Raf. J. Sci.,Vol.28, No.2 Special Issue for the Third Scientific Conference of Chemistry, pp.135-145, 2019

Synthesis and Characterization of Some Novel Hydrazones of N-{11*H*-pyrido[2,1-b]quinazolin-11-one-9-yl} hydrazine

Attallah M. Sheat **Rafid K. Jameel**
Department of Chemistry/ College of Science/ University of Mosul
E-mail: rafiddcy2000@yahoo.com **E-mail:** attalsharifi@yahoo.com

(Received 13/9/2018 ; Accepted 25/10/2018)

ABSTRACT

The 2-[(6-chloro-2-pyridyl) amino]benzoic acid (I) was synthesized viaUllmann-Goldberg coupling by reaction of anthranilic acid with2,6-dichloropyridine. The compound (I) was cyclized by using poly phosphoric acid (PPA) to give 9-chloro-11*H*-pyrido[2,1-b]quinazolin-11-one (II). The compound (II) reacted with hydrazine hydrate to give N-{11*H*-pyrido[2,1-b]quinazolin-11-one-9-yl} hydrazine (III). The compound (III) reacted with various aromatic aldehydes to yield the hydrazones (IVa-p). The reaction progress was followed by thin layer of chromatography (TLC). The physical constants and R_f values were recorded. The synthesized compounds were confirmed via the spectral data (UV,I.R,^{1}H-NMR, ^{13}C-NMR, mass spectra). The possible fragmentation pattrene of GC/MS for the compounds (IVa) were investigated (IVh).

Keywords: anthranilic acid, pyridoquinazoline, hydrazine, hydrazones.

تحضير وتشخيص بعض الهيدرازونات الجديدة لـ N - {11*H*- بيريدو[2,1-b]كوينازولين11-اون-9-يل}هيدرازين

الملخص

يتفاعل حامض الانثرانيليك مع 6,2- ثنائي كلوروبيريدين خلال او لمانكوادبرج لتحضير 2-[(6- كلورو-2-بيريديل)امينو] حامض البنزويك (I). يتحواق المركب (1) بواسطة حامض الفسفوريك المتعدد (PPA) ليعطي 9-كلورو-11*H*-بيريدو[2,1-b] كوينازولين-11-اون (II). يتفاعل المركب (II) مع الهيدرازين المائي ليعطي المركب N - {11*H*-بيريدو[2,1-b]كوينازولين11-اون-9- يل}هيدرازين (III). يتفاعل المركب (III) مع عدد من الالديهايدات الاروماتية ليعطي الهيدرازونات (IVa-p). تم تتبع سير كل التفاعلات بواسطة كروماتوفيا الطبقة الرقيقة (TLC) وتم تحديد قيم (R_f) لجميع المركبات المحضرة. شخصت المركبات المحضرة من خلال النتائج او المعطيات الفيزياوية والطيفية (طيف الأشعة فوق البنفسجية وطيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي وطيف الكتلة).

الكلمات الدالة: حامض الانثرانيليك، بيريدوكوينازولين، هيدرازين، هيدرازون.

INTRODUCTION

Nitrogen - containing heterocycles are present in both natural products and pharmaceuticals. Among the structural analogs of pyridoquinazoline compounds having a diverse biological activity have been discovered. The literatures showed that the pyridoquinazolines derivatives have biological activities such as antitumor agent (Palop *et al*., 2014; Shabana, 2013; Palmer *et al*., 2012), antibacterial (Yassin, 2009), anticonvulsant (Laddha *et al*., 2009), anti – inflammatory and anti – allergic activities (Chandrika *et al*., 2008), analgesic, and anti - inflammatory

(Mikhalev *et al*., 1995), vasodilator effects (Chen *et al*., 2009), COX inhibitory activities (Lee *et al*., 2005), anti-leukemia (Vizirianakis *et al*., 2010), antihypertensive (Jen *et al*., 1972), anti amnesic therapy and inhibition of (AChE) and (BChE) (Decker, 2005).

EXPERIMENT

Melting points were determined using Electro thermal IA9000 Digital-series melting point apparatus, (uncorrected). All reagents and chemicals were used from commercial sources. The solvents were dried by standard methods. The purity of the compounds was ascertained by thin layer chromatography (TLC) on pre-coated silica gel glass plates using either UV radiation or iodine staining for visualization. Column chromatography was carried out using 100–200 mesh silica gel (BDH). UV spectra were recorded on a Shimadzu UV/Vis – 1650 pc spectrophotometer using methanol as a solvent. IR spectra were recorded using FT-IR-600 Bio tech Engineering Management spectrophotometer UK using KBr disc.^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained from a Bruker-avance 300 MHz, NMR spectrometer. The chemical shifts are reported as δ (ppm) for the DMSO- $d_6$solution using TMS as internal standard. The coupling constant, J(Hz) in that order with the use of the following abbreviations; s, singlet; d, doublet; t, triplet; m, multiplet; br, broad(Al-Al-Bayt university, Jordan). Mass spectra (MS) were obtained from perkin Elmer Clarus 500 Gas chromatography-Mass spectrometer (I.I.T Roorkee. India).

Synthesis of 2-[(6-chloro-2-pyridyl) amino]benzoic acid (I) (Jameel *et al*., 2010).

In a 1-litre round bottom flask, equipped with air condenser, a mixture of (8.22 g, 0.06 mol) of anthranilic acid, (8.82 g, 0.06 mol) of 2,6-dichloropyridine, (8.28 g, 0.06 mol) of anhydrous K_2CO_3, 0.2 g of CuO and 2 g of phenol as a solvent. The mixture was heated in an oil bath at 120-130 °C. for 8 hrs. The mixture steam was distilled to remove the excess unreacted starting material, then 1g of decolorizing carbon was added to the hot residual solution. The mixture was boiled for more 15 minutes, filtered at the pump. The filtrate was neutralized by 1:1 (water, acetic acid). The solid was collected by filtration under vacuum then air dried. Crystallization of solid product from ethanol gave the compound (I), m.p=185 °C(dec), R_f = 0.19 (0.5:9.5), (MeOH:$CHCl_3$), yield 67%. (Lit, m.p = 194-19 °C, R_f = 0.17, yield 50%).

Synthesis of 9-chloro-11*H*-pyrido[2,1-b]quinazolin-11-one (II) (Denny *et al*., 1977; Konshin *et al*., 1984).

The compound (I) (5g) was heated with 50 ml of polyphosphoric acid (PPA) in an oil bath at 120-130˚C until homogeneous solution surfaced. The reflux was continued for 3 hrs, the product was precipitated by the addition of cold water, thenbasicified with conc. ammonia solution. The product was filtered offunder reduced pressure and washed several times with cold water then air dried. The brown product was washed with $CHCl_3$, pet-ether (40-60) (0.5:9.5). The final product was pure enough for next experiments, m.p = 170-172 °C (dec.), R_f = 0.6, (0.5:9.5), (MeOH:$CHCl_3$), yield 85%.

Synthesis of N-[11*H*-pyrido[2,1-b]quinazolin-11-one-9-yl]hydrazine (III) (Jameel *et al*., 2009; Moqilaiah, 2010).

The compound (II) (3g) and 30 ml of 80% hydrazine hydrate was dissolved in 75 ml methanol. This mixture was heated under reflux for 3hrs. The completion of the reaction was monitored by TLC. Water (20 ml) was added and the reaction mixture was cooled to room temperature .The precipitated solid was filtered off and washed with water, then recrystallized from ethanol toyieldgray powder, m.p = 133 -135°C, R_f = 0.29, (0.5:9.5),(MeOH:$CHCl_3$), yield 82%.

Synthesis of substituted benzyliden-N-[11*H*-pyrido[2,1-b] quinazolin-11-one]hydrazine (IVa-p) (Kannappan *et al*., 2009; Belwal *et al*., 2012): General procedure

To a solution of compound (III) (0.2 g, 0.88 mmol) in dry methanol (25 ml), 4-tolualdehyd (0.106 g, 0.88 mmol) was added. The resulting solution was refluxed with stirring for at least 6 hrs. The progress of the reaction was monitored by TLC. The mixture was cooled and left overnight. The solid product was filtered off and air dried to yield Brown precipitate [m.p = 113 (dec.), R_f = 0.69, 55%]. The same procedure was used to prepare the compounds (IVb-p) by mixing of (0.88 mmol of compound (III) with appropriate substituted benzaldehyde. Table (1) summarizes the physical properties and R_f values for compounds (IVa-p) (R_f solvent chloroform: methanol 9.5: 0.5).

Table 1: Some physical properties of the compounds (IVa-p)

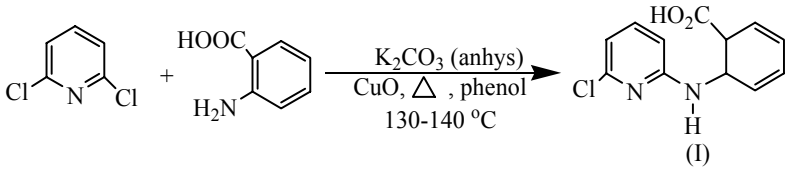
Compd. No.	Ar	m.p°C	R_f	Color	Yield %
IVa	4-$CH_3C_6H_4$-	113-(dec)	0.69	Brown	55
IVb	4-ClC_6H_4-	212-213	0.79	Silver crystal	60
IVc	2-ClC_6H_4-	319-320	0.74	Yellow	57
IVd	2,4-diClC_6H_3-	210-212	0.65	Yellow	58
IVe	4-BrC_6H_4-	160-162	0.75	Pale-yellow	62
IVf	3-$NO_2C_6H_4$-	190-193	0.5	Yellow	65
IVg	4- $NO_2C_6H_4$-	279-280(dec)	0.46	Yellow	70
IVh	2-HOC_6H_4-	219-220	0.2*	Yellow-crystal	45
IVi	3-HOC_6H_4-	169-170	0.21*	Yellow	44
IVj	4-HOC_6H_4-	210-213	0.19*	Yellow	42
IVk	2-$CH_3OC_6H_4$-	170-172	0.48*	Greenish-yellow	60
IVl	4-$CH_3OC_6H_4$-	177-179	0.77*	Greenish-yellow	66
IVm	3,4-di$CH_3OC_6H_3$-	192-194	0.24*	Yellow	62
IVn	4.HO.3.$CH_3OC_6H_3$-	168-170	0.18*	Greenish-red	54
IVo	4-di$CH_3N.C_6H_4$-	220-222	0.63*	Brownish-red	57
IVp	C_6H_5-CH=CH-	177-178	0.98*	Green crystal	60

* TLC by chloroform

RESULTS AND DISCUSSION

Synthesis of 2-[(6-chloro-2-pyridyl) amino]benzoic acid (I)

2-[(6-chloro-2-pyridyl) amino]benzoic acid (I) was synthesized through nucleophilic aromatic substitution of anthranilic acid with 2,6-dichloropyridine using anhydrous K_2CO_3 as a base, CuO as a catalyst and phenol as a solvent (Ullmann reaction) as shown in the following equation.

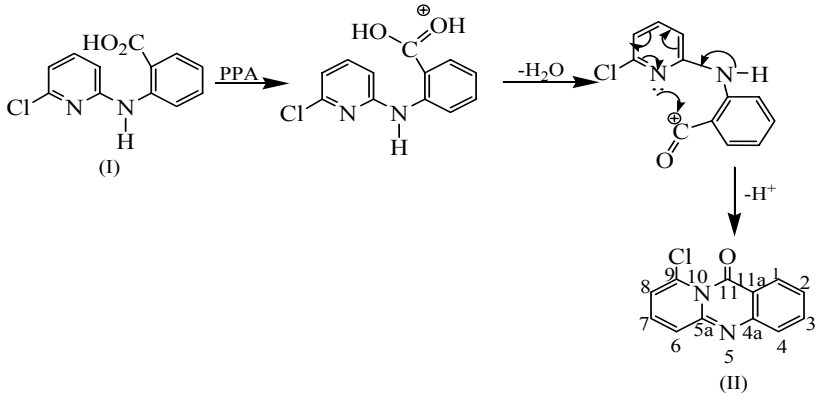


(I)

The structure of the synthesized compound (I) was confirmed by means of physical (m.p, R_f) and spectral data. The IR spectra showed a characteristic absorption band in the region (3350-3100 cm^{-1}, broad) stretching band for (OH, NH) groups respectively, (1670 cm^{-1}) stretching band for (C=O) group, (1610 cm^{-1}) stretching band for (C=N) group, (1595 cm^{-1}) stretchingband for (C=C) group. The ^{1}H-NMR spectral for compound (I) Fig. (1) confirmed the above results. The ^{1}H-NMR spectrum for compound (I)in (DMSO-d_6) δ in ppm showed the significant peaks as the follows: broad at 4.55-6.45 for 1H (NH), multiple at 6.45-8.48 for 7H(ArH), broad peak at 9.82-10.19 due to 1H (CO_2H). (Jameel *et al.*, 2010).

Synthesis of 9-chloro-11*H*-pyrido[2,1-b]quinazolin-11-one (II).

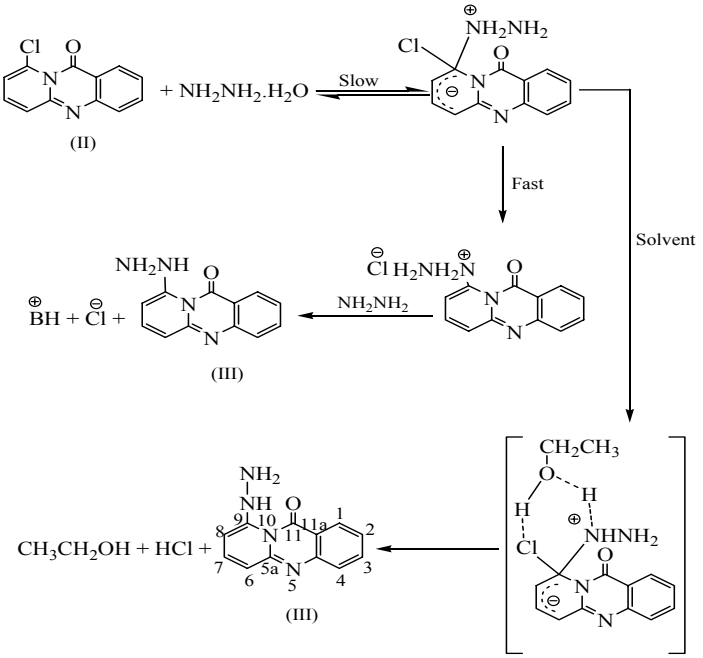
The compound (II) was prepared by cyclization of the acid (I) by using (PPA) according to the following mechanism:



The structure of the synthesized compound (II) was confirmed by means of physical data (m.p, R_f) and spectral data. The IR spectrum showed characteristic absorption band in the region (1665 cm^{-1}) stretching for (C=O amide) group, (1620 cm^{-1}) stretching for (C=N) group, (1590 cm^{-1}) stretching for (C=C) group. The ^{1}H-NMR spectrum for compound (II)in (DMSO-d_6) δ in ppm (Fig. 2) confirmed the above results, showing significant peaks as follows: multiple at 6.97-8.13 for 7H (ArH), D_2O added, no change in NMR spectrumwas found, that means, there is no NH exchangeable protons present. The ^{13}C-NMR for compound (II) in (DMSO-d_6) δ in ppm showed significant peaks as follows: 107(C_8), 116.01 (C_7), 118.32 (C_{11a}), 119.5 (C_6), 122.47 (C_2), 126.09 (C_4), 127.06 (C_1), 130.06 (C_9), 133.47 (C_3), 141.63 (C_{5a}), 147.70 (C_{4a}), 162.65 (C_{11}). (Pellon *et al.*, 2006; Pellon *et al.*, 2007; Meilin *et al.*, 2016).

Synthesis of N-[11*H*-pyrido[2,1-b]quinazolin-11-one-9-yl]hydrazine (III).

This compound has been prepared through reaction of compound (II) with hydrazine hydrate vianucleophilic aromatic substitution reaction in which the chlorine atom (in 9-position) was replaced by hydrazinemoiety as shown in the following mechanism (El-Hashash *et al.,* 2011; Hradil, 1999).

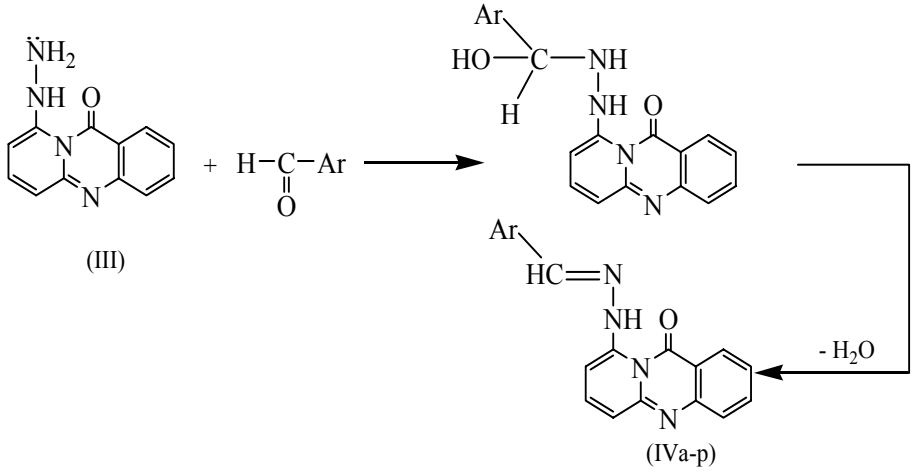


The structure of the synthesized compound (III) was confirmed by means of physical (m.p, R_f) and spectral data. The IR spectrum showed a characteristic absorption bands in the region (3450-3100 cm^{-1}) broad stretching for (NH, NH_2) group, (1640 cm^{-1}) stretching for (C=O amide) group

due to H-bonding with NH group, (1625 cm^{-1}) stretching for (C=N) group, (1595 cm^{-1}) stretching for (C=C) group. The ^{1}H-NMR spectrum Fig. (3) for compound(III) in (DMSO-d_6) δ in ppm confirmed the above results, and showed significant peaks as follows: broad at 2.98-4.46 for 2H due to NH_2, multiple at 6.01-9.10 for 8H due to (NH, ArH) protons. (Jameel *et al.*, 2010; Jameel *et al.*, 2009).

Synthesis of substituted benzyliden-N-[11*H*-pyrido[2,1-b]quinazolin-11-one]hydrazine (IVa-p).

These compounds have been prepared through condensation of compound (III) with various aromatic aldehydes as illustrated in scheme (1) (Jerry March, 1977).



Ar = a , 4-CH_3.C_6H_4 ; b ,4-Cl.C_6H_4 ; c , 2-Cl.C_6H_4 ; d, 2,4-di$Cl.C_6H_3$;
e , 4-Br.C_6H_4 ; f , 3-NO_2.C_6H_4 ; g ,4-NO_2.C_6H_4 ;
h , 2-HO.C_6H_4 ; i , 3-HO.C_6H_4 ; j , 4-HO.C_6H_4 ; k, 2-CH_3O.C_6H_4 ; 4-CH_3O.C_6H_4 ;
m,3,4-diCH_3O.C_6H_3 ;n,4-HO.3-CH_3O.C_6H_3; o, 4-diCH_3N-C_6H_4;
p,C_6H_5-CH = CH-

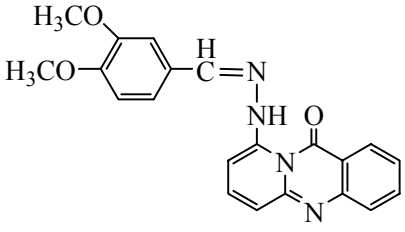
Scheme (1)

The structures of the prepared compounds (IVa-p) were elucidated by means of physical (m.p, R_f) (Table 1) and spectral data (Table 2).

The UV spectra of these compounds(IVa-p) in methanol as a solvent showed two maxima. The first peak between (242-246 nm) with log ε of (4.1364-5.1895 $l.mol^{-1}.cm^{-1}$). This is due to π-π* transition. The second peak appeared between (306-420 nm) with log ε of (4.0940-4.1067) due to n-π* transition and due to CT (charge transfer) of the whole molecule as shown in the Fig. (4).

The IR spectra for these compounds (IVa-p) showed a characteristic absorption bands in the region, (1640-1625 cm^{-1}) stretching for (C=O) group, (1605-1585 cm^{-1}) stretching for (C=C) bond.

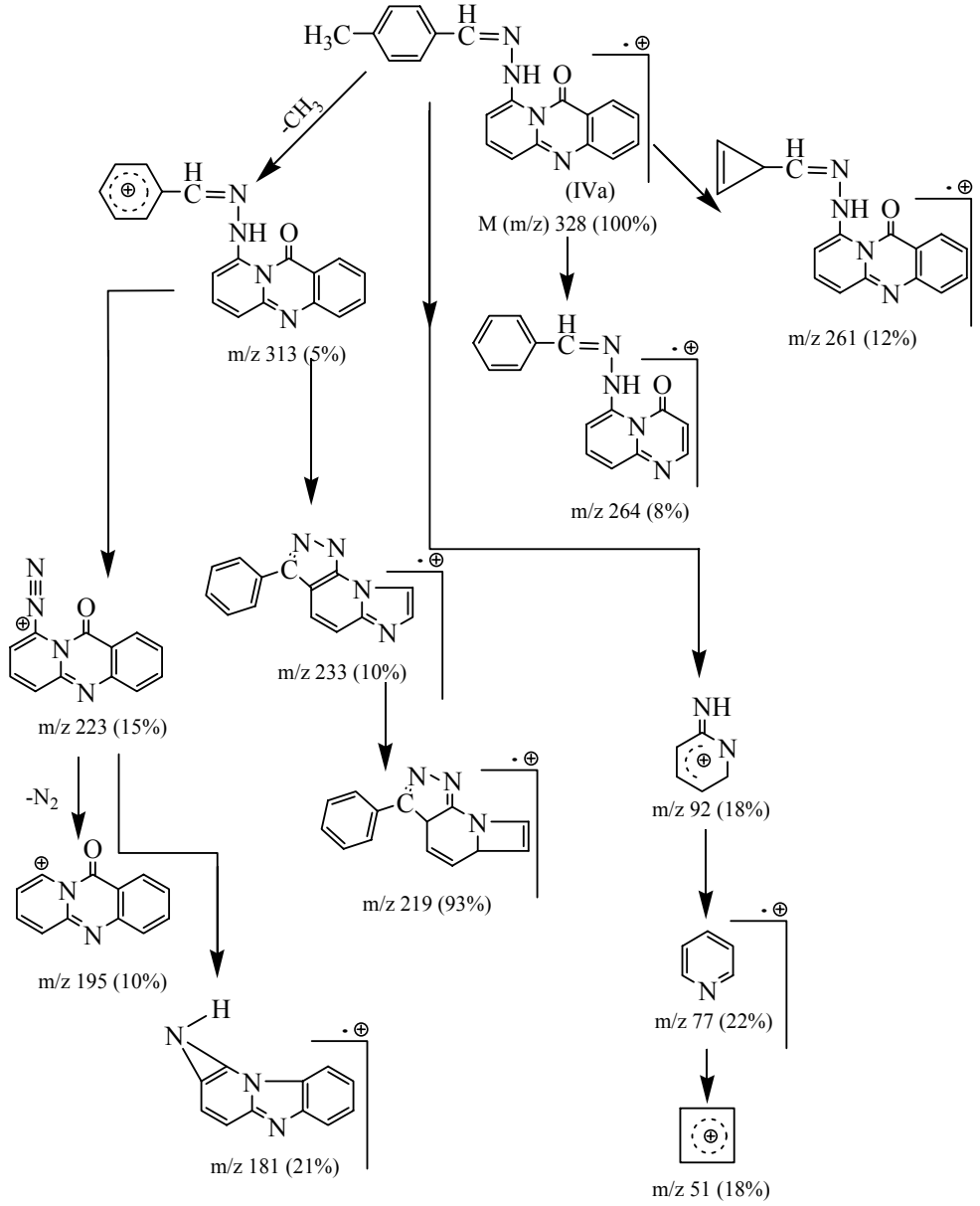
The ^{1}H-NMR spectral confirmed the above results. Compound ((IVm) was selected as a representative for this series. The ^{1}H-NMR spectrumfor compound (IVm) in (DMSO-d_6) δ in ppm showed significant peaks as follows:



(IVm)

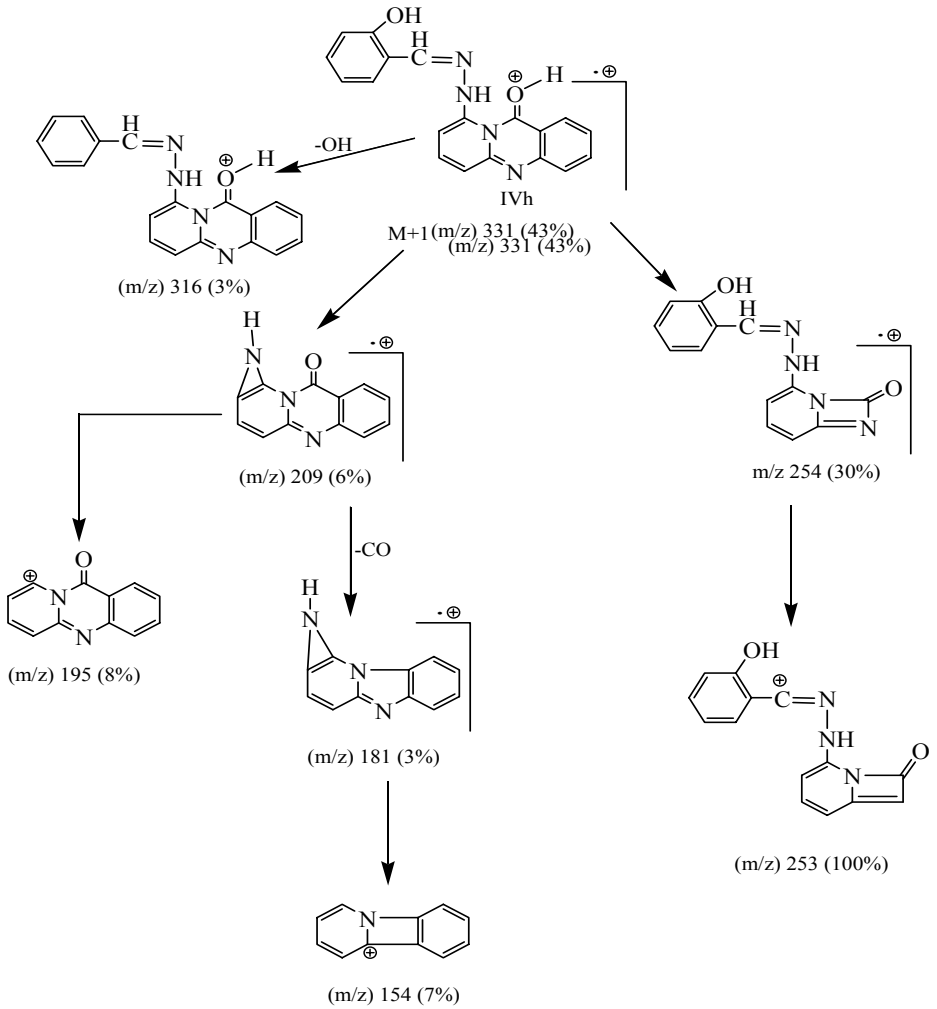
Singlet at 3.8 for 6H ($2OCH_3$), multiple at 6.87 for 3H (HC=N, ArH), multiplet at 7.25 for 3H(ArH), multiple at 7.62 for 3H(ArH), multiple at 8.57 for 2H(ArH), multiplet at 9.72 for 2H (NH, ArH). (Jameel *et al.*, 2014).

The mass spectral confirmed the above results. The mass spectrum for compound (IVa) showed the following possible fragmentation m/z, relative abundance (%) (scheme.2).



Scheme 2: Probability of the fragmentations of compound (IVa)

While the mass spectrum for compound (IVh) showed the following possible fragmentation m/z with relative abundance (%) (scheme. 3)



Scheme 3: Probability of the fragmentations of compound (IVh)

Table 2: Spectral data of the compounds (IVa-p)

Comp. No.	IR (KBr) υ(cm^{-1})		^{1}H-NMR
IVa	**C=O** amide	**C=C**	-------
	1630	1605	
IVb	1630	1604	-------
IVc	1625	1603	-------
IVd	1625	1600	-------
IVe	1630	1595	-------
IVf	1625	1585	-------
IVg	1630	1600	-------
IVh	1630	1602	-------
IVi	1625	1600	-------
IVj	1627	1605	-------
IVk	1625	1600	-------
IVl	1630	1603	3.81 (s, 3H), 7.04 (m, 5H), 7.79-7.81 (m, 5H), 8.62 (m, 3H).
IVm	1625	1585	3.82 (s, 6H), 6.87 (m, 3H), 7.25 (m, 3H), 7.62 (m, 3H), 8.57 (s, 2H).
IVn	1620	1605	-------
IVo	1640	1600	2.98 (s, 6H), 6.66-6.99 (m, 3H), 7.22-7.34 (m, 1H), 7.64 (m, 5H), 8.09-8.49 (m, 4H).
IVp	1627	1595	7.28-7.44 (m, 10H), 7.66 (d, 4H), 8.39 (d, 2H)

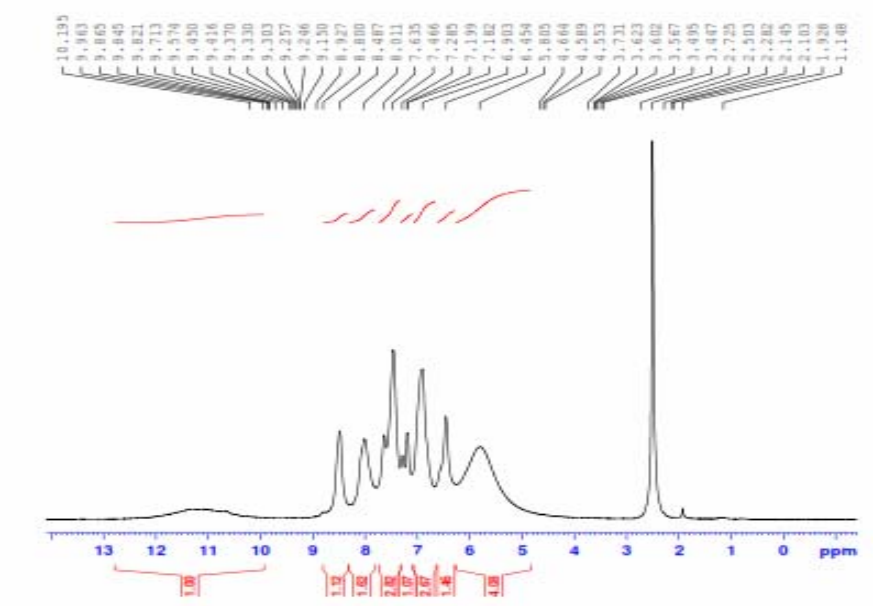


Fig. 1: ^{1}H-NMR spectrum for compound(I)

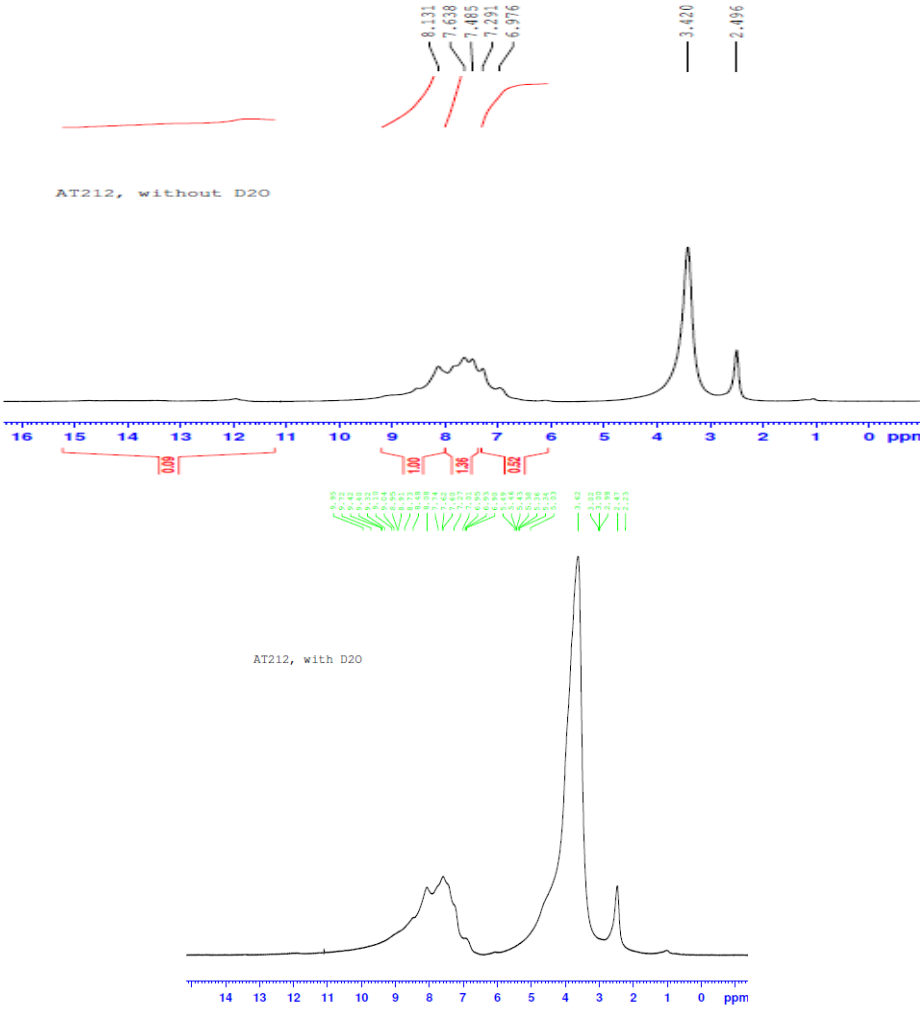


Fig. 2: ^{1}H-NMR spectrum for compound(II)

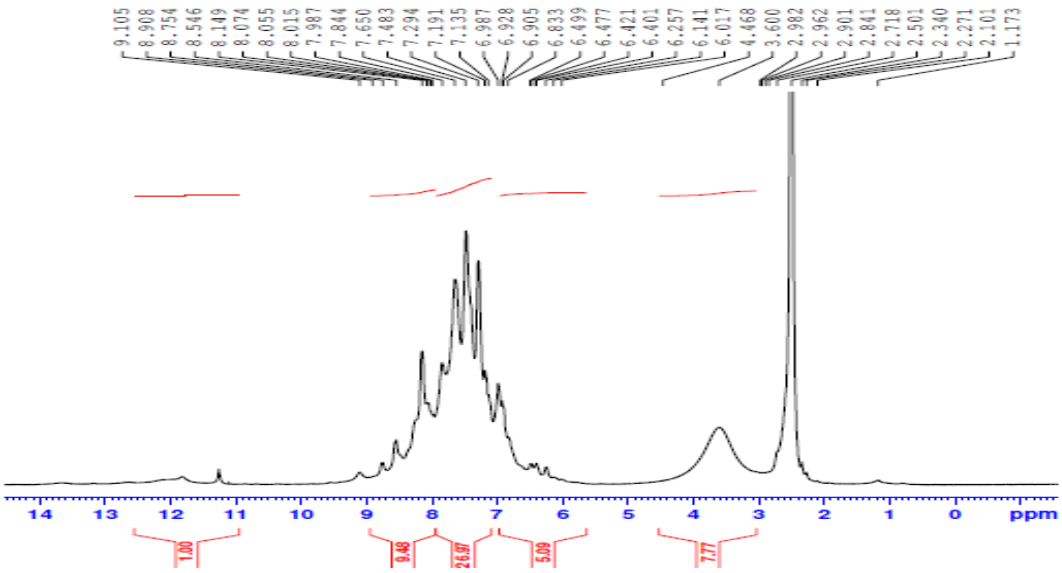


Fig. 3: ^{1}H-NMR spectrum for compound(III)

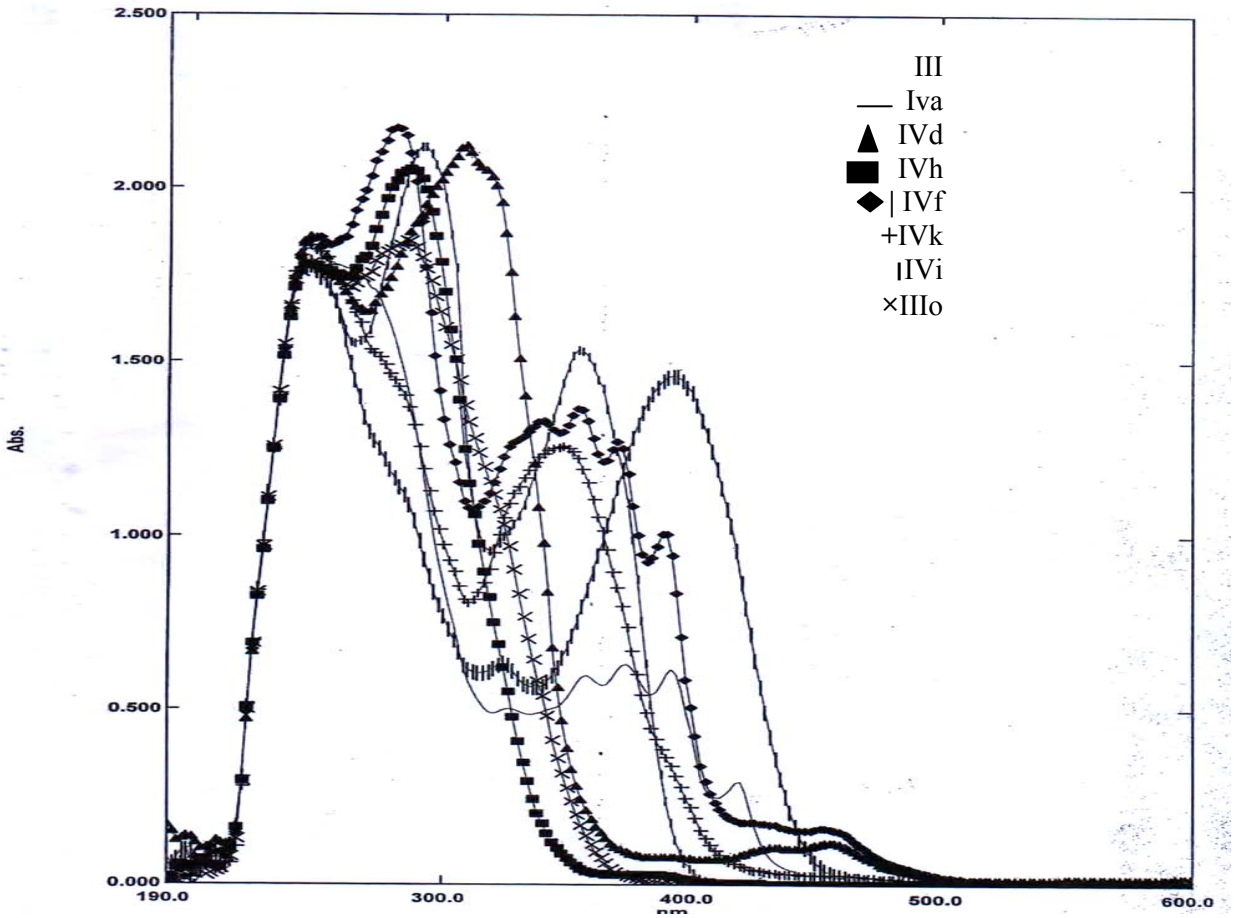


Fig. 4: UV spectrum for compounds (IVa-p)

REFERENCES

Belwal, C.K.; Joshi, K.A. (2012). Synthesis and antifungal activity of some novel thiazolidinonederivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid. *Int. J. Chem. Tech. Res*., **4**(4), 1758 - 1764.

Chandrika, P.M.; Rao, A.R.R.; Narsaiah, B.; Raju, M.B. (2008). Quinazoline derivatives with potent anti-inflammatory and anti-allergic activity. *Int. J. Chem. Sci*., **6**(3), 1119-1146.

Chen, Z.; Hu. G.; Li. D.; Chen. J.; Li. Y.; Zhou, H.; Xie. Y. (2009). Synthesis and vasoldilator effects of rutaecarpine analogues which might be involved transient receptor potential vanilloid subfamily, member 1(TRPV1). *Bioorganic and Med., Chem*., **17**, 2351-2359.

Decker, M. (2005). Novel inhibitors of acetyl–and butyrylcholinesterase derived from the alkaloids dehydroevodiamine and rustaecarpine. *Euro. J. Med. Chem*., **40**, 305-313.

Denny, W.A.; Atwell, G.J.; Caim, B.F. (1977). Potemtialamtitumor agents. 25. Azalogues of the 4'-(9-acridinylamino) methanesulfonanilides. *J. Med. Chem*., **20**(10), 1242- 46.

El-Hashash, M.A.; Darwish, K.M.; Risk, S.A.; El-Bassiouny, F.A. (2011). The reactivity of 2-ethoxy-4-chloroquinolinazoline and its use in synthesis of novel quinazoline derivatives. *Org. Chem. Inter*., 1-7.

Hradil, P. (1999). Synthesis of 2-amino-6-chloropyridine. *Chem*., **38**, 13-16.

Jameel, R.K.; Al-obaydee, S.Z. (2010). Studies on the reaction of some benzonaphthyridine with amine. M.Sc. Thesis, Mosul University, Coll. Sci., Dep. of Chem.

Jameel, R.K.; Al-Hadedi, O.T. (2009). Synthesis of some (10H) benzo[b][1,8]naphthyridin-5-one derivatives. M.Sc. Thesis, Mosul University, Coll. Sci., Dep. of Chem.

Jameel, R.K.; Sheat, A.M. (2014). Synthesis of some new Schiff bases and hydrazones containing benzonaphthyridine / benzonaphthyridine moiety. *Raf. J. Sci*., **25**(3), 56-69.

Jameel, R.K.; Sheat, A.M. (2014). Synthesis of some new Schiff bases derived from 2 and 4-aminoacridin-9(10H) – one. *Inter. J. Enh. Res. Sci. Tech and Eng*., **3**(5), 352-357.

Jen, T.; Dienel, B.; Bowman, H.; Petta, J.; Helt, A.; Love, B. (1972). Amidine. 2. A new class of antihypertensive agent. 1,2,3,5- tetrahydroimidazo[2,1-b]quinazolines. *J. Medicinal Chem*., **15**(7), 727- 31.

Jerry March. (1977). "Advanced Organic Chemistry. Reaction, Mechanism and Structure". 2nd ed.

Kannappan, N.; Reddy, B.S.R.; Sen, S.; Nagarajan, R.; Dashute, S. (2009). Synthesis and chemical characterization of quinoline Imine derivatives. *J. Appl. Chem. Res.,* **9**, 59-68.

Konshin, M.E.; Shramm, N.I. (1984). Synthesis and lonization constants of substituted-10H-Beno[b]-1,8-anphthyrid-5-ones., *Chem. Het. Compds*., **13**, 301-4.

Laddha, S.S.; Bhatnager, S.P. (2009). Novel fused: further studies on the anticonvulsant activity of 1,2,9,11 tetrasubstituted-7H–thieno[2',3':4,5]pyrimido[6,1-b]-quinazolin-7-one and 1,3,10,12-tetrasubstituted-8H–pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one. (ECSOC-13), 1-19.

Lee, E.S.; Kim, S.; Lee, S.H.; Jeong, T.C.; Moon, T.C.; Chang, H.W.; Jahng, Y. (2005). Synthesis and COX inhibitory activities of rutaecarpine derivatives. Bull. Korean. *Chem. Soc*., **26**(12), 1975-1980.

Liu, M.; Shu, M.; Yao, C.; Yin, G.; Wang, D.; Hung, J. (2016). Synthesis of pyrido – fused quinazolinone derivatives via copper – catalyzed domino reaction. *Org. let*., **18**, 824-827.

Mikhalev, A.I.; Kon shin, M.E.; Ovodenko, L.A.; Zaks, A.S. (1995). Synthesis, anti - inflammatory and analgesic activity of pyrido[2,1-b]quinazoline derivatives. *Phar. Chem. J*., **29**(2), 124-126.

Moqilaiah, K.; Dhamaja, K.; Srivami, N.; Chandra, V. Efficiemt. (2010). Synthesis of 9-aryl -6-(2-flourophenyl)-1,2,4-traiazolo{4,3,3-a}{1,8}naphthyridinesusiny chloramines-Tundermicrowace irradiation. *Indian J. Chem*., **49B**, 500-504.

Palmer, B.D.; Rewcastle, G.W.; Atwell, G.J.; Baguley, A.C.; Denny, W.A. (1988). Potential antitumor agent. 54. chromophoro requirements for in vivo antitumor activity among the general class of liner tricyclic carboxamides. *J. Med. Chem.*, **31**, 707-7012.

Palop, J.A.; Plano, D.; Moreno, E.; Sanmartin, C. (2014). Novel pyrido[2,3-b] pyrimidine derivatives and their hydroselenite salts as antitumoral agents. *ARKIVOK*., (ii) 187-206.

Pellon, R.F.; Decampo, M.L.; Fascio, M. (2007). Mild method for Ullmann reaction of 2-chlorobenzoic acid and aminothiazoles or aminobenzothiazoles under ultrasonic irradiation. *Synth. Commun*., **37**, 1853-1764.

Pellon, R.F.; Decampo, M.L.; Kunakbaeva, Z.; Gomez, V.; Casro, H.V. (2006). Synthesis of 9-methyl-11H-pyrido [2,1-b] quinazolin -11-one using the ullmann condensation. *Synth. Commun*., **36**, 481-485.

Shabana, L.A. (2013). Synthesis of novel heterocyclic compounds for antitumor activities. *Inter. J. Phar. Chem.* Res., **2**(3), 2278-8700.

Vizirianakis, I.S.; Chatzopoulou, M.; Bonovolias, I. D.; Nicolaou. I.; Demopoulos, V. J.; Tsifsogou, A.T. (2010). Toward the development of innovative bifunctional agent to induce differentiation and to promote apoptosis in leukemia: clinical candidates and perspectives. *J. Med. Chem*., **53**, 6779-6810.

Yassin, F.A. (2009). Synthesis, reactions and biological activity of 2-substituted 3-cyano-4,6-dimethylpyridine derivatives. *Chem. Het. Com*., **45**(1), 35-42.