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Reliable assignment of absolute configuration of chiral amines based on the analysis of ^{1}H NMR spectra of their CFTA amide diastereomers

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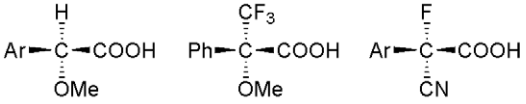
Abstract—Applications of the CFTA method, a new and reliable procedure for the determination of the absolute configuration of chiral primary amines, are described in detail. In addition to the very high reactivity of CFTA chloride, the stable *anti-periplanar* conformers of CFTA amides, associated with the chiral structure of fluorine atom on a stereogenic center, are the key factors that make the technique of using ^{1}H NMR analysis of the CFTA diastereomers very reliable. In particular, this method is useful for the determination of the absolute stereochemistry of isotopically multi-labeled amino acid derivatives.

1. Introduction

The determination of absolute configuration is of fundamental importance to various fields of organic chemistry. Although there have been several methods[1] so far reported for this purpose, extensive research has continued for techniques of more general and practical applicability. X-ray crystallographic analysis is the most reliable method for determining the absolute configuration. However, this is only effective in the case where a single crystal of the sample can be obtained. Therefore, samples obtained in small quantities from natural sources and/or those compounds that are oils cannot be analyzed by X-ray methods. Other procedures including the CD excitation chirality method have been reported. However, all of these procedures also have limitations to their practical applicability.

In order to overcome the drawbacks mentioned above, more convenient methods have been studied which involve diastereomer formation with chiral derivatizing agents (CDAs) followed by NMR spectroscopic examination.[1,2] These CDAs include α-methoxyarylacetic acid analogues **1**–**3** in addition to the well-known α-methoxy-α-trifluoromethylphenylacetic acid **4** (MTPA) (Fig. 1).[3] All of these agents, however, suffer from the problems of low reactivity[4] of the corresponding acid chlorides, possible racemization,[5] and/or poor resolution ability in the NMR of their diastereomers caused by the presence of multiple conformers.[6] We have recently developed a reliable method for the determination of the absolute configuration of chiral amines[7] using α-cyano-α-fluoro-*p*-tolylacetic acid **5**



1: Ar = phenyl (MPA)
2: Ar = 1-naphthyl (1NMA)
3: Ar = 9-anthryl (9AMA)

4: MTPA

5: Ar = *p*-tolyl (CFTA)
6: Ar = phenyl (CFPA)

Figure 1.

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(CFTA). Herein we report in full the details of the CFTA procedure.

2. Results and discussion

2.1. Molecular design of the new CDA

The drawbacks of the existing CDAs seemed to be mainly due to the inherent problems[4] derived from the α-methoxyacetate structure, as shown by **1**–**4**. Upon consideration of the necessary factors for better CDAs, especially greater reactivity so as to allow condensation even with sterically hindered nucleophiles, we focused on α-cyano-α-fluorophenylacetic acid **6** (CFPA). This compound has a unique chiral structure with a fluorine atom located on the stereogenic center.[8] Indeed, CFPA chloride is 500 times more reactive than MTPA chloride, thus allowing reaction even with hindered nucleophiles to give CFPA diastereomers.[9] Furthermore, the ^{19}F NMR chemical shift differences between CFPA diastereomers are in general several times greater than those between the well-known MTPA diastereomers. This enables ee determination by the CFPA method for molecules having their stereogenic centers several bonds remotely disposed from the derivative acid functionality.[8,10]

Although CFPA was useful for the determination of the absolute configuration of chiral molecules, this agent proved to be rather difficult to produce as pure enantiomers. Moreover, the phenyl protons of the CFPA derivatives appear as a complex multiplet that can often complicate the analyses of the proton NMR spectra of a substrate having aromatic substituents. The recognition and analysis of the AB quartet-like proton signals for the *para*-substituted phenyl group is much easier than the proton signals for the other possible substitution patterns. After the examination of several *para*-substituted analogues of CFPA, we have settled on using CFTA **5** for the determination of both ees and absolute configuration.[11]

2.2. Application of the CFTA method to the determination of the absolute configuration of chiral primary amines

We have already reported the formation of a very stable conformer having an all *syn-periplanar* (F–C_α)–(C═O)–O–(C–H) structure in the 'CFTA ester plane' as the predominant rotamer of CFTA esters.[12] We propose that the formation of a very stable *anti-periplanar* (F–C_α)–(C═O)–(N–H)–(C–H) conformer in the 'CFTA amide plane'[7] is the predominant rotamer of CFTA amides, even in $CDCl_3$ solution. Apparently, a consistent relationship exists between the stereochemistry of chiral amines and the chemical shifts of the corresponding diastereomeric CFTA amides. In order to establish this pattern, we investigated various types of chiral amines of known absolute configurations. At first, each chiral amine **7a**–**y** was condensed with both (*S*)- and (*R*)-CFTA chlorides to give (*S*)- and (*R*)-CFTA amide diastereomers, respectively. All proton signals for each of the (*S*)- and (*R*)-CFTA diastereomers **8a**–**y** were assigned and the $\Delta\delta$ ($=\delta_S - \delta_R$) value for every proton was obtained (Fig. 2).

When the amides are depicted such that the two substituents on the stereogenic center are in the plane of the page, and the α-protons are coming out of the plane, the protons with positive $\Delta\delta$ values are invariably on the right

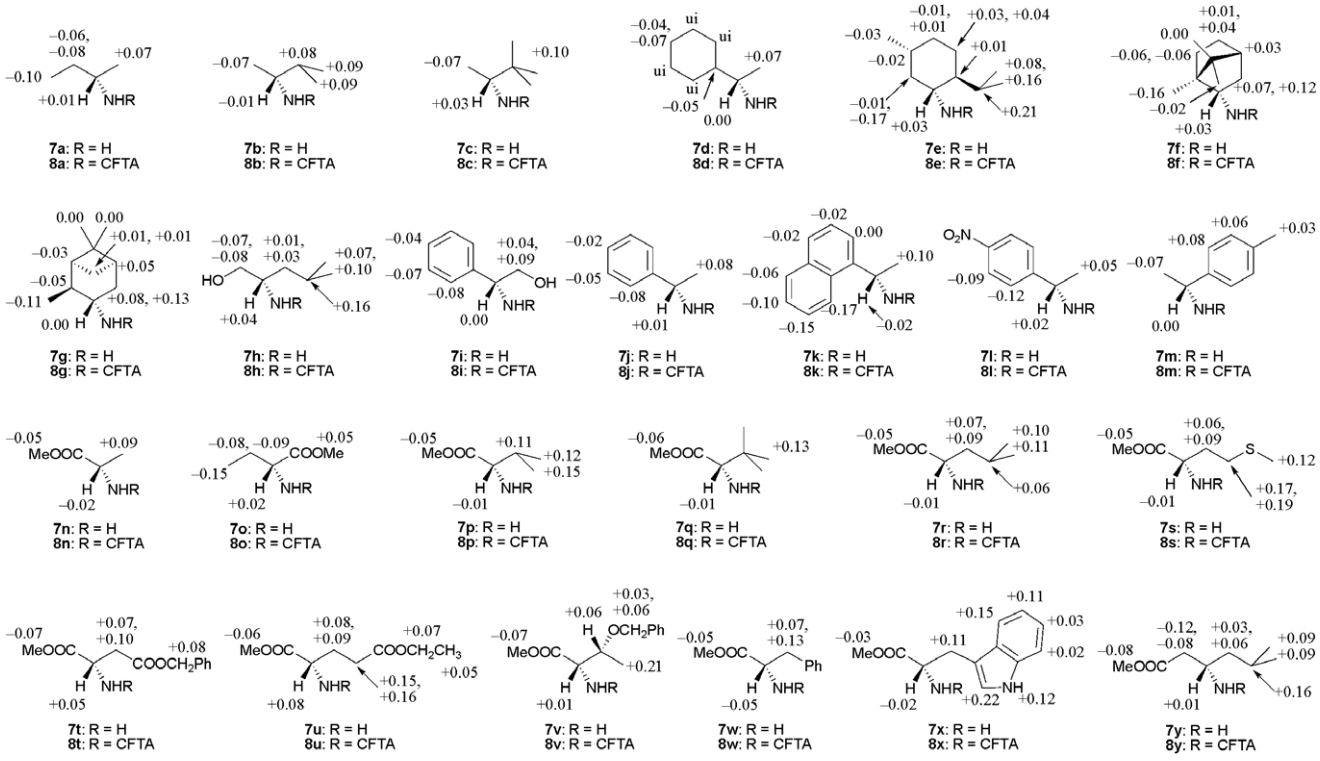

Figure 2. Chemical shift differences ($\Delta\delta_H$) observed for CFTA amide diastereomers of chiral amines **7a**–**y**. ui: unidentified.

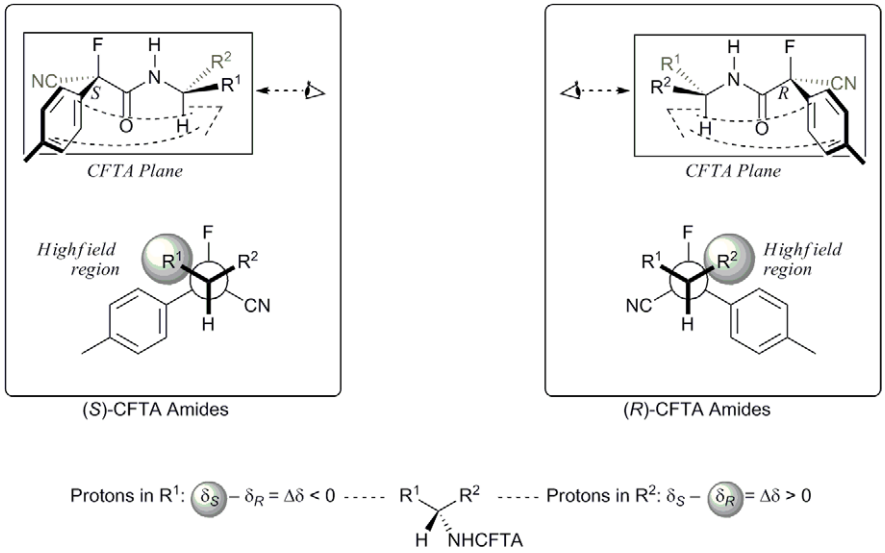

Figure 3. Preferred conformations of (*S*)- and (*R*)-CFTA amides of chiral primary amines ($R^1R^2CHNH_2$).

side of the CFTA amide plane while those having negative $\Delta\delta$ values are on the left side of the plane. We have not found any exception to this pattern. These results can be explained using conformational arguments, as shown in Figure 3.

The structures illustrated show the (*S*)- and (*R*)-CFTA amide diastereomers having an all *anti-periplanar* (*ap*) (F–C_α)–(C=O)–(N–H)–(C–H) array. This *ap* conformation was supported by X-ray crystallographic analyses of the CFTA amide of 1-phenylethylamine[13] and ab initio calculations (GAUSSIAN 98, RHF/6-31+G*) of the CFPA amide of valine methyl ester, taken to be a closely analogous structure.[14]

In order to view the (*S*)-CFTA amides of chiral amines ($R^1R^2CHNH_2$) from the right side, or the (*R*)-CFTA amides from the left side, via an extended Newman projection, the intervening amide linkages are omitted for convenience. In the (*S*)-CFTA diastereomer, the shifts of the protons of the R^1 group should always be upfield, as a result of the anisotropic shielding of the aromatic ring. In contrast, for the (*R*)-diastereomer, the protons of the R^2 group are shielded and therefore should appear upfield. Thus, the $\Delta\delta$ values for the protons on the left side of the CFTA plane should be negative, while those on the right side of the plane should be positive. Reinforcing these differences, the CN group induces an anisotropic deshielding effect[15] on the proximate R^1 and R^2 groups in the (*S*)- and (*R*)-CFTA diastereomers, respectively. Accordingly, the $\Delta\delta$ ($=\delta_S - \delta_R$) values for the protons in the R^2 group, namely, those for all the protons on the right side of the CFTA amide plane, should be positive and those in the R^1 group, namely, those for all the protons on the left side of the plane, should be negative (Fig. 3).

We prepared isotopically multi-labeled amino acids, which we assumed will be useful for medicinal and/or clinical work. We needed to determine the absolute configuration of these compounds **9a** and **9b**. This was also a good opportunity to look further at the scope and limitation of the CFTA method.

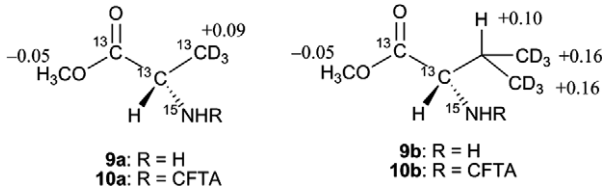

Figure 4. Chemical shift differences ($\Delta\delta_H$ and $\Delta\delta_D$) observed for CFTA amide diastereomers of multi-labeled amino acid methyl esters.

The results of the CFTA derivatization are shown in Figure 4 in a manner similar to Figure 2. We found the expected (*S*)-absolute configuration for both of these multi-labeled amino acids.

3. Conclusion

We have established that the CFTA method can be applied not only to the determination of the absolute configuration of chiral secondary alcohols but also to that of chiral primary amines. Although there are other conceptually similar procedures available, these procedures, in some cases, cannot be applied because the chiral derivatizing agents used for the procedures exhibit insufficient reactivities toward bulky substrates or the absolute configuration using these procedures resulted in ambiguities. The CFTA method has important advantages over them because of the very high reactivity of CFTA chloride[4d] and because the F atom directly connected to the stereogenic center contributes to the conformational control of the amides.[7] The specific stereoelectronic environment that produces this '*ap*' conformation is probably due to the unique F atom and the CN group on the chiral center.[16] We feel that this method should be very reliable and widely applicable. Further clarification of the theoretical basis for the above results

and the acquisition of additional data to study the generality of the CFTA procedure are currently under investigation.

4. Experimental

4.1. General

Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalysis Center of Toyama Medical and Pharmaceutical University. Spectroscopic measurements were carried out with the following instruments: optical rotations, JASCO DIP-1000 digital polarimeter; IR spectra, Perkin–Elmer 1600 Series FTIR; mass spectra (MS), JEOL JMS-GCmate; high resolution mass spectra (HRMS), JEOL JMS-AX 505 HAD or Bruker APEX III; ^{1}H NMR spectra, Varian Unity 500 (500 MHz) or JEOL GSX-400 (400 MHz), in $CDCl_3$ with TMS (=0.00 ppm) as an internal standard; ^{2}D NMR spectra, JEOL GSX-400 (61 MHz), in $CHCl_3$ with $CDCl_3$ (=7.26 ppm) as an internal standard. ^{19}F NMR spectra, Varian Unity 500 (470 MHz), JEOL JNM-GX 270 (254 MHz) or JEOL GSX-400 (376 MHz), in $CDCl_3$ with $CFCl_3$ (=0.00 ppm) as an internal standard. Column chromatography was performed on Fuji Silysia BW-200, Kanto chemical Silica Gel 60N (0.040–0.050 mm), or Merck Silica Gel 60 (0.040–0.063 mm). Thin layer chromatography was performed on Merck 5715.

4.2. Typical procedure for the condensation of α-cyano-α-fluoro-*p*-tolylacetyl chloride with chiral amines

(*R*)-CFTA chloride (30.0 mg, 0.142 mmol) was added to a solution of (*R*)-(+)-1-(*p*-tolyl)ethylamine **7m** (20.4 μL, 0.142 mmol) and pyridine (23.0 μL, 0.284 mmol) in dry CH_2Cl_2 (1 mL) at room temperature. After stirring at room temperature for 2 h, the solvent and excess pyridine were evaporated in vacuo. A solution of the residue in H_2O (0.2 mL) was extracted with EtOAc (3 mL × 3). The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by preparative TLC (eluent; hexane/EtOAc = 1:1) to give *N*-[(*R*)-1-(*p*-tolyl)ethyl]-(*R*)-α-cyano-α-fluoro-*p*-tolylacetamide (44 mg, 100%) as colorless needles: Mp 80–81 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{27} = +110.2$ (*c* 1.2, MeOH); IR (KBr) 3336, 2256, 1678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (3H, d, $J = 7.1$ Hz), 2.34 (3H, s), 2.37 (3H, s), 5.12 (1H, dq, $J = 7.4$, 7.1 Hz), 6.65 (1H, br s), 7.16 (4H, s), 7.22 (2H, br d, $J = 7.9$ Hz), 7.41 (2H, br d, $J = 8.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.99 (s); MS (EI) *m*/*z* 310 (M^+). Anal. Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03. Found: C, 73.55; H, 5.92; N, 8.87.

Other amides were prepared in the same manner in 40–100% yields.

4.2.1. *N*-[(*S*)-2-Butyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7a]. Colorless needles; mp 69–70 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{25} = +18.0$ (*c* 1.3, MeOH); IR (KBr) 3328, 2255, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, $J = 7.5$ Hz), 1.24 (3H, d, $J = 6.6$ Hz), 1.50 (1H, dquint, $J = 15.6$, 7.4 Hz), 1.52 (1H, dqd, $J = 15.6$, 7.4, 7.1 Hz), 2.39 (3H, d, $J = 1.5$ Hz), 3.97 (1H, m), 6.22 (1H, br s), 7.27 (2H, m), 7.49 (2H, m); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.83 (s); MS (EI) *m*/*z* 249 ($M^+ + H$), 248 (M^+). Anal. Calcd for $C_{14}H_{17}FN_2O$: C, 67.72; H, 6.90; N, 11.28. Found: C, 67.35; H, 6.93; N, 11.00.

4.2.2. *N*-[(*S*)-2-Butyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7a]. Colorless needles; mp 93–95 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = +11.0$ (*c* 1.0, MeOH); IR (KBr) 3331, 2256, 1681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, $J = 7.5$ Hz), 1.17 (3H, d, $J = 6.6$ Hz), 1.58 (2H, dq, $J = 14.3$, 7.4 Hz), 2.39 (3H, d, $J = 1.5$ Hz), 3.96 (1H, dqd, $J = 7.4$, 6.6, 1.7 Hz), 6.25 (1H, br s), 7.27 (2H, m), 7.49 (2H, m); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.30 (s); MS (EI) *m*/*z* 248 (M^+). Anal. Calcd for $C_{14}H_{17}FN_2O$: C, 67.72; H, 6.90; N, 11.28. Found: C, 67.89; H, 7.20; N, 11.26.

4.2.3. *N*-[(*R*)-2-(3-Methyl)butyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7b]. Colorless needles; mp 100–102 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = -2.5$ (*c* 2.0, MeOH); IR (KBr) 3324, 2260, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, d, $J = 6.8$ Hz), 0.96 (3H, d, $J = 6.8$ Hz), 1.13 (3H, d, $J = 6.8$ Hz), 1.80 (1H, quint, $J = 6.8$ Hz), 2.40 (3H, br d, $J = 1.7$ Hz), 3.91 (1H, quintd, $J = 6.8$, 1.7 Hz), 6.26 (1H, br s), 7.27 (2H, br d, $J = 8.2$ Hz), 7.49 (2H, br d, $J = 6.8$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.28 (s); MS (EI) *m*/*z* 262 (M^+); HRMS (EI) calcd for $C_{15}H_{19}FN_2O$ (M^+): 262.1481; found: 262.1469.

4.2.4. *N*-[(*R*)-2-(3-Methyl)butyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7b]. Colorless needles; mp 65–67 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = -19.6$ (*c* 1.8, MeOH); IR (KBr) 3668, 2254, 1678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (6H, d, $J = 6.8$ Hz), 1.20 (3H, d, $J = 6.8$ Hz), 1.73 (1H, quint, $J = 6.8$ Hz), 2.39 (3H, br s), 3.92 (1H, quintd, $J = 6.8$, 1.7 Hz), 6.26 (1H, br s), 7.27 (2H, br d, $J = 8.2$ Hz), 7.49 (2H, br d, $J = 7.7$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.30 (s); MS (EI) *m*/*z* 262 (M^+); HRMS (EI) calcd for $C_{15}H_{19}FN_2O$ (M^+): 262.1481; found: 262.1480.

4.2.5. *N*-[(*R*)-2-(3,3-Dimethyl)butyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7c]. Colorless needles; mp 80–82 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = -2.6$ (*c* 1.5, MeOH); IR (KBr) 3316, 2250, 1681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.10 (3H, d, $J = 6.8$ Hz), 2.39 (3H, br s), 3.92 (1H, dqd, $J = 9.8$, 6.8, 1.7 Hz), 6.26 (1H, br s), 7.27 (2H, br d, $J = 9.0$ Hz), 7.49 (2H, d, $J = 7.7$ Hz); ^{19}F NMR (254 MHz; $CDCl_3$) δ −141.06 (s); MS (EI) *m*/*z* 276 (M^+). Anal. Calcd for $C_{16}H_{21}FN_2O$: C, 69.54; H, 7.66; N, 10.14. Found: C, 69.41; H, 7.80; N, 9.85.

4.2.6. *N*-[(*R*)-2-(3,3-Dimethyl)butyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7c]. Pale yellow oil; $[\alpha]_D^{27} = -21.7$ (*c* 2.0, MeOH); IR (neat) 3337, 2253, 1698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (9H, s),

1.18 (3H, d, $J = 6.8$ Hz), 2.39 (3H, br s), 3.90 (1H, dqd, $J = 9.8$, 6.8, 1.7 Hz), 6.26 (1H, br s), 7.27 (2H, br d, $J = 9.0$ Hz), 7.49 (2H, d, $J = 7.7$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −143.13 (s); MS (EI) m/z 276 (M^+); HRMS (EI) calcd for $C_{16}H_{21}FN_2O$ (M^+): 276.1638; found: 276.1621.

4.2.7. *N*-[(*S*)-1-(Cyclohexyl)ethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7d]. Colorless needles; mp 63–64 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -3.8$ (c 1.1, MeOH); IR (KBr) 3315, 2252, 1678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (1H, qd, $J = 12.4$, 3.4 Hz), 0.94 (1H, qd, $J = 12.4$, 3.4 Hz), 1.08 (1H, m), 1.19 (2H, qq, $J = 16.8$, 3.8 Hz), 1.20 (3H, d, $J = 6.8$ Hz), 1.36 (1H, ddq, $J = 15.2$, 12.4, 3.4 Hz), 1.65 (3H, m), 1.73 (2H, br d, $J = 12.5$ Hz), 2.39 (3H, br d, $J = 0.8$ Hz), 3.90 (1H, dqd, $J = 15.4$, 6.8, 1.6 Hz), 6.27 (1H, br s), 7.27 (2H, br d, $J = 7.9$ Hz), 7.49 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.76 (s); MS (EI) m/z 302 (M^+). Anal. Calcd for $C_{18}H_{23}FN_2O$: C, 71.50; H, 7.67; N, 9.26. Found: C, 71.50; H, 7.62; N, 8.96.

4.2.8. *N*-[(*S*)-1-(Cyclohexyl)ethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7d]. Colorless needles; mp 129–130 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -18.2$ (c 1.1, MeOH); IR (KBr) 3321, 2253, 1676 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (1H, m), 1.04 (1H, m), 1.13 (3H, d, $J = 6.8$ Hz), 1.15 (1H, m), 1.26 (2H, m), 1.42 (1H, ddq, $J = 15.0$, 12.2, 3.2 Hz), 1.69 (1H, br d, $J = 13.2$ Hz), 1.71 (1H, br d, $J = 12.4$ Hz), 1.77 (1H, m), 1.78 (2H, m), 2.39 (3H, br s), 3.90 (1H, sext, $J = 6.6$ Hz), 6.28 (1H, br s), 7.27 (2H, br d, $J = 8.1$ Hz), 7.49 (2H, br d, $J = 8.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.18 (s); MS (EI) m/z 302 (M^+). Anal. Calcd for $C_{18}H_{23}FN_2O$: C, 71.50; H, 7.67; N, 9.26. Found: C, 71.46; H, 7.56; N, 9.50.

4.2.9. *N*-[(1*R*,2*S*,5*R*)-Menthyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7e]. Colorless solid; mp 75–77 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = -36.7$ (c 0.7, $CHCl_3$); IR (KBr) 3323, 2255, 1677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, d, $J = 7.2$ Hz), 0.87 (1H, m), 0.88 (3H, d, $J = 6.4$ Hz), 0.91 (1H, m), 0.94 (3H, d, $J = 6.8$ Hz), 1.12 (1H, qd, $J = 12.4$, 3.4 Hz), 1.18 (1H, ddt, $J = 12.1$, 10.1, 2.6 Hz), 1.48 (1H, m), 1.72 (1H, m), 1.73 (1H, m), 1.89 (1H, m), 1.90 (1H, m), 2.39 (3H, d, $J = 1.7$ Hz), 3.82 (1H, m), 6.15 (1H, br d, $J = 6.0$ Hz), 7.27 (2H, br d, $J = 8.8$ Hz), 7.48 (2H, br d, $J = 8.5$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.96 (s); MS (EI) m/z 331 (M^++H). Anal. Calcd for $C_{20}H_{27}FN_2O$: C, 72.70; H, 8.24; N, 8.48. Found: C, 72.90; H, 8.53; N, 8.35.

4.2.10. *N*-[(1*R*,2*S*,5*R*)-Menthyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7e]. Colorless needles; mp 163–165 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = +41.0$ (c 0.7, $CHCl_3$); IR (KBr) 3318, 2257, 1674 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (3H, d, $J = 6.9$ Hz), 0.86 (3H, d, $J = 6.9$ Hz), 0.86 (1H, m), 0.92 (1H, m), 0.92 (3H, d, $J = 6.8$ Hz), 1.08 (1H, qd, $J = 12.8$, 3.4 Hz), 1.17 (1H, ddt, $J = 11.9$, 10.7, 3.0 Hz), 1.50 (1H, m), 1.68 (1H, m), 1.69 (1H, m), 1.74 (1H, m), 2.07 (1H, m), 2.40 (3H, d, $J = 0.9$ Hz), 3.81 (1H, m), 6.14 (1H, br s), 7.28 (2H, br d, $J = 11.1$ Hz), 7.48 (2H, br d, $J = 7.3$ Hz); ^{19}F NMR (254 MHz, $CHCl_3$) δ −141.14 (s); MS (EI) m/z 331 (M^++H). Anal. Calcd for $C_{20}H_{27}FN_2O$: C, 72.70; H, 8.24; N, 8.48. Found: C, 72.62; H, 8.49; N, 8.23.

4.2.11. *N*-[(1*R*,2*S*,4*R*)-Bornyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7f]. Colorless needles; mp 79–80 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{29} = -14.8$ (c 1.1, MeOH); IR (KBr) 3351, 2253, 1682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (3H, s), 0.88 (3H, s), 0.93 (1H, dd, $J = 13.9$, 4.7 Hz), 0.94 (3H, s), 1.24 (1H, m), 1.41 (1H, dt, $J = 13.9$, 5.8 Hz), 1.44 (1H, tdd, $J = 13.7$, 4.8, 1.9 Hz), 1.74 (1H, t, $J = 4.5$ Hz), 1.82 (1H, dddd, $J = 13.9$, 8.1, 6.2, 2.8 Hz), 2.40 (3H, br d, $J = 1.7$ Hz), 2.43 (1H, dddd, $J = 13.7$, 11.2, 4.8, 3.6 Hz), 4.28 (1H, dddd, $J = 11.1$, 4.2, 1.9, 1.1 Hz), 6.44 (1H, br s), 7.28 (2H, br d, $J = 8.5$ Hz), 7.51 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −141.03 (s); MS (EI) m/z 328 (M^+). Anal. Calcd for $C_{20}H_{25}FN_2O$: C, 73.14; H, 7.67; N, 8.53. Found: C, 73.19; H, 7.83; N, 8.80.

4.2.12. *N*-[(1*R*,2*S*,4*R*)-Bornyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7f]. Colorless needles; mp 108–110 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -24.3$ (c 1.1, MeOH); IR (KBr) 3311, 2254, 1676 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (1H, dd, $J = 13.5$, 4.5 Hz), 0.89 (3H, s), 0.90 (3H, s), 0.94 (3H, s), 1.20 (1H, ddd, $J = 13.9$, 7.6, 6.1 Hz), 1.46 (1H, ddd, $J = 14.1$, 7.9, 6.6 Hz), 1.50 (1H, dddd, $J = 14.0$, 8.3, 5.8, 1.8 Hz), 1.71 (1H, t, $J = 4.2$ Hz), 1.82 (1H, m), 2.36 (1H, m), 2.39 (3H, br d, $J = 1.5$ Hz), 4.25 (1H, m), 6.44 (1H, br s), 7.27 (2H, br d, $J = 8.6$ Hz), 7.50 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −142.01 (s); MS (EI) m/z 328 (M^+). Anal. Calcd for $C_{20}H_{25}FN_2O$: C, 73.14; H, 7.67; N, 8.53. Found: C, 73.11; H, 7.69; N, 8.43.

4.2.13. *N*-[(1*R*,2*S*,3*S*)-Isopinocampheyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7g]. Colorless needles; mp 122–123 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = +24.5$ (c 1.1, MeOH); IR (KBr) 3315, 2255, 1677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (1H, d, $J = 10.0$ Hz), 1.04 (3H, s), 1.06 (3H, d, $J = 7.3$ Hz), 1.24 (3H, s), 1.64 (1H, ddd, $J = 14.1$, 6.4, 2.4 Hz), 1.84 (1H, m), 1.85 (1H, br d, $J = 6.4$ Hz), 2.02 (1H, dtd, $J = 8.3$, 3.8, 2.4 Hz), 2.40 (3H, br d, $J = 1.7$ Hz), 2.46 (1H, dddd, $J = 9.8$, 7.2, 6.2, 2.3 Hz), 2.67 (1H, dddd, $J = 13.9$, 10.2, 3.7, 2.3 Hz), 4.32 (1H, m), 6.34 (1H, br d, $J = 8.1$ Hz), 7.28 (2H, br d, $J = 8.6$ Hz), 7.50 (2H, br d, $J = 8.4$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −140.73 (s); MS (EI) m/z 328 (M^+). Anal. Calcd for $C_{20}H_{25}FN_2O$: C, 73.14; H, 7.67; N, 8.53. Found: C, 73.28; H, 7.71; N, 8.58.

4.2.14. *N*-[(1*R*,2*S*,3*S*)-Isopinocampheyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7g]. Colorless needles; mp 111–113 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = +19.0$ (c 1.0, MeOH); IR (KBr) 3276, 2253, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (1H, d, $J = 10.0$ Hz), 1.03 (3H, s), 1.18 (3H, d, $J = 7.1$ Hz), 1.24 (3H, s), 1.51 (1H, ddd, $J = 14.1$, 6.2, 2.4 Hz), 1.88 (1H, m), 1.89 (1H, m), 1.97 (1H, dddd, $J = 7.2$, 6.3, 3.8, 2.4 Hz), 2.39 (3H, br d, $J = 1.7$ Hz), 2.45 (1H, dtd, $J = 9.8$, 6.8, 2.4 Hz), 2.59 (1H, dddd, $J = 13.9$, 10.0, 3.7,

2.3 Hz), 4.32 (1H, dddd, $J = 13.8$, 11.8, 4.6, 3.4 Hz), 6.33 (1H, br s), 7.28 (2H, br d, $J = 8.6$ Hz), 7.50 (2H, br d, $J = 8.4$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −141.67 (s); MS (EI) m/z 328 (M^+). Anal. Calcd for $C_{20}H_{25}FN_2O$: C, 73.14; H, 7.67; N, 8.53. Found: C, 73.08; H, 7.45; N, 8.34.

4.2.15. *N*-[(2*S*)-1-Hydroxy-4-methylpentyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7h]. Colorless needles; mp 77–79 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{26} = -14.8$ (c 0.9, MeOH); IR (KBr) 3483, 3323, 2258, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (6H, d, $J = 6.6$ Hz), 1.43 (1H, br ddd, $J = 14.1$, 8.1, 5.8 Hz), 1.53 (1H, br ddd, $J = 13.9$, 9.0, 6.0 Hz), 1.68 (1H, m), 1.69–1.85 (1H, br s), 2.39 (3H, br s), 3.61 (1H, dd, $J = 11.1$, 5.1 Hz), 3.71 (1H, dd, $J = 11.1$, 1.3 Hz), 4.14 (1H, m), 6.59 (1H, br d, $J = 6.7$ Hz), 7.27 (2H, br d, $J = 8.6$ Hz), 7.53 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.29 (s); MS (EI) m/z 293 (M^++H), 291 (M^+−H), 277 (M^+−15), 274 (M^+−18); HRMS (EI) calcd for $C_{16}H_{21}FN_2O_2$ (M^+): 292.1587; found: 292.1596.

4.2.16. *N*-[(2*S*)-1-Hydroxy-4-methylpentyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7h]. Colorless needles; mp 55–56 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -22.6$ (c 0.9, MeOH); IR (KBr) 3483, 3326, 2258, 1679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, $J = 6.4$ Hz), 0.90 (3H, d, $J = 6.4$ Hz), 1.42 (1H, br ddd, $J = 14.2$, 8.1, 5.6 Hz), 1.49 (1H, br ddd, $J = 14.6$, 8.8, 5.6 Hz), 1.52 (1H, m), 1.76–1.96 (1H, br s), 2.40 (3H, br s), 3.68 (1H, dd, $J = 11.1$, 4.3 Hz), 3.79 (1H, dd, $J = 11.1$, 3.8 Hz), 4.10 (1H, m), 6.64 (1H, br d, $J = 7.2$ Hz), 7.27 (2H, br d, $J = 7.9$ Hz), 7.49 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.29 (s); MS (EI) m/z 274 (M^+−18). Anal. Calcd for $C_{16}H_{21}FN_2O_2$: C, 65.73; H, 7.24; N, 9.58. Found: C, 65.95; H, 7.40; N, 9.33.

4.2.17. *N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7i]. Colorless plates; mp 101–104 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -60.8$ (c 0.8, MeOH); IR (KBr) 3393, 3327, 2266, 1689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79–1.99 (1H, br s), 2.38 (3H, br s), 3.97 (1H, dd, $J = 11.3$, 4.7 Hz), 4.01 (1H, dd, $J = 11.1$, 4.1 Hz), 5.12 (1H, dt, $J = 7.5$, 4.4 Hz), 7.24 (5H, m), 7.32 (1H, br t, $J = 6.8$ Hz), 7.35 (2H, br t, $J = 7.4$ Hz), 7.44 (2H, br d, $J = 7.8$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.12 (s); MS (EI) m/z 294 (M^+−18); HRMS (EI) calcd for $C_{18}H_{17}FN_2O_2$ (M^+): 312.1274; found: 312.1307.

4.2.18. *N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7i]. Pale yellow solid; mp 157–158 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{26} = -98.1$ (c 1.2, MeOH); IR (KBr) 3468, 3278, 2240, 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77–1.90 (1H, br s), 2.41 (3H, br d, $J = 1.5$ Hz), 3.93 (2H, br s), 5.12 (1H, dt, $J = 7.5$, 4.7 Hz), 7.21 (1H, br s), 7.30 (2H, br d, $J = 8.0$ Hz), 7.32 (2H, br d, $J = 7.6$ Hz), 7.36 (1H, tt, $J = 7.4$, 1.5 Hz), 7.42 (2H, tt, $J = 7.5$, 1.3 Hz), 7.56 (2H, br d, $J = 7.8$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.42 (s); MS (EI) m/z 294 (M^+−18); HRMS (EI) calcd for $C_{18}H_{18}FN_2O_2$ (M^+ + H): 313.1352; found: 313.1389.

4.2.19. *N*-[(*S*)-1-Phenylethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7j]. Colorless needles; mp 69–72 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{27} = -88.9$ (c 1.2, MeOH); IR (KBr) 3330, 2252, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, d, $J = 7.1$ Hz), 2.37 (3H, s), 5.16 (1H, quint, $J = 7.1$ Hz), 6.67 (1H, br s), 7.22 (2H, br d, $J = 7.9$ Hz), 7.27 (2H, br d, $J = 6.6$ Hz), 7.31 (1H, m), 7.35 (2H, m), 7.40 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.99 (s); MS (EI) m/z 297 (M^++H), 296 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.87; H, 5.52; N, 9.48.

4.2.20. *N*-[(*S*)-1-Phenylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7j]. Colorless needles; mp 127–129 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{26} = -89.6$ (c 1.6, MeOH); IR (KBr) 3328, 2252, 1676 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (3H, d, $J = 6.8$ Hz), 2.40 (3H, s), 5.16 (1H, dq, $J = 7.1$, 6.8 Hz), 6.68 (1H, br s), 7.29 (2H, br d, $J = 7.9$ Hz), 7.34 (2H, m), 7.39 (1H, m), 7.40 (2H, m), 7.51 (2H, br d, $J = 8.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.27 (s); MS (EI) m/z 297 (M^++H), 296 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.97; H, 5.89; N, 9.31.

4.2.21. *N*-[(*S*)-1-Naphthylethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7k]. Colorless needles; mp 106–107 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{26} = +23.6$ (c 1.6, MeOH); IR (KBr) 3303, 2250, 1679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (3H, d, $J = 6.8$ Hz), 2.37 (3H, d, $J = 1.7$ Hz), 5.94 (1H, dq, $J = 7.1$, 6.9 Hz), 6.69 (1H, br s), 7.16 (2H, br d, $J = 8.1$ Hz), 7.37 (2H, br d, $J = 8.3$ Hz), 7.39 (1H, ddd, $J = 8.4$, 7.0, 1.4 Hz), 7.47 (1H, dd, $J = 7.6$, 7.3 Hz), 7.50 (1H, ddd, $J = 8.1$, 6.9, 1.2 Hz), 7.52 (1H, br d, $J = 8.1$ Hz), 7.84 (1H, d, $J = 8.1$ Hz), 7.85 (1H, d, $J = 8.6$ Hz), 7.88 (1H, br d, $J = 8.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.19 (s); MS (EI) m/z 346 (M^+). Anal. Calcd for $C_{22}H_{19}FN_2O$: C, 76.28; H, 5.53; N, 8.09. Found: C, 76.32; H, 5.26; N, 8.03.

4.2.22. *N*-[(*S*)-1-Naphthylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7k]. Colorless needles; mp 146–148 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{28} = -38.6$ (c 0.5, MeOH); IR (KBr) 3274, 2250, 1665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (3H, d, $J = 6.8$ Hz), 2.41 (3H, d, $J = 1.1$ Hz), 5.96 (1H, dq, $J = 7.1$, 6.8 Hz), 6.74 (1H, br d, $J = 4.7$ Hz), 7.29 (2H, d, $J = 7.9$ Hz), 7.49 (1H, t, $J = 7.8$ Hz), 7.51 (2H, d, $J = 9.0$ Hz), 7.52 (1H, d, $J = 8.3$ Hz), 7.54 (1H, m), 7.60 (1H, ddd, $J = 8.4$, 6.9, 1.5 Hz), 7.86 (1H, d, $J = 8.1$ Hz), 7.90 (1H, dd, $J = 8.1$, 0.6 Hz), 8.05 (1H, d, $J = 8.6$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.21 (s); MS (EI) m/z 346 (M^+). Anal. Calcd for $C_{22}H_{19}FN_2O$: C, 76.28; H, 5.53; N, 8.09. Found: C, 76.05; H, 5.52; N, 7.83.

4.2.23. *N*-[(*S*)-1-(*p*-Nitrophenyl)ethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7l]. Pale yellow oil; $[\alpha]_D^{28} = -77.5$ (c 1.1, MeOH); IR (neat) 3333, 2252, 1692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (3H, d, $J = 7.1$ Hz), 2.39 (3H, br s), 5.22 (1H, quint, $J = 7.1$ Hz), 6.75 (1H, br s), 7.25 (2H, m), 7.38 (4H, br d, $J = 9.0$ Hz), 8.17 (2H, br d, $J = 8.8$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$)

δ −143.36 (s); MS (EI) *m*/*z* 341 (M^+); HRMS (EI) calcd for $C_{18}H_{16}FN_3O_3$ (M^+): 341.1176; found: 341.1147.

4.2.24. *N*-[(*S*)-1-(*p*-Nitrophenyl)ethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7l]. Colorless needles; mp 139–142 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{27}$ = −118.9 (*c* 1.4, MeOH); IR (KBr) 3327, 2253, 1679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (3H, d, *J* = 7.1 Hz), 2.41 (3H, br s), 5.20 (1H, quint, *J* = 7.1 Hz), 6.73 (1H, br s), 7.30 (2H, br d, *J* = 7.9 Hz), 7.50 (4H, m), 8.25 (2H, br d, *J* = 9.0 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −143.36 (s); MS (EI) *m*/*z* 341 (M^+). Anal. Calcd for $C_{18}H_{16}FN_3O_3$: C, 63.34; H, 4.72; N, 12.31. Found: C, 63.13; H, 4.69; N, 12.30.

4.2.25. *N*-[(*R*)-1-(*p*-Tolyl)ethyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7m]. Colorless prisms; mp 177–178 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{26}$ = +119.3 (*c* 1.1, MeOH); IR (KBr) 3328, 2257, 1676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* = 6.8 Hz), 2.36 (3H, s), 2.37 (3H, d, *J* = 0.9 Hz), 5.12 (1H, quint, *J* = 6.8 Hz), 6.62 (1H, br s), 7.20 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 7.9 Hz), 7.51 (2H, d, *J* = 8.3 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −142.15 (s); MS (EI) *m*/*z* 310 (M^+). Anal. Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03. Found: C, 73.55; H, 5.92; N, 8.87.

4.2.26. *N*-[(*S*)-1-Methoxycarbonylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7n]. Colorless needles; mp 111 °C (from hexane/$CHCl_3$); $[\alpha]_D^{25}$ = +1.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3358, 3006, 2959, 1744, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 7.1 Hz), 2.39 (3H, d, *J* = 1.2 Hz), 3.82 (3H, s), 4.62 (1H, dqd, *J* = 7.1, 1.7, 1.0 Hz), 7.15 (1H, br s), 7.28 (2H, br d, *J* = 8.1 Hz), 7.49 (2H, br d, *J* = 8.5 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −143.16 (s); MS (EI) *m*/*z* 278 (M^+). Anal. Calcd for $C_{14}H_{15}FN_2O_3$: C, 60.42; H, 5.43; N, 10.07. Found: C, 60.15; H, 5.52; N, 10.04.

4.2.27. *N*-[(*S*)-1-Methoxycarbonylethyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7n]. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, *J* = 7.1 Hz), 1.54 (3H, d, *J* = 7.1 Hz), 2.39 (6H, d, *J* = 2.0 Hz), 3.77 (3H, s), 3.82 (3H, s), 4.61 (1H, ddq, *J* = 7.1, 1.6, 1.3 Hz), 4.63 (1H, ddq, *J* = 7.1, 1.6, 1.3 Hz), 7.06 (1H, br s), 7.15 (1H, br s), 7.28 (4H, d, *J* = 8.1 Hz), 7.50 (2H, dd, *J* = 8.3, 1.0 Hz), 7.54 (2H, dd, *J* = 8.3, 1.5 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.73 (s), −143.16 (s).

4.2.28. *N*-[(*R*)-1-Methoxycarbonylpropyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7o]. Colorless needles; mp 71 °C (from hexane/Et_2O); $[\alpha]_D^{25}$ = +0.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3346, 3100–2800, 1757, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.6 Hz), 1.86 (1H, dqd, *J* = 14.7, 7.6, 7.3 Hz), 2.02 (1H, dqd, *J* = 14.9, 7.6, 5.1 Hz), 2.39 (3H, d, *J* = 2.0 Hz), 3.77 (3H, s), 4.59 (1H, dddd, *J* = 7.8, 6.8, 5.4, 1.5 Hz), 7.01 (1H, br d, *J* = 3.6 Hz), 7.28 (2H, br d, *J* = 8.2 Hz), 7.53 (2H, dq, *J* = 8.3, 1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.84 (s); MS (EI) *m*/*z* 292 (M^+). Anal. Calcd for $C_{15}H_{17}FN_2O_3$: C, 61.63; H, 5.86; N, 9.58. Found: C, 61.33; H, 6.01; N, 9.57.

4.2.29. *N*-[(*R*)-1-Methoxycarbonylpropyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7o]. ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, *J* = 7.6 Hz), 0.99 (3H, t, *J* = 7.6 Hz), 1.77 (1H, ddq, *J* = 13.9, 7.6, 6.4 Hz), 1.85 (1H, ddq, *J* = 13.9, 7.6, 6.4 Hz), 1.94 (1H, ddq, *J* = 13.9, 7.6, 5.4 Hz), 2.03 (1H, ddq, *J* = 13.9, 7.6, 5.4 Hz), 2.39 (6H, s), 3.76 (3H, s), 3.81 (3H, s), 4.59 (1H, m), 4.61 (1H, m), 7.03 (1H, br s), 7.08 (1H, br s), 7.28 (4H, d, *J* = 7.8 Hz), 7.50 (2H, dd, *J* = 8.6, 1.2 Hz), 7.54 (2H, dd, *J* = 8.3, 1.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.84 (s), −143.84 (s).

4.2.30. *N*-[(*S*)-1-Methoxycarbonyl-2-methylpropyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7p]. Colorless oil; $[\alpha]_D^{25}$ = +2.8 (*c* 1.0, $CHCl_3$); IR (neat) 3341, 2967, 1746, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, *J* = 6.9 Hz), 0.88 (3H, d, *J* = 7.0 Hz), 2.20 (1H, septd, *J* = 6.9, 4.9 Hz), 2.40 (3H, br s), 3.80 (3H, s), 4.58 (1H, ddd, *J* = 8.8, 4.6, 1.2 Hz), 6.99 (1H, br d, *J* = 5.2 Hz), 7.29 (2H, br d, *J* = 8.6 Hz), 7.51 (2H, br d, *J* = 7.5 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −144.58 (s); MS (EI) *m*/*z* 306 (M^+); HRMS (EI) calcd for $C_{16}H_{19}FN_2O_3$ (M^+): 306.1380; found: 306.1407.

4.2.31. *N*-[(*S*)-1-Methoxycarbonyl-2-methylpropyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7p]. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 7.1 Hz), 0.88 (3H, d, *J* = 7.1 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 1.02 (3H, d, *J* = 6.9 Hz), 2.20 (1H, m), 2.31 (1H, m), 2.39 (6H, s), 3.76 (3H, s), 3.81 (3H, s), 4.57 (1H, ddd, *J* = 8.9, 4.4, 1.5 Hz), 4.58 (1H, ddd, *J* = 8.8, 4.4, 1.2 Hz), 7.00 (2H, br s), 7.28 (4H, d, *J* = 7.1 Hz), 7.51 (2H, d, *J* = 7.6 Hz), 7.53 (2H, dd, *J* = 7.6, 1.5 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.95 (s), −144.58 (s).

4.2.32. *N*-[(*S*)-1-Methoxycarbonyl-2,2-dimethylpropyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7q]. Colorless oil; $[\alpha]_D^{25}$ = −15.4 (*c* 1.0, $CHCl_3$); IR (neat) 3422, 3353, 3100–2800, 1742, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (9H, s), 2.39 (3H, br s), 3.79 (3H, s), 4.46 (1H, dd, *J* = 9.5, 1.4 Hz), 6.99 (1H, br d, *J* = 5.4 Hz), 7.29 (2H, br d, *J* = 8.6 Hz), 7.51 (2H, br d, *J* = 7.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ−145.76 (s); MS (EI) *m*/*z* 320 (M^+). Anal. Calcd for $C_{17}H_{21}FN_2O_3$: C, 63.74; H, 6.61; N, 8.74. Found: C, 63.47; H, 6.70; N, 8.68.

4.2.33. *N*-[(*S*)-1-Methoxycarbonyl-2,2-dimethylpropyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7q]. ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (9H, s), 1.05 (9H, s), 2.39 (6H, s), 3.74 (3H, s), 3.80 (3H, s), 4.45 (1H, dd, *J* = 9.2, 1.4 Hz), 4.47 (1H, dd, *J* = 9.2, 1.6 Hz), 7.00 (2H, br d, *J* = 6.2 Hz), 7.28 (4H, d, *J* = 8.6 Hz), 7.50 (2H, d, *J* = 7.8 Hz), 7.51 (2H, d, *J* = 8.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −141.68 (s), −145.75 (s).

4.2.34. *N*-[(*S*)-1-Methoxycarbonyl-3-methylbutyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7r]. Colorless crystals; mp 62 °C (from hexane/Et_2O); $[\alpha]_D^{25}$ = −1.1 (*c* 1.0, $CHCl_3$); IR (KBr) 3337, 2959, 1750, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.1 Hz), 0.90 (3H, d, *J* = 6.3 Hz), 1.53 (1H, m), 1.59

(1H, ddd, $J = 13.8$, 8.8, 6.1 Hz), 1.70 (1H, ddd, $J = 13.9$, 8.3, 5.6 Hz), 2.40 (3H, d, $J = 1.5$ Hz), 3.80 (3H, s), 4.66 (1H, dddd, $J = 8.6$, 8.3, 5.6, 1.5 Hz), 6.90 (1H, br d, $J = 5.4$ Hz), 7.28 (2H, br d, $J = 8.6$ Hz), 7.49 (2H, dq, $J = 8.6$, 1.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −143.76 (s); MS (EI) m/z 320 (M^+). Anal. Calcd for $C_{17}H_{21}FN_2O_3$: C, 63.74; H, 6.61; N, 8.74. Found: C, 63.58; H, 6.74; N, 8.75.

4.2.35. *N*-[(*S*)-1-Methoxycarbonyl-3-methylbutyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7r]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, $J = 6.4$ Hz), 0.90 (3H, d, $J = 6.4$ Hz), 0.99 (3H, d, $J = 6.1$ Hz), 1.00 (3H, d, $J = 5.9$ Hz), 1.48–1.81 (6H, m), 2.39 (6H, s), 3.74 (3H, s), 3.80 (3H, s), 4.63–4.68 (2H, m), 6.89 (2H, br s), 7.28 (4H, d, $J = 8.1$ Hz), 7.49 (2H, d, $J = 8.1$ Hz), 7.54 (2H, d, $J = 7.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.06 (s), −143.76 (s).

4.2.36. *N*-[(*S*)-1-Methoxycarbonyl-4-thiapentyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7s]. Colorless oil; $[\alpha]_D^{25} = +21.7$ (c 1.0, $CHCl_3$); IR (neat) 3335, 3100–2800, 1748, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s), 2.05 (1H, m), 2.17 (1H, m), 2.40 (3H, br s), 2.40 (2H, m), 3.82 (3H, s), 4.74 (1H, br dd, $J = 6.4$, 5.2 Hz), 7.28 (3H, br d, $J = 8.3$ Hz), 7.50 (2H, br d, $J = 7.7$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −145.15 (s); MS (EI) m/z 338 (M^+); HRMS (EI) calcd for $C_{16}H_{19}FN_2O_3S$ (M^+): 338.1100; found: 338.1117.

4.2.37. *N*-[(*S*)-1-Methoxycarbonyl-4-thiapentyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7s]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s), 2.07 (1H, m), 2.13 (3H, s), 2.14 (1H, m), 2.19 (1H, m), 2.27 (1H, dtd, $J = 14.4$, 7.3, 5.1 Hz), 2.38 (1H, m), 2.39 (6H, s), 2.41 (1H, m), 2.56 (1H, m), 2.60 (1H, m), 3.77 (3H, s), 3.82 (3H, s), 4.74 (1H, m), 4.76 (1H, m), 7.27–7.29 (5H, m), 7.36 (1H, br s), 7.51 (2H, d, $J = 7.6$ Hz), 7.54 (2H, dd, $J = 8.3$, 1.2 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.15 (s), −145.15 (s).

4.2.38. *N*-[(*S*)-2-Benzyloxycarbonyl-1-methoxycarbonylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7t]. Colorless oil; $[\alpha]_D^{25} = +48.1$ (c 1.0, $CHCl_3$); IR (neat) 3350, 3100–2800, 1744, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, d, $J = 1.1$ Hz), 2.88 (1H, dd, $J = 17.1$, 4.7 Hz), 2.99 (1H, dd, $J = 17.1$, 4.2 Hz), 3.77 (3H, s), 4.83 (1H, br ddd, $J = 7.8$, 4.7, 4.2 Hz), 5.10 (2H, s), 7.21 (2H, d, $J = 8.3$ Hz), 7.31 (2H, m), 7.35 (3H, m), 7.42 (2H, br d, $J = 8.3$ Hz), 7.54 (1H, br d, $J = 6.0$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −143.34 (s); MS (EI) m/z 412 (M^+). Anal. Calcd for $C_{22}H_{21}FN_2O_5$: C, 64.07; H, 5.13; N, 6.79. Found: C, 63.71; H, 5.40; N, 6.69.

4.2.39. *N*-[(*S*)-2-Benzyloxycarbonyl-1-methoxycarbonylethyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7t]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, d, $J = 1.5$ Hz), 2.39 (3H, d, $J = 2.0$ Hz), 2.88 (1H, dd, $J = 17.1$, 4.4 Hz), 2.96 (1H, dd, $J = 17.7$, 4.4 Hz), 3.10 (1H, dd, $J = 17.2$, 4.4 Hz), 3.20 (1H, dd, $J = 17.5$, 4.4 Hz), 3.70 (3H, s), 3.77 (3H, s), 4.83 (1H, dtd, $J = 7.8$, 4.4, 0.7 Hz), 4.88 (1H, dtd, $J = 8.7$, 4.4, 1.5 Hz), 5.10 (2H, s), 5.17 (2H, s), 7.20 (2H, d, $J = 8.6$ Hz), 7.27–7.39 (12H, m), 7.43 (2H, dd, $J = 8.6$, 1.2 Hz), 7.55 (1H, br s), 7.56 (2H, dd, $J = 8.3$, 1.5 Hz), 7.61 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.82 (s), −143.34 (s).

4.2.40. *N*-[(*S*)-3-Ethoxycarbonyl-1-methoxycarbonylpropyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7u]. Colorless oil; $[\alpha]_D^{25} = +2.7$ (c 1.0, $CHCl_3$); IR (neat) 3337, 3100–2800, 1738, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, $J = 6.8$ Hz), 2.08 (1H, ddd, $J = 14.2$, 8.3, 7.3 Hz), 2.22 (1H, m), 2.27–2.38 (2H, m), 2.40 (3H, br s), 3.80 (3H, s), 4.09 (1H, qd, $J = 6.8$, 3.7 Hz), 4.12 (1H, qd, $J = 6.8$, 3.2 Hz), 4.61 (1H, m), 7.28 (2H, br d, $J = 8.0$ Hz), 7.42 (1H, br d, $J = 5.8$ Hz), 7.51 (2H, br d, $J = 7.6$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −144.77 (s); MS (EI) m/z 364 (M^+). Anal. Calcd for $C_{18}H_{21}FN_2O_5$: C, 59.33; H, 5.81; N, 7.69. Found: C, 59.14; H, 5.81; N, 7.69.

4.2.41. *N*-[(*S*)-3-Ethoxycarbonyl-1-methoxycarbonylpropyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7u]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, $J = 7.1$ Hz), 1.28 (3H, t, $J = 7.1$ Hz), 2.08 (1H, m), 2.17 (1H, m), 2.21 (1H, m), 2.29 (1H, m), 2.31 (1H, m), 2.35 (1H, m), 2.39 (6H, s), 2.45 (1H, m), 2.50 (1H, ddd, $J = 17.0$, 7.3, 7.1 Hz), 3.75 (3H, s), 3.80 (3H, s), 4.10 (2H, dq, $J = 7.1$, 2.9 Hz), 4.18 (2H, q, $J = 7.1$ Hz), 4.61 (1H, m), 4.62 (1H, m), 7.28 (4H, d, $J = 8.7$ Hz), 7.44 (1H, br s), 7.51 (2H, d, $J = 8.1$ Hz), 7.55 (2H, dd, $J = 8.2$, 1.2 Hz), 7.55 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.51 (s), −144.77 (s).

4.2.42. *N*-[(1*S*,2*R*)-1-Methoxycarbonyl-2-benzyloxypropyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7v]. Colorless oil; $[\alpha]_D^{25} = +9.3$ (c 1.0, $CHCl_3$); IR (neat) 3548, 3434, 3100–2800, 1752, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, $J = 6.4$ Hz), 2.39 (3H, br s), 3.71 (3H, s), 4.16 (1H, qd, $J = 6.4$, 1.2 Hz), 4.37 (1H, d, $J = 12.0$ Hz), 4.57 (1H, d, $J = 11.7$ Hz), 4.61 (1H, ddd, $J = 9.1$, 2.2, 1.3 Hz), 7.18 (1H, br d, $J = 7.1$ Hz), 7.21–7.28 (4H, m), 7.29–7.38 (3H, m), 7.53 (2H, d, $J = 6.6$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −144.63 (s); MS (EI) m/z 398 (M^+); HRMS (EI) calcd for $C_{22}H_{23}FN_2O_4$ (M^+): 398.1642; found: 398.1670.

4.2.43. *N*-[(1*S*,2*R*)-1-Methoxycarbonyl-2-benzyloxypropyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7v]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, $J = 6.4$ Hz), 1.31 (3H, d, $J = 6.4$ Hz), 2.39 (6H, s), 3.64 (3H, s), 3.71 (3H, s), 4.16 (1H, dq, $J = 6.4$, 2.2 Hz), 4.23 (1H, dq, $J = 6.4$, 2.2 Hz), 4.37 (1H, d, $J = 12.0$ Hz), 4.40 (1H, d, $J = 12.0$ Hz), 4.56 (1H, d, $J = 12.0$ Hz), 4.61 (1H, m), 4.62 (1H, m), 4.62 (1H, d, $J = 12.0$ Hz), 7.19 (1H, br s), 7.22–7.37 (15H, m), 7.53 (2H, d, $J = 7.6$ Hz), 7.59 (2H, dd, $J = 8.3$, 1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.67 (s), −144.63 (s).

4.2.44. *N*-[(*S*)-1-Methoxycarbonyl-2-phenylethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7w]. Colorless needles; mp 151 °C (from hexane/$CHCl_3$); $[\alpha]_D^{25} = -41.2$ (c 1.0, $CHCl_3$); IR (KBr) 3252, 3100–2900,

2359, 1750, 1698, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, d, $J = 1.0$ Hz), 3.07 (1H, dd, $J = 14.2$, 6.6 Hz), 3.19 (1H, dd, $J = 14.0$, 5.4 Hz), 3.81 (3H, s), 4.91 (1H, dddd, $J = 6.6$, 6.4, 5.4, 1.0 Hz), 6.91 (3H, m), 7.17–7.27 (5H, m), 7.29 (2H, br d, $J = 8.3$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −145.00 (s); MS (EI) m/z 354 (M^+), 353 ($M^+ - 1$). Anal. Calcd for $C_{20}H_{19}FN_2O_3$: C, 67.79; H, 5.40; N, 7.91. Found: C, 67.56; H, 5.61; N, 7.91.

4.2.45. *N*-[(*S*)-1-Methoxycarbonyl-2-phenylethyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7w]. ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, d, $J = 1.7$ Hz), 2.41 (3H, d, $J = 1.2$ Hz), 3.07 (1H, dd, $J = 14.2$, 6.6 Hz), 3.20 (1H, dd, $J = 14.2$, 5.4 Hz), 3.20 (1H, dd, $J = 14.2$, 5.6 Hz), 3.26 (1H, dd, $J = 14.2$, 5.9 Hz), 3.76 (3H, s), 3.81 (3H, s), 4.87 (1H, dtd, $J = 8.1$, 5.6, 1.5 Hz), 4.92 (1H, dddd, $J = 7.8$, 6.6, 5.6, 1.2 Hz), 6.91 (4H, m), 7.11 (2H, dd, $J = 7.6$, 1.2 Hz), 7.18–7.36 (12H, m), 7.48 (2H, dd, $J = 8.3$, 1.2 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −141.42 (s), −145.00 (s).

4.2.46. *N*-[(*S*)-1-Methoxycarbonyl-2-(3-indolyl)ethyl]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*R*)-CFTA amide of 7x]. Colorless crystals; mp 128 °C (from hexane/$CHCl_3$); $[\alpha]_D^{25} = +51.8$ (c 1.0, $CHCl_3$); IR (KBr) 3397, 3316, 3100–2900, 1738, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, br s), 3.33 (2H, d, $J = 5.9$ Hz), 3.75 (3H, s), 4.95 (1H, br dt, $J = 7.8$, 5.9 Hz), 6.81 (1H, d, $J = 2.5$ Hz), 6.99 (1H, br d, $J = 5.8$ Hz), 7.06 (1H, br dd, $J = 8.1$, 7.1 Hz), 7.16 (2H, br d, $J = 7.8$ Hz), 7.20 (1H, t, $J = 7.1$ Hz), 7.28 (2H, br d, $J = 8.3$ Hz), 7.34 (1H, d, $J = 8.0$ Hz), 7.39 (1H, d, $J = 8.1$ Hz), 8.05 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −144.80 (s); MS (EI) m/z 393 (M^+). Anal. Calcd for $C_{22}H_{20}FN_3O_3$: C, 67.17; H, 5.12; N, 10.68. Found: C, 67.21; H, 5.40; N, 10.65.

4.2.47. *N*-[(*S*)-1-Methoxycarbonyl-2-(3-indolyl)ethyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7x]. ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, d, $J = 1.5$ Hz), 2.38 (3H, s), 3.33 (2H, d, $J = 5.6$ Hz), 3.44 (2H, d, $J = 5.4$ Hz), 3.71 (3H, s), 3.75 (3H, s), 4.93 (1H, m), 4.95 (1H, m), 6.80 (1H, d, $J = 2.0$ Hz), 6.99 (1H, br s), 7.02 (1H, d, $J = 2.2$ Hz), 7.05 (1H, br s), 7.06 (1H, dd, $J = 8.1$, 7.1 Hz), 7.16 (1H, dd, $J = 7.6$, 7.1 Hz), 7.17 (2H, d, $J = 7.8$ Hz), 7.20 (1H, dd, $J = 7.8$, 7.1 Hz), 7.22 (1H, dd, $J = 7.8$, 7.1 Hz), 7.23 (2H, d, $J = 7.6$ Hz), 7.29 (2H, d, $J = 7.8$ Hz), 7.35 (1H, d, $J = 7.8$ Hz), 7.37 (1H, d, $J = 7.8$ Hz), 7.40 (1H, d, $J = 8.1$ Hz), 7.48 (2H, d, $J = 7.6$ Hz), 7.55 (1H, d, $J = 7.6$ Hz), 8.04 (1H, br s), 8.16 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.40 (s), −144.80 (s).

4.2.48. *N*-[(*S*)-1-Methoxycarbonyl-4-methylpentyl]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide [(*S*)-CFTA amide of 7y]. Colorless needles; mp 95–96 °C (from hexane/$CHCl_3$); $[\alpha]_D^{27} = -42.2$ (c 0.91, $CHCl_3$); IR (KBr) 3316, 3073, 2251, 1737, 1681 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, d, $J = 6.2$ Hz), 0.96 (3H, d, $J = 6.2$ Hz), 1.38 (1H, m), 1.55–1.69 (2H, m), 2.39 (3H, s), 2.51 (1H, dd, $J = 16.2$, 4.9 Hz), 2.56 (1H, dd, $J = 16.2$, 4.9 Hz), 3.64 (3H, s), 4.34 (1H, m), 7.09 (1H, br d, $J = 5.9$ Hz), 7.26 (2H, d, $J = 7.8$ Hz), 7.50 (2H, d, $J = 8.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −143.16 (s); MS (EI) m/z 335 (M^++H), 334 (M^+); HRMS (EI) calcd for $C_{18}H_{23}FN_2O_3$ (M^+): 334.1693; found: 334.1687.

4.2.49. *N*-[(*S*)-1-Methoxycarbonyl-4-methylpentyl]-(±)-2-cyano-2-fluoro-*p*-tolylacetamide [(±)-CFTA amide of 7y]. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, $J = 6.4$ Hz), 0.87 (3H, d, $J = 6.4$ Hz), 0.94 (3H, d, $J = 6.4$ Hz), 0.96 (3H, d, $J = 6.4$ Hz), 1.35 (1H, m), 1.38 (1H, m), 1.47 (1H, m), 1.56 (1H, m), 1.63 (2H, m), 2.39 (6H, s), 2.51 (1H, dd, $J = 16.1$, 5.4 Hz), 2.56 (1H, dd, $J = 16.1$, 4.9 Hz), 2.59 (1H, dd, $J = 16.4$, 4.6 Hz), 2.68 (1H, dd, $J = 16.4$, 4.9 Hz), 3.64 (3H, s), 3.72 (3H, s), 4.33 (1H, m), 4.35 (1H, m), 7.09 (1H, br s), 7.21 (1H, br s), 7.25–7.28 (4H, m), 7.48–7.50 (4H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −143.11 (s), −143.30 (s).

4.2.50. *N*-[(*S*)-1-(Methoxycarbonyl-α-^{13}C)ethyl-2-d_3-$^{13}C_2$]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide-^{15}N [(*S*)-CFTA amide of 9a]. Colorless needles; mp 78–79 °C (from hexane/$CHCl_3$); $[\alpha]_D^{26} = -14.6$ (c 0.9, $CHCl_3$); IR (film) 3337, 2228, 1701, 1655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (3H, s), 3.77 (3H, d, $J = 3.8$ Hz), 4.60 (1H, dd, $J = 144.2$, 5.8 Hz), 7.06 (1H, dd, $J = 93.6$, 6.4 Hz), 7.28 (2H, d, $J = 7.7$ Hz), 7.54 (2H, d, $J = 8.5$ Hz); ^2D NMR (61 MHz, $CHCl_3$) δ 1.51 (d, $J = 19.8$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.69 (s); MS (EI) m/z 285 (M^+); HRMS (ESI) calcd for $C_{11}{}^{13}C_3H_{13}D_3FN^{15}NO_3$ (M^++H): 286.1404; found: 286.1399.

4.2.51. *N*-[(*S*)-1-(Methoxycarbonyl-α-^{13}C)ethyl-2-d_3-$^{13}C_2$]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide-^{15}N [(*R*)-CFTA amide of 9a]. Colorless needles; mp 112–113 °C (from hexane/$CHCl_3$); $[\alpha]_D^{28} = +0.3$ (c 0.9, $CHCl_3$); IR (film) 3348, 2257, 1700, 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s), 3.82 (3H, d, $J = 3.8$ Hz), 4.61 (1H, dd, $J = 144.0$, 5.6 Hz), 7.16 (1H, dd, $J = 93.3$, 5.3 Hz), 7.28 (2H, d, $J = 8.1$ Hz), 7.50 (2H, d, $J = 8.1$ Hz); ^2D NMR (61 MHz, $CHCl_3$) δ 1.42 (d, $J = 20.1$ Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −143.17 (s); MS (EI) m/z 285 (M^+); HRMS (ESI) calcd for $C_{11}{}^{13}C_3H_{13}D_3FN^{15}NO_3$ (M^++H): 286.1404; found: 286.1399.

4.2.52. *N*-[(*S*)-1-(Methoxycarbonyl-α-^{13}C)2-methyl-d_3-propyl-3-d_3-1-^{13}C]-(*S*)-2-cyano-2-fluoro-*p*-tolylacetamide-^{15}N [(*S*)-CFTA amide of 9b]. Colorless oil; IR (neat) 3345, 2224, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (1H, s), 2.39 (3H, d, $J = 1.3$ Hz), 3.76 (3H, d, $J = 3.8$ Hz), 4.56 (1H, dddddd, $J = 144.0$, 9.0, 6.4, 4.5, 1.7, 1.2 Hz), 7.00 (1H, ddddd, $J = 92.7$, 9.0, 3.0, 1.3, 1.2 Hz), 7.28 (2H, d, $J = 7.7$ Hz), 7.53 (2H, d, $J = 6.8$ Hz); ^2D NMR (61 MHz, $CHCl_3$) δ 0.99 (s); ^{19}F NMR (254 MHz, $CDCl_3$) δ −140.94 (s); HRMS (ESI) calcd for $C_{14}{}^{13}C_2H_{13}D_6FN^{15}NNaO_3$ (M+Na^+): 338.1691; found: 338.1686.

4.2.53. *N*-[(*S*)-1-(Methoxycarbonyl-α-^{13}C)2-methyl-d_3-propyl-3-d_3-1-^{13}C]-(*R*)-2-cyano-2-fluoro-*p*-tolylacetamide-^{15}N [(*R*)-CFTA amide of 9b]. Colorless oil; IR (neat) 3333, 2224, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.16 (1H, s), 2.40 (3H, d, $J = 0.9$ Hz), 3.81 (3H, d, $J = 3.8$ Hz), 4.46 (1H, ddddt, $J = 144.0$, 9.8, 8.5, 4.7,

1.3 Hz), 7.00 (1H, dddt, $J = 92.7$, 8.5, 3.4, 1.7 Hz), 7.29 (2H, d, $J = 8.1$ Hz), 7.51 (2H, d, $J = 7.7$ Hz); ^{2}D NMR (61 MHz, $CHCl_3$) δ 0.83 (s); ^{19}F NMR (254 MHz, $CDCl_3$) δ −144.58 (s); HRMS (ESI) calcd for $C_{14}{}^{13}C_2H_{13}D_6FN^{15}NNaO_3$ ($M+Na^+$): 338.1691; found: 338.1686.

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