Synthesis and Spectroscopic Identification for New Bis-Oxazepines

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Abstract:

Firstly, both compounds ethylmalonate and ethylglutarate (1,2) were prepared via the reaction of di-carboxylic acids(Malonic acid, Glotaric acid) with concentrated sulfuric acid in absolute ethanol, Secondly, both new compounds malonohydrazide and glutarohydrazide (3,4) were prepared through reaction of compounds (1,2) with an excess of hydrazine hydrate at concentration (80%) in absolute ethanol, while the third step involved converting the compounds (3,4) to compounds benzylidenemalonohydrazide (5a-d) and benzylideneglutarohydrazide (6a-d). The convertion occurred via reaction of the compounds (3,4) with different aromatic dehydes in absolute ethanol, Then, the reaction of compounds benzylidenemalonohydrazide (5a-d) and benzylideneglutarohydrazide (6a-d) with maleic anhydride, phthalic and tetra chloro phthalic anhydride in absolute ethanol produces variety of compounds such as bis-substituted(1,3)-oxazepinesmalonamide(7a-d),(9a-d), (11a-d) and bis-substituted(1,3)-oxazepinsglutaramide(8a-d),(10a-d),(12a-d). The compounds of bis-oxazepinesmalonamide and glutaramide are more active and effective than mono-oxazepinesmalonamide and glutaramide. All compounds that prepared in this study were diagnosed using Infrared spectrum (IR) and the protone nuclear magnetic resonance spectrum (1H-NMR) and some physical constants.

Keywords: Bis-oxazepinesmalonamide and glutaramide.

تحضير وتشخيص طيفي لأوكسازبينات ثنائية جديدة

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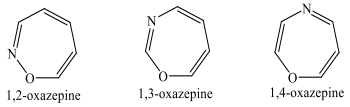
ملخص البحث:

أولاً ، تم تحضير كلا المركبين مالونيت الأثيل و كلوتاريت الأثيل (١،٢) بواسطة تفاعل أحماض ثنائية الكربوكسيل (حامض المالونيك ، حامض الكلوتاريك) مع حامض الكبريتيك المركز في الإيثانول المطلق ، ثانياً ، تم تحضير كل من المركبين الجديدين مالونوهيدرازيد وكلوتاروهيدرازيد (٣،٤) من خلال تفاعل المركبين (١،٢) مع زيادة من الهيدرازين المائي بتركيز (٨٠ ٪) في الإيثانول المطلق ، بينما تضمنت الخطوة الثالثة تحويل المركبات (٣،٤) إلى مركبات بنزيليدين مالونوهيدرازيد (5a–d) وبنزيليدين كلوتاروهيدرازيد(6a–d). حدث التحويل بواسطة تفاعل المركبات (٣،٤) مع ديهيدات أروماتية مختلفة في الإيثانول المطلق. بعد ذلك ، تفاعل المركبات بنزيليدين مالونوهيدرازيد(5a–d) وبنزيليدين كلوتاروهيدرازيد (6a–d) مع أنهيدريدالماليك، فثاليك ورباعي كلورو أنهيدريد الفثاليك في الإيثانول المطلق ينتج مجموعة متنوعة من المركبات مثل ثنائي معوض(١،٣)–أوكسازبينات المالونأمايد(7a–d),(9a–d),(11a–d) وثنائي معوض(١،٣)–أوكسازبينات الكلوتارأمايد(٨a–d),(10a–d),(12a–d). مركبات ثنائي أوكسازبينات المالونأمايد والكلوتارأمايد هي أكثر نشاط وفعالية من أحادي أوكسازبينات المالونأمايد والكلوتارأمايد. جميع المركبات التي حضرت في هذه الدراسة تم تشخيصها باستخدام طيف الأشعة تحت الحمراء (IR) وطيف الرنين المغناطيسي النووي البروتوني (^{1}H–NMR) وبعض الثوابت الفيزيائية.

الكلمات المفتاحية: ثنائي أوكسازبينات المالونأمايد و الكلوتارأمايد.

1. Introduction

Oxazepine compounds are heterocyclic compounds contain five carbon atoms and one atom of both oxygen and nitrogen. There are three isomers for oxazepine compounds are 1,2 , 1,3 and 1,4 oxazepine. This numbering depends on the location of the oxygen and nitrogen atoms in the ring and starting with the oxygen atom and as follows:



The increase in the ring size over six atoms makes it uneven if compared to the hexagonal aromatic benzene ring, therefore the ring takes the shape of the boat in the spatial distribution of the atoms in order to reduce the tension on the ring to be more stable[(1)]. The heterocyclic oxazepine compounds contain in their composition on the nitrogen atom have broad pharmaceutical applications. Among their chemical derivatives are heterogeneous polymers that have activity and effectiveness against cancer[(2)] as well as have effectiveness against fungi and bacteria[(3)], and it was found that some derivatives of oxazepine considered as a medical drug against mental depression as in the derivative (Dibenzoxazepine)[(4)] .

Chemistry of heterocyclic compounds has attracted attention specially 1,3-oxazepine and 1,3-benzooxazepine and its Schiff base (imine) source that showed different biological activities such as anti microbial agents[(5)],inhibitors for some enzymes action[(6)],pharmacological use[(7,8)] in analgesic[(9)]psy choactive drugs[(10)], tricyclic antidepressants (Amoxapine) are used as symptoms depression and anxiety agente treatments[(11,12)].

2. Experimental part

٢.١ Devices and chemicals used

1. Infrared Spectrometer (I.R):

Materials were measured at the University of Mosul / College of Pharmacy with the use of discs (KBr) for solids and the use of discs (NaCl) for liquid materials by adevice:

Bruker Alpha FTIR, Germany, Tenser-27

2. Proton Nuclear Magnetic Resonance Spectrum (^{1}H-NMR):

Proton Nuclear Magnetic Resonance Spectra (^{1}H-NMR) were recorded for a number of compounds prepared at the University of Tehran using adevice:

^{1}H-NMR, Varian Analytische Messtechnik 500MHz, used DMSO-d^6 as solvent and using (TMS) as internal standard reference.

3. Melting Point Devise (M.P):

The melting points of the prepared compounds were measured using adevice: Electrothermal IA 9100 melting point apparatus type(not corrected).

4. All chemicals were produced by BDH and FLUKA.

2.2 Methods of Synthesis

2.2.1 Synthesis of ethylmalonate (1) and ethylglutarate (2)[13].

0.025 mole of (malonic, glutaric acid) was mixed with (50ml) of absolute ethanol, then added with cooling and stirring (6ml) of Conc.H_2SO_4. The mixture was refluxed up to (8) hours, then the solvent was evaporated and the residue was neutralized with 20% sodium bicarbonate. The product is oily liquid and it was extracted by ether, then the organic layer was dried using calcium chloride .The product (1) oily liquid b.p (198-200 C^o) while product (2) oily liquid b.p (236-238 C^o) .

2.2.2 Synthesis of malonohydrazide (3) and glutarohydrazide (4)[14].

0.01mole of compounds (1,2) and (0.1 mole,5 ml) of hydrazine hydrate at concentration (80%) in (50 ml) absolute ethanol were added in round flask then the mixture was refluxed up to (10-12) hours. The solvent was evaporated under a reduced pressure to half the volume and the mixture was cooled, then the precipitate was filtered, recrystallized using ethanol. m.p (148-150 C^o) , (174-176 C^o) and 88% , 82% yield respectivly.

2.2.3 Synthesis of benzylidenemalonohydrazide (5a-d) and benzylidene glutarohydrazide (6a-d)[15,16].

0.005 mole of compounds (3,4) was mixed with (50ml) ethanol, then added (0.01mole) of substituted benzaldehyde in (25ml) ethanol to the mixture and the mixture was refluxed up to (2-4) hours, then it was cooled to obtain precipitate's residue, then it was filtered and recrystallized with ethanol.

Table (1) physical properties of compounds (5a-d),(6a-d).

Comp. No.	n	X	M.p(C^o)	%Yield	Colour
5a	1	m-NO_2	230-232	86	Pale yellow
5b	1	m-OCH_3-p-OH	216-218	84	yellow
5c	1	p-NO_2	222-223	92	yellow
5d	1	p-$N(CH_3)_2$	208-209	80	yellow
6a	3	m-NO_2	250-252	82	Pale yellow
6b	3	m-OCH_3-p-OH	122-124	88	White
6c	3	p-NO_2	2254-257	88	Pale yellow
6d	3	p-$N(CH_3)_2$	234-236	87	Pale yellow

n= CH_2

2.2.4 Synthesis of bis-substituted(1,3)-oxazepinesmalonamide (7a-d),(9a-d),(11a-d) and bis-substituted(1,3)-oxazepinesglutaramide (8a-d),(10a-d),(12a-d)[17,18]

0.001mole of compounds (5a-d),(6a-d) was mixed with (0.002mole) of maleic anhydride, phthalic and tetra chloro phthalic anhydride in (30ml) of absolute ethanol and the mixture was refluxed up to (8)hours, then it was cooled to obtain precipitate's residue, then it was filtered and recrystallized with dioxane.

Table (2) physical properties of compounds (7a-d),(9a-d),(11a-d),(8a-d),(10a-d),(12a-d).

Comp. No.	n	X	Mp(C^o)	%Yield	Colour
7a	1	m-NO_2	214-216	78	Yellowish white
7b	1	m-OCH_3-p-OH	230-232	68	Orange
7c	1	p-NO_2	241-243	56	Orange
7d	1	p-$N(CH_3)_2$	234-236	20	Yellow
8a	3	m-NO_2	244-246	63	Yellowish white
8b	3	m-OCH_3-p-OH	84-86	66	Yellow
8c	3	p-NO_2	250-252	68	Yellow
8d	3	p-$N(CH_3)_2$	216- 218	64	Orange
9a	1	m-NO_2	220-222	65	Yellow
9b	1	m-OCH_3-p-OH	226-228	62	Pale Orange
9c	1	p-NO_2	286-288	42	Yellow

9d	1	p-$N(CH_3)_2$	198-200	67	Dark Orange
10a	3	m-NO_2	238-240	80	White
10b	3	m-OCH_3-p-OH	220-222	40	Pale Yellow
10c	3	p-NO_2	244-246	68	Pale Yellow
10d	3	p-$N(CH_3)_2$	241-243	56	Dark Orange
11a	1	m-NO_2	208-210	70	White
11b	1	m-OCH_3-p-OH	270-272	66	Yellow
11c	1	p-NO_2	226-228	65	Orange
11d	1	p-$N(CH_3)_2$	180-184	68	Dark Orange
12a	3	m-NO_2	236-238	82	White
12b	3	m-OCH_3-p-OH	98-100	45	Yellow
12c	3	p-NO_2	252-254	56	Pale Yellow
12d	3	p-$N(CH_3)_2$	142-144	52	Red

n= CH_2

3. Results & Discussion

Numerous studies have shown that heterocyclic compounds have great importance, as they have been used in the medical field as therapeutic materials and antibiotics[19,20], in the manufacture of paints[21] and a number of polymers[22] in the industrial field and have been used as pesticides[23] and catalysts for growth[24] in the agricultural field.

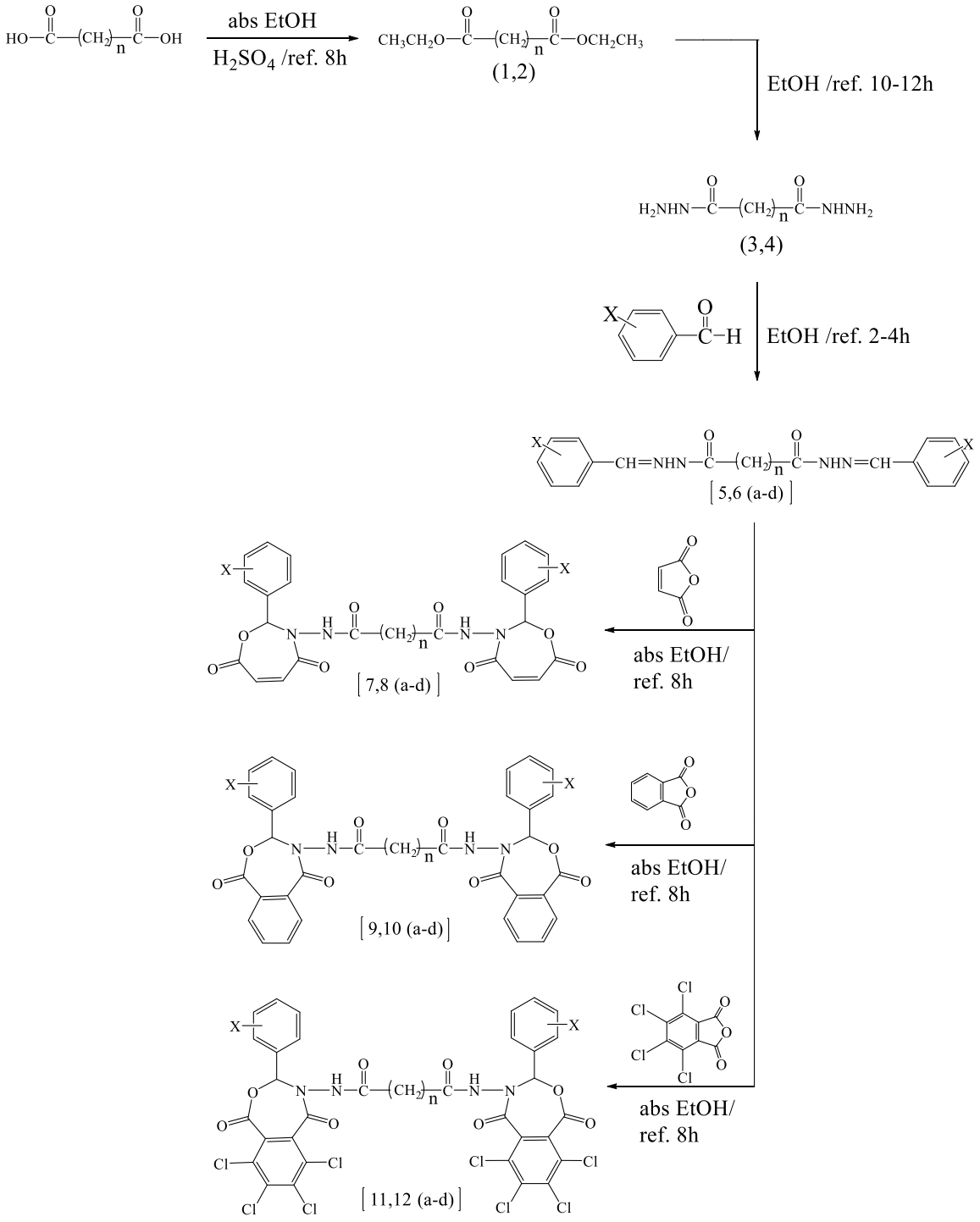
Oxazepine compounds are very important biologically heterocyclic agents[25] as well as its activity as anti cancer agents[26]. The compounds of bis-Oxazepines be more useful as drug or biological agents.

Starting from di-carboxylic acids (Malonic, Glutaric acid). the di-ester(1,2) was prepared *via* reaction with an excess of hydrazine hydrate (80%) in absolute ethanol give malonohydrazide and glutarohydrazide (3,4), Chemical disclosures were used[27] to diagnose the resulting esters *via* ferric hydroxamate and the detection gave apositive result, and esters are diagnosed (R1-3) were prepared by spectra FT-IR, as the spectrum showed beams at (1727-1731cm^{-1}) belong to the ister carbonyl group. symmetric and asymmetric bundles of (C-H) (Aliphatic) at (2981-2984cm^{-1}), and the spectrum showed (C-O) packages individually at (1146-1182cm^{-1}). It was also observed (O-H) group beams that belonged to the carboxylic acids were disappeared, and the carbonyl group stretch values increased in the esters compared to their value in the carboxylic acids[28].

Reaction 1mole of compounds (3,4) with 2mole of different aromatic dehydes to prepare benzylidenemalanohydrazide (5a-d) and benzylidene glutarohydrazide (6a-d) these compounds structure were confirmed by FTIR spectra , packs appeared at (1588-1627cm^{-1}) belong to (C=N) imine group, and packages (N-H) appeared at (3168-3298cm^{-1}) and packages (C=O)

appeared at (1633-1689cm^{-1}). Reaction 1mole of compounds (5a-d),(6a-d) with 2mole of maleic, phthalic and tetra chloro phthalic anhydride in absolute ethanol leades to form bis-substituted(1,3)-oxazepinesmalonamide and bis-substituted(1,3)-oxazepinesglutaramide.

Spectra FT-IR of compounds(7a-d),(9a-d),(11a-d),(8a-d),(10a-d),(12a-d)showed (N-H) peaks at (3170-3275 cm^{-1}), aromatic (C-H) showed peaks at 3030-3080cm^{-1}, aliphatic (C-H) peak appear at (2850-2950cm^{-1}), lactone and lactam carbonyl stretching bands appear at (1649-1782cm^{-1}), as well as C=C(Ar) absorb in the reagion (1570-1600 cm^{-1}). ^{1}H-NMR (500 MH_Z,DMSO-d^6) of compound (11b) exhibts signals (s,2.53ppm, CH_2), (s,3.31ppm, Ar-OCH_3), (m,6.87-7.64ppm, Ar-H), (s,8.9ppm,-N-CH-O-), (s,9.96ppm,Ar-OH) latest (s,10.39ppm, -NH-C=O).



n= CH_2, n= 1,3

x= a= m-NO_2 , b= m-OCH_3-p-OH , c= p-NO_2 , d= p-$N(CH_3)_2$

Scheme (1)

Table (3): FT-IR data for compounds (1,2),(3,4),(5a-d),(6a-d).

Comp. No.	IR(KBr)cm^{-1}				
	n	N-H	C=O	C=N	Others
1	1	-	1731	-	Alph (C-H) 2984 (C-O) 1146
2	3	-	1727	-	Alph (C-H) 2981 (C-O) 1182
3	1	3178	1623	-	3283(NH_2)
4	3	3182	1626	-	3289(NH_2)
5a	1	3232	1675	1617	1520,1385(NO_2)asym,sym
5b	1	3192	1647	1592	3482(OH),1166(O-CH_3)
5c	1	3298	1678	1588	1511,1390(NO_2)asym,sym
5d	1	3211	1656	1599	1227(C-N)
6a	3	3286	1689	1627	1520,1385(NO_2)asym,sym
6b	3	3203	1633	1584	3449(OH),1169(O-CH_3)
6c	3	3244	1671	1590	1514,1389(NO_2)asym,sym
6d	3	3168	1649	1599	1261(C-N)

Table(4): FT-IR data for compounds (7a-d),(9a-d),(11a-d),(8a-d),(10a-d) and (12a-d).

Comp. No.	IR(KBr)cm^{-1}				
	n	N-H	C=O Lactone	C=O Lactam	Others
7a	1	3191	1715	1676	1514,1389(NO_2)asym,sym
7b	1	3243	1718	1657	3455(OH),1159(O-CH_3)
7c	1	3206	1711	1669	1525,1345(NO_2)asym,sym
7d	1	3229	1726	1675	1251(C-N)
8a	3	3221	1722	1674	1521,1345(NO_2)asym,sym
8b	3	3263	1717	1649	3481(OH),1167(O-CH_3)
8c	3	3218	1719	1669	1528,1350(NO_2)asym,sym
8d	3	3170	1729	1650	1261(C-N)
9a	1	3194	1730	1665	1525,1348(NO_2)asym,sym
9b	1	3254	1722	1659	3461(OH),1151(O-CH_3)
9c	1	3185	1731	1676	1515,1370(NO_2)asym,sym
9d	1	3231	1718	1668	1259(C-N)
10a	3	3235	1742	1669	1528,1366(NO_2)asym,sym
10b	3	3258	1719	1661	3472(OH),1175(O-CH_3)
10c	3	3248	1727	1666	1511,1389(NO_2)asym,sym
10d	3	3244	1736	1680	1273(C-N)
11a	1	3202	1739	1671	1520,1352(NO_2)asym,sym

11b	1	3263	1727	1669	3445(OH),1159(O-CH_3)
11c	1	3239	1751	1709	1519,1355(NO_2)asym,sym
11d	1	3242	1745	1690	1268(C-N)
12a	3	3238	1748	1675	1515,1363(NO_2)asym,sym
12b	3	3275	1752	1664	3448(OH),1166(O-CH_3)
12c	3	3265	1769	1715	1513,1364(NO_2)asym,sym
12d	3	3265	1782	1715	1292(C-N)

n= CH_2

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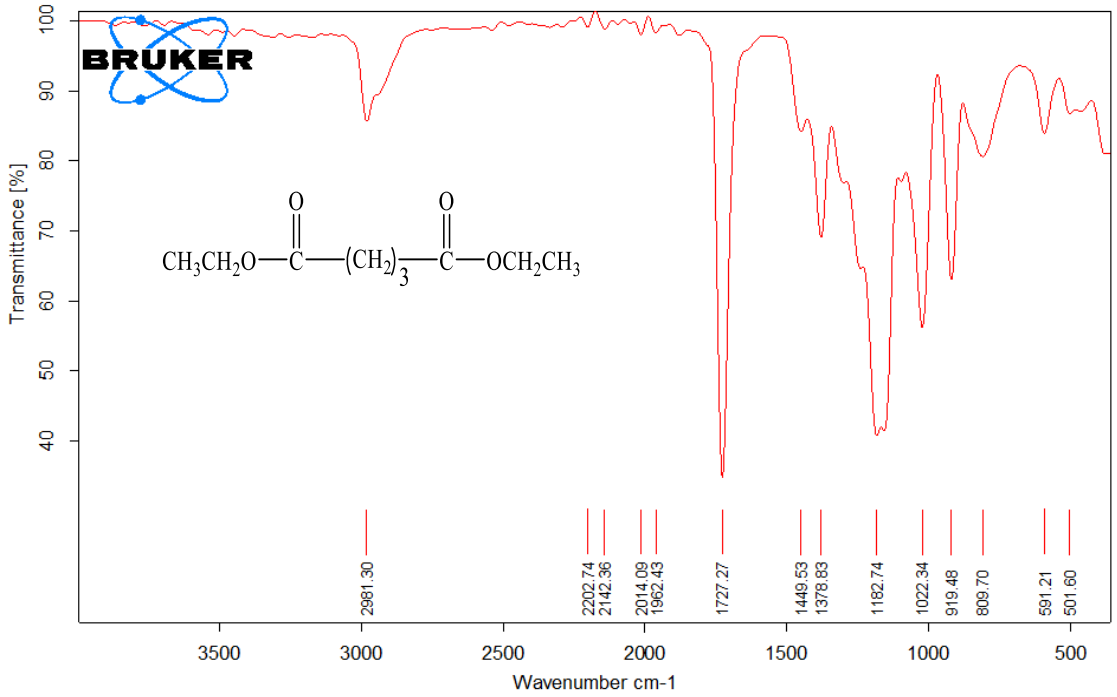

Figure (1): FT-IR spectrum for compound (2)

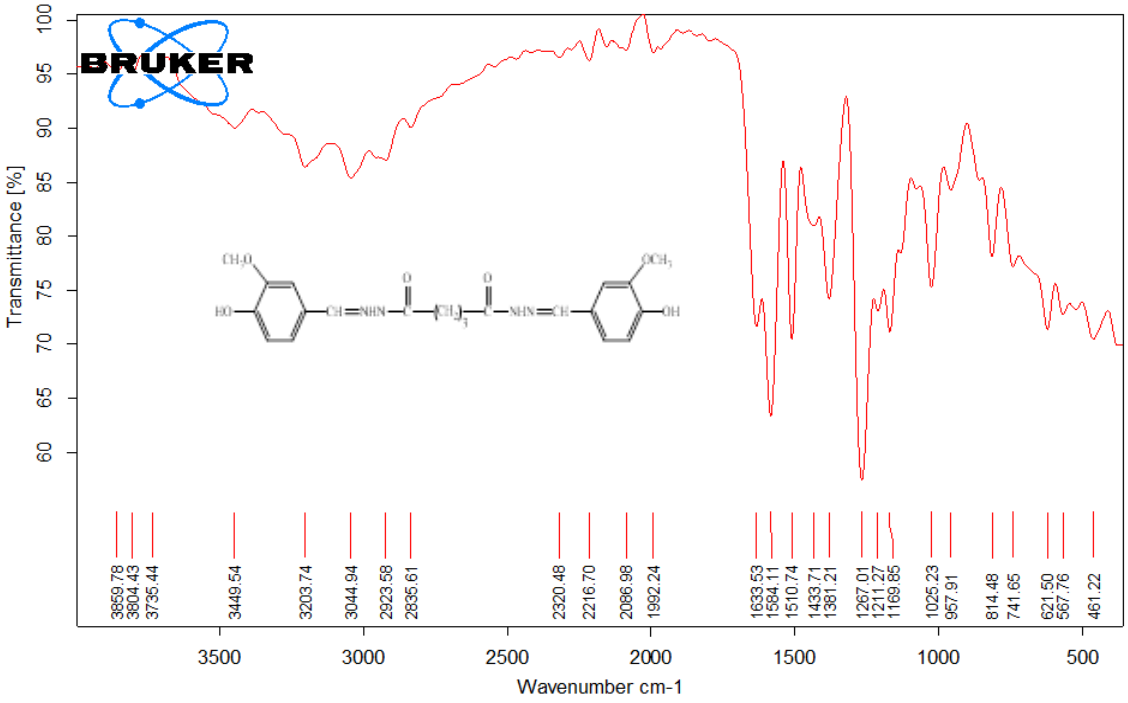

Figure (2): FT-IR spectrum for compound (6b)

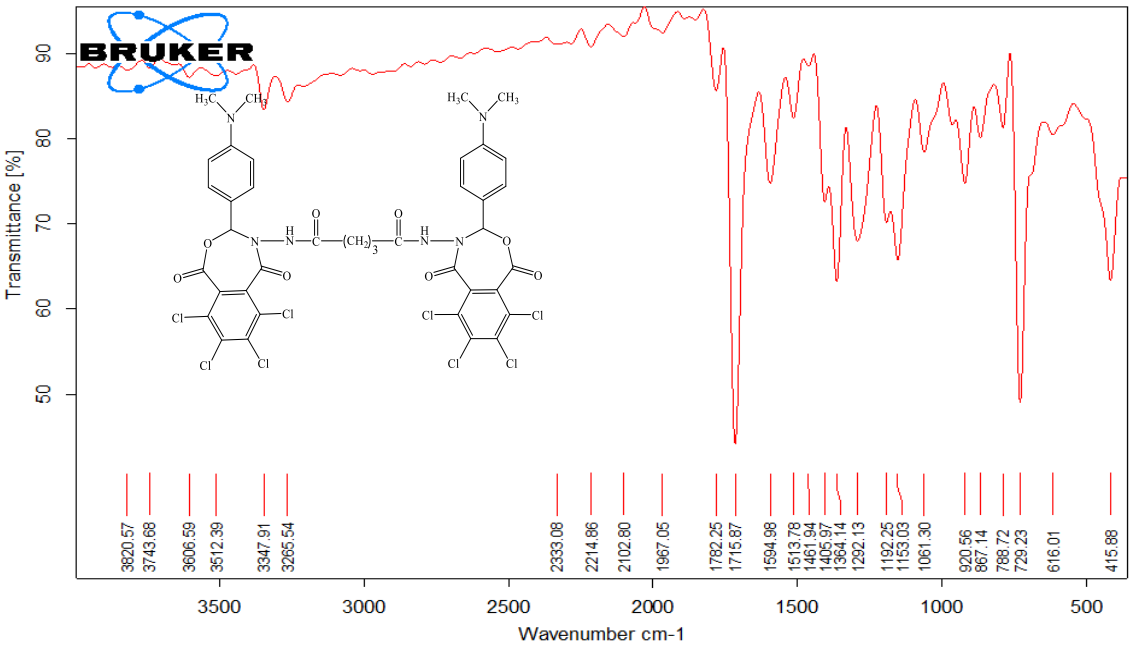

Figure (3): FT-IR spectrum for compound (12d)

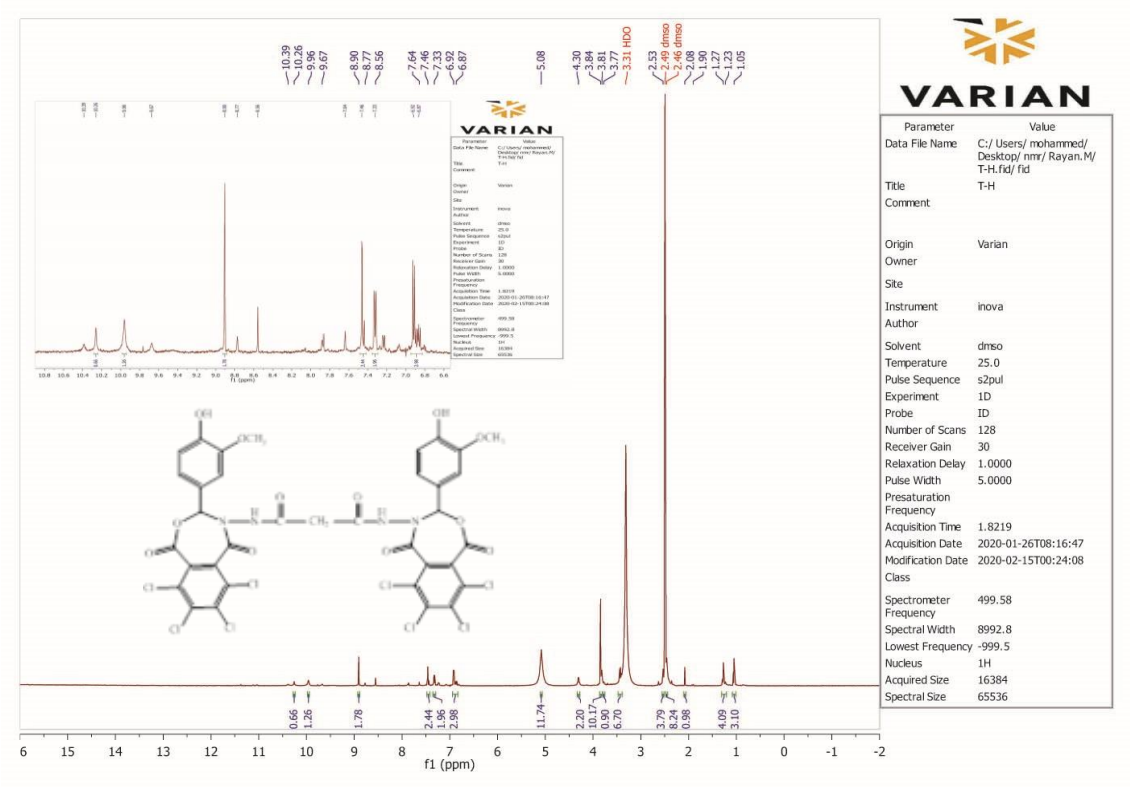

Figure (4): ^{1}H-NMR spectrum for compound (11b)