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Synthesis and Characterization of Some New Morpholine Derivatives

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Abstract:

In this paper a new series of morpholine derivatives was prepared by reacting the morpholine with ethyl chloro acetate in the presence triethylamine as a catalyst in benzene gave morpholin-N-ethyl acetate(1) which reacted with hydrazine hydrate in ethanol, and gave morpholin-N-ethyl acetohydrazide (2) . Morpholin-N-aceto semithiocarbazide (3) were prepared by reacting compound(2) with ammonium thiocyanate , concentrated hydrochloric acid and ethanol as a solvent .Compound (3) reacted with sodium hydroxide and hydrochloric acid to give 5-(morpholin-N-methylene)-1*H*-1,2,4-triazole-3-thiol (4) .The new series of 1,2,4-triazol derivatives (5-8) was synthesized by reaction of compound(4) with formaldehyde , DMF as a solvent and different secondary amines. Preparation of new 1,2,4-triazoline derivatives (9) by reaction compound (4) with bromo acetic acid . Reaction of compound (9) with different aromatic aldehyde and dimethyl sulfoxide as a solvent obtained compounds (10-13).

Key words: Morpholine , 1,2,4-triazole and Mannich Reaction.

Introduction:

Morpholine is a six-membered heterocyclic compound [1]. It has synonyms Tetrahydro-1,4- oxazine; 1-Oxa-4-azacyclohexane; Diethylene oximide [2] and an organic chemical compound having the chemical formula $O(CH_2CH_2)_2NH$, this heterocyclic structure features both amine and ether functional groups.As shown in the following Figure (1):

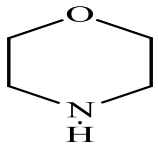


Fig.(1)
Morpholine

Morpholine derivative plays an important role in the treatment of several diseases [3]. Morpholine derivatives find their wide spectrum of antimicrobial activity and insecticidal activity [4]. Morpholine used an emulsifier for cosmetics, rubless waxes,

and polishes, dyes , Pharmaceuticals and catalysts[5,6]. 1,2,4-Triazole has wide range of pharmacological properties[7] and variety of biological activities such as anti-inflammatory [8], Analgesic[9] , antibacterial[10], antifungal, antitumoral [11,12]. Mannich reaction is an organic compounds with the general formula - CH_2-NR_2 they were discovered in 1912 by Mannich and Krosch[13,14]. The Mannich reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or either primary or secondary amine [15]. Mannich base compounds have been studied intersively mainly because of their application of organic synthesis especially for preparing dyes ,industrial, pharmaceutical ,and antimicrobial [16,17].

Materials and Methods:

Chemicals used in this work are supplied from Merck, BDH ,sigma Aldrich ND Fluka companies and are used without further purification. Melting points were recorded by using digital Stuart scientific SMP3 melting point apparatus and are uncorrected. FT-IR spectra were recorded on SHIMAZU FT-IR-8400 Fourier transform Infrared spectrophotometer using KBr discs in the (4000-6000) cm^{-1} spectral range internal reference measurements which were made at College of Pharmacy- Al-Mustansiriya University . ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Burker 500M Hzistrument using DMSO-d_6 as solvent and TMS as internal reference measurements were made at the Chemistry Department, Al-Albyt University, Jordan .

Experimental :

Synthesis of Morpholin-N-ethyl acetate (1)[18]:

A mixture of morpholine (9 ml ,0.1mol) , ethylchloro acetate(12ml ,0.1mol) and triethyl amine(10 ml, 0.1mol) with benzene as a solvent in (100ml) round bottom flask was refluxed for 6 h. at (115^0c).The resultant reaction mixture was cooled at room temperature and the solid was filtered dried and recrystallized from ethanol. The physical properties of compound [1]are listed in Table (1).

Synthesis of Morpholin-N-acetohydrazide (2) [19]:

A mixture of compound (1) (10ml.0.05mol), hydrazine hydrate 80% (3ml, 0.05mol) and ethanol(20ml) were put in round bottom flask and refluxed for 6 h. The mixture was concentrated, cooled and the white crystal was filtered and recrystallized from ethanol. The physical properties of compound (2) are listed in Table (1).

Synthesis of Morpholin-N-aceto semithio carbazide(3)[20]:

In (150ml) round bottom flask dissolved compound (2) and ammonium thiocyanate (5 gm,0.06mol) in 10ml DMF then added 8ml HCL in absolute ethanol(50ml) . The mixture was refluxed for 20h . The solvent was evaporated and the residue poured on crushed ice with stirring. The precipitate was filtered,dried and recrystallized from ethanol .The physical properties of compound (3) are listed in Table (1).

Synthesis of 5-(morpholin-N-methyl)-1*H*-1,2,4-Triazole-3-Thiol (4)[21]:

To a solution of compound (3)(2 gm,0.01mol) in (5ml) DMF and (15ml) of 10%NaOH were refluxed for 3h.The mixture was treated with charcoal and then removed by hot filtration. The solution was acidified by 10%HCl with cooling. The precipitate was filtered, dried and recrystallized from ethanol .The physical properties of compound [4] are listed in Table (1).

General Methods for the Synthesis of 1,2,4-Triazoles(5-13)[22]:

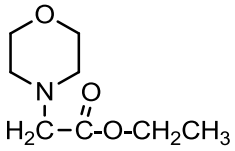
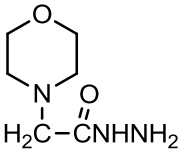
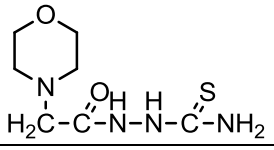
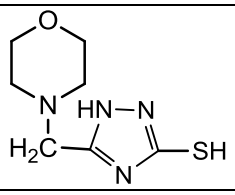
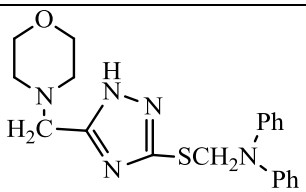
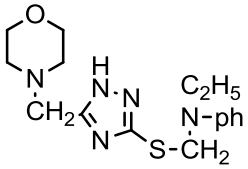
A):-Preparation of Morpholine Substituted 1,2,4-Triazoles (5-8):

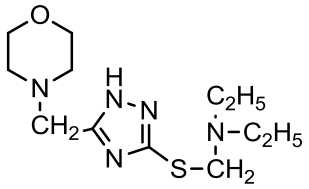
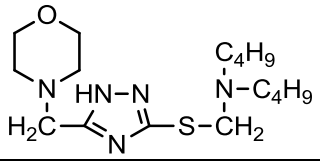
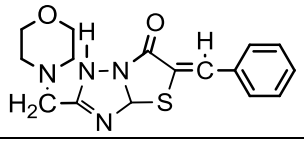
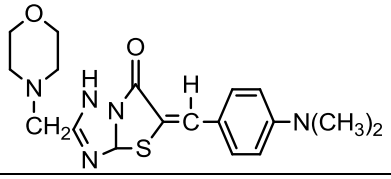
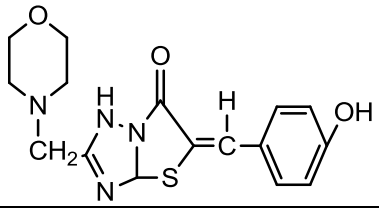
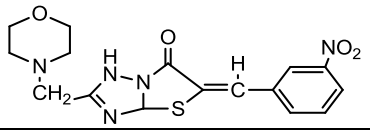
In round bottom, flask was placed solution of compound (4) in 10ml of DMF With (0.002mol) of different amines{N- di-phenylamine, N-ethylaniline, N-diethylamine, N-di-n-butylamine} and formaldehyde (0.02mol) . The mixture was refluxed for 3h. The solvent was evaporated and the residue poured on crushed ice with stirring. The precipitate was filtered,dried and recrystallized from DMSO . The physical properties of compounds (5-8) are listed in Table (1).

B):-Preparation of Morpholine Substituted 1,2,4-Triazoline(9-13):

In the round bottom, flask was dissolved(0.5gm,0.002 mol) of compound (19) an bromo acetic acid (0.3 gm, 0.002 mol) in 10 ml of DMSO then added triethyl amine (1ml) .The product was compound[9]. Then mixture was refluxed for 0:30 h. and added(0.002mol) different aromatic aldehyde{benzaldehyde, 2,4-diethylamine benzeldehyde, m-nitrobenzaldehyde, P-hydroxybenzaldehyde} in presence 10%NaOH then refluxed for 1h .The solvent was evaporated and the residue was poured on crushed ice with stirring . The precipitate was filtered,dried and recrystallized from DMSO . Physical properties of compounds (9-13) are listed in Table (1).

Table (1): The Physical Properties of Prepared Compounds [1-13]

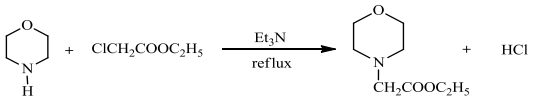
Compd. No.	Nomenclature	Structure formula	Yield %	Color	M. P. °C
1	morpholin-N-ethyl acetate		70	Deep Brown	232-233
2	morpholin-N-acetohydrazide		78	White	105-106
3	morpholin-N-aceto semithio cabazide		88	Light Yellow	216-217
4	5-(morpholin methyl)-1H-1,2,4-triazole-3-thiol		76	Brown	221-222
5	5-(morpholin methyl)-3-thio(methyl-N-diphenyl amine)-1H-1,2,4-triazol		62	Whit	129-130
6	5-(morpholin methyl)-3-thio(methyl-N-ethyl phenylamine)-1H-1,2,4-triazol-3-		55	Light Brown	127-128

7	5-(morpholin methyl)-3-thio(methyl-N-diethylamine)-1H-1,2,4-triazol		78	Yellow	130-131
8	5-(morpholin methyl)-3-thio(methyl-N-dibutylamine)-1H-1,2,4-triazolyl		66	Light Yellow	132-133
10	5-(morpholin methyl)-[2,3-b]-4-oxo-5-benzylidene thiazolidine-1H-[1,2,4]triazol		85	Whit	266-267
11	5-(morpholin methyl)-[2,3-b]-4-oxo-5-(4-dimethylamino benzylidene) thiazolidine-1H-[1,2,4]triazol		56	Yellow	200-201
12	5-(morpholin methyl)-[2,3-b]-4-oxo-5-(4-hydroxybenzylidene) thiazolidine-1H-[1,2,4]triazol		76	Brown	273-274
13	5-(morpholin methyl)-[2,3-b]-4-oxo-5-(3-nitrobenzylidene) thiazolidine-1H-[1,2,4]triazol		77	Light Brown	223-224

Results and Discussion:

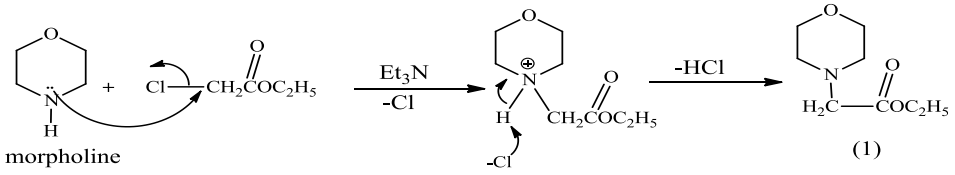
Preparation of Morpholin-N-ethylacetate (1) :

The synthesis is sequences for preparation of series new morpholine derivatives by refluxing morpholine with ethyl chloro acetate in the presence of triethylamine and benzene as a solvent , as shown in the following equation :



(1)

The mechanism for these reaction involves nucleophilic attack of amino group in morpholine on reaction with carbon in ethyl chloro acetate give the final product (1) [23], as shown in the following scheme:



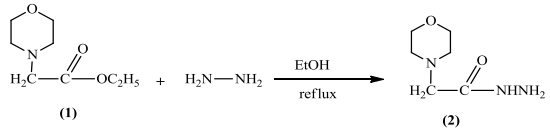
morpholine (1)

The FT-IR spectra as shown in Table (2) and Fig. (2) besidethe (^{1}H-NMR and ^{13}C-NMR) analysis of these compound (1) are listed in Table (3 and 4) .

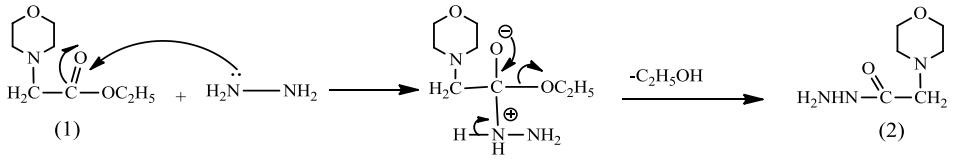
Synthesis of Morpholin-N-acetohydrazide(2):

Hydrazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds and play a very important role owing to their potentially high antifungal, antibacterial,

antiviral and antimalarial activity [24]. Hydrazide derivatives were prepared via treatment of prepared ester (1) with hydrazine hydrate in absolute ethanol, as shown in the following equation:



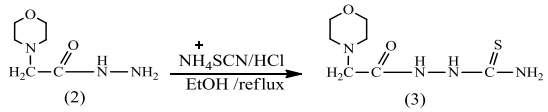
This reaction represents nucleophilic substitution reaction and its mechanism involved nucleophilic attack of amino group in hydrazine on carbonyl group in ester followed by elimination of ethanol molecule [25], as shown in the following Scheme:



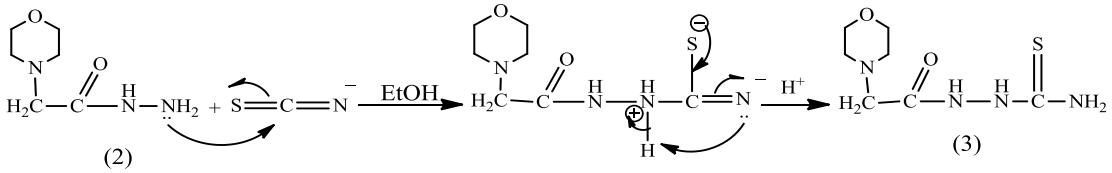
The structure of the synthesized compound has been characterized and confirmed by FT-IR analysis as shown in Table (2).

Synthesis of Morpholin-N-aceto thiosemicarbazide(3) :

The compound (2) was converted to thiosemicarbazide derivative compound (3) by the reaction with ammonium thiocyanate and hydrochloric acid in absolute ethanol as shown in the following equation:



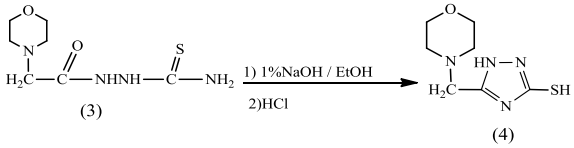
Mechanism of reaction involves nucleophilic attack of amino group of compound (2) on deficient carbon of ammonium thiocyanate followed by rearrangement of molecule [26], as shown in the following Scheme:



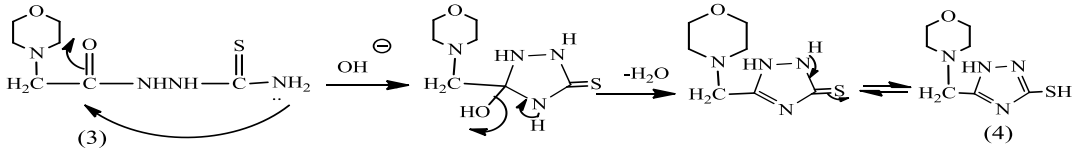
The FTIR spectra data showed in Table (2).

Synthesis of 5-(morpholin methlyl-1H-1,2,4-Triazole-3-Thiol (4):

The compound (3) was converted to compound (4) by reaction with1% NaOH in absolute ethanol and acidified by 10%HCl, as shown in the following equatio



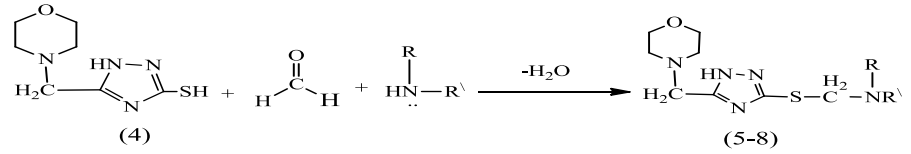
Mechanism of reaction involving nucleophilic attack lead to intramolecular cyclization [27,28] ,as shown in the following Scheme :



The FT-IR spectral data showed in Table (2).

Preparation of 5- [(Morpholin methyl)]-3-thio(methyl-N-Substituted)-1H1,2,4-Triazole (5-8):

A series of new Mannich derivatives was synthesized by the reaction between compound (4), secondary amine and formaldehyde, as shown in the following equation:

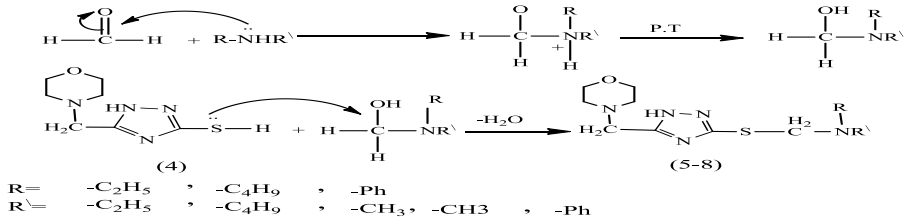


(4) (5-8)

R= $-C_2H_5$, $-C_4H_9$, -Ph

R\= $-C_2H_5$, $-C_4H_9$, $-CH_3$, -CH3 , -Ph

The mechanism of the reaction depends on the nucleophilis addition of amine to the carbon of formaldehyde followed by condensation with compound (4) gives the Mannich base [29,30], the suggested mechanism is shown in the following scheme:



(4) (5-8)

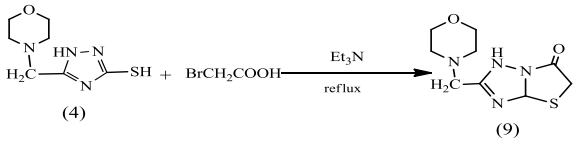
R= $-C_2H_5$, $-C_4H_9$, -Ph

R\= $-C_2H_5$, $-C_4H_9$, $-CH_3$, -CH3 , -Ph

The FT-IR spectra as shown in Table (2) and Fig. (3) besidethe (^{1}H-NMR and ^{13}C-NMR) analysis of these compounds (5-8) are listed in table (3 and 4) and Fig. [4,5].

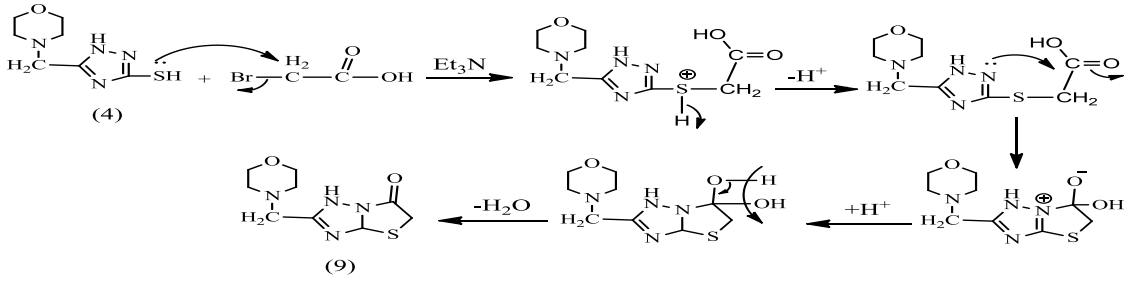
Synthesis of 5-(Morpholin emethyl)-[2,3-b]-4-oxo-5-thiazolidenone-1H-1,2,4-Triazoline (9):

Treatment of compound (4) with bromo acetic acid in presence triethyl amine affords intramolecular cyclization to give compound (9), as shown in the following equation:



(4) (9)

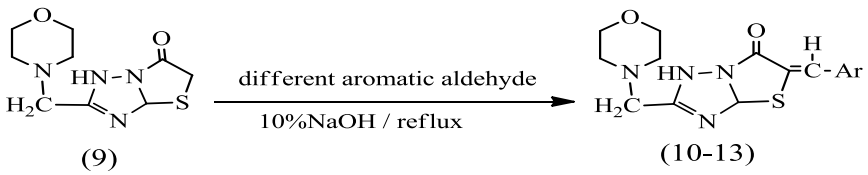
The mechanism of the reaction depends on the nucleophilic addition, as shown in the following mechanism [31]:



(4) (9)

Synthesis of5-(Morpholine methyl)-[2,3-b]-4-oxo-5-thiazolidine-1H-1,2,4-Triazoline (10-13):

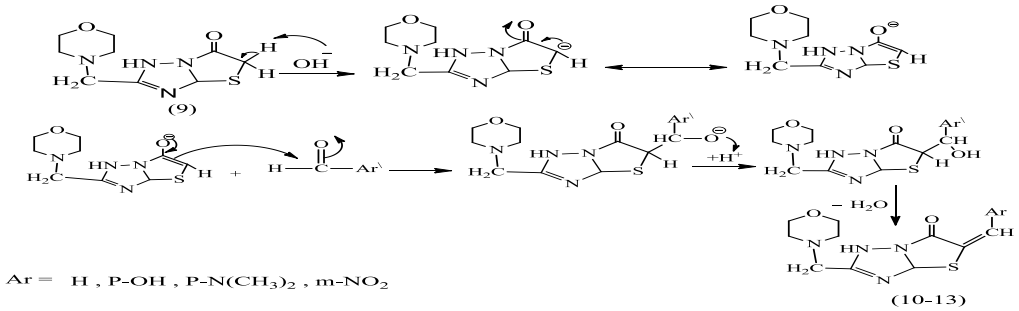
Synthesis compounds (10-13) by reaction of compound (9) with different substituted aromatic aldehyde in presence 10% NaOH resulted the formation of aldol condensation of title compounds (10-13), as shown in the following equation:



(9) (10-13)

Ar =-C_6H_5 p-OHC_6H_4 p-$NO_2C_6H_4$ m-$NO_2C_6H_4$

The first step in condensation reaction,the hydroxyl ion abstract the proton from carbon adjacent the carbonyl to forms an enolate ion .The next step involved nucleophilic addition of enolate ion to another carbonyl group producing intermediate alkoxide ion . This alkoxide ion protonated to form aldol product and the last step form the α, β-unsaturated products (10-13) [32], as shown in the following mechanism:



Ar = H , P-OH , P-$N(CH_3)_2$, m-NO_2

(10-13)

The FT-IR spectra as shown in Table (2) and Fig.(6) beside the (^{1}H-NMR and ^{13}C-NMR) analysis of these compounds (5-8) are listed in Table (3 and 4). and Figure [7,8].

Table (2): FTIR spectral data cm^{-1} of the prepared compounds (1-13)

Com. No.	υ(C-H) cm^{-1} Aromatic	υ(C-H) cm^{-1} Aliphatic	υ(C=O) cm^{-1} amide	υ(C=C) cm^{-1}	υ(N-H) cm^{-1}	υ(C-O-C) cm^{-1}	υ(N-N) cm^{-1}	Other Band cm^{-1}
1	_	2928	-	_	-	1224	-	υ(C-N)1307, υ(C=O)ester1743
2	_	2992	1670	_	3160	1220	1496	υ(NH_2)3350,υ(C-N)1310
3	-	2999	1650	-	3263	1124	1452	υ(NH_2) 3350, υ(C-N) 1350, υ(C-O) 1269 , υ(C=S)1215 , υ(N-C-O)1068
4	-	2997	1680	-	3269	1124	1464	υ(C=N) 1610 , υ(C-N)1348, υ(C-O) 1269 , υ(C-S)692 , υ(N-C-O)1045 ,υ(SH)2682
5	3030	2912	-	1595-1516	3150	1165	1456-1419	υ(C=N) 1645 , υ(C-N)1369, υ(C-S)692 , υ(N-C-O)1058
6	3049	2972	-	1589	3132	1170	1448	υ(C=N) 1653 υ(C-N)1332, υ(C-S)752 , υ(N-C-O)1018
7	-	2912	-	-	3130	1172	1435	υ(C=N) 1653 υ(C-N)1371, υ(C-S)734 , υ(N-C-O)1051
8	-	2997	-	-	3155	1201	1437	υ(C=N) 1660 υ(C-N)1311, υ(C-S)698 , υ(N-C-O)1041
10	3003	2916	-	1527	3190	1199	-	υ(C=N) 1651 ,υ(C-N)1317, υ(C-S)705 , υ(N-C-O)1022 υ(C-NO_2 1410
11	3001	2910	-	1530	3150	1231	-	υ(C=N) 1693 ,υ(C-N)1311, υ(C-S)700 , υ(N-C-O)1066
12	3040	2914	-	1599	3160	1236	-	υ(C=N) 1662 , υ(C-N)1336, υ(C-S)727 , υ(N-C-O)1066
13	3015	2935	-	1550	3228	1130	-	υ(C=N) 1747 , υ(C-N)1350, υ(C-S)781 , υ(N-C-O) 1031,υ(OH) 3477

Table (3): ^{1}H-NMR spectral Data ($^{\delta}$ppm) of Compounds [1,6,7,10,13]

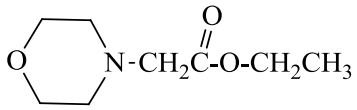
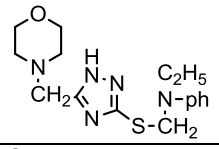
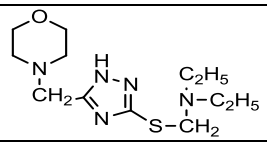
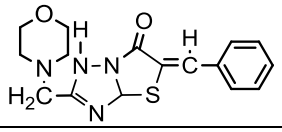
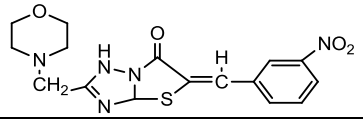
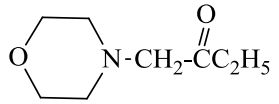
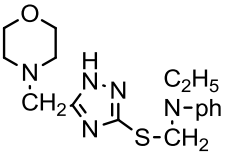
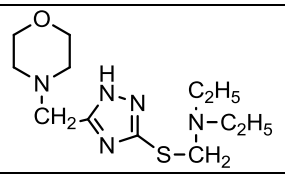
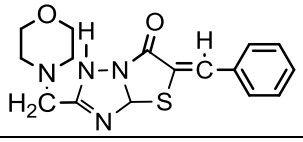
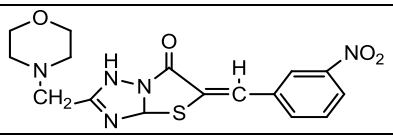
Com. NO	Compound Structure	^{1}H-NMR Spectral data (δ ppm)
1		δ2.5(s,2H,$\underline{CH_2}$-N), δ3(s,3H , $\underline{CH_3}$) , δ3.4(s, 2H, $\underline{CH_2}$-C=Oester) and δ3.7(s, 2H ,$CH_3\underline{CH_2}$-O)
6		δ2.5(t,2H,$\underline{CH_2}$-N) ,δ2.5(q,2H,$CH_3\underline{CH_2}$-N) ,δ3(t,3H,CH_3), δ3.7(t,2H,$\underline{CH_2}$-O) , δ4(S,1H,N-$\underline{CH_2}$-C) ,δ4.7(S,S-$\underline{CH_2}$-N) δ7.5(m,5H,$\underline{CH}$ aromatic) ,δ8.1(S,1H,NH).
7		δ2.2(t,2H,$\underline{CH_2}$-N) ,δ2.5(q,2H,$CH_3\underline{CH_2}$-N) , δ3.60(t,$\underline{CH_2}$-O), δ3.7 (t,2H,$\underline{CH_3}$) , δ4(S,1H,S-$\underline{CH_2}$-N) ,δ7.5(S,1H,$\underline{NH}$).
10		δ2.1(S,IH,NH), δ2.3(S,2H,C-$\underline{CH_2}$-N) ,δ2.5(t,2H,$\underline{CH_2}$-N), δ3.6(t,2H,$\underline{CH_2}$-O) , δ4.1(S,1H,$\underline{N_2}$-CH-S) , δ4.2(S,1H,$\underline{CH}$=) ,δ7.5(S,1H,$\underline{CH}$ aromatic) .
13		δ2(S,IH,NH), δ2.5(S,2H,C-$\underline{CH_2}$-N) ,δ2.54(t,2H,$\underline{CH_2}$-N) , δ3.6(t,2H,$\underline{CH_2}$-O) , δ4.9(S,1H,$\underline{N_2}$-CH-S) , δ7.6(S,1H,$\underline{CH}$=) ,δ8.2(m,5H,$\underline{CH}$ aromatic) .

Table (3-7): ^{13}C-NMR Spectral Data (δppm) of Compounds [1,6,7,10,13]

Com. NO	Compound Structure	^{1}H-NMR Spectral data (δ ppm)
1		14.1($\underline{CH3}$); 61.1(CH3$\underline{CH2}$-O);45($\underline{CH_2}$-N);63($\underline{CH_2}$-O); 163(CH_2-$\underline{C}$=O)
6		14($\underline{CH_3}$) ; 39($CH_3\underline{CH_2}$-N) ; 53(N-$\underline{CH_2}$-C) ; 58(CH_2-N) ; 64(S-CH_2-N) ; 68(CH_2-O);114-129 (6Caromatic) ;161(CH=N)
7		10.8($\underline{CH_3}$) ; 39(N-$\underline{CH_2}$-CH_3) ; 57($\underline{CH_2}$-N) ; 61(N-$\underline{CH_2}$-S) ; 65($\underline{CH_2}$-O) ; 160($\underline{C}$=N)
10		45.5($\underline{CH_2}$-N) ;59.43(N-$\underline{CH_2}$-C); 61.1($\underline{CH_2}$-O) ; 90.19(S-$\underline{CH}$-NN\);124($\underline{CH}$=);128.52-129.17(6$\underline{C}$ aromatic) ; 164(N-$\underline{C}$=O) ; 166($\underline{C}$=N)
13		55(CH_2-N) ; 66(CH_2-O) ; 88(S-CH-NN\) ; 123.1(CH=) ; 129-144(CH aromatic) ; 166(CH-C-NN\)

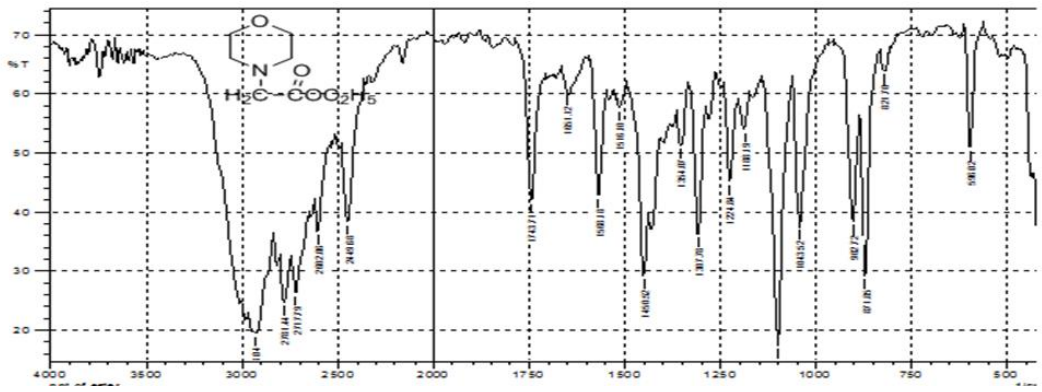


Fig. (2): FT-IR spectrum for compound (1)

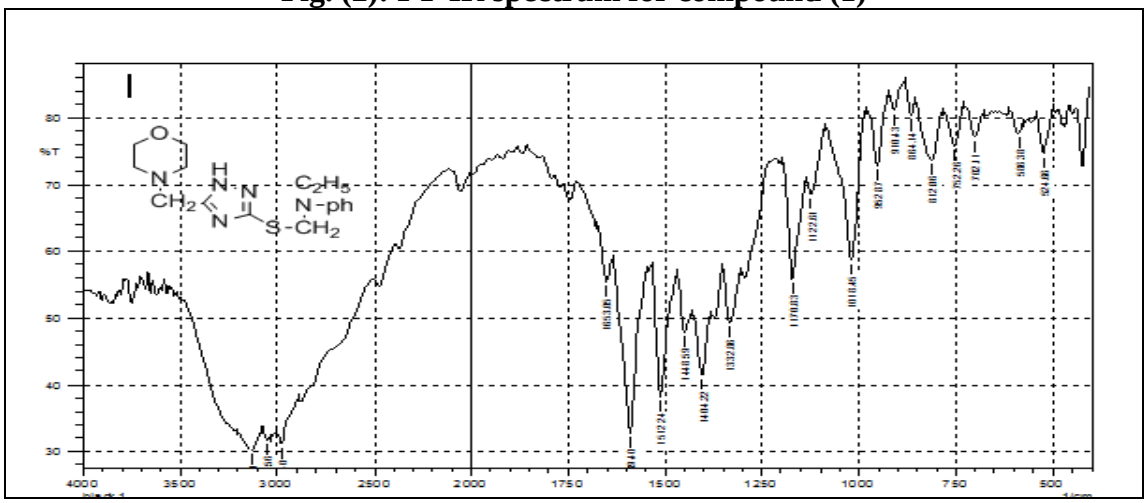


Fig. (3): FT-IR spectrum for compound (6)

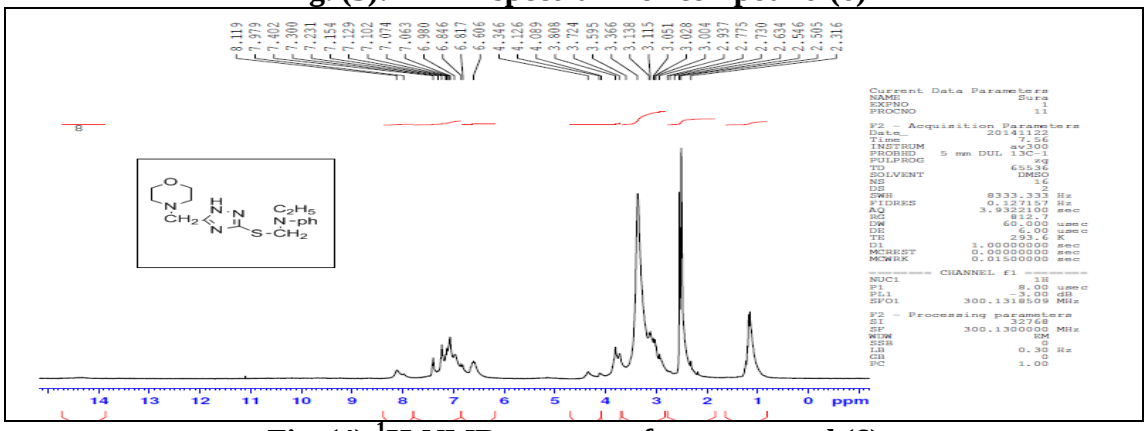


Fig. (4): ^{1}H-NMR spectrum for compound (6)

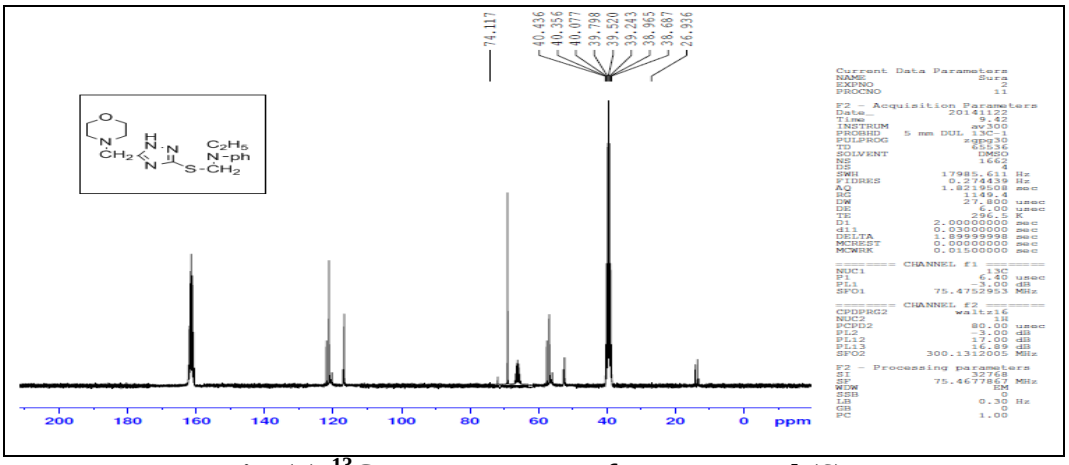


Fig. (5):^{13}C-NMR spectrum for compound (6)

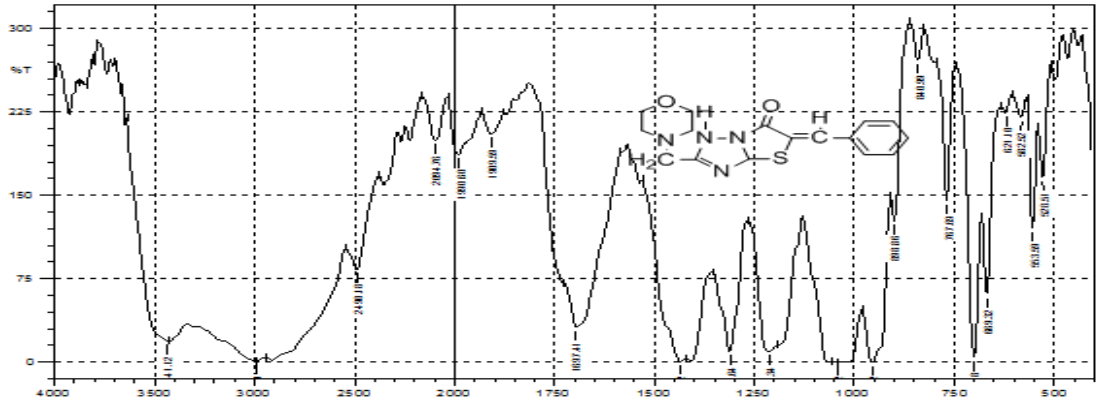


Fig. (6): FT-IR spectrum for compound (10)

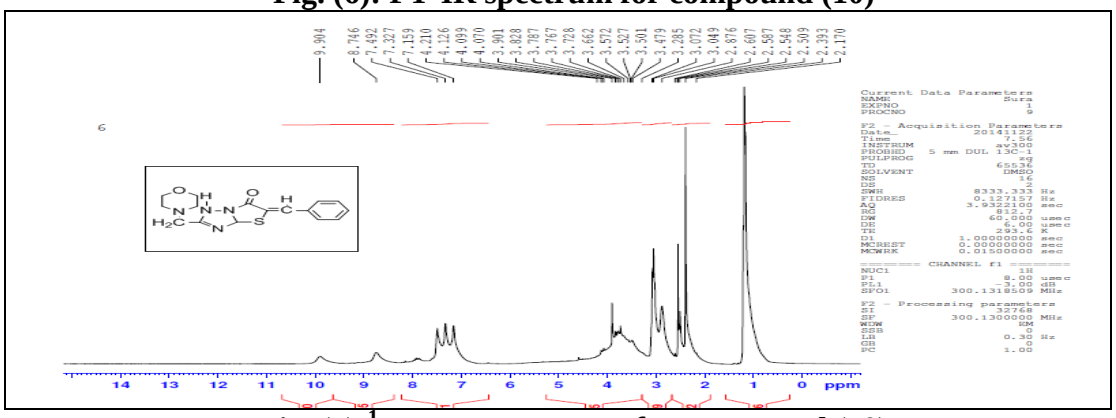


Fig. (7):^{1}H-NMR spectrum for compound (10)

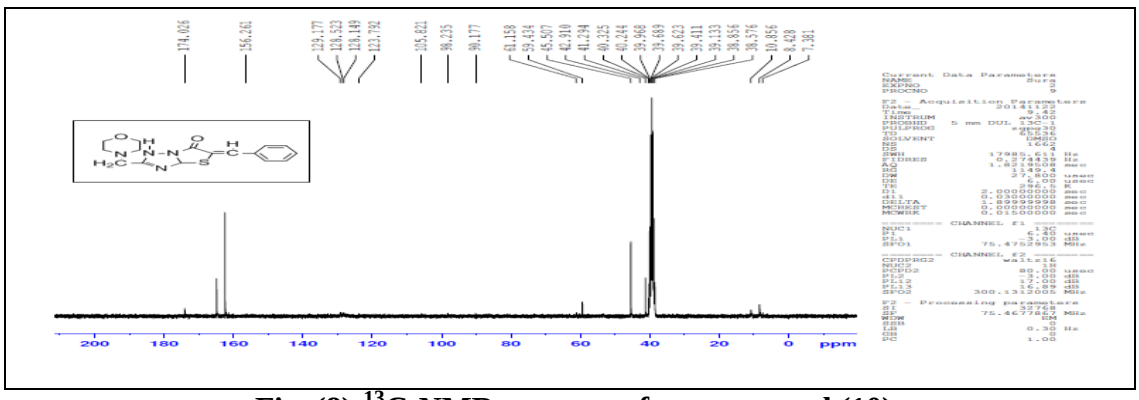


Fig. (8):^{13}C-NMR spectrum for compound (10)

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تحضير وتشخيص بعض المشتقات الجديدة للمورفولين

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الخلاصة:
في هذا البحث تم تحضير سلسلة جديدة من مشتقات المورفولين المحضرة من خلال تصعيد المورفولين مع كلوريد خلات الاثيل وثلاثي اثيل امين كعامل مساعد في البنزين حيث تم الحصول على المركب مورفولين -N-خلات الاثيل (1) وبمفاعلته مع الهايدرازين في الايثانول اعطى مورفولين -N-خلات الهيدرازايد (2) الذي اعطى مورفولين-N-خلات سيمي ثايو كاربازايد(3) من تفاعل المركب (2) مع امونيوثايوسيانايد وحامض الهيدروكلوريك المركز والايثانول كمذيب.تفاعل المركب(3) مع هيدروكسيد الصوديوم وحامض الهيدروكلوريك ليعطي 5-(مورفولين-N-مثيل)-1 -4,2,1-Hترايازول-3- ثايول(4). سلسلة جديدة من مشتقات 4,2,1- ترايازول(5-8) من تفاعل مركب (4) مع الفورمالديهايد وثنائي مثيل فورم امايد كمذيب مع مجموعة من الامينات الثانوية .حضرت مشتق واحد(9) من 4,2,1-ترايازولين من خلال تفاعل المركب (4) مع برومو حامض الخليك. تم مفاعلة المركب (9) مع الديهايدات اروماتية مختلفة بوجود ثنائي مثيل سلفوكسايد كمذيب لتحضير سلسلة من مركبات (10-13). حيث تم تشخيص هذه المشتقات بواسطة درجات الانصهار واطياف، FT-IR 13C-NMR 1H-NMR and.

الكلمات المفتاحية: مورفولين،4,2,1- ترايازول ، تفاعلات مانخ