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Synthesis and *In Vitro* Cytotoxic Evaluation of 7-Chloro-4-anilino-quinoline Amide Derivatives

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A series of new amide derivatives of 4-anilino-quinoline have been synthesized and evaluated *in vitro* cytotoxic activity against the human hepatocellular carcinoma (HepG2), human lung carcinoma (SK-LU-1) and human breast cancer (MCF-7). Compound **5g** was found to be most potent cytotoxic activity against HepG2 and MCF-7 cell lines with IC_{50} values of 2.09 and 4.63 µg/mL, respectively. Compound **5e** exhibited significant cytotoxic activity against three cell lines with IC_{50} values ranging from 5-10 µg/mL.

Key Words: Anticancer, Amide, Cell line, Cytotoxic, Quinoline.

INTRODUCTION

The recent statistical data have revealed that cancer-diseases characterized by uncontrolled cell growth, metastasis and invasion are responsible for approximate 13 % of all human deaths throughout the world[1]. Three most fatal cancers are lung, liver and breast cancer. It is documented that in many cellular processes, including cell proliferation, metabolism, survival and apoptosis, there are involvements of protein tyrosine kinase enzymes. The tumor growth and progression are known to be driven by several protein tyrosine kinases, which are activated in cancer cells[2]. The uncontrolled cell growth is known to result from over expression, constitutive activation or mutation caused by inappropriate or uncontrolled activation of these kinases[3].

Quinoline, a heterocyclic aromatic compound, is considered to be an important scaffold and prevalent in variety of pharmacologically active synthetic compounds as well as in naturally occurring products[4]. Studies have shown that quinoline derivatives possess a wide range of biological activities, including antimalarial[5], antibacterial[6], antitumor[7,8], anticancer[9], antidepressant activities[10]. Recent continued researches about cytotoxic activities of quinoline derivatives have resulted in a lot of encouraging results[11].

Among different structural classes of tyrosine kinase inhibitions, 4-anilino-quinazoline and its bio-isosteric, 4-anilino-quinolines have been reported to be the most promising molecules, which were selective inhibition to epidermal cell growth factor receptor (EGFR)[12]. Some recently synthesized anilino-quinoline derivatives exhibited potent inhibitory activity against MCF-7 cell line[13].

In continuing program in the search for new candidates as potential cytotoxic agents, we design the synthesis of two new series of amides of 4-anilino-quinoline **4a-g**, **5a-g** and report the results in this communication.

EXPERIMENTAL

All chemicals and reaction solvents were purchased from Merck and Aldrich. Melting points were determined in open capillaries on Electrothermal IA 9200 Shimazu apparatus and uncorrected. IR spectra were recorded on FT-IR IMPACT-410 using neat or KBr discs. ^{1}H NMR spectra were recorded on Bruker AVANCE 500 MHz spectrometer in $CDCl_3$ and DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS and coupling constants (*J*) are expressed in hertz (Hz). Mass spectra were recorded on FTICR MS Varian. Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with Ultraviolet (UV) fluorescent silica gel (Merck 60 F_{254}) and spots were visualized by Dragendoff reagent. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), brd (broad doublet) t (triplet), m (multiplet). Column chromatography was carried out using silica gel 40-230 mesh. Solvents were commercially available materials of reagent grade.

General procedure for the synthesis of 2 and 3: A mixture of 4,7-dichloroquinoline (1 g, 5.05 mmol) and 3 and 4-aminobenzoic acid (0.691 g, 5.05 mmol) in MeOH (25 mL) was refluxed for 6 h. The solvent was evaporated under vacuum and solid mass was obtained. The solid was recrystallized by methanol to obtain compound **2** and **3** as yellow solids.

4-(7-Chloro-quinolin-4-yl)-benzoic acid (2): m.p. ≥ 300 ºC. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11,16 (br, 1H), 8.86 (d, *J* = 9 Hz, 1H), 8.61 (d, *J* = 7 Hz, 1H), 8.17 (d, *J* = 2Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 9.90 (dd, *J* = 2Hz, 9Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.5, 153.8, 144.2, 141.4, 139.8, 138.2, 128.8, 127.4, 126.1, 124.2, 119.7, 117.8, 101.2.

4-(7-Chloro-quinolin-3-yl)-benzoic acid (3): m.p. ≥ 300 ºC. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.4 (br, 1H, NH), 8.95 (d, *J* = 9 Hz, 1H), 8.55 (d, *J* = 7 Hz, 1H), 8.21 (d, *J* = 2 Hz, 1H), 8.01 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.87 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.5, 154.7, 143.6, 139.2, 138.3, 137.5, 132.5, 130.3, 129.5, 128.0, 127.4, 126.3, 125.8, 119.3, 116.2, 100.4.

General procedure for the synthesis of amide derivatives: 4a-g and 5a-g: A mixture of **2** or **3** (1 mmol) in CH_2Cl_2 (15 mL) and amines (1 mmol), EDC (1 mmol), DMAP (0.3 mmol) were stirred at room temperature for 24 h. The reaction mixture was then extracted with water. The organic phase was separated and dried on anhydrous Na_2SO_4. The solvent was evaporated to obtain residues which after recrystallization in methanol or column chromatography on silica gel using proper solvent mixtures as eluting systems to give target compounds.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-phenyl-piperazine-1-yl)-methanone (4a): m.p. 226-227 ºC. IR (KBr, ν_{max}, cm^{-1}): 3429, 3062, 2971, 2899, 1651, 1566, 1457, 1346, 1269, 1120, 871. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.58 (d, *J* = 5.5 Hz, 1H), 8.04-8.02 (m, 2H), 7.44 (m, 3H), 7.31-7.25 (m, 4H), 7.06 (d, *J* = 5Hz, 1H), 6.96-6.91 (m, 3H), 3.85 (brs, 4H), 3.23 (br, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 151.8, 150.9, 149.8, 146.9, 141.7, 135.5, 130.9, 129.3, 128.9, 128.8, 126.3, 121.9, 121.4, 120.8, 118.6, 116.8, 103.5. 57.7, 49.4. ESI-MS m/z 443 $[M + H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-methyl-piperidin-1-yl)-methanone (4b): m.p. 233-234 ºC. IR (KBr, ν_{max}, cm^{-1}): 3422, 2978, 2879, 1644, 1577, 1464, 1345, 1256, 1157, 1111, 874. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.51 (d, *J* = 5 Hz, 1H), 8.20 (d, *J* = 9.5 Hz, 2H), 7.97 (d, *J* = 2Hz, 1H), 7.36 (dd, *J* = 2Hz, 9Hz, 1H), 7,29 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 5 Hz, 1H), 4.69 (brs, 1H), 3.83 (brs, 1H), 2.86-2.65 (br, 2H), 1.77-1.67 (br, 3H), 1.25 (br, 2H), 0.99 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.1, 151.6, 149.7, 147.7, 141.5, 135.2, 131.5, 128.4, 128.2, 125.8, 122.7, 121.8, 118.7, 102.7, 44.5, 31.1, 27.6, 21.6. ESI-MS m/z 380 $[M + H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-piperidin-1-yl-methanone (4c): m.p. 247-248 ºC. IR (KBr, ν_{max}, cm^{-1}): 3404, 3060, 1665, 1560, 1444, 1375, 1311, 1260, 1118, 875. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52 (d, *J* = 5 Hz, 1H), 8.15 (d, *J* = 9Hz, 1H), 8.0 (d, *J* = 1.5 Hz, 1H), 7.40 (dd, *J* = 2Hz, 9Hz, 1H), 7.33 (d, *J* = 8.5Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 5Hz, 1H), 3.74-3.47 (m, 4H), 1.71-1.59 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 151.6, 149.7, 141.3, 135.4, 131.8, 128.6, 128.4, 126.0, 125.9, 122.3, 121.8, 118.6, 102.9, 46.9, 25.9, 24.6. ESI-MS m/z 366 $[M+H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-ethyl-piperazin-1-yl)-methanone (4d): m.p. 232-234 ºC. IR (KBr, ν_{max}, cm^{-1}): 3201, 2886, 1665, 1561, 1455, 1362, 1295, 1097, 815. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (d, *J* = 5.5Hz, 1H), 8.05-8.02 (m, 2H), 7.44 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 5.5 Hz, 1H), 3.82-3.5 (brs, 4H), 2.50-2.45 (br, 4H), 2.04 (br, 2H, CH_2), 1.12 (t, *J* = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 151.7, 149.7, 147.2, 141.5, 135.5, 131.3, 128.8, 128.7, 126.3, 121.9, 121.6, 118.6, 103.3, 52.3 (3C), 11.9. ESI-MS m/z 395 $[M + H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-methyl-piperazin-1-yl)-methanone (4e): m.p. 224-2250C. IR (KBr, ν_{max}, cm^{-1}): 3200, 1658, 1544, 1455, 1329, 1217, 1098, 866. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (d, *J* = 5 Hz, 1H), 8.06 (d, *J* = 9 Hz, 1H), 8.02 (d, *J* = 2 Hz, 1H), 7.44 (dd, *J* = 2 Hz, 9Hz, 1H), 7.39 (d, *J* = 8 Hz, 2H), 7.24 (d, *J* = 8 Hz, 2H), 7.03 (d, *J* = 5 Hz, 1H), 3.80-3.48 (br, 4H, $2CH_2$), 2.47 (brs, 4H, $2CH_2$), 2.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 151.7, 149.7, 147.2, 141.5, 135.5, 131.1, 128.8, 128.7, 126.2, 122.1, 121.6, 118.6, 103.2, 55.6, 46.0, 39.7. ESI-MS m/z 381 $[M + H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-pyrrolidin-1-yl-methanone (4f): m.p. 288-289 ºC. IR (KBr, ν_{max}, cm^{-1}): 3229, 2833, 1665, 1500, 1444, 1366, 1200, 1081, 827, 775. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 500 MHz): δ 8.63 (s, 1H), 8.55 (d, *J* = 5 Hz, 1H), 8.29 (d, *J* = 9 Hz, 1H), 7.95 (d, *J* = 2 Hz, 1H), 7.58 (d, *J* = 8 Hz, 2H), 7.43 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.38 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 5 Hz, 1H), 3.64 (brs, 2H), 3.64 (m, 2H), 3.54 (m, 2H), 1.99 (m, 2H), 1.92 (m, 2H). ^{13}C NMR ($CDCl_3$, + DMSO-d_6, 125 MHz): δ 168.5, 151.3, 149.4, 147.1, 141.8, 134.4, 131.5, 128.2, 127.8, 124.9, 123.2, 120.4, 118.5, 102.7, 49.1, 23.8. ESI-MS m/z 352 $[M + H]^+$.

[4-(7-Chloro-quinolin-4-ylamino)-phenyl]-(2-methyl-piperidin-1-yl)-methanone (4g): m.p. 222-223 ºC. IR (KBr, ν_{max}, cm^{-1}): 3425, 2888, 2777, 1646, 1519, 1454, 1326, 1203, 1054, 906, 816, 740. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.53 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 9 Hz, 1H), 8.00 (d, *J* = 2 Hz, 1H), 7.83 (br, 1H), 7.41 (dd, *J* = 2.5 Hz, 9 Hz, 9 Hz, 1H), 7.29 (d, *J* = 9 Hz, 2H), 7.18 (d, *J* = 9 Hz, 2H), 6.98 (d, *J* = 5.5 Hz, 1H), 3.06 (br, 1H), 2.12 (br, 1H), 1.74-1.69 (br, 5 H), 1.59 (br, 1H), 1.51(br, 1H), 1.29 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2, 151.8, 149.8, 147.6, 141.1, 135.3, 132.3, 128.7, 127.9, 125.9, 122.4, 122.1, 118.6, 102.8, 46.7, 44.6, 30.4, 26.1, 18.9, 16.2. ESI-MS m/z 380 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-phenyl-piperazin-1-yl)-methanone (5a): m.p. 223-224 ºC. IR (KBr, ν_{max}, cm^{-1}): 3439, 2971, 2899, 1659, 1457, 1306, 1269, 1120, 871. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 500 MHz): δ 8.55 (d, *J* = 5.5 Hz, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 9 Hz, 1H), 7.98 (d, *J* = 2 Hz, 1H), 7.46-7.40 (m, 4H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.18-7.16 (m, 1H), 7.05 (d, *J* = 5 Hz, 1H), 6.94-6.89 (m, 3H), 3.93 (br, 2H), 3.65 (br, 2H), 3.25 (br, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 151.6, 150.6, 149.7, 147.5, 140.8, 136.8, 134.9, 129.4, 128.9, 128.3, 125.4, 122.9, 121.9, 120.4, 120.3, 118.6, 116.5, 113.6, 102.7, 57.6, 49.4. ESI-MS m/z 443 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-methyl-piperidin-1-yl)-methanone (5b): m.p. 147-149 ºC. IR (KBr, ν_{max}, cm^{-1}): 3431, 2979, 2890, 1654, 1457, 1336, 1269, 1120. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.53 (d, *J* = 5 Hz, 1H), 8.02-8.00 (m, 2H), 7.43 (dd, *J* = 2 Hz, 9 Hz, 2H), 7.35 (t, *J* = 8 Hz, 1H), 7.29 (d, *J* = 2 Hz, 1H), 7.22 (s, 1H), 7.10 (d, *J* = 7 Hz,

1H), 6.95 (d, *J* = 5 Hz, 1H), 4.67 (brd, *J* = 10Hz, 1H), 3.77 (brd, *J* = 11.5 Hz, 1H), 3.02 (brs, 1H), 2.77 (brs, 1H), 1.77 (br, 1H), 1.69-1.62 (m, 2H), 1.27-1.22 (m, 1H), 1.11 (s, 1H), 0.98 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 151.8, 149.8, 147.5, 140.3, 137.9, 135.4, 129.6, 128.8, 126.1, 123.1, 122.4, 122.0, 120.7, 118.5, 102.8, 48.2, 34.7, 31.1, 21.6. ESI-MS m/z 380 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(piperidin-1-yl)-methanone (5c): m.p. 127-129 ºC. IR (KBr, ν_{max}, cm^{-1}): 3339, 2989, 2890, 1656, 1457, 1306, 1266, 1120. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.48 (d, *J* = 5.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 2Hz, 1H), 7.83 (brs, 1H), 7.37(dd, *J* = 2 Hz, 9 Hz, 1H), 7.32-7.28 (m, 2H), 7.20 (s, 1H), 7.07 (d, *J* = 7 Hz, 1H), 6.92 (d, *J* = 5Hz, 1H), 3.70 (brs, 2H), 3.38 (brs, 2H), 2.31 (brs, 2H), 1.68 (brs, 2H), 1.53 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 151.7, 149.8, 147.6, 140.4, 137.7, 135.3, 129.6, 128.6, 125.9, 123.1, 122.3, 122.2, 120.7, 118.5, 102.6, 48.8, 26.5, 24.5. ESI-MS m/z 366 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-ethyl-piperazin-1-yl)-methanone (5d): IR (KBr, neat, ν_{max}, cm^{-1}): 3369, 2988, 2891, 1651, 1457, 1326, 1266, 1122. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.53 (d, *J* = 5.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 8.0 (d, *J* = 2Hz, 1H), 7.83 (brs, 1H), 7.37 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.32-7.28 (m, 2H), 7.18 (s, 1H), 7.07 (d, *J* = 7 Hz, 1H), 6.92 (d, *J* = 5Hz, 1H), 3.80-3.5 (brs, 4H), 2.50-2.45 (br, 4H), 2.14 (br, 2H, CH_2), 1.17 (t, *J* = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 151.5, 149.7, 147.3, 140.4, 137.8, 135.3, 129.6, 128.6, 126.0, 123.1, 122.3, 122.2, 120.5, 118.6, 102.6, 52.2 (3C), 12.1. ESI-MS m/z 395 $[M + H]^+$.

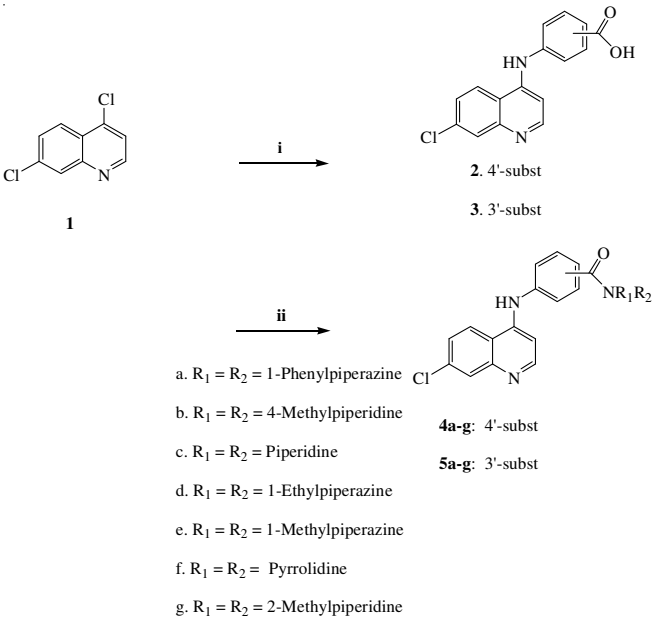
[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(4-methyl-piperazin-1-yl)-methanone (5e): IR (KBr, neat, ν_{max}, cm^{-1}): 3427, 2998, 1665, 1437, 1313, 1266, 1122. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.55 (d, *J* = 5 Hz, 1H), 8.02 (d, *J* = 9 Hz, 1H), 7.99 (d, *J* = 2 Hz, 1H), 7.43 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.10 (d, *J* = 5 Hz, 1H), 3.78-3.40 (br, 4H, $2CH_2$), 2.44 (brs, 4H, $2CH_2$), 2.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 151.9, 149.7, 147.6, 140.3, 138.5, 135.3, 129.4, 128.5, 125.8, 123.6, 122.5, 122.3, 121.3, 118.5, 102.4, 55.8, 46.2, 39.8. ESI-MS m/z 381 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(pyrrolidin-1-yl)-methanone (5f): m.p. 188-189 ºC. IR (KBr, ν_{max}, cm^{-1}): 3421, 2990, 1666, 1439, 1311, 1266, 1122. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.49 (d, *J* = 5 Hz, 1H), 8.12 (d, *J* = 9 Hz, 1H), 7.99 (d, *J* = 2 Hz, 1H), 7.84 (s, 1H), 7.39 (dd, *J* = 2 Hz, 9 Hz, 1H), 7.35-7.32 (m, 3H), 7.21-7.19 (m, 2H), 6.90 (d, *J* = 5 Hz, 1H), 3.62 (t, *J* = 7.0 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 1.98-1.94 (m, 2H), 1.91(m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.2, 151.7, 149.7, 147.7, 140.3, 138.5, 135.3, 129.4, 128.6, 125.9, 123.6, 122.6, 122.4, 121.3, 118.5, 102.6, 46.3, 24.4. ESI-MS m/z 352 $[M + H]^+$.

[3-(7-Chloro-quinolin-4-ylamino)-phenyl]-(2-methyl-piperidin-1-yl)-methanone (5g): m.p. 139-140 ºC. IR (KBr, ν_{max}, cm^{-1}): 3431, 2998, 1656, 1433, 1314, 1266, 1121. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.48 (d, *J* = 5 Hz, 1H), 8.08 (d, *J* = 9 Hz, 1H), 7.99 (d, *J* = 2 Hz, 1H), 7.79 (br, 1H), 7.40 (dd, *J* = 2 Hz, 8.5 Hz, 1H), 7.23-7.28 (m, 2H), 7.16 (m, 1H), 7.05-7.03 (m, 1H), 6.92 (d, *J* = 5 Hz, 1H), 3.01 (br, 1H), 2.23 (brs, 2H), 1.76-1.60 (br, 4H), 1.55-1.38 (m, 2H), 1.24 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 151.7, 149.8, 147.7, 140.4, 138.2, 135.3, 129.6, 128.6, 125.9, 122.9, 122.4, 121.8, 120.4, 118.5, 102.6, 46.6, 44.4, 30.3, 26.0, 25.2, 16.1. ESI-MS m/z 380 $[M + H]^+$.

RESULTS AND DISCUSSION

The synthetic route for the preparation of novel amide derivatives of quinoline **4a-f**, **5a-f** is described in **Scheme-I**. At first, 4,7-dichloroquinoline (**1**) was reacted with **3** and 4-aminobenzoic acid in methanol under reflux for 6 h. The precipitated solids resulting from reaction mixture were filtered, dried and recrystallized from methanol to yield the intermediate compounds **2** and **3** in good yields as yellow solids.



Scheme-I: Reagents and condition: (i) aminobenzoic acids, MeOH, reflux, 6 h. (ii) amines, CH_2Cl_2, EDC, DMAP, rt, 24 h

These compounds were then reacted with secondary amines in dichloromethane at room temperature for 24 h in the presence of EDC and DMAP as catalysts to furnish the target compounds **4a-g** and **5a-g** in moderate to good yields. Compound **4a** and **5a** were obtained by recrystallization in methanol after a work-up with water and dichloromethane. Compounds **4b-e**, **5b**,**c** were purified by column chromatography on silica gel using dichloromethane:methanol (96:4) as an eluting system. Other compounds after a work-up with water and dichloromethane were purified by column chromatography on silica gel using dichloromethane:methanol:Et_3N (98:2:0.2) as an eluting system. The structure of compounds was confirmed by the ^{1}H NMR, ^{13}C NMR, IR and MS. For structural elucidation, the compound **5a** was an example. The presence of more five prontons of the phenyl ring and eight protons of piperazine group was observed in the ^{1}H NMR spectra. In the ^{13}C NMR spectra, four more carbons of phenyl ring were also observed. In addition, the carbon peak of amide carbon was observed at 169.5 ppm in the ^{13}C NMR and a strong peak of amide and broad peak of NH at 1659 and 3439 cm^{-1} in the IR spectra supports the structure of **5a**.

TABLE-1
IN VITRO CYTOTOXIC ACTIVITY DATA FOR COMPOUNDS: **4a-g** AND **5a-g**

No	Compounds	Substituents (R)	IC_{50} (μg/mL)		
			HepG2	SK-LU-1	MCF-7
1	**4a**	1-Phenylpiperazine	>128	>128	>128
2	**4b**	4-Methylpiperidine	72.33	97.96	40.61
3	**4c**	Piperidine	76.86	>128	98.41
4	**4d**	1-Ethylpiperazine	86.61	89.93	98.68
5	**4e**	1-Methylpiperazine	>128	>128	>128
6	**4f**	Pyrrolidine	>128	>128	>128
7	**4g**	2-Methylpiperidine	>128	>128	>128
8	**5a**	1-Phenylpiperazine	>128	>128	>128
9	**5b**	4-Methylpiperidine	>128	>128	>128
10	**5c**	Piperidine	19.29	66.17	47.99
11	**5d**	1-Ethylpiperazine	21.46	55.11	48.55
12	**5e**	1-Methylpiperazine	6.72	5.35	9.50
13	**5f**	Pyrrolidine	>128	>128	>128
14	**5g**	2-Methylpiperidine	2.09	>128	4.63
15	Ellipticine	–	0.99	0.78	0.82

Note: The reference substance, ellipticine, exhibited cytotoxic activity against HepG2 (ATCC-HB-8065), SK-LU-1 (ATCC-HTB-57) and MCF-7 (ATCC-HTB-22) cells with IC_{50} values of 0.99, 0.78 and 0.82 μg/mL, respectively. The values shown for these compounds are the average of three determinations.

The bio-assay of the synthesized compounds **4a-g** and **5a-g** was carried out at the Institute of Chemistry, Vietnam Academy of Science and Technology.

Though compounds **4a** and **4e** were synthesized and tested for antimalarial and antifilarial activity[14], in this communication, two series of **4a-g** and **5a-g** were evaluated for *in vitro* cytotoxic activity against three human cancer cell lines (HepG2, SK-LU-1 and MCF-7) according to a described protocol[15]. The results are shown in Table-1. The initial structure-activity observations revealed that seven derivatives: **4a**, **4e-g**, **5a-b** and **5f** exhibited no cytotoxic activity against all three cell lines and none of the other derivatives can compare with the reference drug, ellipticine in terms of IC_{50} values. Some derivatives **4c-d** showed weak activity against three cell lines tested. Some other derivatives showed quite noteworthy cytotoxicity. For example, **5c** and **5d** exhibited IC_{50} values of less than 22 μg/mL against HepG2 cell line. Compound **5d** was more active than **4d** with moderate cytotoxicity against HepG2 cell line at IC_{50} value of 21.46 μg/mL while **4d** possessing the same ethylpiperazine group exhibited weak cytotoxic activity against three cell lines. Among the synthesized compounds, compound **5e** exhibited significant cytotoxic activity against three cell lines with the IC_{50} values of 6.72, 5.35 and 9.50 μg/mL, respectively. Especially, compound **5g** showed most potent cytotoxic activity against HepG2 and MCF-7 cell lines with IC_{50} values of 2.09 and 4.63 μg/mL, respectively, but showed no activity against SK-LU-1 cell line. Unexpectedly, compound **4g**, which possessed the same 2-methylpiperidine group, was inactive against three cell lines tested.

Conclusion

We have synthesized a series of new amide anilino-quinoline derivatives through a simple procedure and screened for *in vitro* cytotoxic activity. The results showed that the compound **5g** exhibited most potent cytotoxic activity against HepG2 and MCF-7 cell lines with IC_{50} values of 2.09 and 4.63 μg/mL, respectively. In addition, compound **5e** exhibited significant activity against three cell lines tested.

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REFERENCES

1. For statistical information about cancer, see: WorldHealth Organisation: http://www.who.int/mediacentre/factsheets/fs297/en/.
2. J.D. Jordan, E. M. Landau and R. Iyengar, *Cell*, **103**, 193 (2000).
3. P. Blume-Jensen and T. Hunter, *Nature*, **411**, 355 (2001).
4. T. Eicher and S. Hauptmann, The Chemistry of Heterocycles, Wiley-VCH, Weinheim, edn. 2, p. 316 (2003).
5. P.G. Bray, S.A. Ward and P.M. O'Neill, *Curr. Top. Microbiol. Immunol*., **295**, 3 (2005).
6. (a) P. Narender, U. Srinnivas, M. Ravinder, A.B. Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U.S.N. Murthy and J.V. Rao, *Bioorg. Med. Chem*., **14**, 4600 (2006); (b) A. Nayyar, A. Malde, E. Couthinho and R. Jain, *Bioorg. Med. Chem*., **14**, 7302 (2006).
7. G. Roma, M.D. Braccio, G. Grossi, F. Mattioli and M. Ghia, *Eur. J. Med. Chem*., **35**, 1021 (2000).
8. R. Kakadiya, H. Dong, A. Kumar, D. Narsinh, X. Zhang, T.C. Ting-Chao Chou, T.C. Lee, A. Anamik Shah and T.L. Su, *Bioorg. Med. Chem*., **18**, 2285 (2010).
9. A. Dlugosz and D. Dus, *Farmaco*, **51**, 367 (1996).
10. S. Kumar, S. Bawa, S. Drabu, H. Gupta, L. Machwal and R. Kumar, *Eur. J. Med. Chem*., **46**, 670 (2011).
11. (a) R.C. Montenegro, L.V. Lotufo, M.O. Moraes, C. do O Pessoa, F.A.R. Rodrigues, M.L.F. Bispo, L.N.F. Cardoso, C.R. Kaiser and M.V.N. Souza, *Med. Chem.*, **7**, 599 (2011); (b) J. Bernzweig, B. Heiniger, K. Prasain, J. Lu, D.H. Hua and T.A. Nguyen, *Med. Chem*., **7**, 448 (2011).
12. (a) J.A. Adams, *Chem. Rev*., **101**, 2271 (2001); (b) J. Dumas, *Curr. Opin. Drug Discov. Develop*., **4**, 378 (2001).
13. E.I. Aly, *J. Am. Sci*., **6**, 73 (2010).
14. P.M.S. Chauhan, S. Sharma and D.S. Bhakuni, *Indian J. Chem.*, **25B**, 828 (1986).
15. D.A. Scudiero, R.H. Shoemaker, D.P. Kenneth, A. Monks, S. Tierney, T.H. Nofziger, M.J. Currens, D. Seniff and M.R. Boyd, *Cancer Res*., **48**, 4827 (1988).