Research Article

Synthetic Studies on [2, 6]Naphthyridine Compounds and its Derivatives – Synthesis of 5-Hydroxybenzo [*c*][2,6]Naphthyridine 1,4-dione

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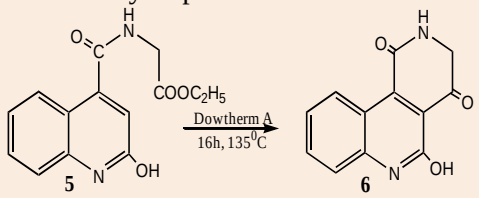
Abstract

A new route was evaluated for the synthesis of 2-oxo quinoline-4-carboxylic acid from 2-oxo 4-methyl quinoline, which could be a potential precursor for the synthesis of 5-hydroxybenzo [*c*] [2, 6] naphthyridine 1, 4-dione, and its derivatives. 2-oxo quinoline-4-carboxylic acid obtained by oxidation, then converted to 5-hydroxybenzo [*c*][2,6]naphthyridine 1,4-dione using Dowtherm A. Thus a new methodology has been worked out for the synthesis of [2, 6] benzo[*c*]naphthyridines.

Keywords: 2-oxo quinoline-4-carboxylic acid, 2-oxo 4-methyl quinoline, *N*- (Carbethoxy methyl)-2-hydroxyquinoline 4-carboxamide , dichloro benzo[*c*][2,6]naphthyridine, 5-hydroxy benzo [*c*] [2,6]naphthyridine 1,4-dione and Dowtherm A.

The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, Mass spectra and elemental analysis. Compounds (6, 6a, 6b) were screened for their antibacterial activity against, Salmonella species, Escherichia coli and Aeromonas hydrophila**.**



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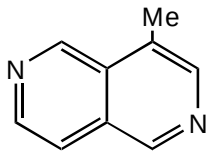
Introduction

Nitrogen hetero cycles possess a wide spectrum of antimicrobial and anti-pharmaceutical activities. Among the nitrogen hetero cycles naphthyridines and their derivatives possess vital importance in the field of medicinal chemistry. Naphthyridine derivatives were also used for the diagnosis and therapy of diseases of human including AIDS for combating exo and endo parasites in agriculture and in cattle breeding.2,6- naphthyridine (I) was isolated from the aerial parts of antirrhinum species and aronticus also possess potent antimicrobial activities[1]



I

4-methyl[2,6]naphthyridine

Scheme 1

Our first attempt to Synthesis of 2-oxo-4-formylquinoline from 2-oxo-4-methylquinoline was tried with (i) SeO_2-oxidation method[2-4], (ii) Using I_2/DMSO[5], (iii) DMSO with 2-oxo-4-bromomethyl quinoline[6-7] and (iv) Using DDQ in dioxane[8] with 2-oxo-4-hydroxymethyl quinoline. SeO_2 oxidation method resulted the formation of 2-oxo

quinoline-4-carboxylic acid. Since all the attempts made for synthesis of aldehyde were failing to give the expected 2-oxo-4-formylquinoline, but gave 2-oxo quinoline-4-carboxylic acid as a product.
This was explored for the synthesis of novel naphthyridines. During the investigations of the above reactions, we observed that the conversion of 2-oxo-4-methylquinoline (2) to 2-oxo-quinoline-4-carboxylic acid (3) can be done smoothly. So we intend to prepare the 2-oxo-quinoline-4-carboxylic acid (3), which could be a precursor for the synthesis of 2, 6-naphthyridines.

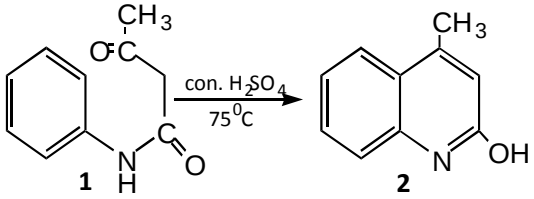
Benzo[*c*][2,6]naphthyridine and their derivatives were confirmed by spectral and analytical data. Biological screening of few of the selected compounds showed promising antibacterial activities.

Experimental Analysis

Purification of the crude samples was carried out using chromatographic columns packed with silica gel. TLC was performed by using silica gel. Petroleum ether and ethyl acetate were used as irrigant.IR Spectra were recorded on Shimadzu FT IR PC (S) 8201 spectrophotometer using KBr disc and absorption frequencies quoted in reciprocal centimeters. NMR Spectra were taken on AMX-400(400MHz) spectrophotometer using TMS as internal reference. The chemical shifts are expressed parts per million.The mass spectra were determined on a Autospec EI+ mass spectrophotometer. The solvents and reagents used for the synthesis were of reagent grade and purified by standard methods.

Results and Discussion

Firstly, the acetoacetanilide (1) was cyclised to 2-oxo-4-methylquinoline (2).The cyclisation was carried out by adding acetoacetanilide (1) (0.012 mol) in portions to con.sulphuric acid (0.001 mol) by maintaining the temperature not above 75 ^{o}C. After the complete addition of acetoacetanilide (1), the reaction mixture was heated at 95 ^{o}C for half an hour. Then the reaction mixture was cooled and poured into crushed ice, filtered and dried. The crude obtained was recrystallised from methanol [10].m.pt:208^{o}C.

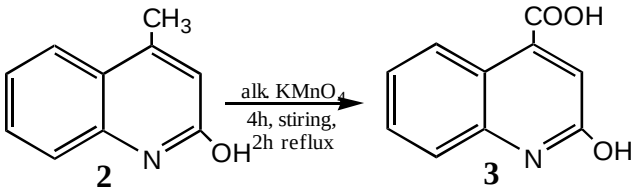


Scheme 2

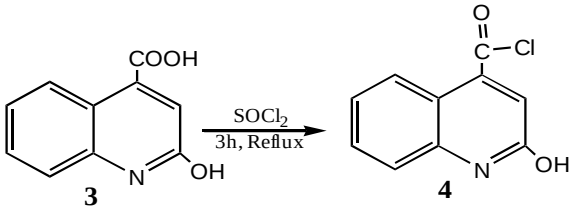
2-oxo-4-methylquinoline (2) was oxidized by alk. $KMnO_4$ [11] resulting in the formation of 2-oxo-quinoline-4-carboxylic acid (3), which was then converted into 2-oxo-quinoline-4-carbonyl chloride(4). To 1.5g (0.0094 mol) of 2-oxo-4-methylquinoline (2) in water, 2.84g (0.018 mol) of alk. $KMnO_4$ was added with stirring for 4 hours and kept on the water bath for 2 hours till the colour of the mixture changes to brown. The reaction was then filtered and neutralized with 1:1 hydrochloric acid. The precipitate formed was washed with water and dried and recrystallised from hot water.IR (KBr) spectrum of the compound (3) showed absorption bands at 1707 cm^{-1} for (C=O) of acid, and 3067 cm^{-1}, 3200 cm^{-1} for (-OH) group, 1656 cm^{-1} for (C=N). MS: 188.25 (M+ 100) .
The compounds gave effervescence with sodium bicarbonate and red colour with neutral ferric chloride. Elemental analysis of the compound confirms the molecular formula of the compound to be $C_{10}H_7NO_3$. This confirms the formation of acid namely 2-oxo-quinoline-4-carboxylic acid (3). The reaction was extended to their derivatives.

To 1g (0.0053 mol) of acid (3), 0.077mL (0.016 mol) thionyl chloride was added and refluxed on a water bath. After the reaction excess thionyl chloride was removed by co distillation with benzene. IR (KBr) absorption

bands of compound (4) at 3307 cm^{-1} for (OH) group and 1649 cm^{-1} for (C=O). A peak at 1031 cm^{-1} for (C-Cl). The disappearance of band at 1707cm^{-1} confirms the formation of acid chloride. The reaction was extended to their derivatives.

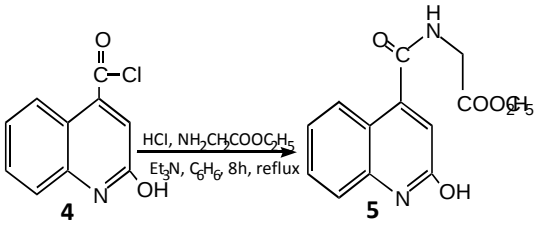


Scheme 3



Scheme 4

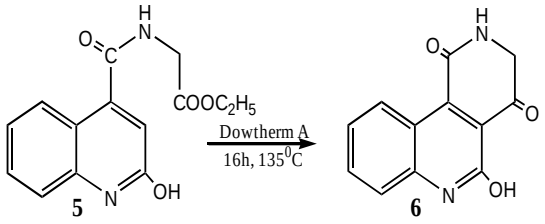
Though the reaction was expected to be tough since it involves the condensation of two acidic moieties, we thought that the use of tri ethyl amine which is an excellent acid quenches would result in the successful condensation of the reactants into *N*- (carbethoxy)-2-hydroxyquinoline-4-carboxamide (5). Accordingly tri ethylamine was maintained 2-5 times than that of carbonyl chloride. To 1g (0.0054 mol) of acid chloride (4) in benzene 0.547g (0.00464 mol) of ethyl glycinate hydrochloride and triethylamine were added and refluxed on a water bath for 6-8 hours. TLC monitored the reaction. After the completion of the reaction, the reaction mixture was poured into crushed ice, and extracted with benzene. The organic layer thus separated was washed with water, dried over anhydrous sodium sulphate. Evaporation of excess solvent resulted in a gummy product with an yield of 60%. IR spectrum of the compound (5) showed absorption bands at 1748cm^{-1} (C=O) of (-$COOC_2H_5$), 1662 cm^{-1} for (-CONH) group, 1618 cm^{-1} for (C=N) group, 2884 cm^{-1} for NH group and 3624 cm^{-1}, 3685cm^{-1} for (-OH) group. MS: 274.19 (M+1). The elemental analysis of the compound (5) was found to be $C_{14}H_{14}N_2O_4$.



Scheme 5

The spectral and analytical data confirmed the compound (5) to be *N*-(carbethoxy)-2-hydroxyquinoline-4-carboxamide (5). The reaction was extended to their derivatives. Then we thought that to achieve the targeted compound *viz.*., benzo[*c*][2,6]naphthyridine 1,4-dione. "Dowtherm A" would be a better reagent for cyclisation.

Accordingly, the condensed product (5) *N*-(carbethoxy)-2-hydroxyquinoline-4-carboxamide was added in to refluxing "Dowtherm A" [Eutectic mixture of biphenyl and Biphenyl oxide (27.5%and 72.5%)] at temperature 135^oC and 16 hours the reaction continued, the reaction was monitored by using TLC. After the completion of the reaction, the resulting mixture was washed well with petroleum ether, which resulted in a brown solid. m.pt:180^0C.



Scheme 6

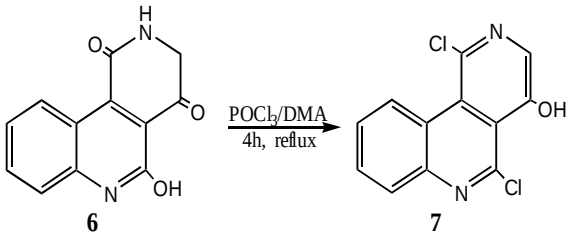
IR spectrum of the compound (6) showed bands at 1657 cm^{-1} for (C=O) group, 1554$cm^{-1}$for (C=N) group, 3415 cm^{-1} for (-OH) group, 2813 cm^{-1} for (NH) group and the disappearance at 1748 cm^{-1} corresponding to ester shows the cyclisation.

^{1}H-NMR spectrum of the compound (6) showed signal at δ 2.6 (s, 2H, -CH_2), δ 12.2 (s, NH) unresolved multiplets δ 7.2-7.7 (m, 4H, Ar-H), δ 6.6(s,OH). MS: 228.17(M+,100). The elemental analysis of the compound (6) was found to be $C_{12}H_8N_2O_3$.From the analytical and spectral data the compound was confirmed to be 2-hydroxybenzo[*c*][2,6] naphthyridine 1,4-dione (6). The reaction was extended to their derivatives (6a, 6b)

2-hydroxy 5- methoxy benzo [*c*] [2,6] naphthyridine (2H)-3-dihydro 1,4-dione(6a) IR: 1655.6 cm^{-1}(-CONH),2919 cm^{-1}(NH-CO), 3413 cm^{-1}(OH). ^{1}H-NMR spectrum of the compound (6a) showed signal δ 2.5 (s, 2H, CH_2), 6.5 (s, OH) ,δ 7.1-7.3 (m, 4H, Ar-H) δ11.3((s, NH).MS: 258.18 (M+, 93). The elemental analysis of the compound (6) was found to be $C_{13}H_{10}N_2O_4$.

2-hydroxy 7- methyl benzo [*c*] [2,6] naphthyridine (2H)-3-dihydro 1,4-dione(6b)
IR: 13651 cm^{-1}(-CONH),2922 cm^{-1}(NH-CO), 3319 cm^{-1}(OH), ^{1}H-NMR : δ 2.6 (s, 2H, CH_2), 6.4 (s, OH) ,δ 7.1-7.5 (m, 4H, Ar-H) δ11.1((s, NH). MS: 242.17 (M+,78). The elemental analysis of the compound (6) was found to be $C_{13}H_{10}N_2O_3$.

The aromatization of 5-hydroxybenzo[*c*][2,6] naphthyridine1,4-dione (6), using $POCl_3$ and Dimethyl aniline was also attempted. To 0.1g of 5-hydroxybenzo[*c*][2,6]naphthyridine[2H] 3-dihydro 1,4dione (6), 2mL of $POCl_3$ and 1 drops of *N,N*- dimethyl aniline was added refluxed on a water bath for about 4 hours. After the completion of the reaction, the reaction mixture was poured into crushed ice, the solid separated was washed with water, dried and recrystallised from methanol. m.pt: 167 ^oC.



Scheme 7

The product obtained answer for the presence of chlorine, IR spectrum of the compound (7) showed bands at, 1102 cm^{-1} & 1151 cm^{-1} for (C-Cl), 3404 cm^{-1} for (-OH), 2372 cm^{-}1 for (C=C stretching). Elemental analysis of compound (7) confirms the formula to be $C_{12}H_6N_2OCl_2$. From the above spectral and analytical data the compound (7) was confirmed to be 1,5-dichloro benzo[*c*][2,6]naphthyridine.

The reaction sequence has been extended to synthesis the derivatives of 5-hydroxybenzo[*c*][2,6] naphthyridine[2H] 3-dihydro 1,4-dione.

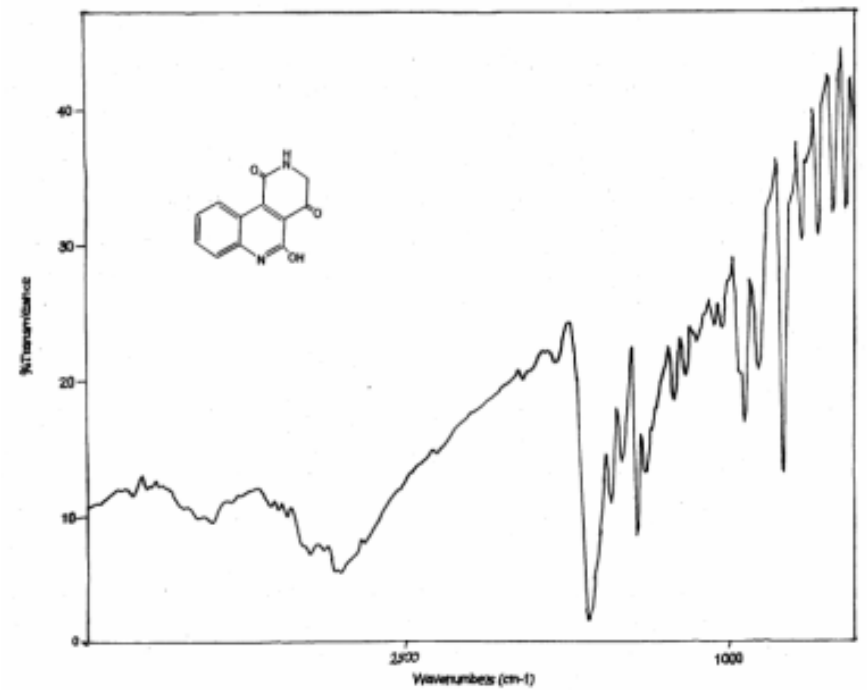


Figure 1 FTIR spectrum of 5

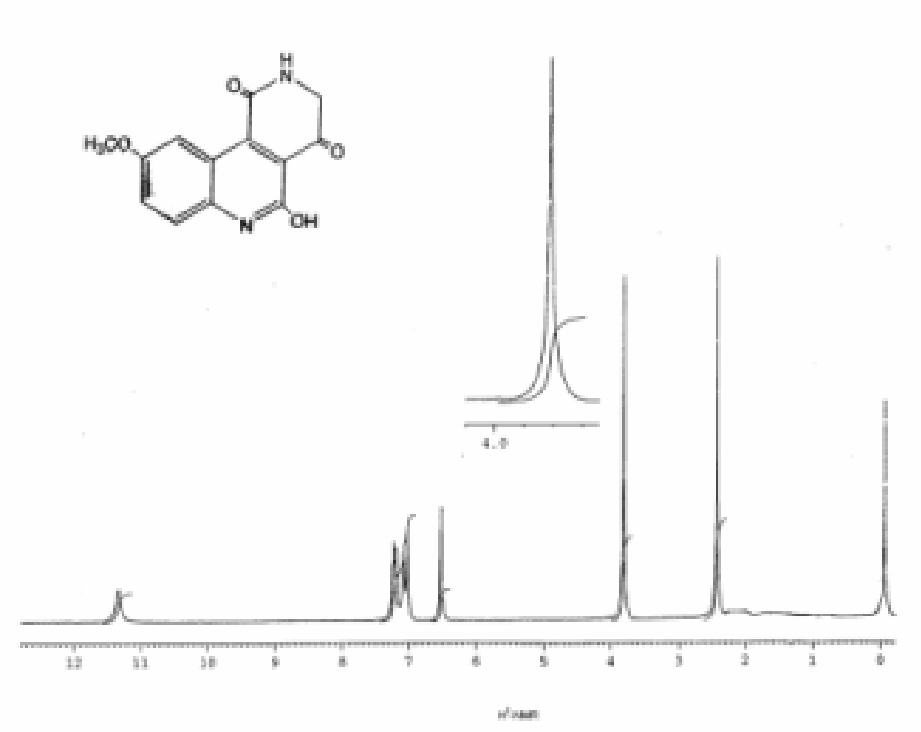
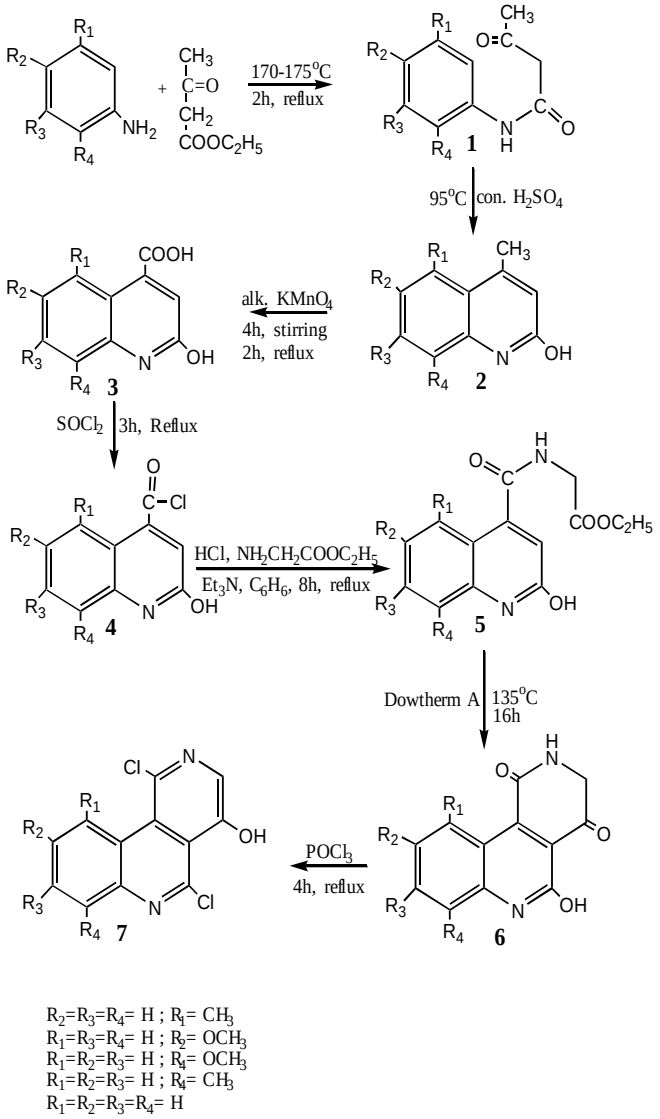


Figure 2 ^{1}H NMR spectrum of **5**



Scheme 8

General preparation methods

Preparation of acetoacetanilides (1)

Aniline (0.01 mol) was added drop wise to the preheated ethyl acetoacetate (0.04 mol) with constant stirring for about 30 minutes, kept at 170 – 175°C. The heating was continued for another 2 hours. Then the mixture kept on ice for overnight. The resulting residue was washed with petroleum ether and recrystallized from petroleum ether and benzene.

Preparation of 2–hydroxy 4–methylqunioline (2)

Acetoacetanilide (0.0123 mol) was added in portions to conc. sulphuric acid (0.001 mol) (the temperature not exceeding 75°C) at 75°C. After the complete addition of acetoacetanilide, the reaction mixture was heated 95°C for 2 hours. After the completion of the reaction, the reaction mixture was cooled, poured into crushed ice, filtered and dried.

Preparation of 2-hydroxyquinoline 4-carboxylic acid (3)

2-Hydroxy 4-methylquinoline (0.01 mol) was stirred well with water (40mL). Alkaline $KMnO_4$ (0.02 mol) in 10% NaOH was added slowly. The flask was surrounded by hot water and stirring continued for 3-4hours. After the last addition of $KMnO_4$ is decolorized, raise the temperature at 85^oC. Thereafter, the reaction mixture was filtered. The filtrate was neutralized with 1:1 HCl, the acid formed was filtered and dried.

Preparation of 2-hydroxyquinoline 4-carbonyl chloride (4)

2-Hydroxy quinoline 4-carboxlic acid (0.01 mol) and thionylchloride (0.02 mol) was refluxed on a water bath, for 3 hours. After 3 hours excess thionylchloride was removed by Co-distillation with benzene and the carbonyl chloride was taken in dry benzene.

Preparation of *N*-(Carbethoxy methyl)-2- hydroxyquinoline 4-carboxamide (5)

To the solution of 0.01 mol of carbonyl chloride in benzene, 0.01 mol of ethyl glycinate hydrochloride and 0.025 mol of triethyl amine were added and refluxed on a water bath for about 8-10 hours. The reaction monitored by TLC, after the completion of the reaction, the reaction mixture was poured into crushed ice and extracted with benzene. The solvent from the organic layer is removed by distillation. The obtained product is purified by column chromatography using petroleum ether and ethyl acetate.

Cyclisation of *N*-(Carbethoxy methyl)-2-hydroxyquinoline-4-carboxamide (6)

N-(Carbethoxy methyl)-2-hydroxyquinoline-4-carboxamide was added to a solution of refluxing Dowthem A (2 mL) (Eutectic mixture of 26.5% biphenyl and 73.5% diphenyl oxide). The mixture was then refluxed at 135^oC for 16 hours. The proceeding of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture cooled and on washing with petroleum ether thoroughly, results in a brown residue, which on column chromatography with petroleum ether and ethyl acetate, yielded an amorphous yellow coloured powder

Preparation of dichloro benzo[*c*][2,6]naphthyridine(7)

A mixture of 0.05 mol of benzo[*c*][2,6]napthyridine-1,4-dione, 5 mL of $POCl_3$ and 3 drops of *N*,*N*-dimethyl aniline was refluxed on a water bath for about 4 hours. Then the reaction mixture was poured into crushed ice, the solid was filtered and washed with water and dried.

Table 1 Physical data of the compounds (6, 6a, 6b)

Title Compound	**2-hydroxy benzo [*c*] [2,6] naphthyridine (2H)-3-dihydro 1,4-dione(6)**			**2-hydroxy 5- methoxy benzo [*c*] [2,6] naphthyridine (2H)-3-dihydro 1,4-dione(6a)**			**2-hydroxy 7- methyl benzo [*c*] [2,6] naphthyridine (2H)-3-dihydro 1,4-dione(6b)**		
Parent compound	*N*-(Carbethoxy methyl)-2-hydroxyquinoline 4-carboxamide			*N*-(Carbethoxy methyl)-5- methoxy 2-hydroxyquinoline 4-carboxamide			*N*-(Carbethoxy methyl)- 7-methyl 2-hydroxyquinoline 4-carboxamide		
Yield	62.5%			62.5%			83%		
Melting point	180^{0}C			185^{0}C			Above 260^{0}C		
Molecular Formula	$C_{12}H_8N_2O_3$.			$C_{13}H_{10}N_2O_4$.			$C_{13}H_{10}N_2O_3$.		
Molecular Weight	228.17			258.18			242.17		
Elemental Analysis	% C	% H	% N	% C	% H	% N	% C	% H	% N
Calculated	63.16	3.5	12.27	60.47	3.9	10.84	64.47	4.2	11
Found	63.09	3.10	11.68	60.04	3.61	9.96	63.91	3.86	10.62

Antibiogram

Antibacterial activities of compounds (6, 6a, 6b) were screened for their in invitro growth inhibitory activity against, Salmonella species, Escherichia coli and Aeromonas hydrophila(Table-2)**.** The compound (6) showed moderate activity against Salmonella species, Aeromonas hydrophila and is inactive towards Escherichia coli. The compound (6a) is active towards all three species and their derivatives are good when compared to the other tested compounds. The compound (6b) is active towards all bacterial, but their activities are enhanced. The anti bacterial activities of the compounds were found to be reasonable against all bacteria. The enhanced activity of compounds (6a) and (6b) might be due to the substitution of methoxy and methyl groups in quinoline ring respectively**.**

Table 2 Antibacterial activities of the compounds (6, 6a, 6b)

	Diameter of inhibition zone in mm								
Antibiogram	25 µ/ml	50 µ/ml	100 µ/ml	25 µ/ml	50 µ/ml	100 µ/ml	25 µ/ml	50 µ/ml	100 µ/ml
Escherichia coli	11	12	11	-	-	16	12	13	15
Aeromonas hydrophila	-	-	12	13	13	16	-	-	12
Salmonella species	11	11	11	-	-	17	12	14	18

Conclusion

Benzo[c][2,6]naphthyridine and their derivatives were confirmed by spectral and analytical data(Table-1). Biological screening of few of the selected compounds showed promising antibacterial activities (Table-2)

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