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Syntheses of quinolone hydrochloride enantiomers from synthons (*R*)- and (*S*)-2-methylpiperazine

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Abstract—A series of *R* and *S* enantiomers of 7-(3-methylpiperazin-1-yl) quinolone derivatives were synthesized from (*R*)- and (*S*)-*tert*-butyl 2-methylpiperazine-1-carboxylate and tested for their antibacterial activities on 14 kinds of bacteria. Although no distinct difference in in vitro antibacterial activities was observed, 2–64-fold difference between *R* and *S* enantiomers was observed in approximately 52% of cases.

1. Introduction

Piperazine derivatives are particularly important to medicinal chemist. They were found to be used as substituents to impart the desired pharmacological and pharmacokinetic properties to quinolone antibiotics. In recent years, many evidence proved that 7-(substituted-piperazin-1-yl)quinolone derivatives has the lower CNS toxicity than 7-(piperazin-1-yl)quinolone antibiotics.[1] So many clinical quinolone antibacterials contain the 3-methylpiperazin-1-yl group at C_7. Examples can be found in the Gatifloxacin **1**[2] and Temafloxacin **2**[3] (Chart 1). They are racemate having a chiral center at C_3 of the 7-piperazin-1-yl group. In 1991, Daniel T.W.C. and his colleagues reported the synthesis and properties of the enantiomers of temafloxacin hydrochloride. To their conclusion, no difference in in vitro antibacterial activities but a minor difference in in vivo antibacterial activities was observed. However, ((*R*)-pyrrolidin-2-yl)methanol,[4] (*S*)-3-aminopyrrolidine[5] and (*S*)-7-amino-5-azaspiro[2.4]heptane[6] are known to be more potent than their antipodes of some but not all quinolone derivatives in terms of antibacterial activity and pharmacokinetic profiles. These limited data

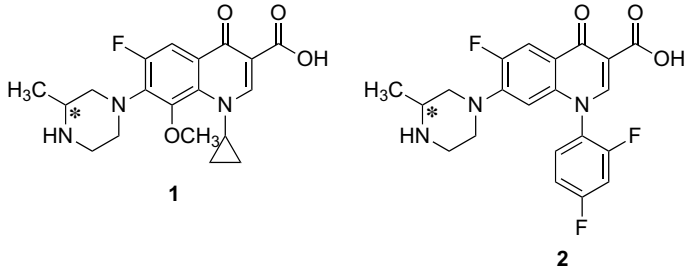

Chart 1.

Keywords: Quinolone; Synthon; Methylpiperazine; Antibacterial activity.
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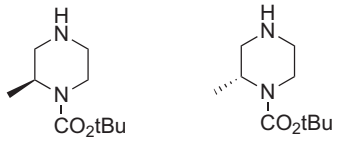
prompted us to explore further if there exists steric influence on biological activities in quinolone series of compounds. In this paper, we report the synthesis and in vitro activities of a series of (*R*)- and -(*S*)-7-(3-methylpiperazin-1-yl)quinolone compounds.

2. Chemistry

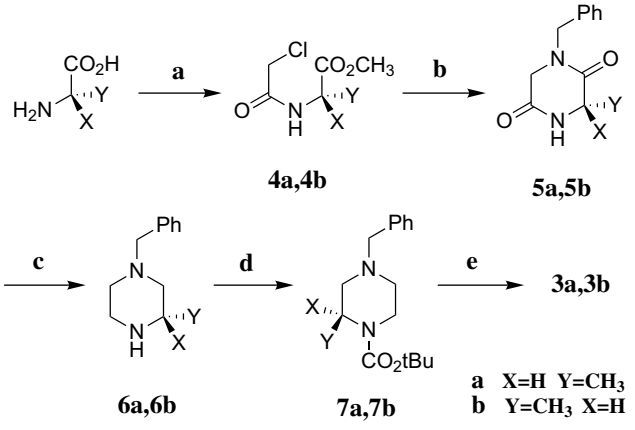
The general method used for the preparation of quinolone derivatives involving an intermolecular nucleophilic displacement ammonification reaction has been previously described.[7] However, the displacement of the quinolone parent nucleus by chiral 2-methylpiperazine provided the target compound in low yield.[3] And the chiral 2-methylpiperazine was not easy to store because of its hygroscopicity. In order to improve the selectivity of amino-group in 2-methylpiperazine and the synthetic yield, we used the enantiomerically pure *tert*-butyl 2-methylpiperazine-1-carboxylate **3a** and **3b** (Chart 2) as synthons for the chiral 2-methylpiperazines' analogs.

In our previous work, we have reported a novel and facile method to synthesize **3a** and **3b**.[8] The synthetic route was depicted in Scheme 1. Comparing to other works, we used cheaper material and reagent to get the enantiomerically pure 1-protected 2-methylpiperazine in higher yield. Moreover, the operation process was facile and suitable for large scale production.



3a **3b**

Chart 2.



Scheme 1. Reagents and conditions: (a) (1) $SOCl_2$, CH_3OH, rt, overnight; (2) $ClCH_2COCl$, $NaHCO_3$, H_2O/C_6H_6, rt, 3 h; (b) benzylamine, TEA, CH_3OH, reflux, 24 h; (c) LAH, THF, 0 °C–rt, 36 h; (d) $(BOC)_2O$, TEA, CH_2Cl_2, overnight; (e) 10% Pd/C, H_2, CH_3OH, rt, overnight.

Table 1. The structure of quinolone nuclear parents

Compound	R_8	R_1
8	(*S*)-$OCH_2CH(CH_3)$	
9	(*R*)-$OCH_2CH(CH_3)$	
10	H	*c*-C_3H_5
11	F	*c*-C_3H_5
12	F	$C_6H_3F_2$-2,4
13	F	$C_6H_3F_2$-3,4
14	F	C_6H_4F-3

Next, we used the general method to prepare a series of 9-fluoro or 7-fluoro quinolone parent nucleus (Table 1), for the reason that the fluorine atom is the preferred leaving group. The synthesis of compound **8**,[9] **9**,[9] **10**,[10] **11**,[11] **12**[12] have been reported, and compound **13**, **14** were synthesized according to Scheme 2.

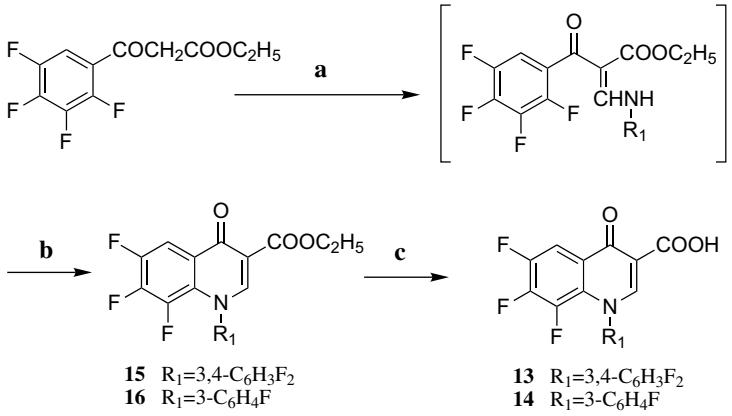
Finally, we connected the quinolone parent nucleus (**8** to **14**) with **3a** and **3b** to get the *N*-*tert*-butoxycarbonyl protected quinolone compounds[13] (**17a**,**b** to **23a**,**b**), followed by deprotection in acid medium to get the quinolone hydrochlorides. The general route to synthesize the target compounds was described in Scheme 3 and the compounds synthesized were listed in Table 2.

3. Results and discussion

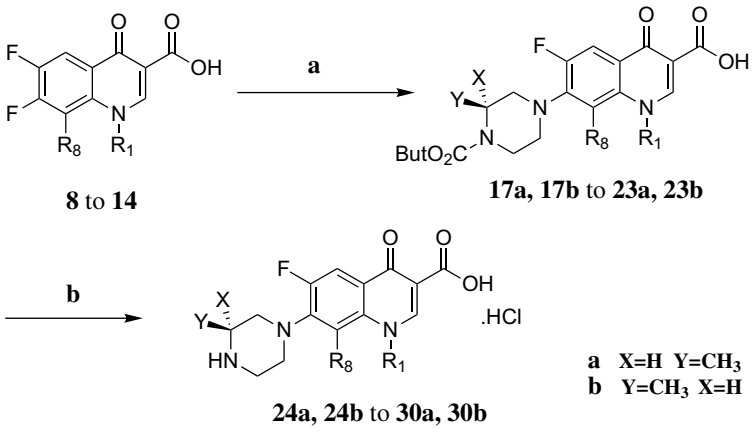
From Table 2, we can see that 8-fluoro parent nucleus led to better results than *S*- and *R*-ofloxacin parent nucleus. This is due to the −I effect and −C effect of 8-substituent on the aromatic ring. As the −I effect of fluoro atom is more powerful than −C effect, the 8-fluoro group reduces the electron density of Meisenheimer and makes the S_N2 nucleophilic substitution reaction easier and faster. Just on the contrary, the alkoxy group increases the electron density of transition complex and makes the reaction more difficult and slower. However, even in the reaction of *S*- and *R*-ofloxacin parent nucleus, the yield is higher than the synthesis of Temafloxacin **2**.

The comparative in vitro antibacterial activity of the enantiomers of quinolone hydrochlorides against 14 representatives of Gram-negative and Gram-positive organisms was shown in Tables 3 and 4. Data for *S*-ofloxacin hydrochloride (**S-1**) and ciprofloxacin hydrochloride (**S-2**) are provided for comparison. The in vitro antibacterial activities are reported as minimum inhibitory concentration (MIC) in micromole per liter. The MIC's were determined by the 2-fold agar dilution in the MUELLER–HINTON substrate by using standard microtitration techniques.[14]

In the total 98 groups of *R* and *S* enantiomers listed in Tables 3 and 4, 2–512-fold difference between enantiomers was observed in 51 groups. And this is more distinct in drug resistant strains, most remarkable examples can be observed in the row of *S. epidermidis* 69. Among the 51 groups, in some case *S* enantiomers are better than their antipodes, but in other cases *R* enantiomers seem better. So there is no regularity to fol-



Scheme 2. Reagents and conditions: (a) (1) $CH(OC_2H_5)_3/Ac_2O$; (2) $NH_2–R_1/CH_2Cl_2$; (b) K_2CO_3/DMF; (c) HCl/AcOH.



Scheme 3. Reagents and conditions: (a) **3a** or **3b**, *N*-methylmorpholine/DMSO; (b) 3 NHCl/EtOH.

Table 2. The structure of products **24a**–**30b** and yields via Scheme 3

Product	R_8	R_1	Side chain	Material	Intermediate	Yield of step a (%)	Yield of step b (%)	Overall yield (%)
24a	(*S*)-$OCH_2CH(CH_3)$		*S*-3-Methylpiperazin-1-yl	8	**17a**	84.1	80.5	67.7
24b	(*S*)-$OCH_2CH(CH_3)$		*R*-3-Methylpiperazin-1-yl	8	**17b**	83.6	81.2	67.9
25a	(*R*)-$OCH_2CH(CH_3)$		*S*-3-Methylpiperazin-1-yl	9	**18a**	78.4	81.3	63.7
25b	(*R*)-$OCH_2CH(CH_3)$		*R*-3-Methylpiperazin-1-yl	9	**18b**	82.7	77.8	64.3
26a	H	*c*-C_3H_5	*S*-3-Methylpiperazin-1-yl	10	**19a**	71.4	79.2	56.5
26b	H	*c*-C_3H_5	*R*-3-Methylpiperazin-1-yl	10	**19b**	69.5	80.5	55.9
27a	F	*c*-C_3H_5	*S*-3-Methylpiperazin-1-yl	11	**20a**	98.6	80.7	79.6
27b	F	*c*-C_3H_5	*R*-3-Methylpiperazin-1-yl	11	**20b**	95.7	81.4	77.9
28a	F	$C_6H_3F_2$-2,4	*S*-3-Methylpiperazin-1-yl	12	**21a**	96.8	80.5	77.9
28b	F	$C_6H_3F_2$-2,4	*R*-3-Methylpiperazin-1-yl	12	**21b**	95.9	84.1	80.6
29a	F	$C_6H_3F_2$-3,4	*S*-3-Methylpiperazin-1-yl	13	**22a**	94.6	89.7	84.6
29b	F	$C_6H_3F_2$-3,4	*R*-3-Methylpiperazin-1-yl	13	**22b**	96.1	89.6	86.1
30a	F	C_6H_4F-3	*S*-3-Methylpiperazin-1-yl	14	**23a**	90.3	90.1	81.4
30b	F	C_6H_4F-3	*R*-3-Methylpiperazin-1-yl	14	**23b**	89.7	87.2	78.2

low, though a regular pattern can be found in **24a** versus **24b**, **25a** versus **25b**, and **26a** versus **26b**.

In comparison with *S*-ofloxacin hydrochloride (**S-1**) and ciprofloxacin hydrochloride (**S-2**), **24a**, **24b**, **26a**, **26b**, **27a**, **27b**, **28a**, **28b**, **29a**, and **29b** showed no less activity than **S-1** versus *P. aerug* 10211, **26a** and **27a** demonstrated 8-fold activity than **S-2** and 2-fold activity than **S-1** versus *P. aerug* 10211. Furthermore, **24a**, **24b**, **26a**, **26b**, **27a**, **27b**, **28a**, and **28b** have excellent data in all

Table 3. Biological testing results from Gram-negative organisms (MIC μmol/L)

Compd	*E. coli* 46117	*E. coli* 323*	*K. pneum* 25922	*K. pneum* 440*	*S. typh* 50097	*P. aerug* 10211	*P. aerug* 322*	*Sh. flexneri* 51573
24a	0.125	16	0.25	128	0.125	4	8	0.5
24b	0.25	16	0.5	128	0.25	8	16	0.5
25a	2	>128	16	>128	8	128	>128	32
25b	1	>128	8	>128	4	128	128	128
26a	0.125	4	0.125	128	0.125	1	2	0.125
26b	0.125	8	0.125	128	0.125	4	4	0.25
27a	0.125	4	0.125	64	0.125	1	2	0.125
27b	0.125	2	0.125	16	0.125	4	4	0.125
28a	0.125	32	0.25	128	0.125	8	16	0.5
28b	0.125	16	0.25	128	0.125	4	16	0.5
29a	0.125	64	0.25	>128	0.25	8	32	64
29b	0.125	64	1	>128	0.25	8	32	1
30a	0.25	128	2	128	0.5	32	64	32
30b	0.25	64	2	64	1	64	64	4
S-1	0.125	4	0.125	32	0.125	8	2	0.125
S-2	0.125	4	0.125	128	0.125	2	2	0.125

The strain tagged by * is the clinical drug resistance strain.

Table 4. Biological testing results from Gram-positive organisms (MIC μmol/L)

Compd	*S. aureus* 25923	*S. aureus* 22*	*S. epidermidis* 26069	*S. epidermidis* 69*	*Streptococcus* 32210	*Streptococcus* 27*
24a	1	4	1	2	2	0.25
24b	2	4	1	0.5	2	1
25a	128	>128	128	64	128	32
25b	64	>128	64	0.125	128	16
26a	0.5	2	0.5	0.25	4	0.125
26b	0.5	4	1	1	4	0.25
27a	0.5	1	0.5	0.25	2	0.125
27b	0.5	1	0.5	0.5	32	0.125
28a	1	16	2	1	4	2
28b	1	8	4	128	128	0.5
29a	4	64	4	2	16	1
29b	1	32	4	0.25	128	2
30a	8	64	16	8	64	4
30b	8	32	16	0.125	64	4
S-1	0.5	1	0.5	0.125	2	0.125
S-2	1	2	0.5	0.25	0.5	0.125

The strain tagged by * is the clinical drug resistance strain.

tests. Especially, **27a** showed better results than **S-1** and **S-2** in all tested strains.

4. Conclusion

A series of *R* and *S* enantiomers of 7-(3-methylpiperazin-1-yl)quinolone derivatives were synthesized and tested against 14 representative Gram-negative and Gram-positive organisms. It was found that steric influences do exist in this series though not very significant.

5. Experimental

5.1. General

The ^{1}H NMR spectra were recorded on a Varian Mercury-400 High Performance Digital FT-NMR with TMS as internal standard, and the mass spectra were determined using Finnigan MAT 95, EI: 70 eV. Melting points were obtained at a Büchi 510 melting point apparatus and are uncorrected. Microanalyses were carried out on a Leco CHN-2000 elemental analyzer and the IR spectra were determined using Nicolet-FTIR-750. The optical rotation value $[\alpha]_D$ was determined with PerkinElmer-341 (589 nm).

5.1.1. Synthesis of the quinolone nuclear parents 13 and 14

5.1.1.1. Ethyl 6,7,8-trifluoro-1-(3,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (15). A solution of ethyl 3-(2,3,4,5-tetrafluorophenyl)-3-oxopropanoate (9.03 g, 34.1 mmol) in triethylorthoformate (8.5 mL, 51.2 mmol) and acetic anhydride (21.3 mL, 153 mmol) was heated at 130 °C for 2 h with removal of the ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to a mobile oil that was dissolved in methylene chloride (50 mL). 3,4-Difluoroaniline (5.28 g, 40.9 mmol) was added to the solution. After 1 h, the solution was evaporated to a residue that was dissolved in anhydrous DMF (50 mL). Anhydrous K_2CO_3 (14 g, 101.4 mmol) was added to the solution. After heating at 110 °C for 10 h, the solution was poured into ice/water (200 mL) and stirred for 0.5 h. The suspension was filtered and

washed by water (40 mL) three times to get crude product. Crystallization from 1,4-dioxane (150 mL) gave 7.96 g (60.9%) of **15** as a white solid. Mp 268–269 °C; ^{1}H NMR ($CDCl_3$): δ 1.39 (3H, t, J = 7.1 Hz), 4.38 (2H, q, J = 7.1 Hz), 7.24–7.26 (1H, m), 7.33–7.42 (2H, m), 8.14-8.19 (1H, m), 8.34 (1H, s). MS(EI), *m*/*z* (%) 383 (M^+, 8), 338 (25), 311 (100).

5.1.1.2. Ethyl 6,7,8-trifluoro-1-(3-fluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (16). This compound was prepared in 53.9% yield from 3-fluoroaniline as a white solid according to the procedure described above. Mp 228–229 °C; ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.2 Hz), 4.38 (2H, q, J = 7.2 Hz), 7.19–7.22 (1H, m), 7.25–7.31 (2H, m), 7.53–7.57 (1H, m), 8.17 (1H, m), 8.37 (1H, s). MS(EI), *m*/*z* (%) 365 (M^+, 6.5), 320 (23), 293 (100).

5.1.1.3. 6,7,8-Trifluoro-1-(3,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (13). Compound **15** (1.53 g, 4 mmol) was dissolved in hot acetic acid (20 mL) and a half volume of 3 NHCl was added over 2 h at 100 °C. The mixture was stirred an additional 2 h at this temperature and cooled slowly. The white solids formed were filtered and washed with cold water, 2-propanol, and ether to give 1.24 g (87.5%) of **13**. Mp 260–261 °C. ^{1}H NMR (DMSO-d_6): δ 7.67–7.71 (2H, m), 7.99–8.03 (1H, m), 8.20–8.25 (1H, m), 8.69 (1H, s), 14.05 (1H, br). MS(EI), *m*/*z* (%) 355 (M^+, 6), 311 (100), 294 (32).

5.1.1.4. 6,7,8-Trifluoro-1-(3-fluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (14). This compound was prepared in 93.4% yield from **16** as a white solid according to the procedure described above. Mp 270–271 °C. ^{1}H NMR (DMSO-d_6): δ 7.51–7.55 (1H, m), 7.63–7.72 (2H, m), 7.76–7.79 (1H, m), 8.24–8.29 (1H, m), 8.66 (1H, s), 14.25 (1H, br). MS(EI), *m*/*z* (%) 337 (M^+, 6), 293 (100), 276 (31).

5.1.2. General procedure for the preparation of the *N*-*tert*-butoxycarbonyl protected quinolone compounds 17a,b to 23a,b

5.1.2.1. Method A: (*S*)-10-((*S*)-4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (17a). To *N*-methylmorpholine (0.1 mL, 0.9 mmol) and (*S*)-*tert*-butyl 2-methylpiperazine-1-carboxylate (**3a**) (120 mg, 0.6 mmol) in DMSO (3 mL) was added (*S*)-9,10-difluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (**8**) (112 mg, 0.4 mmol). The mixture was heated at 120 °C for 24 h and cooled slowly. The solution was diluted by ethyl acetate (70 mL) and washed by water (10 mL) twice and brine (10 mL) twice, dried with Na_2SO_4, and concentrated to a yellow solid. Ethanol (2 mL) was added to digest it at boiling for 1 h. The mixture was cooled and filtered, yielding 155.2 mg (84.1%) of **17a** as a yellow solid. Mp 250–251 °C. ^{1}H NMR (DMSO-d_6): δ 1.24 (3H, d, J = 6.59 Hz), 1.40 (9H, s), 1.42 (3H, d, J = 6.87 Hz), 3.11–3.28 (5H, m), 3.76 (1H, d, J = 10.44 Hz), 4.17 (1H, m), 4.36 (1H, dd, J_1 = 2.2 Hz, J_2 = 11.35 Hz), 4.55 (1H, dd, J_1 = 1.92 Hz, J_2 = 11.55 Hz), 4.90 (1H, m), 7.58 (1H, d, J = 12.1 Hz), 8.96 (1H, s), 15.11 (1H, br). MS(EI), *m*/*z* (%) 461 (M^+, 52), 404 (60), 361 (100), 305 (76), 261 (96). $[\alpha]_D^{21}$ −40 (*c* 0.1, $CHCl_3$).

5.1.2.2. Method B: 7-((*S*)-4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (20a). To *N*-methyl-morpholine (0.1 mL, 0.9 mmol) and (*S*)-*tert*-butyl 2-methylpiperazine-1-carboxylate (**3a**) (120 mg, 0.6 mmol) in DMSO (3 mL) was added 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**11**) (113 mg, 0.4 mmol). The mixture was heated at 120 °C for 24 h and cooled slowly. The mixture was filtered. The pale yellow solid was washed with ethyl acetate (5 mL) three times and dried under vacuum, yielding 116 mg of **20a**. The mother liquor was diluted with ethyl acetate (55 mL) and washed with water (10 mL) twice and brine (10 mL) twice. It was dried with Na_2SO_4 and concentrated. Crystallization from ethanol gave further 66.7 mg of **20a**. The total yield was 98.6%. Mp 234–235 °C. ^{1}H NMR (DMSO-d_6): δ 1.15–1.22 (4H, m), 1.26 (3H, d, J = 6.8 Hz), 1.43 (9H, s), 3.18–3.45 (5H, m), 3.83 (1H, m), 4.13 (1H, m), 4.23 (1H, m), 7.85 (1H, d, J = 11.9 Hz), 8.69 (1H, m), 14.81 (1H, br). MS(EI), *m*/*z* (%) 463 (M^+, 14), 363 (96), 307 (100), 263 (92) 57 (87). $[\alpha]_D^{20}$ +43 (*c* 0.12, CH_3OH).

5.1.2.3. (*S*)-10-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxa-zino[2,3,4-*ij*]quinoline-6-carboxylic acid (17b). This compound was prepared in 83.6% yield from **3b** and **8** as a yellow solid according to method A. Mp 250–251 °C. ^{1}H NMR (DMSO-d_6): δ 1.24 (3H, d, J = 6.73 Hz), 1.43 (9H, s), 1.46 (3H, d, J = 6.74 Hz), 3.17–3.36 (5H, m), 3.79 (1H, d, J = 11.41 Hz), 4.19 (1H, m), 4.38 (1H, dd, J_1 = 2.4 Hz, J_2 = 11.4 Hz), 4.57 (1H, dd, J_1 = 1.9 Hz, J_2 = 11.4 Hz), 4.90 (1H, m), 7.60 (1H, d, J = 12.24 Hz), 8.94 (1H, s), 15.13 (1H, br). MS(EI), *m*/*z* (%) 461 (M^+, 34), 404 (38), 361 (71), 305 (90), 261 (100). $[\alpha]_D^{21}$ −155 (*c* 0.12, $CHCl_3$).

5.1.2.4. (*R*)-10-((*S*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxa-zino[2,3,4-*ij*]quinoline-6-carboxylic acid (18a). This compound was prepared in 78.4% yield from **3a** and **9** as a yellow solid according to method A. Mp 247–248 °C. ^{1}H NMR (DMSO-d_6): δ 1.24 (3H, d, J = 6.59 Hz), 1.40 (9H, s), 1.43 (3H, d, J = 6.87 Hz), 3.13-3.29 (5H, m), 3.76 (1H, d, J = 10.99 Hz), 4.17 (1H, m), 4.35 (1H, dd, J_1 = 2.2 Hz, J_2 = 11.35 Hz), 4.56 (1H, dd, J_1 = 1.92 Hz, J_2 = 11.55 Hz), 4.90 (1H, m), 7.59 (1H, d, J = 12.1 Hz), 8.96 (1H, s), 15.11 (1H, br). MS(EI), *m*/*z* (%) 461 (M^+, 30), 404 (36), 361 (68), 305 (84), 261 (100). $[\alpha]_D^{21}$ +148 (*c* 0.1, $CHCl_3$).

5.1.2.5. (*R*)-10-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxa-zino[2,3,4-*ij*]quinoline-6-carboxylic acid (18b). This compound was prepared in 82.7% yield from **3b** and **9** as a yellow solid according to method A. Mp 245–246 °C. ^{1}H NMR (DMSO-d_6): δ 1.25 (3H, d, J = 6.58 Hz), 1.42 (9H, s), 1.44 (3H, d, J = 6.86 Hz), 3.12–3.27 (5H, m), 3.78 (1H, d, J = 10.43 Hz), 4.18

(1H, m), 4.38 (1H, dd, J_1 = 2.16 Hz, J_2 = 11.34 Hz), 4.57 (1H, dd, J_1 = 1.93 Hz, J_2 = 11.53 Hz), 4.92 (1H, m), 7.60 (1H, d, J = 12.35 Hz), 8.98 (1H, s), 15.17 (1H, br). MS(EI), *m/z* (%) 461 (M^+, 26), 404 (32), 361 (64), 305 (81), 261 (100). $[\alpha]_D^{23}$ +40 (*c* 0.1, $CHCl_3$).

5.1.2.6. 7-((*S*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (19a). This compound was prepared in 71.4% yield from **3a** and **10** as a yellow solid according to method A. Mp 240–242 °C. ^{1}H NMR (DMSO-d_6): δ 1.11–1.18 (2H, m), 1.24 (3H, d, J = 6.87 Hz), 1.27–1.32 (2H, m), 1.41 (9H, s), 2.91–3.09 (3H, m), 3.53–3.65 (2H, m), 3.75–3.92 (2H, m), 4.26 (1H, m), 7.55 (1H, d, J = 7.70 Hz), 7.91 (1H, d, J = 12.92 Hz), 8.65 (1H, s). MS(EI), *m/z* (%) 445 (M^+, 28), 401 (36), 345 (100), 289 (57), 245 (68). $[\alpha]_D^{21}$ −36 (*c* 0.055, $CHCl_3$).

5.1.2.7. 7-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (19b). This compound was prepared in 69.5% yield from **3b** and **10** as a yellow solid according to method A. Mp 241–242 °C. ^{1}H NMR (DMSO-d_6): δ 1.11–1.18 (2H, m), 1.24 (3H, d, J = 6.87 Hz), 1.27–1.32 (2H, m), 1.41 (9H, s), 2.91–3.09 (3H, m), 3.53–3.65 (2H, m), 3.75–3.92 (2H, m), 4.26 (1H, m), 7.55 (1H, d, J = 7.70 Hz), 7.91 (1H, d, J = 12.92 Hz), 8.65 (1H, s). MS(EI), *m/z* (%) 445 (M^+, 28), 401 (36), 345 (100), 289 (57), 245 (68). $[\alpha]_D^{21}$ +32 (*c* 0.13, $CHCl_3$).

5.1.2.8. 7-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (20b). This compound was prepared in 95.7% overall yield from **3b** and **11** as a pale yellow solid according to method B. Mp 234–235 °C. ^{1}H NMR (DMSO-d_6): δ 1.16–1.23 (4H, m), 1.25 (3H, d, J = 6.6 Hz), 1.43 (9H, s), 3.18–3.45 (5H, m), 3.82 (1H, m), 4.12 (1H, m), 4.22 (1H, m), 7.84 (1H, d, J = 11.9 Hz), 8.68 (1H, m), 14.81 (1H, br). MS(EI), *m/z* (%) 463 (M^+, 14), 363 (96), 307 (100), 263 (92), 57 (87). $[\alpha]_D^{20}$ −45 (*c* 0.11, CH_3OH).

5.1.2.9. 7-((*S*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (21a). This compound was prepared in 96.8% overall yield from **3a** and **12** as a yellow solid according to method B. Mp 244–245 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (3H, d, J = 6.7 Hz), 1.36 (9H, s), 3.05–3.33 (5H, m), 3.72 (1H, m), 4.09–4.18 (1H, m), 7.34 (1H, m), 7.62 (1H, m), 7.95 (1H, d, J = 12.4 Hz), 7.94–7.98 (1H, m), 8.69 (1H, m), 14.45 (1H, br). MS(EI), *m/z* (%) 535 (M^+, 13), 478 (34), 435 (44), 379 (34.5), 335 (34), 63 (100), 57 (47). $[\alpha]_D^{21}$ +39 (*c* 0.065, CH_3OH).

5.1.2.10. 7-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (21b). This compound was prepared in 95.9% overall yield from **3b** and **12** as a yellow solid according to method B. Mp 243–244 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (3H, d, J = 6.6 Hz), 1.37 (9H, s), 3.05–3.33 (5H, m), 3.72 (1H, m), 4.09–4.18 (1H, m), 7.33 (1H, m), 7.62 (1H, m), 7.95 (1H, d, J = 12.4 Hz), 7.94–7.98 (1H, m), 8.69 (1H, m), 14.45 (1H, br). MS(EI), *m/z* (%) 535 (M^+, 4), 478 (12), 435 (33), 379 (100), 335 (88), 57 (74). $[\alpha]_D^{21}$ −40 (*c* 0.07, CH_3OH).

5.1.2.11. 7-((*S*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(3,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (22a). This compound was prepared in 94.6% overall yield from **3a** and **13** as a pale yellow solid according to method B. Mp 257–258 °C. ^{1}H NMR (DMSO-d_6): δ 1.14 (3H, d, J = 6.5 Hz), 1.40 (9H, s), 3.05–3.39 (5H, m), 3.75 (1H, m), 4.11–4.19 (1H, m), 7.64–7.73 (2H, m), 7.95 (1H, d, J = 12.5 Hz), 7.99–8.05 (1H, m), 8.59 (1H, m). MS(EI), *m/z* (%) 535 (M^+, 17), 478 (76), 435 (100), 379 (78), 335 (73), 57 (72). $[\alpha]_D^{20}$ +36 (*c* 0.055, CH_3OH).

5.1.2.12. 7-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(3,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (22b). This compound was prepared in 96.1% overall yield from **3b** and **13** as a pale yellow solid according to method B. Mp 257–258 °C. ^{1}H NMR (DMSO-d_6): δ 1.17 (3H, d, J = 6.7 Hz), 1.43 (9H, s), 3.08–3.41 (5H, m), 3.77 (1H, m), 4.13–4.21 (1H, m), 7.66–7.75 (2H, m), 7.97 (1H, d, J = 11.75 Hz), 8.03–8.07 (1H, m), 8.61 (1H, m). MS(EI), *m/z* (%) 535 (M^+, 12), 478 (40), 435 (58), 379 (73), 335 (71), 57 (100). $[\alpha]_D^{20}$ −31 (*c* 0.065, CH_3OH).

5.1.2.13. 7-((*S*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(3-fluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (23a). This compound was prepared in 90.3% overall yield from **3a** and **14** as a yellow solid according to method B. Mp 252–253 °C. ^{1}H NMR (DMSO-d_6): δ 1.13 (3H, d, J = 6.7 Hz), 1.38 (9H, s), 3.04–3.31 (5H, m), 3.72–3.74 (1H, m), 4.13 (1H, m), 7.45–7.49 (1H, m), 7.57–7.66 (2H, m), 7.73 (1H, m), 7.94 (1H, d, J = 11.80 Hz), 8.53 (1H, s). MS(EI), *m/z* (%) 517 (M^+, 36), 460 (84), 417 (100), 361 (65), 317 (46), 57 (51). $[\alpha]_D^{21}$ +40 (*c* 0.07, CH_3OH).

5.1.2.14. 7-((*R*)-4-(*tert*-Butoxycarbonyl)-3-methylpiperazin-1-yl)-6,8-difluoro-1-(3-fluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (23b). This compound was prepared in 90.3% overall yield from **3b** and **14** as a yellow solid according to method B. Mp 253–254 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (3H, d, J = 6.6 Hz), 1.37 (9H, s), 3.03–3.30 (5H, m), 3.70–3.72 (1H, m), 4.14 (1H, m), 7.43–7.48 (1H, m), 7.56–7.65 (2H, m), 7.71–7.73 (1H, m), 7.93 (1H, d, J = 11.82 Hz), 8.51 (1H, s), 14.59 (1H, br). MS(EI), *m/z* (%) 517 (M^+, 16), 460 (45), 417 (74), 361 (71), 317 (100), 57 (57). $[\alpha]_D^{21}$ −40 (*c* 0.075, CH_3OH).

5.1.3. General procedure for the preparation of the quinolone hydrochlorides 24a,b to 30a,b

5.1.3.1. (*S*)-9-Fluoro-3,7-dihydro-3-methyl-10-((*S*)-3-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxylic acid hydrochloride (24a). To **17a** (92 mg, 0.20 mmol) in ethanol (4 mL) was added

3 NHCl (2 mL). The mixture was heated at boiling for 10 h and concentrated under reduced pressure to dryness. The residue was crystallized from ethanol–water to yield 65.9 mg (80.5%) of **24a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.32 (3H, d, J = 6.46 Hz), 1.51 (3H, d, J = 6.60 Hz), 3.29–3.58 (7H, m), 4.40 (1H, d, J = 11.14 Hz), 4.54 (1H, d, J = 11.14 Hz), 4.70 (1H, m), 7.22 (1H, d, J = 12.23 Hz), 8.65 (1H, s). IR (KBr) ν 3473.2, 2950.6, 2767.4, 1708.6, 1621.9, 1053.0, 804.2 cm^{-1}. MS(EI), *m/z* (%) 361 (M^+, 31), 305 (100), 261 (91). $[\alpha]_D^{22}$ −82 (*c* 0.13, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_4$·HCl·1.1H_2O: C, 51.76; H, 5.60; N, 10.06. Found: C, 51.48; H, 5.45; N, 9.94.

5.1.3.2. (*S*)-9-Fluoro-3,7-dihydro-3-methyl-10-((*R*)-3-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxylic acid hydrochloride (24b). This compound was prepared in 81.2% yield from **17b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.43 (3H, d, J = 6.38 Hz), 1.63 (3H, d, J = 6.55 Hz), 3.38–3.46 (2H, m), 3.54–3.72 (5H, m), 4.52 (1H, d, J = 11.75 Hz), 4.66 (1H, d, J = 12.09 Hz), 4.70 (1H, m), 7.46 (1H, d, J = 11.92 Hz), 8.81 (1H, s). IR (KBr) ν 3419.2, 2939.0, 2775.1, 1708.6, 1621.9, 1054.9, 804.2 cm^{-1}. MS(EI), *m/z* (%) 361 (M^+, 28), 305 (98), 261 (100). $[\alpha]_D^{22}$ −25 (*c* 0.115, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_4$·HCl·H_2O: C, 51.99; H, 5.57; N, 10.10. Found: C, 51.95; H, 5.83; N, 10.33.

5.1.3.3. (*R*)-9-Fluoro-3,7-dihydro-3-methyl-10-((*S*)-3-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid hydrochloride (25a). This compound was prepared in 81.3% yield from **18a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.44 (3H, d, J = 6.33 Hz), 1.64 (3H, d, J = 6.73 Hz), 3.39–3.44 (2H, m), 3.55–3.72 (5H, m), 4.52 (1H, d, J = 11.00 Hz), 4.67 (1H, d, J = 10.26 Hz), 4.71 (1H, m), 7.44 (1H, d, J = 12.09 Hz), 8.82 (1H, s). IR (KBr) ν 3423.1, 2941.0, 2807.9, 1706.7, 1621.9, 1054.9, 804.2 cm^{-1}. MS(EI), *m/z* (%) 361 (M^+, 30), 305 (100), 261 (93). $[\alpha]_D^{21}$ +21 (*c* 0.12, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_4$·HCl·H_2O: C, 51.99; H, 5.57; N, 10.10. Found: C, 51.85; H, 5.84; N, 10.23.

5.1.3.4. (*R*)-9-Fluoro-3,7-dihydro-3-methyl-10-((*R*)-3-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid hydrochloride (25b). This compound was prepared in 77.8% yield from **18b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.44 (3H, d, J = 5.04 Hz), 1.63 (3H, d, J = 6.88 Hz), 3.42–3.47 (2H, m), 3.55–3.71 (5H, m), 4.52 (1H, d, J = 11.74 Hz), 4.66 (1H, d, J = 11.76 Hz), 4.70 (1H, m), 7.43 (1H, d, J = 11.92 Hz), 8.80 (1H, s). IR (KBr) ν 3471.3, 2950.6, 2769.3, 1708.6, 1621.9, 1477.2, 1053.0, 804.2 cm^{-1}. MS(EI), *m/z* (%) 361 (M^+, 28), 305 (100), 261 (70). $[\alpha]_D^{21}$ +75 (*c* 0.12, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_4$·HCl·H_2O: C, 51.99; H, 5.57; N, 10.10. Found: C, 51.87; H, 5.80; N, 10.21.

5.1.3.5. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-((*S*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (26a). This compound was prepared in 79.2% yield from **19a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.23–1.35 (4H, m), 1.42 (3H, d, J = 6.67 Hz), 3.17–3.53 (7H, m), 4.21 (1H, m), 7.38 (1H, d, J = 7.60 Hz), 7.76 (1H, d, J = 12.43 Hz), 8.78 (1H, s). IR (KBr) ν 3437.6, 2950.4, 2703.7, 1725.6, 1620.4, 1363.2, 1046.8, 805.9 cm^{-1}. MS(EI), *m/z* (%) 345 (M^+, 31), 289 (100), 245 (88). $[\alpha]_D^{21}$ +24 (*c* 0.12, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_3$·HCl·H_2O: C, 54.07; H, 5.80; N, 10.51. Found: C, 53.92; H, 5.93; N, 10.72.

5.1.3.6. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-((*R*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (26b). This compound was prepared in 80.5% yield from **19b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.23–1.35 (4H, m), 1.42 (3H, d, J = 6.67 Hz), 3.17–3.53 (7H, m), 4.21 (1H, m), 7.38 (1H, d, J = 7.60 Hz), 7.76 (1H, d, J = 12.43 Hz), 8.78 (1H, s). IR (KBr) ν 3442.5, 2941.2, 2704.8, 1726.8, 1620.4, 1362.7, 1045.6, 805.9 cm^{-1}. MS(EI), *m/z* (%) 345 (M^+, 31), 289 (100), 245 (88). $[\alpha]_D^{21}$ −25 (*c* 0.09, H_2O). Anal. Calcd for $C_{18}H_{20}FN_3O_3$·HCl·0.8H_2O: C, 54.56; H, 5.75; N, 10.60. Found: C, 54.38; H, 5.86; N, 10.47.

5.1.3.7. 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-((*S*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (27a). This compound was prepared in 80.7% yield from **20a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.27–1.36 (4H, m), 1.44 (3H, d, J = 6.60 Hz), 3.44–3.78 (7H, m), 4.18 (1H, m), 7.70 (1H, d, J = 11.41 Hz), 8.82 (1H, s). IR (KBr) ν 3430.8, 2937.1, 2699.9, 1727.9, 1625.7, 1475.3, 1324.9, 1033.7, 806.1, 551.6 cm^{-1}. MS(EI), *m/z* (%) 363 (M^+, 27), 307 (100), 263 (60). $[\alpha]_D^{20}$ −26 (*c* 0.233, H_2O). Anal. Calcd for $C_{18}H_{19}F_2N_3O_3$·HCl·0.2H_2O: C, 53.59; H, 5.10; N, 10.42. Found: C, 53.47; H, 5.24; N, 10.37.

5.1.3.8. 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-((*R*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (27b). This compound was prepared in 81.4% yield from **20b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.27–1.36 (4H, m), 1.44 (3H, d, J = 6.60 Hz), 3.44–3.78 (7H, m), 4.18 (1H, m), 7.70 (1H, d, J = 11.41 Hz), 8.82 (1H, s). IR (KBr) ν 3453.9, 2931.3, 2699.9, 1727.9, 1618.0, 1479.2, 1326.8, 1035.6, 806.1, 551.6 cm^{-1}. MS(EI), *m/z* (%) 363 (M^+, 25), 307 (100), 263 (66). $[\alpha]_D^{23}$ +34 (*c* 0.105, H_2O). Anal. Calcd for $C_{18}H_{19}F_2N_3O_3$·HCl·0.3H_2O: C, 53.35; H, 5.12; N, 10.37. Found: C, 53.53; H, 5.46; N, 10.64.

5.1.3.9. 6,8-Difluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-((*S*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (28a). This compound was prepared in 80.5% yield from **21a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.37 (3H, d, J = 6.6 Hz), 3.30–3.38 (2H, m), 3.48–3.66 (5H, m), 7.27–7.37 (2H, m), 7.73–7.79 (1H, m), 7.99 (1H, d, J = 10.86 Hz), 8.80 (1H, s). IR (KBr) ν 3446.2, 2939.0, 2709.5, 1731.8, 1618.0, 1459.9, 1438.7, 1322.9, 806.1, 536.1 cm^{-1}. MS(EI), *m/z* (%) 435 (M^+, 24), 379 (100), 335 (80). $[\alpha]_D^{21}$ −27 (*c* 0.12, H_2O). Anal. Calcd for $C_{21}H_{17}F_4N_3O_3$·HCl·H_2O: C, 51.49; H, 4.12; N, 8.58. Found: C, 51.36; H, 4.25; N, 8.76.

5.1.3.10. 6,8-Difluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-((*R*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (28b). This compound was prepared in 80.5% yield from **21b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.35 (3H, d, J = 6.46 Hz), 3.28–3.36 (2H, m), 3.46–3.64 (5H, m), 7.25–7.35 (2H, m), 7.71–7.77 (1H, m), 7.96 (1H, d, J = 12.09 Hz), 8.79 (1H, s). IR (KBr) ν 3446.2, 2939.0, 2738.5, 1731.8, 1618.0, 1508.1, 1438.7, 1322.9, 806.1, 536.1 cm^{-1}. MS(EI), *m/z* (%) 435 (M^+, 24), 379 (100), 335 (80). $[\alpha]_D^{23}$ +30 (*c* 0.10, H_2O). Anal. Calcd for $C_{21}H_{17}F_4N_3O_3$·HCl·0.6H_2O: C, 52.26; H, 4.01; N, 8.71. Found: C, 52.45; H, 4.19; N, 8.98.

5.1.3.11. 6,8-Difluoro-1-(3,4-difluorophenyl)-1,4-dihydro-7-((*S*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (29a). This compound was prepared in 89.7% yield from **22a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.37 (3H, d, J = 6.46 Hz), 3.31–3.37 (2H, m), 3.47–3.65 (5H, m), 7.49 (1H, m), 7.54–7.61 (1H, m), 7.64–7.68 (1H, m), 8.00 (1H, d, J = 11.55 Hz), 8.81 (1H, s). IR (KBr) ν 3419.2, 2941.0, 2717.3, 1726.0, 1623.8, 1510.0, 1448.3, 1274.7, 802.3, 775.3, 563.1 cm^{-1}. MS(EI), *m/z* (%) 435 (M^+, 24), 379 (100), 335 (77). $[\alpha]_D^{21}$ −29 (*c* 0.095, H_2O). Anal. Calcd for $C_{21}H_{17}F_4N_3O_3$·HCl·H_2O: C, 51.49; H, 4.12; N, 8.58. Found: C, 51.72; H, 4.13; N, 8.61.

5.1.3.12. 6,8-Difluoro-1-(3,4-difluorophenyl)-1,4-dihydro-7-((*R*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (29b). This compound was prepared in 89.6% yield from **22b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.35 (3H, d, J = 6.46 Hz), 3.27–3.35 (2H, m), 3.46–3.64 (5H, m), 7.48 (1H, m), 7.52–7.59 (1H, m), 7.63–7.66 (1H, m), 7.98 (1H, d, J = 10.86 Hz), 8.79 (1H, s). IR (KBr) ν 3423.1, 2935.2, 2736.5, 1726.0, 1623.8, 1510.0, 1452.2, 1274.7, 804.2, 775.3, 563.1 cm^{-1}. MS(EI), *m/z* (%) 435 (M^+, 23), 379 (100), 335 (90). $[\alpha]_D^{23}$ +36 (*c* 0.105, H_2O). Anal. Calcd for $C_{21}H_{17}F_4N_3O_3$·HCl·H_2O: C, 51.49; H, 4.12; N, 8.58. Found: C, 51.60; H, 4.15; N, 8.65.

5.1.3.13. 6,8-Difluoro-1-(3-fluorophenyl)-1,4-dihydro-7-((*S*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (30a). This compound was prepared in 90.1% yield from **23a** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.37 (3H, d, J = 6.47 Hz), 3.29–3.37 (2H, m), 3.48–3.66 (5H, m), 7.48–7.52 (3H, m), 7.68–7.72 (1H, m), 7.93 (1H, d, J = 11.82 Hz), 8.80 (1H, s). IR (KBr) ν 3434.7, 2933.2, 2713.4, 1735.6, 1619.9, 1596.8, 1484.9, 1446.4, 1322.9, 1027.9, 804.2, 684.6 cm^{-1}. MS(EI), *m/z* (%) 417 (M^+, 14), 361 (96), 317 (100). $[\alpha]_D^{22}$ −29 (*c* 0.1, H_2O). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$·HCl·0.1H_2O: C, 55.36; H, 4.25; N, 9.22. Found: C, 55.23; H, 4.20; N, 9.15.

5.1.3.14. 6,8-Difluoro-1-(3-fluorophenyl)-1,4-dihydro-7-((*R*)-3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride (30b). This compound was prepared in 87.2% yield from **23b** as a white solid. Mp >290 °C. ^{1}H NMR (D_2O): δ 1.37 (3H, d, J = 6.46 Hz), 3.26–3.34 (2H, m), 3.45–3.63 (5H, m), 7.45–7.49 (3H, m), 7.65–7.71 (1H, m), 7.95 (1H, d, J = 11.62 Hz), 8.79 (1H, s). IR (KBr) ν 3444.3, 2929.4, 2701.8, 1735.6, 1619.9, 1596.8, 1477.2, 1446.4, 1322.9, 1027.9, 804.2, 684.6 cm^{-1}. MS(EI), *m/z* (%) 417 (M^+, 24), 361 (100), 317 (79). $[\alpha]_D^{23}$ +25 (*c* 0.099, H_2O). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$·HCl·0.3H_2O: C, 54.92; H, 4.30; N, 9.15. Found: C, 55.04; H, 4.33; N, 9.40.

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