SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-CYCLOPROPYL-6,8-DIFLUORO-7-(2-SUBSTITUTED 4,6-DIHYDRO-1*H*-PYRROLO[3,4-*d*]THIAZOL-5-YL)-1,4-DIHYDRO-4-OXOQUINOLINE-3-CARBOXYLIC ACID

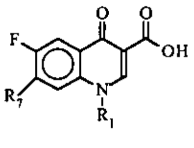
Wan-Joo Kim*, Bong-Jin Kim, Tae-Suk Lee, Keun-Soo Nam, and Keun-Jae Kim**

*Korea Research Institute of Chemical Technology, Pharmaceuticals Division.
P O box 107, Yu-Sung ku, Taejeon, Korea 305-606

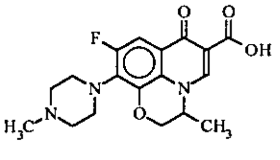
**Han Nam University, Department of Chemistry, 133 O-Jung Dong, Daedeog-ku, Taejeon, Korea 300-791

Abstract-Quinolone derivatives (**9** and **10**) substituted with bicyclothiazole (**7**) and (**8**) at C-7 position were synthesized. Bicyclothiazole derivatives (**7** and **8**) were prepared through 9 steps by way of the 4-bromo-3-oxopyrrolidine (**16**) was a key intermediate and introduced into the title compounds as new C-7 substituents. *In vitro* antibacterial activity of **9** and **10** was also reported.

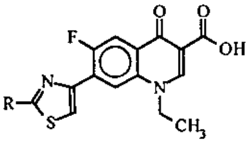
The importance of quinolone antibacterial agents has been demonstrated for the last 10 years.[1] Quinolone antibacterial agents such as Norfloxacin (**1**),[2] Ciprofloxacin (**2**),[3] and Ofloxacin (**3**)[4] are examples of those introduced.
Figure **12**



1. R_1= ethyl, R_7= piperazinyl
2. R_1= cyclopropyl, R_7= piperazinyl



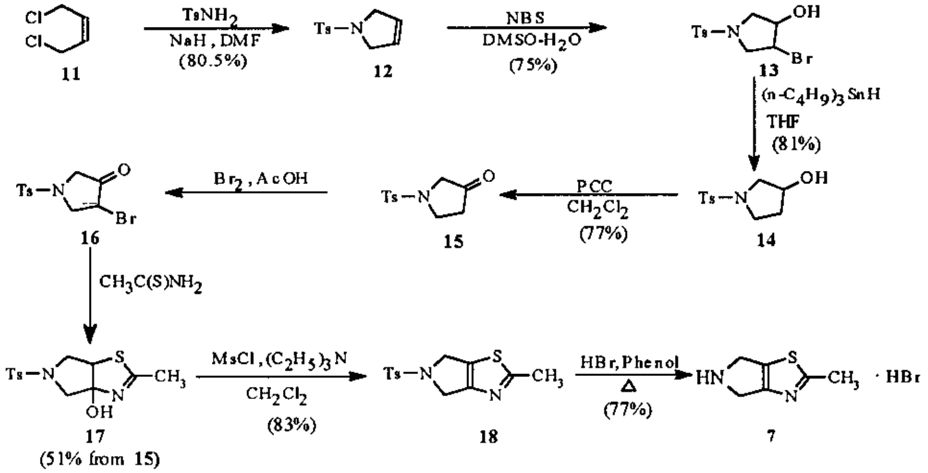
3. Ofloxacin



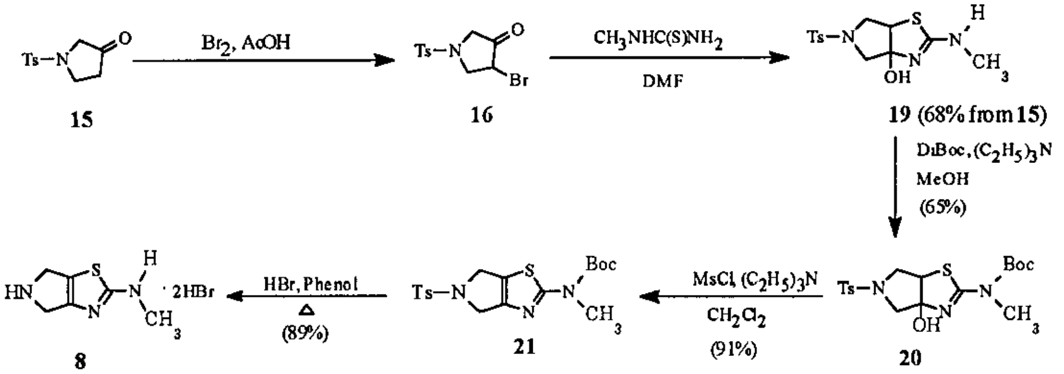
4. R ; $-NH_2$,
5. R ; $-CH_2NH_2$,
6. R ; $-CH_2NHCH_3$

(Et_3N) as a base in CH_2Cl_2, the compound (**18**) was obtained from **17** in 83 % yield (Scheme **1**). In general synthetic method of a thiazole ring, condensation of an α-bromo ketone and a thioamide is frequently employed, but in this reaction, hydroxythiazoline type compound (**17** and **19**) were obtained probably due to the high ring strain and unfavorable configuration between the bridged proton and the hydroxyl group.

According to the estabilished method, the compound (**19**) was obtained in 68 % yield by the reaction of **16** and methylthiourea in DMF. After protection of the amino group of **19** with *di-tert*-bytyl-dicarbonate (DiBOC), elimination of the hydroxyl group by MsCl and Et_3N as a base afforded **21** in 91 % yield. As a general deprotection method for *N*-tosyl group, 48 % HBr and phenol was used, providing **7** and **8** from **18** and **21**, respectively (Scheme **1** and **2**).



Scheme 1



Scheme 2

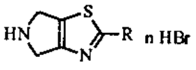
These compounds represent a distinct structural variation wherein antibacterial activity is preserved. Thus, the antibacterial activity of quinolone depends upon the proper combination of substituents at each site of quinolone.[5] Based on QSAR studies, C-7 cyclic amine derivatives appears to be the most important substituent for showing antibacterial activity of quinolone including the essential groups such as C-3 carboxyl, C-4 carbonyl and C-6 fluorine atom.[6] In order to improve the spectrum of antibacaterial activity and the bioavailability, a large number of cyclic amine derivatives have been synthesized and introduced to quinolones. As the result, some of them such as piperazine[7] and pyrrolidine derivatives[8] showed broad spectra and good pharmacokinetics.

Thiazole derivatives have frequently been used in pharmaceutical drugs. Especially, in β-lactam antibacterial agents, the thiazole derivatives show excellent antibacterial activity.[9]

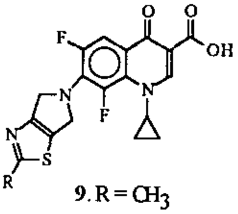
In 1987, researchers at Warner-Lambert[10] reported the new quinolones (**4** ~ **6**) substituted with aminothiazole derivatives at C-7 position (Figure **1**). These quinolones were found to exhibit a relatively antibacterial activity (MIC ; <1 μg/ml in Gram-(-) and Gram-(+) organisms).

We are interested in developing efficient synthetic routes to bicyclothiazole derivatives (**7** and **8**) for their biological evaluation.

Figure **2**



7. R = CH_3 (n=1)
8 R = $NHCH_3$ (n=2)



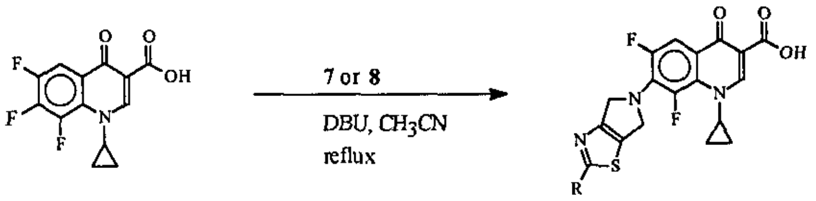
9. R = CH_3
10. R = $NHCH_3$

Herein we report an expedient synthesis of 7 and **8**, and their quinolone derivatives (**9** and **10**) (Figure **2**). Antibacterial activity of **9** and **10** is also presented (Table **I**).

CHEMISTRY

Our synthetic sequences to **7** and **8** are outlined in Scheme 1 and **2**. Bicyclothiazole derivatives (**7** and **8**) were synthesized as salt forms through 8 and 9 steps, respectively, by way of the 4-bromo-3-oxopyrrolidine (**16**). The compound (**16**) which was employed as a key intermediate in the syntheses of bicyclothiazole derivatives was unstable under acidic conditions such as in a HBr solution and its stability was found to depend upon the *N*-protective group.[11] Direct oxidation of **13** with pyridinium chlorochromate (PCC) was prepared by treatment of **13** with tributyltinhydride[12] in THF. Subsequent oxidation of **14** with PCC in dichloromethane (CH_2Cl_2) at room temperature produced **15** in 77 % yield. The compound (**15**) was treated with Br_2(1 eq.) in acetic acid at 46~50°C for 5 min to afford **16** in 96 % yield. Without purification, the compound (**16**) was treated with thioacetamide in DMF at 46~50°C for 3 h to afford **17** (51 % yield from **15**). By use of methanesulfonyl chloride (MsCl) and triethylamine

The coupling reaction of **22** and the compound (**7**) and (**8**) in refluxing MeCN by use of diazabicyclo[5.4.0]undec-7-ene (DBU) as a base furnished **9** and **10** in 62 % or 63 % yields, respectively (Scheme **3**).



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9. R= CH_3, 62%
10. R= $NHCH_3$, 63%

Scheme **3**

ANTIBACTERIAL ACTIVITY

Table **I** summarized in vitro antibacterial activity of **9** and **10** against four Gram-(+) and five Gram-(-) micro-organisms. For comparison, the activity of ofloxacin is also shown. The compounds (**9** and **10**) exhibited very good activity against *Gram-(+) bacteria but they are much less potent against* Gram-(-) bacteria.

Table **I**

In vitro Antibacterial Activity of (**9**) and (**10**)

MIC, μg/ml [a]

Compound	Sa(A)[b]	Sa(s)[c]	S(f)[d]	S(c)[e]	E(A)[f]	E(D)[g]	Pa 9027[h]	Sa(t)[i]	Kl(a)[j]
(9)	0.007	<0.002	0.391	0.004	100.00	1.563	25.00	0.781	6.250
(10)	0.098	0.098	0.781	0.098	6.250	0.391	12.5	0.195	0.781
Ofloxacin	0.195	0.391	1.563	0.195	0.391	0.049	1.563	0.049	0.049

[a] Minimum Inhibitory Concentration (MIC) is the lowest concentration of the quinolone that inhibits visible growth of microorganisms after 48 h at 37°C, [b] Staphylococcus aureus SG 511, [c] Staphylococcus aureus 285, [d] Streptococcus faeciumMD 8b, [e] Staphylococcus aureus 503, [f] Escherichia Coli DC 0, [g] Echerichia Coli 1507E, [h] Pseudomonas aeruginosa 9, [i] Salmonella typhimurium, [j] *Klebsiella aerogenes 1522E*

EXPERIMENTAL

^1H (300 MHz) and ^{13}C (75.5 MHz) nmr spectra were recorded on a Bruker AM-300 NMR Spectrometer in the solvent indicated with TMS as an internal standard. Chemical shifts are reported in ppm (δ) and *J* values are in Hz. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded on a *Shimadzu IR-435 spectrometer* in a potassium bromide pellet or neat, and frequencies are expressed in cm^{-1}. Mass spectra were obtained on Jeol JMS-DX 303 GC/MS and Shimadzu GCMS-QP 5000 spectrometers.

1-(Toluene-4-sulfonyl)-2,5-dihydro-*1H*-pyrrole (**12**)

To a stirred mixture of 12.5 g (0.10 mol) of **11** and *p*-toluenesulfonamide 18.8 g (0.11 mole) in 125 ml of DMF, 8.36 g (0.10 mol) of sodium hydride (60 % dispersion in mineral oil) was gradually added at room temperature. Stirring was continued for an additional 1 h at the same temperature. The mixture was poured into 500 ml of water and the whole was stirred for 30 min. The solid appeared was collected by filtration, and washed with water and hexane to give 21.2 g (95 %) as crude product. The crude product was recrystallized from ethyl acetate(EtOAc)-ethanol(EtOH) solution to give 1.94g (80.5 %) of **12** as a needle form, mp 121 - 122 °C. Ir (KBr) 1588, 1328, 1154, 674, 596, 542 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.45 (s, 3H), 4.15 (s, 4H), 5.63 (s, 2H), 7 36 (d, 2H, *J*=17 Hz), 7.75 (d, 2H, *J*=17 Hz). Mass (*m/z*) 223, 155, 92, 91. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17 ; H, 5.80 ; N, 6.27, Found : C, 59.11 ; H, 5.84 ; N, 6.11.

4-Bromo-1-(toluene-4-sulfonyl)pyrrolidin-3-ol (**13**)

To a stirred mixture of 11.2 g (0.05 mol) of **12** in 150 ml of DMSO and 2.5 ml of H_2O, 17.8 g (0.1 mol) of *N*-bromosuccinimide (NBS) was gradually added over 10 min at room temperature. The reaction mixture was poured into 500 ml of water. The white precipitate appeared was collected by filtration, and washed with water and hexane to give 12.8 g (80 %) as a crude product. The crude product was purified with fresh column chromatography (Eluent · $CHCl_3$ / MeOH=100/1) to afford 12.0 g (75 %) of **13** as a white solid, mp 135 - 136°C . Ir (KBr) 3435, 1446, 1318, 1146, 666, 603, 545 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.45(s, 3H), 3.41(d, 1H, *J*=18 Hz), 3.60-3.86(m, 2H), 4.05(s, 1H), 4 15-4.50 (m, 3H), 7.35(d, 2H, *J*=17 Hz), 7 75(d, 2H, *J*=17 Hz). Mass (*m/z*) 322, 320, 240, 184, 155. Anal. Calcd for $C_{11}H_{14}NO_3BrS$: C, 41.26 ; H, 4.40 ; N, 4.37, Found : C, 41.49 ; H, 4.44 ; N, 4.30 .

1-(Toluene-4-sulfonyl)pyrrolidin-3-ol (**14**)

To a solution of 3.20 g (0.01 mol) of **13** in 10 ml of dry THF solution, 8.07 ml (0.03 mol) of tributyltin hydride was added dropwise under N_2 atmosphere. After refluxing for 5 h, 2 ml of water was added, and the THF was removed under a reduced pressure. 20 ml of hexane was added to the mixture and the white solid appeared was collected by filtration. The crude product was recrystallized from ethyl acetate (EtOAc)-ethanol to give 1.94 g (81 %) of **14** as needles, mp 105 - 106°C Ir (KBr) 3449, 1317, 1153, 656, 591, 543 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.70-2.00(m, 3H), 2.40(s, 3H), 3.20-3 46(m, 4H), 4.40(br s, 1H), 7.35(d, 2H, *J*=17 Hz), 7.75(d, 2H, *J*=17 Hz). Mass (*m/z*) 242, 224, 222, 155, 139. Anal. Calcd for $C_{11}H_{15}NO_3S$; C, 54.75 ; H, 6.27 ; N, 5.80, Found : C, 54.49 ; H, 6.31 ; N, 5 73

1-(Toluene-4-sulfonyl)pyrrolidin-3-one (**15**)

To a solution of 0.60 g (2.5 mmol) of **14** in 10 ml of dry CH_2Cl_2, 0.80 g (3.8 mmol) of PCC and powdered molecular sieves (0.5 g) were added at room temperature. Additional stirring was continued overnight. 10 ml of ether were added, and the mixture was stirred for additional 1 h. The black solid was filtered and washed with ether (10 ml x 2). the filtrate was concentrated under a reduced pressure. The crude residue was purified by flash column chromatography (Eluent: $CHCl_3$: MeOH =100 : 1) to afford 0.45 g (77 %) of **15** as a white solid, mp 118 - 119°C. Ir (KBr) 3386, 1746, 1591, 1329, 1149 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.45(s, 3H), 2.50(t, 2H, *J*=11 Hz), 3.48(s, 2H), 3.55(t, 2H, *J*=11 Hz), 7.35(d, 2H, *J*=13 Hz), 7.74(d, 2H, *J*=13 Hz). Mass (*m/z*) 239,211, 212, 156, 155, 147, 146. Anal.Calcd for $C_{11}H_{13}NO_3S$; C, 55.21 ; H, 5.48 , N, 5.85, Found : C, 55.14 ; H, 5.47 ; N, 5.62.

2-Methyl-5-(toluene-4-sulfonyl)-4,5,6,6a-tetrahydropyrrolo [4,3-*d*]thiazol-3a-ol (**17**)

To a solution of 3 ml of acetic acid and 0.24 g (1.0 mmol) of **15**, 0.16 g (1.0 mmol) of bromine (Br_2) diluted with 3 ml of AcOH were added dropwise at 10 °C and heated to 46 ~50 °C for 5 min. The color of the mixture disappeared at this temperature. 20 ml of water were added, and the mixture was extracted with $CHCl_3$ (20 ml x 3). The organic layer was washed with water (20 ml) and dried over anhydrous $MgSO_4$. The concentration under a reduced pressure gave, without purification, 0.31 g (96 %) of crude **16** as a oil. The crude product was directly used for the next reaction.

The compound (**16**) (0.31 g, 0.96 mmol) and 0.07 g (0.96 mmol) of thioacetamide were dissolved in 3 ml of DMF. The mixture was stirred at 50 ~ 55 °C for 5 h, then cooled to room temperature. 0.08 g of $NaHCO_3$ were added, and the solvent was concentrated under a reduced pressure. 10 ml of ethyl acetate (EtOAc) were added to the residue, and the solid appeared was collected by filtration, and washed with EtOAc (10 ml x 2) to give 0.15 g (51 %) of **17** as a white solid, mp 148-150°C Ir (KBr) 3051, 1626, 1336, 1176, 1592 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2 18(s, 3H), 2.45(s, 3H), 3.18(d, 1H, *J*=10 Hz), 3 32(dd, 1H, *J*=4 Hz and *J*=4 Hz)), 3.50-3.60(m, 2H), 3.96(dd, 1H, *J*=4 Hz and *J*=4 Hz), 5.56(br s, 1H), 7.35(d, 2H, *J*=8 Hz), 7.70(d, 2H, *J*=8 Hz). ^{13}C-Nmr ($CDCl_3$, 75.5 MHz) 20.00, 21.6, 55.7, 56.8, 59.6, 116.4, 128 0, 129.8, 131.6, 144.2, 171.5 ppm. Mass (*m/z*) 313, 198, 157, 155, 116, 88. Anal. Calcd for $C_{13}H_{16}N_2O_3S_2$: C, 49.98 , H, 5.16 ; N, 8 97, Found : C, 49 98 ; H, 5.15 ; N, 8.72.

2-Methyl-5-(toluene-4-sulfonyl)-4,6-dihydro-5*H*-pyrrolo[3,4 -*d*]thiazole (**18**)

To a solution of 0.38 g (1.21 mmol) of **17** in 3.8 ml of dry CH_2Cl_2, 0.42 ml (2.42 mmol) of MsCl was added at 0 °C, and then 1.4 ml (10.04 mmol) of Et_3N were gradually added at the same temperature. After the addition was over, the mixture was stirred at room temperature for 1 h. 5 ml of water were added, and the mixture was extracted with CH_2Cl_2 (10 ml x 2). The organic layer was dried over anhydrous $MgSO_4$, and concentrated to give **18** as a crude product. The crude product was purified by flash column chromatography (Eluent : Hexane / EtOAc = 1 : 1) to afford 0.3 g (83 %) of **18** as a white solid, mp 192-194°C. Ir (KBr) 1746($\nu_{C=N}$), 1336, 1160, 669 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.45(s, 3H), 2.65(s, 3H), 4.51(s, 2H), 4.61(s, 2H), 7.33(d, 2H, *J*=9 Hz), 7.78(d, 2H, *J*=9 Hz). ^{13}C-Nmr ($CDCl_3$, 75.5 MHz) 19.7, 21.5, 46.3, 50.0, 126 5, 127.4, 129.9, 133.9, 143.8, 154.0, 171.5 ppm. Mass (*m/z*) 295, 261, 155, 139. Anal. Calcd for $C_{13}H_{14}N_2O_2S_2$; C, 53.04 ; H, 4.79 ; N, 9.52, Found : C, 53.17 ; H, 4.80 ; N, 9.49.

2-Methyl-4,6-dihydro-5*H*-pyrrolo[3,4-*d*]thiazole · hydrobromide **(7)**

0.20 g (0.68 mmol) of **18**, 0.14 ml of phenol and 1 ml of 48% HBr were mixed, and the mixture was heated at reflux for 1 h. The mixture was cooled to room temperature and concentrated under a reduced pressure. To the residue, 1 ml of water and 2 ml of ether were added and the mixture was stirred for 1 h. The organic layer was separated, and the water layer was concentrated under a reduced pressure. 3 ml of MeCN were added, and the appeared solid was filtered, and washed with MeCN (3 ml x 3) to give 0.17 g (77 %) of **7** as a gray solid, mp > 227°C (decomp.). Ir (KBr) 3244, 2655, 1621, 1519, 1041 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 2.69(s, 3H), 4.38(s, 2H), 4.52(s, 2H), 5.40(br s, 1H). Mass (*m/z*) 139, 107, 98, 82. Anal. Calcd for $C_6H_{10}N_2Br_2S$, C, 32.59 ; H, 4.10 ; N, 12.67, Found . C, 32.61 ; H, 4.09 ; N, 12.55.

2-(*N*-*t*-Butyoxycarbonylmethylamino)-5-(toluene-4-sulfonyl)-4,5,6,6a-tetrahydropyrrolo[3,4-*d*]thiazol-3a-ol **(20)**

A solution of 0.60 g (1.88 mmol) of **16** and 0.18 g (1.97 mmol) of methylthiourea in 7 ml of DMF was heated to 50 °C for 10 h. The mixture was cooled to room temperature and concentrated. 10 ml of EtOAc were added to the residue. The precipitate appeared was collected by filtration, and washed with EtOAc (10 ml x 3) to give 0.52 g (68 %) of **19** as a crude product. A solution of 0.52 g (1.27 mmol) of **19**, 0.28 g (1.27 mmol) of DiBOC, and 0.2 ml (1.43 mmol) of Et_3N in 5 2 ml of MeOH was stirred at 40 °C for 3 h. The mixture was cooled to 5 °C and further stirred for 2 h. The precipitate appeared was collected by filtration and washed with cold MeOH. Drying under a reduced pressure afforded 0.35 g (65 %) of **20** as a white powder, mp 174 - 175°C . Ir (KBr) 3501,1709, 1580, 1333, 1152, 659 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.55 (s, 9H), 2.47 (s, 3H), 3.29 (s, 3H), 3.40 (m, 2H), 3.42 (s, 1H), 3.50 - 3.60 (m, 2H), 3.80 (m, 1H), 7.45 (d, 2H, *J*=8 Hz), 7 68 (d, 2H, *J*= 8 Hz). ^{13}C-Nmr ($CDCl_3$, 75.5 MHz) 21 6, 28.0, 35.3, 55.2, 56.2, 59.8, 84.2, 109.8, 128.0, 129 7, 131.9, 143 9, 153.0, 161 8 ppm. Mass (*m/z*) 428, 372, 328, 310, 272. Anal Calcd for $C_{18}H_{25}N_3O_5S_2$; C, 50.57 ; H, 5.89 ; N, 9.83, Found : C, 50.31 ; H, 5.89 ; N, 9.84.

2-(*N*-*t*-Butoxycarbonylmethylamino)-5-(toluene-4-sulfonyl)-4,6-dihydro-5*H*-pyrrolo[3,4-*d*]thiazole **(21)**

To a solution of 0.52 g (1.22 mmol) of **20** in 7 ml of CH_2Cl_2, 0.19 g (2.44 mmol) of MsCl and 0.31 ml (3.66 mmol) of Et_3N were added dropwise at room temperature. After stirring was continued for additional 30 min, 7 ml of water were added, and the mixture was extracted with CH_2Cl_2 (10 ml x 2). The organic layer was concentrated and ether (5 ml) was added to the residue. The white solid appeared was collected by filtration and dried under a reduced pressure to give 0.45 g (91 %) of **21** as a white solid, mp 168~169 °C. Ir (KBr) 1696, 1487, 1419, 1343, 1150, 672, 597, 561 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.55(s, 9H), 2.40(s, 3H), 3.46(s, 3H), 4.45(m, 2H), 4.60(m, 2H), 7.30(d, 2H, *J*=9 Hz), 7.72(d, 2H, *J*=9 Hz). ^{13}C-Nmr ($CDCl_3$, 75.5 MHz) 21.5, 28.1, 34 5, 50.2, 50.4, 121.7, 127.4, 129.9, 134 0, 143.7, 148.3, 166.4 ppm. Mass (*m/z*) 410, 354, 309, 153. Anal. Calcd for $C_{18}H_{23}N_3O_4S_2$; C, 52.79 ; H, 5.66 ; N,10.26, Found : C, 52.18 ; H, 5 68 ; N, 10.09.

2-Methylamino-4,6-dihydro-5*H*-pyrrolo[3,4-*d*]thiazole · dihydrobromide (**8**)

0.30 g (0.73 mmol) of **21** and 0.21 ml (2.39 mmol) of phenol were mixed with 1.5 ml of 48% HBr and the mixture was stirred at 110 °C for 2 h. The mixture was cooled to room temperature, and 3 ml of ether was added to separate an organic layer. The lower water layer was concentrated under a reduced pressure, and then 3 ml of MeCN and 3 ml of ether were added to the residue. Stirring is continued for additional 1 h and precipitate appeared was collected by filtration, and washed with 5 ml of MeCN and ether. Drying under a reduced pressure afforded 0.21 g (89 %) of **8** as a pure solid by nmr and mass spectra without purificarion, mp 210 - 215 °C. Ir (KBr) 2943, 1637, 1555, 1119 cm^{-1}. ^{1}H-Nmr (DMSO-d$_6$) δ 3.05(s, 3H), 3.70-4.01(m, 2H), 4.28-4.45(m, 2H), 8.05-8.20(br s, 2H), 9.60 - 9.75(br s, 2H). ^{13}C-Nmr (D_2O, 75.5 MHz) 30.0, 49.9, 52.7, 100.4, 103.9, 169.1 ppm. Mass (*m/z*) 155, 131, 98, 74. Anal. Calcd for $C_6H_{11}N_3Br_2S$; C, 22.73 ; H, 3.50 ; N, 13.25, Found : C, 22.67 ; H, 3.58 ; N, 12.90.

1-Cyclopropyl-6,8-difluoro-7-(2-methyl-4,6-dihydro-5*H*-pyrrolo[3,4-*d*]thiazol-5-yl)-1,4-dihydro-4-oxoquinolin-3-carboxylic acid (**9**)

A mixture of 0.15 g (0.54 mmol) of **22**, 0.12 g (0.54 mmol) of (**7**), and 2 ml (1.08 mmol) of DBU in 2 ml of MeCN were heated at reflux for 2 h. The mixture was cooled to room temperature and stirred for 1 h. The solid appeared was collected by filtration and washed with MeCN (5 ml x 3). Drying under a reduced pressure afforded 0.14 g (63 %) of **9** as a pure solid by nmr and mass spectra without purification, mp > 250 °C (decomp.). Ir (KBr) 1717, 1617, 1595, 1436 cm^{-1}. ^{1}H-Nmr (CDCl$_3$) δ 1.20-1 40(m, 4H), 2.81(s, 3H), 4.05(m, 1H), 5.02(s, 2H), 5.18(s, 2H), 7.95(d, 1H, *J*=16 Hz), 8.79(s, 1H), 14.8(s, 1H). Mass (*m/z*) 403, 359, 326, 220. Anal. Calcd for $C_{19}H_{15}N_3O_3F_2S_1$; C, 56.57 ; H, 3.75 ; N, 10.42, Found : C, 56.54 ; H, 3.68 ; N, 10.24.

1-Cyclopropyl-6,8-difluoro-7-(2-methylamino-4,6-dihydro-5*H*-pyrrolo[3,4-*d*]thiazol-5-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**10**)

A mixture of 0.45 g (1.5 mmol) of **22**, 0.47 g (1.5 mmol) of **8**, and 0.456 g (3 mmol) of DBU in 10 ml of pyridine was heated at 70 °C for 12 h. The mixture were cooled to room temperature and the solvent was removed under a reduced pressure. To the residue, 10 ml of MeCN was added, and the mixture was stirred at room temperature for 2 h. The solid appeared was collected by filtration and washed with MeCN (10 ml x 3). Recrystallization from DMF gave 0.40 g (64 %) of **10** as a yellowish solid, mp > 250 °C (decomp.). Ir (KBr) 1715, 1620, 1589, 1431, 1306 cm^{-1}. ^{1}H-Nmr (DMSO-d$_6$) δ 1.10-1.29(m, 4H), 2.75(s, 3H), 3.70-3.81(m, 2H), 3.95(m, 1H), 4.06-4.20(m, 2H), 6.20(s, 1H), 7.76(d, 1H, *J*=13 Hz), 8.65(s, 1H), 14.60(s, 1H) Mass (*m/z*) 418, 387, 374, 343, 127. Anal. Calcd for $C_{19}H_{16}N_4O_3F_2S_1$; C, 54.54 ; H, 3.85 ; N, 13.39, Found : C, 54.06 ; H, 3.80 ; N, 12.96.

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