Synthesis of Some New Mannich Bases Containing Acetylenic Amines Derived from Piperazine

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Received 26 May 2014 ; Accepted 24 November 2014

Abstract

In regard to the biological effectiveness of the piperazine and the acetylenic compounds derived from the secondary amines such as piperidine and morpholine. These acetylenic amines are very important class compounds for their pharmacological properties such as activity, low toxicity and fast absorption by body. More over these compounds are electron rich and easy to bond with protein receptor.

A number of pharmacologically important acetylenic amines derived from piperazine with expected activity as oxotremorine antagonist have been synthesized through Mannich reaction[(1)]. The compounds prepared by reaction of substituted propynes and butynes with substituted piperazine and paraformaldehyde in the presence of cuprous chloride as a catalyst. All the prepared compounds are characterized by elemental analysis, physical data and spectroscopic methods (IR, H^1-NMR), and physical and spectral data were tabulated showed in tables (1-3).

Key words: Acetylenic amines, Mannich reaction, Mannich bases, Piprazine derivatives.

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تحضير بعض قواعد مانخ الجديدة والمحتوية على أمينات أستلينية مشتقة من الببرازين

عفراء صابر شهاب الزوبعي

قسم الكيمياء، كلية العلوم، جامعة تكريت، تكريت، العراق

الملخص

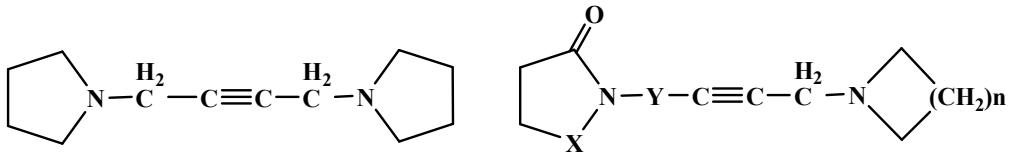
بالنظر للفعالية البايولوجية للببرازين والمركبات الاسيتلينية المشتقة من الامينات الثانوية، مثل ببريدين والمورفيلين واهتم الباحثون لهذه المركبات. تعتبر الامينات الاسيتلينية من اصناف المركبات المهمة جدا بسبب خاصيتها البايولوجية مثل الفعالية، سميتها الواطئة وسهولة امتصاصها من قبل الجسم. وتعتبر هذه المركبات غنية بالالكترونات وتكون آواصر بسهولة مع مستقبلات البروتين.

لقد حضر عدد من هذه الامينات الاستلينية ذات الفعالية البايولوجية والمشتقة من الببرازين ذات فعالية متوقعة كمضاد للاوكستريمورين بواسطة تفاعل مانخ[1]. فقد تمت مفاعلة مشتقات البروباين والبيوتاين مع مشتقات الببرازين ومع بارافورمالديهايد بوجود كلوريد النحاسوز كعامل مساعد. وقد شخصت جميع هذه المركبات المحضرة بواسطة التحليل الدقيق للعناصر والطرق الطيفية. ان قيم التحاليل الفيزيائية والطيفية موضحة في الجداول (1-3).

الكلمات المفتاحية: الامينات الاسيتلينية، تفاعل مانخ، قواعد مانخ، مشتقات الببرازين.

Introduction

Acetylenic amines derivatives have received considerable attention due to the fact that a number of them are pharmacologically activity compounds[2-4]. For example, a number of acetylenic amines are known to be pharmacologically important compounds[5-7]. For example, various prop-2-ynylamines are used as drugs or pesticides[8]. Some of the acetylenic amines that contain (-CH_2–C≡C–CH_2-) as moiety function have been found to possess a high degree of specificity as central cholinergic or anticholinergic agents, among these are tremorine (1, 4-dipyrrolidino-2-butyne) (1) and a number of N-(dialkylamino-2-alkynyl) substituted succinimido[9,10] (2a) and pyrrolidones (2b)(Fig.1.).



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(2a) X = CO Y = CH_2, $(CH_2)_2$, $C(CH_3)_2$
(2b) X = CH_2 n = 2 - 4

Figure (1): Tremorine and N-(tert-aminoalkynyl) substituted succinimides and 2-pyrrolidone

The importance of the acetylenic bond in oxotremorine and antagonists of oxotremorine has been the subject of discussion. It has been known that the triple bond is electron rich which is capable of binding to the muscarinic receptors at the same site as the furan oxygen of muscarine and ester oxygen of acetylcholine[11]. It has also been claimed that the acetylenic bond is not considered essential for activity but favors entry in the central nervous system (CNS) by reducing the base strength[12].

We report here with, the synthesis of a number of organic compounds that comprise both piperazine ring and acetylenic moiety in the same molecule.

Experimental

Preparation of Mannich bases (compounds a-h)[13,14].

These compounds where prepared through Mannich reaction between the acetylenic compounds, paraformaldehyde, piperazine derivatives, and cuprous chloride as a catalyst as follows:

To a mixture of (0.01) mole of the propargylic derivatives and (0.01) mole of para formaldehyde in (50) ml peroxide – free dioxane as a solvent was added (0.005) mole of the appropriate piperazine compound and a catalytic amount (0.001 mole, 0.12 g) of cuprous chloride. The mixture was heated at 90° C for (90) minutes. After cooling, the mixture was

filtered and the filtrate was poured into (100) ml of cold water. The solid compound was isolated and passed on a column of neutral alumina and eluted with chloroform. A pale yellow to brown crystalline solid of Mannich bases (a-h) was obtained in each case.

The physical and analytical data and spectroscopic data (FT-IR analyzed in the North Oil Company in Kirkuk and the H^1-NMR, C.H.N analyzed in Al- Albait University in Jordan) are collected in tables (1, 2 and 3).

Results and Discussion

A number of compounds comprising both amino and ethynyl functions have been reported to possess a potential pharmacological value in blocking the motor effects of the mascarinic agent oxotrcmorine[9,10,15], such as N-(tert-aminoalkynyl) substituted succinimides and 2-pyrrolidones (Fig.1) were reported to be potent.

As a variation of the above structures three series comprising eight acetylenic amines (series I-III) that are drug candidates with expected activity as oxotremoring antagonists have been synthesized through Mannich reaction using piperazine as the secondary amine component[16,17]. Those acetylenic compounds that are prepared in this work consist in their structure a phenyl (substituted) compounds (a-c), tert-butyl (d and e), saccarin moiety (f-h). Thus the reaction between the piperazine (secondary amines) with acetylenic derivatives and paraformaldehyde in the presence of a catalytic amount of cuprous chloride to give compounds (a-h). (Scheme 1 & 2).

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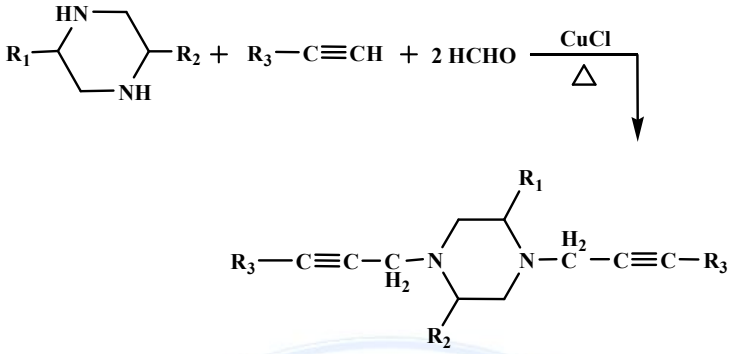


Scheme (1)

Series I : N,N´-Bis-[3-phenyl-prop-2-ynyl] piprazine derivatives

(a) $R_1 = R_2 = H$, R_3= ph

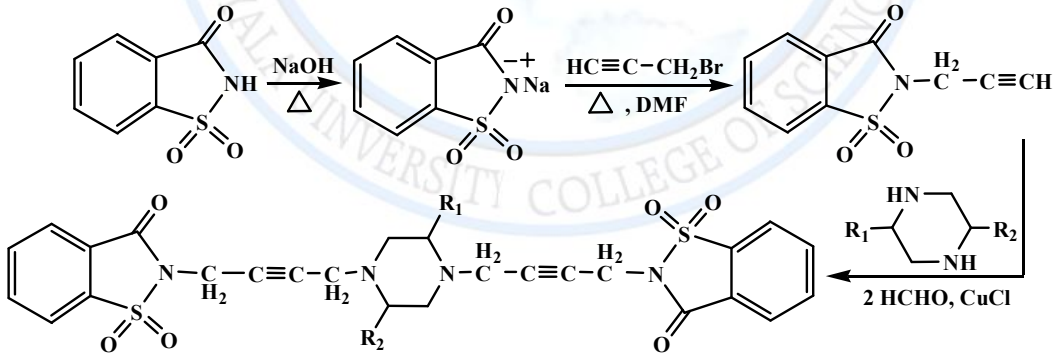
(b) $R_1 = H$, $R_2 = CH_3$, R_3= ph

(c) $R_1 = R_2 = CH_3$, R_3= ph

Series II : N,N´-Bis-[4,4-dimethyl-pent-2-ynyl] piprazine derivatives

(d) $R_1 = R_2 = H$, $R_3 = (CH_3)_3C$-

(e) $R_1 = H$, $R_2 = CH_3$, $R_3 = (CH_3)_3C$-



Scheme (2)

Series III : N,N´-Bis-[4-(N-saccharено)- but-2-ynyl] piprazine derivatives

(f) $R_1 = R_2 = H$

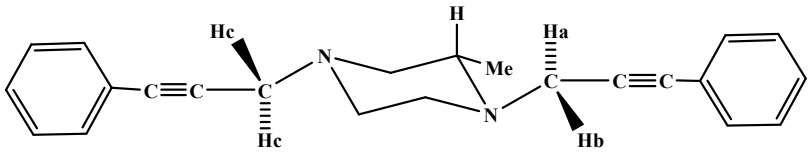
(g) $R_1 = H$, $R_2 = CH_3$

(h) $R_1 = R_2 = CH_3$

These compounds were characterized by elemental analysis and spectroscopic means. The results of elemental analysis agree quite well with the assigned formulas for these compounds. The physical, analytical and spectroscopic data of the acetylenic amines described in this work are listed in tables (1, 2 and 3).

The infrared spectra clearly showed the absence of acetylenic absorption in all the compounds and this is not surprising in view of the highly symmetrical structure of the molecules so small or no change in dipole moment occurs during vibration.

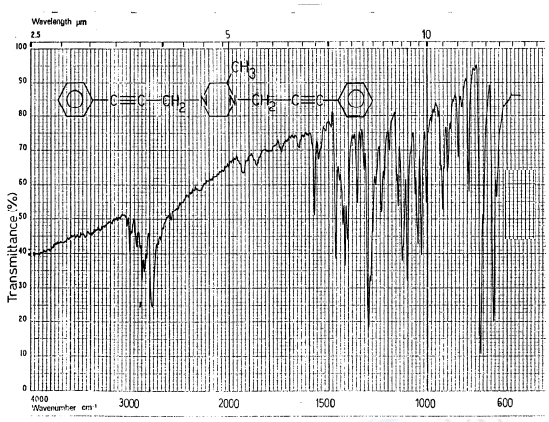
In the H^1-NMR spectra, the two (CH_2) protons that are connected to the (C≡C) function appeared as triplets (somewhat poorly resolved) due to long range coupling. However in compounds (b, c, and e) where the piperazine ring carries one or two groups of (-CH_3) at positions 2 and 5, the diastereotopic (N-CH_2-) protons are anisochronous due to the presence of methyl group at position (2) of the heterocyclic ring and thus appear as a triplet of quartet (tq) that is an AB part of the ABX_2 system due to coupling with (≡C-CH_2-) protons across the triple bond as shown in the figure (4) for the compounds (a - e). For example the H^1-NMR spectrum for the compound (a) gives multiplet signal for the aromatic protons at (δ = 7.1-7.6 ppm), singlet for four (N-CH_2) protons at (δ = 3.55 ppm) and singlet for eight piprazine ring protons at (δ = 2.79 ppm). The H^1-NMR spectrum for the compound (b) different from the compound (a), it show's multiplet signals for seven piperazine ring protons at (δ = 2.7-3.0 ppm) and singlet for (N-CH_2) protons at (δ = 3.5 ppm) that they are isochronous. The (N-CH_2) protons (H_a, H_b) show's (AB - quartet signals at (δ = 3.55 ppm) because they are an isochronous according to AB system and these signals overlapping with the singlet signal for the (H_c) protons. The singlet signal for the isochronous protons (H_c) (N-CH_2) disappear as in the compound (b) at (δ = 3.5 ppm) as in the figure (4). The same an isochronous protons signal will appears in the compounds (d and e) as showing in the figures (4) [18].



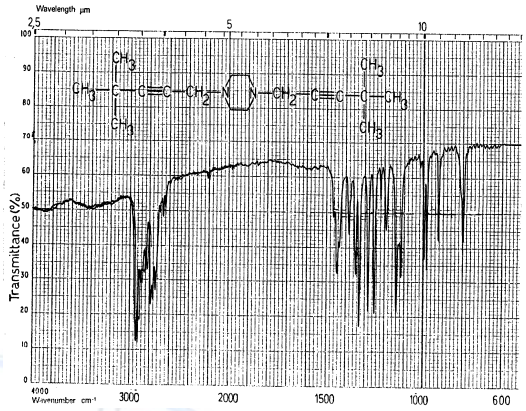
compond (b)

Figure (2): The stereochemistry of the compound (b)

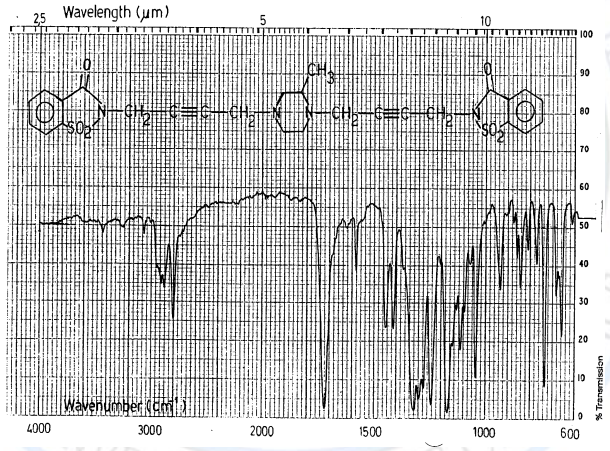
The pharmacological importance of these compounds is to be tested later and needs further work.



Compound (b)



Compound (d)



Compound (g)

Figure (3): The IR spectra for the compounds (b, d & g)

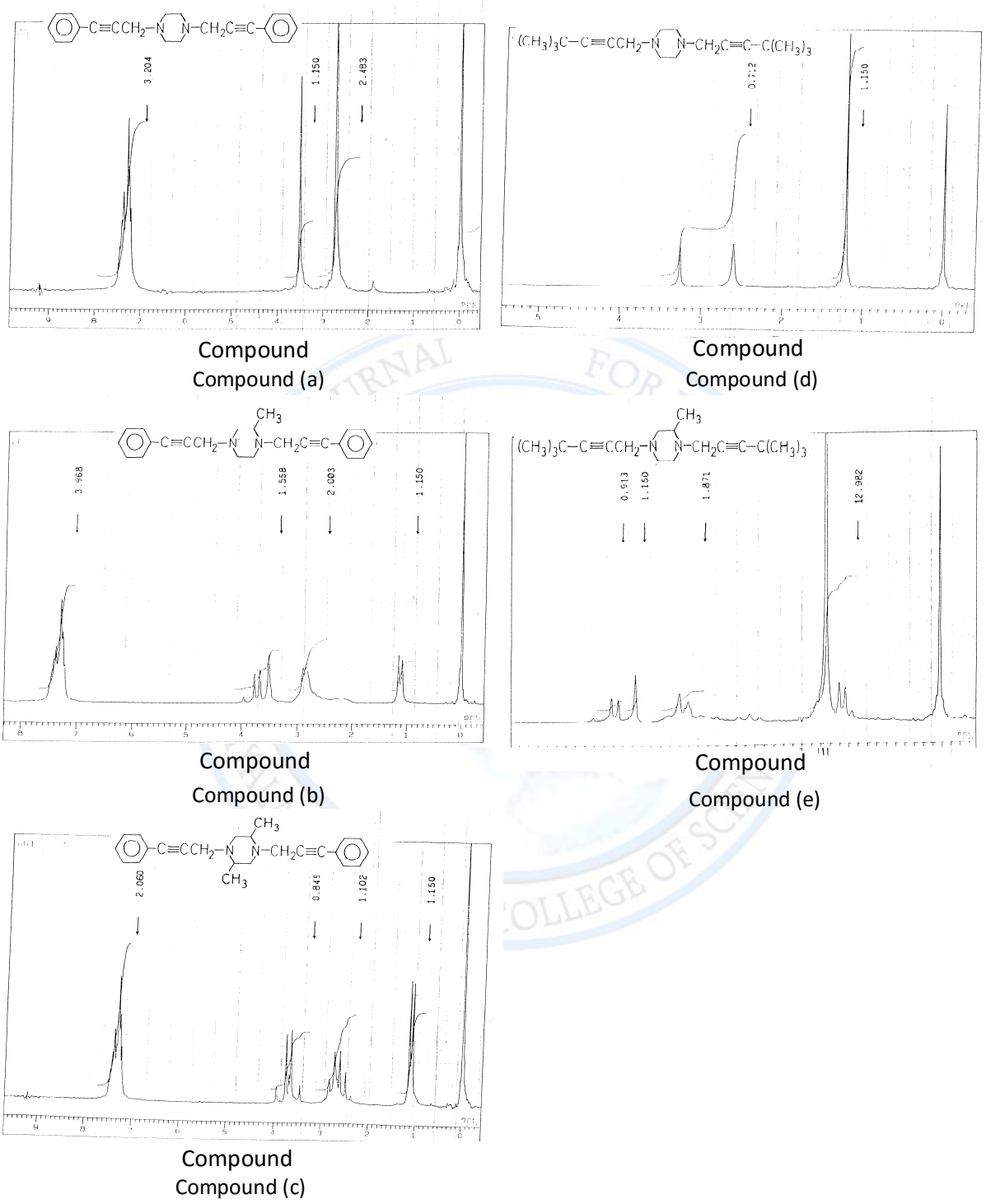


Figure (4): The H^1-NMR spectra for the compounds (a-e)

Table (1): Physical and analytical data of Mannich bases (a-h)

Comp. No.	*% Yield*	*Color*	*M.P. °C*	*(C.H.N) / cal. (found)*		
				% C	*% H*	*% N*
a	94	Yellow	103-105	84.03 (83.63)	7.05 (7.07)	8.90 (8.27)
b	80	Yellow	71-73	84.10 (83.26)	7.36 (7.65)	8.52 (8.16)
c	65	Pale yellow	140-142	84.16 (84.26)	7.65 (7.64)	8.17 (8.12)
d	75	Yellow to brown	96-98	78.77 (77.73)	11.01 (10.13)	10.20 (10.50)
e	60	Brown	60-62	79.10 (78.19)	11.18 (10.90)	9.71 (9.21)
f	55	Brown	182-184	56.50 (56.88)	4.37 (4.59)	10.13 (9.97)
g	80	Pale yellow	181-183 (dec.)	57.23 (56.97)	4.63 (4.15)	9.88 (9.67)
h	78	Dark brown	190-193 (dec.)	57.91 (57.00)	4.86 (4.80)	9.64 (9.30)

Table (2): IR spectroscopic data of Mannich bases (a-h)

Comp. No.	*IR (cm^{-1})*				
	C-H(al.) str.	C-H(ar.) str.	C-C(al.) str.	C-H(al.) ben.	SO_2(str.)
a	2981	3180	1440 1600	1485	-
b	2807	3030	1440 1600	1480	-
c	2936	3090	1440 1600	1480	-
d	2921	3179	-	1460	-
e	2990	3092	-	1470	-
f	2928	3138	-	1460	1180(s) 1340(as)
g	2910	3100	-	1465	1180(s) 1330(as)
h	2912	3180	-	1467	1185(s) 1335(as)

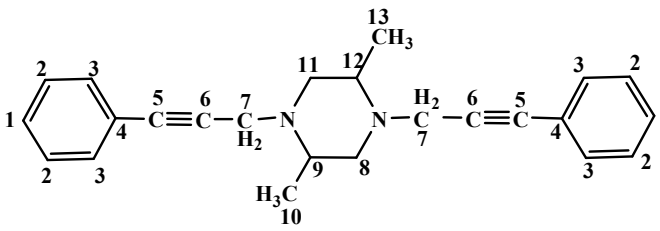
str.: stretching, ben.: bending, ar.: aromatic, al.: aliphatic

Table (3): H^1-NMR spectroscopic data of Mannich bases (a-h)

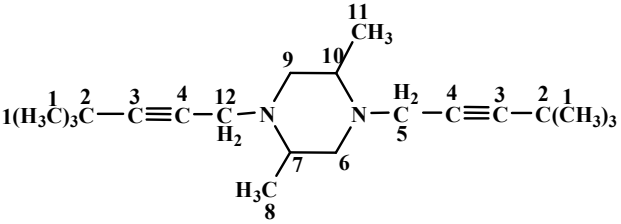
Comp. No.		*NMR (δ, ppm), (D_2O)*			
	CH_3 piper. ring	CH_2 piper. ring	CH_2–N	$-C(CH_3)_3$	aromatic
a	-	2.79 (s,8H)	3.55 (s,4H)	-	7.1-7.6 (m,10H)
b	1.13 (d,3H)	2.7-3.0 (m,7H)	3.63 (d,2H) 3.84 (d,2H)	-	7.3-7.6 (m,10H)
c	1.15 (d,6H)	2.3-2.9 (q,6H)	3.60 (d,2H) 3.82 (d,2H)	-	7.4-7.8 (m,10H)
d	-	2.62 (s,8H)	3.29 (s,4H)	1.27 (s, 18H)	-
e	1.08 (d,3H)	2.5-2.9 (m,7H)	3.12 (p.r.t,4H)	1.27 (s, 18H)	-
f	-	2.65 (s,8H)	3.11 (p.r.t,4H)	-	7.5-7.8 (m,10H)
g	1.14 (d,3H)	2.45 (s,7H)	3.11 (p.r.t,4H)	-	7.7-8.3 (m,10H)
h	1.23 (d,6H)	2.3-2.6 (m,6H)	3.12 (p.r.t,4H)		7.7-8.4 (m,10H)

s: singlet, d: doublet, t: triplet, m: multiplet, p.r.t.: poorly resolved triplet, piper.: piperazine

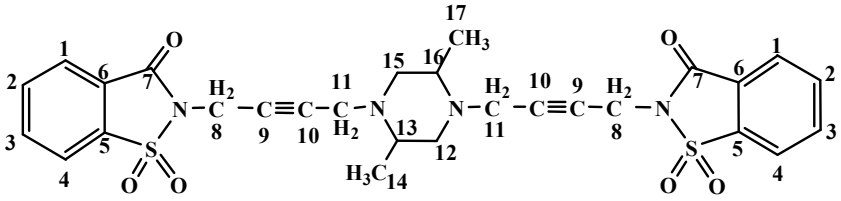
Table (4): C^{13} - NMR data of Mannich bases (a-h)



Compounds (a,b,c)



Compounds (d,e)



Compounds (f,g,h)

Comp. No.	Carbon atoms symbol																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
a	128.5	128.4	132.3	122.7	81.0	82.6	43.2	50.9	50.9	-	50.9	50.9	-	-	-	-	-
b	128.5	128.4	132.3	122.7	81.0	82.6	40.7	48.4	51.2	-	60.5	53.1	15.9	-	-	-	-
c	128.5	128.4	132.3	122.7	81.0	82.6	41.0	58.0	53.4	15.9	58.0	53.4	15.9	-	-	-	-
d	31.1	28.2	89.4	78.3	44.2	50.9	50.9	-	50.9	50.9	-	44.2	-	-	-	-	-
e	31.1	28.2	89.4	78.3	41.7	48.4	51.2	-	60.5	53.1	15.9	44.5	-	-	-	-	-
f	127.8	132.1	132.5	127.4	140.1	127.6	168.0	26.8	79.8	79.8	43.3	50.9	50.9	-	50.9	50.9	-
g	127.8	132.1	132.5	127.4	140.1	127.6	168.0	26.8	79.8	79.8	40.8	48.4	51.2	-	60.5	53.1	15.9
h	127.8	132.1	132.5	127.4	140.1	127.6	168.0	26.8	79.8	79.8	41.1	58.0	53.4	15.9	58.0	53.4	15.9

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