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A FACILE APPROACH FOR THE SYNTHESIS OF QUINOLINE-4-CARBOXYLIC ACID DERIVATIVES AND ITS ANTICANCER EVALUATION

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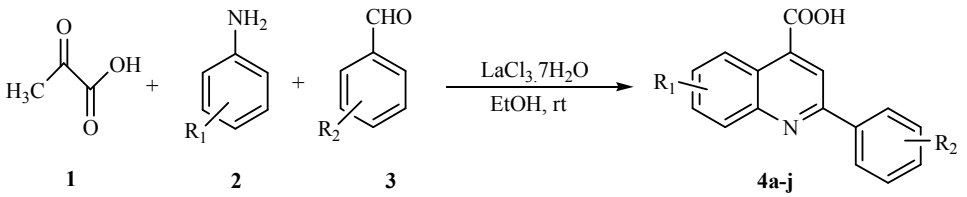
Abstract: An effective methodology was established using lanthanum chloride as catalyst to obtainedquinoline-4-carboxylic acid derivatives under ambient temperature condition. The synthesis of quinoline-4-carboxylic acids has been achieved *via* one-pot reaction of pyruvic acid, anilines and aromatic aldehyde using lanthanum chloride as catalyst in solvent ethanol. All the synthesized derivatives were evaluated for inhibition of cancer cell. The initial assays reveals that some of the newly synthesized compounds displayed significantly good inhibition activities against human breast cancer cell (MCF-7), cell lines compared with the control (Adriamysin), which might be developed as novel lead scaffold for potential anticancer agents.

Keywords: Anticancer activity, Quinoline-4-carboxylic acid, Aromatic aldehyde, Lanthanum chloride, Pyruvic acid.

Introduction:

Nitrogen containing heterocycles are abundant in nature and reveal a variety of significant chemical and biological activities. Among them quinoline derivatives characterize a major class of heterocyclic compound and several preparations have been recognized since the late 1800s. The quinoline ring system occurs in a number of natural products, especially in alkaloids. Quinoline moiety is very concerned owing to their broad spectrum as anti-cancer,[I-II] anti-malarials,[III-VI] antibacterial,[VII-VIII] anti-microbial,[IX] anti-fungal,[X-XI] and use as an inhibiting agent.[XII]

There are various synthetic methods are reported in literature for the synthesis of quinoline-4-carboxylic acid derivatives under several conditions such as microwaves,[XIII] ytterbium perfluorooctanoate catalyzed,[XIV] and base catalyzed.[XV] Many of these methods proceeded in presence of catalyst and required long reaction time, low yields, large amount of organic solvent, harsh reactions conditions and extensive workup procedure. Therefore herein, we have developed a lanthanum chloride catalyzed synthesis of quinoline-4-carboxylic acids by the one-pot reaction of pyruvic acid, anilines and aromatic aldehyde in solvent ethanol at room temperature condition (**Scheme1**).



1 **2** **3** **4a-j**

Scheme1

Experimental

All solvents were employed as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (100-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ solvent.

General procedure for the synthesis quinoline-4-carboxylic acid derivatives: In 50ml round-bottom flask, a mixture of pyruvic acid (1.2 mmol), amine (1.1 mmol), and aromatic aldehyde (1.0 mmol) were added in 20 ml ethanol. Further (10 mol %) lanthanum chloride as catalyst was added to the reaction mixture. This mixture was then stirred at room temperature for appropriate time (Table2). After the completion of reaction indicated by TLC, the resulting solid was collected by filtration and dissolved in 20 ml dichloromethane and combined organic layer was dried over anhydrous calcium chloride and filtered. Evaporation of the solvent afforded crude product which was purified by column chromatography with pet ether and ethyl acetate (4:1) to give pure product.

2-(4-Chlorophenyl)-6-methylquinoline-4-carboxylic acid (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37(s, 3H), 7.12-7.21 (m, 4H), 7.42-7.45(d, 2H), 7.82-7.84 (d, 2H), 8.43 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 120.9, 122.8, 128.3, 129.1, 129.9, 130.0, 132.1, 135.0, 136.2, 137.3, 149.2, 158.0, 168.2.

2-(2-Chlorophenyl)-7-nitroquinoline-4-carboxylic acid (4f): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.38 (d,1H) ,7.40-7.47 (m, 2H), 7.53-7.61 (m,2H), 8.07-8.14 (m, 2H), 8.24-8.26 (d, 1H), 8.95 (s, 1H); ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.1, 121.0, 123.8, 125.9, 127.4, 127.5, 128.9, 130.1, 130.3, 132.6, 133.1, 136.7, 145.8, 153.1, 159.3, 168.8.

Results and discussion

Herein an effective approach was developed for the synthesis of quinoline-4-carboxylic acid derivatives using lanthanum chloride as catalyst under room temperature condition. Initially for the optimization study, we screened the various solvent on the model reaction of pyruvic acid, 4-methyl aniline and 4-chloro benzaldehyde using 10 mol % catalytic amount of lanthanum chloride at room temperature condition. The polar protic solvents ethanol and methanol were found to be the good solvent for the reaction particularly ethanol. In the solvent methanol, product 4c was obtained in 69% yield within reaction time 5h (Table 1, Entry 1). The reaction performance improved when reaction carried out in solvent ethanol which afforded excellent 91 % yield within reaction time 2 hours (Table 1, Entry 2). Furthermore the reaction in the solvent acetonitrile and water afforded 52% and 30 % yields with longer reaction time (Table 1, Entries 3 and 4 respectively).In the solvents toluene and dichloromethane, the corresponding product 4c was obtained in lower yield with extended reaction time (Table 1, Entries 5 and 6 respectively). Afterward, we investigated the influence of catalytic loading on the model reaction with ethanol as solvent. At the catalytic loading of 5 mol % of catalyst, the reaction offered 78% yield of the corresponding product 4c (Table 1, Entry 7).

In our investigation, the best result for the reaction was observed at the catalytic loading of 10 mol % of the catalyst lanthanum chloride in solvent ethanol. The reaction was completed within 2 hours and afforded the product in excellent yield of 90% (Table 1, Entry 2). Further increase in the catalytic loading up to 15 mol % did not show significant progress in the yield even with extended reaction time (Table 1, Entry 8). To ensure the necessity of the catalyst in the reaction, the model reaction was carried out without catalyst in solvent ethanol. The reaction was completed with extended reaction time 18 hours but poor yield of product was the observed (Table 1, Entry 9).

Table 1. The screening of solvent and catalytic loading on the synthesis of quinoline-4-carboxylic acid derivatives

Entry	Solvent	$LaCl_3.7H_2O$ (mol %)	Time(h)	Yield[a] (%)
1	Methanol	10	5	69
2	**Ethanol**	**10**	**2**	**91**
3	Acetonitrile	10	10	52
4	Water	10	16	30
5	Toluene	10	14	34
6	DCM	10	14	38
7	Ethanol	5	4	78
8	Ethanol	15	2.5	88
9	Ethanol	-	18	26

[a]Isolated Yield

Optimistic by these noteworthy results, we screened a variety of aromatic aldehyde for the synthesis of corresponding quinoline-4-carboxylic acid derivatives. We observed that all products were obtained with good to excellent yields (Table2, Entries 1-10).

Table 2: An efficient synthesis of quinoline-4-carboxylic acid derivatives catalyzed by lanthanum chloride

Entry	Amine (R_1)	Aldehyde (R_2)	Products(4a-j)	Time (h)	Yield[a] (%)
1	H	4-Cl	4a	4.30	87
2	4-CH_3	4-NO_2	4b	4.00	86
3	4-CH_3	4-Cl	4c	2.00	91
4	4-Cl	3-NO_2	4d	3.20	88
5	2-NO_2	2-Cl	4e	4.45	87
6	3-NO_2	2-Cl	4f	4.50	92
7	4-Br	2-Cl	4g	4.55	88
8	4-Cl	4-Cl	4h	3.00	84
9	4-Cl	2-Cl	4i	3.00	87

10	4-Br	4-OCH_3	4j	4.00	86

[a]Isolated yield

Anticancer activity

The potent anticancer activity of various heterocycles derivatives of quinoline have studied by various researchers which targets specifically on sites like farnasyl transferase, protein kinase CK-II , telomerase, topoisomerase I, Src tyrosine kinase, etc. Vittorio Caprio *et al.* have synthesized Indole fused 10H-indolo[3,2-b]quinoline bearing bis-dimethylaminoethyl chain when evaluated for anticancer activity it show inhibition telomerase with IC_{50} of 16Um.[XVI] The invitro anticancer studied of Various pyrazolo[3,4-b]quinoline ribofuranosides synthesised by Ronald Wolin *et al.* have ability to inhibit the nucleotide exchange process on oncogenic Ras gene.[XVII] The new derivatives of 2-phenyl quinoline having [(2- aminoethyl)aminomethyl] group synthesised by YuziMikata *et al.* shows the ability to intercalate into double stranded DNA and thus prevent the cancer cells from proliferation.[XVIII] The similar DNA binding activity was also shown by Pyridine fused pyrido[3,2-g] quinoline derivative synthesised by Sharples D *et al.*[XIX] In the same way Yanong D W *et al.* have developed the moiety with 4-anilino-3-cyanoquinolines having Src Tyrosine Kinase inhibition with IC_{50} of 5.3Um.[XX] Charles Z. Ding *et al.* have designed and synthesised A series of 3-imidazolymethylaminophenylsulphonyl tetrahydro quinoline which act as FTI (farnesyl transferase inhibitors) was found to be most active with $FTIC_{50}$ of 0.13 Um.[XXI] Likewise The compound 6-hydroxy-10- chlorobenzo[c]quinololizinum synthesized by Y. Mettey *et al.* found to be Inhibitors of protein kinase CK-II with IC50 0.005 Um.[XXII]

Material and methods

In vitro MTT assay for Anticancer activity

MTT is a quantitative colorimetric assay which is based on the phenomenon of enzymatic reduction of MTT dye [(3-(4,5-dimethylthiazol -2-yl)-2,5-diphenyl tetrazolium bromide)]. MTT is a pale yellow substrate that is reduced by living cells to yield a dark blue formazan product. This process requires active mitochondria, and even freshly dead cells do not cleave significant amount of MTT. Thus the amount of MTT cleaved is directly proportional to the number of viable cells present, which is quantified by colorimetric methods. The antiproliferative activities of the compounds on MCF-7 breast cancer cells were determined using MTT assay was performed at Deshpande Laboratories, Bhopal using the standard operating procedures. The assay provides a direct relationship between the cell viability and color formation (absorbance). Among the10 synthesized compound, the compound 3D (4c) and 6D (4f) with high yield of 90 and 91% respectively were studied for anticancer activity. Briefly the compounds were dissolved in DMSO at a concentration of 0.1% and serially diluted with complete medium to get the concentrations a range of test concentration (i.e. 0.001, 0.01, 0.1, 1.0 and 10uM). MCF-7 breast cancer cells maintained in appropriate conditions were seeded in 96 well plates and treated with different concentrations of the test samples and incubated at 37°C humidified, 5% CO_2 for 96 hours. MTT reagent was added to the wells and incubated for 4 hours; Supernatant from each well containing the dark blue formazan product formed by the cells was carefully removed was dissolved in 100ul of DMSO under a safety cabinet and absorbance was read at 550nm by UV-Visible spectrophotometer to determine the cell viability. Percentage inhibitions were calculated using following formula and plotted against the concentrations used to calculate the IC_{50} values (Table 3).

$$\% \textbf{ cell inhibition} = \frac{(\textbf{OD control} - \textbf{OD treated})}{\textbf{OD control}} \times \textbf{100}$$

Results

The synthesized quinoline-4-carboxylic acid derivatives were tested for *in vitro* anticancer activity against MCF7 (human breast cancer) cells using MTT reduction assay. The anticancer drug Adriamysin was used as reference standard. The compounds studied for anticancer activity only compounds 3D (4c) and 6D (4f) was found to be the most potent with IC_{50} values of 6 and 3uM **Figure 1** respectively against MCF-7 cell line. In comparison to the derivative 3D (4c), compound 6D (4f) showed two fold greater anti-proliferative potency against MCF-7 cell growth inhibition clearly indicating that the growth inhibitory activity of quinoline-4-carboxylic increases drastically when 4-methyl and 4-Chloro were substituted by 3-Nitro and 2-Chloro at R_1 and R_2 position respectively which benefits anticancer activity.

Table 3: IC50 values for synthesized derivatives against cell line MCF7.

Drug Concentration(mg/ml) / **Compound**	**0.001**	**0.01**	**0.1**	**1**	**10**	**IC-50**
4a	1.52	5.98	16.27	23.69	42.05	11.32
4b	1.05	3.28	15.04	24.36	39.35	12.03
4c	1.59	2.39	13.28	23.62	58.96	6.21
4d	1.72	2.98	12.65	24.58	37.92	12.46
4e	1.85	3.56	10.56	23.24	34.25	13.76
4f	2.11	6.35	21.62	32.58	68.95	3.97
4g	2.02	6.56	13.58	25.02	37.85	12.47
4h	1.98	7.01	13.20	24.25	33.02	14.19
4i	1.15	6.95	14.35	23.64	34.06	13.80
4j	1.25	5.01	14.20	26.04	41.89	11.33
ADR	11.41	29.58	49.98	80.27	92.61	0.27

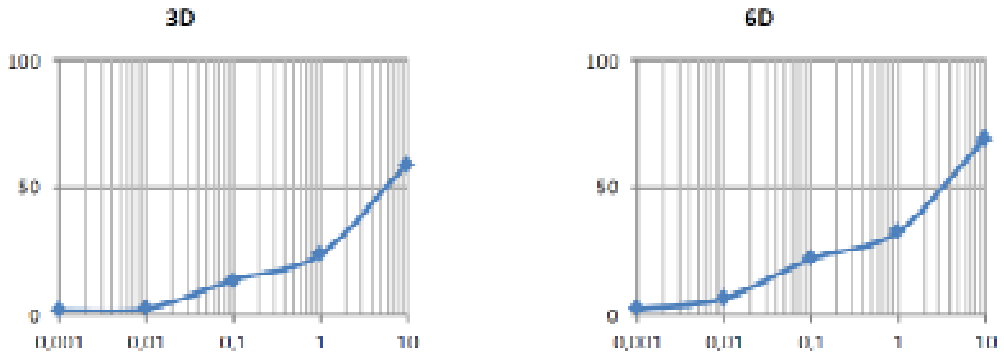


Figure 1: Percent cell inhibition activity of compounds 3D (4c) and 6D (4f)

Conclusion

In conclusion, we have developed an expedient approach for the synthesis of quinoline-4-carboxylic acid derivatives by the one-pot reaction of pyruvic acid, anilines and aromatic aldehyde in solvent ethanol at room temperature condition using lanthanum chloride as catalyst. The delightful features of this protocol are easy work up, use of environmentally benign catalyst, cost efficiency and excellent yields of the corresponding quinoline derivatives. Synthesized derivatives 3D (4c) and 6D (4f) were evaluated for their anticancer activities. The initial assays indicated that both newly synthesized compounds displayed significantly good inhibition activities against human breast cancer cell (MCF-7), cell lines compared with the control (Adriamysin), which might be developed as novel lead scaffold for potential anticancer agents.

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