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Synthesis and Antibacterial Activity of New Tetracyclic Triazolo-thiadiazino Fluoroquinolones

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Abstract: A series of novel 9-fluoro-10-(4-methylpiperazin-1-yl)-3-substituted-8-oxo-8*H*-[1,2,4] triazolo[3,4-b]thiadiazino[6,5,4-ij]quinoline-7-carboxylic acids was prepared by a facile synthetic method and the *in vitro* antibacterial activity against Gram-postive (G^+) and Gram negative (G^-) bacteria was primarily evaluated.

Keywords: Antibiotics, tetracyclicquinolone, synthesis, antibacterial agents.

Since nalidixic acid[1] was first clinically used as a potent antibacterial agent, many analogues, such as bicyclic ciprofloxacin[2], tricyclic ofloxacin[3], have become an important class of therapeutical compounds. Recently, novel tetracyclic fluoroquinolones having a thiazolooxazine ring with potent antibacterial activity against both G^+ and G^- have been reported[4]. In order to find better antibacterial agents for our urgent research of the multidrug resistant (MDR)[5], we herein describe a facile synthetic method of novel tetracyclic fluoroquinoline carboxylic acids containing triazolothiadiazine ring at 1,8 positions of quinoline carboxylic acids (**Scheme 1**).

2, 3, 4, 5-Tetrafluorobenzoyl methyl acrylate **1** was condensed with methyl ortho- formate in acetic anhydride to give the corresponding ether compound **2 ,** followed by the condensation with 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (AMT)[6], respectively, to afford the key intermediates **3**, which were cyclized with K_2CO_3 in DMF to obtain tetracyclic esters **4** and followed by the hydrolysis under acidic condition to form bifluorotetracyclic carboxylic acids **5,** the direct replacement of 10-fluorine atom of compounds **5** with methylpiperazine in *i*-Pr-OH (without going through general borine complexes of **4)** to achieve the free base **6,** which were recrystallized from 3 % hydrochloric acid to obtain the corresponding salts. The structure of the products was confirmed by elemental analysis (EA),^{1}H NMR, IR and MS[7].

The *in vitro* antibacterial activity of compounds **6.**HCl against G^+ and G^- demonstrated that the increase in the size of the alkyl substituents at 3-position of **6a~f**

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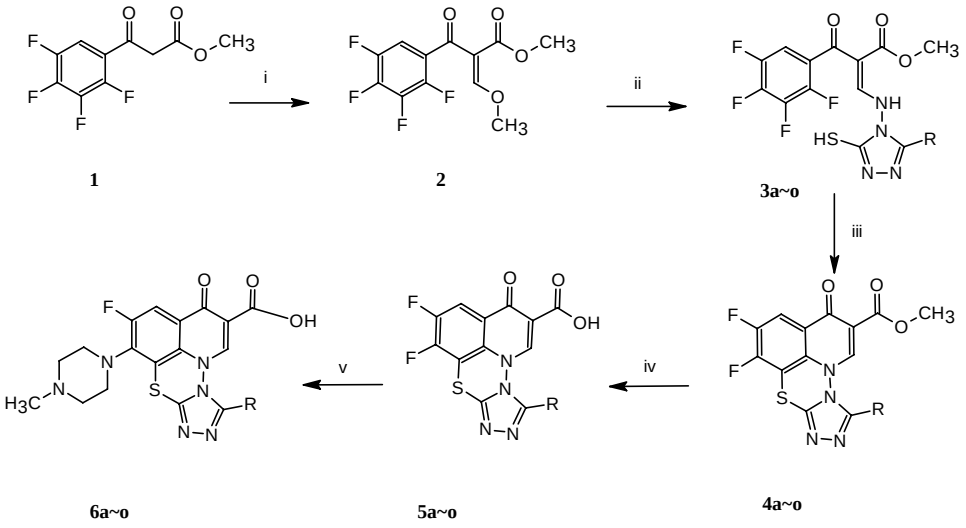
Scheme 1



R: **a,** H; **b**, CH_3; **c**, CH_2CH_3; **d**, *n*-C_3H_7; **e**, *n*-C_4H_9; **f**, *n*-C_5H_{11}; **g**, C_6H_5; **h**, *p*-$CH_3OC_6H_4$; **i**, *m*-$CH_3OC_6H_4$; **j**, *p*-$CH_3C_6H_4$; **k**, 3,4-*(*$CH_3O)_2C_6H_3$; **l**, 3,4-$(OCH_2O)_2C_6H_3$; **m**, 3,4,5-$(CH_3O)_3C_6H_2$; **n**, *p*-FC_6H_4; **o**, *p*-ClC_6H_4.
reagents and conditions: i, $CH(OCH_3)_3$, Ac_2O, xyl, reflux, 6h; ii, AMT, MeOH, rt ~ reflux,5h; iii, DMF, K_2CO_3, rt ~ 120°C, 12h; iv, HAc-HCl, reflux, 10h; v, methylpiperazine, *i*-PrOH, 140°C,8h.

obviously reduce the antibacterial activity. The activity against both G^+ and G^- bacterial of those compounds with substituent R (H or CH_3) is comparable to that of ofloxacin; for aryl substituents, most compounds with aryl substituent R show no effect or poor activity against G^+ and G^- bacterial, except **6h**, **i**, **l**. The detailed studies on their inhibitory activity on gyrase and structure activity relationship (SAR) are progressing.

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7. **6a** m p 278~280°C as pale yellow crystal, IR (KBr, *v* cm^{-1}): 3445, 1689,1463, 1108 ; ^{1}HNMR(D_2O, *δ* ppm): 9.56(s,1H), 8.84(s,1H), 7.28(d,1H,*J*=12.6Hz), 3.56~3.82(m,8H), 2.83(s,3H); MS(*m/z*): 402(M^+); EA calcd. for $C_{17}H_{15}FN_6O_3S$•HCl: C,46.53, H, 3.67; N, 19.15.

Found C,46.72; H, 3.77; N, 19.02.

6b m p 258~260°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3445, 1686,1472, 1106 ; ^{1}HNMR(D_2O, *δ* ppm): 8.86(s,1H), 7.62(d,1H, *J*=12.6Hz), 3.64~3.80(m,8H), 2.80(s,3H), 2.86(s,3H); MS(*m/z*): 416(M^+); EA calcd. for $C_{18}H_{17}FN_6O_3S$•HCl: C,47.74, H, 4.01; N, 18.56. Found C,47.48; H, 4.15; N, 19.06.

6c m p 246~247°C as light yellow crystal, IR(KBr, *v* cm^{-1}): 3448, 1682,1463, 1106; ^{1}HNMR(D_2O, *δ* ppm): 8.78(s,1H), 7.75(d,1H, *J*=13Hz), 3.34~3.80 (m,8H), 3.17 (q,2H,*J*=7.2Hz),2.76(s,3H), 1.37(t,3H, *J*=7.5Hz); MS(*m/z*): 430(M^+); EA calcd. for $C_{19}H_{19}FN_6O_3S$•HCl: C,48.87, H, 4.32; N, 18.00. Found C,48.62; H, 4.47; N, 18.16.

6d m p 243~245°C as light yellow crystal, IR (KBr, *v* cm^{-1}): 3048, 1682,1463, 1103; ^{1}HNMR(D_2O, *δ* ppm): 8.84(s,1H), 7.65(d,1H, *J*=13Hz), 3.38~3.87(m,8H),3.12(t,2H,*J*=6Hz), 2.74(s,3H),1.76~1.85 (m,2H),1.02(t,3H, *J*=7.2Hz); MS(*m/z*): 444(M^+); EA calcd. for $C_{20}H_{21}FN_6O_3S$•HCl: C,49.95, H, 4.61; N, 17.47. Found C,50.12; H, 4.70; N, 17.67.

6e m p 212~214°C as light yellow crystal, IR (KBr, *v* cm^{-1}): 3448, 1686,1465, 1087; ^{1}HNMR(D_2O, *δ* ppm): 8.75(s,1H), 7.65(d,1H, *J*=12.6Hz), 3.28~3.86(m,8H), 3.14(t,2H), 2.87 (s,3H), 1.53(m,2H),1.35 (m,2H),0.93 (t,3H, *J*=7.5Hz); MS(*m/z*): 458(M^+); EA calcd. for $C_{21}H_{23}FN_6O_3S$•HCl: C,50.96, H, 4.89; N, 16.98. Found C,51.17; H, 5.00; N, 17.23.

6f m p 202~204°C as light yellow crystal, IR(KBr, *v* cm^{-1}): 3378, 1678,1457, 1107; ^{1}HNMR(D_2O, *δ* ppm): 8.85(s,1H), 7.72(d,1H, *J*=13Hz), 3.42~3.86(m,8H), 3.12(t,2H), 2.84(s,3H),1.50~1.27(m,6H), 0.91(t,3H, *J*=7.6Hz); MS(*m/z*): 472(M^+); EA calcd. for $C_{22}H_{25}FN_6O_3S$•HCl: C,51.95, H, 5.15; N, 16.51. Found C,51.77; H, 5.04; N, 16.82.

6g m p 289~291°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3448, 1674,1453, 1086; ^{1}HNMR(D_2O, *δ* ppm): 8.84(d,1H, *J*=12.5Hz), 7.28~7.74(m,6H), 3.35~3.87(m,8H), 2.84(s,1H); MS(*m/z*): 478(M^+); EA calcd. for $C_{23}H_{19}FN_6O_3S$•HCl : C,53.64; H, 3.91; N, 16.32. Found C, 53.88; H, 4.14; N, 16.54.

6h m p 278~281°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3456, 1676,1452, 1084 ; ^{1}HNMR(D_2O, *δ* ppm): 8.86(s,1H), 7.26~7.68(m,5H), 3.65~3.97(m,11H), 2.84(s,3H); MS(*m/z*): 508(M^+); EA calcd for $C_{24}H_{21}FN_6O_4S$•HCl: C,52.89; H, 4.07; N, 15.42. Found C,53.17; H, 4.18 N, 15.70.

6i m p 268~270°C as yellow crystal, IR(KBr, *v* cm^{-1}): 3448, 1672, 1450, 1103; ^{1}H NMR(D_2O, *δ* ppm): 8.86(s,1H), 7.26~ 7.82(m,5H), 3.35~3.96(m,11H), 2.88(s,3H); MS(*m/z*): 508(M^+); EA calcd. for $C_{24}H_{21}FN_6O_4S$•HCl: C,52.89; H, 4.07; N, 15.42. Found C,53.13; H, 4.34 N, 15.62.

6j m p 301~302°C as yellow crystal, IR(KBr, *v* cm^{-1}): 3378, 1678,1453, 1076; ^{1}H NMR(D_2O, *δ* ppm): 8.86(s,1H), 7.26~7.74(m,5H), 3.32~3.87(m,8H), 2.87(s,3H), 2.54(s,3H); MS(*m/z*): 492(M^+); EA calcd. for $C_{24}H_{21}FN_6O_3S$•HCl: C,54.49; H, 4.19; N, 15.89. Found C,54.72; H, 4.18 N, 16.12.

6k m p 282~284°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3378, 1676,1463, 1082; ^{1}HNMR (D_2O, *δ* ppm): 8.78(s,1H), 7.23~7.74(m,4H), 3.28~3.97(m,14H), 2.86(s,3H); MS(*m/z*): 538(M^+); EA calcd. for $C_{25}H_{23}FN_6O_5S$•HCl: C,52.22; H, 4.21; N, 14.62. Found C,52.53; H, 4.36 N, 14.36.

6l m p 328~330°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3425, 1683,1453, 1100; ^{1}HNMR (D_2O, *δ* ppm): 8.81(s,1H), 7.32~7.83 (m,4H), 5.98(s,2H),3.35~3.94(m,8H), 2.82(s,3H); MS(*m/z*): 522(M^+); EA calcd. for $C_{19}H_{24}FN_6O_5S$•HCl: C,51.57; H, 3.61; N, 15.03. Found C,51.74; H, 3.52 N, 15.17.

6m m p 254~255°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3446, 1674,1462, 1084; ^{1}HNMR(D_2O, *δ* ppm): 8.81(s,1H), 7.16~7.73(m,3H), 3.25~3.94 (m,17H), 2.86(s,3H); MS (*m/z*):568(M^+); EA calcd. for $C_{26}H_{25}FN_6O_6S$•HCl: C,51.61; H, 4.33; N, 13.89. Found C,51.53; H, 4.56 N, 14.12.

6n m p 301~303°C as yellow crystal, IR (KBr, *v* cm^{-1}): 3440, 1675,1458, 1079; ^{1}HNMR(D_2O, *δ* ppm): 8.84(s,1H), 7.28~7.73(m,5H), 3.36~3.84(m,8H), 2.87(s,3H); MS(*m/z*): 496(M^+); EA calcd. for $C_{23}H_{18}F_2N_6O_3S$•HCl: C,51.83; H, 3.59; N, 15.77. Found C,52.08; H,3.72; N, 15.64.

6o m p 274~276°C as yellow crystal, IR(KBr, *v* cm^{-1}): 3386, 1685,1462, 1075; ^{1}HNMR(D_2O, *δ* ppm): 8.89(s,1H), 7.25~7.86(m,5H), 3.28~3.84 (m,8H), 2.85(s,3H),; MS(*m/z*): 512/514(M^+); EA calcd. for $C_{23}H_{18}ClFN_6O_3S$•HCl : C,50.28; H, 3.49; N, 15.30. Found C,50.46; H,3.61; N, 15.12.

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