IRAQI Academic Scientific Journals
Samarra Journal of Pure and Applied Science
SJPAS
www.sjpas.com
p ISSN: 2663-7405
e ISSN: 2789-6838

Synthesis and Identification of Some New bi-azetidine 2,2'- dione and bi-quinazoline-4,4 '-dione Compounds derived from bis Schiff Base derivatives.

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https://doi.org/10.54153/sjpas.2025.v7i2.994

Article Information
Received: 24/07/2024
Revised: 18/08/2024
Accepted: 20/09/2024
Published: 30/06/2025

Keywords:
Heterocyclic compounds *1, Schiff bases2, Azetidine 3,* Quinazoline*4, and* biological activities*5.*

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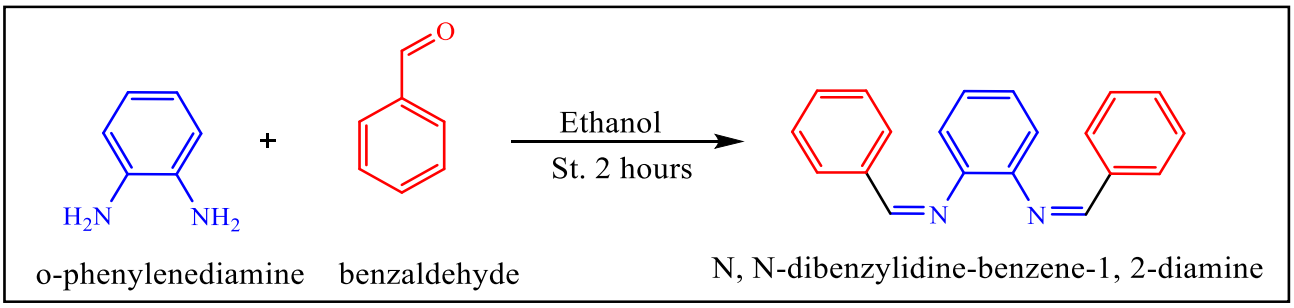
Abstract

This research Included the preparation and characterization of new Four and Six membered Heterocyclic Compounds (bi-azetidine 2,2'- dione and bi-quinazoline-4,4 '-dione) by using two steps. The first step includes reaction of benzaldehyde derivatives with hydrazine hydrate in presence of glacial acetic acid to give 1,2-bis (Substituted-benzylidene) hydrazine derivative (A_1-A_7). The second step includes reaction of compounds (A_1-A_7) with (chloroacetylchloride) in the presence of triethylamine to give 4,4'-bis (substitutedphenyl)-3,3'-dichloro-[1,1'-biazetidine]-2,2'-dione (A_8-A_{14}). Then, compounds (A_1-A_7) reacted with (2-amino benzoic acid) in ethanol as solvent to gives 2,2'- bis (substitutedphenyl) -1,1',2,2'-tetrahydro-4H,4'H-[3,3'-biquinazoline]-4,4'-dione (A_{15}-A_{21}). The prepared compounds were characterized by their physical properties, melting points, FT-IR, 1H-NMR and 13C-NMR.

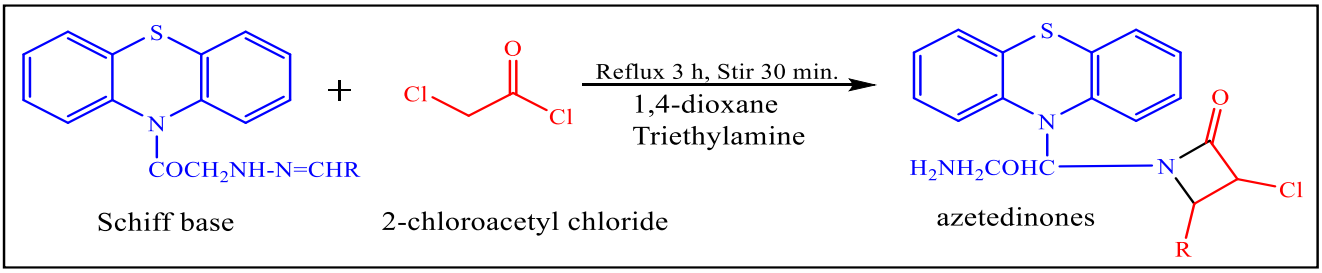
Introduction:

Heterocyclic compounds and their derivatives are considered the greatest biologically active because of their unlimited importance in the fields of drug, as they have been used as antibacterial, cancerous tumors, spasmodics, fungi and viruses [1]. Schiff base (known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group [2], They are a wide group of compounds characterized by the presence of a double bond linking carbon and nitrogen atoms [3]. Schiff bases are prepared from the condensation of aromatic or aliphatic amines and compounds (ketone, aldehyde, or acetyl compound) containing a carbonyl group by nucleophilic addition [2]. Schiff bases have been synthesized through the reaction of benzaldehyde and ethanolic solution of o-phenylenediamine [4]. Equation1. Schiff base have biological activities such as anticancer, antioxidant [5], anti-microbial [6], anti-inflammatory [7] and analgesic, anxiolytic [8].



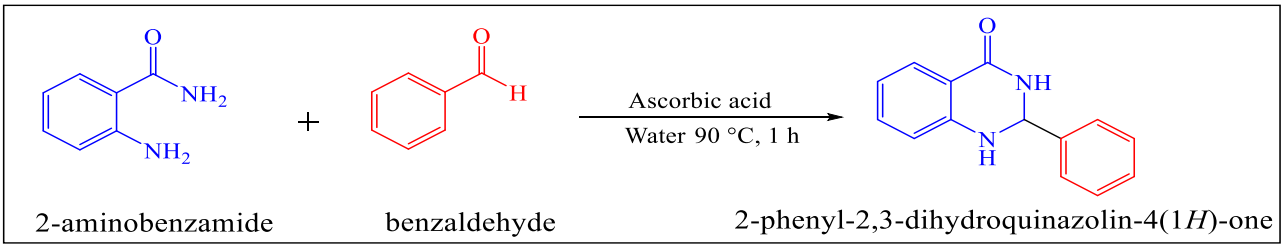
Equation 1 : Synthesis of Schiff Base

Azetidinone is chemically 2-Azacyclobutanon, it is the four membered heterocyclic compound which contain one Nitrogen atom in their ring. It is have caught the attention of chemists and medical researchers [9]. Azetidinones are of great biological interest, especially as antibacterial [10], antifungus [11], antitubercular [12], antioxidant [13], antidepressant [14], anti-inflammatory [15] and against Parkinson's disease [16], showed other important biological effects such antidiabetic [17] and hypolipemiant [18]. Azitidinone derivatives were prepared by cyclocondensation of azomethine compounds with chloroacetyl chloride in the presence of Et_3N.[19]. Equation 2.



Equation 2: Synthesis of azetedinones

Quinazolines are a compounds conjured of two merged six-membered aromatic rings, pyrimidine and benzene rings [20], They are very useful heterocyclic compound have a wide range of biological activities such as antitubercular [21-22], anti-cancer [23], anti-inflammatory [24], antifungal [25], antibacterial [26], antileukemic [27], antileishmanial [28], antioxidant [29] and antibiofilm [30]. Quinazoline derivatives have been synthesized through reaction of benzaldehyde and 2-aminobenzamide, equation 3. [31]



Equation 3: Synthesis of quinazoline-4(1H)-one

Aim of work.

To synthesize bi-azetidine 2,2'- dione and bi-quinazoline-4,4 '-dione derivatives through the reaction of Schiff base with chloro actylchlorides and 2-amino benzoic acid respectively and the Study of the physical properties and the results of spectroscopic measurements (FT.IR., ^{1}H-NMR. and ^{13}C-NMR).

Experimental

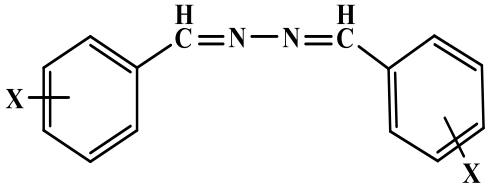
Aryl aldehydes, hydrazine hydrate 80% chloroacetylchloride, 2-amino benzoic acid, ethanol, trimethylamine, acetic acid and dioxane are provided that from Aldrich and Fluka they used without further purification. The melting points of the prepared compounds were measured using a melting point device (uncorrected). IR spectra were recorded on a Shimadzo FTIR-8100 spectrophotometer using KBr discs-and ^{1}H.N.M.R and ^{13}C.N.M.R spectra were recorded on Bruker spectroscopic ultra-shield magnets 300 MHz instruments using DMSO-d6 as a solvent and tetramethyl silane (TMS) as an interior standared**.**

Methods of Synthesis:

Synthesis of Diarylidine hydrazine Compounds(A_1-A_{10}).[32]

A mixture of aryl aldehydes (0.02 mol), hydrazine hydrazine (0.01 mol, 0.5 g) and a drop of acetic acid was dissolved in ethanol and refluxed (8) hours. The reaction mixture was concentrated and poured into crushed ice. The solid product was obtained, separated and dried. The synthesized product was recrystallized from ethanol. listed in Table 1.

Table 1. Physical properties of compounds (A_1-A_7).

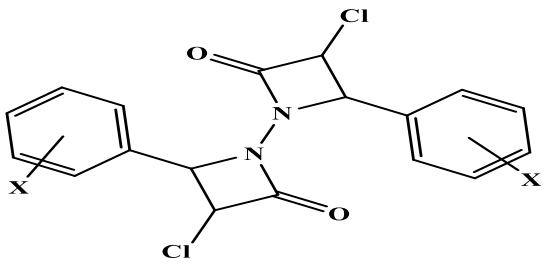


Comp. No.	X	Molecular formulation	M. p.(Cº)	Yield (%)	Colour
A_1	H	$C_{14}H_{12}N_2$	60 - 62	87	Yellow
A_2	4-Br	$C_{14}H_{10}N_2Br_2$	216 – 218	95	Yellow
A_3	4-Cl	$C_{14}H_{10}N_2Cl_2$	198 – 200	95	White yellow
A_4	4-N$(CH_3)_2$	$C_{18}H_{22}N_4$	202 – 204	95	Orange
A_5	3-OH	$C_{14}H_{12}N_2O_2$	94 – 96	77	Yellow
A_6	3-Cl,2-OH	$C_{14}H_{10}N_2O_2Cl_2$	98 – 100	91	Yellow
A_7	3-OCH_3,4-OH	$C_{16}H_{16}N_2O_2$	74 – 76	75	Greenish yellow

Synthesis of: 4,4'-bis(subs.phenyl)-3,3'-dichloro-[1,1'-biazetidine]-2,2'-dione (A_8-A_{14}).[33]

A mixture of compounds (A_1-A_7) (0.01 mol) and triethylamine (0.02 mol) in 1,4-dioxane (20 mL) at (5) °C was stirred for (5) hours, During stirring, chloroacetyl chloride (0.02 mol, 2.6 g) in dioxan (10 mL) was added dropwise, The mixture was refluxed for (8) hours. The resulted mixture was cooled and the obtained precipitate was filtered, Recrystallization was done with ethanol to give the 3,3'- dichloro-[1,1'-biazetidine]-2,2'-dione (A_8-A_{14}) compounds. listed in Table (2).

Table 2. Physical properties of compounds (A_8-A_{14}).

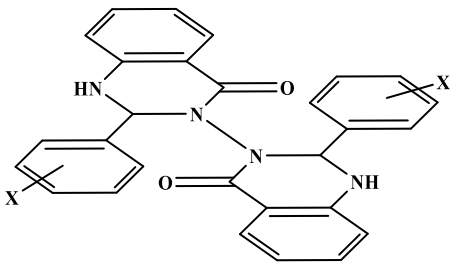


Comp. No.	X	Molecular formulation	M. p. (Cº)	Yield (%)	Colour
A_8	H	$C_{18}H_{14}N_2O_4\ Cl_2$	245-247	71	Dark brown
A_9	4-Br	$C_{18}H_{14}N_2O_2Br_2\ Cl_2$	230-232	83	Light brown
A_{10}	4-Cl	$C_{18}H_{14}N_2O_4Cl_4$	226-228	96	Light brown
A_{11}	4-$N(CH_3)_2$	$C_{22}H_{24}N_4O_2\ Cl_2$	195-197	79	Dark brown
A_{12}	3-OH	$C_{20}H_{18}N_2O_6\ Cl_2$	220-222	78	Light brown
A_{13}	3-Cl,2-OH	$C_{18}H_{12}N_2O_4\ Cl_2$	240-242	89	Brown
A_{14}	3-OCH_3,4-OH	$C_{18}H_{12}N_2O_2Cl_4$	229-231	92	Light brown

Synthesis of: 2,2'-bis(subs.phenyl)-1,1',2,2'-tetrahydro-4H,4'H-[3,3'-biquinazoline]-4,4'-dione (A_{15}-A_{21}).[34]

Solution of Schiff bases [A_1-A_7] (0.01 mol.) in absolute ethanol (10 mL) and (0.02 mole, 2.74 g) 2-amino benzoic acid in absolute ethanol (5 mL) was refluxed for (15 h), then, The product was appropriately washed with cold-water and filtered, re-crystallized with a suitable solvent. listed in Table (3).

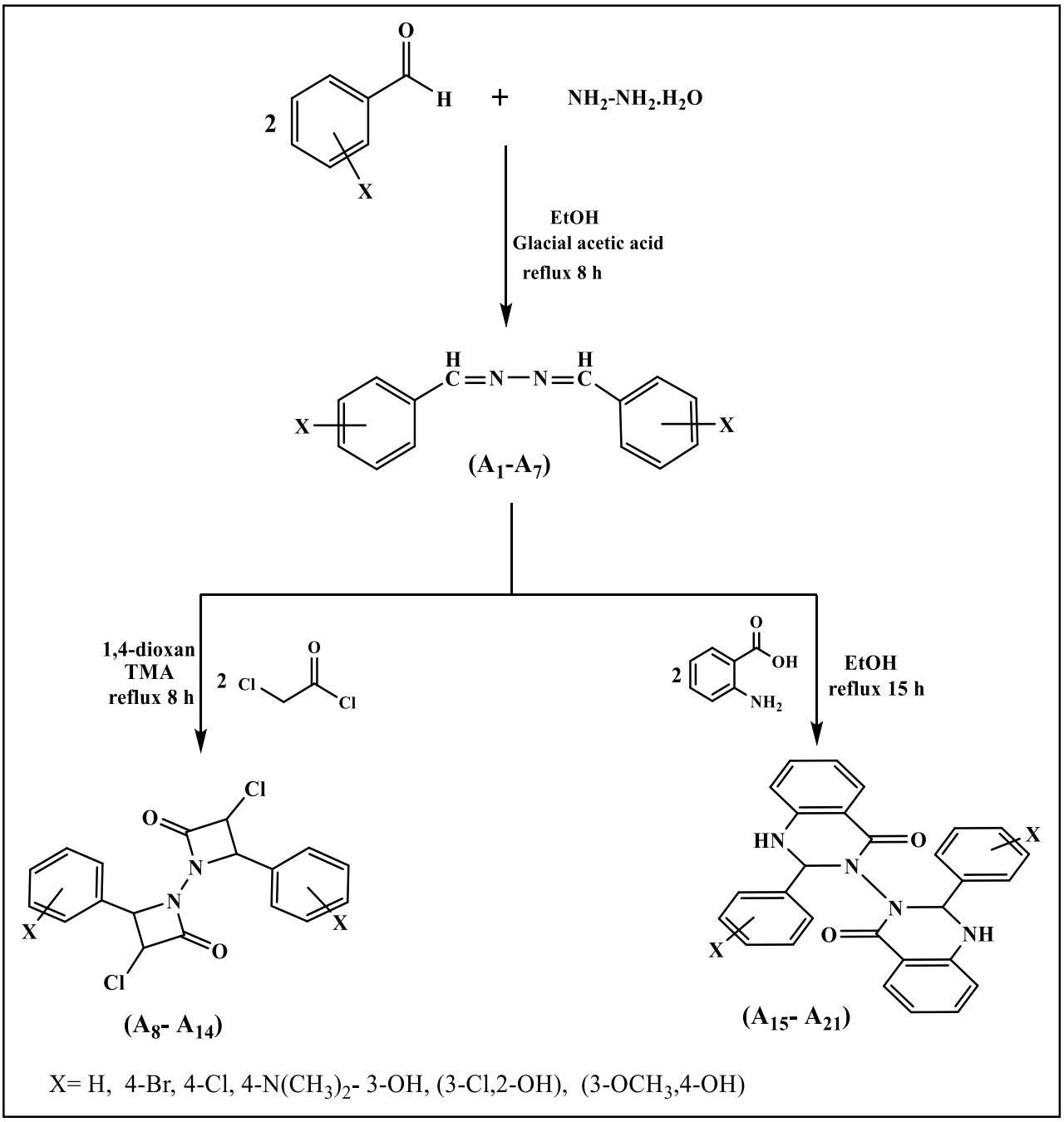
Table 3. Physical properties of compounds (A_{15}-A_{21}).



Comp. No.	X	Molecular formulation	M. p. (Cº)	Yield (%)	Colour
A_{15}	H	$C_{28}H_{20}N_4O_2Cl_2$	149-151	78	Bright green
A_{16}	4-Br	$C_{28}H_{22}N_4O_4$	66-68	65	Orange
A_{17}	4-Cl	$C_{28}H_{20}N_4O_4Cl_2$	158-160	89	Orange
A_{18}	4-$N(CH_3)_2$	$C_{28}H_{20}N_4O_2Br_2$	214-216	90	Brown
A_{19}	3-OH	$C_{28}H_{20}N_4O_2Br_2$	100-102	83	Brown
A_{20}	3-Cl,2-OH	$C_{28}H_{22}N_4O_4$	196-198	76	Orange
A_{21}	3-OCH_3,4-OH	$C_{28}H_{22}N_4O_2$	116-118	67	Orange

Results and Discussion:

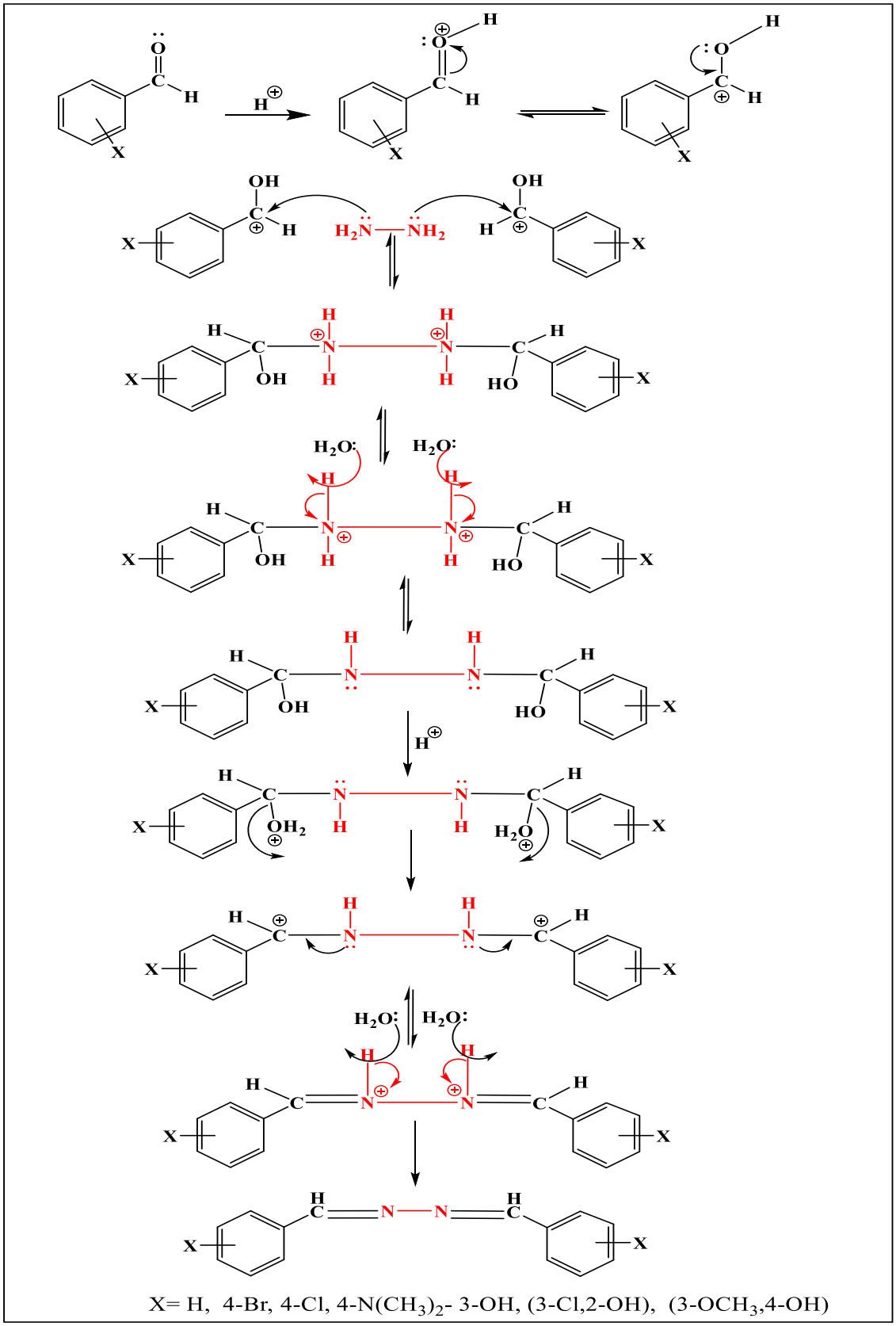
The main reason for the high interest in this class of compounds is that the lactam moiety and quinazoline is present in various natural and synthetic compounds that possess a broad spectrum of biological properties, especially those of three to seven members. The construction of the β-lactam ring (2-azetidinone) is the most studied synthesis of lactams carried out by synthetic organic chemists and medicinal chemists due to its medicinal value [35-36]. This study prepared quaternary and hexagonal rings of azetidine and quinazoline derivatives by reacting Schiff base derivatives with chloroacetyl chloride and 2-amino benzoic acid with molar numbers (1:2) respectively, as shown in Scheme 4.



Scheme 4. Synthesis of compounds (A_1-A_{21}).

Characterization of the Diarylidine hydrazine Compounds(A_1-A_7).

The new Diarylidine hydrazine were synthesized from the reaction of hydrazine hydrate with 2 mole of aryl aldehydes in absolute ethanol and in the catalytic amount of glacial acetic acid, The suggested m**e**chanism as shown in Scheme 5.



Scheme 5. mechanism of preparation of Diarylidine hydrazine (A_1-A_7)

The FT-IR spectra of Diarylidine hydrazine (A_1-A_7): A clear decrease in the melting points was recorded, which may be attributed to the decrease in the possibility of forming interfacial hydrogen bonds with the disappearance of the NH_2 group, The prepared compounds(A_1-A_7) were characterized by the infrared spectrum, as it showed an absorption band within the range IR(cm^{-1}) as: (3034, 3091) cm^{-1} (= CH stretching aromatic) ; (C=N)

stretch band(1616-1656) cm^{-1} [37], (1452,1602)cm^{-1} (C=C aromatic ring) ; (C-N) was appeared at (1253-1357) cm^{-1}, (935-1085)cm^{-1} (N-N stretching). as shown in Table 4, Figure 1 and 2.

Table 4. Some spectral data for compounds (A_1- A_7)

I.R., υ (cm^{-1}), KBr Comp. No.	X	(=CH) arom.	(C=N)	(C=C) arom.	(C-N)	(N-N)	Others
A_1	H	3034	1624	1577,1452	1292	935	-
A_2	4-Br	3112	1616	1515,1470	1269	1070	(C-Br),825
A_3	4-Cl	3047	1633	1589,1485	1298	1085	(C-Cl),956
A_4	4-$N(CH_3)_2$	3074	1624	1575,1477	1254	1002	(C-H), 2992,2833,
A_5	3-OH	3074	1618	1513,1472	1357	1009	(OH),3473
A_6	3-Cl,2-OH	3091	1631	1578,1487	1355	989	(C-Cl),966 (OH),3278
A_7	3-OCH_3 , 4-OH	3056	1656	1596,1515	1253	1029	(OH),3363

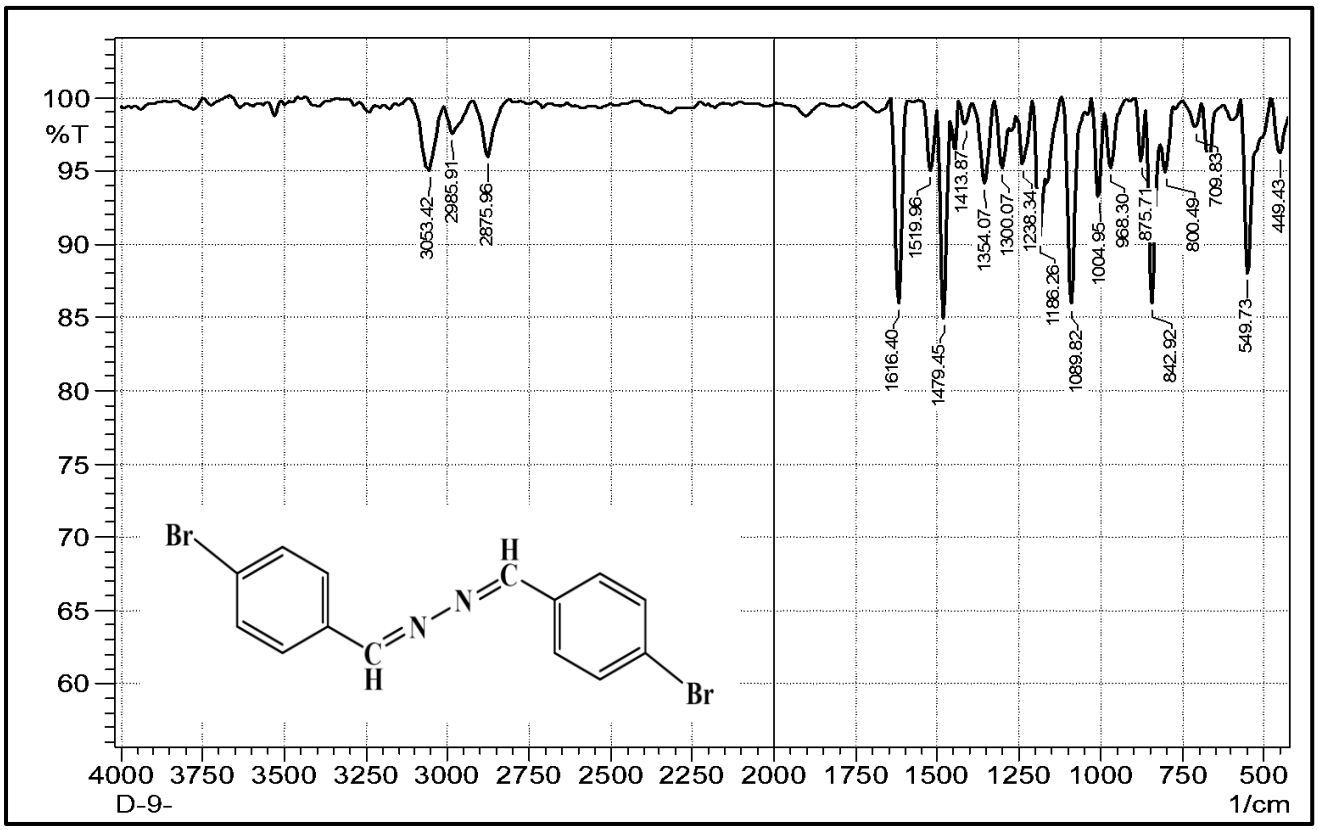


Fig. 1: Show the IR for compound (A_2)

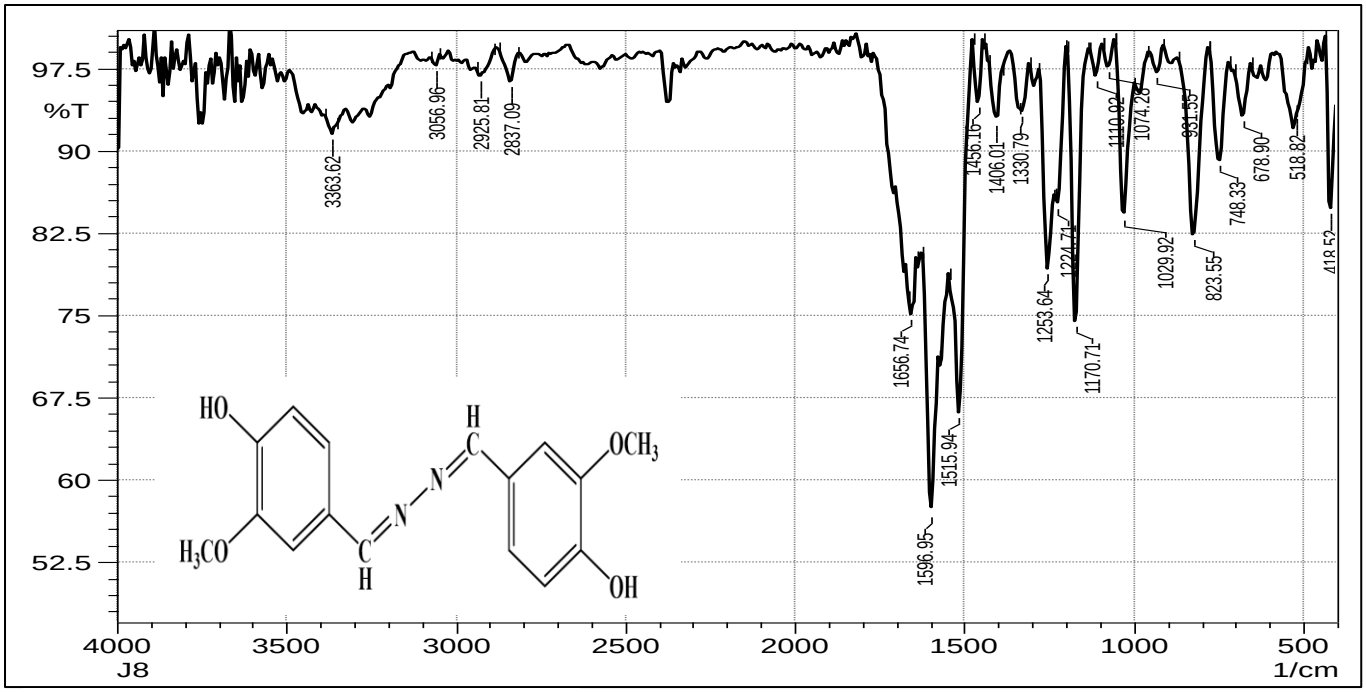
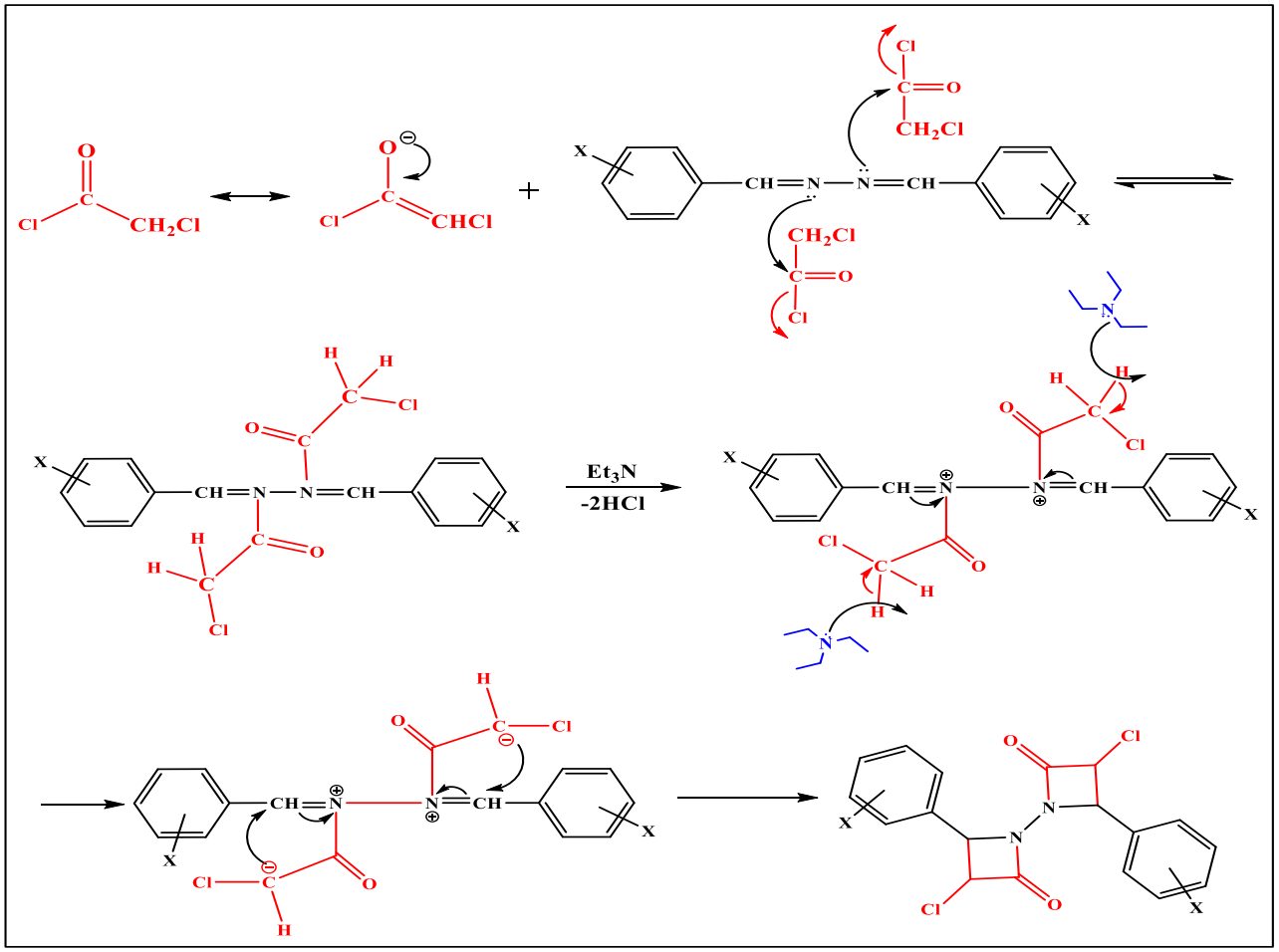


Fig. 2: Show the IR for compound (A_7)

Characterization of the: 4,4'-bis (subs. phenyl)-3,3'-dichloro-[1,1'-biazetidine]-2,2' -dione (A_8-A_{14})

The bi-azetidine 2,2'- dione were synthesized from the reaction of Diarylidine hydrazine (A_1-A_7) with 2 moles of chloroacetyl chloride in dioxin as a solvent, The suggested mechanism as shown in Scheme 6.



Scheme 6. mechanism of the preparation of of compounds (A_8-A_{14})

The above reaction included a nucleophilic attack by the electron pair of the nitrogen atom in azomethine compounds (A_1- A_7) on the carbon of the carbonyl group (C=O) forming chloroacetyls, followed by closing the intermediate material to form azetidinone derivatives and attack was repeated again on the second mole of chloroacetyl chloride . According to the above mechanism. The prepared compounds (A_8-A_{14}) were characterized by the infrared spectrum, as it showed an absorption band within the range IR: 3031,3107 (=CH stretching aromatic), (1649-1708)cm^{-1} (C=O lactam)[38] , (1462,1594)cm^{-1} (C=C stretching aromatic ring) , (C-N) was appeared at (1297-1398)cm^{-1}, (1024-1086)cm^{-1} (N-N) . as shown in Table 5, Figure 3 and 4.

Table 5. Some spectral data for compounds (A_8- A_{14})

I.R., υ (cm^{-1}), KBr Comp. No	X	(=CH) arom.	(C=O)	(C=C) arom.	(C-N)	(N-N)	(C-Cl)	Others
A_8	H	3038	1708	1585, 1481	1398	1080	866	-
A_9	4-Br	3060	1704	1594, 1502	1297	1030	991	(C-Br),867
A_{10}	4-Cl	3053	1649	1593, 1492	1340	1072	983	(C-Cl),694
A_{11}	4-N(CH_3)$_2$	3050	1667	1590, 1491	1385	1086	867	(C-H),2974-2938
A_{12}	3-OH	3074	1733	1588, 1462	1358	1031	957	(OH),3302
A_{13}	3-Cl,2-OH	3031	1684	1586, 1512	1355	1024	885	(OH),3452
A_{14}	3-OCH_3,4-OH	3107	1708	1647, 1583	1326	1074	842	(OH),3247

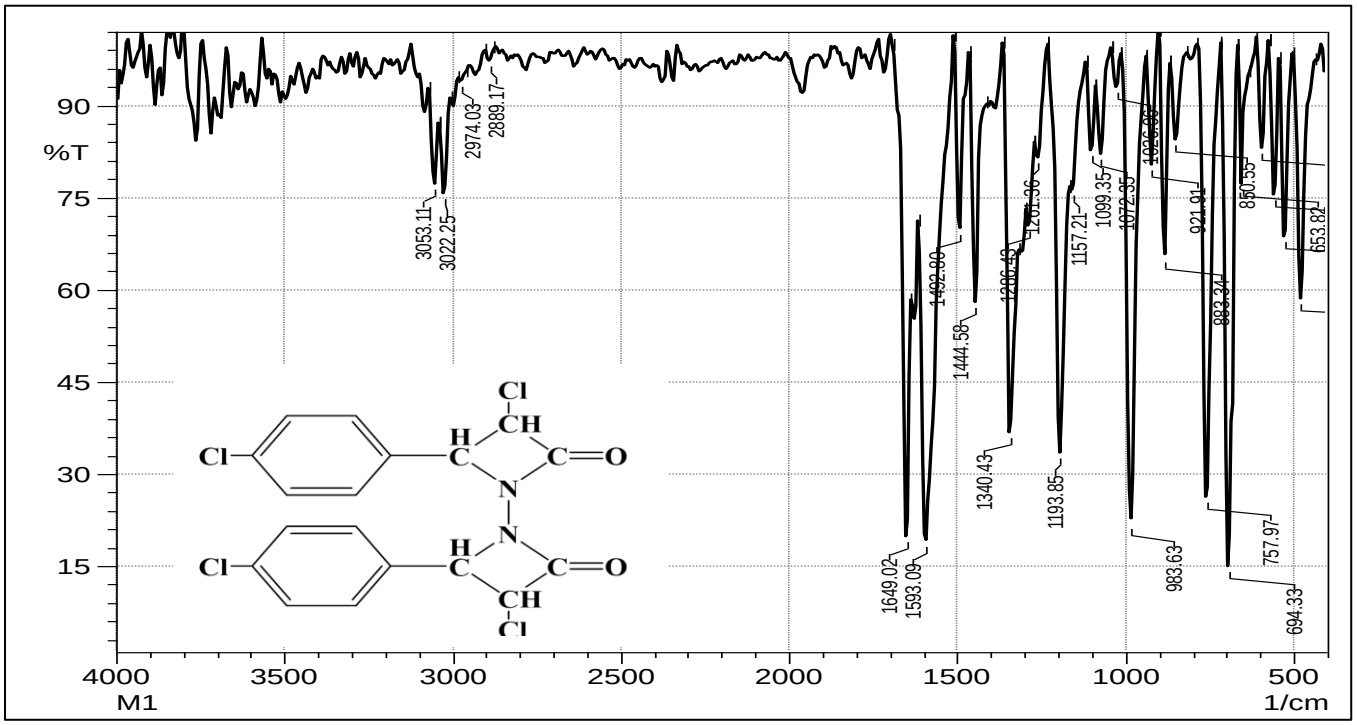


Fig. 3. Show the IR for compound (A_{10})

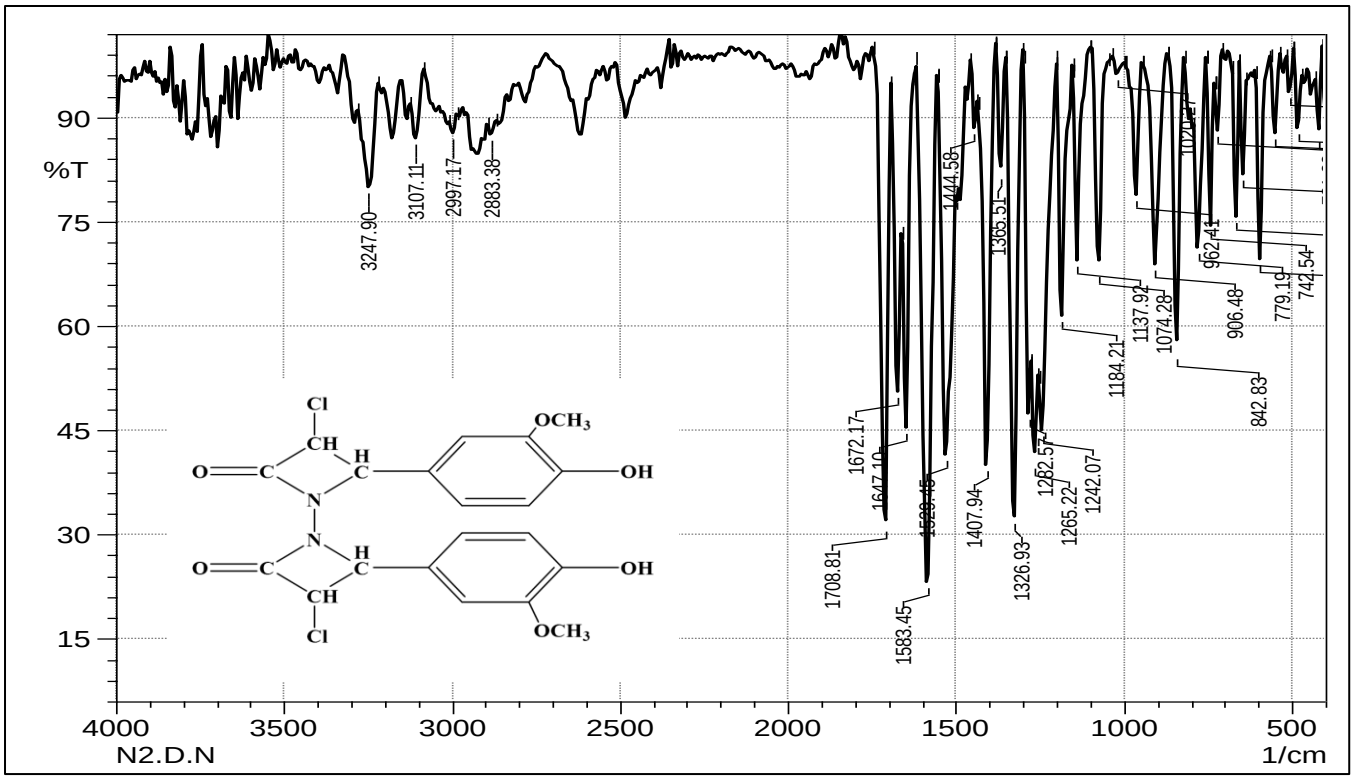
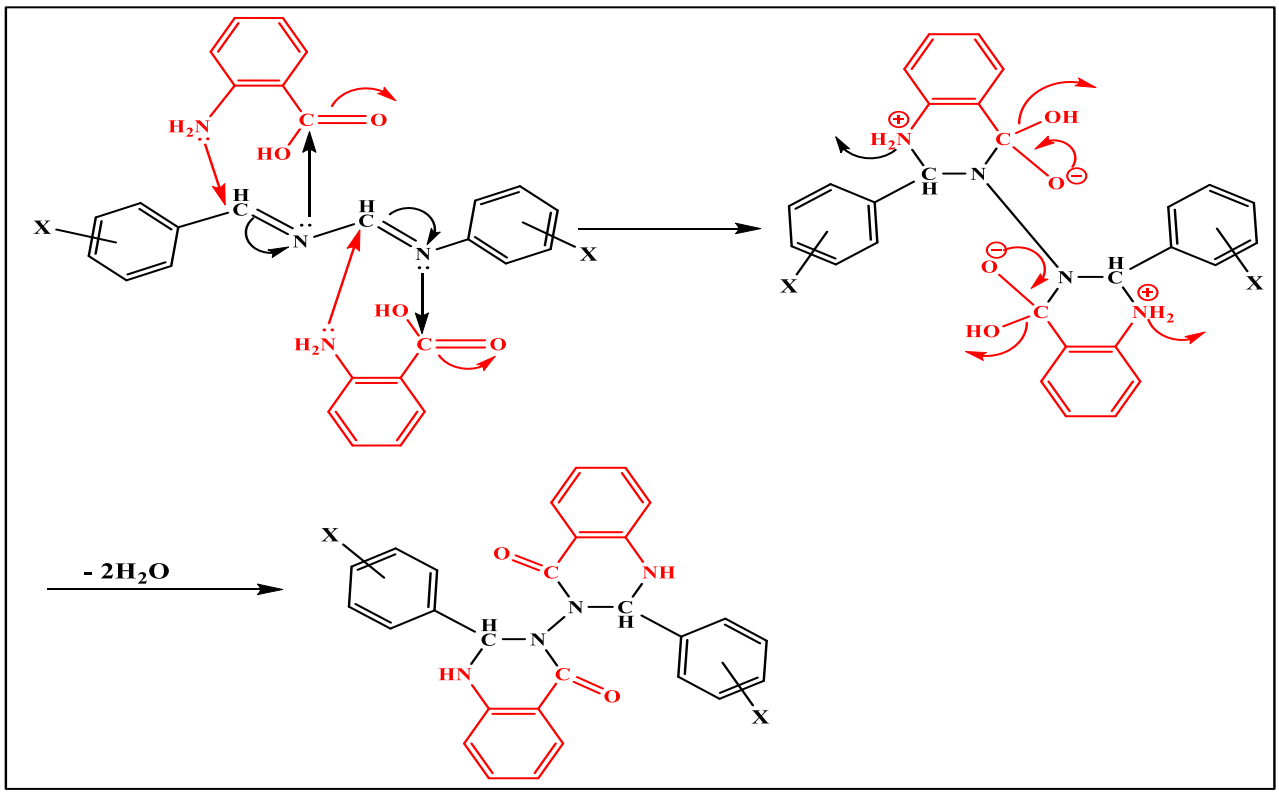


Fig. 4. Show the IR for compound (A_{14})

Characterization of the: 2,2'-bis(subs.phenyl)-1,1',2,2'-tetrahydro-4H,4'H-[3,3'-biquinazoline]-4,4'-dione (A_{15}-A_{21})

The bi-quinazoline-4,4'-dione were synthesized from the reaction of Diarylidine hydrazine (A_1-A_7) with 2 moles of 2-amino benzoic acid in absolute ethanol as a solvent was refluxed for (15 h), The suggested mechanism as shown in Scheme 7.



Scheme 7. mechanism of preparation of compounds (A_{15}-A_{21}).

The above reaction included a nucleophilic attack by the electron pair of the nitrogen atom in azomethine compounds (A_1- A_7) on the carbon of the carbonyl group (C=O) , followed by closing the intermediate material to form biquinazoline derivatives and attack was repeated again on the second mole of 2-amino benzoic acid.The prepared compounds(A_{15}-A_{21}) were characterized by the infrared spectrum, as it showed an absorption band within the range IR: (3332-3440) cm^{-1}(NH_2 stretching), (3061-3088) cm^{-1}(= CH stretching), (2727-2958) cm^{-1} C-H aliph. stretching), (1652-1693) cm^{-1} (C=O Ktone quinazoline ring,(1584-1620)cm^{-1} (N-H bending), (1465,1589) cm^{-1} (C= C aromatic ring), (1174-1359) cm^{-1} (C-N stretching). as shown in Table 6, Figure 5 and 6.

Table 6. Some spectral data for compounds (A_{15}- A_{21})

I.R., υ (cm^{-1}), KBr Comp. No.	X	(N-H)	(=CH) arom.	(C=O)	(C=C) arom.	(C-N)	Others
A_{15}	H	3342	3077	1664	1522,1468	1342	-
A_{16}	4-Br	3402	3064	1674	1579,1469	1355	(C-Br),799
A_{17}	4-Cl	3366	3102	1672	1511,1482	1326	(C-Cl), 932
A_{18}	4-$N(CH_3)_2$	3312	3074	1689	1517,1465	1334	(C-H), 2954-2853
A_{19}	3-OH	3355	3068	1683	1589,1552	1199	(O-H),3197
A_{20}	3-Cl,2-OH	3440	3088	1693	1622,1533	1174	(OH),3199 (C-Cl),965
A_{21}	3-OCH_3, 4- OH	3332	3061	1652	1589,1492	1359	(OH),3263

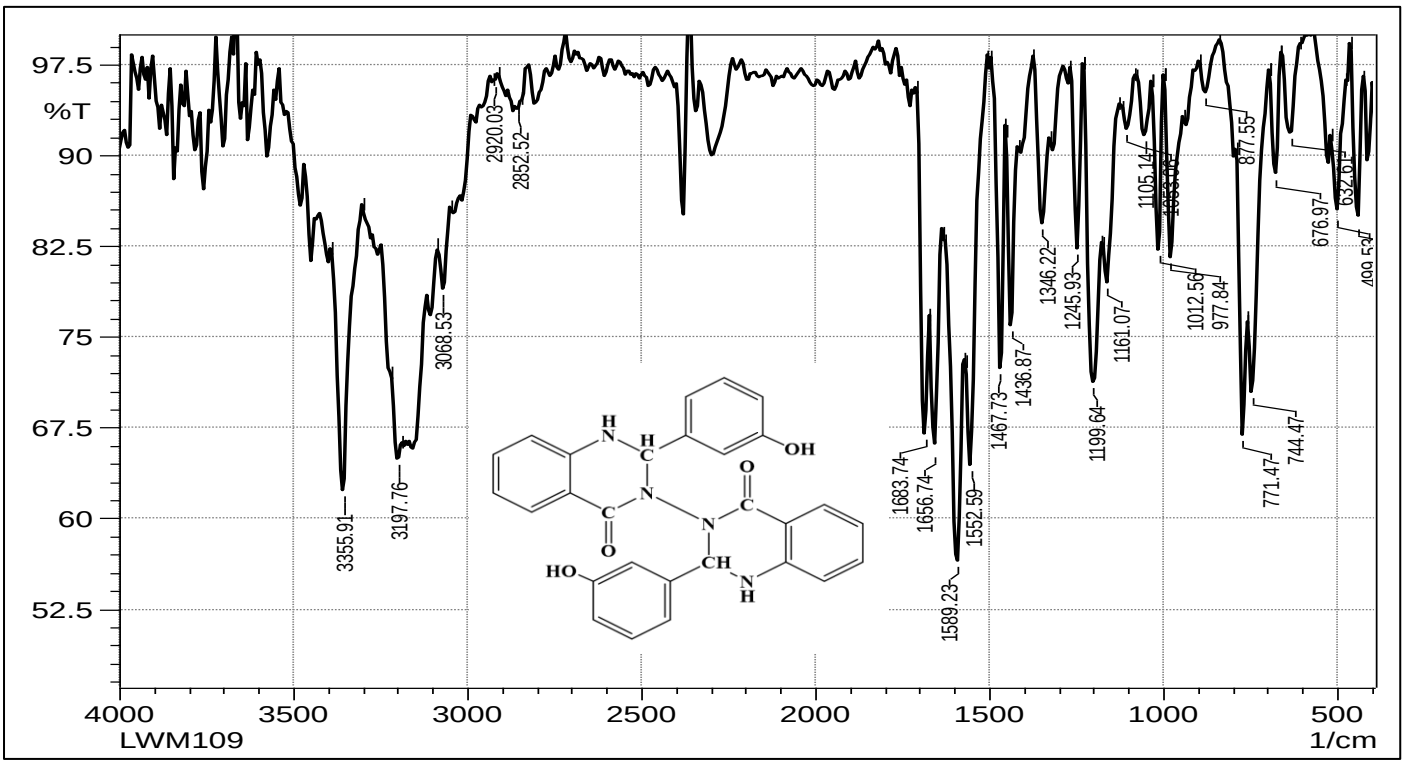


Fig. 5. Show the IR for compound (A_{19})

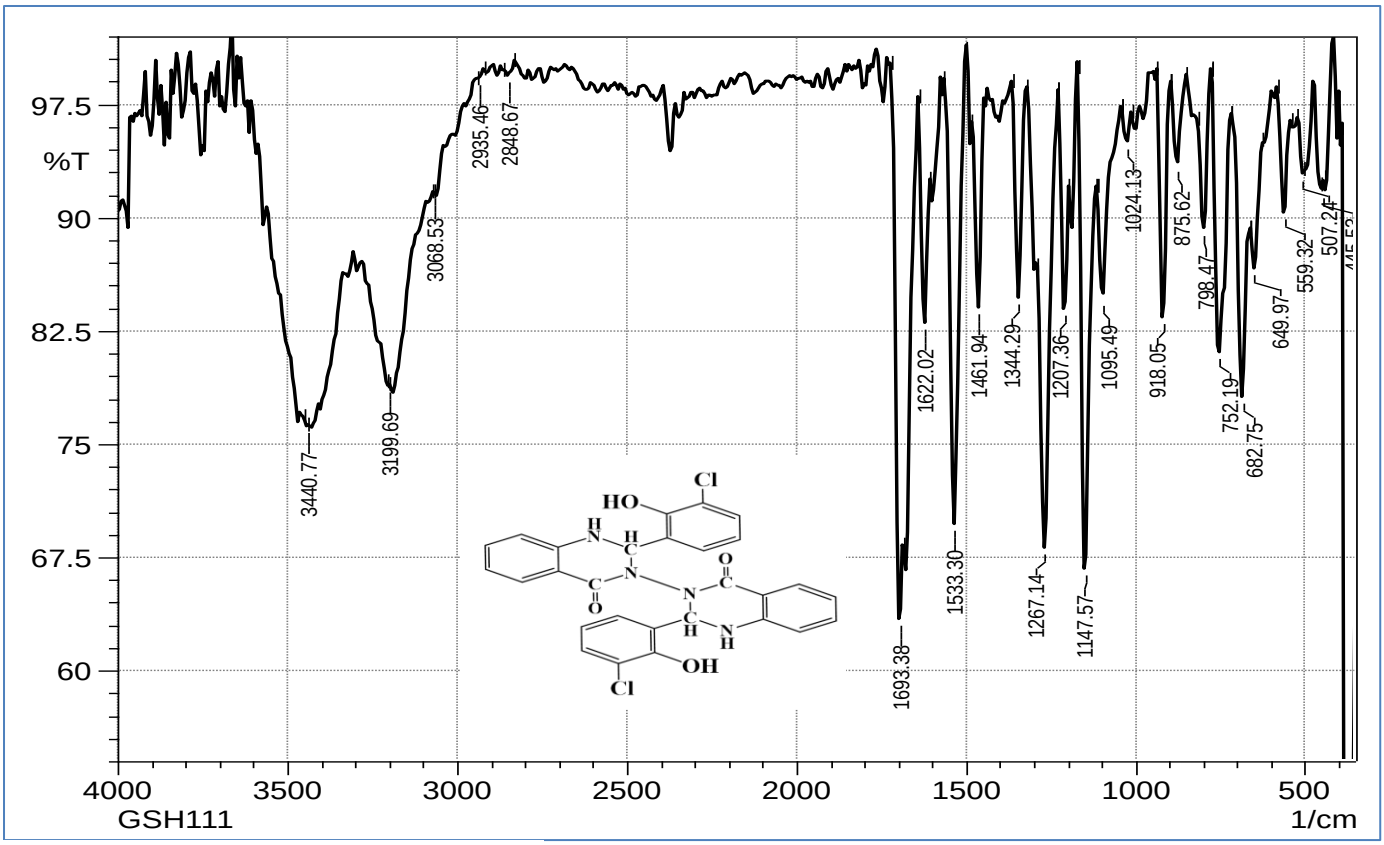


Fig. 6. Show the IR for compound (A_{20})

Discussion of nuclear magnetic resonance of proton spectra (^{1}H-NMR).

The compound (A_2) were diagnosed by proton spectra (1H-NMR), as the spectrum showed Single package (8.17 -8.16 ppm) due to azomethine group N=CH; and multi package at rang ; (7.88 – 7.01 ppm, m, 4H benzene ring). figure (7) Show the 1HNMR for compound (2). While the compound (A_7) as the spectrum showed Single-band (8.70- 8.53 ppm) belongs to azomethine group N=CH; single packet at ppm (3.76) ppm due to OCH_3 group; Single package at (10.70) ppm due to OH groups, Multiple bands split at rang (8.51 -8.08) ppm of 6 protons of the derivatives benzene ring. figure (8) Show the 1HNMR for compounds (A_2 , A_7).

The compound (A_{10}) as the spectrum showed Single package at (6.63) ppm due CH adjacent to Cl); Single package at (6.15) ppm due CH on the ring) and multi package at rang (8.31 - ,7.638 ppm, due 8H benzene ring). figure (9) Show the 1HNMR for compound (A_{10}). While the compound (A_{14}) as the spectrum showed Single package at (6.76) ppm due CH adjacent to Cl); Single package at (6.61) ppm due CH on the ring), single packet at ppm (3.03) ppm due to OCH_3 group, Single package at (9.66) ppm due to OH groups, and multi package at ((7.39,7.41,7.27,7.14 ppm, due 6H benzene ring). figure (10) Show the 1HNMR for compound (A_{14}).

The compound (A_{19}) as the spectrum showed Single-band (6.15 ppm) belongs to N-CH-N; single packet at ppm (3.84) ppm amide NH group; Multiple bands split at rang (8.32 -7.68) ppm of 14 protons of the derivatives benzene ring and Single package at (10.32) ppm due to OH groups ; figure (11) Show the 1HNMR for compound (A_{19}).

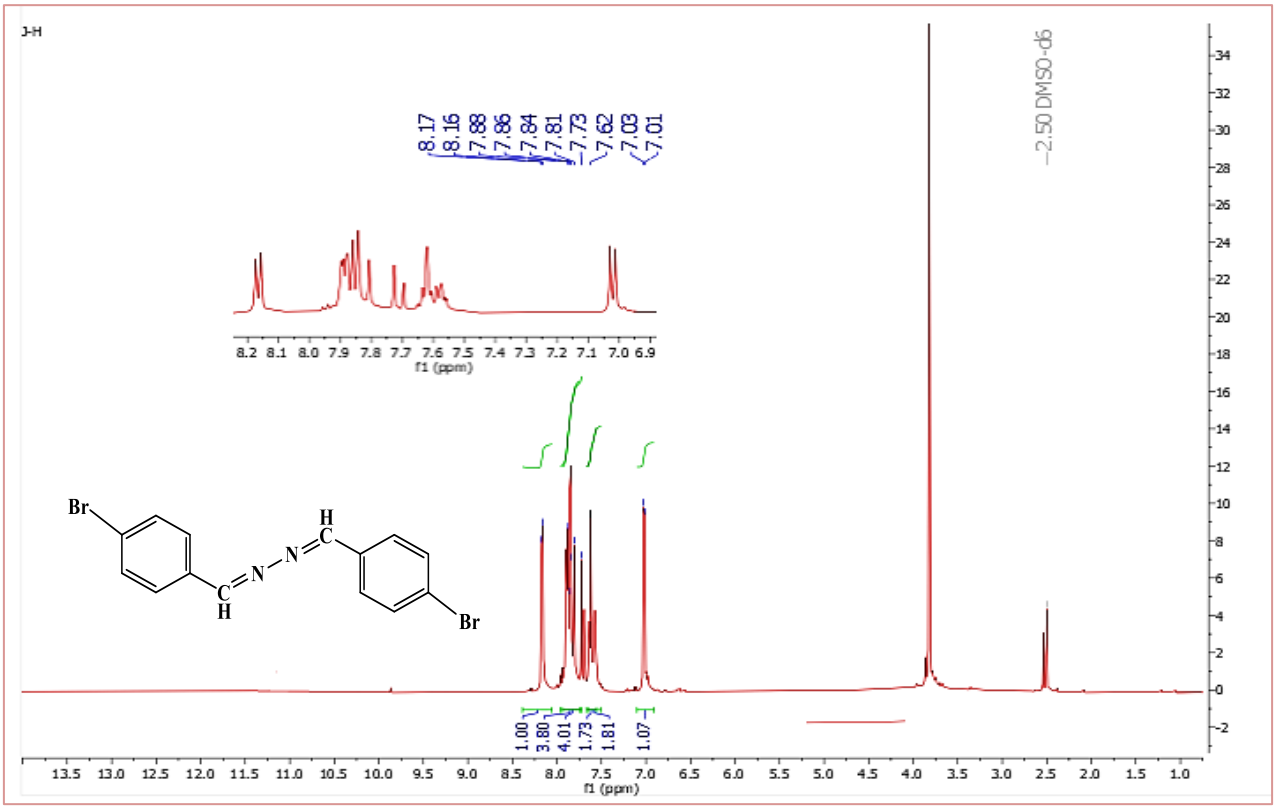


Fig. 7. Show the ^{1}HNMR for compound (A_2)

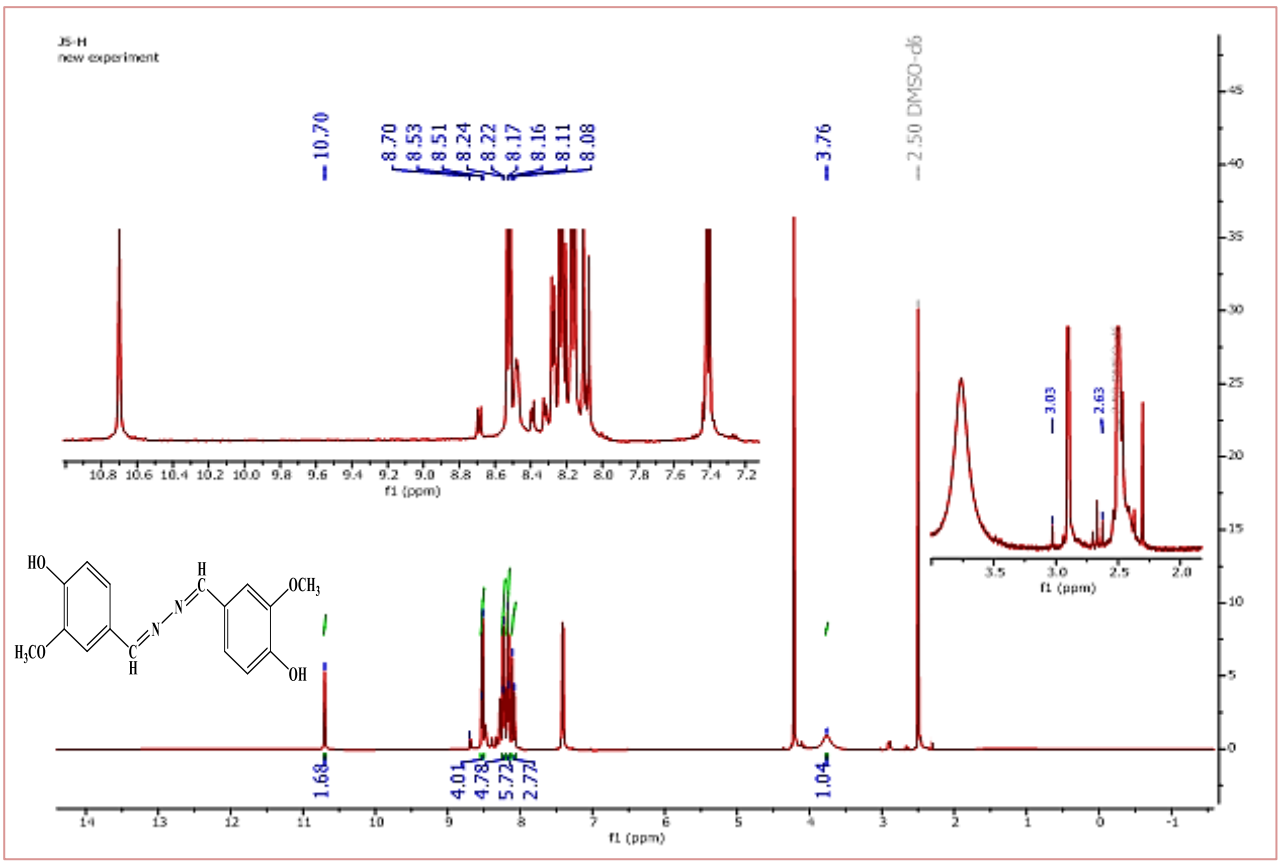


Fig. 8 Show the ^{1}HNMR for compound (A_7)

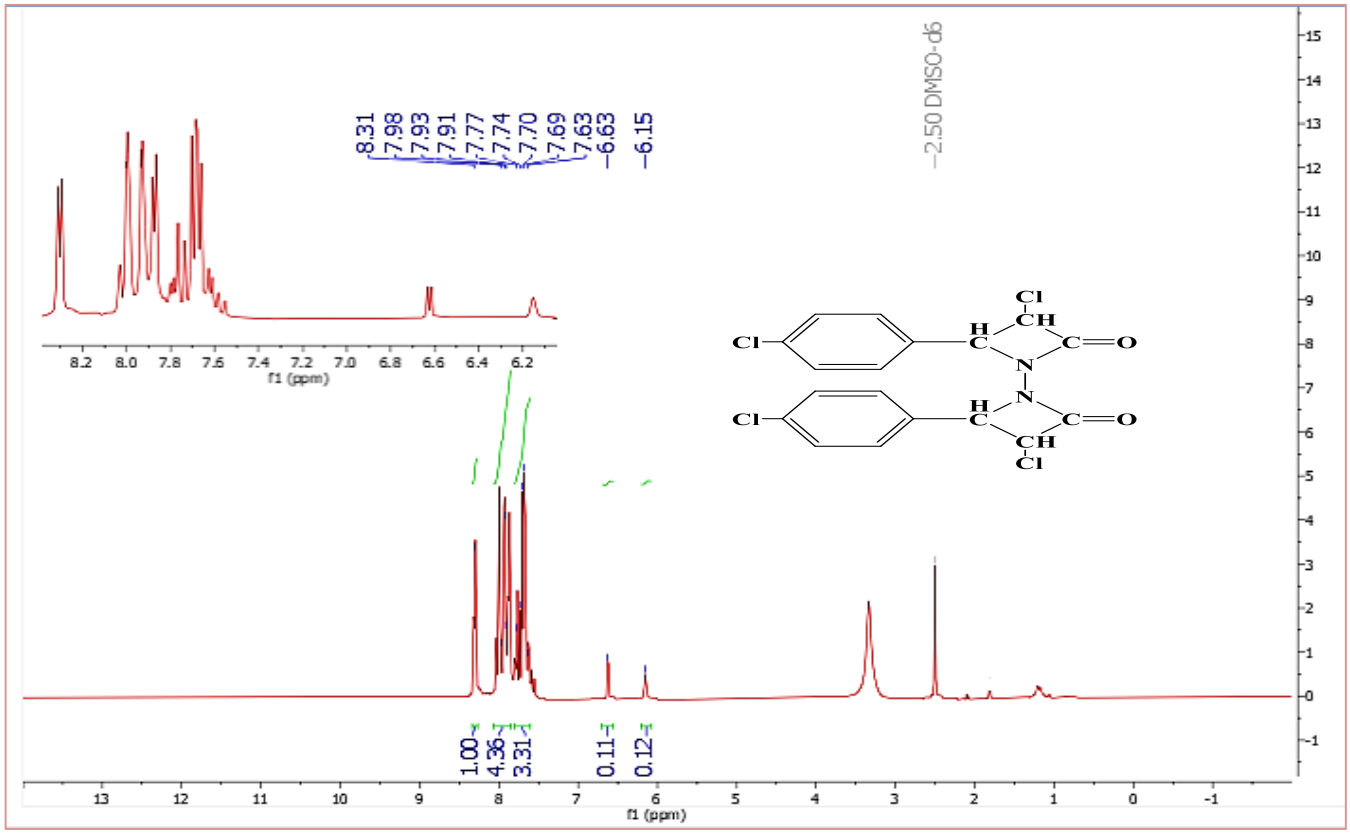


Fig. 9 Show the ^{1}HNMR for compound (A_{10})

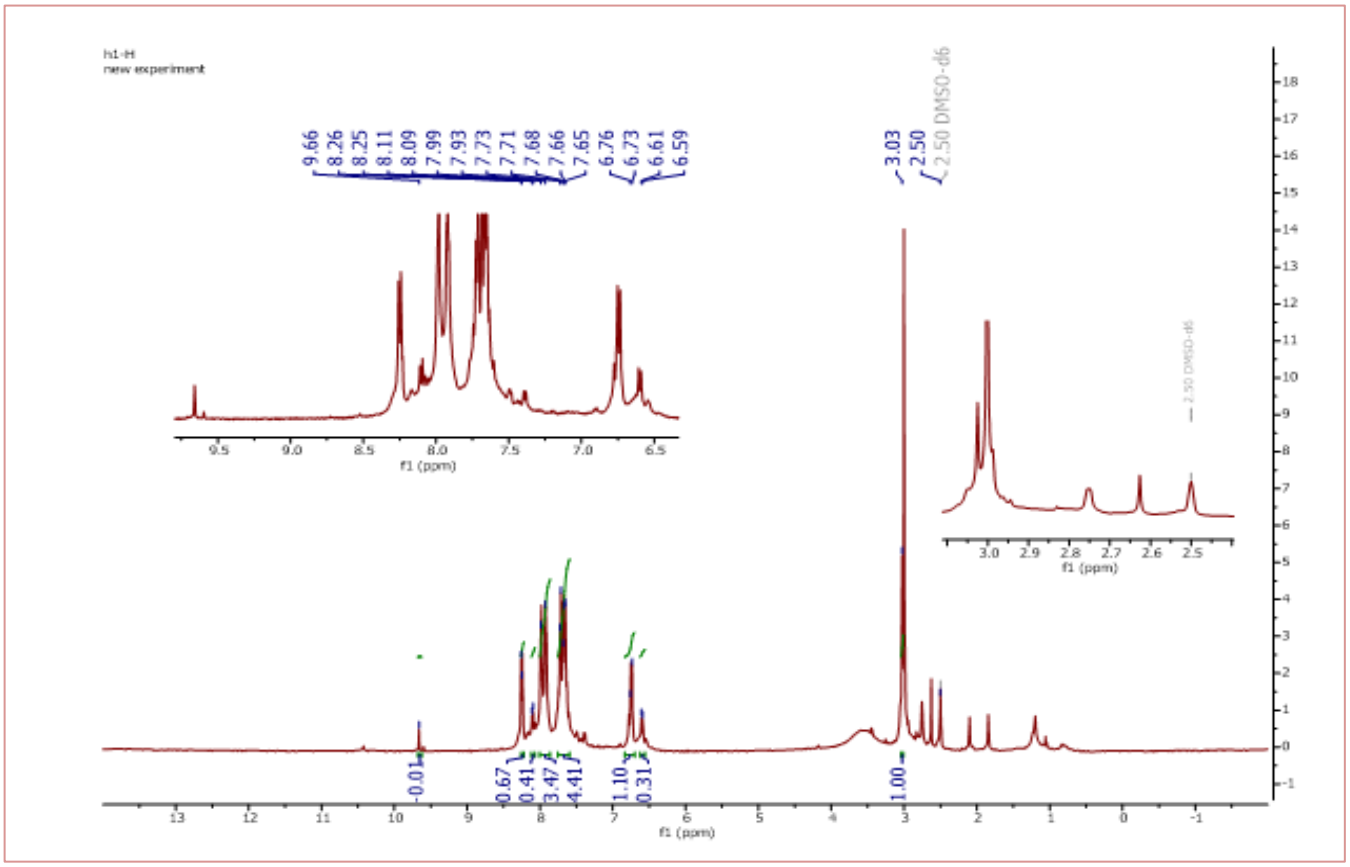


Fig. 10 Show the ^{1}HNMR for compound (A_{14})

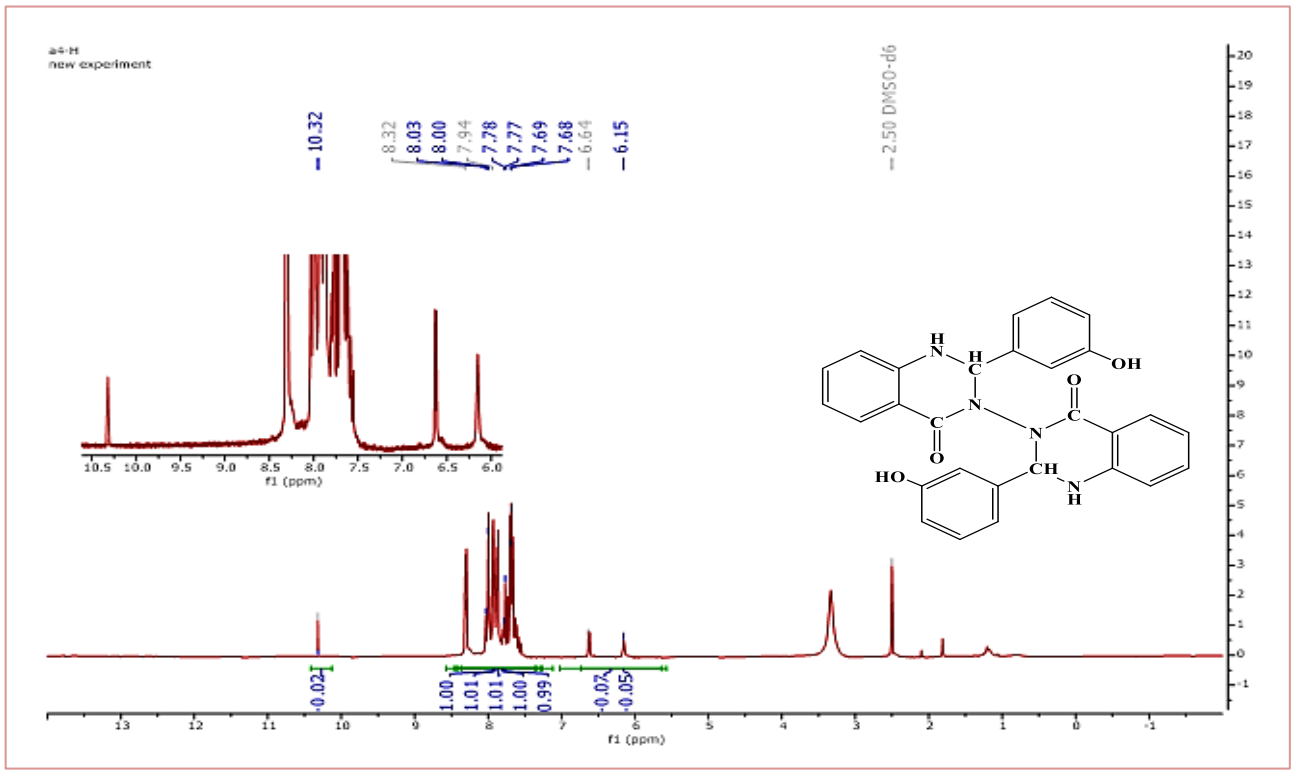


Fig. 11 Show the ^{1}HNMR for compound (A_{19})

Discussion of nuclear magnetic resonance of proton spectra (^{13}C-NMR)

The 13C- NMR spectra of compound (A_{10}) were obtained in DMSO-*d*6. the CH signal adjacent to Cl detected at (55.81) ppm, signal at (55.85) ppm due CH on the azetidine ring, signal at (168.43) ppm due Carbonyl group C=O on the azetidine ring, The aromatic carbon signals were observed at (119.28 – 144.35) ppm. as shown in Figure (12). While the compound (A_{19}) were obtained signal at (167.47) pmm due Carbonyl group C=O on the quinazoline ring and the signal at (118.87 – 144.05) ppm due aromatic carbon. as shown in Figure (13).

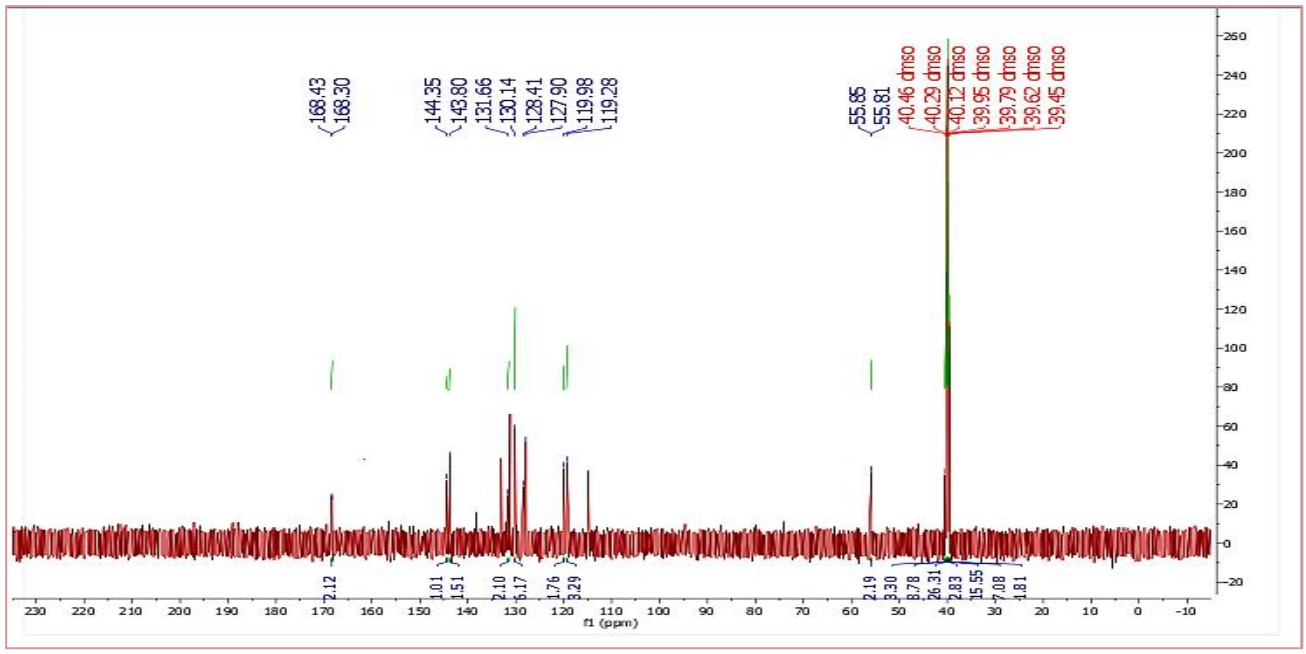


Fig. 12 Show the ^{13}C-NMR for compound (A_{10})

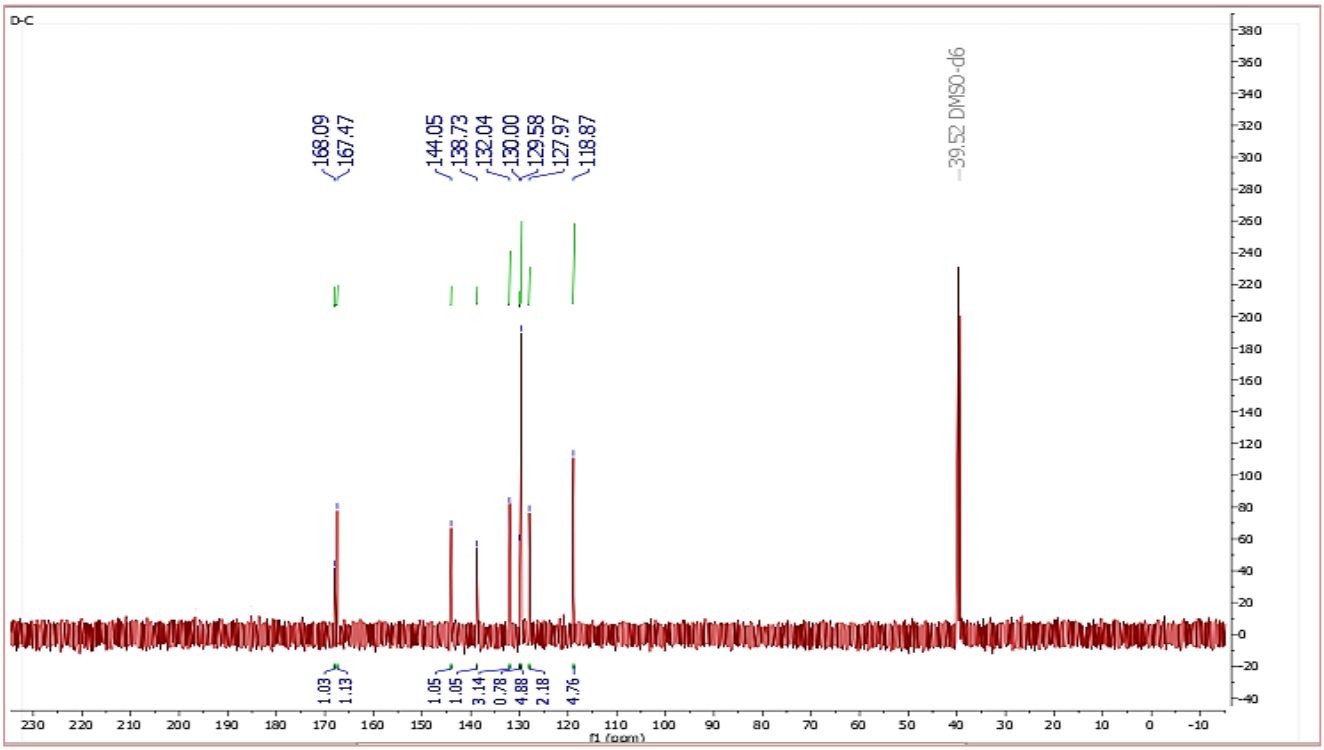


Fig. 13 Show the ^{13}C-NMR for compound (A_{19})

Conclusion

In conclusion, On the bases of the previous results New organic compounds with two groups were prepared from bi-azetidine 2,2'- dione and bi-quinazoline-4,4'-dione derivatives.That is through two first steps: New compounds with two groups of azomethine were prepared, through the reaction of benzaldehyde compounds of different substitutions with hydrazine hydrate (di-amino groups). The second step: The azomethine compounds prepared in the previous step were reacted with acetic acid dichloride and 2-amino benzoic acid with different molar numbers (1:2) Respectively. Physical and spectroscopic measurements demonstrated the prepared compounds' structures' accuracy.

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p ISSN: 2663-7405
e ISSN: 2789-6838

تحضير وتشخيص بعض مركبات ثنائي أزيتيدين 2,2'- دايون وثنائي كينازولين-4,4'- دايون الجديدة المشتقة من قواعد شيف.

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مديرية تربية كركوك، وزارة التربية، العراق

معلومات البحث:
تاريخ الاستلام: 2024/07/24
تاريخ التعديل: 2024/08/18
تاريخ القبــول: 2024/09/20
تاريخ الـنشر: 2025/06/30
الكلمات المفتاحية:
مركبات حلقية غير متجانسة1 ،قواعد شيف2، ازيتيدين 3، كينازولين 4، فعالية بيولوجية 5.

معلومات المؤلف
الايميل:
الموبايل:

الخلاصة:
تضمن هذا البحث تحضير وتشخيص بعض مشتقات المركبات ذات الحلقات الرباعية والخماسية غير المتجانسة (ثنائي أزيتيدين 2,2'- دايون) و(ثنائي كينازولين-4,4'- دايون). تتضمن الخطوة الأولى تفاعل مشتقات البنزالديهايد مع الهيدرازين المائي بوجود حامض الخليك الثلجي وباستخدام الإيثانول كمذيب مناسب للحصول على 2,1- بس (معوضات بنزاليدين) هايدرازين (A_1-A_7). الخطوة الثانية تتفاعل المركبات (A_1-A_7) مع (كلوريد كلورو الاسيتيل) بوجود ثلاثي إيثيل أمين للحصول على 3,3'- ثنائي كلورو- 4,4'(معوضات ثنائي الفينيل)-[1,1'- ثنائي ازيتيدين]-2-2'- داي ون (A_8-A_{14}) ويتفاعل أيضاً (A_1-A_7) مع (2- امينوحامض البنزويك) بوجود ثلاثي مثيل امين للحصول على معوضات (2- (3- معوضات فينيل)-2'- (3- معوضات فينيل)-1,1',2,2'- رباعي هيدرو4H ,,4'H - [3,3- ثنائي كينازولين-4,4'- داي ون] (A_{15}-A_{21}) .تم التعرف على تركيب المركبات المحضرة حديثا بالطرق الطيفية [FTIR وبعضها بـ 1HNMR و13C-NMR] وقياس بعض خواصها الفيزيائية.