Chapter IV

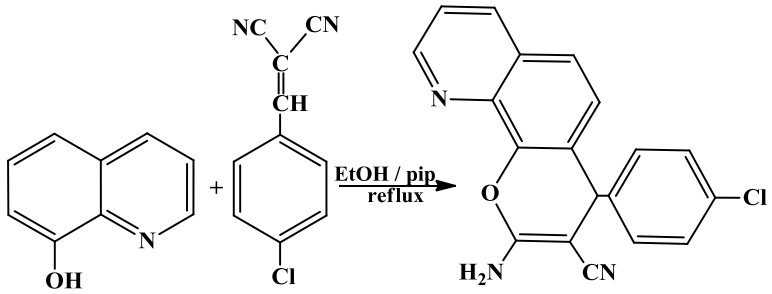
Background

Heterocyclic systems possess strong impact in bioactive substances and it is available in natural product *Dicbamnus dasycarpus* (*Rutaceae)*[1]. Pyrano quinoline skeleton are the main N-heteroaromatics incorporated into the structure of many pharmaceuticals.

Pyrano quinoline also acts as antimicrobial activities[2-6], antimalarial[7], psychotropic, antiallergenic, anti-inflammatory[8-10], antiproliferative activity against HCT 116[11], antitubercular agents[12] and good synthones[13] which was used for the preparation of fused ring such as imidazole, triazolo, quinazalino, tetrazolo, triazino pyrano quinolines.

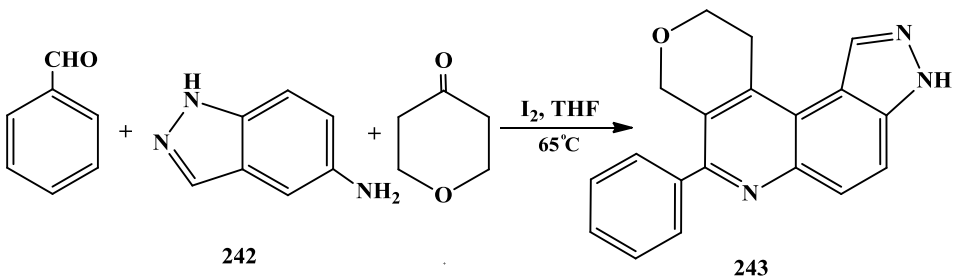
The development of efficient synthesis of pyrano quinolines has been the focus of much research for several decades and continues to be an active and rewarding research area. However, most of the existing methods suffer from limited scope or availability of starting materials[14-16].

Agrady *et al*[17] have developed 4*H*-pyrano-[3,2-*h*]- quinoline and 7*H*-pyrimido[4′,5′ :6,5]pyrano[3,2-*h*]quinoline(**241**) from 8-hydroxy quinolines. The synthesised compounds were studied for their antitumor activity.



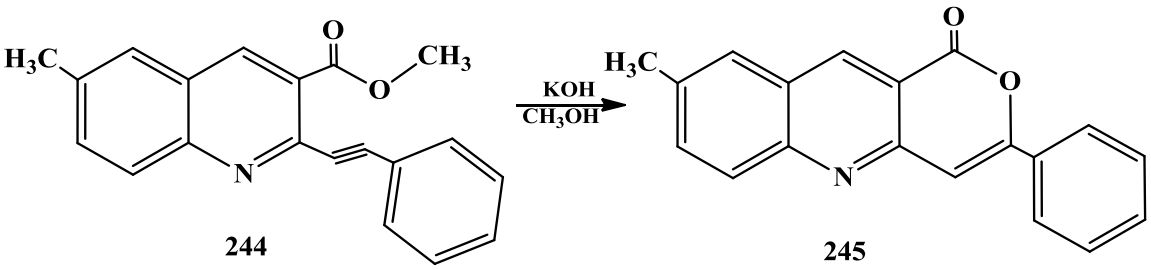
240 **241**

One pot synthesis of 7-phenyl-3,8,10,11-tetrahydropyrano[3,4-*c*]pyrazolo[4,3-*f*] quinoline(**243**) under metal free catalyst with mild reaction condition was reported by Wang[18].



242 **243**

Sharma *et al*[19] synthesised 8-methyl-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline-1-one(**245**) through intermolecular cyclization of 6-methyl-2-arylethynyl-quinoline-3-carbaldehyde(**244**).



244 **245**

Literature survey has been carried out for the synthesis, biological and pharmacological importance of various pyrano [2,3-b] quinolines and pyrano[3,2-c] quinolines and their reactions are developed as chemical equations as below

Asghari *et al* [20] ethyl 2-amino-6-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinolin-3-carboxylate(**247**)

Chang *et al*[21] ethyl-4-oxo-3,4-dihydro-1H-pyrano[3,4-*b*] quinolin-3-carboxylate(**252**)

Singh *et al* [22] iodo substituted 1*H*-pyrano-[4,3-*b*] quinolines **254**

Palaniappan[23] (4aS, 5S, 10bR)-5-argio-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*] quinoline(**256**)

Agrody *et al* [24] (*E*)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives **258**

Majumdar *et al* [25] 7-ethyl-8,8-dimethyl-8,9-dihydro-3*H*-pyrano[3,2-*f*]quinolin-3,10 (7*H*)-dione(**261**)

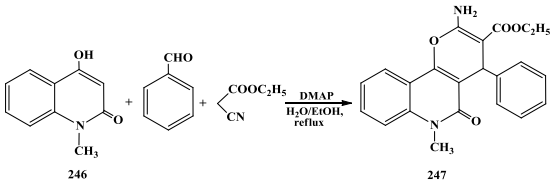
Maghadam *et al* [26] 3,4-dihydro-6*H*-pyrano[3,2-*c*]quinoline-2,5-diones **262**.

Majumdar *et al* [27]pyrano[3,2-*f*]quinoline-3,10(7*H*)-dione **264**.

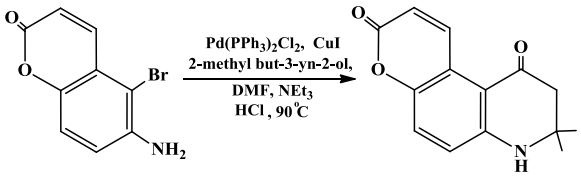
Hazra *et al* [28] tetracyclic pyrrolidine and isoxazo lidine fused pyrano[3,2-*h*]quinolines **268**

Bogami *et al* [29] 4*H*-pyrano[3,2-*h*] quinoline **269**

Bhawana *et al* [30] furo[2′,4′:4,6] pyrano[2,3-*b*]quinoline(**271**).



246 247



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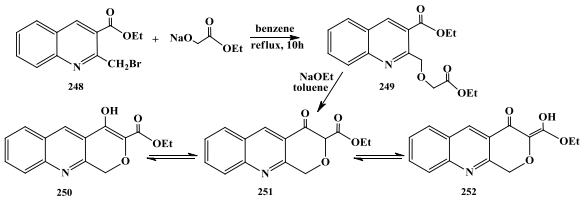
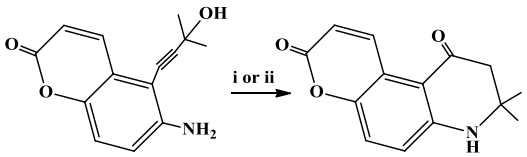
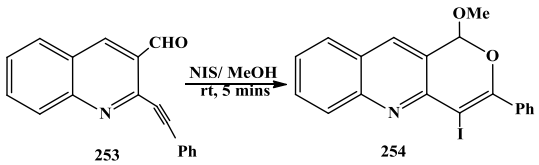


248 249 250 251 252



265 266

i) HCl, △ / M.W. ii) HCl / H_2O 100°C, 30 mins



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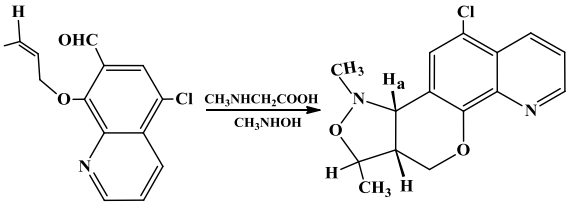
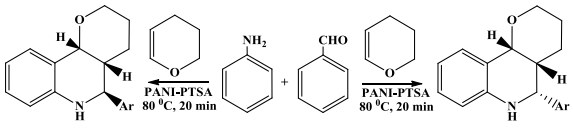
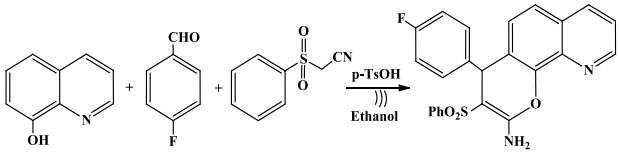


267 268



100% trans 255 100% cis 256



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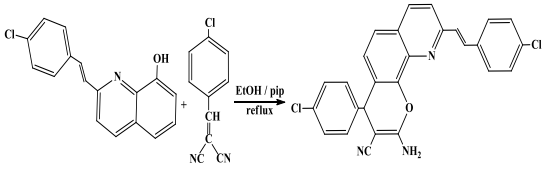
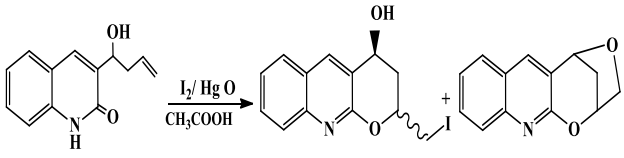
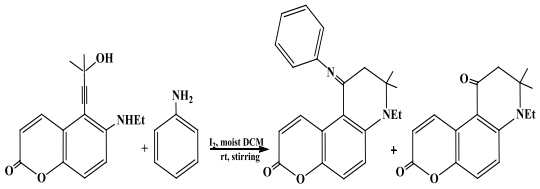


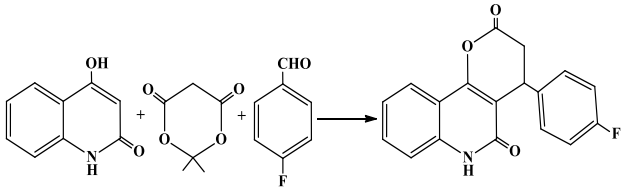
257 258



270 271



259 260 261



262

Result and Discussion

Synthesis of pyrano quinoline from the precursor 2-hydroxyquinoline-4-carboxylic acid would be worthwhile to explore newer method to construct the various substitution patterns that would provide a facile access to a wide class of compounds.

4.1. Synthesis of 4-hydroxypyrano[4,3-*c*]quinolin-2,10(3*H*)-dione(46)

At this juncture, we planned to synthesis of angular pyrano quinoline from 2-hydroxy-4-methyl quinoline via their corresponding carboxy chloride.

4.1.1. Synthesis of 2-hydroxy-8-methylquinolin-4-carboxylic acid(272b)

Accordingly, to the solution of 4,8-dimethyl-2-hydroxyquinoline, 3g (0.0174mol) on alk. $KMnO_4$ 3.2823g(0.02088mol) oxidation yield a white coloured solid which was further recrystallised with hot water gave a crystalline white solid. Yield-2.5964g (73.8%) with m.p-262˚C.

The IR spectrum **(fig.219)** of the compound **272b** showed absorption bands at 1740cm^{-1} for (C=O) of acid 3204 cm^{-1} for OH and 1654 cm^{-1} for (C=N). **^{1}H-NMR** (**fig.220**) **(DMSO-D_6) δ(ppm)** spectrum of the compound **272b** revealed singlet at δ 1.45 for methyl proton, broad singlet at δ 4.5 for OH, multiplet at δ 6.9-7.8 for aromatic proton C_3, C_5, C_6, C_7 -H, singlet at δ 9.3 for NH, broad singlet at δ 10.8 for acid OH. **^{13}C-NMR (DMSO-D_6) δ(ppm)spectrum** (**fig.221)** of the compound **272b** showed signals at δ 174 for carbonyl carbon(C_4), δ 168 for carbonyl carbon(C_2), δ 152(C_8), δ 142(C_9), δ 134(C_7), δ 131(C_6), δ 123(C_5), δ 118(C_{10}), δ 117(C_3) for aromatic carbon, δ 11 for methyl carbon.

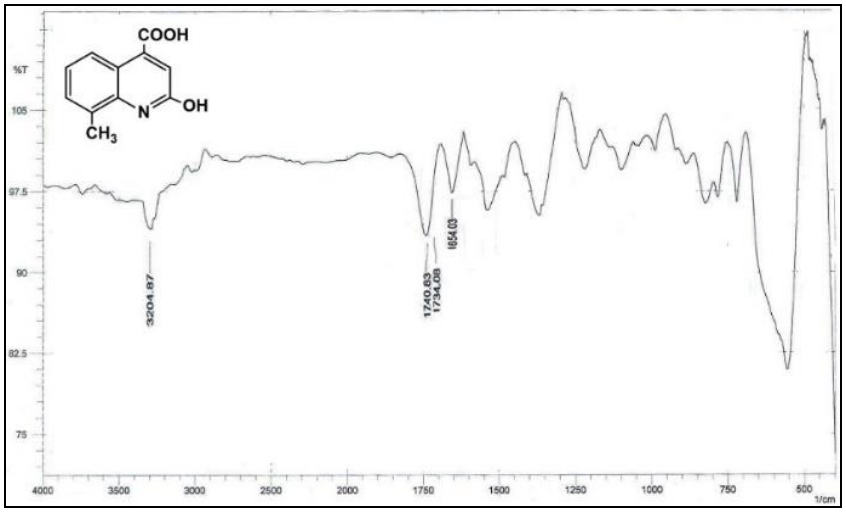


Fig.219-IR spectrum of 2-hydroxy-8-methylquinolin-4-carboxylic acid

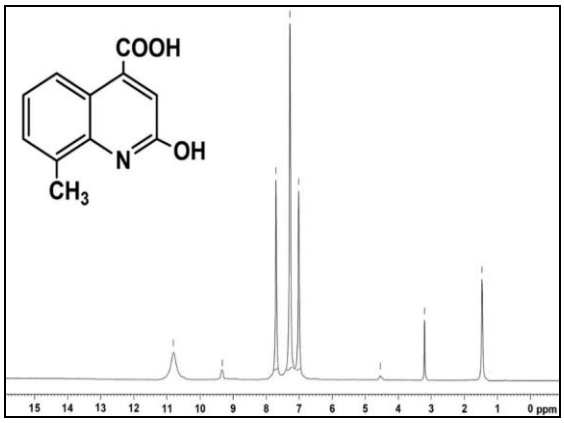


Fig.220-^{1}H-NMR spectrum of 2-hydroxy-8-methylquinolin-4-carboxylic acid

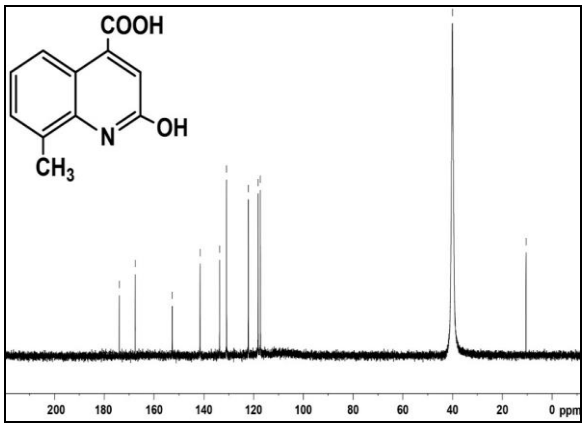
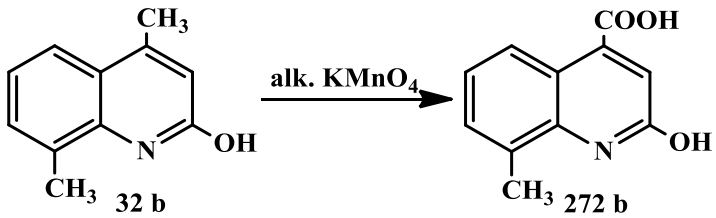


Fig.221-^{13}C-NMR spectrum of 2-hydroxy-8-methylquinolin-4-carboxylic acid

The compound **272b** was answered positive to acid. Hence, the above discussed the spectral and analytical data helped us **272b** was identified as 2-hydroxy-8-methyl quinolin-4-carboxylic acid. (**Scheme XXVI**) (**Chart XIII**).



Scheme XXVI

Similarly, the derivatives of quinoline carboxylic acid was synthesised **272**(**a-k**) (**Scheme XXVI**) (**Chart XIII**).

The conversion of acid to acid chloride was carried out which was used as the potential intermediate for the synthesis of pyrano quinolines.

4.1.2. Synthesis of 2-hydroxy-8-methylquinolin-4-carboxy chloride(273b)

For this, 2-hydroxy-8-methylquinoilin-4-carboxylic acid thus obtained was then refluxed with $SOCl_2$. 2g (0.009839mol) of acid, of 2.34mL (0.02mol)thionyl chloride was refluxed on a water bath. The progress of the reaction was carried out by TLC. After completion of the reaction, excess thionyl chloride was removed by codistillation with benzene. A yellow coloured solid was obtained. 1.78g (81.58%, 8.02mmol), mp: 245˚C.

The IR (**fig.222**) absorptions of the compound **273b** at 3171 cm^{-1}, 1721 cm^{-1}, 1633 cm^{-1} and 1096cm^{-1} supports the presence of OH, C=O, C=N and C-Cl respectively.

^{1}H-NMR (DMSO-D_6) (**fig.223) (ppm)**spectrum of the compound **273b** showed singlet at δ 1.25 for methyl proton, broad singlet at 4.1 for OH, singlet at δ 6.17 for aromatic proton C_3-H, multiplet from δ 7.46-7.66 for 4 aromatic proton C_5, C_6, C_7-H, and singlet at 8.96 for NH. **^{13}C-NMR (DMSO-D_6) δ (ppm)spectrum (fig.224)** of the compound **273b** assigned at δ 152 for carbonyl carbon(C_2), δ 147 for hydroxyl carbon(C_4), δ 142(C_8), δ 137(C_7), δ 129(C_6), δ 128(C_5), 119(C_{10}), δ 111(C_3), δ 13 for methyl carbon. The above spectral and analytical results supported the formation of the compound **273b** and it was attested to be 2-hydroxy-8-methylquinolin-2-carboxy chloride (**Scheme XXVII**) (**Chart XIII**).

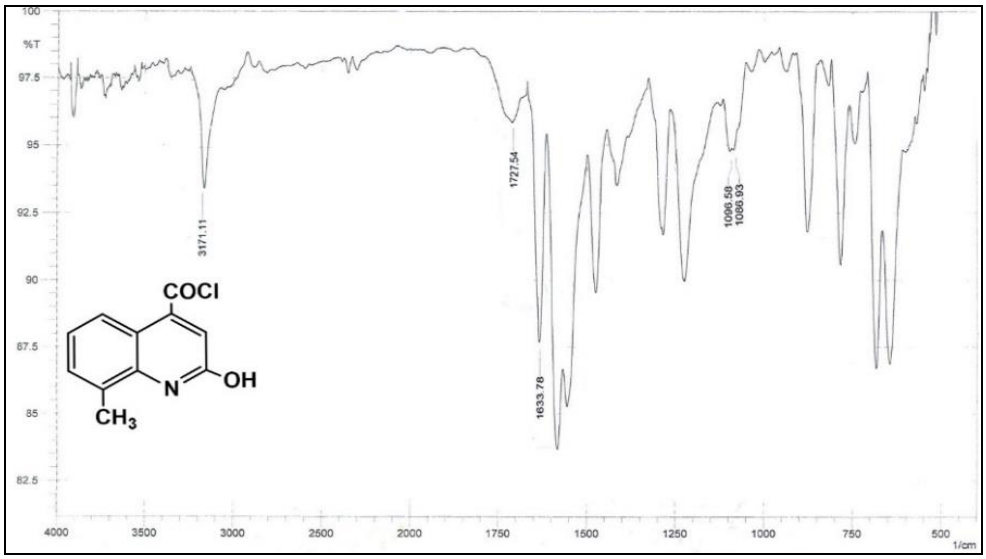


Fig.222-IR spectrum of 2-hydroxy-8-methylquinolin-4-carboxy chloride

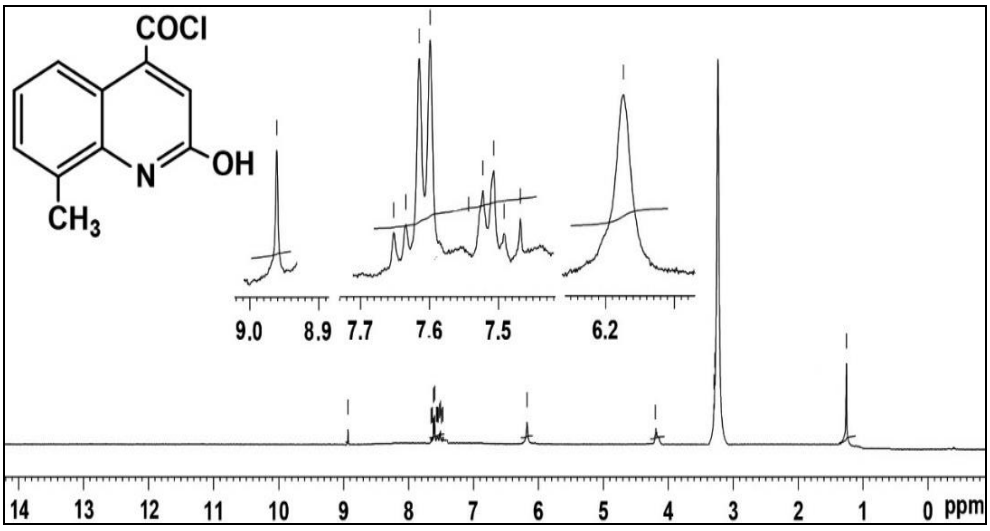


Fig.223-^{1}H-NMR spectrum of 2-hydroxy-8-methylquinolin-4-carboxy chloride

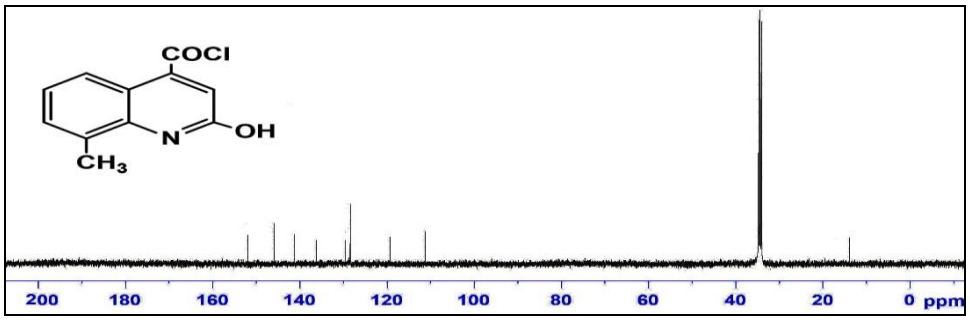
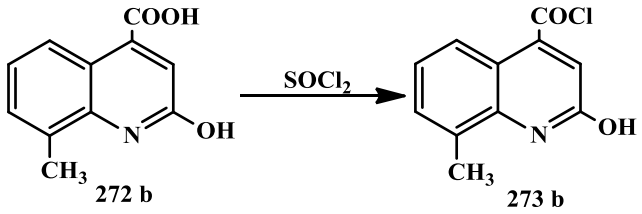


Fig.224-^{13}C-NMR spectrum of 2-hydroxy-8-methylquinolin-4-carboxy chloride



Scheme XXVII

The same reaction was carried out to synthesise their derivatives **273(a-k)** (**Scheme XXVII**) (**Chart XIII**)

4.1.3. Synthesis of 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(46)

In the next step, the solution of 2-hydroxy-8-methylquinolin-4-carboxychloride 1.1g (4.961mmol) and chloro acetic acid 0.4686g (4.961mmol) in ethanol and two drops of triethylamine was added and refluxed at 160˚C for 16 hours. The reaction was monitored by TLC until the disappearance of the reactant. After completion of the reaction, the excess solvent was evaporated and dried. The pale-yellow solid was obtained at (**97**:**3**) PE: EA. The product obtained was recrystallised from ethanol and yielded 0.8804g (72.94%, 3.6188mmol) with mp-239˚C.

IR absorptions **(fig.225)** at 1668 cm^{-1}, 1639 $cm^{-1,}$ 1179 $cm^{-1,}$ 3299 cm^{-1} which are attributed to the presence of C=O, C=N, C-O-C, OH respectively.

^{1}H-NMR (DMSO-D_6)(ppm)spectrum of (**fig.226)** of the compound **46b** showed singlet at δ 1.5 for methyl proton, singlet at δ 2.5 (C_3-H)for methylene proton, broad singlet at δ 4.1 for OH, triplet at δ 6.96 for aromatic proton C_8-H with coupling constant *J* = 7 Hz, 7.5 Hz, doublet at δ 7.18 for aromatic proton C_7-H with coupling constant *J* = 7.5Hz, doublet at δ 7.8 for aromatic proton C_9-H with coupling constant *J* = 8Hz, singlet at δ 10.15 (C_4-H) for hydroxy proton.

^{13}C-NMR (DMSO-d_6)(δ,ppm) (**fig.227**): 173 for carbonyl carbon (C=O) (C_2), 171 for carbonyl carbon (C=O) (C_{10}), 153 for hydroxyl carbon (C-OH) (C_4), 137(C_6), 132(C_{13}), 130(C_{14}), 129(C_7), 128(C_8), 126(C_9), 123(C_{11}), 121(C_{12}), 22(C_3) for methylene group, 18(CH_3) for methyl group. Mass m/z(M^+)(**fig.228**)-243. Elemental analysis of the compound has revealed the molecular formula of the compound **$C_{13}H_9O_4N$**.

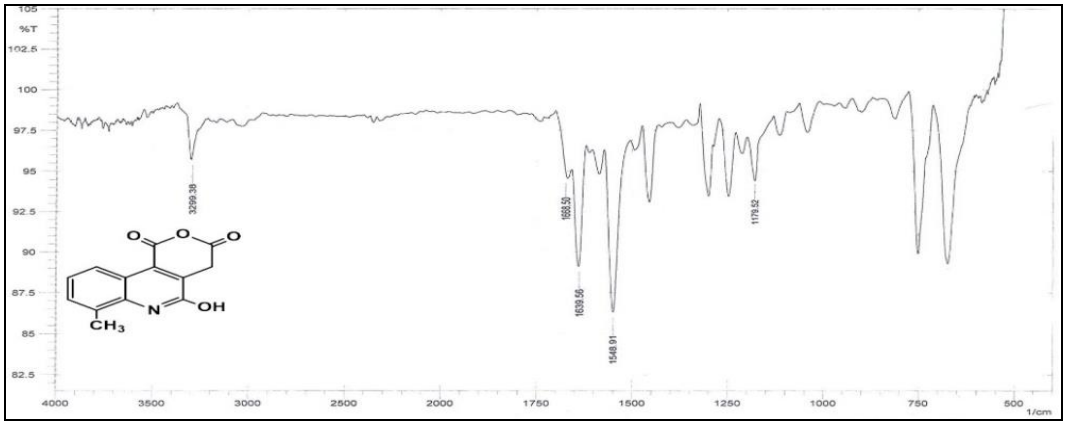


Fig.225-IR spectrum of 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1, 3(4*H*)-dione

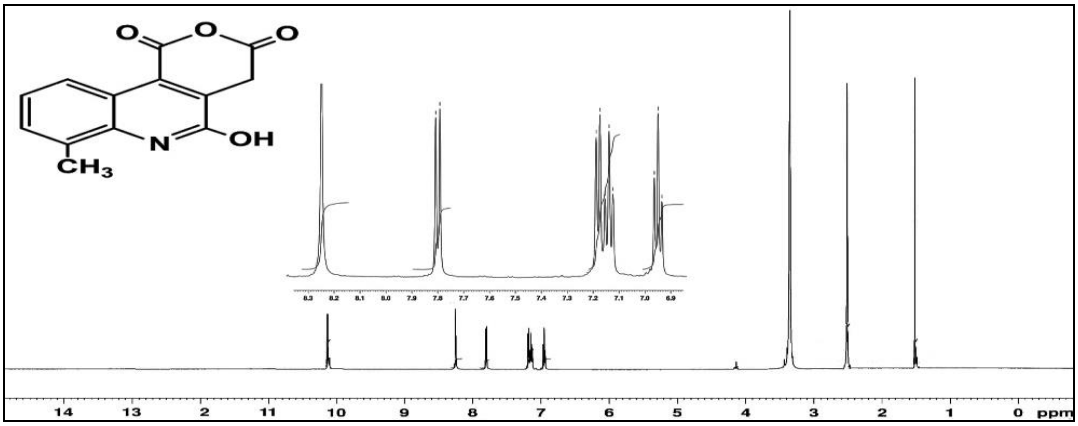


Fig.226 - ^{1}H-NMR spectrum of 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1, 3(4*H*)-dione

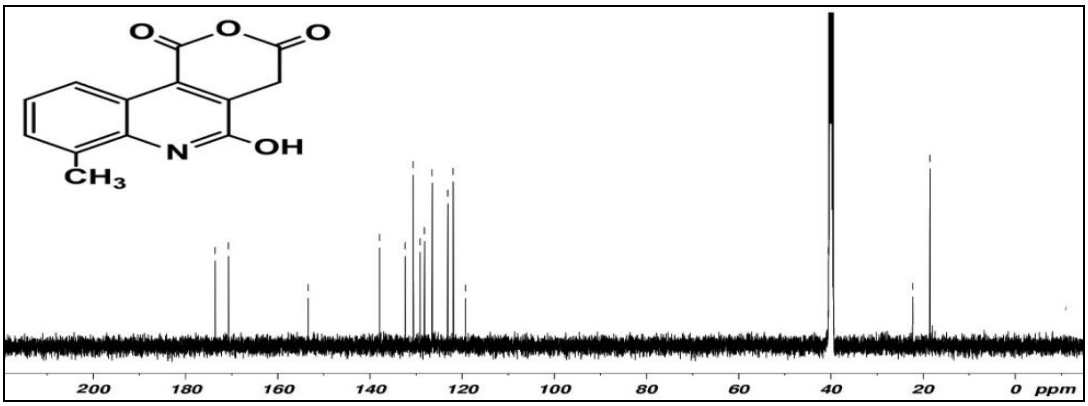


Fig.227- ^{13}C-NMR spectrum of 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1, 3(4*H*)-dione

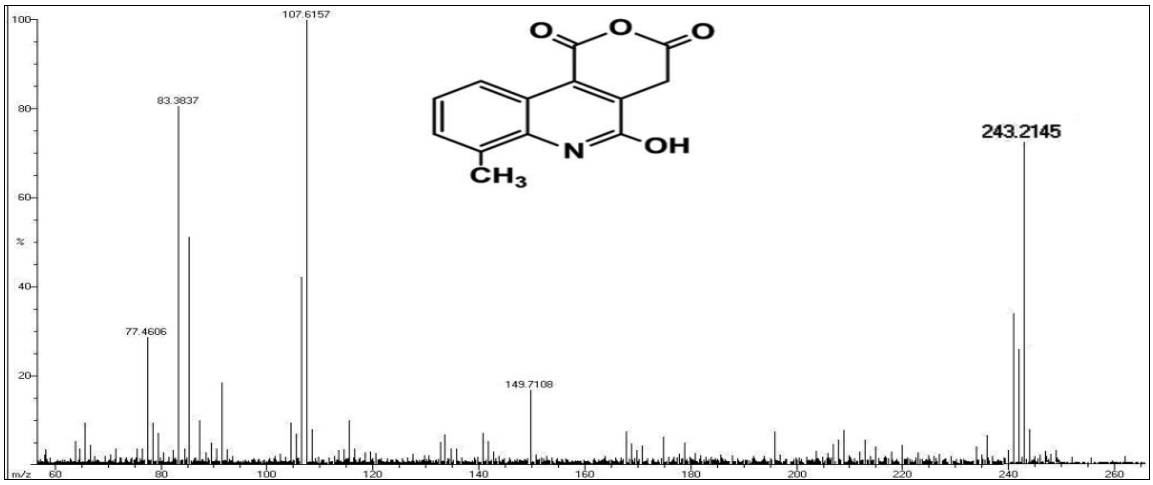
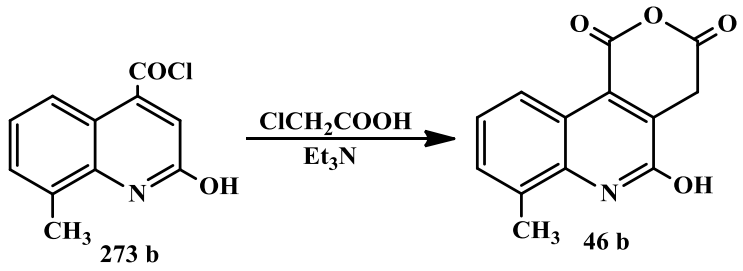


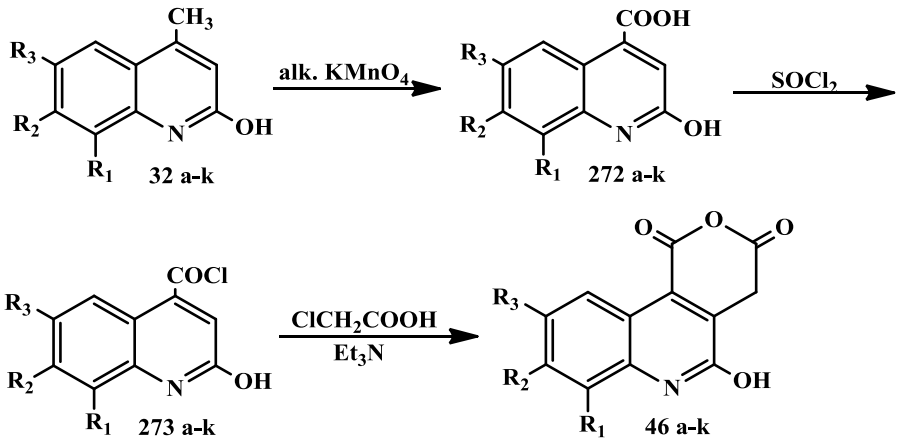
Fig.228- Mass spectrum of 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1, 3(4*H*)-dione



Scheme XXVIII

The reaction sequence was extended to synthesise their derivatives **46**(**a-k**) (**Scheme XXVIII**) (**Chart XIII**)

Chart XII



a) $R^1 = R^2 = R^3 = H$ **b) $R^1 = CH_3 R^2 = R^3 = H$** **c) $R^2 = CH_3$ $R^1 = R^3 = H$**

d) $R^3 = CH_3$ $R^1 = R^2 = H$ **e) $R^1 = Cl$ $R^2 = R^3 = H$** **f) $R^2 = Cl$ $R^1 = R^3 = H$**

g) $R^3 = Cl$ $R^1 = R^2 = H$ **h) $R^1 = OCH_3$ $R^2 = R^3 = H$** **i) $R^3 = OCH_3$ $R^1 = R^2 = H$**

j) $R^1 = OH$ $R^2 = R^3 = H$ **k) $R^3 = OH$ $R^1 = R^2 = H$**

Mass m/z (**fig.79**) -198The above spectral and analytical data has unambiguously attested to be 5-hydroxy-7-methylpyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46b**) (**Scheme XXVIII**) (**Chart XIII**).

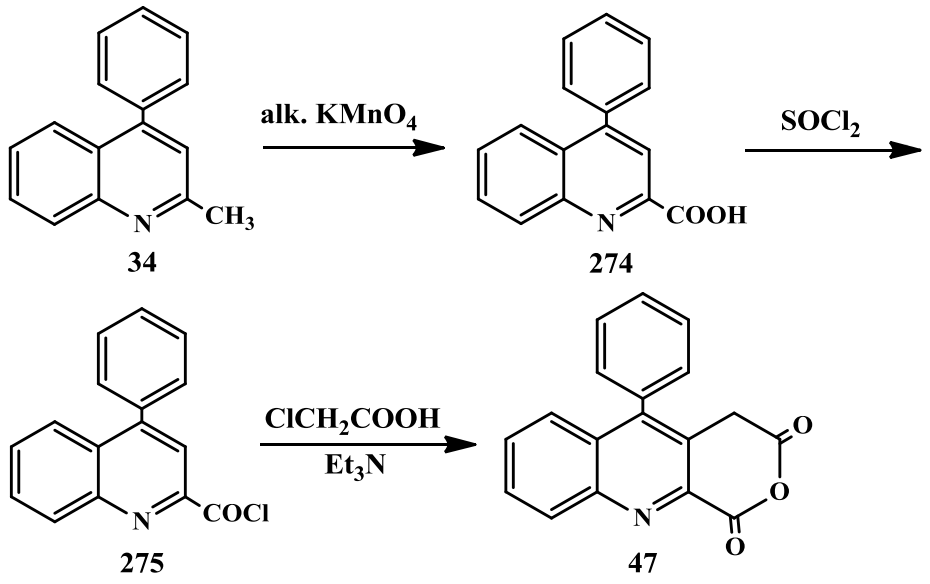
4.1.4. Synthesis of 5-phenylpyrano[3,4-*b*]quinolin-1,3(4*H*)-dione(47)

Synthesis of 2-methyl-4-phenylquinoline(34)

Benzoyl acetone(5g) was refluxed with aniline(5mL) in the presence of p-toluene sulphonic acid(0.5g) at 160ºC for 14hours. Then the reaction mixture was poured into crushed ice filtered, dried and recrystallised from ethanol yielded 2.32g (84.35%) with m.p.118º C.

The same reaction procedure of the synthesis of angular pyrano quinoline was worked up for the synthesis of linear pyrano quinoline **47** from the precursor 2-methyl-4-phenyl quinoline(**34**) via acetyl chloride **275**.

Chart XIII



Experimental

4.1. 5-hydroxypyrano[4, 3-c]quinolin-1, 3(4*H*)-dione 46(a-k)

4.1.2. Preparation of 2-hydroxy-quinolin-4-carboxylic acid 272(a-k)

2-hydroxy-4-methyl quinoline was oxidised with alk. $KMnO_4$ taken in the mole ratio 1.2moles. was added with the filtrate was neutralized with Conc. HCl gave a white coloured solid then filtered and dried. The spectral data were given in **Table**. **32**

2-hydroxy-quinolin-4-carboxylicacid(**272a**),2-hydroxy-8-methylquinolin-4-carboxylic acid (**272b**), 2-hydroxy-7-methylquinolin-4-carboxylicacid(**272c**), 2-hydroxy-6-methyl quinolin-4-carboxylicacid(**272d**), 8-chloro-2-hydroxy-quinolin-4-carboxylic acid(**272e**), 7-chloro-2-hydroxy-quinolin-4-carboxylicacid(**272f**),6-chloro-2-hydroxy-quinolin-4-carboxylic acid (**272g**), 2-hydroxy-8-methoxyquinolin-4-carboxylicacid(**272h**) 2-hydroxy-6-methoxy quinolin-4-carboxylicacid(**272i**), 2,8-dihydroxyquinolin-4-carboxylic acid(**272j**), 2,6-di hydroxy-quinolin-4-carboxylicacid (**272k**).

4.1.3. Preparation of 2-hydroxyquinolin-4-carboxy chloride 273(a-k)

A solution of 2-Hydroxy quinolin-4-carboxylic acid and thionyl chloride was refluxed on a water bath, for 3 hours. The excess thionyl chloride was removed by codistillation with benzene. Pale white solid was obtained. The physical and spectral details were shown in **Table**.**33**

2-hydroxyquinolin-4-carboxy chloride(**273a**), 2-hydroxy-8-methylquinolin-4-carboxy chloride(**273b**), 2-hydroxy-7-methylquinolin-4-carboxy chloride(**273c**), 2-hydroxy-6-methyl quinolin-4-carboxy chloride(**273d**), 8-chloro-2-hydroxyquinolin-4-carboxy chloride(**273e**), 7-chloro-2-hydroxyquinolin-4-carboxy chloride(**273f**),6-chloro-2-hydroxyquinolin-4-carboxy chloride(**273g**), 2-hydroxy-8-methoxyquinoline-4-carboxychloride(**273h**), 2-hydroxy-6-methoxyquinoline-4-carboxy chloride(**273i**), 2,8-dihydroxy-quinolin-4-carboxychloride (**273j**), 2,6-dihydroxyquinoline-4-carboxychloride(**273k**).

4.1.4. Preparation of 5-hydroxypyrano[4, 3-c]quinolin-1, 3(4*H*)-dione 46(a-k)

Equal moles of 2-hydroxy- quinolin-4-carboxy chloride and chloro acetic acid were dissolved in ethanol. One drop of triethylamine was added. Then it was refluxed at 160˚C for 16h. After completion of the reaction, the excess solvent was evaporated and

Table 32. Synthesis of substituted 2-hydroxy-quinolin-4-carboxylic acid 272(a-k)

	2-hydroxy-4-methylquinoline	$KMnO_4$	Yield	m.p (˚C)	Spectral data
272a	**32a** -2.5g (0.0157mol	2.9765g (0.0188mol)	2.1098g (71.04%)	266	IR υmax cm^{-1}: 1742(C=O), 1646(C=N), 3226(OH)
272b	**32b** -3g(0.0173mol)	3.2823g (0.0208mol)	2.5964g (73.8%)	262	
272c	**32c** -2.5g (0.0144mol)	2.7353g (0.0173mol)	2.0675g (70.52%)	259	IR υ_{max} cm^{1}: 1738(C=O), 1634(C=N), 3298(OH)
272d	**32d** - 2.5g (0.0144mol)	2.7353g (0.0173mol)	2.0992g (71.6%)	256	IR υ_{max} cm^{1}: 1735(C=O), 1638(C=N), 3299(OH)
272e	**32e** -2.3g (0.0119mol	2.2517g (0.0142mol)	1.85g (69.48%)	252	IR υ_{max} cm^{1}: 1743(CO), 1637(CN), 1048(C-Cl), 3300(OH)
272f	**32f** -2.5g(0.013mol)	2.4475 (0.016mol)	2.0233g (70.09%)	256	IR υ_{max} cm^{1}(**fig**.**252**): 1742(C=O), 1635(C=N), 1095(C-Cl), 3291(OH). ^{1}H-NMR ($CDCl_3$) (δ,ppm) (**fig**.**253**): 4.2(s, NH, 1H), 6.8(s, 1H, ArH) 7.05-8.1(m, 5H, ArH, C_3, C_5, C_7, C_8-H), 10.68(s, 1H, OH); ^{13}C-NMR ($CDCl_3$) (δ,ppm) (**fig**.**254**): 162(C_2-OH),156(C_4-OH), δ 148 (C_7),132 (C_9), 131 (C_8), 130 (C_6), 129 (C_5), 122 (C_{10}), 119 (C_3)
272g	**32g** -2.5g (0.013mol	2.4475g (0.016mol)	2.0827g (72.15%)	266	IRυ_{max} cm^{1}(**fig**.**262**): 1743(C=O), 1636(C=N), 1094(C-Cl), 3291(OH)
272h	**32h** -2.2g (0.01mol),	2.2037g (0.013 mol)	1.7438g (68.44%)	262	IR υ_{max} cm^{-1}: 1741(C=O), 1648(C=N), 3301(OH)
272i	**32i** -2.2g (0.0116mol)	2.2722g (0.0144mol)	1.73g (67.98%)	261	IR υ_{max} cm^{-1}: 1741(C=O), 1648(C=N), 3301(OH)
272j	**32j** -2.1g (0.012mol	2.2722g (0.0144mol)	1.6331g (66.42%)	262	IR υ_{max} cm^{1}: 1741(C=O), 1650(C=N), 3131(OH)
272k	**32k** -2.1g (0.012mol	2.2722g (0.0144mol)	1.6557g (67.34%)	265	IR υ_{max} cm^{1}(**fig**.**268**): 1741(C=O), 1650(C=N), 3131(OH)
274	**34**-3g(0.0174mol)	3.2013g	2.1044g	242	IR υ_{max} cm^{1}: 1743(C=O), 1646(C=N), 3301(OH)

Table 33. Synthesis of substituted 2-hydroxyquinolin-4-carboxy chloride 273 (a-i)

	2-hydroxy-quinolin-4-carboxylic acid	Thionyl chloride	Yield	m.p (˚C)	Spectral data
273a	**272a** -1.5g (0.007927mol	1.88mL (0.016mol)	1.35g (82.11%)	240	IR υ_{max} cm^{-1}:1726(C=O), 1606(C=N), 3266(OH), 1096(C-Cl)
273b	**272b** -2g (0.009839mol	2.34mL (0.02mol)	1.78g (81.58%)	245	
273c	**272c** -1.5g (0.0074mol	1.75mL (0.015mol)	1.27 (77.62%)	245	IR υ_{max} cm^{1}: 1721(C=O), 1633(C=N), 3171(OH), 1096(C-Cl)
273d	**272d** - 1.5g (0.007mol	1.75mL (0.015mol)	1.28g (78.51%)	244	IR υ_{max} cm^{-1}: 1721(C=O), 1633(C=N), 3171(OH), 1096(C-Cl)
273e	**272e** -1.3g (0.0058mol	1.382mL (0.012mol)	1.07g (76.21%)	249	IR υ_{max} cm^{-1}: 1721(C=O), 1633(C=N), 3289(OH), 1096(C-Cl)
273f	**272f** -1.5g (0.006706mol	1.59mL (0.013mol)	1.238g (76.25%)	242	IR υ_{max} cm^{-1}(**fig**.**255**): 1721(C=O), 1633(C=N), 3289(OH), 1096(C-Cl); ^{1}H-NMR ($CDCl_3$) (δ,ppm) (**fig**.**256**): 9.32 (s, 1H, OH), 7.07-7.36 (m, 5H, ArH, C_3, C_5, C_6, C_8-H); ^{13}C-NMR ($CDCl_3$) (δ,ppm) (**fig**.**257**): 164(C_2-OH), 151(C_4-OH), δ 149 (C_7),132 (C_9), 131 (C_8), 130 (C_6), 119 (C_5), 117 (C_{10}), 112 (C_3)
273g	**272g** -1.5g (0.0067mol	1.6mL (0.013mol)	1.28g (78.69%)	242	IR υ_{max} cm^{-1}(**fig**.**263**):1721(C=O), 1630(C=N), 3225(OH), 1085(C-Cl)
273h	**272h** -1.2g 0.0055mol	1.3mL (0.011mol)	0.996g (76.54%)	245	IR υ_{max} cm^{-1}:1726(C=O), 1659(C=N), 1600(OCH_3), 3198(OH), 1093(C-Cl)
273i	**272i** -1.2g (0.0054mol	1.3mL (0.011mol)	0.986g (75.8%)	246	IR υ_{max} cm^{-1}:1726(C=O), 1659(C=N), 1601(OCH_3), 3198(OH), 1093(C-Cl)
273j	**272j** 1.1g (0.00536mol	1.27mL (0.011mol)	0.898g (74.91%)	245	IR υ_{max} cm^{-1}: 1721(C=O), 1634(C=N), 3258(OH), 1038(C-Cl)
273k	**272k -** 1.1g (0.00536mol)	1.27mL (0.011mol)	0.89g (74.53%)	247	IR υ_{max} cm^{-1}(**fig**.**269**): 1726(C=O), 1637(C=N), 3297(OH), 1030(C-Cl)
275	**274** - 1.2g, 0.004812mol)	1.14mL, 0.0096mol)	1.1091g (86.06%)	220	IR υ_{max} cm^{-1}: 1721(C=O), 1654(C=N), 1039(C-Cl)

dried and column chromatographed at (**97**:**3**). The white solid was obtained. The spectral details in **Table**.**34**

5-hydroxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46a**), 5-hydroxy-7-methylpyrano [4,3-*c*] quinolin-1,3(4*H*)-dione(**46b**), 5-hydroxy-8-methylpyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46c**), 5-hydroxy-9-methylpyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46d**), 7-chloro-5-hydroxypyrano [4,3-*c*]quinolin-1,3(4*H*)-dione(**46e**), 8-chloro-5-hydroxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione (**46f)**, 9-chloro-5-hydroxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46g**),5-hydroxy-7-methoxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46h**),5-hydroxy-8-methoxypyrano[4,3-*c*] quinolin-1,3(4*H*)-dione(**46i**),5,7-dihydroxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46j**), 5,9-dihydroxy pyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46k**).

4-phenyl-quinolin-2-carboxylicacid(**274**), 4-phenylquinolin-2-carboxychloride(**275**), 5-phenylpyrano[3,4-*b*]quinolin-1,3(4*H*)-dione(**47)**.

Table 34. Synthesis of substituted 5-hydroxypyrano[4, 3-c]quinolin-1, 3(4*H*)-dione 46 (a-k)(continued)

	2-hydroxy quinolin-4-carboxy chloride	Chloro acetic acid	Yield	m.p (˚C)	Spectral data
46a	**273a** -0.9g (4.334mmol)	0.4686g (4.961mmol)	0.7203g (72.5%)	239	IR υ_{max} cm^{-1}: 1699 (C=O), 1187 (C-O-C), 1643 (C=N), 3286(OH); ^{1}H-NMR (DMSO-d_6) (δ,ppm): 2.1 (s, 2H, CH_2), 6.5(t, *J*=8Hz, 1H, ArH, C_9-H), 7.2 (d, *J*=7Hz, ArH, C_6-H), 7.8(t, *J*=8, 8Hz, H, ArH, C_7, C_8-H), 9.8(s, 1H, NH)
46b	**273b** -1.1g (4.961mmol)	0.4686g (4.961mmol)	0.8804g (72.94%)	237	
46c	**273c** -0.8g (3.608mmol)	0.3409g (3.608mmol)	0.6168g (70.26%)	235	IR υ_{max} cm^{1}:1675(C=O), 1172 (C-O-C),1631(C=N), 3305(OH)
46d	**273d** -0.8g (3.608mmol)	0.3409g (3.608mmol)	0.631g (71.88%)	231	IRυ_{max} cm^{1}1683 (C=O), 1189 (C-O-C), 1654(C=N), 3298(OH)
46e	**273e** -0.7g 2.891mmol)	0.2732g (2.891mmol)	0.5329g (69.9%)	239	IR υ_{max} cm^{1}:1690(C=O), 1173(C-O-C) 1574(C=N), 3270(OH), 1030 (C-Cl)
46f	**273f** -0.7g (2.891mmol)	-0.2732g (2.891mmol)	0.544g (71.36%)	231	IR υ_{max} cm^{1}(**fig**.**258**):1666(CO), 1178(C-O) 1640(CN), 3299(OH), 1036 (C-Cl); ^{1}H-NMR (DMSO-d_6) (δ,ppm) (**fig**.**259**): 2.5(s, 2H,CH_2), 7.04(d, *J*=7.5Hz, 2H,C_8, C_9-H),7.25(m, ArH, 3H, C_6, C_8 ,C_9 -H), 7.7(s,1H, ArH, C_6-H) 8.97(s,1H, NH);^{13}C-NMR (DMSO-d_6) (δ,ppm) (**fig**.**260**): 153(C_2=O), 148(C_{10}=O), 142(C_4), 134(C_7), 131(C_{13}), 130(C_{11}), 127(C_8), 122(C_6), 118(C_5), 110(C_{12}), 102(C_{14}), 29(CH_2); MS(m/z): 263 $[M]^{+}$, 235, 219, 203, 161, 127, 101, 75
46g	**273g** -0.8g (3.304mmol)	0.3123g (3.304mmol)	0.6278g (72.05%)	232	IR υ_{max} cm^{1}(**fig**.**264**):1705 (CO), 1172(C-O-C), 1603(CN), 3329(OH), 1090 (C-Cl); ^{1}H-NMR (DMSO-d_6) (δ,ppm) (**fig**.**265**): 2.49(s,2H, CH_2), 6.54(d, *J*=10.5 Hz, 1H, ArH, C_6-H), 7.0(d, *J*=11Hz ,1H, ArH, C_7-H), 7.4(s, 1H, ArH, C_9-H), 10.89(s,1H,NH);^{13}C-NMR(DMSO-d_6)(δ,ppm)(**fig**.**266**):162C_2=O), 161 (C_{10}=O),156(C_4),148(C_8), 145(C_{13}), 138(C_{11}), 129(C_7), 128(C_6), 123(C_5), 119(C_{12}),117(C_{14}), 25(CH_3)
46h	**273h** -0.6g (2.524mmol)	0.2385g (2.524mmol)	0.4489g (68.6%)	234	IR υ_{max} cm^{1}:1705(C=O), 1179(C-O-C), 1620(C=N), 3329(OH); ^{1}H-NMR (DMSO-d_6) (δ,ppm): 2.7(s, 2H, CH_2), 3.8(s, 3H, OCH_3) 7.2(t, *J*=8Hz, 1H, ArH), 7.5(d, *J*=8Hz, 1H, ArH), 7.6(d, *J*=8 Hz, 1H, ArH), 9.1(s,1H,NH)
46i	**273i** -0.6g (2.524mmol)	0.2385g (2.524mmol)	0.4446g (67.94%)	231	IR υ_{max} cm^{1}:1677 (C=O), 1179(C-O-C), 1620(C=N), 3298(OH)

	2-hydroxy quinolin-4-carboxy chloride	Chloro acetic acid	Yield	m.p (˚C)	Spectral data
46j	**273j** -0.6g (2.683mmol)	0.2535g (2.683mmol)	0.4442g (67.53%)	236	IR υ_{max} cm^1:1644 (C=O), 1179(C-O-C), 1624(C=N), 3121 (OH)
46k	**273k** -0.6g (2.683mmol)	0.2535g (2.683mmol)	0.4422g (67.21%)	239	IR υ_{max} cm^1(**fig**.**270**):1644 (C=O), 1179(C-O-C) 1624(C=N), 3121(OH); ^{1}H-NMR(DMSO-d_6) (δ,ppm) (**fig**.**271**):2.3(s, 2H, CH_2), 3.8(s,1H, C_4-OH) 4.26(s,1H, C_8-OH) 6.17(s,1H, ArH, C_9-H), 6.69(d, *J*=10.5Hz, 1H, ArH, C_6-H), 7.5(d, *J*=9 Hz, 1H, ArH, C_7-H), 11.5(s,1H, NH); ^{13}C-NMR (DMSO-d_6) (δ,ppm) (**fig**.**272**): 162C_2=O), 161(C_{10}=O), 155(C_4), 149(C_8), 141(C_{13}), 138(C_{11}), 128(C_7), 118(C_6), 115(C_5), 114(C_{12}),102(C_{14}), 21(CH_3)
47	**275 -** 0.7g ((2.614mmol)	0. 0.247g (2.614mmol)	0.5477g (72.41%)	233	IR υ_{max} cm^1(**fig**.**273**):1731 (C=O), 1682(C=O),1217(C-O-C) 1585(C=N); ^{1}H-NMR(DMSO-d_6) (δ,ppm) (**fig**.**274**): 6.92-8.15(m, 9H, ArH, $C_{7,}$ $C_{8,}$ $C_{6,}$ $C_{5,}$ $C_{2',}$ $C_{3',}$ $C_{1'}$ -H), 2.3(s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) (δ,ppm) (**fig**.**275**): δ 153 (C_2=O), 141 CO), 133 C_4), 132 C_9), 129 C_{13}), 128 C_{12}), 127 C_7), 126 $C_{2'}$), 122 C_8), 120 $C_{1'}$), 119 C_{10}), 118 (C_{11})

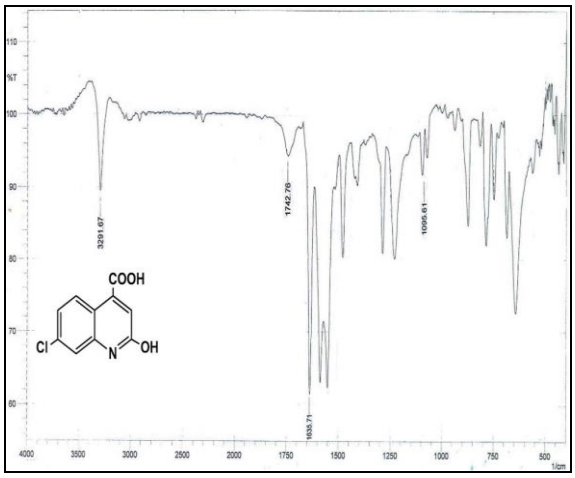


Fig.252-IR spectrum of7-chloro-2-hydroxy-quinolin-4-carboxylic acid

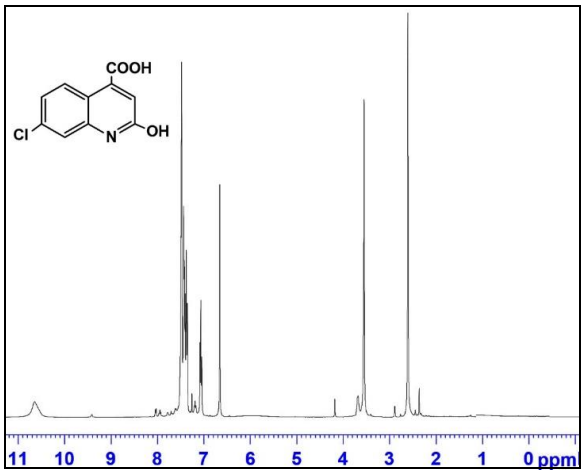


Fig.253-^{1}H-NMR spectrum of 7-chloro-2-hydroxy-quinolin-4-carboxylic acid

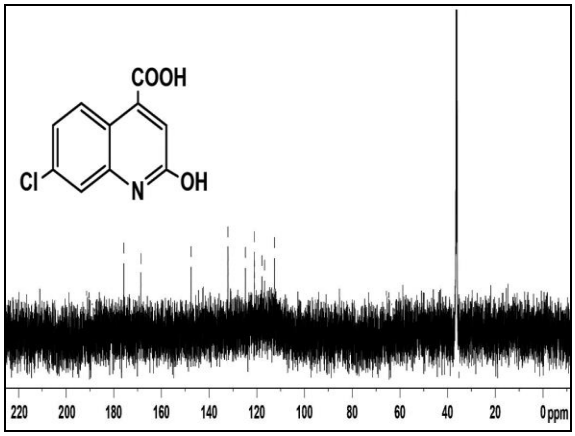


Fig.254-^{13}C-NMR spectrum of 7-chloro-2-hydroxy-quinolin-4-carboxylic acid

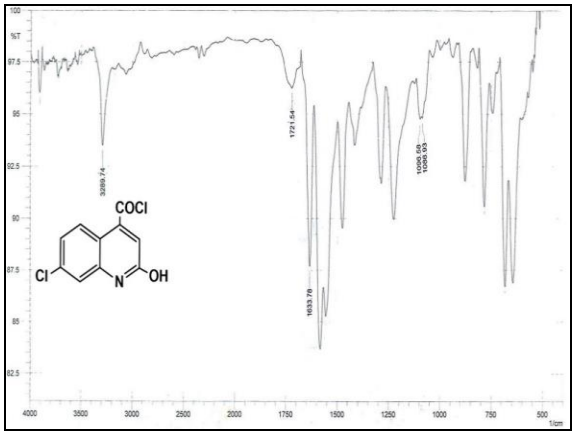


Fig.255-IR spectrum of7-chloro-2-hydroxy-quinolin-4-carboxy chloride

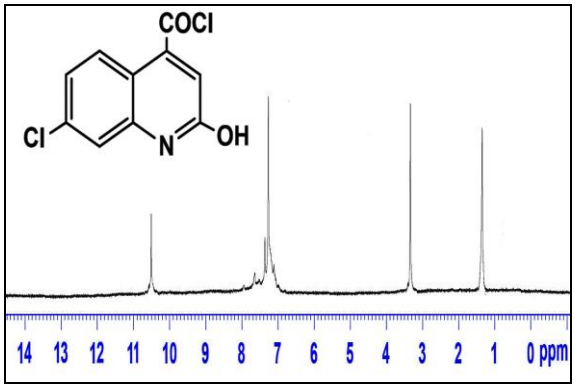


Fig.256-^{1}H-NMR spectrum of 7-chloro-2-hydroxy-quinolin-4-carboxy chloride

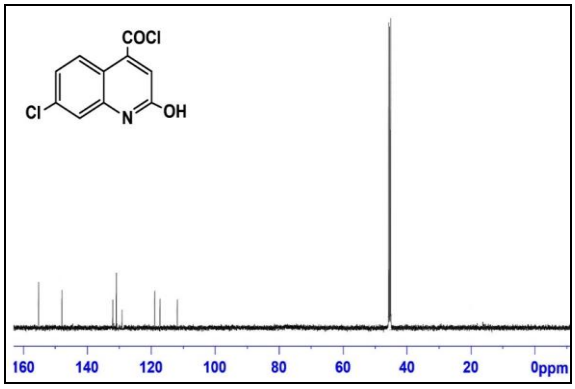


Fig.257-^{13}C-NMR spectrum of 7-chloro-2-hydroxy-quinolin-4-carboxy chloride

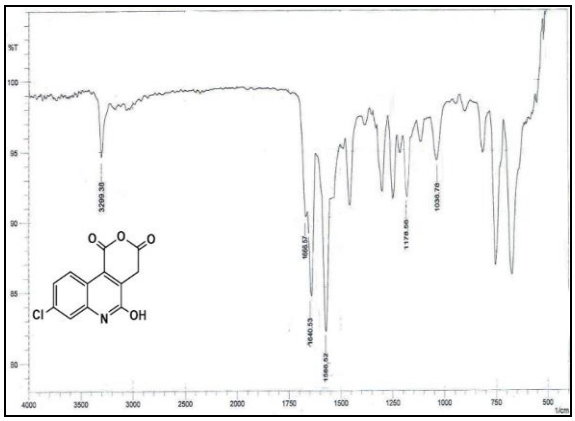


Fig.258-IR spectrum of 7-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

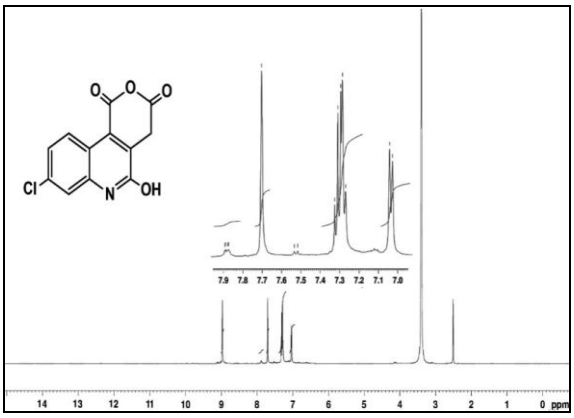


Fig.259-^{1}H-NMR spectrum of 7-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10--dione

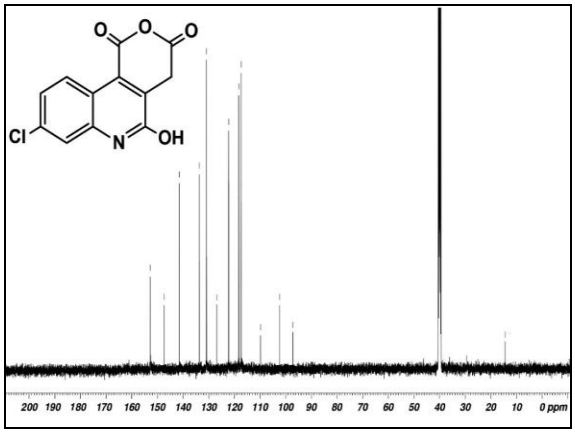


Fig.260-^{13}C-NMR spectrum of 7-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10--dione

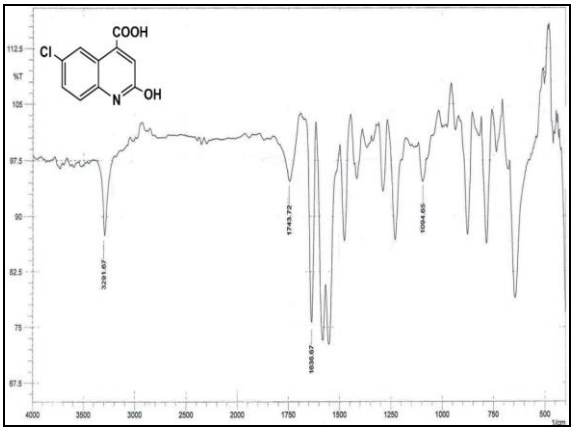


Fig.262-IR spectrum of6-chloro-2-hydroxy-quinolin-4-carboxylic acid

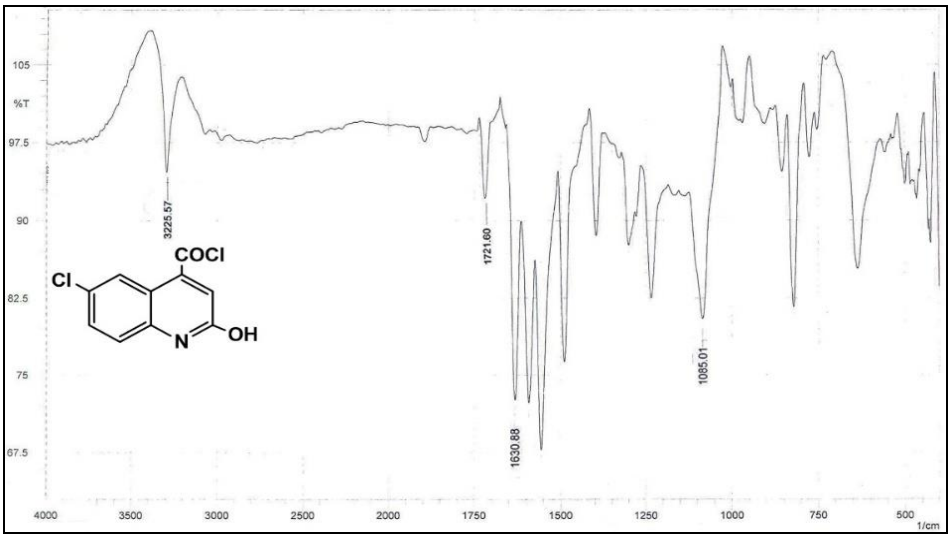


Fig.263-IR spectrum of 6-chloro-2-hydroxy-quinolin-4-carboxy chloride

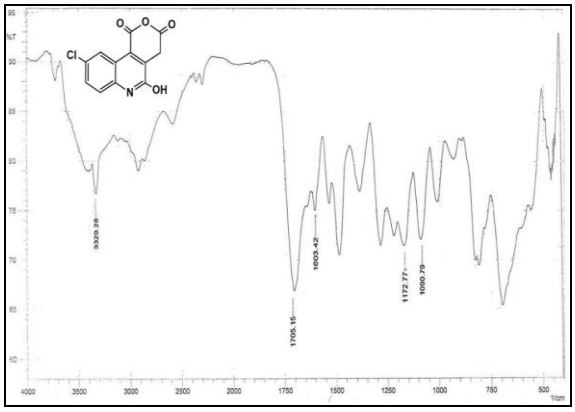


Fig.264-IR spectrum of 8-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

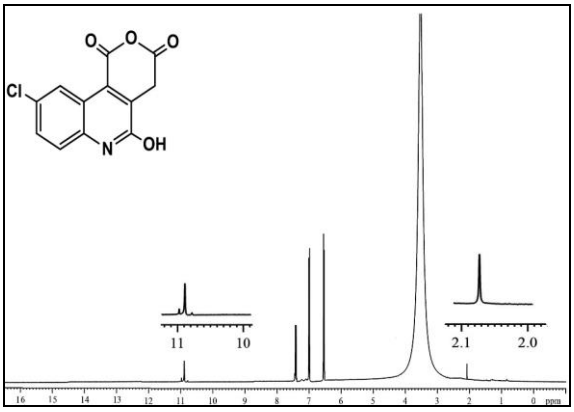


Fig.265-^{1}H-NMR spectrum of 8-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

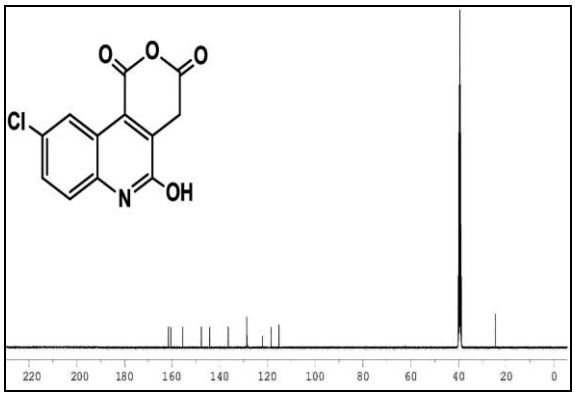


Fig.266-^{13}C-NMR spectrum of 8-chloro-4-hydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10- dione

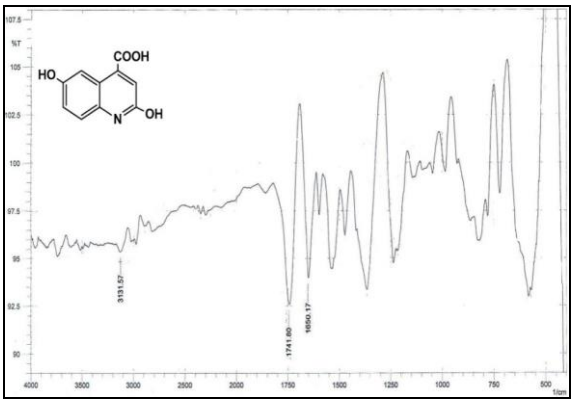


Fig.267-IR spectrum of 2,6-dihydroxy-quinolin-4-carboxylic acid

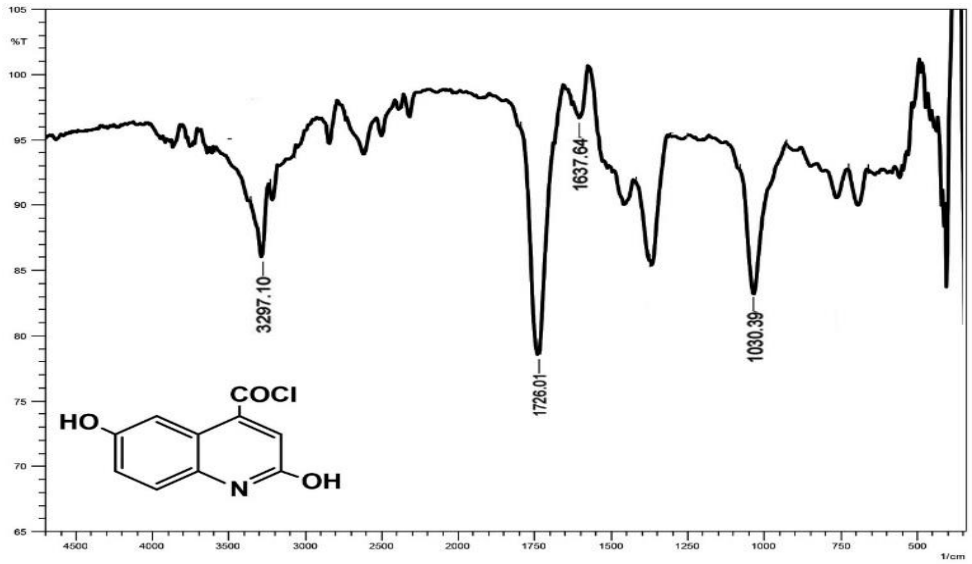


Fig.268-IR spectrum of 2,6-dihydroxy-quinolin-4-carboxy chloride

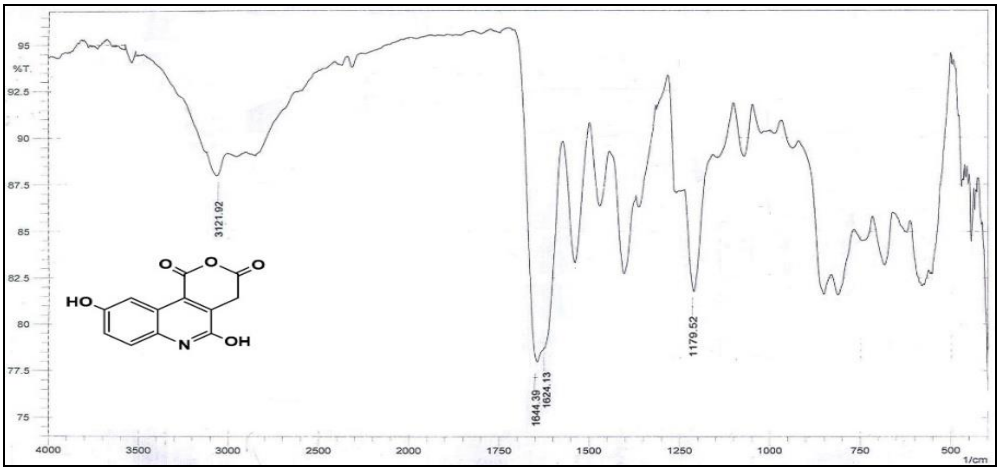


Fig.269-IR spectrum of 4,8-dihydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

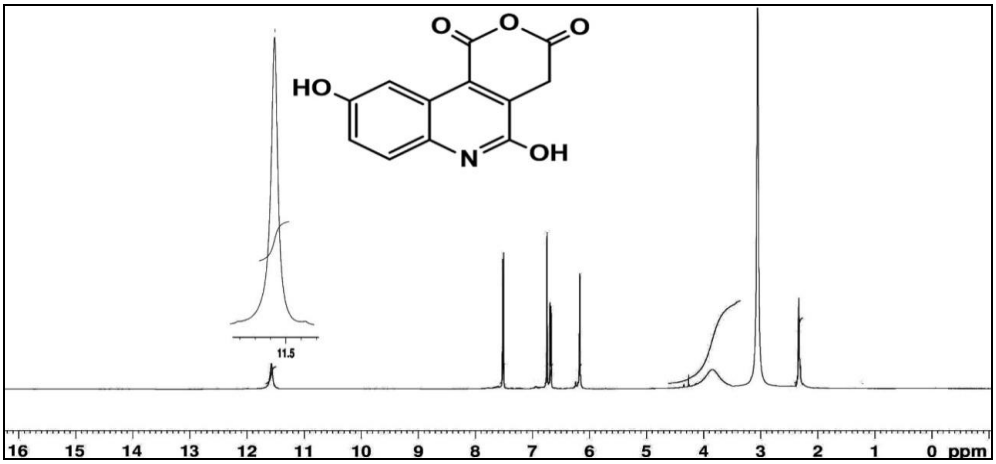


Fig.270-^{1}H-NMR spectrum of 4,8-dihydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

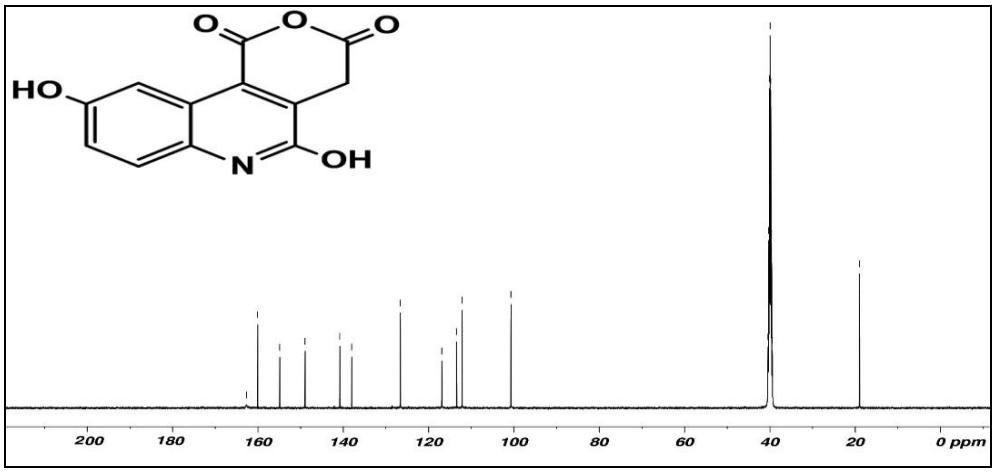


Fig.271-^{13}C-NMR spectrum of 4,8-dihydroxy-3*H*-pyrano-[4,3-*c*]-quinolin-1, 10-dione

References

1. Jun-Li Yang, Lei-Lei Liu, Yan-Ping Shi, *Planta Med*, **2011,**77, 271–276.
2. Vetrivel Nadaraj, Senniappan Tharmaraj Selvi, Helen Pricilla Bai, Sellappan Mohan, Thangaian Daniel Thangadurai, *Med. Chem. Res*., **2012**, 21, 2902-2910.
3. M.M. Ghorab, S.G. Abdel-hamide and Hala. A. Farrag, *Acta Polon. Pharmac. Drug Res*., **2001**, 58, 175-184.
4. Ahmed M. El-Agrody, Hisham S. M. Abd-Rabboh, Abdullah M. Al-Ghamdi, *Med. Chem. Res*., **2013**, 22, 1339-1355.
5. Narsidas J. Parmar, Rikin A. Patel, Bhagyashri D. Parmar, Navin P. Talpada, Bio. org *Med. Chem. Lett*, **2013,** 23, 656–1661.
6. Jose Marco-Contelles, Rafael Leon, Manuela G. Lopez, *Euro. J. Med. Chem*., **2006**, 41, 1464-1469.
7. M.Isaka, M.Tanticharoen, P.Kongsaeree, Y.Thebtaranonth, *J. Org. Chem*., **2001**, 66, 4803-4808.
8. J.J. Chen, P.H. Liao, C. H. Huang, S. Y. Chen. *J. Nat.Prod.*, **2007**, 70, 1444-1448.
9. F. Koizumi, N. Fukumitsu, J. Zhao, R. Chanklan, T.Miyakawa, S. Kawahara, S. Iwamoto, M. Suzuki, S. Kakita, E.S. Rahayu, S. Hosokawa, K. Tatsuta, M. Ichimura, *J. Antibiot*., **2007**, *60*, 455-458.
10. C. J. Magesh. S. V. Makesh. and P. T. Perumal, *Bioor. Med. Chem. Lett.*, **2004**, 14, 2035-2040.
11. Kai Schiemann, Dirk Finsinger, Frank Zenke, Christiane Amendt, Thorsten Knochel, David Bruge, Hans-Peter Buchstaller, Ulrich Emde, Wolfgang Stahle, Soheila Anzali, *Bio.org. Med. Chem. Lett*, **2010,** 20, 1491–1495.
12. Srinivas Kantevari, Thirumal Yempala, Govardhan Surineni, Balasubramanian Sridhar, Perumal Yogeeswari, Dharmarajan Sriram, *Euro. J. Med. Chem*, **2011,** 46, 4827-4833.
13. V.V.Mulwad, Manojkumar V Lohar, *Ind. J. Chem*., **2003**, 42B, 2568.
14. J.Marco-Contelles, R.Leon, M.G.Lopez, A.G.García, M.Villarroya, *Eur. J. Med. Chem*. **2006**, 41, 1464–1469.
15. I.Butenschon, K. Moller,W. Hansel, *J. Med. Chem*. **2001**, 44, 1249–1256.
16. K.P. Kalita, B.Baruah, P.J. Bhuyan, *Tetrahedron Lett*., **2006**, 47, 7779–7782.
17. Ahmed M. El-Agrody, Hisham S. M. Abd-Rabboh, Abdullah M. Al-Ghamdi, *Med Chem Res*, **2013,** 22, 1339-1355.
18. Wei Wang, Yu-Ling Li, and Xiang-Shan Wang, *ARKIVOC*, **2012**, (vi), 214-221.

19. Neha Sharma, Mrityunjaya Asthana, Durgesh Nandini, R.P. Singh, Radhey M. Singh, *Tetrahedron*, **2013,** 69, 1822-1829.

20. Sakineh Asghari, Samaneh Ramezani, Mojtaba Mohseni, *Chinese Chem. Lett.* **2014,** 25 431-434.

21. Ming-Qin Chang, Feng Gao, Yang Li, Wen-Tao Gao, *Chemical Papers,* **2013,** 67 (4), 437- 443.

22. Bhawana Singh, Atish Chandra, Seema Singh, Radhey M. Singh, *Tetrahedron*, **2011,** 67, 505-511.

23. Srinivasan Palaniappan, Boddula Rajender, Male Umashankar, *J. of .Mol. Catalysis A: Chemical*, **2012,** 352,70-74.

24. Ahmed M. El-Agrody, Essam Shawky A. E. H. Khattab, Ahmed M. Fouda, Abdullah M. Al-Ghamdi, *Med Chem Res,* DOI 10.1007/s00044-011-9965-x, 2012.

25. K. C. Majumdar, SudiptaPonra, Tapas Ghosh, *Tetrahedron Lett*., **2013,** 54, 5586-5590.

26. Kurosh Rad-Moghadam, Seyyedeh Cobra Azimi, EsmayeelAbbaspour-Gilandeh *Tetrahedron Lett*, **2013,** 54, 4633-4636.

27. K.C. Majumdar, SudiptaPonra, Tapas Ghosh, Ratan Sadhukhan, Utpal Ghosh *Euro. J. Med. Chem*, **2014,** 71, 306-315.

28. Abhijit Hazra, Yogesh P. Bharitkar, Arindam Maity, Shyamal Mondal, Nirup B. Mondal, *Tetrahedron Lett*, **2013,**54, 4339-4342.

29. Abdullah S. Al-Bogami, Tamer S.Saleh, Ehab M.Zayed, *Ultrasoni. Sonochem.*, **2013** 20,1194-1202.

30. Bhawana Singh, Atish Chandra, Shraddha Upadhyay, Radhey M. Singh, M. C. Puerta, Pedro Valerga, *Tetrahedron Lett*, **2008**, 49, 6423-6425.