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Synthesis and *In vitro* Testing of Novel Quinoline Derivatives and for Cancer Cells

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ABSTRACT

Quinoline and its derivatives represent an important class of nitrogen-containing heterocycles because they are useful intermediates in organic synthesis and biological activities such as antiasthmatic, anti-inflammatory, anticancer, and antimalarial activity. A quinoline containing eight compounds was successfully synthesized and characterized by FT-IR, 1H NMR, 13C NMR and mass spectral analysis. Therefore, the synthesis of new quinoline derivatives with strong pharmacological activity is important in medicine. There is significant research focused on the development of new quinoline-based structures and new methods of synthesis. In this research study, new quinoline derivatives were synthesized and the synthesized compounds were characterized by several spectroscopic techniques, the biological activity of these compounds was evaluated using lung cancer cell lines and molecular modeling in an enzymatic system. The synthesized eight new compounds were tested for their potential activity in lung cancer cell lines. Eight synthesized compounds (K1-K8) were evaluated for their cytotoxic activities. The anticancer test showed that the quinoline compounds K2, K3 and K4 show good anticancer activity. Among them, K2 and K4 were shown to be dose-dependent, with K4 having the highest toxicity at 250 μM and K8 having the highest toxicity at 125, 250, and 500 μM, while K1, K2, K5, K6, and K7 were not cytotoxic.

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INTRODUCTION

Chemistry occupies an awesome region in our knowledge of the universe and its Composition; it is the technology of molecules present in count number and area. But organic chemistry, even though a department of chemistry is a thrilling and dynamic discipline of science which literally creates itself because it grows. The look at of natural chemistry regularly includes a have look at new molecules that give statistics both to be had or unavailable from the molecules without a doubt found in residing things [1]. Quinoline and their derivatives represent an important class of nitrogen-containing heterocycles as they are useful dyes and intermediates in organic synthesis [2]. Cancer, is an epidemic and second main causes of death within the word, is chargeable for approximately 25% of all deaths [3, 4]. The identification of lung cancer in human beings may be adverse, confronting them with adjustments in identification, social interactions and offering

them with an uncertain destiny [5]. Now it's miles the leading disease both in charge and mortality. Each year, 1.2 million new instances of lung most cancers are diagnosed (12.3% of all cancers worldwide) and 1.1 million patients die because of lung cancer (17.8% of all cancer deaths worldwide) [6]. Regardless of the reality that effective anti-most cancer pills exist, drug resistance has to turn out to be a substantial crisis. This has necessitated the look for novel and value-powerful drugs with high structural variant. Compounds with heterocyclic ring have chemical structural similarity with appreciate to the biologically active compounds inside our body along with all of the nucleic acids, hormones, neurotransmitters and many others, so it will become a pivotal part of drug molecules [7]. Beginning inside the early 1900s, drug discovery became increasingly more centered on discovering and growing chemical entities that on their personal have a favored pharmaceutical effect. To start with this was fuelled by way of tries to extract and discover the active thing in extracts from natural merchandise that had been being used to treat infection. A number of trends, but, have resulted in the multi-disciplinary science that drug discovery is today, including molecular biology [8]. Docking is a technique which predicts the preferred orientation of 1 molecule to a 2d whilst certain to every other to shape a stable complicated; it is a key tool in structural molecular biology and laptop-assisted drug layout. The intention of ligand-protein docking is to expect the predominant binding mode of a ligand with a protein of recognized 3-dimensional shape [9]. Quinoline and its derivatives are acknowledged for their anti-most cancers and programs of quinoline derivatives have unfolded unexpectedly from being in anti-most cancers tablets, to almost every branch of medicinal chemistry [10]. Knowing the medicinal importance of quinoline primarily based compounds, we undertook an investigation to synthesize novel quinoline derivatives and take a look at their application in organic structures [11]. The purpose of this look at is to synthesize quinoline derivatives, examine their bacterial and anticancer capacity and adopt molecular docking evaluation of high-quality scoring selected compounds [12].

MATERIALS AND METHODS

Solvents and commercially available reagents such as aniline, *o*-anisidine, *m*-toluidine, phosphoryloxychloride, fluoroaniline, aniline hydrochloride, dimethyl formamide, petroleum ether, ethanol, ethyl acetate, hexane and methanol were purchased from S.A, Aldrin and Merck. These reagents and solvents were used without further purification. Thin Layer Chromatography (TLC) was performed using TLC plates. When conducting TLC analysis, a pencil line was drawn 2cm above and below the rim of a pre-cut TLC plate and approximately10 μL of a solution of the crude mixture was placed on the bottom line and air dried. The mobile phase consisting of petroleum ether and ethyl acetate (4:1, v/v) was placed in a TLC chamber, closed and allowed to equilibrate until the atmosphere was saturated with the solvent vapour. The TLC plate was placed gently in the chamber and allowed to run until the mobile phase reached the top pencil mark. It was removed, air dried and viewed under the UV lamp followed by staining in an iodine chamber containing sea sand and iodine crystals.

General Procedure for the Synthesis of 2-chloro-3-formyl quinoline

Dry 3 mmol of DMF (35 mL) cooled at 0ºC in a round backside flask geared up with a drying tube and then 12 mmol POCl3 (168.2 mL) became introduced drop-sensible with stirring. To this answer, 1 mmol of acetanilide (20.27gm) became delivered in small portions after 30 minutes. The reaction aggregate turned into heated for 24-25 hours on water bath. The reaction mixture became poured into ice water, stirred for half-hour. The work-up changed into executed with aqueous NaOH to shape a precipitate, to hydrolyse the imine salt and take away any acid shaped. The product turned into filtered, dried and purified and yield turned into located (92 %).

Synthesis of Quinoline Derivatives

Procedure for the Synthesis of (K1-K8)

Mixture of 2 mmol 2-chloro-3-formyl quinoline (0.3831 g), 2 mmol malononitrile (, 0.144 g) and 2 mmol triethylamine (0.202 g), dissolved 50 mL of ethanol and stirred at room temperature for 30-40 minutes. Then added mixer of 2 mmol arylamine (0.2mL) and 2 mmol dimethyl acetylenedicarboxylate (0.284 g) dissolved in 25 mL ethanol.

Biological Studies

This examine investigated the cytotoxicity of synthesized quinoline derivatives (K1-K8) within the K549 lung cancer cellular line. These compounds differed in substituents like OCH3, CH3, F and Cl attached to the benzene ring. Herein we wished to analyze the effect of these compounds based on the one of a kind practical companies to observe their anticancer capacity. The cytotoxicity of the compounds in cancerous K549 lung cells became assessed with the use of the MTT assay. This assay measures mobile proliferation/metabolic hobby in vitro. The technique is especially useful for cells which are metabolically energetic based on their redox capac-

ity and capability of dehydrogenase enzymes to convert yellow water-soluble salt right into a purple water-insoluble formazan product. The insoluble crystals are then dissolved in DMSO and the absorbance is examined on a spectrophotometer. K549 cells have been uncovered to diverse concentrations of the synthesized compounds. A management of cells incubated with complete culture media handiest become used. The effects were expressed as optical density. The remedy companies at numerous concentrations (31.25–500 μM) were in comparison to the control to decide the capability as an anti-most cancers drug.

The determined compound K1 (with no substituent inside the benzene ring) is not cytotoxic however, alternatively will increase metabolic pastime as all concentrations examined showed more pastime than manipulate. The compound K2 (with an electron donating institution, OCH3 substituent in the benzene ring), shows a dose established toxicity because of its substituent as the effects offers proof that the compound has capacity as an anti-most cancers drug. The compound K3 (with an electron donating group, CH3 substituent in the benzene ring) suggests high toxicity but only at higher concentrations, has capability as an anti-most cancers drug. Compound K4 (with the chloro institution, which withdraws electrons with the aid of induction, however donates electrons via resonance inside the benzene ring) indicates dose-based toxicity with the best toxicity at 250 μM. The compound has capacity as an anti-most cancers drug. Compounds K5, K6 and K7 (with the fluoro group within the benzene ring) were now not cytotoxic, whilst K8 (with the 2 chloro organizations, which withdraw electrons through induction, however donate electrons through resonance in the benzene ring) show a dose dependent toxicity with the very best toxicity at one hundred twenty five, 250 and 500 μM. The compound has potential as an anti-most cancers drug [13].

RESULTS AND DISCUSSION

The identification of all of the compounds (K1-K8) structures becomes confirmed using IR, Mass 1H NMR and 13C NMR. All the spectra were well resolved. We decided on compound K1 because the template and characterised the shape completely with the resource of 2d NMR strategies in particular HSQC, HMBC, cosy and NOESY which led to the unambiguous assigning of all protons and carbons. We used the characterization of K1 as a template to explain the opposite 7 derivatives.

Hence 2D NMR was performed on K1 and the chemical shifts were unambiguously assigned. Furthermore, mass spectroscopy analysis was performed on, K1, K2, K3, K4, K6, K7 and K8 while ^{19}F NMR was performed on K6 and K7. As a typical example the optical activity of K1 was measured using light having a wavelength of 589 nm. The IR spectra of K1-K8 exhibited an absorption band around 1748-1652 cm^{-1} which was assigned to C=O stretch whilst 1105-1153 and 932-778 cm^{-1} were assigned as the C-Cl and C-F stretch for the chloro and fluoro derivatives, respectively. The characteristic absorption bands for K1-K8 were observed in the range 3449-3309 cm^{-1} and 3369-3218 cm^{-1} corresponding to the asymmetric and symmetric stretching of the NH_2 group whilst the CN stretch was observed at 2185-2171 cm^{-1}.

The ^{1}H NMR spectrum of K1, shows singlets at δ 3.44 and δ 3.51 for two acetoxy groups (H-9', H-10'). The singlets at δ 4.13 and δ 5.36 are assigned to the amino (NH_2) and aliphatic proton (H-4') on the dihydropyridine ring, respectively. Ten aromatic protons were observed and unambiguously assigned by using 2D NMR techniques. The chemical shifts, spin multiplicities and coupling constants (in Hertz) were assigned as: δ 8.14 (H-4, s); δ 7.85 (d, H-6, 8.1); δ 7.71 (t, H-7, 7.6); δ 7.55 (t, H-8, 7.4); δ 8.02 (d, H-9, 8.4); δ 7.39 (m, H-2"); δ 7.52 (m, H-3"); δ 7.38 (m, H-4", 7.4); δ 7.52 (m, H-5") and δ 7.39 (m, H-6"). In the NMR spectra of all the related derivatives, the quinoline and dihydropyridine were similar. The differences were seen in the phenyl ring attached to the "N due to the different substituents in the ring. For instance, in the ^{1}H NMR spectra for K2, presented in the aromatic group methoxy proton H-7" (δ 3.50) of compound K2 appears deshielded due to OCH_3 electron density attached to the nearby carbon C-7"; the H-3" resonance is now *ortho* to the OCH_3 group, is also deshielded and now occurring as a doublet at δ 7.84 (J = 8.1) due to OCH_3 electron density attached to the nearby carbon atom as shown in the expanded. Shows an *m/z* of 504 and the isotopic ratio of 3:1 for ^{35}Cl; ^{37}Cl was observed at *m/z* 427 and 429. Also, the loss of *m/z* 427 shows the benzene fragment at *m/z* 77.

In the ^{1}H NMR spectra for K3, presented in there is a methyl proton resonance (H-7") occurring as a singlet at δ 2.39. Unlike in K1 where there was only one singlet observed in the aromatic region, a noticeable resonance H-2" (7.23) in was observed. The mass spectra of K3 which is presented in the molecular ion peak was observed at *m/z* 488. Loss of 2H· radicals gave the peak at *m/z* 486 which also showed the isotopic chlorine ratio of ^{35}Cl: ^{37}Cl as 3:1. The tropylium ion was observed at *m/z* 91.

Table 1: ^{1}H NMR Chemical Shifts for Compounds K1-K8, δ of ^{1}H (J, Hz)

No.	K1	K2	K3	K4	K5	K6	K7	K8
NH_2	4.13(s)	4.17(s)	4.23(s)	5.86(s)	5.99(s)	5.86(s)	5.83(s)	6.02(s)
CH	5.36(s)	5.36(s)	5.33(s)	5.24(s)	5.22(s)	5.25(s)	5.23(s)	5.25(s)
OCH_3	3.51(s)	3.46(s)	3.50(s)	3.45(s)	3.46(s)	3.45(s)	3.38(s)	3.43(s)
OCH_3	3.44(s)	3.49(s)	3.44(s)	3.43(s)	3.46(s)	3.40(s)	3.43(s)	3.39(s)
4	8.14(s)	8.39(s)	8.12(s)	8.34(s)	8.33(s)	8.40(s)	8.38(s)	8.45(s)
6	7.85(d, 8.1)	7.80(d, 8.1)	7.84(d,8.2)	7.98(d, 8.5)	7.59(m)	7.99(d, 8.5)	8.17(d, 8.0)	7.99(d, 8.4)
7	7.71(t, 7.6)	7.69(7.6)	7.69(t, 10.1)	7.70(t, 7.9)	7.67(t, 7.1)	7.70(t, 6.9)	7.82(t, 7.3)	7.84(t, 7.7)
8	7.55(t, 7.4)	7.53(t, 7.1)	7.53(t, 11.2)	7.84(t, 6.9)	7.67(t, 7.1)	7.84(t, 7.0)	7.66(t, 7.2)	7.70(t, 7.6)
9	8.02(d, 8.4)	8.01(d, 8.4)	8.00(d, 9.7)	8.17(d, 8.1)	7.84(d, 7.3)	8.19(d, 8.4)	7.96(d, 7.6)	8.20(d, 8.1)
2”	7.39(m)	-	7.23(s)	7.60(d, 11.2)	-	7.41(d, 4.7)	7.50(d, 8.2)	7.47(d, 2.3)
3”	7.52(m)	7.84(d, 8.1)	-	7.49(d, 8.8)	7.33(d,d, 7.7)	-	7.34-7.36(d, 8.6)	-
4”	7.38(t, 3.5)	7.06-7.02(m)	7.16(d,7.6)	-	7.64-7.37(m)	7.44(dd, 4.8)	-	-
5”	7.52(m)	7.48(t, 7.8)	7.36(t, 9.9)	7.49(d, 8.8)	7.64-7.37(m)	7.60(d, 4.8)	7.34-7.36(d, 8.0)	7.87(d, 9.9)
6”	7.39(d, 3.4)	7.30(d, 7.3)	7.29(d,7.6)	7.60(d, 11.2)	7.64-7.37(m)	7.32(d, 7.8)	7.50(d, 8.2)	7.80(d, 7.7)
7”	-	3.50(s)	2.39(s)	-	-	-	-	-
8”	-	-	-	-	-	-	-	-

In the expanded ^{1}H NMR spectra for K4, presented in, resonances (H-2”, H-6”) and (H-3”, H-5”) on the phenyl ring now appears as doublets at δ 7.60 (J = 11.2) and δ 7.49 (J = 8.8), respectively. It shows an *m/z* of 510. The peaks at *m/z* 509 and 508 are due to the loss of hydrogen and the two hydrogens by rearrangements, respectively. In the ^{1}H NMR spectra for K5, presented in where a fluorine atom is substituted at the 2” position, causing splitting of the adjacent aromatic proton by short as well as long-range coupling. The H-3” appears as a doublet at δ 7.33 (J = 7.7). The H-4”, H-5” and H-6” appear at δ 7.37-7.64 but these assignments are not well resolved. In the ^{13}C NMR spectrum, presented in the C-F coupling is observed for C-2” and appears as a doublet at δ 160.6 (J = 254.1). The C-3” appears as doublet of doublets at δ 128.3 (J = 120.2).

In the ^{1}H NMR expanded spectra for K6, presented in the fluoro group is at the 3” position, causes splitting of the adjacent aromatic proton by short as well as long range coupling. The H-6” proton occurs as a doublet at δ 7.32 (J = 7.8). The H-5” occurs as a doublet doublet at δ 7.60 (J = 4.8). The H-2” and H-4” protons are split by fluorine and occurs as a doublet and doublet of doublet at δ 7.41 (J = 4.7) and δ 7.44 (J = 4.8), respectively. In the ^{19}F NMR spectra for K6, presented in it shows a singlet at δ 111.2 is attributed to C-F function. The C-2” and C-4” appears as doublets at δ 127.8 (J = 29.8) and δ 127.9 (J = 15.9), interchangeably. The mass spectra of K6 which is presented in it shows an *m/z* of 494. The peaks at *m/z* 493 and 492 are due to the loss of hydrogen and the two hydrogens by rearrangements, respectively. In the ^{1}H NMR spectra for K7, presented the fluoro group is at the 4” position; causing splitting of the adjacent aromatic proton by short as well as long range coupling. The H-2” and H-6” protons are equivalent and integrated to 2 protons appearing at δ 7.50 (J = 8.2). In the ^{13}C NMR spectrum, presented in the C-F coupling is observed for C4” and appears as a doublet at δ 210.0 (J = 20.0). The C-3” and C-5” are equivalent and appears as doublet at δ 127.9 (J = 68.9). The mass spectra of K7 which is presented in it shows an *m/z* of 494. The peaks at *m/z* 493 and 492 are due to the loss of hydrogen and the two hydrogens by rearrangements, respectively. In the expanded ^{1}H NMR spectrum for K8, presented in the chlorine atoms are

Table 2: ^{13}C NMR Chemical Shifts (δ in ppm) for Compounds K1-K8

No.	K1	K2	K3	K4	K5	K6	K7	K8
2	150.9	150.9	150.4	151.4	151.4	151.6	149.1	151.1
3	137.3	130.4	136.5	137.7	143.2	118.7	127.4	131.3
4	138.4	138.7	138.5	139.1	146.6	139.1	142.9	131.6
5	134.9	127.6	127.7	128.0	128.7	128.0	133.3	131.8
6	139.6	139.1	128.3	128.5	128.9	131.6	133.4	132.3
7	130.2	127.0	129.8	130.2	129.1	131.6	133.3	133.5
8	130.9	128.5	131.5	132.9	133.4	131.4	133.0	133.8
9	130.5	128.3	130.4	131.4	131.5	128.6	131.1	127.9
10	149.0	149.9	149.9	149.6	143.2	149.6	149.0	142.9
2’	164.7	165.4	165.3	165.2	164.1	165.2	150.9	165.2
3’	58.0	61.8	60.8	58.5	79.6	58.8	61.7	58.6
4’	39.0	36.4	36.7	39.6	44.9	37.1	36.8	37.1
5’	120.3	119.9	127.1	120.8	120.7	120.7	120.4	120.7
6’	143.1	146.9	143.1	146.5	151.3	143.2	142.9	139.4
7’	162.6	163.3	163.2	165.2	165.7	163.3	149.1	163.1
8’	162.6	163.3	163.2	163.1	165.0	163.1	149.1	163.1
9’	52.3	52.1	52.1	52.0	53.6	52.1	57.3	52.4
10’	51.9	52.5	52.6	52.4	53.2	52.9	57.8	53.1
1”	146.0	146.9	146.9	143.3	133.5	146.6	143.1	146.5
2”	127.3	150.1	127.2	127.9	160.6 (d, 254.1)	127.8 (d, 29.8)	127.3 (d, 33.5)	128.5
3”	127.5	127.6	140.5	135.3	128.3 (dd,120.2)	161.7 (d, 248)	127.3-127.9 (dd, 180.2, 33.5)	139.4
4”	127.5	121.0	127.6	127.9	128.1 (dd, 49.9)	127.9 (d, 29.8)	151.0 (d, 29.4)	137.8
5”	127.5	126.9	130.7	134.4	127.8 (dd, 180.3, 12.8)	137.9 (dd, 29.8, 15.9)	127.3-127.9 (dd, 175.0, 33.5)	135.4
6”	128.0	127.3	119.9	127.9	128.4 (d, 41.6)	128.0 (d, 52.9)	128.0 (d, 30.1)	130.1
7”	-	52.0	21.2	-	-	-	-	-

Table 3: Physicochemical Data for Quinoline Derivatives

Compound	Ar	%Yield	Melting Point (^{0}C)
K1	C_6H_4	90	275-280
K2	$OCH_3C_6H_4$	40	263-268
K3	$CH_3C_6H_4$	73	237-242
K4	ClC_6H_4	79	287-292
K5	FC_6H_4	64	247-252
K6	FC_6H_4	31	269-274
K7	FC_6H_4	60	253-258
K8	$diClC_6H_4$	72	280-285

substituted at the 3" and 4" positions, resonances H-2" and H-5" on phenyl ring now appears as doublets at δ 7.48 (J =7.8) and δ 7.47 (J = 8.2), respectively. The mass spectra of K8 which is presented shows an m/z of 544; the base peak appears at m/z 485 is due to the loss of the acetoxy group. Table 1 represents the chemical shifts and coupling constants of the protons of K1-K8. The chemical shift of the carbons of K1-8 is presented in Table 2. In Table 3 mentioned Synthesized compounds Physicochemical data for quinoline derivatives.

CONCLUSION

2-Chloro-3-formyl quinoline was synthesized from *N*-phenylacetamide by the Vilsmeier-Haack reaction and it was characterized by IR, 1H NMR and 13C NMR spectroscopy. Eight new quinoline derivatives were synthesized from 2-chloro-3-formyl quinoline, malononitrile, arylamine and dimethyl acetylenedicarboxylate by one pot multi-component reaction. These compounds were produced in yields of 37-90% and were characterized by IR, 1H NMR, 13C NMR and MS. Eight novel quinoline derivatives were synthesized using a one-pot multi-component reaction were tested for their anti-cancer potential. The anti-cancer assays indicated that compounds K2, K3, K4 and K8 have good potential as anti-cancer drugs by showing antiproliferative activity. Compounds K1, K5 and K7 were not cytotoxic.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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