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Synthesis and antitumor evaluation of fluoroquinolone C3 fused heterocycles (II): From triazolothiadiazines to pyrazolotriazoles

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Abstract

To further expand an effective modified route for the shift from an antibacterial fluoroquinolone (FQ) to an antitumor FQ, two series of title compounds based on an isostere of the FQ C3 carboxylic group with two fused heterocyclic rings, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine and pyrazolo[5,1-*c*][1,2,4]triazole, respectively, were designed and synthesized starting from the current antibacterial FQs, and their *in vitro* antitumor activity against L1210, CHO cell lines were evaluated *via* their respective IC_{50} values.

Keywords: Fluoroquinolone; Triazolothiadiazine; Pyrazolotriazole; Antitumor evaluation

Recently, an attempt on the shift from an antibacterial fluoroquinolone (ABFQ) to an antitumor fluoroquinolone (ATFQ) has been also paid an attractive attention based on the mechanistic similarities and sequence homologies exhibited for targeting topoisomerases as the eukaryotic topoisomerases [1]. However, many ATFQs were mainly derived from the structural modifications of clinical ABFQs related to the nitrogen-ring, such as piperazine, bearing the 7-position and the 2-position of FQ scaffold [2,3], whereas few of modifications for the carboxylic group at the 3-position were reported [3,4]. Indeed, it does not seem necessary for an ATFQ to remain the carboxylic group, moreover, a (fused) heterocyclic ring as an isostere of the carboxylic group perfectly showed an anticancer activity as well as an excellent water solubility [5]. Nevertheless, it is less known that heterocylces might be used as efficient isosteres for carboxlate acid. Thus, the lasted attempt on discovery of ATFQs as potential new lead compounds derived from ABFQ C3 fused *s*-triazolothiadiazines **3a**–**3e** and pyrazolo *s*-triazoles **5a**–**5e** (Scheme 1) was reported.

Five starting materials 4-amino-5-mercapto-3-FQ-3-yl-1,2,4-triazole **1a**–**1e** derived from clinical ABFQs corresponding to norfloxacin, ciprofloxacin, enrofloxacin, ofloxacin and levofloxacin, respectively, were prepared according to the known procedure [5]. A condensation of **1** with 4-(chloroacetyl)catechol in sodium hydroxide-ethanol–water solvents at room temperature formed the opening products **2a**–**2e**, respectively. Then, these opening products were directly subjected to an acid catalyzed intramolecular cyclocondensation to yield the corresponding closed-ring products, 3-(6-catechol-4-yl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-quinolon-4(1*H*)-ones **3a**–

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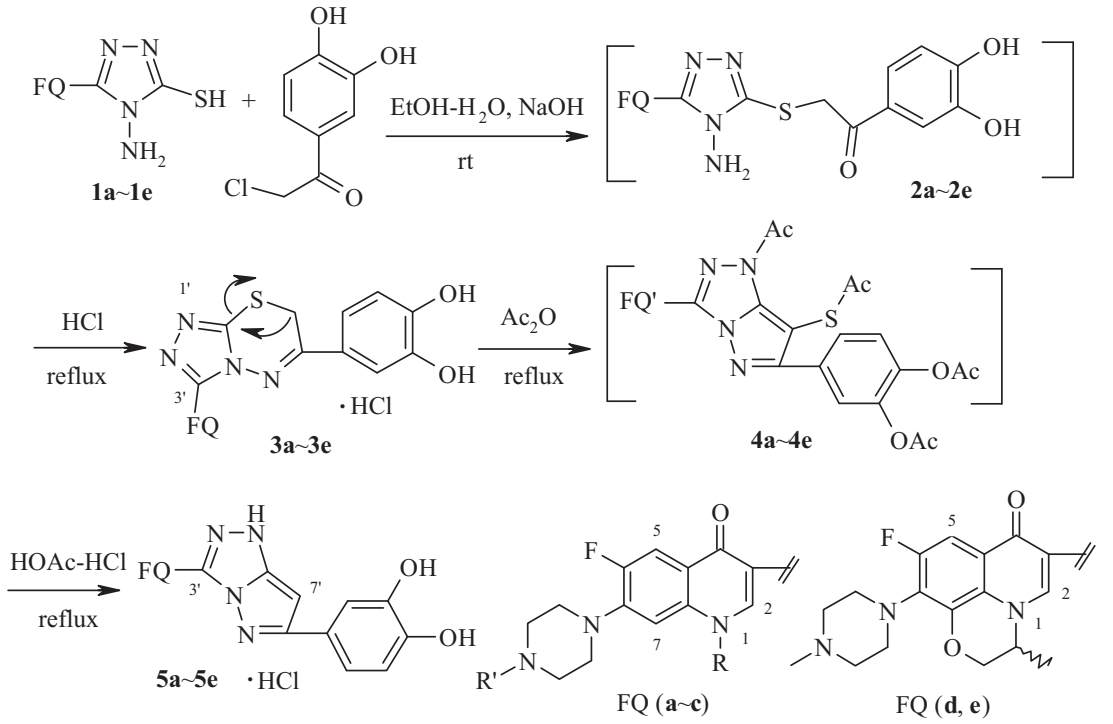

Scheme 1. R/R′ for FQ: C_2H_5/H (**3a**, **5a**); cyclopropyl/H (**3b**, **5b**); cyclopropyl/C_2H_5 (**3c**, **5c**); (±)-S/R (**3d**, **5d**); (−)-S (**3e**, **5e**).

3e, as their respective hydrochloride. But, it is unsuccessful at preparing this known fused heterocyclic system according to a general procedure [6] due to a slight solubility in refluxing ethanol. Occasionally, while heating the fused heterocycles **3a**–**3e** in acetic acid readily resulted in a ring-contraction of fused six-membered thiadiazine by a sulfur extrusion reaction leading to formation of fused five-membered pyrazole corresponding to new fused heterocycles, 3-(1-acetyl-6-diacetylcatechol-4-yl-7-acetylsulfanyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl)-(*N*-acetyl)-quinolon-4-(1*H*)-ones **4a**–**4e**, followed by one-pot conversion of **4a**–**4e** by an acetic acid and a hydrochloric acid catalyzed hydrolysis occurring desulfurization and deacetylation reactions to give the title compounds, 6-catechol- 4-yl-3-FQ-3-yl-1*H*-pyrazolo [5,1-*c*][1,2,4]triazole **5a**–**5e** as the respective hydrochloride.

The *in vitro* antitumor activity for compounds **3a**–**3e** and **5a**–**5e** against L1210 (murine leukemia) and CHO (Chinese hamster ovary) cell lines was evaluated *via* their respective IC_{50} values by the standard MTT assay [7]. The results demonstrated that five parent fluoroquinolones had a poor inhibitory activity against the above tested cancer line cells ($IC_{50} > 150$ μmol/L), but the ten isolated fused heterocycles **3a**–**3e** and **5a**–**5e** had a potential activity with an IC_{50} values within 10.0 μmol concentration, especially compounds **3b**, **3e**, **5b** and **5e** displayed a better potent against L1210 with an IC_{50} value of 1.4, 1.8, 0.14 and 1.2 μmol/L than against CHO with an IC_{50} value of 3.6, 5.7, 2.2 and 3.5 μmol/L, respectively. Conclusion, the construction of the FQ flavanoids by three structural units corresponding to FQ scaffold, fused heterocyclic core and catechol moiety for a promising development of new antitumor lead compounds are value for further study.

The structures of the title compounds **5a**–**5e** were confirmed by elemental and spectral data [8].

Acknowledgments

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[8] (a) A general procedure for synthesis of 3-(6-catechol-4-yl-3-FQ-3-yl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **3a**–**3e**:To a mixture of each of the starting materials **1a**–**1e** (10 mmol) and 4-(chloroacetyl)catechol (2.0 g, 10 mmol) in ethanol (50 mL) was added 30% sodium hydroxide (1.5 g, 11 mmol), and stirred at room temperature for 12 h. Then, a concentrated hydrochloric acid (5 mL) was added to the above reaction solution, the resultant mixture was refluxed for 6 h. The resultant solid was collected, and recrystallized from ethanol to give the title compounds **3a**–**3e** as respective hydrochloride. (b) A general procedure for synthesis of 6-catechol-4-yl-3-FQ-3-yl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole **5a**–**5e**: Each of compounds **3a**–**3e** hydrochloride (5 mmol) in refluxing acetic anhydride (10 mL) was stirred for 1 h, a concentrated hydrochloric acid (5 mL) was then added to the above reaction solution. Refluxing was continued for 3 h. After removal of the solvents on a rotary evaporator, the residue was recrystallized from ethanol to give the title compounds **5a**–**5e** as respective hydrochloride. 3-(6-Catechol-4-yl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl)-1-ethyl-6-fluoro-7-piperazin-1-yl-quinolin-4(1*H*)-one HCl 5a: yield 52%, mp >260 °C. IR (KBr, υ): 3458, 3158, 1626, 1574, 1457, 1248 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 13.16 (s, 1H, NH), 11.45 (brs, 1H, HCl), 9.66, 9.53 (2 s, 2H, 2 × OH), 9.07 (s, 1H, H-2), 7.84 (d, 1H, *J* = 5.4 Hz, H-8), 7.75 (s, 1H, Ph–H), 7.62 (d, 1H, *J* = 13.2 Hz, H-5), 7.52 (dd, *J* = 7.2 Hz, Ph-H), 7.44 (dd, *J* = 7.2 Hz, Ph-H), 6.76 (s, 1H, 7′-H), 3.48–3.22 (m, 8H, piperazine-H), 2.67 (q, 2H, *J* = 7.2 Hz, N–CH_2), 1.38(t, *J* = 7.2 Hz, 3H, CH_3); MS *m/z*: Found 490 (M^+ + H), Calcd. 489.51 (M^+) for $C_{25}H_{24}FN_7O_3$. Anal. Calcd. for $C_{25}H_{24}FN_7O_3$ HCl: C 57.09, H 4.79, N 18.64; Found C 57.32, H 4.61, N 18.83. 3-(6-Catechol-4-yl-1H-pyrazolo[5,1-*c*][1,2, 4]triazol-3-yl)-1-cyclopropyl-6-fluoro-7-piperazin-1-yl-quinolin-4-(1H)-one·HCl 5b: yield 52%, mp >260 °C. IR (KBr, υ): 3528, 3356, 2894, 1632, 1568, 1455, 1268 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 12.67 (s, 1H, NH), 11.36 (br s, 1H, HCl), 9.58, 9.50 (2 s, 2H, 2 × OH), 8.97 (s, 1H, H-2), 8.04 (d, 1H, *J* = 5.5 Hz, H-8), 7.86 (d, 1H, *J* = 13.2 Hz, H-5), 7.68–7.47 (m, 3H, Ph–H), 6.54 (s, 1H, 7′-H), 3.74–3.68 (m, 1H, CH-cyclopropyl), 3.36–2.58 (m, 8H, piperazine-H), 1.36–1.21 (m, 4H, CH_2CH_2-cyclopropyl); MS *m/z*: Found 524 (M^+ + Na), Calcd. 501.52 (M^+) for $C_{26}H_{24}FN_7O_3S$. Anal. Calcd. for $C_{26}H_{24}FN_7O_3$ HCl: C 58.05, H 4.68, N 18.22; Found C 58.29, H 4.47, N 18.40. 3-(6-Catechol-4-yl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl)-1-cyclopropyl-6-fluoro-7-(4-ethyl-piperazin-1-yl)-quinolin-4-(1*H*)-one HCl **5c**: yield 46%, mp 255–257 °C. IR (KBr, υ): 3368, 3057, 2854, 1627, 1562, 1457, 1264 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 13.17 (s, 1H, NH), 11.26 (brs, 1H, HCl), 9.66, 9.53 (2 s, 2H, 2 × OH), 8.96 (s, 1H, H-2), 8.24 (d, 1H, *J* = 5.7 Hz, H-8), 7.79 (d, 1H, *J* = 13.2 Hz, H-5), 7.68–7.52 (m, 3H, Ph–H), 6.68 (s, 1H, 7′-H), 3.72–3.38 (m, 1H, CH-cyclopropyl), 3.36–3.17 (m, 8H, piperazine-H), 2.58 (q, *J* = 7.2 Hz, 2H, N-CH_2), 1.45–1.17 (m, 7H, NCH_2CH_3 and CH_2CH_2-cyclopropyl); MS *m/z*: Found 530 (M^+ + H), Calcd. 529.58 (M^+) for $C_{28}H_{28}FN_7O_3$. Anal. Calcd. for $C_{28}H_{28}FN_7O_3$ HCl: C 59.41, H 5.16, N 17.32; Found C 59.66, H 5.32, N 17.48. (±)-3-(6-Catechol-4-yl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl)-1,8-(2,1-propoxy)-6-fluoro-7-(4-methyl-piperazin-1-yl)-quinol- in-4-(1*H*)-one HCl **5d**: yield 47%, mp >260 °C. IR (KBr, υ): 3426, 3057, 1636, 1574, 1458, 1266 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 13.28 (s, 1H, NH), 11.36 (brs, 1H, HCl), 9.57, 9.52 (2 s, 2H, 2 × OH), 9.12 (s, 1H, H-2), 8.26 (d, 1H, *J* = 13.3 Hz, H-5), 7.80–7.52 (m, 3H, Ph-H), 6.64 (s, 1H, 7′-H), 4.57–4.53 (m, 3H, OCH_2CH), 3.50–3.28 (m, 8H, piperazine-H), 2 .56 (s, 3H, N-CH_3), 1.46–1.35 (m, 3H, CH_3); MS *m/z*: Found 554 (M^+ + Na), Calcd. 531.55 (M^+) for $C_{27}H_{26}FN_7O_4$. Anal. Calcd. for $C_{27}H_{26}FN_7O_4$ HCl: C 57.09, H 4.79, N 17.26; Found C 57.33, H 4.60, N 17.45. (S)-3-(6-Catechol-4-yl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl)-1,8-(2,1-propoxy)-6-fluoro-7-(4-methyl-piperazin-1-yl)-quinol- in-4-(1*H*)-one HCl **5e**: yield 42%, mp 253–255 °C. IR (KBr, υ): 3415, 3054, 1625, 1557, 1455, 1266 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 13.15 (s, 1H, NH), 11.30 (brs, 1H, HCl), 9.64, 9.58 (2 s, 2H, 2 × OH), 9.07 (s, 1H, H-2), 8.17 (d, 1H, *J* = 13.3 Hz, H-5), 7.68–7.47 (m, 3H, Ph-H), 6.68 (s, 1H, 7′-H) 4.62–4.56 (m, 3H, OCH_2CH), 3.55–3.36 (m, 8H, piperazine-H), 2.62 (s, 3H, N-CH_3), 1.44–1.32 (m, 3H, CH_3); MS *m/z*: Found 532 (M^+ + H), Calcd. 531.55 (M^+) for $C_{27}H_{26}FN_7O_4$. Anal. Calcd. for $C_{27}H_{26}FN_7O_4$ HCl: C 57.09, H 4.79, N 17.26; Found C 57.28, H 4.84, N 17.48.