Synthesis and Characterization of Novel 4-oxo-1, 4-dihydroquinoline-3-carboxamide Derivatives from Diazomethane and HCl (g)

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Abstract
Reaction of thionyl chloride with 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid 1 gave acid chloride 2. Compound 2 was reacted with glycine and D-glutamic acid to afford 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)aminopantandioic acid 3a and 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)aminoacetic acid 3b. These compounds were changed to chloromethyl ketone derivatives 5a-b from diazomethane and then HCl (g) in dry diethyl ether.

Keywords: Quinoline, glycine, D-glutamic acid, Diazomethane, Chloromethyl ketone.

Introduction
Heterocyclic compounds containing nitrogen have significant applications in medicinal, biological, industrial and synthetic organic chemistry. Quinolones are among the most widely of pharmaceutical compounds, and they are known because of their anti-malarial [1-3], leishmanicidal [4], antibacterial [5], and anticancer activities [6-9]. These groups of compounds are also used for the preparation of structures with electronic and photonic properties [10]. Fluoroquinolone derivatives are a successful achievement in biological and pharmaceutical activities [11-12], while some related derivatives exhibit antitumor activity [13-15]. In this part, 7-chloro-6-fluoro-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids and 6,7-difluoro-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids are useful intermediates for the synthesis of quinolone antibacterial agents [16]. On the other hand chloromethyl...
ketone compounds are known as an inhibitor of pig heart acetoacetyl-CoA thiolase [17] and severe acute respiratory syndrome coronavirus main protease (SARS-CoV Mpro) [18]. In view of the above facts our current interest is focused on the synthesis of some heterocyclic compounds containing nitrogen atom [19]. So, we decided to study chloromethyl ketonate of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid 1 from diazomethane and dry HCl (g).

**Experimental**

All of Chemical compounds and Solvents were purchased from Merck without further purification. TLC silica gel 60, aluminum sheets were purchased from Merck. The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (the samples as KBr disks for the range 4000–400 cm⁻¹). The 1H and 13C NMR spectra were recorded on a Bruker AC-500 spectrometer (¹H, 500 MHz; ¹³C, 125.75 MHz) using TMS as an internal standard. Mass-spectrometric measurements were made on an Agilent 6890 N Network GC system. The C, H, N analyses were performed by the microanalytical service of the N.I.O.C. Research Institute of Petroleum Industry.

**Synthesis of 2-(7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)aminopentandioic acid (3a)**

Compound 2 (2 mmol, 0.63 g) was dissolved in 4 ml of benzene and slowly Sodium carbonate (3.7 mmol, 0.39 g), D-glutamic acid (2.3 mmol, 0.16 g) and 3 ml water were added to it in ice bath and the reaction vessel was stirred overnight. The mixture was acidified using hydrochloric acid 2N to pH=5-6 and extracted with chloroform. The solvent in organic phase was removed on a rotary evaporator and the residue was recrystallized from ethyl acetate. Slowly, water phase was arrived to pH=2 and the vessel was kept overnight in refrigerator. The crystals formed were separated. The progress of the reaction was monitored by TLC using n-hexane–ethyl acetate (1:2) and detected by UV lamp (254 & 366 nm). Colorless prism crystals. Yield 58 %, m.p. 210 °C, Rf=0.4.

FT-IR (ν/cm⁻¹): 2500-3000 (COOH), 3274 (NH), 1719 (C=O), 1663 (C=O Amide), 1613 (C=C). ¹H NMR (CDCl₃, 500 MHz) δH: 13.20 (s, 1H, COOH), 12.50 (s, 1H, COOH), 10.82 (s, 1H, COOH), 12.50 (s, 1H, COOH), 10.82 (s, 1H, NH), 8.56 (s, 1H, CH Aromatic), 8.20 (d, 1H, CH Aromatic, J=9 Hz), 7.99 (d, 1H, CH Aromatic, J=9 Hz), 7.99 (d, 1H, CH Aromatic, J=30 Hz), 3.45 (m, 1H, CH in cyclopropane), 2.22-2.50 (m, 2H, CH₂), 1.53 (m, 4H, 2CH₂). ¹³C NMR (125.75 MHz) δC: 175.08 (C-4), 175.04 (C-14), 173.12 (C-18), 165.60 (C-13), 157.06 (C-6), 155.06 (C-2), 149.22 (C-9), 137.59 (C-7), 129.03 (C-10), 127.42 (C-8), 119.37 (C-3), 114.29 (C-5), 61.45 (C-
Synthesis of 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)amino acetic acid (3b)

Compound 2 (2 mmol, 0.63 g) was dissolved in 4 ml of benzene and slowly Sodium carbonate (3.7 mmol, 0.39 g), glycine (2.3 mmol, 0.17 g) and 3 ml water were added to it in ice bath and the reaction vessel was stirred overnight. The mixture was acidified using hydrochloric acid 2N to pH=5-6 and then extracted with chloroform. The solvent in organic phase was removed on a rotary evaporator and the residue was recrystallized from ethyl acetate. Slowly, water phase was arrived to pH=2 and the vessel was kept overnight in refrigerator. The crystals formed were separated. The progress of the reaction was monitored by TLC using n-hexane–ethyl acetate (1:2) and detected by UV lamp (254 & 366 nm). The product was separated as colorless plate crystals. Yield 63%, m.p. 190 °C, Rf=0.5.

FT-IR (ν/cm⁻¹): 2400-3500 (COOH), 3283 (NH), 2995 (CH), 1707 (C=O). ¹H NMR (CDCl₃, 500 MHz) δ_H: 10.30 (s, 1H, NH), 8.64 (s, 1H, CH Aromatic), 8.25 (d, 1H, CH Aromatic, J=9 Hz), 8.03 (d, 1H, CH Aromatic, J=5.5 Hz), 4.45 (s, 2H, CH₂), 3.49 (m, 1H, CH in cyclopropane), 1.41 (m, 2H, CH₂ in cyclopropane), 1.20 (m, 2H, CH₂ in cyclopropane). MS: m/z 410/412 [M⁺]. Anal Calcd. for C₁₈H₁₆C₇FN₂O₆: C, 52.68; H, 3.90; N, 6.82. Found: C, 52.56; H, 3.98; N, 6.78.

Diazomethane was synthesized by using the reported procedure [21].

Synthesis of 7-Chloro-1-cyclopropyl-N-[5-diazo-1-(diazoacetyl)-4-oxopantyl]-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxamide (4a)

N-methyl morpholine (NMM) (1.6 mmol, 0.2 ml) was added to a solution of 3a (0.8 mmol, 0.32 g) in dry tetrahydrofuran (THF) (12 ml) in -20°C (acetone, N₂ (Liq)) under anhydrous conditions. Isobutyl chloroformate (IBCF) (1.6 mmol, 0.24 ml) was added, stirred for 15 min at -20°C. Cold THF (10ml) was added and the solution was filtered. The filtered was added to a cold solution of diazomethane in diethyl ether (48ml) Reaction mixture was kept 2h in 0 °C and then allowed to warm to room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and detected by UV lamp (254 & 366 nm). The solvent was removed under reduced pressure.

The crude product was subjected to column chromatography on silica gel using ethyl acetate as an eluent affording pure compound 4a as yellow powder. Yield 78 %, m.p. 243 °C, Rf= 0.3.

FT-IR (ν/cm⁻¹): 3253 (NH), 2804 (CH Aromatic), 1701 (C=O), 1626 (C=C). ¹H NMR (CDCl₃, 500 MHz) δ_H: 10.38 (s, 1H,

NH), 8.86 (s, 1H, CH Aromatic), 8.21 (m, 2H, CH Aromatic), 5.78 (s, 1H, CH), 5.48 (s, 1H, CH), 4.66 (m, 1H, CH), 3.68 (m, 1H, CH in cyclopropane), 2.00-2.28 (m, 2H, CH), 1.74 (m, 2H, CH₂), 1.40 (m, 4H, 2CH₂), MS: m/z 458/460 (M⁺).

Anal Calcd. for C₂₀H₁₆ClFN₆O₄: C, 52.40; H, 3.49; N, 18.34. Found: C, 52.58; H, 3.39; N, 18.41.

**Synthesis of 7-Chloro - 1 - cyclopropyl -N³-(diazo-2-oxopropyl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (4b)**

N-methyl morpholine (NMM) (1.6 mmol, 0.2 ml) was added to a solution of 3b (0.8 mmol, 0.27 g) in dry tetrahydrofuran (THF) (12 ml) in -20°C (acetone, N₂ (Liq)) under anhydrous conditions. Isobutyl chloroformate (IBCF) (1.6 mmol, 0.24 ml) was added, stirred for 15 min at -20°C. Cold THF (10ml) was added and the solution was filtered. The filtered was added to a cold solution of diazomethane in diethyl ether (48ml) Reaction mixture was kept 2h in 0 °C and then allowed to warm to room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and detected by UV lamp (254 & 366 nm). The solvent was removed under reduced pressure. The crude product was subjected to column chromatography on silica gel using ethyl acetate as an eluent affording pure compound 4b as white powder. Yield 68 %, m.p. 200 °C, RF=0.5.

FT-IR (ν/cm⁻¹): 3259 (NH), 1725 (C=O), 1675 (C=O Amide), 1621 (C=C). ¹H NMR (CDCl₃, 500 Hz) δ: 10.12 (s, 1H, NH), 8.87 (s, 1H, CH Aromatic), 8.23 (m, 2H , CH Aromatic), 8.59 (s, 1H, CH=N=N), 4.50 (s, 2H, CH₂), 3.60 (m, 1H, CH in cyclopropane), 1.48 (m, 2H, CH₂ in cyclopropane), 1.26 (m, 2H ,CH₂ in cyclopropane). MS: m/z 362/364 [M⁺].

¹³C NMR (125.75 MHz) δ: 177.39 (C-15), 166.20 (C-14), 157.45 (C-13), 154.93 (C-6), 148.63 (C-2), 137.78 (C-9), 135.82 (C-16), 129.15 (C-7), 128.33 (C-10), 117.54 (C-8), 113.10 (C-3), 108.84 (C-5), 58.12 (C-14), 35.64 (C-11), 9.41 (C-12,12'). Anal Calcd. for C₁₆H₁₂ClFN₄O₃: C, 53.03; H, 3.31; N, 15.46. Found: C, 52.95; H, 3.52; N, 15.32.

**Synthesis of 7-Chloro-N-[5-chloro-1-(2-chloroacetyl)-4-oxopantyl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (5a)**

Compound 4a (1 mmol, 0.46 g) was inserted into ice bath, then HCl (gas) in dry diethyl ether was added dropwise to it and the progress of the reaction was monitored by TLC using n-hexane–ethyl acetate (1:2) and detected by UV lamp (254 & 366 nm). The solution was filtered and dried. The crude product was subjected to column chromatography on silica gel using n-hexane–ethyl acetate (1:3) as an eluent affording pure compound 5a as yellow powder. Yield 72 %, m.p. 195 °C, RF=0.6.

FT-IR (ν/cm⁻¹): 3297 (NH), 3259 (NH), 1725 (C=O), 1675 (C=O Amide), 1621 (C=C).
(C=O), 865 (CH\textsubscript{2}Cl).

**\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz)** \(\delta_H\): 9.73 (s, 1H, NH), 8.74 (s, 1H, CH Aromatic), 8.25 (d, 1H, CH Aromatic, \(J = 10\) Hz), 7.93 (d, 1H, CH Aromatic, \(J = 5\) Hz), 4.44 (s, 2H, CH\textsubscript{2}Cl), 4.13 (s, 2H, CH\textsubscript{2}Cl), 3.97 (m, 1H, CH), 3.40 (m, 1H, CH in cyclopropane), 1.78 -2.00 (m, 2H, CH\textsubscript{2}), 1.44 (m, 2H, CH\textsubscript{2}), 1.37 (m, 4H, CH2).

**\textsuperscript{13}C NMR (125 MHz)** \(\delta_C\): 176.99 (C-19), 165.97 (C-15), 157.03 (C-4), 153.73 (C-13), 150.22 (C-6), 136.73 (C-2), 127.78 (C-9), 126.45 (C-7), 121.57 (C-10), 112.67 (C-8), 112.55 (C-3), 108.37 (C-5), 59.87 (C-16), 54.46 (C-20), 54.36 (C-14), 45.93 (C-18), 34.96 (C-11), 15.37 (C-17), 10.85 (C-12, 12'). MS: \(m/z\) 474/476/478/480 [M]\textsuperscript{+}. Anal Calcd. for C\textsubscript{18}H\textsubscript{18}Cl\textsubscript{3}FN\textsubscript{2}O\textsubscript{4}: C, 50.63; H, 3.79; N, 5.90. Found: C, 50.57; H, 3.71; N, 5.87.

**Synthesis of 7-Chloro-N3-(2-chloro-2-oxopropyl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (5b)**

Compound 4b (1 mmol, 0.36 g) was inserted in ice bath, then HCl\textsubscript{(gas)} in dry diethyl ether (25ml) was added dropwise to it and the progress of the reaction was monitored by TLC using \(n\)-hexane–ethyl acetate (1:2) and detected by UV lamp (254 & 366 nm). The solution was filtered and dried. The crude product was subjected to column chromatography on silica gel using \(n\)-hexane–ethyl acetate (1:3) as an eluent affording pure compound 5b as White powder. Yield 75 %, m.p. 186 °C, RF=0.7.

**FT-IR (\nu/cm\textsuperscript{–1})**: 3220 (NH), 3049 (=CH), 2842 (CH Aromatic), 1714 (C=O), 1620 (C=C), 854 (CH\textsubscript{2}Cl). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 Hz) \(\delta_H\): 9.82 (s, 1H, NH), 8.86 (s, 1H, CH Aromatic), 8.21 (m, 2H, CH Aromatic), 5.21 (s, 2H, CH\textsubscript{2}Cl), 4.76 (s, 2H, CH\textsubscript{2}), 3.62 (m, 1H, CH in cyclopropane), 1.47 (m, 2H, CH in cyclopropane), 1.26 (m, 2H, CH\textsubscript{2} in cyclopropane).

**\textsuperscript{13}C NMR (125.75 MHz)** \(\delta_C\): 177.21 (C-15), 175.62 (C-4), 165.8 (C-13), 158.65 (C-6), 149.58 (C-2), 138.45 (C-9), 125.68 (C-7), 122.43 (C-10), 120.58 (C-8), 118.73 (C-3), 112.62 (C-5), 108.02 (C-14), 36.30 (C-16), 20.95 (C-11), 10.96 (C-12, 12'). MS: \(m/z\) 370/372/374 [M]\textsuperscript{+}. Anal Calcd. for C\textsubscript{16}H\textsubscript{15}Cl\textsubscript{2}FN\textsubscript{2}O\textsubscript{3}: C, 51.89; H, 3.51; N, 7.57. Found: C, 51.81; H, 3.48; N, 7.58.
Results and discussion

In order to synthesize these new derivatives of chloromethyl ketone compounds, D-glutamic acid and glycine were designed and these compounds synthesized via the route outlined in Scheme (1-3) starting from compound 1. The key intermediate 7-Chloro-1-cyclopropyl-N-[5-diazo-1-(diaoacetyl)-4-oxopantyl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide 4a 7-Chloro-1-cyclopropyl-N3-(diazo-2-oxopropyl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide 4b were obtained via the sequence of acylation, nucleophilic substitution and diazomethylation. These were followed by reaction with acid hydrochloride (gas) [20] in dry diethyl ether to give chloromethyl ketone derivatives of compounds 5a-b.

Besides, the IR, 1H NMR, 13C NMR, Mass spectrometry and Microanalysis data of all the synthesized compounds were in full agreement with the proposed structures. Initially, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbonyl chloride 2 was synthesized by using the reported procedure [17]. Then, we carried out the reaction of compound 2 with D-glutamic acid and glycine in benzene and in the presence of sodium carbonate to obtain two compounds, which were characterized to be 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)aminopantandioic acid 3a in 58% yield and 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)aminoacetic acid 3b in 63% yield, respectively. The structures of compounds 3a-b were determined by NMR, IR, mass spectrometry and Microanalysis (Scheme 2). The 1H NMR spectra of 3a and 3b showed three and two exchangeable protons, respectively. The COOH protons of the amino acid 3a residue resonated at lower field than that of the NH proton which was assigned to the singlet at δ 10.82 ppm. The 13C NMR spectra of 3a and 3b showed two types of signals, in the downfield and upfield region. The FT-IR spectra of compound 3b exhibited a broad vibration bond at 3283 cm⁻¹ (NH) and sharp vibration bond at 1707 cm⁻¹ (C=O). The mass spectra of 3a (which showed double signals for monochlorinated in accordance with the contents of the stable natural isotopes, Cl35 and Cl37 at m/z 410/412 that is characteristic for molecular ion) are in agreement with the molecular formula C18H16ClF3N2O6. The fragment at m/z 365 (23%) can be attributed to the loss of COOH from the molecular ion.
In continuation, the reaction of compounds 3a-b with diazomethane afforded 7-Chloro-1-cyclopropyl-N-[5-diazo-1-(diazoacetyl)-4-oxopantyl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide 4a in 78% yield and 7-Chloro-1-cyclopropyl-N3-(diazo-2-oxopropyl)-6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxamide 4b in 68% yield. These compounds were fully characterized by IR, NMR, MS spectroscopy and elemental analysis (Scheme 3).

The elemental analysis result of compounds 4a and 4b were satisfactory. The infrared spectrum of compound 4b showed broad absorption for NH stretching vibrations in 3259 cm$^{-1}$, CO vibrations (amide) in 1675 cm$^{-1}$, and C=C vibration in 1621 cm$^{-1}$. The
$^1$H NMR spectra of 4a exhibited two sharp signals at $\delta$ 5.78 and $\delta$ 5.48, 4b exhibited a sharp signal at $\delta$ 5.59 ppm for protons of CH=N=N. The mass spectra of compounds 4a and 4b displayed a molecular ion peak at m/z 458/460 and 362/364, respectively. Any initial fragmentation involves loss from or complete loss of the side chain and part of the quinoline ring system.

Finally, we reacted compounds 4a-b with anhydrous HCl to afford 7-chloro-N-[5-chloro-1-(2-chloroacetyl)-4-oxopantyl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide 5a in 72% yield and 7-chloro-N$^3$-(2-chloro-2-oxopropyl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide 5b in 75% yield. The structure of compounds 5a-b was deduced from elemental analyses, IR, NMR spectra and MS spectroscopy (Scheme 3).

These compounds 5a-b revealed the methylene chloride bond in the IR spectrum at 865 cm$^{-1}$ and 854 cm$^{-1}$, respectively. The $^1$H NMR of compound 5b revealed a sharp signal at 5.21 ppm for protons of methylene chloride and $^{13}$C NMR of compound 5a indicates two sharp signals for methylene chloride carbons at 54.46 and 54.36 ppm. The mass spectra of this compound revealed a molecular ion peak at m/z 474/476/478/480 for trichlorinated compound. Any initial fragmentation involves loss from or complete loss of the side chain and part of the quinoline ring system.

**Conclusion**

In summary, the presented reactions carried the advantage of being performed under mild conditions and good yields. These compounds could be interesting in pharmacology and biology.

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**References**

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