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Studies in the synthesis and applications of 4-(aminomethyl)quinolin-2(1*H*)-one derivatives as anti-cancer agents.

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ABSTRACT

2-quinolone derivatives find applications as antimicrobial, anti-viral and anticancer agents. 3-Aryl and N-methyl derivatives of 2-quinolone have been reported as most potent anti-cancer agents. Present study involves synthesis, characterization of novel4-(aminomethyl)quinolin-2(1H)-onederivatives, ***7a-e,*** *devoid of 3-aryl and N-methyl substitutions and their application as anti-cancer agents. MTT assay of the synthesized new chemical entities against A549 cell line was carried out and compound* ***7e*** *was found to be the most potent anti-cancer agent in the series.*

Keywords: 2-quinolone, glycine amide, anti-cancer agent, MTT assay.

INTRODUCTION

With the advances in medicine, life expectancy of individuals has increased many folds, yet Cancer is still regarded as the most dreaded disease.Other than cardiovascular diseases, cancer accounts for highest mortality rate[1]. From the medicinal chemistry point of view, the drug administered to patients suffering from cancer should cause selective induction of apoptosis in cancerous cells while leaving normal cells unaffected. Thus safe yet selective drug for the treatment of cancer is the need of the hour.Various natural and synthetic molecules are reported to exhibit anti-cancer activity. Quinolone derivatives are widely exploredand have gained importance for their promising pharmacological potential attributed to its drug-like properties and structural similarity to some specific targets thereby rendering them selective in their action.

Quinolones form the basic framework of many biologically active molecules exhibiting a broad spectrum of bioactivities, primarily, antimicrobial [2, 3], anti-cancer [4-6] and anti-viral [7, 8] activity. Since past five decades, 4(1*H*)-quinolone-3-carboxylic acid derivativesare widely used as antibiotics. Also,4-(aminomethyl)quinolin-2(1*H*)-onederivatives and various quinolone linked with coumarins via ether linkage have been studied for their anti-microbial and analgesic activities [9, 10]. Various 2-quinolone derivatives have been reported as inducible nitric oxide synthase (iNOS) inhibitors and potent anti-platelet agents [11, 12].

Fluoroquinolones have been approved by WHO as a second line drug for the treatment of tuberculosis.The potential of fluroquinolones as first line drug due to its good pharmacological profile, absorption and penetration into host macrophages is still being investigated. Farnesyltransferase inhibitor, tipifarnib, a 3-aryl-2-quinolone derivative is in its clinical trial stage for the treatment of leukemia and breast cancer [13]. Joseph *et al.*, havereported 3-aryl-2-quinolone derivatives as anti-tumor agents [14]. Recently, N. Kumar and co-workers have reported novel 2-quinolonederivatives exhibiting anti-cancer activity [15, 16].

Thus, 2-quinolone derivatives are reported to show anti-cancer activity. However, to the best of our knowledge, anti-cancer activity of 4-(aminomethyl)quinolin-2(1*H*)-one derivatives has not been studied so far. Present work has been designed for the synthesis of substituted 4-(aminomethyl)quinolin-2(1*H*)-one derivatives with an aim to explore its anti-cancer potency.

MATERIALS AND METHODS

Chemistry:
Reagent grade chemicals and solvents were purchased from commercial supplier and used after purification. TLC was performed on silica gel F254 plates (Merck). Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX 1 spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 400 spectrometer (400 MHz) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. *J* values are in Hz. Mass of the compounds were determined by ESI-MS, using a Shimadzu LCMS 2020 apparatus. All reactions were carried out under nitrogen atmosphere.

Synthesis of 4-(bromomethyl)quinolin-2(1H)-one (3)
To a solution of acetoacetanilide**1** (0.056 mmol) in glacial acetic acid (10 mL) containing catalytic amount of iodine, bromine (0.056 mmol) in glacial acetic acid (30 mL) was added at 0-5 ^{o}C, over a period of 30 minutes and then the reaction mixture was stirred at room temperature till the completion of reaction as monitored on TLC. On completion of reaction, it was poured onto crushed ice and the solid thus separated was filtered and washed with cold water several times and dried to yield3-oxo-3-(phenylamino)propanoyl bromide**2**. A solution of compound **2** (1 g) inconc. H_2SO_4(2 mL) on heating at 90-100 ^{o}C for 2 hours, poured into crushed ice, gave crude product which on recrystallization from absolute ethanol gave, off-white fluffy mass of 4-(bromomethyl)quinolin-2(1*H*)-one **3**.

General procedure for the synthesis of compounds 5a-f
A mixture of boc-glycine **4** (1.11 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(1.67 mmol) (EDCI), 1-hydroxybenzotriazole (1.11 mmol) (HOBt), 4-dimethylaminopyridine (1.34mmol) (DMAP) and amine (1^0 and 2^0) (1.22 mmol) in dichloromethane (50 mL) (DCM) was stirred at room temperature for 16 hours. The reaction was monitored using TLC. On completion of the reaction, it was washed with water (2x20 mL), brine (1x10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give the crude product which was then purified by column chromatography using silica gel, employing methanol in dichloromethane (5:95) as eluent to yield desired product as white solid **5a-f**.

General procedure for preparation of compounds 7a-e
Compounds**5a-e**weredeprotected by stirring in a solution of 10% trifluoroacetic acid (TFA) in dichloromethane (DCM). On deprotection of amine, the solvent was evaporated under reduced pressure to give corresponding bases**6a-e**(1.1 mmol), to which a solution of compound **3** (1.0 mmol) in dimethyl formamide (DMF) was added followed by lithium hydroxide monohydrate (2.0 mmol) and the resulting mixture was stirred at room temperature till completion of reaction, as monitored on TLC. On completion of reaction, it was poured onto crushed ice and the solid filtered, dried and recrystallized from absolute ethanol to yield product **7a-e**.

Spectral Data:
4-(bromomethyl)quinolin-2(1H)-one (3)
Yield: 65%; off-white solid; m.p.: 258-260 ^{o}C;IR (KBr): 3316, 3141,3098, 3017, 2968, 2891, 2856, 2742, 1669, 1616, 1552, 1511, 1473, 1435, 1403, 1267, 1206, 1145, 1130, 982, 899, 881, 750, 585cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 4.90 (s, 2H), 6.74 (s, 1H), 7.24 (t, 1H, *J* = 7.6 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.2 Hz), 7.84 (d, 1H, *J* = 8.0 Hz), 11.86 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 59.96, 116.14, 117.19, 117.89, 122.33, 124.17, 130.78, 131.22, 138.92, 147.32, 152.34, 162.37;ESI-MS: *m/z* 237.8 $[M]^+$and 239.8 $[M+2]^+$.

***tert*-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate (5a)**
Yield: 70%; white solid; m.p.: 182-184 ^{o}C;IR (KBr): 3370, 3320, 3204, 3136, 2999, 2968, 2938, 1681, 1673, 1613, 1555, 1520, 1492, 1403, 1391, 1290, 1247, 1180, 1163, 1087, 935, 831, 725cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (s, 9H), 3.71 (d, 2H, *J* = 6.4 Hz), 7.09 (br s, 1H), 7.36 (d, 2H, *J* = 8.8 Hz), 7.61 (d, 2H, *J* = 8.8 Hz), 10.08 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 18.92, 28.61, 44.14, 49.05, 56.52, 78.66, 121.08, 127.20, 129.12, 138.26, 156.45, 168.91;ESI-MS: *m/z*307.0 $[M+Na]^+$.

***tert*-butyl 2-(4-bromophenylamino)-2-oxoethylcarbamate (5b)**
Yield: 75%; white solid; m.p.: 172-174 ^{o}C;IR (KBr):3372, 3320, 3281, 3204, 3134, 2996, 1678, 1611, 1545, 1523, 1491, 1391, 1290, 1246, 1180, 827 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (m, 2H), 7.03-7.06 (m, 1H), 7.11-

7.16 (m, 2H), 7.56-7.59 (m, 2H), 10.01 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 18.92, 28.62, 44.07, 49.05, 56.52, 78.64, 115.65, 115.87, 121.25, 121.33, 135.70, 156.44, 168.65;ESI-MS : *m/z*350.9[M+Na]$^+$.

***tert*-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate(5c)**
Yield: 55%; white solid; m.p.: 156-158 ^{o}C;IR (KBr): 3379, 3319, 3208, 3141, 2987, 2971, 2936, 1690, 1674, 1612, 1549, 1525, 1393, 1316, 1289, 1250, 1170, 935, 821, 729, 580, 505 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 2.22 (s, 3H), 3.95 (br s, 2H), 5.49 (br s, 1h), 7.12 (d, 2H, *J* = 8.4 Hz), 7.40 (d, 2H, *J* = 8.4 Hz), 8.34 (br s, 1H);^{13}C NMR (400 MHz,$CDCl_3$):δ 20.90, 28.32, 45.36, 80.62, 120.09, 129.50, 134.15, 134.89, 156.51, 167.76;ESI-MS: *m/z*265.1[M+H]$^+$.

***tert*-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate (5d)**
Yield: 69%; white solid; m.p.: 166-164 ^{o}C;IR (KBr): 3367, 3323, 3226, 3163, 3103, 3004, 2990, 2941, 1688, 1672, 1619, 1565, 1529, 1508, 1391, 1367, 1292, 1251, 1171, 1155, 1049, 837 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (s, 9H), 3.70 (d, 2H, *J* = 6.0 Hz), 7.05-7.08 (m, 1H), 7.12-7.16 (m, 2H), 7.57-7.61 (m, 2H), 10.01 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 28.62, 44.09, 78.57, 115.64, 115.86, 121.21, 121.28, 135.76, 156.42, 157.17, 159.55, 168.64; ESI-MS: *m/z*291[M+Na]$^+$.

***tert*-butyl 2-(dimethylamino)-2-oxoethylcarbamate (5e)**
Yield: 50%; white solid; m.p.: 66-68 ^{o}C;IR (KBr):3563, 3259, 2939, 1569, 1732, 1683, 1645, 1569, 1551, 1534, 1503, 1454, 1431, 1365, 1335, 1248, 1176, 1044, 956, 939, 868, 814, 736, 642, 551cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.94 (s, 3H), 2.96 (s, 3H), , 3.92 (s, 2H), 5.51 (s, 1H);^{13}C NMR (400 MHz, $CDCl_3$):δ 28.33, 35.55, 35.82, 42.24, 79.52, 155.83, 168.26; ESI-MS: *m/z* 203.0 [M+H]$^+$.

***tert*-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate(5f)**
Yield: 45%; viscous liquid;IR (KBr): 3283, 3044, 2978, 2935, 2879, 1722, 1636, 1535, 1450, 1403, 1364, 1340, 1287, 1267, 1253, 1226, 1158, 1041, 940, 869, 856, 804, 766, 643, 548 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.86-1.91 (m, 2H), 1.96-2.01 (m, 2H), 3.37 (t, 2H, *J* = 6.8 Hz), 3.50 (t, 2H, *J* = 6.8 Hz), 3.89 (d, 2H, *J* = 4.4 Hz), 5.52 (br s, 1H);^{13}C NMR (400 MHz, $CDCl_3$):δ 24.15, 25.97, 28.37, 39.43, 43.07, 45.34, 45.94, 155.88, 166.76;ESI-MS: *m/z* 229.0[M+H]$^+$.

N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide (7a)
Yield: 25%; white solid; m.p.: 246-248 ^{o}C;IR (KBr):3336, 3260, 2844, 1660, 1559, 1525, 1432, 1400, 1305, 1173, 1059, 871, 824, 755, 676, 506cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 2.8-3.0 (m, 2H), 3.98 (s, 2H), 6.58 (s, 1H), 7.18-7.82 (m, 10H), 9.90 (s, 1H), 11.60 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 49.51, 52.53, 1116.00, 118.75, 119.99, 121.04, 121.13, 122.10, 124.82, 127.24, 129.05, 130.61, 138.06, 139.33, 149.57, 162.22, 170.73; ESI-MS: *m/z*364.0 [M+Na]$^+$.

N-(4-bromophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide (7b)
Yield: 15%; white solid; m.p.: 260 ^{o}C (decomposes);IR (KBr):3338, 3250, 2854, 1666, 1531, 1435, 1314, 1072, 892, 818, 751cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 2.8-3.0 (m, 2H), 3.98 (s, 2H), 6.58 (s, 1H), 7.07-7.93 (m, 8H), 9.72 (s, 1H), 11.67 (s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 49.54, 52.57, 116.01, 118.76, 120.00, 121.15, 122.11, 124.82, 127.25, 129.05, 130.61, 138.07, 139.34, 149.57, 162.23, 170.74; ESI-MS: *m/z*407.9[M+Na]$^+$.

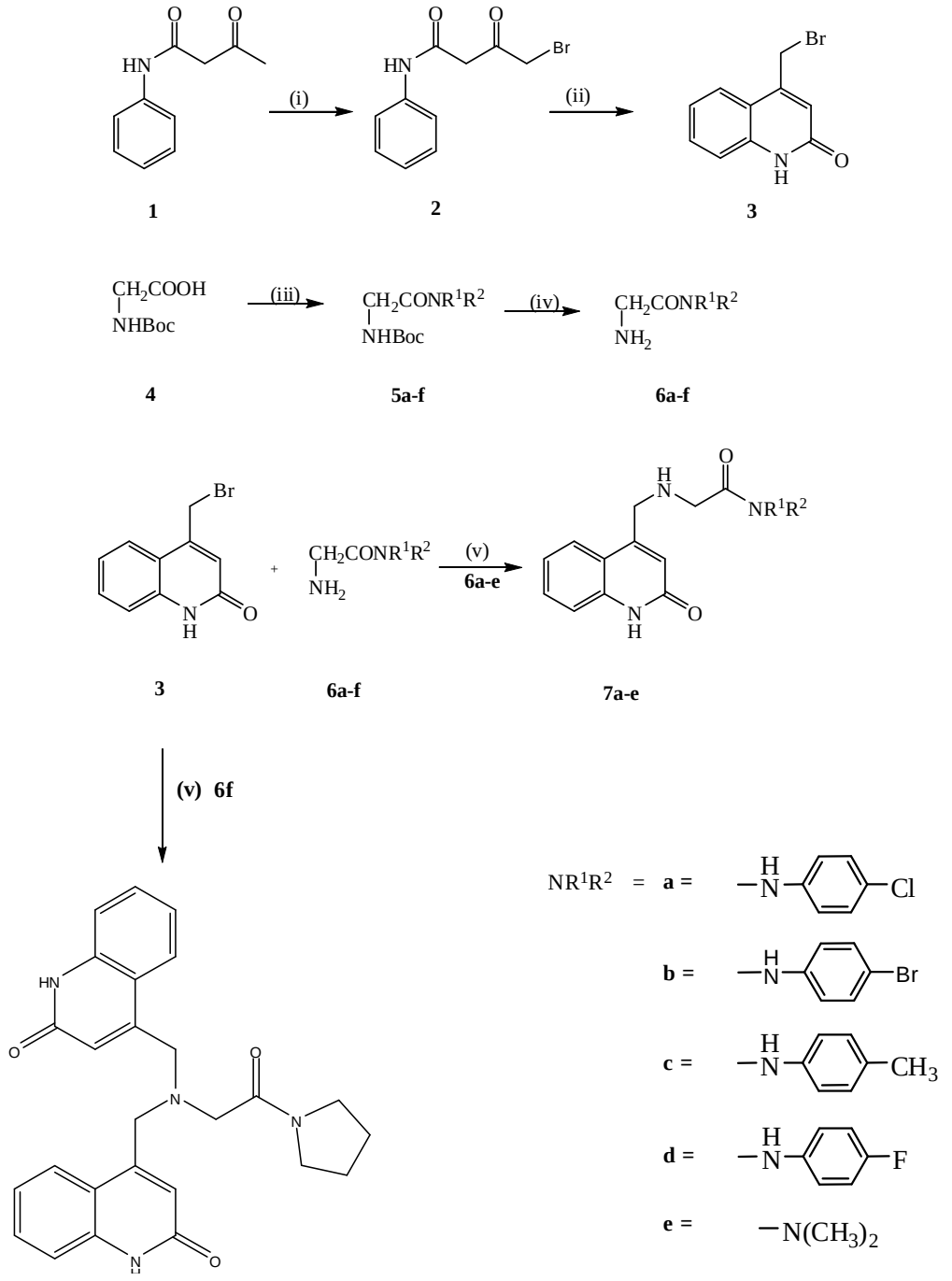
2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)-N-p-tolylacetamide (7c)
Yield: 25%; white solid; m.p.: 240-242 ^{o}C;IR (KBr):3337, 3248, 3000, 2852, 1668, 1661, 1559, 1532, 1436, 1408, 1355, 1316, 1206, 1133, 914, 892, 817, 752, 674 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 2H), 3.99 (s, 2H), 6.58 (s, 1H), 7.07-7.91 (m, 9H), 9.71 (s, 1H), 11.67 (s, 1H); ESI-MS: *m/z*344.0 [M+Na]$^+$.

N-(4-fluorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide (7d)
Yield: 35%; white solid; m.p.: 220 ^{o}C (decomposes);IR (KBr): 3265, 1671, 1614, 1559, 1509, 1468, 1407, 1295, 1216, 1155, 958, 836, 754, 689 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 2.5 (s, 2H), 3.97 (s, 2H), 6.58 (s, 1H), 7.06-7.84 (m, 10H), 9.92 (s, 1H), 11.75 (br s, 1H);^{13}C NMR (400 MHz, DMSO-d_6):δ 26.04, 49.50, 115.55, 115.77, 116.06, 118.76, 119.93, 121.34, 121.42, 122.12, 124.79, 130.60, 135.59, 139.32, 149.62, 157.21, 162.29, 170.53, 174.95; ESI-MS: *m/z*364.0 [M+K]$^+$.

N,N-dimethyl-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide (7e)
Yield: 25%; yellow solid; m.p.: 200 ^{o}C (decomposes);IR (KBr):3260, 2849, 1655, 1557, 1408, 748cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 6H), 4.24 (br s, 2H), 4.49 (br s, 2H), 6.53 (s, 1H), 7.00-7.82 (m, 4H), 11.67 (s, 1H); ESI-MS: *m/z*282.0 [M+Na]$^+$.

4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one (7f)

Yield: 28%; off-white solid; m.p.: 230 ^{o}C (decomposes);IR (KBr):3444,2958, 2845, 1735, 1659, 1556, 1501, 1443, 1421, 1356, 1294, 1262, 1168, 1151, 1036, 941, 883, 772, 679, 632, 572cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 1.70-1.74 (m, 4H), 3.15-3.50 (m, 4H), 4.04 (s, 4H), 6.53 (s, 1H), 6.98-7.87 (m, 8H), 11.62 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): 24.04, 26.08,45.34, 45.94, 55.64, 115.83, 118.94, 121.74, 121.96, 125.70, 130.67, 139.37, 148.36, 162.03, 168.33; ESI-MS: *m/z*465.1[M+Na]$^{+}$.



Scheme 1: **Reagents: (i) Br_2, CH_3COOH, I_2; (ii) conc.H_2SO_4; (iii) EDCI, HOBt, DMAP, various amines, DCM; (iv) 10% TFA in DCM; (v) LiOH.H_2O, DMF**

Cytotoxicity assay:

For testing cytotoxicity potential of test compounds **7a-e**, MTT assay was performed. In a 96 well plate A549 cells were plated(104cells/well in 100 µL of medium) in their exponential growth phase, the cells were incubated for 24 hr. Test compounds were prepared in 1% DMSO at two fold concentration (12.5, 25.0, 50.0 and 100.0µg/mL) and

cells were exposed to different concentration of test compounds. Post incubation media was removed and cell were incubated with 100µL MTTreagent (1 mg/mL) at 37 ^{o}C for 160 min. DMSO (100 µL) was used to solubilize formazan, produced by only viable cells. Plate was placed on micro-vibrator for 5 min to assist solublization; absorbance at 540nm was read by microplate reader. Percentage cytotoxicity was calculated against control (media with DMSO only) for test compounds **7a-e.**

RESULTS AND DISCUSSION

Chemistry

Bromination of acetoacetanilide**1** using bromine in glacial acetic acid gavebromoacetoacetanilide**2** which on cyclization with concentrated sulphuric acid (conc. H_2SO_4) gave4-(bromomethyl)quinolin-2(*1H*)-one**3**. The structure of compound **3** was confirmed from its IR spectrum which showed a strong band at 1653 cm^{-1} for the lactam carbonyl while its ^{1}H NMR spectrum showed two singlets, one at δ 4.90 for the methylene protons at C-4 and another at δ 11.86 for the –NH lactam proton. Presence of M^+ and $[M+2]^+$ peak of equal intensity confirmed the presence of bromine in the structure of **3.**

Commercially available boc-protected glycine **4** was reacted with various amines in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), 4-dimethyl aminopyridine (DMAP) to yield the corresponding C-substituted amide derivatives of glycine **5a-f**as shown in Scheme 1.

The IR spectrum of **5a** showed two bands at 1681 and 1673 cm^{-1} for the amide carbonyls while in its^{1}H NMR spectrum a peak at δ 3.71 for the methylene protons of glycine and two doublets at δ 7.36 and 7.61 for the aromatic protons and molecular ion peak at *m/z* 307.0 $[M+Na]^+$ in the ESI-MS spectrum confirmed the formation of **5a.** The IR, ^{1}H NMR, ^{13}C NMR and ESI-MS spectra of compounds **5b-f**confirmed their structures. Deprotection of boc-protected glycine amides **5a-f** by trifluoroacetic acid (TFA) gave corresponding bases **6a-f**which were not isolated and used for subsequent reaction directly after concentration.

Reaction of **3** with aromatic and cyclic aliphatic bases has been reported to be a facile one. But due to the incorporation of glycyl moiety, further reaction of **3** with **6a-f**in the presence of a base was unsuccessful. Initially, organic bases like triethyl amine (TEA) and diisopropyl ethylamine (DIPEA) and later inorganic bases like potassium carbonate (K_2CO_3) were used from 3 to 10 equivalents.Effect of change of solvent and temperature on the progress of reaction was also studied but all the reactions failed.

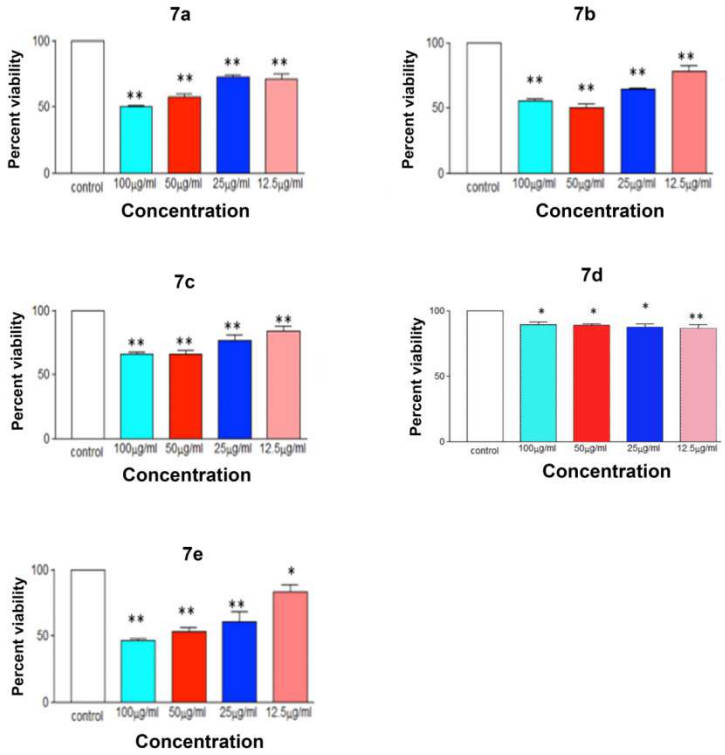
Later, the reaction succeeded by use of a very strong inorganic base, lithium hydroxide monohydrate using dimethylformamide (DMF) as a solvent, at room temperature itself. Thus use of strong base, gave the desired substituted 4-(bromomethyl)quinolin-2(1*H*)-onederivatives **7a-e**as shown in Scheme 1. The IR spectrum of **7a** showed two strong bands at 3336 and 3260 cm^{-1} for –NH stretching vibrations of amide group and a strong band at 1660 cm^{-1} for the amide carbonyl group. The ^{1}H NMR spectrum of **7a** showed two singlets at δ 2.9 and 3.9 for the –CH_2 groups, three singlets at δ 6.58, 9.90 and 11.60 indicated three –NH protons and the remaining aromatic protons were observed from δ 7.18-7.82, thus confirmed the structure of **7a**.

An interesting observation under similar reaction conditions was,disubstitution of the glycyl amino –NH_2 group by **3** thereby leading to formation of **7f** which due to its poor solubility was not evaluated for its anti-cancer potency. The structure of **7f** was confirmed by its IR spectrum which showed bands at 3414 cm^{-1} for –NH of amide group and a strong band at 1659 cm^{-1} indicating lactam carbonyl group. The ^{1}H NMR spectrum of **7f** showedmultiplet from δ 1.70-1.74 for four protons (C2-C3) and other multiplets at δ 3.15-3.50 for the remaining four protons (C1, C4) of the pyrrolidine moiety; a singlet at δ 4.04 indicated the two sets of –CH_2 protons attached to the quinolinone system and multiplets from δ 6.53 to 7.87 for the ten aromatic protons thus confirmed the formation of disubstituted product **7f**. Further, ESI-MS spectrum of **7f** showed a peak at *m/z* 465 for $[M+Na]^+$ also supported the formation of **7f**.

Biological activity

All the compounds **7a-e**were then tested against lung cancer cell line A549 cell line employing MTT assay. The results are shown in Figure 2.

Figure 1: MTT assay of compounds 7a-e



Data expressed as mean ± S.E.M. for n=3.
**P<0.05, **P<0.01, ***P<0.001 compared with control (DMSO)*

CONCLUSION

For the better understanding of the structure activity relationship various *para*- substituted aniline, an aliphatic secondary amine and a cyclic aliphatic amine derivativesof the 4-bromoquinolone motif were synthesized, **7a-e**. From the MTT assay it can be concluded that amongst the test compounds **7a-e**, *para*- substituted aniline derivatives showed good cytotoxicityand amongst them*p*-bromo aniline derivative **7b** is the most cytotoxic, while the aliphatic dimethyl amine derivative **7e** is the most potent anti-cancer agent synthesized in the series.

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REFERENCES

[1] J. A. Salomon, H. Wang, M. K. Freeman, T. Vos, A. D. Flaxman, A. D. Lopez, C. J. L. Murray, *Lancet*, **2012**,380, 2144.
[2] B. Letafat, S. Emami, N. Mohammadhosseini, M. A. Faramarzi, N. Samadi, A. Shafiee, A. Foroumadi, *Chem. Pharm. Bull.* (Tokyo), **2007**,55, 894.
[3] B. K. Srivastava, M. Solanki, B. Mishra, R. Soni,S. Jayadev, D. Valani, M. Jain, P. R. Patel, *Bioorg. Med. Chem.Lett.*, **2007**, 17, 1924.
[4] A. Ryckebusch, D. Garcin, A. Lansiaux, J. Goossens, B. Baldeyrou, R. Houssin, C. Bailly, J.Hénichart, *J. Med. Chem.*,**2008**,51, 3617.
[5] M. G. Ferlin, G. Chiarelotto, V. Gasparotto, L. Dalla Via, V. Pezzi, L. Barzon, G. Palù, I. Castagliuolo, *J. Med. Chem.*,**2005**, 48, 3417.
[6] V. Gasparotto, I. Castagliuolo, G. Chiarelotto, V. Pezzi, D. Montanaro, P. Brun, G. Palù, G. Viola, M. G. Ferlin, *J. Med. Chem.*, **2006**, 49, 1910.
[7] O. Tabarrini, M. Stevens, V. Cecchetti, S. Sabatini, M. Dell'Uomo, G. Manfroni, M. Palumbo, C. Pannecouque, E. De Clercq, A.Fravolini,*J. Med. Chem.*, **2004**,47, 5567.

[8] V. Cecchetti, C. Parolin,S. Moro, T. Pecere, E. Filipponi, A. Calistri,O. Tabarrini, B. Gatto, M. Palumbo, A. Fravolini,*J. Med. Chem.*,**2000**, 43, 3799.
[9] R. G. Kalkhambkar, G. M. Kulkarni, C. M., Kamanavalli, N. Premkumar, S.M.B. Asdaq, C. M. Sun, *Eur. J. Med. Chem.*,**2008**, 43,2178.
[10] R. G. Kalkhambkar, G.Aridoss, G. M. Kulkarni, R. M.Bapset, T. Y. Mudaraddi, N. Premkumar, Y. T. Jeong, *Monatsh Chem.*,**2011**, 142,305.
[11] C. Bonnefous, J. E. Payne, J. Roppe, H. Zhuang, X. Chen, K. T. Symons, P. M. Nguyen, M. Sablad, N. Rozenkrants, Y. Zhang, L. Wang, D. Severance, J. P. Walsh, N. Yazdani, A. K. Shiau, S. A. Noble, P. Rix, T. S. Rao, C. A. Hassig, N. D. Smith,*J. Med. Chem.*,**2009**,52,3047.
[12] N. Priya, A. Gupta, K. Chand, P. Singh, A. Kathuria, H. G. Raj, V. S. Parmar, S. K. Sharma, *Bioorg.Med. Chem.*,**2010**,18, 4085.
[13] J.A. Sparano, S. Moulder, A. Kazi, D. Coppola, A. Negassa, L. Vahdat, T. Li, C. Pellegrino, S. Fineberg, P. Munster, M. Malafa, D. Lee, S. Hoschander, U. Hopkins, D. Hershman, J. J. Wright, C. Kleer, S. Merajver, S. M. Sebti,*Clin. Cancer Res.*, **2009**, 15, 2942.
[14] B. Joseph,F. Darro,A. Behard,B. Lesur,F. Collignon,C. Decaestecker, A. Frydman, G. Guillaumet, R. Kiss, *J. Med. Chem.*,**2002**,45, 2543.
[15] N. Kumar, P. V. Raj, B. S. Jayshree, S.S., Kar, A. Anandam, S. Thomas, P. Jain, A. Rai, C. M. Rao, *Chem. Biol. Drug Des.*, **2012**, 80, 291.
[16] N. Kumar, I. Dhamija, P. V. Raj, B. S. Jayashree, V. Parihar, S. N. Manjula, S. Thomas, N. G. Kutty, C. M.Rao, *Arabian Journal of Chemistry*,**2014**, 7, 409.