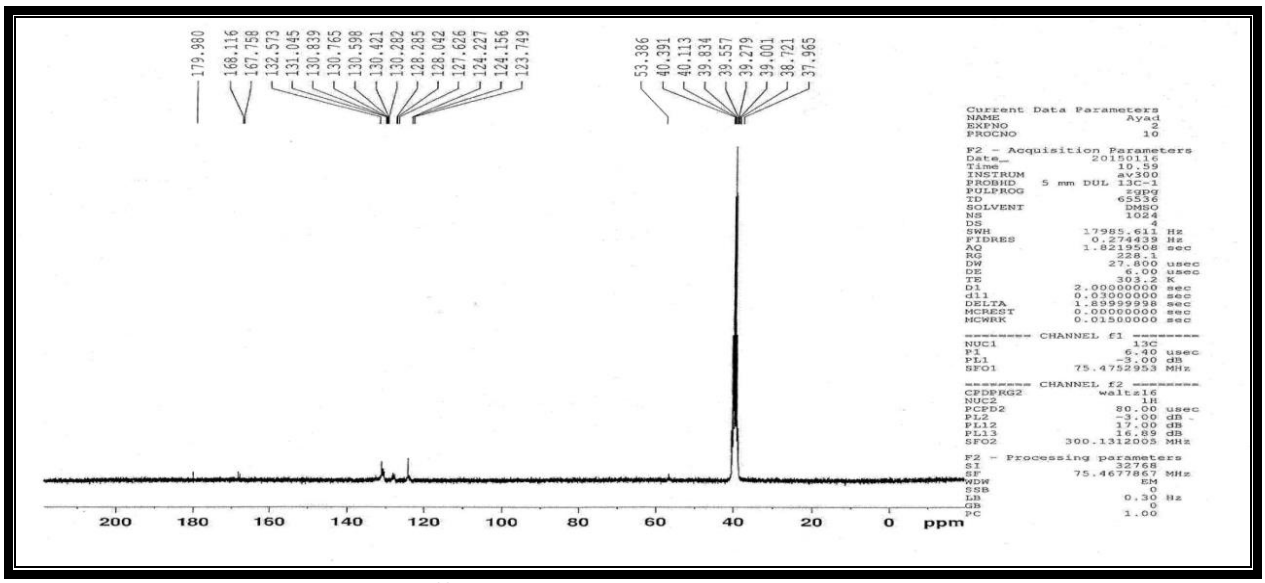


Fig.(4): ^{13}CNMR Spectrum for compound (10).

Antibacterial Screening

All the newly synthesized compounds were screened for their antibacterial activity. For antibacterial studies microorganisms employed were *Streptococcuss pneumoniae*, *Enterococcus faecalis*, *Salmonella typhi.*, *Acinetobacte sp.* were used as microorganisms.

The antibacterial activities were assessed by minimum inhibitory concentration (MIC). The data are summarized in Table (5), and show that many compounds display certain activity against the tested microorganisms.

Table (5)
Antibacterial Data for the Selected Synthesized Compounds.

Compound no.	*Antibacterial activity data in MIC (µg/mL)*			
	Streptococcuss Pneumoniae	*Enterococcus faecalis*	*Salmonella typhi.*	*Acinetobacte sp.*
7	25	20	15	25
8	50	25	20	50
9	10	25	25	20
10	25	15	20	15
11	20	20	50	20
12	20	15	15	25
Ceftriaxone (std.)	5	5	10	1
DMSO(control)	-	-	-	-

We can see from Structure-activity relationship (SAR) that the antibacterial activity of the prepared compounds may be due the presence of the versatile pharmacophore which increase the lipophilic character of the molecules, which facilitate the crossing through the biological membrane of the microorganism and thereby inhibit their growth.

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الخلاصة

تضمن هذا البحث تحضير مشتقات حلقية غير متجانسة جديدة لـ ١-امينوانثراكوينون معوضة بـ ٢- امينوبنزوثايازول، تم الحصول على مشتقات ٢-امينوبنزوثايازول المعوضة في الموقع ٦ على الحلقة الاروماتية من تفاعل الانيلين المعوض في الموقع (٤) مع ثايو سيانيت الامونيوم في البروم وحامض الخليك الثلجي. استخدمت هذه المشتقات بعد ذلك لتحضير ٢-(٢-كلورو اسيتيل امينـو)-٦- بنزوثايازول معوض المركبات [١-٦] بمعاملتها مع كلورو اسيتيل كلورايد في الكلوروفورم. تصعيد هذه المركبات مع 1- امينوانثراكوينون في الايثانول المطلق انتج N (٢-(٢-اسيت اميدو)-٦- معوضة بنزوثايازول -٢-ايل ١- امينوانثراكوينون المركبات [٧-١٢]. شخصت المركبات المحضرة بواسطة درجات الانصهار، طيف الاشعة تحت الحمراء الدقيق وطيف الرنين النـووي المغناطيسي بنوعيـه. اختبـرت بعض المركبـات المحضرة الجديدة فعالياتها المضادة للبكتريا لنوعين من البكتريا موجبة الصبغة ونوعين اخرين سالبة الصبغة وتم مقارنتها مع سيفترياكسزون الذي استخدم كدواء قياسى حيث اظهرت النتائج ان معظم المركبات التي تم اختبارها تمتلك فعالية جيدة الى متوسطة في تثبيط هذه الاجناس من البكتريا مقارنة بالدواء القياسي اعلاه.