Journal of Applied Chemical Research, 9, 4, 31-40 (2015)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

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

Navabeh Nami*, Seyed Marziyeh Kazemi

Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Mazandaran, Iran

(Received 23 Feb. 2015; Final version received 16 May 2015)

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) aminopantandioicacid 3a and 2-(7-chloro-1-cyclopropyl-6-fluoro -4- oxo-1,4-dihydroquinoline-3-carbonyl)aminoaceticacid **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

***Corresponding author:** Navabeh Nami, Associate Professor, Department of Chemistry, Qaemshahr Branch, Islamic Azad University, P.O.Box: 47631–35953 Mazandaran, Iran. E-mail: Navabehnami@yahoo.com, Tel. 00989111133578, Fax: +98 123 214504.*

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 (^{1}H, 500 MHz; ^{13}C, 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 in overnight. The mixture was acidified using hydrochloric acid 2N to *p*H=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 *p*H=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). ^{1}H NMR ($CDCl_3$, 500 MHz) δH: 13.20 (s, 1H, COOH), 12.50 (s, 1H, COOH), 10.82 (s, 1H, NH), 8.56 (s, 1H, CH Aromatic), 8.20 (d, lH, CH Aromatic, *J*=9 Hz), 7.99 (d , lH, CH Aromatic, *J*= 5.5Hz), 4.55 (t, lH, CH, *J*=30 Hz), 3.45 (m, lH, CH in cyclopropane), 2.22-2.50 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.53 (m, 4H, $2CH_2$). ^{13}C NMR (125.75 MHz) δ_C: l75.08 (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-

15), 35.20 (C-17), 14.82 (C-11), 14.6 (C-16), 8.67 (C-12, 12'). MS: *m/z* 410/412 $[M]^+$. Anal Calcd. for $C_{18}H_{16}C_lFN_2O_6$: C, 52.68; H, 3.90; N, 6.82. Found: C, 52.56; H, 3.98; N, 6.78.

*Synthesis of 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbonyl)amino aceticacid (**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 *p*H=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 *p*H=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). ^{1}H NMR ($CDCl_3$, 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, CH_2 in cyclopropane), 1.20 (m, 2H, CH^2 in cyclopropane). MS: *m/z* 338/340 (M^+). Anal Calcd. for $C_{15}H_{12}C_lFN_2O_4$: C, 53.25; H, 3.55; N, 8.27. Found: C, 53.14; H, 3.68; N, 8.35.

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, $N_{2\ (Liq)}$) 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). ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 10.38 (s, 1H,

NH), 8.86 (s, 1H, CH Aromatic), 8.2l (m, 2H, CH Aromatic), 5.78 (s, 1H, CH), 5.48 (s, 1H, CH), 4.66 (m, lH, CH), 3.68 (m, lH, CH in cyclopropane), 2.00-2.28 (m, 2H, CH), 1.74 (m, 2H, CH_2), 1.40 (m, 4H, $2CH_2$). MS: m/z 458/460 (M^+).

Anal Calcd. for $C_{20}H_{16}C_lFN_6O_4$: 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 -N^3-(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 -20oC (acetone, $N_{2\ (Liq)}$) under anhydrous conditions. Isobutyl chloroformate (IBCF) (1.6 mmol, 0.24 ml) was added, stirred for 15 min at -20oC. 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). ^{1}H NMR ($CDCl_3$, 500 Hz) δ_H: 10.12 (s, 1H, NH), 8.87 (s, 1H, CH Aromatic), 8.23 (m, 2H , CH Aromatic), 5.59 (s, lH, CH=N=N), 4.50 (s, 2H, CH_2), 3.60 (m, lH, CH in cyclopropane), 1.48 (m, 2H, CH_2 in cyclopropane), 1.26 (m, 2H ,CH_2 in cyclopropane). MS: ***m/z*** 362/364 [M] $^+$. ^{I3}C NMR (125.75 MHz) δ_C: 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 $C_{16}H_{12}C_lFN_4O_3$: 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), 1700 (C=O), 1628

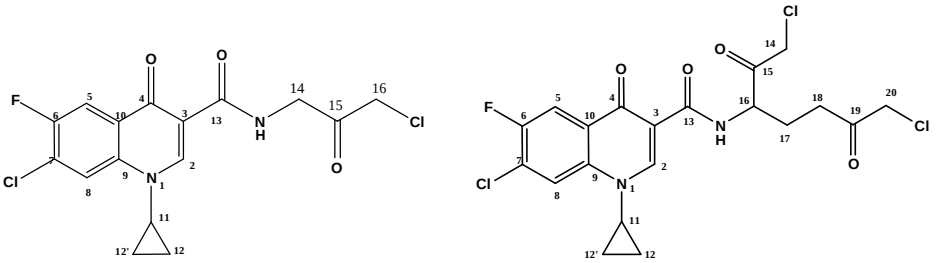
(C=C), 865 (CH_2Cl). ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 9.73 (s, 1H, NH), 8.74 (s, 1H, CH Aromatic), 8.25 (d, l H, CH Aromatic, *J* =10 Hz), 7.93 (d, lH, CH Aromatic, *J* =5 Hz), 4.44 (s, 2H, CH_2C1), 4.13 (s, 2H, CH_2C1), 3.97 (m, 1H, CH), 3.40 (m, lH, CH in cyclopropane), 1.78 -2.00 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 1.37 (m, 4H, CH2). ^{13}C NMR (125 MHz) δC: 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 $[M]^+$. Anal Calcd. for $C`H_{18}C_{l3}FN_2O_4$: 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-caboxamide (**5b**)*

Compound **4b** (1 mmol, 0.36 g) was inserted in ice bath, then $HCl_{(gas)}$ 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 crud 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 (ν/cm^{-1}): 3220 (NH), 3049 (=CH), 2842 (CH Aromatic), 1714 (C=O), 1620 (C=C), 854 (CH_2Cl). ^1H NMR ($CDCl_3$, 500 Hz) δ_H: 9.82 (s, 1H, NH), 8.86 (s, 1H. CH Aromatic), 8.21 (m, 2H, CH Aromatic), 5.21 (s, 2H, CH_2C1), 4.76 (s, 2H, CH_2), 3.62 (m, lH, CH in cyclopropane), 1.47 (m, 2H, CH in cyclopropane), 1.26 (m, 2H, CH_2 in cyclopropane).

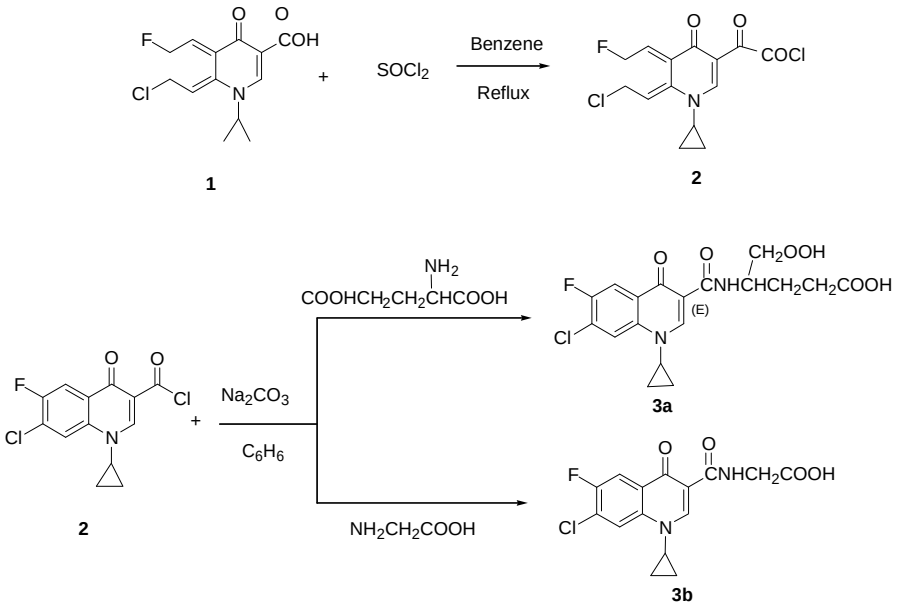
^{13}C NMR (125.75 MHz) δ_C: 177.21 (C-15), 175.62 (C-4), 165.8 (C-13), 158.65 (C-6), 149.58 (C-2), 138.45 (C-9), 125.68 (C-7), 122.43 (C-10), 120.58 (C-8), 118.73 (C-3), 112.62 (C-5), 108.02 (C-14), 36.30 (C-16), 20.95 (C-11), 10.96 (C-12, 12'). MS: *m/z* 370/372/374 $[M]^+$. Anal Calcd. For $C_{16}H_{13}Cl_2FN_2O_3$: C, 51.89; H, 3.51; N, 7.57. Found: C, 51.81; H, 3.48; N, 7.58.



Scheme1. The structure of compound 5a-b

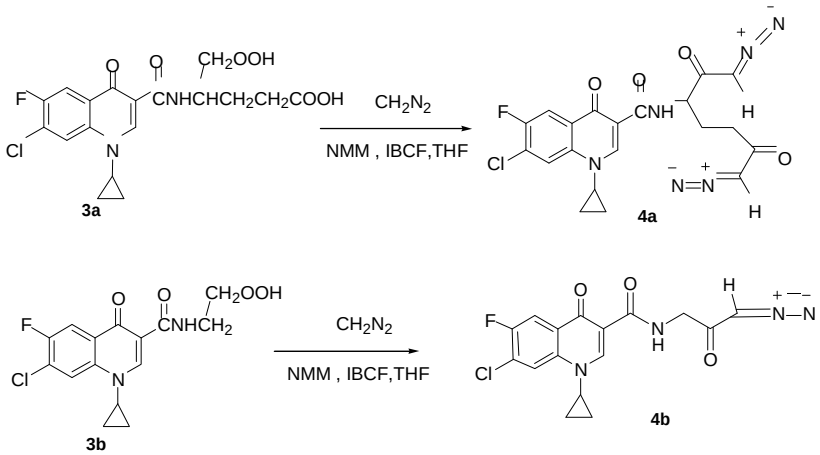
Results and discussion

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-(diazoacetyl)-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, ^{1}H NMR, ^{13}C 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-dihydro quinoline-3-carbonyl)aminopantandioicacid 3a in 58% yield and 2-(7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro quinoline-3-carbonyl)aminoaceticacid **3b** in 63% yield, respectively. The structures of compounds **3a-b** were determined by NMR, IR, mass spectrometry and Microanalysis (Scheme 2). The $_{1}$H 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 ^{13}C 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 $C_{18}H_{16}ClFN_2O_6$. The fragment at m/z 365 (23%) can be attributed to the loss of COOH from the molecular ion.



Scheme 2. Synthesis of compound **2** and **3a-b**

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-dihydro quinoline-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).

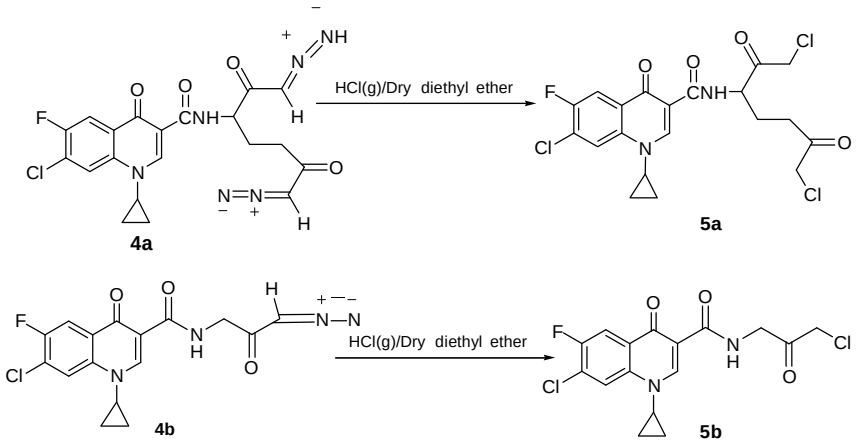


Scheme 3. Synthesis of compound **4a-b**

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 δ 5.78 and δ 5.48, 4b exhibited a sharp signal at δ 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).



Scheme4. Synthesis of compound 5a-b

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.

Acknowledgements

This work was supported by Islamic Azad University, Qaemshahr Branch.

References

[1] M.P. Lamontagne, A. Markovac, M.S.

Khan, *J. Med. Chem*., 25, 964 (1982).

[2] M.P. Lamontagne, P. Blumbergs, R.E. Strube, *J. Med. Chem*., 25, 1094 (1982).

[3] J. Wiesner, R. Ortmann, H. Jomaa, M.M. Schlitzer, *Angew. Chem., Int. Ed*. 42, 5274 (2003).

[4] J. Dade, O. Provot, H. Moskowitz, J. Mayrargue, E. Prina, *Chem. Pharm. Bull*., 49, 480 (2001).

[5] P. Veyssier, A. Bryskier, Dihydrofolate reductase inhibitors, nitroheterocycles (furans), and 8-hydroxyquinolines. In A. Bryskier (ed.), *Antimicrobial agents: Antibacterials and Antifungals*. ASM Press, Washington, DC, 941 (2005).

[6] N.H.P. Cnubben, H.M. Wortelboer, van J.J. Zanden, I.M.C.M. Rietjens, van P.J. Bladeren, *Expert Opin. Drug Metab. & Toxicol*., 1, 219 (2005).

[7] R.G. Boyle, S. Travers, *Anticancer Agents Med. Chem*., 6, 281 (2006).

[8] M. Kawase, N. Motohashi, C*urr. Drug Targets*, 4, 31 (2003).

[9] M.L. Levitt, P.P. Koty, *Invest. New Drugs*. 17, 213 (1999).

[10] (a) X. Zhang, A.S. Shetty S.A., Jenekhe, *Macromolecules*, 32, 7422 (1999). (b) S.A. Jenekhe, L. Lu, M.M. Alam, *Macromolecules*, 34, 7315 (2001).

[11] (a) K. Nakatani, S. Sando, I. Saito, *Bioorg. Med. Chem*., 2001, 9, 2381. (b) C. He, S.J. Lippard, *Inorg. Chem*., 40, 1414 (2001).

[12] (a) A.D. Da Silva, M.V. De Almeida, M.V.N. De Souza, M.R.C. Couri, Curr. *Med. Chem*., 10, 21 (2003). (b) L.A. Mistcher, *Chem. Rev*., 105, 559 (2005).

[13] (a) H.S. Elsea, P.R. McGuirk, T.D. Gootz, M. Moynihan, N. Osheroff, *Antimicrob. Agents Chemother*., 37, 2179 (1993). (b) K.D. Bromberg, A.B. Burgin, N. Osheroff, *Biochemistry*, 42, 3393 (2003).

[14] T. Yoshinari, E. Mano, H. Arakawa, M. Kurama, T. Iguchi, S. Nakagawa, N. Tanaka, A. Okura, *Jpn. J. Cancer Res*., 84, 800 (1993).

[15] (a) H. Arakawa, E. Mano, N. Hakoda, T. Yoshinari, S. Nakagawa, A. Okura, *Anti-cancer Drug Des.* 11, 221 (1996). (b) A.M. Kamat, J.I. DeHaven, D.L. Lamm, Urology, 54, 56 (1999). (c) C. Nishijima, K. Kawada, K. Ohara, T. Shinomiya, S. Fukuda, A. Nakamura, T. Sawai, M. Ikekita, *Res. Comm. Biochem. Cell Mol. Biol*., 6, 21 (2002). (d) D. Huang, K. Okada, C. Komori, E. Itoi, T. Suzuki, *Cancer Sci*., 95, 845 (2004).

[16] (a) R. Wise, J.M. Andrews, L.J. Edwards, *Antimicrob. Agents Chemother*., 23, 559 (1983). (b) D. Felmingham, M.D. O'Hare, M.J. Robbins, R.A. Wall, A.H. Williams, A.W. Cremer, G.L. Ridgeway, R.N. Gruneberg, *Drugs Exp. Clin. Res*., 11, 317 (1985).

[17] D.P. Bloxham, R.A. Chalkley, J.S. Coghlin, W. Salam, *Biochem. J*., 175, 999 (1978).

[18] K. Phakthanakanok, K. Ratanakhanokchai, K.L. Kyu, P. Sompornpisut, A. Watts, S. Pinitglang, A computational analysis of SARS

cysteine proteinase-octapeptide substrate interaction: implication for structure and active site binding mechanism of Seventh *Asia Pacific Bioinformatics Conference (APBC 2009) Beijing, China*, 13-16 Jan 10, S48 (2009).

[19] H.A. Oskooie, M.M. Heravi, N. Nami, A. Nazari, *Heterocycl. Commun*., 11, 101 (2005).

[20] Pascal (Ed), P. Noveau Traité de Chimie Minérale, Masson: Paris, XVI, 194 (1960).

[21] F. Arndt, *Org Syntheses Coll*., 2, 461 (1935).