Available online at www.sciencedirect.com

SciVerse ScienceDirect

Chinese Chemical Letters 23 (2012) 515–517

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

Synthesis and antitumor and antibacterial evaluation of fluoro-quinolone derivatives (III): Mono- and bis-Schiff-bases

Guo Qiang Hu [a,*], Xiao Kui Wu [a], Guo Qiang Wang [a], Nan Nan Duan [a], Xiao Yi Wen [a], Tie Yao Cao [a], Yin Jun [a], Wang Wei [a], Song Qiang Xie [a], Wen Long Huang [b]

[a] *Institute of Chemistry & Biology, Henan University, Kaifeng 475001, China*
[b] *China Pharmaceutical University, Nanjing 210009, China*

Received 16 November 2011
Available online 29 March 2012

Abstract

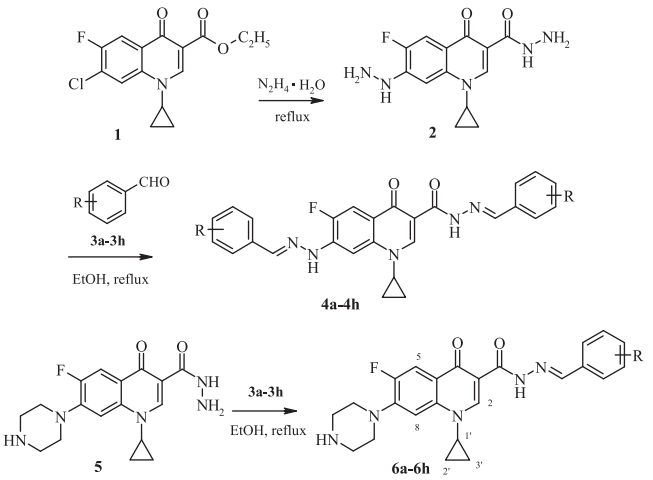
To further explore an efficient modified route for the shift from an antibacterial fluoroquinolone to an antitumor one, mono-Schiff bases **6a–6h** related to ciprofloxacin C3 carbonylhydrazone and bis-Schiff bases **4a–4h** corresponding to C3/C7 carbonylhydrazone/hydrazone attached on a skeleton of ciprofloquinolone were designed and synthesized, and their *in vitro* antitumor activity against CHO, HL60, L1210 cells and antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* were also reported.

Keywords: Fluoroquinolone; Schiff base; Antitumor evaluation

The discovery of new anticancer lead compounds is an important strategy for further development of new antitumor drugs to overcome clinically common disadvantages such as a poor selectivity and/or multi-drug resistance in the treatment of cancers [1]. Simultaneously, a mechanism- or structure-based rational design from currently available drugs also plays an important role in going to success [2]. Coincidentally, in view of the mechanistic similarities of targeting topoisomerases as eukaryotic ones, a study on the shift from an antibacterial fluoroquinolone to an antitumor one has been an important branch in the topoisomerase inhibitors [3]. Moreover, many attempts mainly focused on the structural changes of current fluoroquinolone drugs related to nitrogen heterocyclic rings attached at the 7-position of quinoline scaffold [4]. In addition, a few of modifications for the carboxylic group at the 3-position were also investigated, and it has been proved that it is not necessary for an antitumor fluoroquinolone to remain a carboxylic group, which could be replaced with a (fused) heterocyclic ring as bioisosterism in our laboratory and others [5]. Unfortunately, it is less known whether a piperazine group at the 7-position should be replaced with an efficient bioisosterism. So, in order to answer if necessary to remain the piperazine ring for an antitumor fluoroquinolone, we designed and synthesized two series of mono Schiff-bases **6a–6h** related to ciprofloxacin C3 carbonylhydrazone and bis Schiff-bases **4a–4h** corresponding to ciproflo-quinolone C3/C7 carbonylhydrazone/hydrazone with their antibacterial and antitumor evaluations (Scheme 1).

* Corresponding author.
E-mail addresses: hgqxy@sina.com.cn, hgq@henu.edu.cn (G.Q. Hu).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2012.01.029



Scheme 1. R: H (**a**); 2-OH (**b**); 4-CH_3O (**c**); 3, 4-OCH_2O (**d**); 3,4,5-$(CH_3O)_3$ (**e**); 3-OH-4-CH_3O (**f**); 4-F (**g**); 4-O_2N (**h**).

Precursor ester **1** of ciprofloxacin in refluxing hydrazine hydrate occurred simultaneously a hydrazinolysis of ester and an nucleophilic substitution of chlorine atom to form 1-cycloproyl-6-fluoro-7-hydrazinoquinolin-4(1*H*)-one-3-carboxylic acid hydrazide **2**. Similarly, ciprofloxacin in refluxing hydrazine hydrate yielded the corresponding hydrazide **5** [6]. A condensation of hydrazides **2** and **5** with appropriate aromatic aldehydes **3a–3h** gave the title compounds bis Schiff bases **4a–4h**, 3-[(substituted benzylidene hydrazino) carbonyl]-7-(*N*′-substituted benzylidene hydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-ones, and mono Schiff bases **6a–6h** [7], 3-[(substituted benzyl-idene hydrazino) carbonyl]-1-cycloproyl-6-fluoro-7-piperazin-1-ylquinolin-4(1*H*)-ones, respectively.

The *in vitro* antitumor activity for compounds **4a–4h** and **6a–6h** against CHO (Chinese hamster ovary), HL60 (human leukemia) and L1210 (murine leukemia) cells was evaluated comparison to cirprofloxacin by the standard MTT assay [5b]. The results demonstrated that both mono- and bis-Schiff bases had an IC_{50} value within 25.0 μmol concentration without a significant difference between them, but comparison ciprofloxacin had a poor activity ($IC_{50} > 150$ μmol/L). Meaningfully, the activity of bis Schiff bases **4a–4h** against L1210 was obviously better than mono Schiff bases **6a–6h** against CHO. In addition, the *in vitro* antibacterial activity showed that both mono and bis Schiff bases had no activity ($MIC_{50} > 64$ μg/mL) against Gram-positive bacteria (*Staphylococcus aureus* ATCC29213) and Gram-negative bacteria (*Escherichia coli* ATCC25922) as compared to that of ciprofloxacin ($MIC_{50} \leq 1.0$ μg/mL) by the means of double tube dilution method [8]. In conclusion, it is unnecessary for a C3 carboxyl and a C7 piperazine ring in an antitumor fluoroquinolone, an intensive study on structure–activity relationship (SAR) of antitumor fluoro-quinolones is value for further development.

The structures of the title compounds **4a–4h** and representative compounds **4a** and **4e** were confirmed by their spectral data [9].

Acknowledgment

This project was supported by the National Natural Science Foundation of China (Nos. 20872028 and 21072045).

References

[1] Y. Zhang, J. Feng, Y. Jia, et al. J. Med. Chem. 54 (2011) 2823.
[2] (a) C.J. Hela, Z. Kang, X. Hou, et al. J. Med. Chem. 54 (2011) 4536;
(b) K.M. Huttunen, H. Raunio, J.L. Rautio, Pharmacol. Rev. 63 (2011) 750.
[3] S.A. Al-Trawneh, J.A. Zahra, M.P. Kamal, et al. Bioorg. Med. Chem. 18 (2010) 5873.
[4] P. Yogeeswari, D. Sriram, R. Kavya, et al. Biomed. Pharmacother. 59 (2005) 501.
[5] (a) G.Q. Hu, L.L. Hou, Y. Yang, et al. Chin. Chem. Lett. 22 (2011) 804;
(b) G.Q. Hu, Y. Yang, L. Yi, et al. Acta Pharm. Sin. B 1 (2011) 172;
(c) Q.D. You, Z.Y. Li, H.Y. Wang, et al. J. Med. Chem. 52 (2009) 5649.
[6] G.Q. Hu, X.K. Wu, X. Wang, et al. Acta Pharm. Sin. 43 (2008) 1112 (in Chinese).

[7] J.H. Zheng, M.S. Thesis, Henan University, 2009.
[8] K. ManjunathaK, B. Poojary, P.L. Lobo, et al. J. Med. Chem. 32 (1989) 537.
[9] 3-(Benzylidene hydrazino-carbonyl)-7-(*N*′-benzylidenehydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-one **4a**: yield 91%, mp 291–293 °C. IR (KBr, *ν*): 3447, 1616, 1527, 1433 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.26 (s, 1H, CONH), 10.37 (s, 7H, NH), 8.68 (s, 1H, H-2), 8.46 (s, 1H, H-5), 8.40 (brs, 2H, 2× CH═N), 8.20 (s, 1H, H-8), 7.77–7.40 (m, 10H, Ph-H), 3.81–3.84 (m, 1H, H′-1), 1.32–1.20 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 468 (M^++H), calcd. 467.51 (M^+). Anal. for $C_{27}H_{22}FN_5O_2$: C 69.37, H 4.74, N 14.98; Found C 69.62, H 4.55, N 15.13. 3-(2-Hydroxybenzylidene hydrazinocarbonyl)-7-(*N*′-2-hydroxy benzylidenehydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-ones **4b**: yield 93%, mp > 300 °C. IR (KBr, *ν*): 3421, 1655, 1547, 1448 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.29 (s, 1H, CONH), 11.34 (s, 7H, NH), 10.40 and 10.32 (2s, 2H, 2× OH), 8.69 (s, 1H, H-2), 8.57 (s, 1H, H-5), 8.32 (brs, 2H, 2× CH═N), 8.21 (s, 1H, H-8), 7.70–6.94 (m, 8H, Ph-H), 3.82 (m, 1H, H′-1), 1.30–1.15 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 500 (M^++H), calcd. 499.51 (M^+). Anal. for $C_{27}H_{22}FN_5O_4$: C 64.92, H 4.44, N 14.02; Found C 65.18, H 4.20, N 14.28. 3-(4-Methoxybenzylidenehydrazinocarbonyl)-7-(*N*′-4-methoxybenzylidene hydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-one **4c**: yield 90%, mp 265–267 °C. IR (KBr, *ν*): 3021, 1632, 1544, 1433 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.19 (s, 1H, CONH), 10.20 (s, 7H, NH), 8.67 (s, 1H, H-2), 8.58 (s, 1H, H-5), 8.32 (brs, 2H, 2× CH═N), 8.19 (s, 1H, H-8), 7.67–7.04 (m, 8H, Ph-H), 3.36 (m, 1H, H′-1), 1.30–1.14 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 528 (M^++H), calcd. 527.56 (M^+). Anal. for $C_{29}H_{26}FN_5O_4$: C 66.03, H 4.97, N 13.27; Found C 66.27, H 4.74, N 13.52. 3-(3, 4-Methylenedioxybenzylidenehydrazinocarbonyl)-7-(*N*′-3, 4-methylenedioxybenzylidenehydrazino)-1-cycloproyl-6-fluoro-quinolin-4(1*H*)-one **4d**: yield 92%, mp > 300 °C. IR (KBr, *ν*): 3086, 1626, 1535, 1449 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.18 (s, 1H, CONH), 10.22 (s, 7H, NH), 8.74 (s, 1H, H-2), 8.36 (s, 1H, H-5), 8.18 (brs, 2H, 2× CH═N), 8.01 (s, 1H, H-8), 7.36–7.00 (m, 6H, Ph-H), 6.11 (s, 4H, 2×OCH_2O), 3.82 (m, 1H, H′-1), 1.31–1.16 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 556 (M^++H), calcd. 555.53 (M^+). Anal. for $C_{29}H_{22}FN_5O_6$: C 62.70, H 3.99, N 12.61; Found C 62.91, H 4.14, N 12.88. 3-(3, 4, 5-Trimethoxybenzylidenehydrazinocarbonyl)-7-(*N*′-3, 4, 5-trimethoxybenzylidenehydrazino)-1-cycloproyl-6-fluoroquinolin- 4(1*H*)-one **4e**: yield 84%, mp 272–274 °C. IR (KBr, *ν*): 3073, 1628, 1546, 1447 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.16 (s, 1H, CONH), 10.24 (s, 7H, NH), 8.63 (s, 1H, H-2), 8.32 (s, 1H, H-5), 8.16 (brs, 2H, 2× CH═N), 8.04 (s, 1H, H-8), 7.43–7.21 (m, 4H, Ph-H), 3.86 and 3.89 (2s, 18H, 6× OCH_3), 3.80 (m, 1H, H′-1), 1.32–1.18 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 648 (M^++H), calcd.647.67 (M^+). Anal. for $C_{33}H_{34}FN_5O_8$: C 61.20, H 5.29, N 10.81; Found C 61.46, H 5.12, N 11.06. 3-(3-Hydroxy-4-methoxybenzylidenehydrazinocarbonyl)-7-(*N*′-3-hydroxy-4-methoxybenzylidenehydrazino)-1-cycloproyl- 6-fluoroquinolin-4(1*H*)-one **4f**: yield 94%, mp > 300 °C. IR (KBr, *ν*): 3365, 1632, 1557, 1448 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.20 (s, 1H, CONH), 11.22 (s, 7H, NH), 9.96 and 10.15 (2s, 2H, 2× OH), 8.68 (s, 1H, H-2), 8.42 (s, 1H, H-5), 8.17 (brs, 2H, 2× CH═N), 8.05 (s, 1H, H-8), 7.52–7.23 (m, 6H, Ph-H), 3.87 (brs, 6H, 2× OCH_3), 3.82 (m, 1H, H′-1), 1.33–1.20 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 560 (M^++H), calcd. 559.56 (M^+). Anal. for $C_{29}H_{26}FN_5O_6$: C 62.25, H 4.68, N 12.52; Found C 62.51, H 4.46, N 12.80. 3-(4-Fluorobenzylidenehydrazinocarbonyl)-7-(*N*′-4-fluorobenzylidene hydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-one **4g**: yield 92%, mp 270–272 °C. IR (KBr, *ν*): 3038, 1630, 1548, 1437 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.24 (s, 1H, CONH), 11.25 (s, 7H, NH), 8.72 (s, 1H, H-2), 8.51 (s, 1H, H-5), 8.20 (brs, 2H, 2× CH═N), 8.12 (s, 1H, H-8), 7.81–7.53 (m, 8H, Ph-H), 3.85 (m, 1H, H′-1), 1.37–1.22 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 504 (M^++H), calcd.503.49 (M^+). Anal. for $C_{27}H_{20}F_3N_5O_2$: C 64.41, H 4.00, N 13.91; Found C 64.68, H 4.13, N 14.12. 3-(4-Nitrobenzylidene hydrazine-carbonyl)-7-(*N*′-4-nitrobenzylidenehydrazino)-1-cycloproyl-6-fluoroquinolin-4(1*H*)-one **4h**: yield 83%, mp > 300 °C. IR (KBr, *ν*): 3047, 1636, 1555, 1445 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 13.28 (s, 1H, CONH), 11.26 (s, 7H, NH), 8.68 (s, 1H, H-2), 8.47 (s, 1H, H-5), 8.23 (brs, 2H, 2× CH═N), 8.16 (s, 1H, H-8), 7.83–7.54 (m, 8H, Ph-H), 3.86 (m, 1H, H′-1), 1.38–1.24 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 558 (M^++H), calcd. 557.50 (M^+). Anal. for $C_{27}H_{20}FN_7O_6$: C 58.17, H 3.62, N 17.59; Found C 58.42, H 3.46, N 17.82. 3-(Benzylidenehydrazinocarbonyl)-1-cycloproyl-6-fluoro-7-piperazin-1-yl-quinolin-4(1*H*)-one **6a**: yield 84%, mp 234–236 °C. IR (KBr, *ν*): 3368, 3038, 1668, 1625, 1473 cm^{-1}; ^1H NMR ($CDCl_3$) *δ*: 13.24 (s, 1H, CONH), 8.84 (s, 1H, H-2), 8.21 (s, 1H, CH═N), 8.06–7.26 (m, 7H, H-5, H-8 and Ph-H), 3.67 (m, 1H, H′-1), 3.34–2.68 (m, 8H, piperazine-H), 1.25–1.20 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 434 (M^++H), calcd. 433.49 (M^+). Anal. for $C_{24}H_{24}FN_5O_2$: C 66.50, H 5.58, N 16.16; Found C 66.76, H 5.38, N 16.44. 3-(3, 4, 5-Trimethoxybenzylidene hydrazinocarbonyl)-1-cycloproyl-6-fluoro-7-piperazin-1-yl-quinolin-4(1*H*)-one **6e**: yield 80%, mp 251–252 °C. IR (KBr, *ν*): 3446, 2941, 1667, 1626, 1479 cm^{-1}; ^1H NMR ($CDCl_3$) *δ*: 13.25 (s, 1H, CONH), 8.77 (s, 1H, H-2), 8.23 (s, 1H, CH═N), 8.01 (d, *J* = 13.2 Hz, H-5), 7.32 (d, *J* = 7.2 Hz, H-8), 7.15 (s, 2H, Ph-H), 3.89, 3.93 (2s, 9H, 3× OCH_3), 3.56 (m, 1H, H′-1), 3.30–3.15 (m, 8H, piperazine-H), 1.38–1.21 (m, 4H, H′-2 and H′-3); MS *m/z*: Found 524 (M^++H), calcd. 523.57 (M^+). Anal. for $C_{27}H_{30}FN_5O_5$: C 61.94, H 5.78, N 13.38; Found C 62.17, H 5.54, N 13.57.