Synthesis and characterization of some new N-mannich bases for clonazepam

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Abstract:

The N- Mannich bases (1-10) have been synthesized by reaction of clonazepam with formaldehyde or benzaldehyde and different secondary amines. The N-Mannich bases were subjected to physicochemical studies like melting point determination, TLC and yield%. The structures of mannich bases were characterized by IR, ^{1}HNMR and ^{13}CNMR spectroscopy.

تحضير وتشخيص بعض N- قواعد مانيخ الجديدة للكلونازيبام

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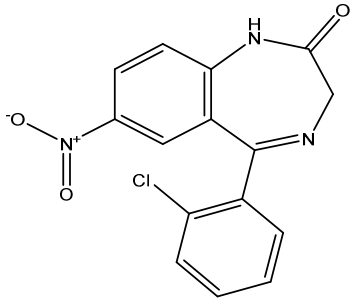
الخلاصة :

تم في هذا البحث تحضير N- قواعد مانيخ (1-10) للكلونازيبام من تفاعله مع الفورمالديهايد او البنزلديهايد واامينات ثانوية مختلفة . تم اثبات وتشخيص التراكيب المحضرة بالطرائق الفيزيائية مثل تعين درجة الانصهار , تقنية الـ TLC ونسبة المنتوج وباستعمال الطرائق الطيفية (طيف الاشعة تحت الحمراء , طيف الرنين النووي المغناطيسي للبروتون والكاربون 13) .

الكلمات المفتاحية :N- قواعد مانيخ , كلونازيبام

Introduction

The scientific name of Clonazepam [1] is 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one. It is medication of the benzodiazepine class. It conceders a derivative of nitrazepam and its structural formula as below [2,3]:

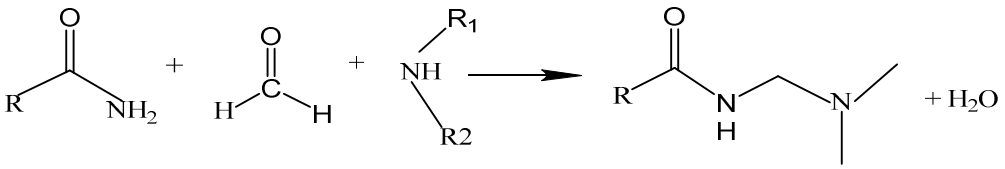


Clonazepam is given for the management of panic[4], depression[5],sleep- associated movements[6] and epilepsy disorders[7] .It has anti-anxiety, sedative, relaxant of muscle, against convulsion and sleepiness properties[8]. The elimination of its plasma half-life range from 18–50 hours to 19–60 hours, and it is known as to be a long-acting benzodiazepine [9]. The profile of pharmacologic action of clonazepam is similar to those other benzodiazepines, ties to particular site on the GABA gamma aminobutyric acid receptor [10] .

A Mannich base involves a worthy position in the generation of many pharmaceutical products and common compounds in natural products which have aminoalkyl chain. The examples of different therapeutic agents for Mannich bases are tramadol as an analgesic, molindone as a neuroleptic, procyclidine as an antiparkinsonic, ranitidine and triprolidine an antihistaminic agent [11-13] . They are known for their broad gamut of

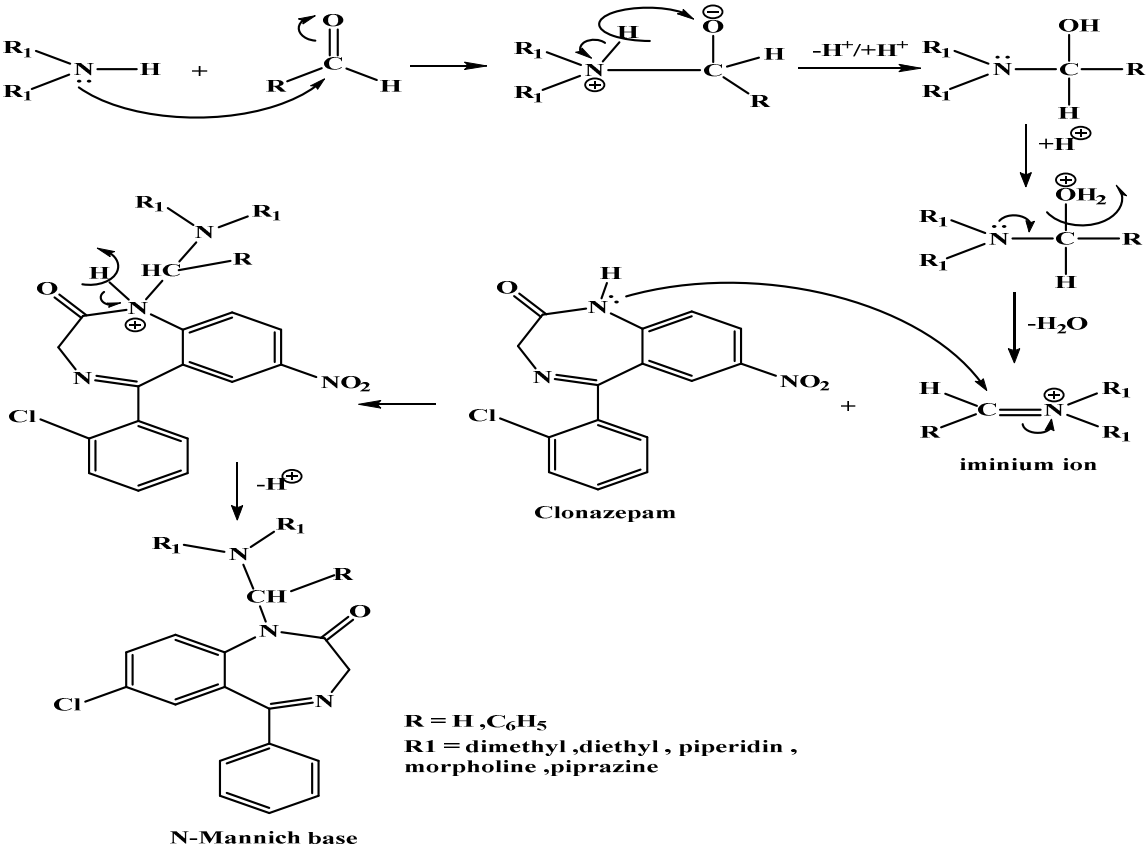
biological activities range from against inflammation [14,15], against malaria [16], against cancer [17,18], against bacteria [19,20], against fungi [21], against convulsion [22], against Helminthic [23], and against TB [24,25].

N-Mannich bases are prepared through the Mannich reaction, which involves a NH-acidic compound, an aldehyde (usually formaldehyde) and an amine Scheme1.



Scheme1. Equation preparation of N-Mannich bases

The present work involved prepared ten of N-Mannich bases derivatives from clonazepam the compounds (1-10), by condensing NH- group of clonazepam with formaldehyde or benzaldehyde and some secondary amines (dimethyl amine, diethyl amine, piperidine , morpholine and piprazine) scheme 2.



Scheme 2. Recommend Mechanism for Synthesis N-Mannich of clonazepam

Experimental:

Starting materials and reagent were from commercial chemical suppliers. Melting points were determined in open capillary tube and are uncorrected. The IR spectra

(KBr,cm^{-1}) were recorded on Perkin Elmer spectrometer ,^{1}H NMR and ^{13}CNMR (δ, ppm) spectra were recorded on a Bruker 400 MHz spectrometer using TMS as an internal standard and DMSO as a solvent .The purity of compounds and progress of the reaction were checked by TLC using silica gel (60-230) mesh as stationary phase and (ethyl acetate : n-hexane) (1:1) as mobile phase .

Procedure for preparation of N-mannich bases:

Equimolar quantity of Clonazepam , formaldehyde or benzaldehyde and various secondary amines (dimethyl amine , diethyl amine , piperidine , morpholine , piprazine) were dissolved in 20ml methanol , then add 4-5 drops of glacial acetic acid and the mixture was refluxed for (3-8) hours, then the mixture was stirred at room temperature for 24 hours .The precipitates were obtained after several days ageing at 0^0C refrigerator, the product was washed with acetone then recrystallized by using ethanol. Completion of reaction was monitored by TLC analysis for several times . Melting point, Rf value and yield were noted. Physical data of various N-Mannich derivatives are shown in table 1 .

Table 1 : Physical data of the synthesized compounds (1-10)

Comp. No	Amine	Aldehyde	Mol.formula	Mol.wt	m.p^{0}C	%yield	Rf* value
1	Dimethyl amine	formaldehyde	$C_{18}H_{17}ClN_4O_3$	372.8	186-188	55	0.88
2	Diethyl amine	formaldehyde	$C_{20}H_{21}ClN_4O_3$	400.8	200-201	67	0.68
3	piperidine	formaldehyde	$C_{21}H_21ClN_4O_3$	412.8	198 dec.	73	0.85
4	morpholine	formaldehyde	$C_{20}H_{19}ClN_4O_4$	414.8	192-190	65	0.77
5	piprazine	formaldehyde	$C_{20}H_{20}ClN_5O_3$	413.8	240-245	52	0.79
6	Dimethyl amine	benzaldehyde	$C_{24}H_{21}ClN_4O_3$	448.9	199-202	44	0.77
7	Diethyl amine	benzaldehyde	$C_{26}H_{25}ClN_4O_3$	476.9	177-179	60	0.69
8	piperidine	benzaldehyde	$C_{27}H_{25}ClN4O_3$	488.9	150-152	70	0.78
9	morpholine	benzaldehyde	$C_{26}H_{23}ClN_4O_4$	490.9	123-125	54	0.85
10	piprazine	benzaldehyde	$C_{26}H_{24}ClN_5O_3$	489.9	180-182	75	0.68

*(ethyl acetate : n-hexane) (1:1)

Results and Discussion

The spectral data reveals that structures of all the synthesized compounds are in good agreement with the proposed ones. The FTIR spectra of compounds show absence of NH band at around 3430 cm^{-1} for benzodiazepine ring except compounds (5,10) which have piprazine rings. The appearance of signal δ5- 4.8(s,2H ,N-CH_2-N) in^{1}HNMR spectra of compounds (1-5) and signal δ (5.9-4.6) (s, 1H) in^{1}HNMR spectra of compounds (6-10) reveals the formation of CH_2 ,CH bridge between clonazepam and secondary amine which supports the formation of N-Mannich bases .

In ^{13}CNMR spectra, DEPT-135 of N- Mannich bases (1-5) show negative signal at around δ 69-62 for(N-CH2-N)bridge beside CH_2 for amine and CH_2 for benzodiazepine ring .The DEPT-90 spectrum of N- Mannich bases (6-10) shows positive signal at around δ 69-62 for CH (N-CH-N)bridge beside CH for aromatic ring. The spectral results of synthesized compounds (1-10) are given in table 2.

Table 2: Spectral data of N- Mannich bases (1-10)

Comp. No	IR (KBr ,cm^{-1})	^{1}HNMR & ^{13}CNMR (δ ,ppm))
1	3040(CH-Ar,(2970,2835) (CH-aliphatic),1685(C=O), 1620(C=N),(1570,1540) (N=O),1345(C-NO_2), 1025 (C-N), 730 (Ar-CI)	^{1}HNMR: 2.4(s,3Ha), 4.3 (s,2H, ringHb), 4.8(s,2Hc,N-CH_2-N), 7.4-7.5(m,3H, Ar-Hd) , 7.6(s,1H, Ar-He), 7.7(s,1H, Ar-Hf) , 8.3(d,2H,Ar-Hn) ^{13}CNMR : 46.1(N-CH_3), 56.7(CH_2, ring) , 62.2(N-CH_2-N)bridge , 141-122(C,Ar), 144(C-NO_2), , 167.8(C=N) , 169.2 (C=O)
2	3060(CH-Ar), (2940,2890) (CH-aliphatic), 1680 (C=O), 1628 (C=N) , (1580,1543) (N=O),1335(C-NO_2), 1023 (C-N), 750 (Ar-CI)	^{1}HNMR: 0.8-.1.1(t,6H,CH_3,Ha) , 2.4-2.3(q,,4H,CH_2, Hb) , 4.3 (s,2H, ringHc), 4.8(s,2Hd,N-CH_2-N), 7.4-7.5(m,3H, Ar-He) , 7.6(s,1H, Ar-Hf), ,7.7(s,1H, Ar-Hn) ,8.3(d,2H,Ar-Hh) ^{13}CNMR : 18.1(CH_3-N), 48.2(CH_2-N) , 56.7(CH_2, ring) , 62.2(N-CH_2-N)bridge ,141-122(C,Ar), 144(C-NO_2), 167.8(C=N) , 169.2 (C=O)
3	(3103,3050)(CH- Ar), (2956,2850)(CH-aliphatic), 1693 (C=O), 1612 (C=N), (1529,1519) (N=O),1340(C-NO_2), 1040 (C-N), 760 (Ar-CI)	^{1}HNMR: 1.03-1.22 (m,6H,CH_3,Ha) , 2.1-2.3(t,,4H,CH_2, Hb) , piperidine:, 4.31 (s,2H, ringHc) , 5.07(s,2Hd,N-CH_2-N),7.4-7.5(m,3H, Ar-He) ,7.6(d,1H, Ar-Hf),7.73-7.74(d,1H, Ar-Hn) ,8.36-8.39(dd,2H,Ar-Hh) ^{13}CNMR :, 25.1 -26(CH_2-N) piperidine, 56.7(N-CH_2), 58.7(CH_2, ring) , 62.3(N-CH_2-N)bridge , 121.9-141.3 (C,Ar), 144(C-NO_2), 167.6(C=N) ,168.9(C=O)
4	3103(CH-Ar), (2968,2850) (CH-aliphatic), 1695 (C=O), 1616 (C=N), (1575,1535) (N=O),1338(C-NO_2), (1163,1099)(C-O-C), 1018(C-N), 730 (Ar-CI)	^{1}HNMR:, 2.7-.3(t,4H,CH_2β morpholine, Ha), 3.2-3.5(t,4H,CH_2α morpholine, Hb), 4.3(s, 2H, Hc), 4.83(s,2H, N-CH_2-N, Hd), 7.4-7.5(m,3H, Ar-He) , 7.6(s,1H, Ar-Hf),7.7(s,1H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 54.08(CH_2-N-CH_2) morpholine, 57.07(CH_2, ring) , 60.2(CH_2-O-CH_2) morpholine, 63.1(N-CH_2-N)bridge , 122-141(CH,Ar), 144(C-NO_2) ,167.8(C=N) , 169.2 (C=O)
5	3420 (N-H) ,3049(CH-Ar), (2927,2860)(CH-aliphatic), 1693(C=O) , 1618 (C=N), (1556,1530) (N=O),1340(C-NO_2), 1060 (C-N), 734 (Ar-CI)	^{1}HNMR: 1.09 (s,1H,N-Ha) , 2.4-.2.6(t,4H,CH_2β piprazine, Hb), 2.8-3.1(t,4H,CH_2α piprazine, Hc), 4.3(s, 2H, Hd), 4.81(s,2H, N-CH_2-N) bridge, He, 7.4-7.5(m,8H, Ar-Hf) ,7.6-7.7 (s,2H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 52. 9(CH_2-N-CH_2) piprazine, 53. 8(CH_2-N-CH_2) piprazine, 56.8(CH_2, ring) , 69.9(N-CH-N)bridge , 119-141(CH,Ar), 144.3(C-NO_2) , 168.1(C=N) , 169.1 (C=O)
6	3107(CH-Ar),2970(CH--aliphatic), 1695 (C=O), 1618 (C=N),(1562,1540) (N=O), 1338(C-NO_2), 1018 (C-N), 730 (Ar-CI)	^{1}HNMR: 2.4(s,3Ha) , 4.3(s,2H, ringHb) , 4.8(s,1Hc,N-CH-N) bridge, 7.4-7.5(m,8H, Ar-Hd) ,7.6(s,1H, Ar-He), 7.7(s,1H, Ar-Hf) ,8.3(d,2H,Ar-Hn) ^{13}CNMR : 46.1(N-CH3), 56.7(CH_2, ring)), 62.2(N-CH-N)bridge , 122-141(C,Ar), 144(C-NO_2), 167.8(C=N) , 169.2 (C=O)
7	(3105,3020)(CH-Ar), (2973 ,2885)(CH-aliphatic), 1690 (C=O),1618(C=N), (1570 ,1535) (N=O),1337(C-NO_2), 1020 (C-N), 760 (Ar-CI))	^{1}HNMR: 0.84-1.2(t,6H,CH_3,Ha), 2.1-2.5(q,4H,CH_2, Hb) , 4.3(s,2H, ring Hc) , 4.6(s,2Hd,N-CH_2-N bridge), 7.3-7.5(m,8H, Ar-He) ,7.6(d,1H, Ar-Hf), 7.7(s,1H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 15.8(CH_3-N), 54.07(CH_2-N) , 57.07 (CH_2, ring) , 62.4(N-CH-N)bridge , 119-141(C,Ar), 144(C-NO2), 167.8(C=N) , 169.2 (C=O)
8	(3107,3030)(CH-Ar), (2962 ,2870)(CH-aliphatic), 1685(C=O),1620(C=N), (1573,1537) (N=O),1339(C-NO_2),(1080,1040)(C-N), 755 (Ar-CI)	^{1}HNMR:, 1.1-.1.3(t,6H,CH_3,Ha), 2.3-2.5(q,,4H,CH_2, Hb) , 4.3(s,2Hb,N-CH_2-N,Hc) , 5.9(s,1H, N-CH-N bridge, Hd), 7.2-7.5(m,8H, Ar-He) , 7.6(S,1H, Ar-Hf), 7.7(S,1H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 18.1(CH_3-N), 46.1(N-CH_2), 49.2(CH_2-N) , 56.7(CH_2, ring) , 62.2(N-CH-N)bridge , 122-141(C,Ar), 144(C-NO_2), 167.8(C=N) , 169.2 (C=O)

9	(3109,3050)(CH-Ar), (2983,2840)(CH-aliphatic), 1690 (C=O), 1630 (C=N), (1570,1545) (N=O),1337(C-NO_2),(1116,1090(C-O-C), 1040 (C-N), 750 (Ar-CI)	^{1}HNMR:, 2.7-.3(t,4H,CH_2β morpholine, Ha), 3.2-3.5(t,4H,CH_2α morpholine, Hb), 4.3(s, 2H, Hc), 4.8(s,2H, N-CH_2-N, Hd), 7.4-7.5(m,8H, Ar-He) , 7.6(s,1H, Ar-Hf),7.7(s,1H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 57.07(CH_2, ring), ,54.08(CH_2-N-CH_2) morpholine 60.2(CH_2-O-CH_2) morpholine, 63.1(N-CH-N)bridge , 122-141(CH,Ar), 141(C-NO_2) ,167.8(C=N) , 169.2 (C=O)
10	3427(N-H),3050(CH-Ar), 2927(CH-aliphatic),1710 (C=O),1614(C=N), (1579, 1535) (N=O),1326(C-NO_2), 1060 (C-N), 750 (Ar-CI)	^{1}HNMR: 1.09 (s,1H,N-Ha) , 2.4-.2.6(t,4H,CH_2β piprazine, Hb), 2.8-3.1(t,4H,CH_2α piprazine, Hc), 4.3(s, 2H, Hd), 5.9(s,1H, N-CH-N bridge, He), 7.4-7.5(m,8H, Ar-Hf) , 7.6-7.7 (s,2H, Ar-Hn) , 8.3(d,2H,Ar-Hh) ^{13}CNMR : 52. 9(CH_2-N-CH_2) piprazine ,53. 8(CH_2-N-CH_2) piprazine, 56.8(CH_2, ring) , 69.9(N-CH-N)bridge , 119-141(CH,Ar), 144.3(C-NO_2) ,168.1(C=N) , 169.1 (C=O)

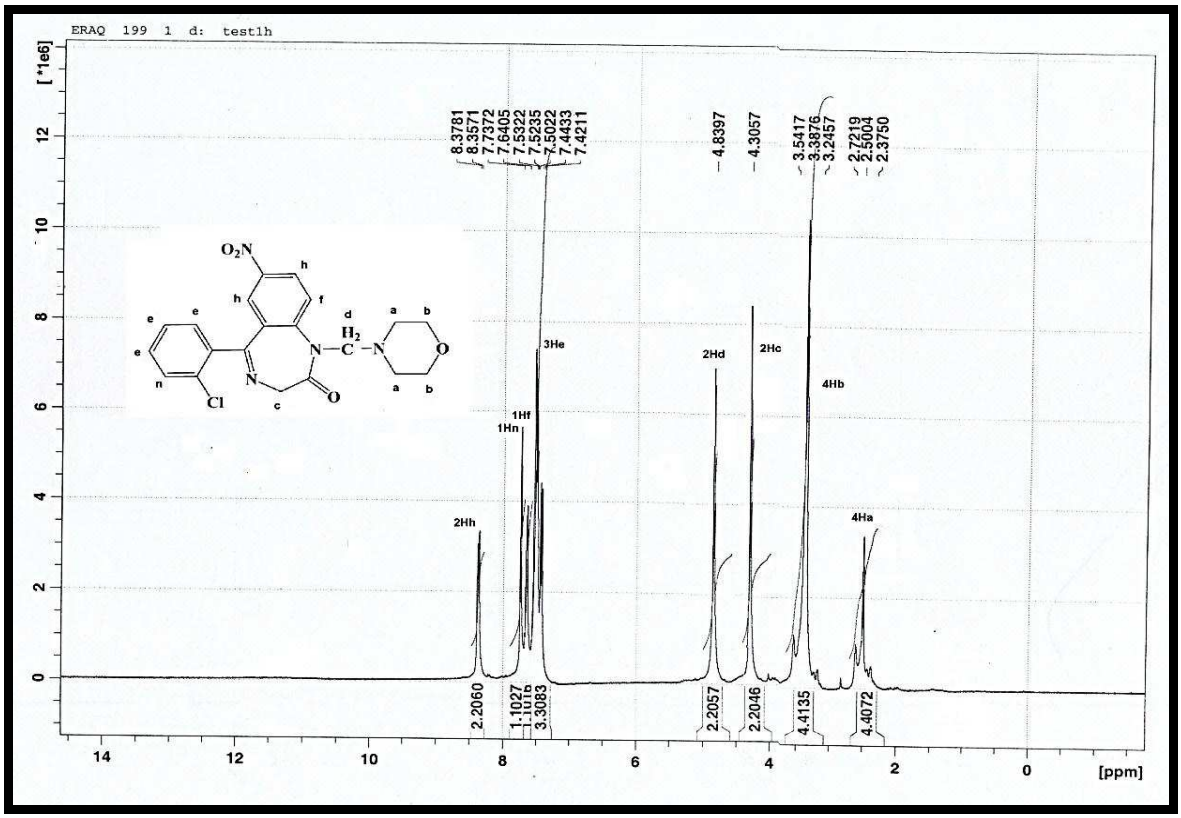


Fig. 1 ^{1}HNMR of compound 4

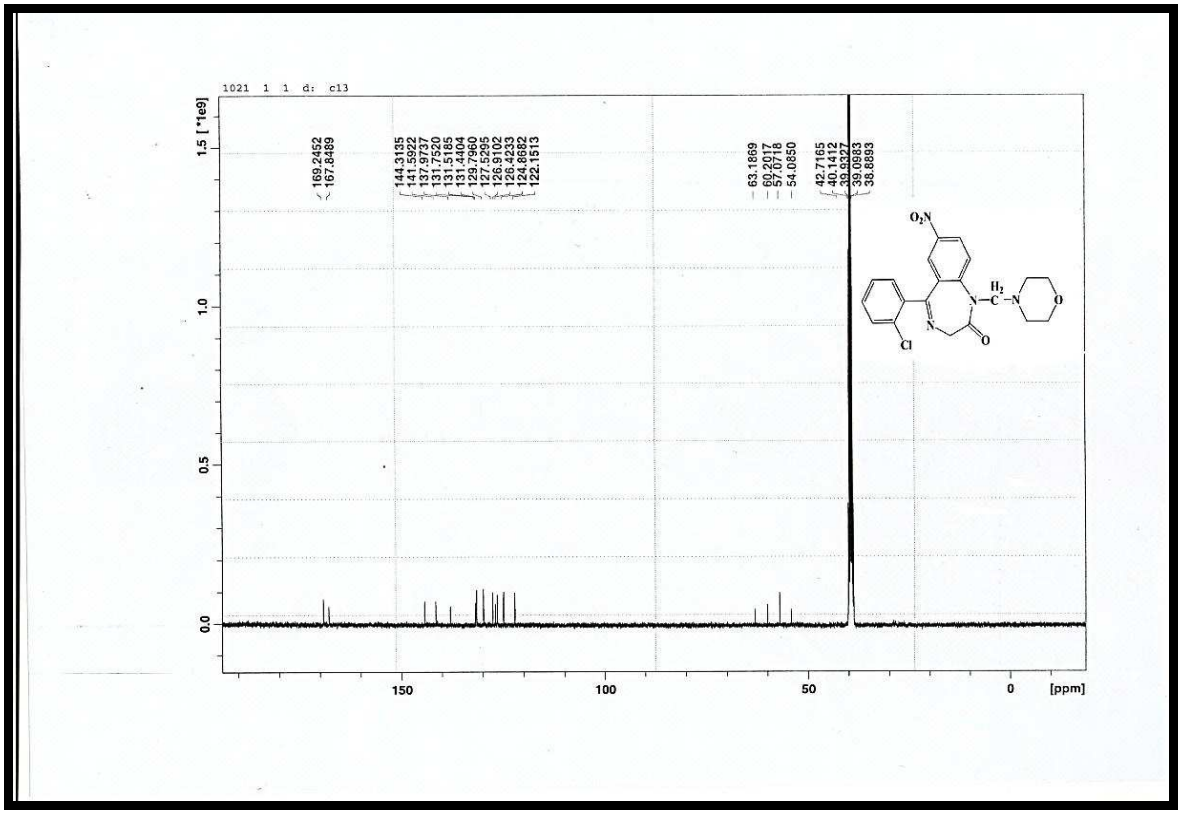


Fig. 2 ^{13}CNMR of compound 4

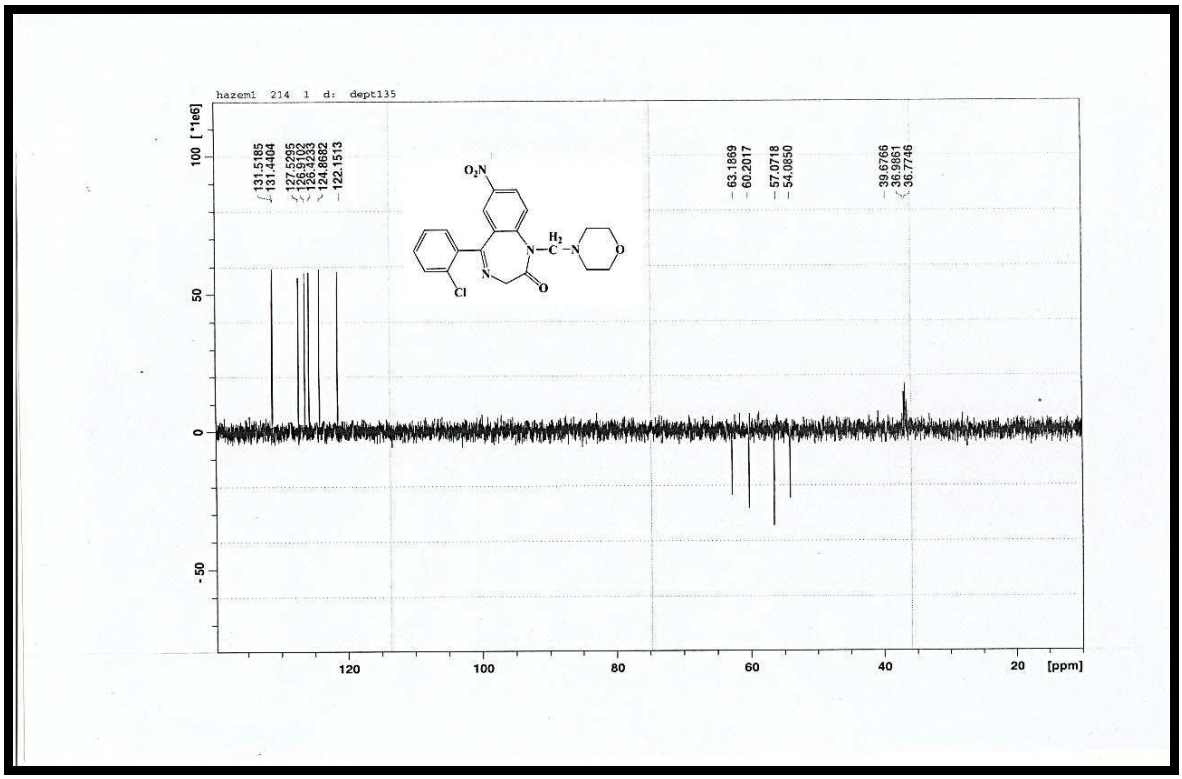


Fig.3 ^{13}CNMR (DEPT135) of compound 4

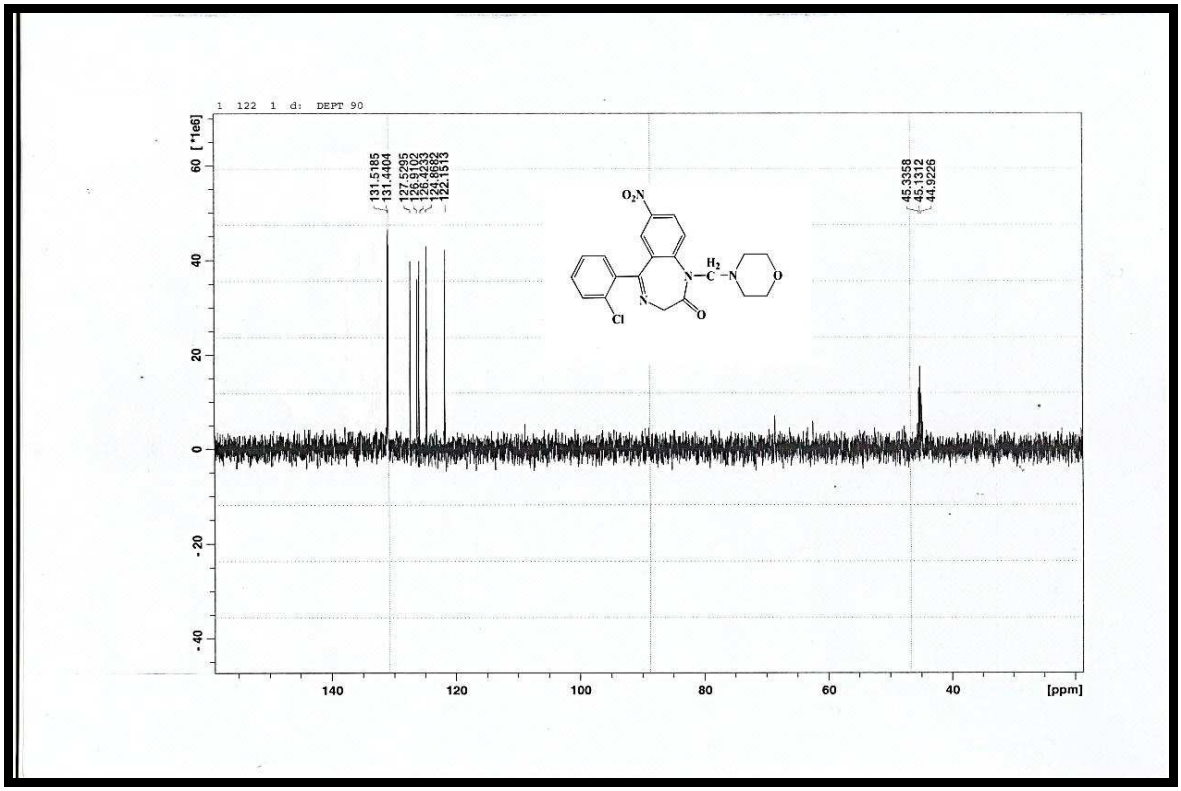


Fig.4 ^{13}CNMR (DEPT90) of compound 4

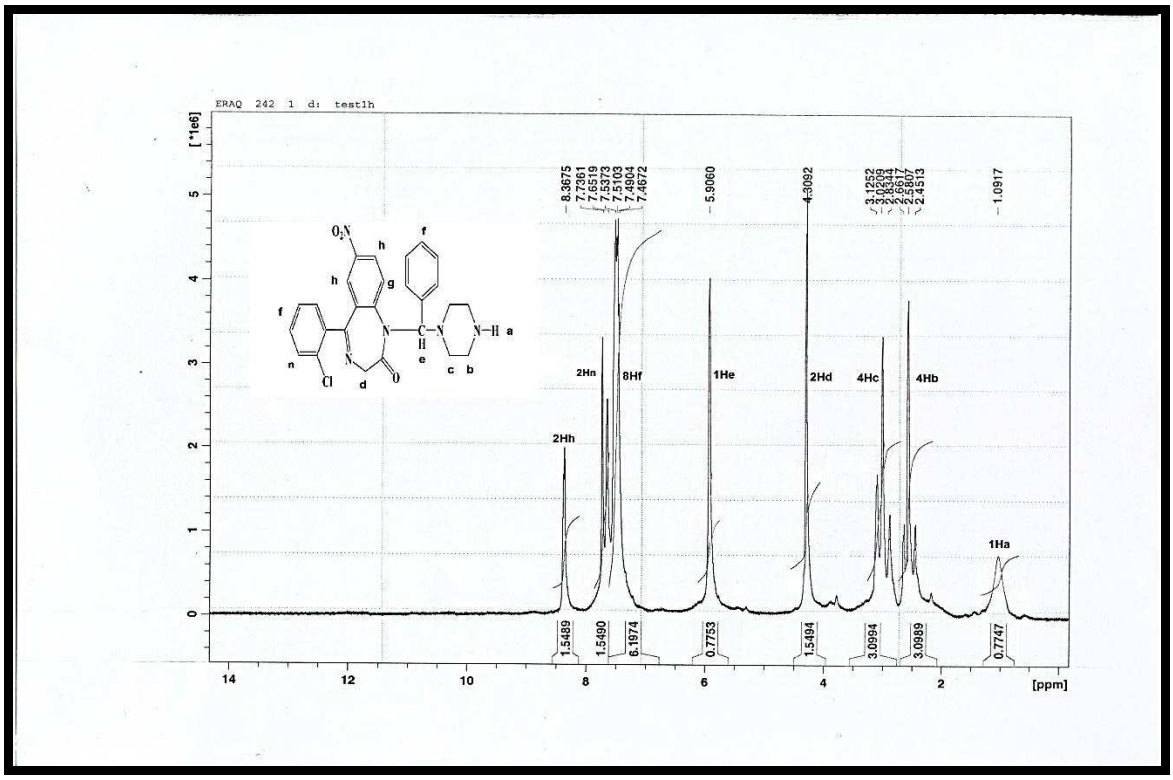


Fig. 5 ^{1}HNMR of compound 10

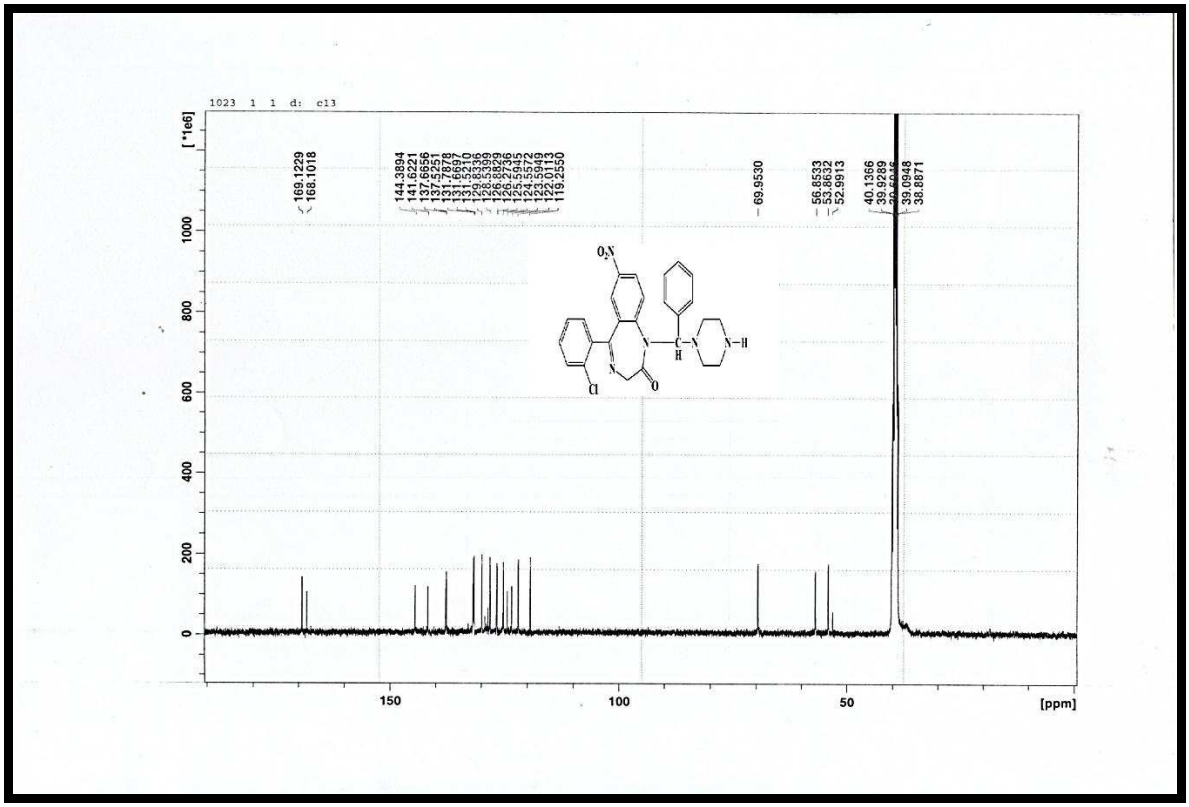


Fig. 6 ^{13}CNMR of compound 10

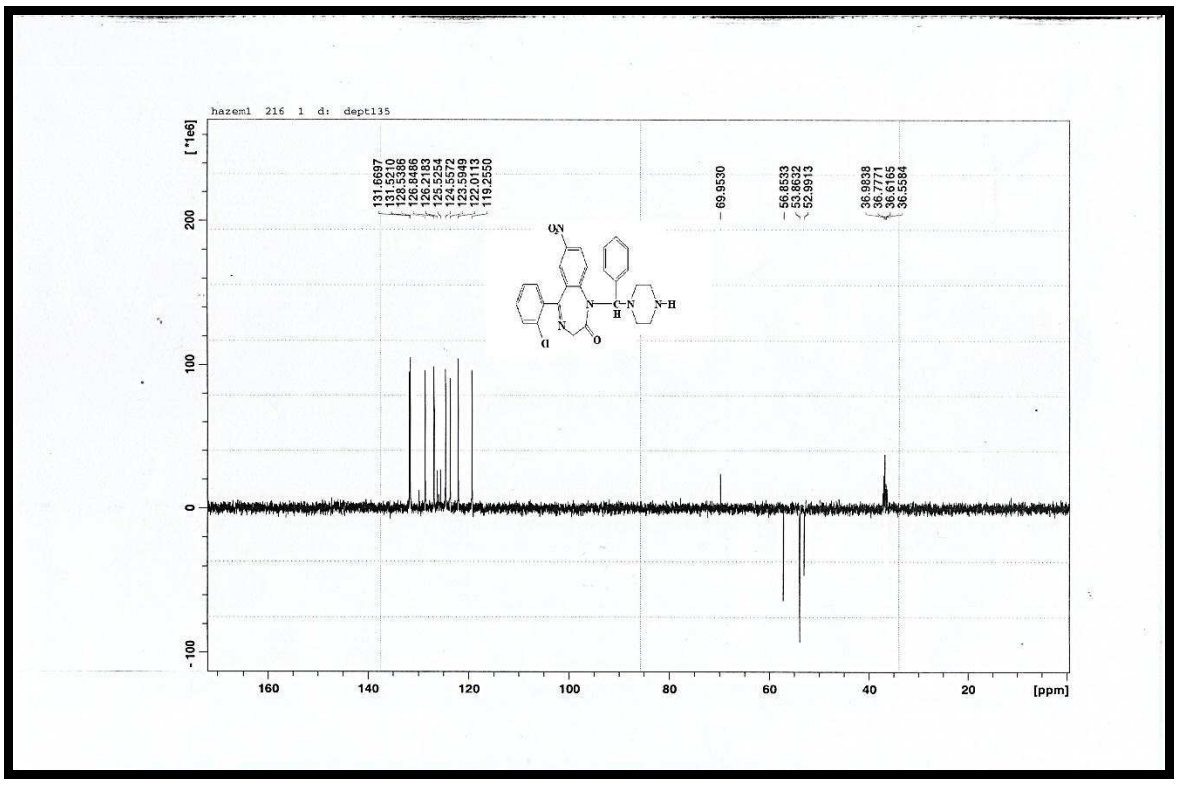


Fig.7 ^{13}CNMR (DEPT135) of compound 10

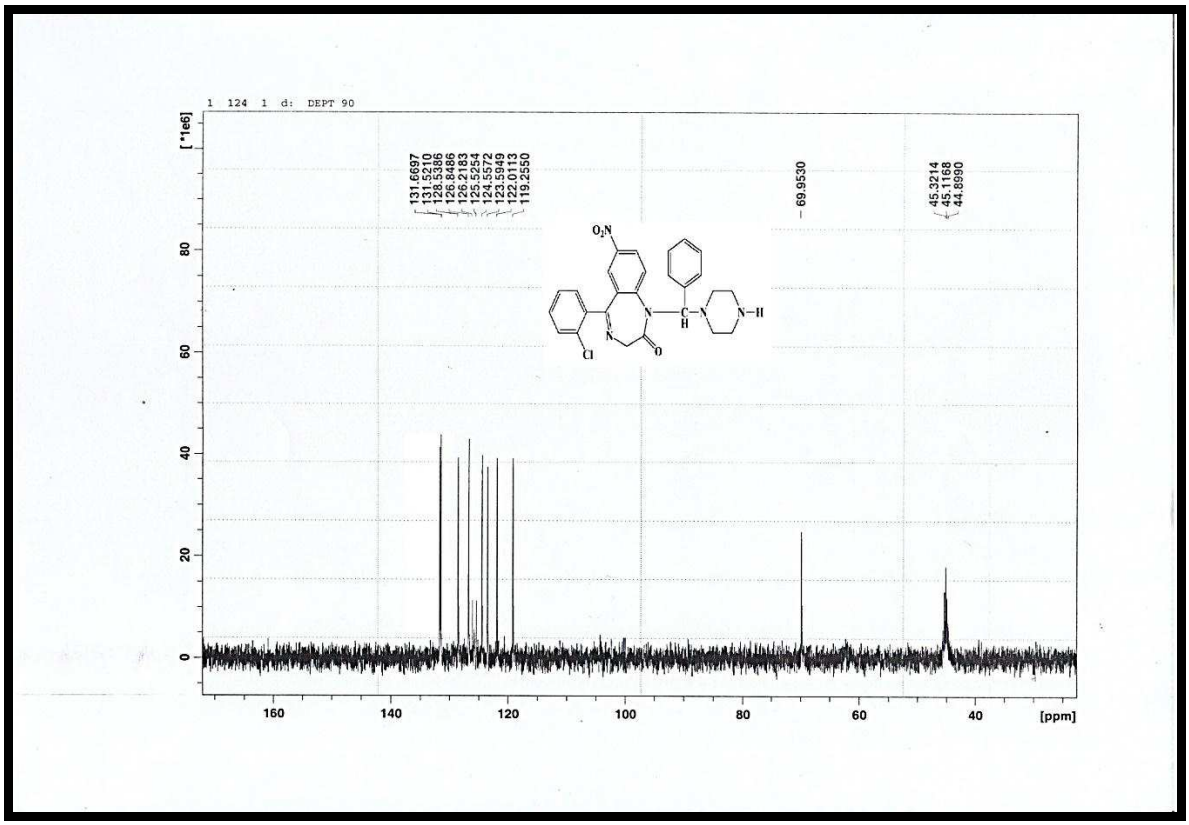


Fig.8 ^{13}CNMR (D

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