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Synthesis, Characterization and Antibacterial Studies of New Carboxamide Derivatives of Dapsone

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Abstract:

The project aims at the synthesis of Carboxamide derivatives of Dapsone. Three derivatives of benzoic acid, 4-hydroxybenzoic acid and 4-chlorobenzoic acid are used to prepare carboxamides of dapsone (I, II and III respectively). All the product is characterized by spectrophotometer. Fourier transmission Infra red (FTIR) shows the distinguish bands of carboxamide, amine, carboxyl and hydroxyl group. The UV-Spectra shows two types of transition л → л* and n→ л*. Proton Nuclear magnetic resonance spectra (^{1}H-NMR) of carboxamide derivatives shows signals of aromatic protons and broad singlet to the amide proton. Mass spectra of amides have same base peaks due to the loss of C_6H_6SNO from second fragmentation. Diffusion agar method is used in biological activities. Three types of bacteria (*Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*) are used in this studies , the carboxamide III has high biological activity than others. By using Density functional theory (DFT) studies explain the stability the carboxamide compounds.

Keywords: Dapsone, carboxamide, characterization, carbonyl.

تحضير وتشخيص ودراسة الفعالية الاحيائية لمشتقات الكاربوكسي امايد الجديدة للدابسون

رحيم جميل محسن ، لقاء عبدالرضا رحيم الربيعي

الكيمياء الصيدلانية / كلية الصيدلة جامعة البصرة

الخلاصـــــــــة:

يهدف هذا البحث الى تحضير بعض مشتقات الكاربوكسي امايد للدابسون. استخدمت مركبات حامض البنزويك ، ٤-هيدروكسي حامض البنزويك و ٤-كلورو حامض البنزويك. لتحضير مشتقات الكاربوكسي امايد من الدابسون (I, II,III) بالتوالي . شخصت جميع المركبات طيفيا. اعطى طيف الأشعة تحت الحمراء الحزم المميزة لمركبات الكاربوكسي امايد مثل الامايد والكاربونيل والهيدروكسيل . شخص طيف الأشعة فوق البنفسجية نوعين من الانتقالات ($n \rightarrow \pi^*$ و $\pi \rightarrow \pi^*$) . استخدم طيف الرنين النووي المغناطيسي للبروتونات لتشخيص المركبات المحضرة واعطى الحزم المميزة لبروتونات الحلقة الأروماتية وكذلك لبروتونات الامايد. استخدمت طريقه الانتشار في تحديد الفعاليات الحيوية التي اجريت على ثلاث انواع من البكتريا المتضمنة المكورات العنقودية ، اشريشيا القولونية والزائف الزنجارية واظهرت النتائج ان الكاربوكسي (III) امايد هو الاكثر فعالية بالمقارنة مع بقية المركبات .

والتي اثبتت استقرارية مركبات الكاربوكسي امايد المحضرة (DFT) كما اظهرت الدراسة النظرية باستخدام الدالة

الكلمات المفتاحية : دابسون ، الكاربوكسي امايد ، تشخيص ، كاربونيل

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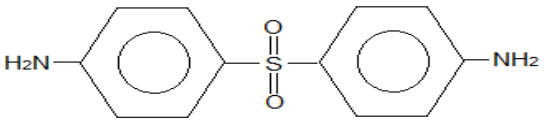
Introduction

The sulfones are primarily of interest as antibacterial agents, though there are some reports of their use in the treatment of malarial and rickettisial infections. They are less effective than the sulfonamides. Several sulfones have proved useful in the treatment of leprosy, but among them only dapsone is clinically used today [(1)].



Dapsone also a sulphone analog, has been proved to be a powerful narrow antibacterial agent [(2)]. A series of Dapsone derivative has been prepared as Schiff base as antimicrobial agents [(3)], acyl derivatives as new inhibitors of the arginine methyl transferase $hPRMT_1$ [(4)]. Amide derivatives of dapsone and non-steroidal anti-inflammatory were prepared as

compound have anti-inflammatory and antibacterial activity with low ulcerogenic action[5]. The derivatives and analogs of dapsone against mycobacterium leprae as antimicrobial agents were studied [6].

The carboxamide groups (-CONR-) occur in many drugs, natural products and peptides, therefore, over the past century, we have seen development of many methods for synthesizing this important functional group [7]. There are many methods for synthesizing this important functional group such acid halides, acid anhydrides, activated amides, acyl azides and activated ester.

The goal of the research is to study synthesis and characterization of new amides derivative of dapsone and study its biological activities.

Experimental:

Materials

All materials were supplied from Fluka and BDH , Benzoic acid,4-chlorobenzoic acid, 4-hydroxy benzoic acid , sodium matel , Dapsone, tetrahydrofuran (THF), methanol , dichloromethane , Ethyl acetate and sodium bicarbonate.

Analyses and physical measurement:

Infrared spectra in the range 4000-400 cm^{-1} were obtained from samples in the form of KBr pellets using a Unicam FTIR spectrometer. 1HNMR spectra were recorded with a Bruker AMX-500 Spectrometer in DMSO-d_6. Chemical shifts for proton resonances are reported in ppm (δ) relative to tetramethylsilane. The mass spectra of compounds were recorded Using Agilent Technologies-597SC spectrometer instrument using dimethylsulfoxide as solvents. Both H-NMR and Mass spectrophotometer were performed at the analytical laboratory of Tarbiat Modares, University of Tahran, Iran.

Preparation esters of benzoic acid and its derivatives [8]:

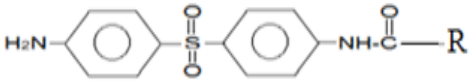
(0.1 mol) (12.2 gm) benzoic acid,(0.1 mol) (13.8gm) 4-hydroxybenzoic acid or (0.1 mol) (15.65gm) 4-chlorobenzoic acid were dissolved in 20 ml

methanol at a 100 ml round flask , then added 3 ml of con.H_2SO_4.The mixture was refluxing with stirring for 1 hour, then cool the mixture. It was separated by adding 50 ml dichloromethane. Washing the organic layer with 20 ml of water and 20 ml of sodium bicarbonate solution (5%) respectively. The melting point (m.p.) or boiling point (b.p.) of ester products were recorded as the following:

Ester product	Properties	.p./ b.p. (°C)
Methyl benzoate	**Liquid colorless**	**197-199**
Methyl-4-hydroxybenzoate	**White crystalline powder**	**125-127**
Methyl-4-chloro benzoate	**White crystal**	**42- 45**

Preparation of carboxamides of dapsone [9]:

Carboxamide of dapsone was prepared via aminolysis reaction. The solution of ester (0.001 mol) (0.136 gm, 0.152 gm and 0.17 gm) of methyl benzoate, (methyl-4-hydroxy benzoate,methyl-4-chlorobenzoate) respectively and 0.001 mole (0.24 gm) of dapsone was dissolved in 20 ml tetrahydrofuran (THF),in stopper flask with stirr were heated at 35 ºC . Then it was treated with the requiresite volume of freshly prepare saturated methanolic sodium methoxide dropwise, then left overnight with stirrer at 25˚C. The reaction mixture was then treated with ethyl acetate ,methanol to form the products with mp. (165, 142 and 150)˚C, respectively.



when R = Ph Carboxamide I

R = 4-hydroxy phenyl Carboxamide II

R = 4-Chloro phenyl Carboxamide III

Antibacterial Studies:

The synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* , *Escherichia coli*, and *Pseudomonas aeruginosa* at a concentration of 100 mg/ml by using agar diffusion method[10].

Results and Discussion:

The methyl benzoate derivatives were used in the preparation of carboxzmide. The aminolysis reaction is very useful method to synthesis af amide. Single amide of dapsone are prepare by (1:1) molar ratio, but there is achance to react both amine groups of dapsone to formation doublet carboxamide. Both single or doublet carboxamide of dapsone can be estimated in FTIR, NMR and Mass spectra [8].

Carboxamide contain carbonyl (C=O) and ether (N-C) dipoles arises from covalent bonding between electronegative oxygen or nitrogen atoms and electro-neutral carbon atoms. The direct conversion of a carboxylic acid to an amide is difficult, because amines tend to convert carboxylic acids to their highly unreactive carboxylates[11].

The UV spectra (in THF, figure 2) of the dapsone show that bands at 260 *nm* and 290 *nm* assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ of the conjugated system of dapsone respectively.

The dapsone derivatives spectrum shows that absorption of amide group confirm with in literature, л → л*, n→ л* transition, at 210-220 and 300 *nm* respectively [12]. The high intensity of all transition in all carboxamide derivatives is due to increase conjugation between both amide and aromatic ring compared with dapsone.

Generally, amide is characterize by a conjugated system in which the delocalization of the electrons of the nitrogen. The diphenyl rings of dapsone and benzoate ring in carboxamide were given strong $n \rightarrow$ л* transition at 300 nm[ʌ].

In amides, acids,esters or acid halides, the substituents viz. NR2, OH, OR, or X on carbonyl groups show pronounced hypsochromic effect on the $n \rightarrow \pi^*$ transitions. The hypsochromic effect is due to inductive effect of nitrogen, oxygen or halogen atoms. The heteroatom withdraws electrons from carbonyl carbon and makes carbonyl oxygen lone pair of electrons morestabilized due to

its involvement in increasing C=O bond order. As a result, then n → л* transitions of these compounds is shifted to 200-215 nm range relative to 270 nm in aldehydes and ketones. Conjugation of the carbonyl group with double bond shifts both n → л* and π → π* transition to longer wavelengths. The effect on π → π* band is more pronounced[١٣].

From FTIR spectra of dapsone and its carboxamide derivatives are shown in figures (3 to 5) , table 2. Assignments when comparing the main IR frequencies of dapsone and its derivative, showed prominent peaks for $–SO_2$, $-NH_2$, -CO-NH- and NH- groups in the table-2. The stretching vibration of the sulfone group O=S=O (in dapsone) is at 1338 and 1146 cm^{-1}, the bending vibration of p-disubstituted aromatic ring at 831cm^{-1}. The peaks at 1598cm^{-1} and 3367cm^{-1} correspond to the N-H bending vibration and stretching vibration respectively. The streaching vibration of hydroxyl group in compound (II) is overlaped with streaching vibration of amine group.

Proton Nuclear magnetic resonance spectra (^{1}H-NMR) of all carboxamides of dapsone were performed in deuterated dimethylsulfoxide (DMSO) with tetramethylsaline as an internal standard. All spectra showed a signal at δ= 2.5 ppm for DMSO solvent and sharp singlet δ=3.33 ppm for water in DMSO. From literature, the assignment ^{1}H-NMR data for dapsone was explained as following in figure (6) [١٤].The signals at the rang (6-7.5) ppm were assigned to the aromatic protons, a multiplet being observed because the protons are not equivalent , the broad singlet at the range(8-8.5 ppm) is attributed to the amide proton.

Mass spectra of all carboxamides exhibit parent peaks, and the base peaks of carboxamides are dependent on the substituted benzoic acid. Aromatic carboxylic acids show strong molecular ion of carboxamide I, II and III are seen at m/z 352, 368 and 387 mass unit with intensity of (20 %), (25 %) and (18 %) respectively[١٥].The mass spectra of the carboxamides have base peak at m/z 108 (90 %) due to the loss of C_6H_6SNO from second fragmentation which results in m/z 108 as shown in scheme (1), m/z 248 corresponding to $C_{12}H_{12}N_2O_2S$, dapsone structure and m/z 140 corresponding to C_6H_6NOS species [16].

The carboxamide derivatives of dapsone under study were subjected to antibacterial activity against *E.Coli.* , *S.aureus, P.aeruginosa* and *proteus* at a concentration of 100 mg/mL, dapsone was used as standard drug for comparision as in the table (3). Carboxamide (III) , has more biological activity against E.Coli, and proteous, and it doesn't have any biological activity against pseudomonas aeruginosa and S.aureus. The carboxamide(II) doesn't have biological activities against above species.

DFT calculations of dapsone carboxamide derivatives (figure 13) have been done using the optimized geometry molecular structures, molecular orbital calculation provide a detailed description of orbitals including spatial characteristics .The energy of highest occupied molecular orbital (HOMO) of all dapsone carboxamide derivatives are :

(E_{HOMO} = -9.043694 ev, E_{HOMO}= -9.039297 ev and E_{HOMO}= -9.06631ev) respectively ,whereas the energy of lowest unoccupied molecular orbital(LUMO) are (E_{LUMO} = - 0.8086302 ev , E_{LUMO}= -0.7763753 ev and E_{LUMO}= -1.002968 ev) respectively, the highest value in the HOMO and LUMO energy gap explains the high stability of these compounds, and other physical properties can be shown in table 4 .

Conclusion:

Carboxamide derivatives of dapsone were prepared .The products were characterized by UV., FTIR, H^1NMR and Mass spectra. The biological activates against several type of bacterial were studied. The highest energy value in both HOMO and LUMO energy gap estimate the high stability of these compounds.
The carboxamide (III) showed higher biological activity than others. The highest energy value in both HOMO and LUMO energy gap estimate the high stability of these compounds.

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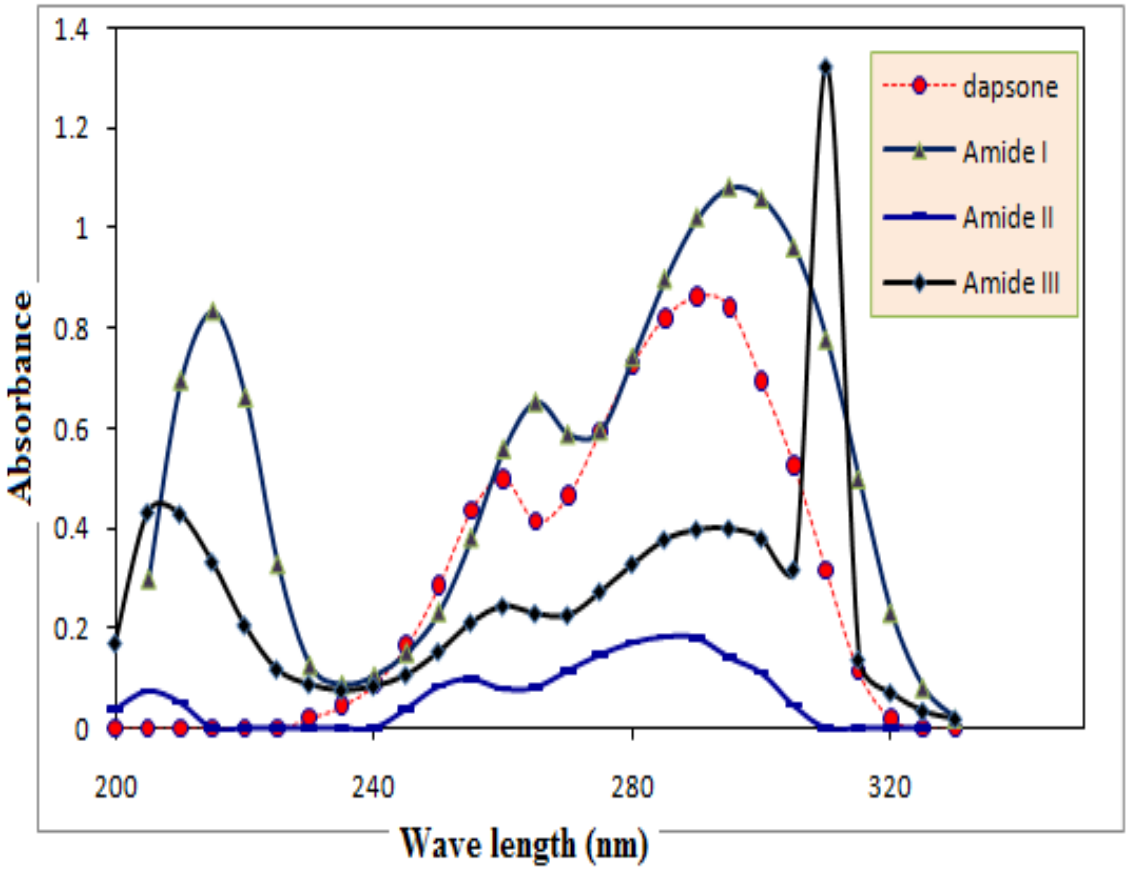


Figure (2): UV absorption of Carboxamides I, II and III.

Table (2): The characteristic FT-IR spectra bands in carboxamides.

compounds	Stretching vibration (ν_{NH2})	ν_{SO2}	ν_{C-S}	ν_{NH2} bending	$\nu_{C=O}$(-NH-CO-)
Dapsonebenzamide I	(free NH) Sym 3392, asym.3456 . (NH amide) sym. 3336 , asym. 3367 .	sym. 1145 s asym. 1335	648	1595 s	1631 s
Dapsone-4-hydroxy benzamide II	(free NH) sym. 3396 b. a sym. 3456 b. (NH amide) sym.3334 m asym. 3365 m	sym. 1147 asym. 1338 w	648	1589	1631 s
Dapsone-4-chloro benzamide III	(free NH) Sym.3456 s asym.3325 (NH amide) Sym. 3240 br. a sym. 3367 br.	sym.1147 s asy.1338 w	648	1593	1627

s= strong , m = medium , br. =broad

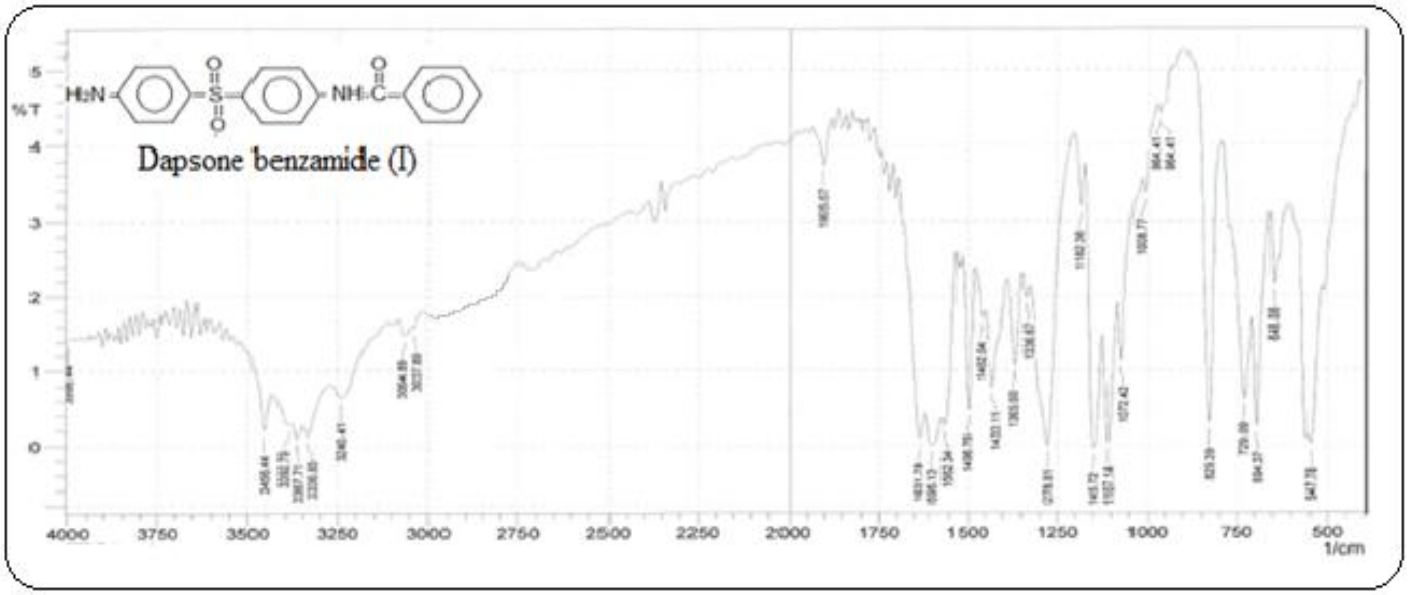


Figure (3): FTIR spectra of dapsone benzamide (I).

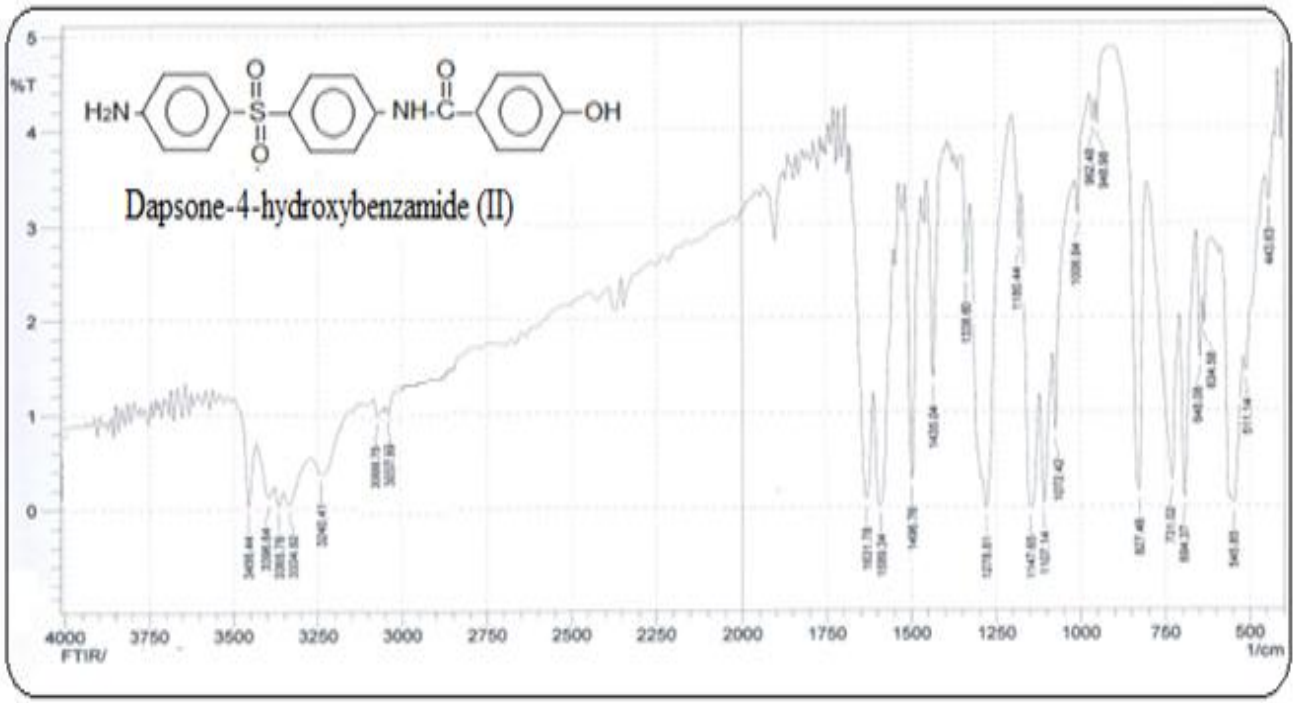


Figure (4): FTIR spectra of dapsone-4-hydroxybenzamide (II).

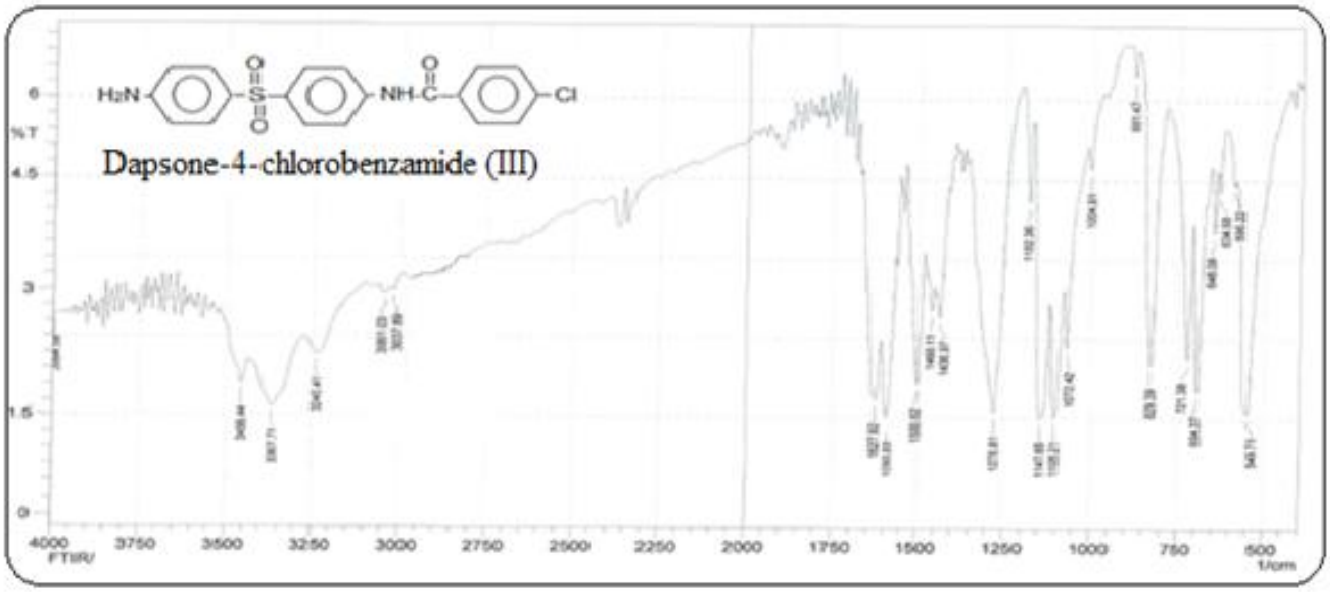


Figure (5): FTIR spectra of dapsone 4-chlorobenzamide (III).

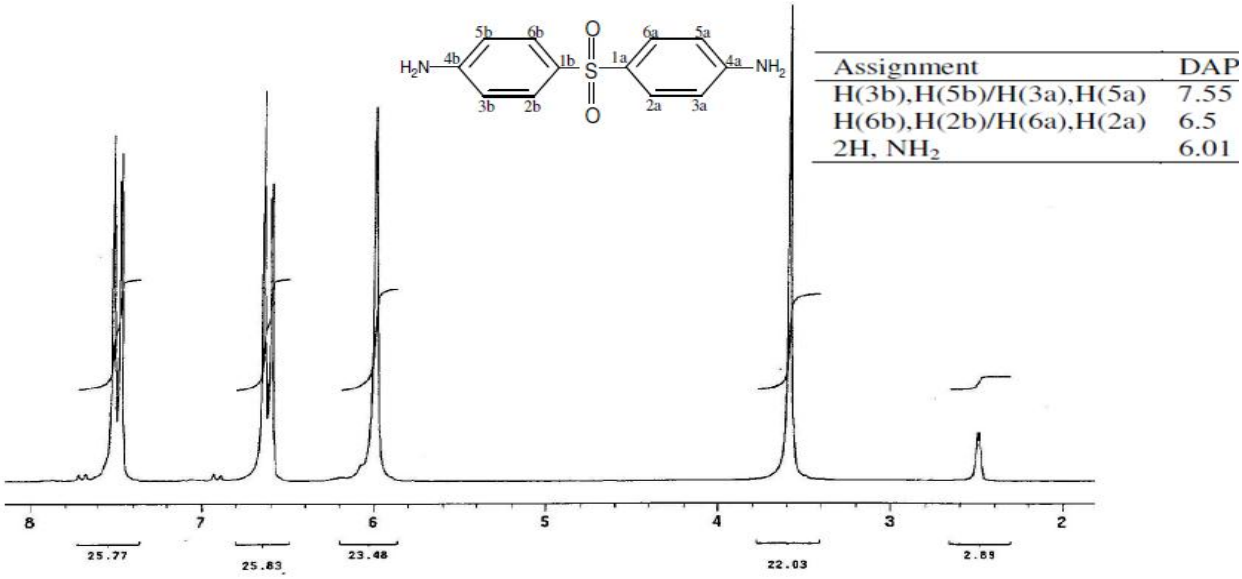


Figure (6): ^{1}H-NMR spectra of dapsone.

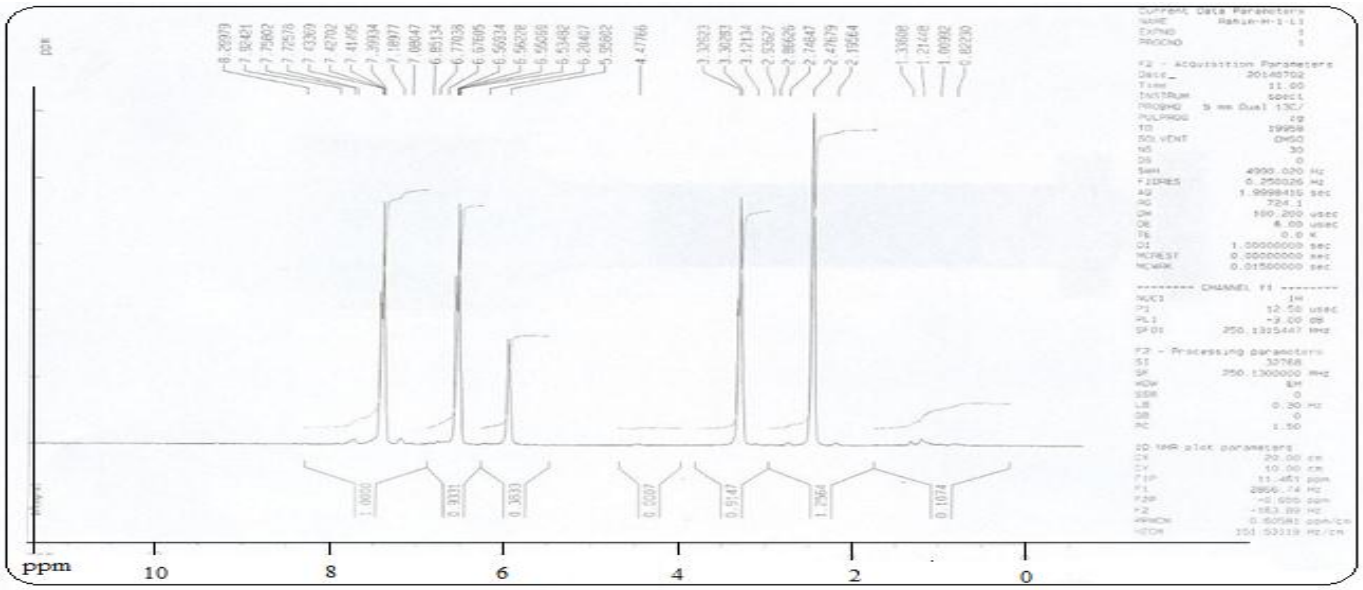
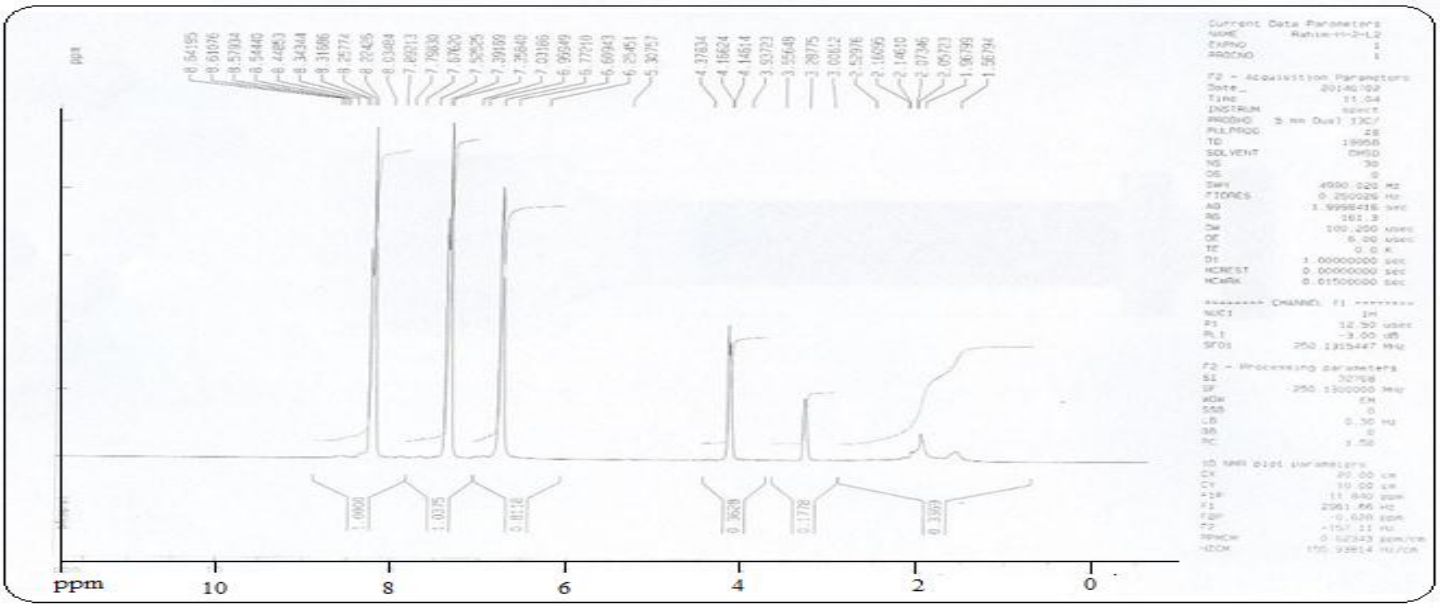


Figure (7): ^{1}H-NMR- Spectra of Dapsone Benzcarboxamide (I).



Figure(8): ^{1}H-NMR- Spectra of Dapsone 4-hydroxybenzamide (II).

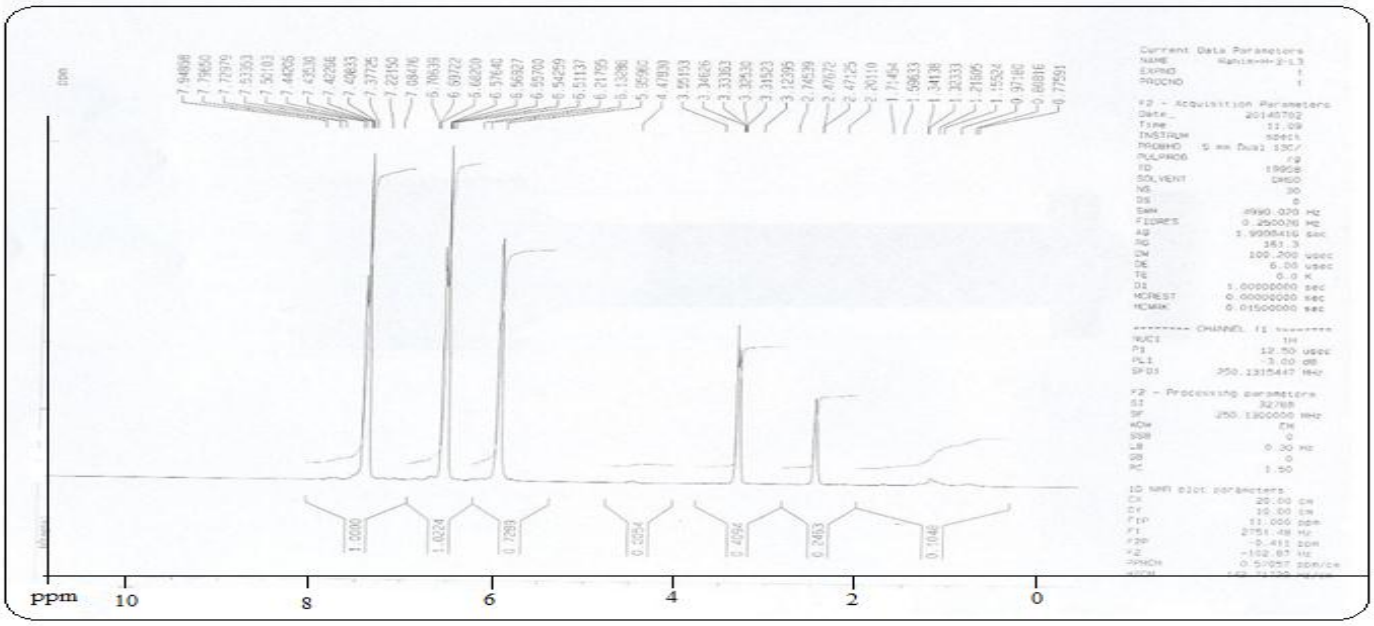
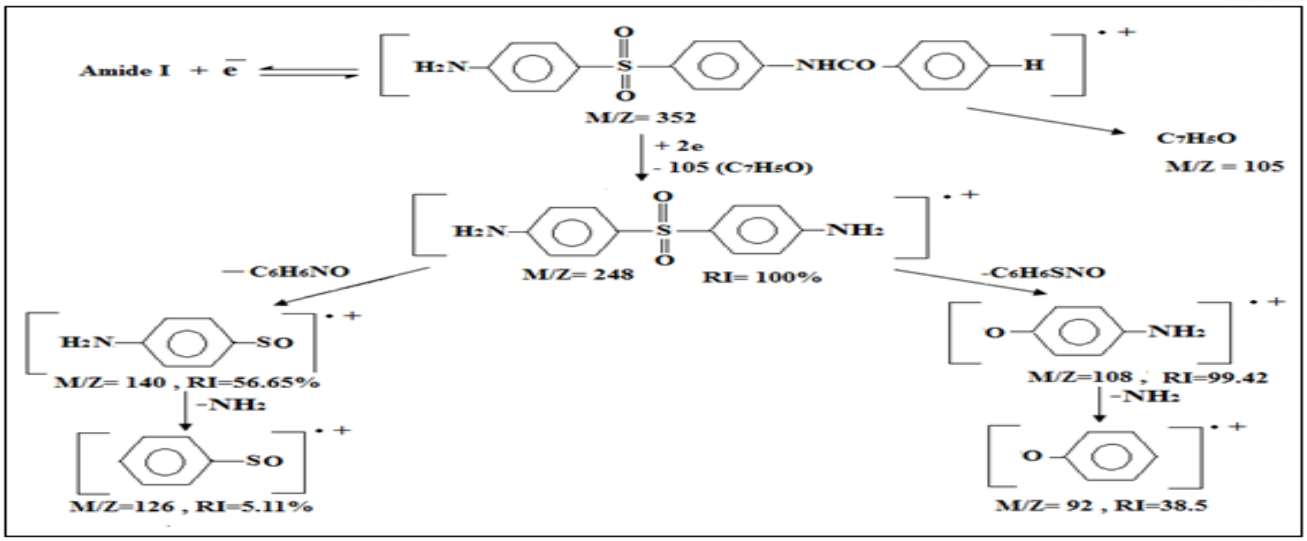


Figure (9): ^{1}H-NMR- Spectra of Dapsone 4-Chlorobenzamide (III).



Scheme (1): The suggest major fragmentation path of carboxamides of dapsone.

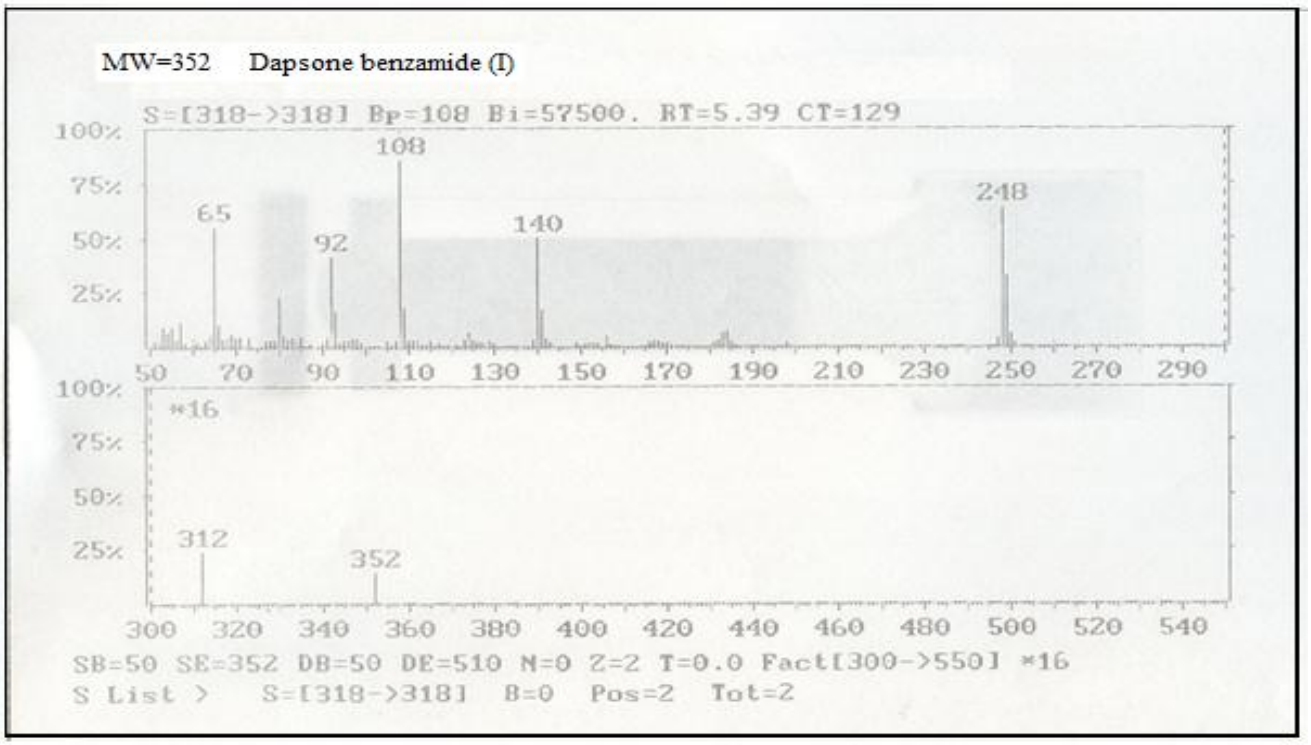


Figure (10): Mass spectrum of Dapsone benzamide (I).

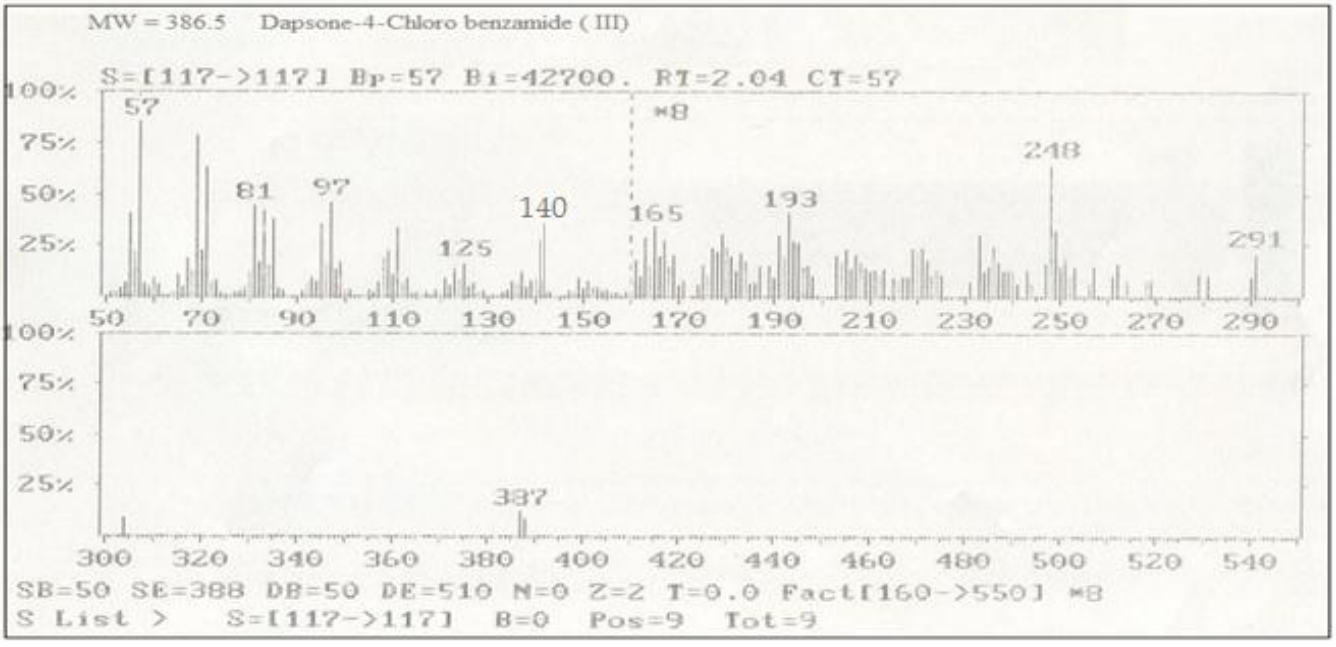


Figure (11): Mass spectrum of Dapsone 4-hydroxybenzamide (II).

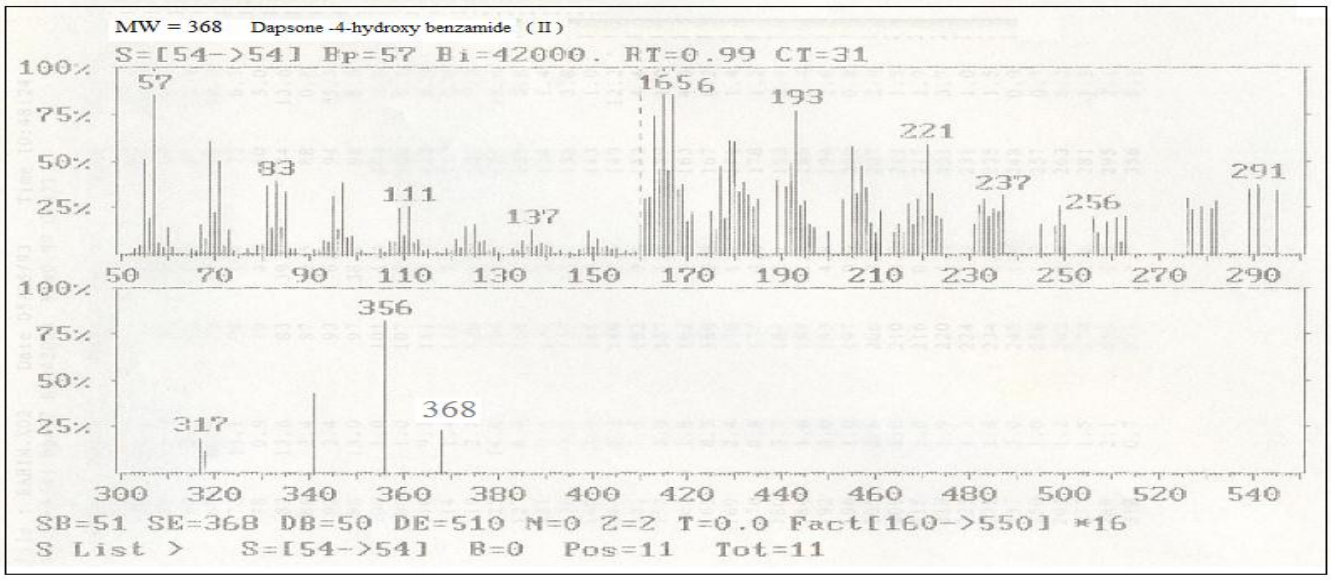
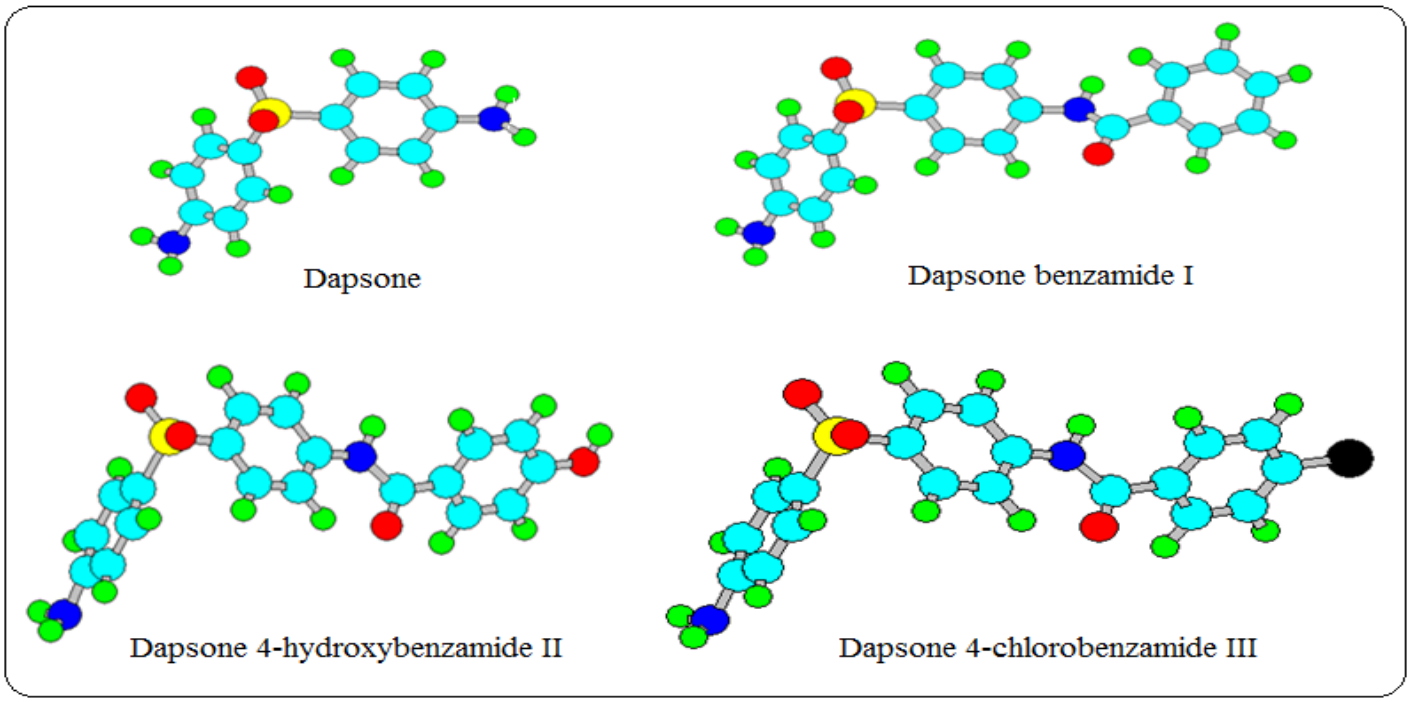


Figure (12): Mass spectrum of Dapsone 4-chlorobenzamide (III).

Table (3): Show zone inhibition in antibacterial activity of dapsone and its carboxamide derivatives.

Compounds	*E.Coli*	*S. aureus*	*Pse. aeruginosa*	*proteus*
Dapsone benzamide (I)	0.9 mm	1.2 mm	*no*	no
Daosone-4-hydroxy benzamide (II)	no	no	*no*	no
Dapsone-4-chlorobenzamide (III)	2.5 mm	no	no	1.6 mm
Dapsone	1.5 mm	0.9 mm	no	1.4 mm

[Note: Paper disk with a diameter of 0.٦ mm, no = no effect]



Figure(13): Optimized 3D structures of Dapsone and its carboxamide derivatives(I, II and III).

Table (4): Physical properties of studying compounds.

Compounds / Physical properties	Dapsone	Dapsone-benzamide	Dapsone-4-hydroxy benzamide	Dapsone-4-chloro benzamide
Total Energy (kcal/mol)	-62343.7355651	-89647.286719	-96425.1651829	-96598.0514023
Binding Energy (kcal/mol)	-3099.9804431	-650396.4354776	-4674.9473149	-4553.1139543
Heat of Formation (kcal/mol)	- 12.5584431	-18.2945416	-63.7693149	-24.6069543
Dipole moment (Debyes)	5.159	6.435	6.387	5.778
Surface Area (appprox.) (A^2)	361.75	494.35	509.07	529.46
Surface Area (Grid) (A^2)	437.37	580.99	589.76	604.48
Volume (A^3)	700.35	966.54	986.41	1007.57
Mass (a.m.u.)	248.3	352.41	368.41	386.85
log p	-2.94	-1.97	-2.99	-2.19
Polarizability (A^3)	23.93	35.52	36.15	37.44
Refractivity (A^3)	76.31	110.06	111.67	114.78
Hydration energy (kcal/mol)	-16.72	-14.65	-21.52	-14.31
E_{LUMO} (ev)	-0.3859762	-0.8086302	-0.7763753	-1.002968
E_{HOMO} (ev)	-9.05035	-9.043694	-9.039297	-9.06631