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DESIGNING, SYNTHESIS, AND ANTICANCER EVALUATION OF SOME NEW QUINOLINE BASED CHALCONES

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ABSTRACT:
A novel series of the quinoline chalcone derivatives containing pyrrole and pyridine nucleus **5a-5i** with different substituent were synthesized by employing efficient protocol and characterized by the spectral analysis techniques ^{1}H NMR and^{13}C NMR. The derivatives **5a-5i** was tested for in vitro anticancer activity against two different cell lines **MCF7** and **A549**. The derivatives **5a-5i** was synthesized out of which, **5g** and **5e** displayed considerable to promising anticancer activity with IC50 values of 31.08 and 31.92 **µg** against MCF7 cell lines and countable anticancer activity against A549 cell lines with IC50 values of 41.32 and 42.92 **µg** respectively which were compared with the standard control cisplatin. As far as considered this is the first-ever attempt for the synthesis and anticancer activity evaluation of the quinoline based pyrrole or pyridine chalcone derivatives.
KEYWORDS: Quinoline-Chalcone, Anticancer activity, MCF7, A549, Acetyl Pyridine, Acetyl Pyrrole.

INTRODUCTION

Worldwide, Cancer is the biggest threat to humankind because it is the main reason for death, which is due to the uncontrolled growth of human cells [1]. Cancer progresses *via* multistep carcinogenesis, which involves various physiological processes of the human body like uncontrolled growth of cells due to the deregulation of essential enzymes, cell signalling, and apoptosis. Cancer is extremely complicated to combat [2]. The root cause was found to be the pattern of lifestyle adopted such as excessive use of tobacco, physical inactivity, and improper diet [3]. The increase in cancer incidence proves that even today it is not curable with the available therapy and medication. The major downsides of current therapy available to treat cancer include side effects, lack of tumor specificity, and multi-drug resistance. Focusing on it, the designing and synthesis of new anticancer drugs with potent anticancer activity and fewer side effects are the factors that demand detailed investigation in medicinal chemistry. Quinoline nucleus has many pharmacological functions, such as antibacterial, antifungal, anti-malarial, anti-inflammatory, and especially as an anticancer agent, therefore the synthesis and biological evaluation of quinoline moiety has more demand for organic chemists [4-15]. Quinoline derivatives may act as anticancer agents through a variety of

mechanisms such as cell cycle arrest in the G2 phase [16], topoisomerase inhibition [17], inhibition of tubulin polymerization [18], and inhibition of tyrosine kinases which is the most common mechanism [19, 20].

A α, β-unsaturated ketones, commonly known as chalcones are an important class of natural as well as synthetic products which show a variety of biological activities. During the last few decades, chalcone derivatives have been reported as having potent anticancer activity with low side effects and better solubility for therapeutic applications [21-22]. Simple structural modification in chalcone moiety with heterocycles, polyarene compounds, or organometal complexes may lead to new anticancer agents with promising activity [23-24]. Chalcone-based small molecules provide an advantage over others due to their low toxicity and mutagenicity profile. Yu *et al* showed that 4-(dimethylamino)-4-amino chalcone can interact with base pairs and created a new method to determine the trace amount of DNA [25].

EXPERIMENTAL:

General details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F254, Merck grade was used for thin layer chromatography to determine progress of reaction. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AV-400 MHz spectrometer in $CDCl_3$ solvent.

General Procedure

General procedure for the Synthesis of substituted acetanilide (2a-c):

Substituted acetanilide was prepared according to the literature [1]. Acetic anhydride (1.5 mmol) was gradually added to the Substituted aniline (26.8 mmol) in the ice bath and the mixture was stirred for 10 min to 2 hours. Upon completion of the reaction (monitored by TLC), water is poured into the mixture, and the formed precipitate is filtrated, washed with several times water, and dried to yield substituted acetanilide 2a-2c. The compound was identified by TLC with an authentic sample and used in the next reaction without any purification.

General procedure for the Synthesis of 2-chloro 3-Formyl Quinoline derivatives (3a-3c):

Dimethylformamide (DMF) (3 mmol) was added to substituted acetanilide (2a-2c, 1 mmol) in an ice bath, then phosphoryl chloride ($POCl_3$) (15 mmol) was added drop wise to the mixture and was stirred at ice bath for 20 min, then the reaction mixture refluxed at temperature 80-90 ^{o}C for 7-10 hours. After completion of the reaction as monitored by thin layer chromatography (TLC), ice was added to the reaction mixture and then reaction mixture was stirred. The precipitate obtained was filtered, then washed several times with cold water and, re-crystallized in ethanol to get substituted 2-chloro-quinoline-3-carbaldehyde (3a-3c) [2]. The 2-chloro-quinoline-3-carbaldehyde (3a-3c) was confirmed by TLC with astandard sample and used in the next reaction without any purification.

General procedure for the preparation of Quinoline-Pyridine and Pyrrole Chalcone derivatives (5a-5i):

To a solution of substituted 2-chloro-3-formyl quinoline (3a-3c) (10 mmol) and acetyl pyridine or pyrrole (10 mmol), in absolute ethanol (50 mL), sodium hydroxide solution (5 mL, 20%) was added dropwise by dropping funnel. The reaction mixture was stirred for 4-6 hours at room temperature. The reaction was monitored by thin layer chromatography(TLC), after completion of reaction as indicated by TLC, the obtained solid was collected by filtration, washed with water, dried, and crystallized from ethanol to afford compound 5a-5i as a yellow powder and yield (64-86%).

(E)-3-(2-chloroquinolin-3-yl)-1-(pyridin-4-yl)-prop-2-en-1-one (5a)

Yield; 89**; ^{1}H NMR**($CDCl_3$) 400 MHz: δ ppm,7.42-7.46, (d, 1H), 7.59-7.62, (d, 1H), 7.78-7.80 (d, 1H),7.89-7.91 (d, 1H), 8.03-8.05(d, 1H), 8.22-8.26(d, 1H),8.48 (s, 1H), 8.76-8.78,(d,

2H),8.87-8.89, (d, 2H);**^{13}C NMR,**($CDCl_3$)100 MHz; δ ppm,124.2, 124.4, 126.9, 128.0, 128.3, 129.8, 131.2, 132.1, 136.8, 142.0, 146.3, 147.6, 150.2, 152.0, 190.1.

(E)-3-(2-chloro-6-methylquinolin-3-yl)-1-(pyridin-4-yl)-prop-2-en-1-one (5b)

Yield; 80**; ^{1}H NMR**($CDCl_3$): δ ppm,2.53, (s, 3H), 7.39-7.42, (d, 1H),7.61-7.62,(d, 1H),7.67, (s, 1H), 7.90-7.92, (d, 1H),8.21-8.24, (d, 1H), 8.40 (s, 1H), 8.74-8.75 (d, , 2H),8.85-8.87, (d,2H),**^{13}C NMR**, ($CDCl_3$)100 MHz; δ ppm; 22.1, 123.6, 123.7, 126.4, 127.0, 128.3, 130.7, 131.5, 136.2, 137.5, 141.5, 145.9, 146.2, 149.6, 151.8, 189.2

(E)-3-(2-chloro-6-methoxyquinolin-3-yl)-1-(pyridin-4-yl)-prop-2-en-1-one (5c)

Yield; 77**; ^{1}H NMR**($CDCl_3$): δ ppm,2.94, (s, 3H), 7.13-7.15, (d,1H), 7.42-7.44, (d,1H), 7.60-7.62, (d, 1H), 7.64, (s, 1H), 8.06-8.08, (d, 1H), 8.37, (s,1H),(8.74-8.76, d,2H),8.83-8.85, (d,2H); **^{13}C NMR**, 100 MHz; δ ppm;**^{13}C NMR**,($CDCl_3$) 100 MHz; δ ppm; 56.0, 107.3, 123.0, 123.1, 128.3, 129.0, 129.7, 130.9, 135.9, 140.8, 145.2, 145.6, 148.9, 151.3, 159.2, 188.9

(E)-3-(2-chloroquinolin-3-yl)-1-(pyridin-3-yl)-prop-2-en-1-one (5d)

Yield; 76**; ^{1}H NMR**($CDCl_3$): δ ppm, 7.42-7.46, (d, 1H), 7.59-7.62, (d, 1H), 7.79-7.81, (d, 1H), 7.89-7.91, (d, 1H), 8.79-8.81, (d, 1H), 8.03-8.05, (d, 1H),8.22-8.26, (d,1H), 8.39-8.41, (t,1H), 8.48, (s, 1H),8.90-8.91, (d, 1H), 9.21, (s, 1H); **^{13}C NMR**,($CDCl_3$) 100 MHz; δ ppm; 125.0, 125.1, 128.2, 128.5, 129.5, 130.4, 132.8, 133.3, 134.6, 137.5, 138.2, 146.9, 148.7, 151.6, 154.1, 156.0, 190.5.

(E)-3-(2-chloro-6-methylquinolin-3-yl)-1-(pyridin-3-yl)-prop-2-en-1-one (5e)

Yield; 75**; ^{1}H NMR**($CDCl_3$): δ ppm, 2.65, (s,3H), 5.77-5.79, (d,1H), 7.14-7.15, (d, 1H), 7.65, (s, 1H), 7.91-7.93, (d, 1H), 8.22-8.26, (d, 1H), 8.37-8.39, (t, 1H),8.48, (s, 1H), 8.79-8.81, (d,1H), 8.83-8.85, (d, 1H), 9.28, (s, 1H); **^{13}C NMR**,($CDCl_3$) 100 MHz; δ ppm; 23.2, 124.5, 124.7, 127.6, 128.1, 128.9, 132.0, 132.9, 133.8, 136.8, 137.7, 138.7, 146.3, 147.9, 151.0, 153.7, 155.4, 189.6

(E)-3-(2-chloro-6-methoxyquinolin-3-yl)-1-(pyridin-3-yl)-prop-2-en-1-one (5f)

Yield; 74**; ^{1}H NMR**($CDCl_3$): δ ppm,3.95, (s, 3H), 5.74-5.76, (d, 1H), 7.13-7.14, (d, 1H), 7.36-7.37, (d, 1H), 7.38-7.40, (d,1H), 7.43-7.45, (t,1H), 7.91-7.93, (d,1H), 8.25-8.27, (d,1H), 8.41, (s,1H), 8.81-8.82, (d,1H), 9.20, (s, 1H); **^{13}C NMR**,($CDCl_3$) 100 MHz; δ ppm;56.8, 108.1, 123.9, 124.0, 126.9, 129.1, 131.4, 132.0, 132.7, 136.0, 136.5, 145.8, 147.3, 150.2, 152.7, 154.9, 160.2, 189.2.

(E)-3-(2-chloroquinolin-3-yl)-1-(1H-pyrrol-2-yl)-prop-2-en-1-one (5g)

Yield; 74**; ^{1}H NMR**($CDCl_3$): δ ppm,6.38-6.40, (m,1H), 7.14-7.16, (d, 2H), 7.43-7.45, (d,1H), 7.76-7.78, (t,1H), 7.79-7.81, (t, 1H), 7.89-7.91, (d,1H), 8.03-8.05, (d,1H), 8.22-8.26, (d, 1H), 8.49, (s,1H), 9.68, (s, 1H);**^{13}C NMR**,($CDCl_3$) 100 MHz; δ ppm;112.4, 123.8, 125.3, 126.5, 126.7, 127.5, 128.1, 128.3, 128.5 129.8, 133.9, 134.0 145.6, 146.8, 148.5, 189.4.

(E)-3-(2-chloro-6-methylquinolin-3-yl)-1-(1H-pyrrol-2-yl)-prop-2-en-1-one (5h)

Yield; 69**; ^{1}H NMR**($CDCl_3$): δ ppm, 2.55, (s,3H), 6.37-6.41, (m, 1H), 7.12-7.16, (d,2H), 7.40-7.44, (d,1H), 7.61-7.63, (d,1H), 7.65, (s, 1H), 7.90-7.93, (d, 1H), 8.39, (s, 1H), 8.21-8.23, (d, 1H), 9.72, (s,1H); **^{13}C NMR**,($CDCl_3$), 100 MHz; δ ppm; 21.8, 111.8, 123.1, 124.6, 126.0, 126.1, 126.2, 126.9, 127.6, 127.7, 129.5, 132.4, 133.6, 144.9, 145.5, 147.8, 188.8.

(E)-3-(2-chloro-6-methoxyquinolin-3-yl)-1-(1H-pyrrol-2-yl)-prop-2-en-1-one (5i)

Yield; 64**; ^{1}H NMR**($CDCl_3$): δ ppm, 3.94, (s,3H), 6.28-6.33, (m,1H), 6.96-6.99, (d,2H), 7.30-7.31, (d,1H), 7.38-7.39, (d,1H), 7.40-7.45, (d,1H), 7.45, (s,1H), 8.19-8.23, (d,1H), 8.39, (s,1H), 9.63, (s,1H);**^{13}C NMR**, ($CDCl_3$), 100 MHz; δ ppm; 53.8, 106.4, 111.2, 122.6, 123.7, 125.5, 125.6, 126.1, 127.0, 127.2, 129.0, 131.8, 132.8 144.2, 144.3, 146.1, 188.1.

Anticancer Evaluation study

Introduction:

Measurement of cell viability and proliferation forms the basis for numerous in vitro assays of a cell population's response to external factors. The MTT Cell Proliferation Assay measures the cell proliferation rate and conversely, when metabolic events lead to apoptosis or necrosis, the reduction in cell viability. The anti-cancer activity of quinoline-chalcone compounds was determined in vitro by MTT Assay.

Materials and Methods:

DMEM (Dulbecco's modified Eagles medium), MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide], trypsin, EDTA Phosphate Buffered Saline (PBS) and were purchased from Sigma Chemicals Co. (St. Louis, MO) and Fetal Bovine Serum (FBS) were purchased from Gibco. 25 cm^2 and 75 cm^2 flask and 96 well plated purchased from Eppendorf India.

Maintenance of Cell Line:

The Cancer cell lines were purchased from NCCS, Pune, and the cells were maintained in MEM supplemented with 10 % FBS and the antibiotics penicillin/streptomycin (0.5 mL-1), in the atmosphere of 5 % CO_2 / 95 % air at 37 ^oC.

Preparation of Test Compound:

For the MTT assay, Each Test compounds were weighed separately and dissolved in DMSO. With media made up the final concentration to 1 molar and the cells were treated with a series of concentrations from 5 to 100 µM.

MTT ASSAY

MTT Assay is a colorimetric assay that measures the reduction of yellow 3-(4, 5-dimethythiazol- 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The assay depends both on the number of cells present and, on the assumption, that dead cells or their products do not reduce tetrazolium. The MTT enters the cells and passes into the mitochondria where it is reduced to insoluble, dark purple-coloured formazan crystals. The cells are then solubilized with a DMSO and the released, solubilized formazan reagent is measured spectrophotometrically at 570 nm.

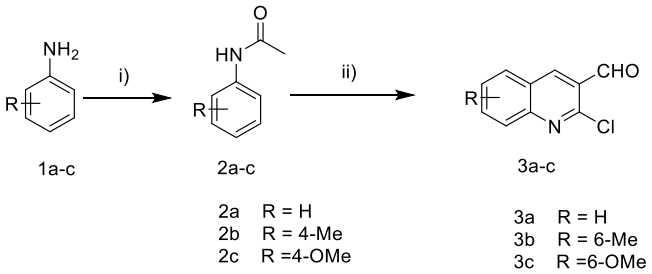
Cell viability was evaluated by the MTT Assay with three independent experiments with six concentrations of compounds in triplicates. Cells were trypsinized and perform the tryphan blue assay to know viable cells in the cell suspension. Cells were counted by haemocytometer and seeded at a density of 5.0 X 103 cells / well in 100µl media in 96 well plate culture medium and incubated overnight at 37 ^oC. After incubation, take off the old media and add fresh media 100 µl with different concentrations of the test compound in represented wells in 96 plates. After 48 hrs, discard the drug solution and add the fresh medic with MTT solution (0.5 mg / mL-1) added to each well, and plates were incubated at 37 ^oC for 3 hrs. At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula.

$$\% \text{ Inhibition} = \frac{100\ (\text{Control} - \text{Treatment})}{\text{Control}}$$

The IC50 value was determined by using linear regression equation i. e, y = m x + c. Here, y= 50, m and c values were derived from the viability graph. Compounds treated with MCF 7 and A549 cell lines and showing the IC50/(µg) values are as follows in the table provided.

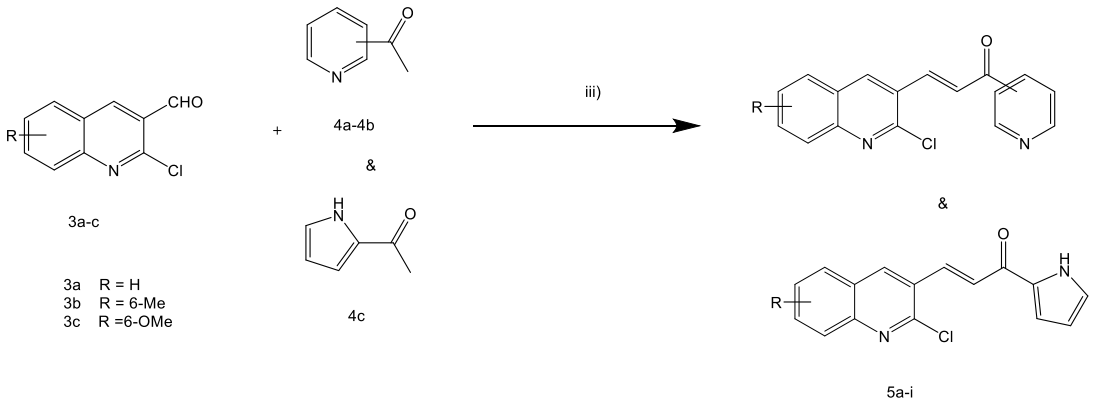
RESULT AND DISCUSSION:

The imperious active quinoline precursor (3) was obtained by making some changes to the reported methods as shown in the **Scheme 1.** The compound 3 was synthesized by the cyclisation of acetanilide, which was obtained from acetylation of aniline. Derivatives 5a-5i was obtained by the condensation of quinoline compound 3 and acetyl pyridine and acetyl pyrrole in the presence of 40% NaOH and Ethyl alcohol **(Scheme 2)**. The synthesized compounds were confirmed by spectral studies like ^{1}H NMR, and ^{13}C NMR.



Scheme 1 Synthesis of 2-Chloro-3-formyl quinoline derivatives.
Reagent and Conditions: i) Ac_2O ii) DMF, $POCl_3$.

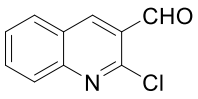
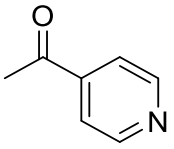
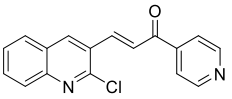
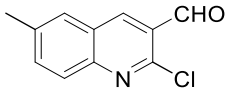
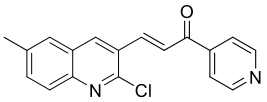
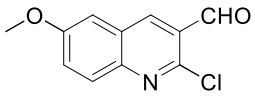
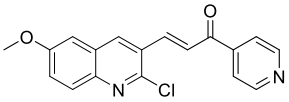
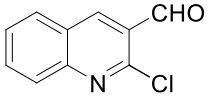
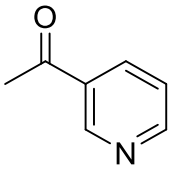
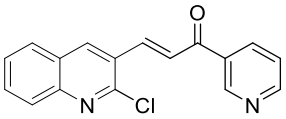
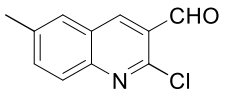
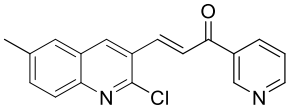
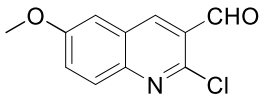
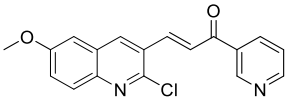
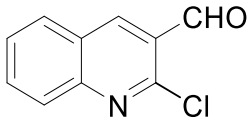
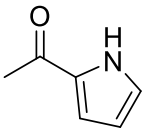
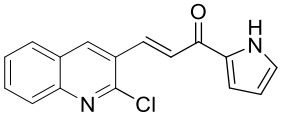
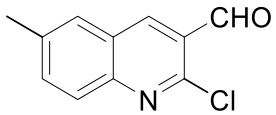
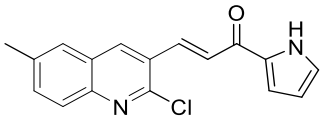
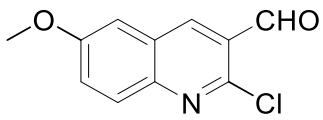
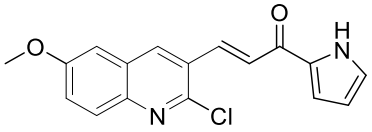
Focusing on the biological importance of quinoline and chalcone and in continuation to our research interest to design and synthesize new anticancer compounds, we herein report an effective protocol for the synthesis of quinoline based chalcone derivatives **5a-5i** in moderate yields. The designed and synthesized quinoline chalcone hybrids **5a-5i** were tested for their anticancer activity against two cell lines as follows MCF7 (mammary gland) and A549 (lung) by MTT assay method. Considerably, out of nine derivatives (5a-5i) synthesized 5g and 5e displayed considerable to encouraging anticancer activity with IC50 values of 31.08 and 31.92 µg against MCF7 cell lines and analogue 5g and 5e shown countable anticancer activity against A549 cell lines with IC50 values of 41.32 and 42.92 µg respectively which were compared with control cisplatin.



Reagent and Conditions: iii) EtOH, 40 % NaOH.

Scheme 2 A series of quinoline based chalcone derivatives

Table 1. Synthesized quinoline based chalcone derivatives

SN	Reactant	Reactant	Products	Yield (%)
1	 **3a**	 **4a**	 **5a**	**89**
2	 **3b**		 **5b**	**80**
3	 **3c**		 **5c**	**77**
4	 **3a**	 **4b**	 **5d**	**76**
5	 **3b**		 **5e**	**75**
6	 **3c**		 **5f**	**74**
7	 **3a**	 **4c**	 **5g**	**74**
8	 **3b**		 **5h**	**69**
9	 **3c**		 **5i**	**64**

The anticancer activity of the designed and synthesised compounds **5a-5i** with the cancer cell line MCF7 (mammary gland) and A549 (lung) are given in **Table 2**. Depending upon IC50 values obtained from the MTT assay the ranges between 31.08 to 139.75 μg for MCF7 and 41.32 to 158.65 μg for A549 human cancer cell lines. In this quinoline based chalcone hybrids were studied for their anticancer activity. In this study, we focused mainly on the effect of the presence of different substituents at the 3rd position and, at 6th position on the 2-chloro-3-formyl quinoline. On the other hand, we aimed to study the effect of the position of the acetyl group on the pyridine, and ring size of nitrogen-containing heterocycles. We glad to see the results, specifically, the derivatives 5e and 5g displayed encouraging results in the

evaluation of anticancer activity with IC50 values 31.92 and 31.08 µg against MCF7 (mammary gland) cell lines. The same compounds *i. e* 5g and 5e have shown encouraging IC50 values 41.32 and 42.92 µg against A549 human lung cell lines. The anticancer activity evaluation indicates 5g analogue exhibited better anticancer activity against MCF7 cell line than the 5e analogue. The anticancer activity evaluation for 5g analogue unveiled good anticancer activity against A549 cell line than the 5e analogue. The structural aspects of the compound 5g and 5e were compared, the analogue 5g contains a pyrrole ring, which is five-membered nitrogen-containing heterocycles displayed better anticancer activity among all derivatives 5a-5i of the quinoline based chalcone hybrids. The analogue 5e which having second number activity, having the acetyl group at the 3rd position on the pyridine ring of the quinoline chalcone structure, and there is methyl group present at 6th positon on quinoline ring (Table 2).

As far as considered this is the first-ever attempt for the synthesis and anticancer activity evaluation of quinoline based chalcone derivatives containing pyridine and pyrrole nucleus.

Table 2. IC_{50} values of synthesized quinoline chalcone derivatives.

SAMPLENAME	**MCF 7 IC_{50} (µg)**	**A549 IC_{50} (µg)**
D5a	69.88 ± 0.032	99.48 ± 0.024
D5b	93.51 ± 0.041	124.42 ± 0.036
D5c	48.17 ± 0.057	78.47 ± 0.054
D5d	139.75 ± 0.049	158.65 ±0.048
D5e	31.92 ± 0.058	42.92 ± 0.035
D5f	69.96 ± 0.062	79.76 ± 0.081
D5g	31.08 ± 0.087	41.32 ± 0.024
D5h	49.79 ± 0.023	58.69 ± 0.095
D5i	84.07 ± 0.0 37	78.06 ± 0.068
Cisplatin **(µM)**	5.46 ± 0.047	8.59 ± 0.021

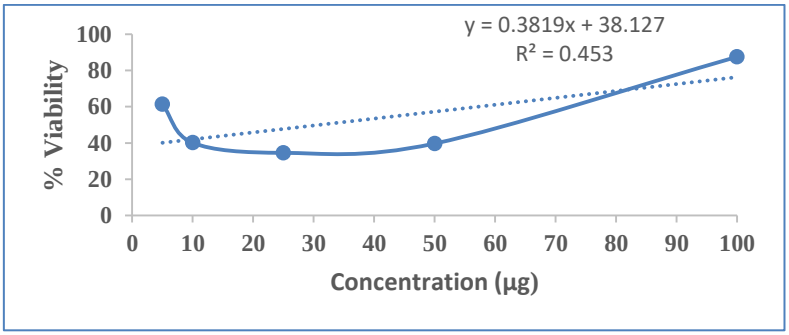


Figure: Graph showing the % Viability of 5g derivative against MCF7 Cell line.

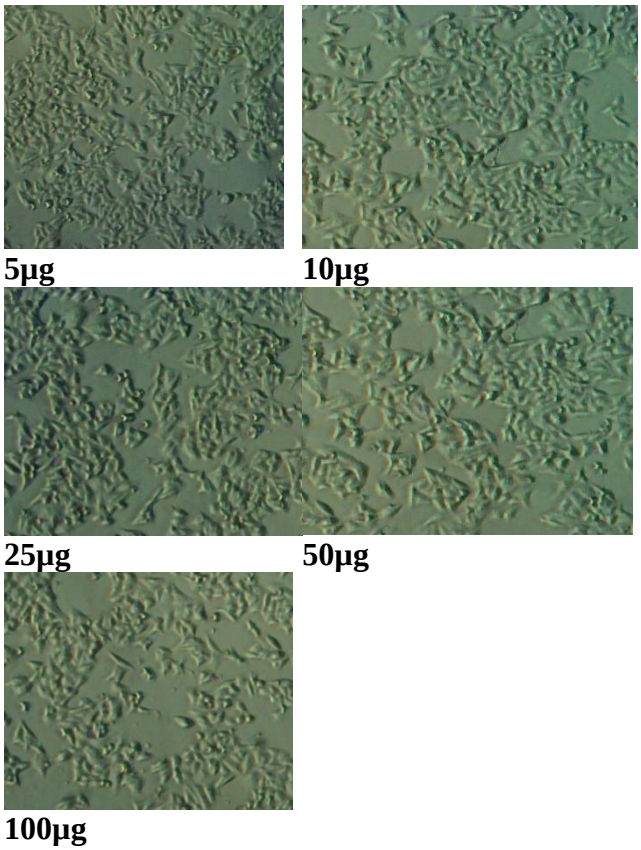


Figure: Images of the **5g** derivatives at different concentration during in vitro anticancer evaluation.

CONCLUSION:

Lastly, concluded that a series of designed and synthesized quinoline-chalcone hybrid derivatives 5a-5i in moderate to excellent yields (64-89 %) and evaluated for their in vitro anticancer activity against two different cell lines MCF7 and A549 respectively. Remarkably, the compound 5g unveiled the best anticancer activity against MCF7 which compared to Cisplatin. The initial results could offer an excellent framework in this area that may mainly focus on the discovery of new potent antitumor agents.

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