Supporting Information for

Selective Covalent Targeting of SARS-CoV-2 Main Protease by Enantiopure Chlorofluoroacetamide

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| Crystal data and structure refinement for *syn*-**18** |
|------------------------------------------------------|
| **Empirical formula** | C_{22}H_{18}ClF_7N_4O_2S |
| **Formula weight** | 570.91 |
| **Temperature** | 100.0 K |
| **Radiation wavelength** | 0.71073 Å |
| **Crystal system** | Monoclinic |
| **Space group** | P2_1/n |
| **Unit cell dimensions** | |
| a = 9.4276(3) Å | α = 90° |
| b = 19.5575(5) Å | β = 93.634(4)° |
| c = 50.822(2) Å | γ = 90° |
| **Volume** | 9351.7(6) Å³ |
| **Z** | 16 |
| **Density (calculated)** | 1.622 g/cm³ |
| **Absorption coefficient** | 0.338 mm⁻¹ |
| **F(000)** | 4640.0 |
| **Crystal size** | 0.333 × 0.086 × 0.026 mm³ |
| **Crystal color, habit** | Colorless, plate |
| **2θ range for data collection** | 3.828 to 59.52° |
| **Index ranges** | −12 ≤ h ≤ 12, −26 ≤ k ≤ 27, −69 ≤ l ≤ 69 |
| **Completeness to theta = 27.42°** | 98.60% |
| **Reflections collected** | 93272 |
| **Independent reflections** | 24343 [R(int) = 0.0717, R(sigma) = 0.0736] |
| **Data / restraints / parameters** | 24343 / 31 / 1361 |
| **Goodness-of-fit on F²** | 1.185 |
| **R indices** | R₁ = 0.1379, wR₂ = 0.3258 |
| **Largest diffraction peak and hole** | 1.59 and −0.78 e.Å⁻³ |

**Figure S1.** Crystallographic structure of *syn*-**18** (top) and crystal data and structure refinement (bottom)
Table: Crystal data and structure refinement for 21B

| Property                              | Value                                      |
|---------------------------------------|--------------------------------------------|
| Empirical formula                     | \( \text{C}_{11}\text{H}_{11}\text{ClFNO}_2 \) |
| Formula weight                        | 231.65                                     |
| Temperature                           | 110.0 K                                    |
| Radiation wavelength                  | 0.71073 Å                                  |
| Crystal system                        | Orthorhombic                               |
| Space group                           | \( P2_1 2_1 2_1 \)                         |
| Unit cell dimensions                  | \( a = 5.1224(2) \text{ Å}\) \( \alpha = 90° \) |
|                                        | \( b = 8.2680(3) \text{ Å}\) \( \beta = 90° \) |
|                                        | \( c = 24.1637(10) \text{ Å}\) \( \gamma = 90° \) |
| Volume                                | 1023.38(7) Å\(^3\)                        |
| \( Z \)                               | 4                                          |
| Density (calculated)                  | 1.503 g/cm\(^3\)                          |
| Absorption coefficient                | 0.366 mm\(^{-1}\)                         |
| \( F(000) \)                          | 480.0                                      |
| Crystal size                          | 0.409 × 0.354 × 0.138 mm\(^3\)             |
| Crystal color, habit                  | Colorless, prism                           |
| 2θ range for data collection          | 5.208 to 54.954°                           |
| Index ranges                          | \(-6 \leq h \leq 6, -10 \leq k \leq 10, -31 \leq l \leq 30\) |
| Completeness to theta = 27.42°        | 99.87%                                     |
| Reflections collected                 | 9089                                       |
| Independent reflections               | 2351 [\( R_{\text{wp}} = 0.0259, R_{\text{sign}} = 0.0224 \)] |
| Data / restraints / parameters        | 2351 / 0 / 137                             |
| Goodness-of-fit on \( F^2 \)          | 1.049                                      |
| \( R \) indices                       | \( R_c = 0.0247, wR_c = 0.0593 \)         |
| Largest diffraction peak and hole     | 0.23 and \(-0.21\) e.Å\(^{-3}\)           |

Figure S2. Crystallographic structure of 21B (top) and crystal data and structure refinement (bottom)
Figure S3. Determination of kinetic parameters for irreversible inactivation of M^pro by \((R,R)-18\). A) The chemical structure of \((R,R)-18\). B) A plot of first-order rate constants \(k_{\text{obs}}\) versus the inhibitor concentrations \([I]\) and non-linear regression gave the \(k_{\text{inact}}/K_I\) value of 4,167 M\(^{-1}\)s\(^{-1}\). C) A plot of the initial state velocity versus \([I]/(1+(S)/K_m)\) and non-linear regression gave the \(K_i\) value of 1.34 μM. The \(k_{\text{inact}}\) value of 0.0056 s\(^{-1}\) was calculated from the \(k_{\text{inact}}/K_i\) value of 4,167 M\(^{-1}\)s\(^{-1}\).
**Figure S4.** Determination of kinetic parameters for irreversible inactivation of M<sup>pro</sup> by (S,R)-18. A) The chemical structure of (S,R)-18 and time-course plot of M<sup>pro</sup>-catalyzed hydrolysis of Ac-Abu-Tle-Leu-Gln-MCA in the presence of various concentrations of (S,R)-18. B) A plot of first-order rate constants $k_{\text{obs}}$ versus the inhibitor concentrations [I] and non-linear regression gave the $k_{\text{inact}}/K_i$ value of 66.0 M<sup>-1</sup>s<sup>-1</sup>. C) A plot of the initial state velocity versus [I]/(1+([S]/$K_m$)) and non-linear regression gave the $K_i$ value of 64.7 μM. The $k_{\text{inact}}$ value of 0.0043 s<sup>-1</sup> was calculated from the $k_{\text{inact}}/K_i$ value of 66.0 M<sup>-1</sup>s<sup>-1</sup>. 

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**A**

![Chemical structure of (S,R)-18 and time-course plot](image)

**B**

![Plot of $k_{\text{obs}}$ versus [I]](image)

**C**

![Plot of initial state velocity versus [I]/(1+([S]/$K_m$))] (image)
Figure S5. Determination of kinetic parameters for irreversible inactivation of Mpro by (R,S)-18. A) The chemical structure of (R,S)-18 and time-course plot of Mpro-catalyzed hydrolysis of Ac-Abu-Tle-Leu-Gln-MCA in the presence of various concentrations of (R,S)-18. B) A plot of first-order rate constants $k_{\text{obs}}$ versus the inhibitor concentrations [I] and non-linear regression gave the $k_{\text{inact}}/K_i$ value of 20.0 M$^{-1}$s$^{-1}$. C) A plot of the initial state velocity versus [I]/(1+([S]/$K_m$)) and non-linear regression gave the $K_i$ value of 53.6 μM. The $k_{\text{inact}}$ value of 0.0011 s$^{-1}$ was calculated from the $k_{\text{inact}}/K_i$ value of 20.0 M$^{-1}$s$^{-1}$. 
**Figure S6.** Determination of kinetic parameters for irreversible inactivation of $M^{\text{pro}}$ by 1. A) The chemical structure of 1 and time-course plot of $M^{\text{pro}}$-catalyzed hydrolysis of Ac-Abu-Tle-Leu-Gln-MCA in the presence of various concentrations of 1. B) A plot of first-order rate constants $k_{\text{obs}}$ versus the inhibitor concentrations [I] and non-linear regression gave the $k_{\text{inact}}/K_i$ value of 81.2 M$^{-1}$s$^{-1}$. C) A plot of the initial state velocity versus [I]/(1+(S)/$K_m$) and non-linear regression gave the $K_i$ value of 10.0 μM. The $k_{\text{inact}}$ value of 0.00082 s$^{-1}$ was calculated from the $k_{\text{inact}}/K_i$ value of 81.2 M$^{-1}$s$^{-1}$. 
**Figure S7.** Coomassie Brilliant Blue (CBB) staining of the gel shown in Figure 5C.

**Figure S8.** Coomassie Brilliant Blue (CBB) staining of the gel shown in Figure 5D.
Figure S9. Determination of the $K_m$ value for $\text{Ac-Abu-Tle-Leu-Gln-MCA}$ with the recombinant SARS-CoV-2 M\textsuperscript{pro}. The Michaelis–Menten plot and non-linear regression gave the $K_m$ value of 126.8 $\mu$M.
Synthetic Procedures

General synthetic methods

Reagents and solvents were obtained from commercial suppliers and used without further purification, unless otherwise stated. Reactions were carried out under a positive atmosphere of nitrogen, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on Merck TLC Silica gel 60 F254, using shortwave UV light as the visualizing agent and phosphomolybdic acid in EtOH and heat as developing agent. Flash column chromatography was performed using Kanto Chemical Silica gel 60 N (spherical, 40-50 μm). 1H and 13C NMR spectra were recorded on Bruker Avance III HD 500 MHz spectrometer and were calibrated using residual undeuterated solvent as the internal references (CDCl3: 7.26 ppm; CD3OD: 3.31 ppm; DMSO-d6: 2.50 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. Low-resolution and high-resolution mass spectra were recorded on Bruker micrOTOF focus II mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. X-ray crystallographic experiments were performed using Rigaku FR-E+ instrument.
Preparation of isocyanides

\[
\begin{align*}
\text{HCO}_2\text{Et, reflux} & \quad \text{POCl}_3, \text{TEA} \\
\text{S1} & \quad \text{DCM, 0 °C}
\end{align*}
\]

1-Fluoro-3-(2-isocyanoethyl)benzene (S1)

2-(3-Fluorophenyl)ethylamine (3.01 g, 21.6 mL) was dissolved in ethyl formate (40 mL) and the mixture was heated at reflux overnight. The excess ethyl formate was removed in vacuo and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:1 to 1:2) to give the corresponding formamide (3.28 g, 91% yield).

To a stirred solution of the above formamide (2.10 g, 12.6 mmol) and triethylamine (5.6 mL, 40.2 mmol) in dry DCM (100 mL) was added POCl\(_3\) (1.25 mL, 13.4 mmol) dropwise at 0 °C. After stirred for 3 h at 0 °C, the reaction mixture was diluted with DCM and sat. NaHCO\(_3\). The aqueous phase was separated and extracted twice with DCM. The combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 9:1) to give S1 (1.78 g, 95% yield) as colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34–7.29 (m, 1H), 7.03–6.92 (m, 3H), 3.62 (tt, \(J = 7.0, 1.5\) Hz, 2H), 2.89 (tt, \(J = 7.0, 2.0\) Hz, 2H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.1 (\(d, J(C-F) = 245.0\) Hz), 157.2 (\(t, J(C-N) = 5.4\) Hz), 139.1 (\(d, J(C-F) = 7.4\) Hz), 130.5 (\(d, J(C-F) = 8.5\) Hz), 124.5 (\(d, J(C-F) = 2.8\) Hz), 115.7 (\(d, J(C-F) = 21.4\) Hz), 114.4 (\(d, J(C-F) = 20.9\) Hz), 42.8 (\(t, J(C-N) = 6.8\) Hz), 35.5.

HRMS (ESI) \(m/z [M+Na]^+\) calcd for C\(_9\)H\(_8\)FNNa 172.0533; Found 172.0541.

2-(2(Isocyanoethyl)pyridine (S2)

S2 was prepared from 2-(2-pyridyl)ethylamine in a similar manner to S1.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.57 (\(d, J = 4.5\) Hz, 1H), 7.66 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.22 (d, \(J = 8.0\) Hz, 1H), 7.21–7.18 (m, 1H), 3.85 (tt, \(J = 6.5, 2.0\) Hz, 2H), 3.15 (tt, \(J = 7.0, 2.0\) Hz, 2H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 156.5, 149.8, 136.8, 123.8, 122.4, 41.1 (\(t, J(C-N) = 6.9\) Hz), 37.7.

HRMS (ESI) \(m/z [M+Na]^+\) calcd for C\(_8\)H\(_8\)N\(_2\)Na 155.0580; Found 155.0609.
3-(2-Isocyanooethyl)pyridine (S3)

S3 was prepared from 2-(3-pyridyl)ethylamine in a similar manner to S1. Colorless oil.

$^{1}H$ NMR (500 MHz, CDCl$_3$) $\delta$ 8.56 (d, $J = 4.5$ Hz, 1H), 8.52 (s, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.31–7.28 (m, 1H), 3.65 (t, $J = 7.0$ Hz, 2H), 3.00 (t, $J = 6.5$ Hz, 2H).

$^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 157.7 (t, $J(\text{C-N}) = 5.8$ Hz), 150.1, 149.0, 136.4, 132.2, 123.7, 42.7 (t, $J(\text{C-N}) = 6.8$ Hz), 32.9.

HRMS (ESI) $m/z$ [M+Na]$^{+}$ calcd for C$_8$H$_8$N$_2$Na 155.0580; Found 155.0610.

7-Isocyanooisoquinoline (S4)

A mixture of formic acid (377 $\mu$L, 9.99 mmol) and acetic anhydride (945 $\mu$L, 10.0 mmol) was heated at 55 °C for 2 h. The resulting mixture was diluted with dry THF (3.0 mL) and cooled to 0 °C. To the mixture was added 7-aminoisoquinoline (617 mg, 4.28 mmol) and stirred for 2 h at ambient temperature. The reaction mixture was diluted with AcOEt and sat. NaHCO$_3$ and the separated aqueous phase was extracted twice with AcOEt. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was suspended in diethyl ether and the solid was collected by suction filtration, washed with diethyl ether, and dried under vacuum to give the corresponding formamide (551 mg, 75%).

The formamide was converted in a similar manner to S1 to afford S4 (75% yield) as an off-white solid.

$^{1}H$ NMR (500 MHz, CDCl$_3$) $\delta$ 9.28 (s, 1H), 8.64 (d, $J = 5.5$ Hz, 1H), 8.03 (d, $J = 8.5$ Hz, 1H), 7.69 (d, $J = 5.5$ Hz, 1H), 7.64 (dd, $J = 8.5$, 1.5 Hz, 1H).

$^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 165.9, 152.4, 144.9, 135.2, 128.6, 127.9, 127.8, 125.4, 124.9, 120.2.

HRMS (ESI) $m/z$ [M+H]$^{+}$ calcd for C$_{10}$H$_7$N$_2$ 155.0604; Found 155.0628.
1-Ethynyl-3-(2-isocyanatoethyl)benzene (S5)

N-[(3-Iodophenethyl)formamide was prepared from 2-(3-iodophenyl)ethylamine and ethyl formate. To a stirred solution of the formamide (1.13 g, 4.10 mmol), (triisopropylsilyl)acetylene (2.0 mL, 8.92 mmol), and triethylamine (1.7 mL, 12.2 mmol) in degassed dry THF was added Pd(PPh₃)₄ (474 mg, 0.410 mmol, 10 mol%) and CuI (71.5 mg, 0.375 mmol, 9 mol%) at ambient temperature. After stirred at 50 °C overnight, the reaction mixture was diluted with AcOEt and sat. NH₄Cl, and the separated aqueous phase was extracted twice with AcOEt. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 2:1 to 1:1) to give the intermediate (745 mg, 55% yield) as pale-yellow viscous oil.

To a stirred solution of the intermediate (745 mg, 2.26 mmol) in THF (6.0 mL) was added TBAF (1.0 M in THF, 2.5 mL, 2.50 mmol) dropwise at 0 °C. After stirred for 1 h at 0 °C, the reaction mixture was diluted with AcOEt and sat. NH₄Cl, and the separated aqueous phase was extracted twice with AcOEt. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was dissolved in dry DCM (22 mL) and added triethylamine (1.0 mL, 7.17 mmol). To the mixture was added POCl₃ (320 μL, 3.43 mmol) dropwise at 0 °C. After stirred for 3 h at ambient temperature, the reaction mixture was diluted with DCM and sat. NaHCO₃, and the aqueous phase was separated and extracted twice with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 15:1 to 10:1) to give S5 (292 mg, 83% yield over 2 steps) as colorless oil.

\[ ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 7.42 (dt, J = 7.5, 1.5 \text{ Hz, 1H}), 7.36 (s, 1H), 7.30 (t, J = 8.0 \text{ Hz, 1H}), 7.23 (d, J = 8.0 \text{ Hz, 1H}), 3.61 (tt, J = 7.0, 1.5 \text{ Hz, 1H}), 2.97 (tt, J = 7.0, 1.5 \text{ Hz, 1H}). \]

\[ ^13C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 157.1 (t, J(C-N) = 5.4 \text{ Hz}), 137.0, 132.4, 131.2, 129.4, 129.0, 122.8, 83.3, 77.7, 42.8 (t, J(C-N) = 6.8 \text{ Hz}), 35.5. \]

HRMS (ESI) \( m/z [M+Na]^+ \) calcd for C₁₁H₉NNa 178.0627; Found 178.0650.
General procedure for Ugi multi-component reaction

Aniline (0.300 mmol, 1.0 eq) and aldehyde (0.300 mmol, 1.0 eq) were dissolved in MeOH (0.5 mL). To the mixture was added carboxylic acid (0.360 mmol, 1.2 eq) and isocyanide (0.315 mmol, 1.05 eq). After stirred for 3 h at ambient temperature, MeOH was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the dipeptide product.

Spectral data for Ugi MCR-generated dipeptides

1H NMR (500 MHz, CDCl3): δ 8.42 (dd, J = 4.5, 1.5 Hz, 1H), 8.23 (s, 1H), 7.36 (dd, J = 7.5, 1.0 Hz, 1H), 7.23–7.16 (m, 3H), 7.02 (dd, J = 7.5, 5.0 Hz, 1H), 6.91-6.83 (m, 6H), 6.35 (dd, J = 16.8, 1.8 Hz, 1H), 6.33 (s, 1H), 5.96 (dd, J = 16.8, 10.3 Hz, 1H), 5.54 (dd, J = 10.5, 2.0 Hz, 1H), 3.67–3.61 (m, 1H), 3.55–3.50 (m, 1H), 2.83 (t, J = 6.8 Hz, 2H), 1.27 (s, 9H).

13C NMR (125 MHz, CDCl3): δ 169.8, 166.4, 162.8 (d, 3J(C-F) = 244.5 Hz), 151.8, 151.0, 149.4, 141.4 (d, 3J(C-F) = 7.1 Hz), 137.9, 136.1, 130.6, 129.9 (d, 2J(C-F) = 8.1 Hz), 129.8, 128.7, 128.3, 126.1, 124.5, 122.8, 115.7 (d, 2J(C-F) = 20.8 Hz), 113.3 (d, 2J(C-F) = 20.8 Hz), 62.9, 53.4, 40.7, 35.2, 34.6, 31.2.

HRMS (ESI) m/z [M+Na]⁺ calcd for C28H30FN3O2Na 482.2214; Found 482.2239.

1H NMR (500 MHz, CDCl3): δ 8.45 (dd, J = 4.8, 1.8 Hz, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.47 (tt, J = 8.0,
Diastereomer B

$\text{H NMR}$ (500 MHz, CDCl$_3$): $\delta$ 8.45 (d, $J = 5.0$ Hz, 1H), 8.27 (s, 1H), 7.37 (br s, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.24–7.18 (m, 1H), 7.13 (br s, 1H), 7.03–6.99 (m, 1H), 6.92–6.80 (m, 3H), 6.50 (br s, 1H), 6.23 (br d, $J = 5.0$ Hz, 1H), 6.09 (d, $J_{(H-F)} = 50.5$ Hz, 1H), 5.87 (s, 1H), 3.66–3.52 (m, 2H), 2.83 (t, $J = 7.0$ Hz, 2H), 1.27 (s, 9H).

$^{13}$C NMR (125 MHz, CD$_3$OD): $\delta$ 167.9, 164.5 (d, $^{2}J_{(C-F)} = 25.8$ Hz), 163.0 (d, $^{1}J_{(C-F)} = 244.6$ Hz), 153.3, 151.4, 150.3, 141.2 (d, $^{3}J_{(C-F)} = 7.0$ Hz), 138.0, 133.4, 130.4 (br s), 130.2 (d, $^{3}J_{(C-F)} = 8.1$ Hz), 129.4, 126.7 (br s), 124.6 (d, $^{4}J_{(C-F)} = 2.6$ Hz), 123.1, 115.8 (d, $^{5}J_{(C-F)} = 20.9$ Hz), 113.6 (d, $^{2}J_{(C-F)} = 20.8$ Hz), 90.5 (d, $^{1}J_{(C-F)} = 246.3$ Hz), 63.4, 40.9, 35.4, 34.9, 31.3.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{27}$H$_{28}$ClF$_{2}$N$_{3}$O$_{3}$Na 522.1730; Found 522.1756.

Diastereomer B

$\text{H NMR}$ (500 MHz, CDCl$_3$): $\delta$ 8.45 (dd, $J = 2.0$, 0.5 Hz, 1H), 7.25 (d, $J = 9.0$ Hz, 2H), 7.18–7.14 (m, 1H), 7.06 (d, $J = 8.0$, 4.5 Hz, 1H), 6.94–6.84 (m, 5H), 6.56 (br s, 1H), 6.17 (dd, $J = 3.5$, 1.5 Hz, 1H), 6.06 (s, 1H), 5.42 (d, $J = 4.0$ Hz, 1H), 3.61–3.53 (m, 2H), 2.85 (t, $J = 7.0$ Hz, 2H), 1.29 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.8, 162.9 (d, $^{1}J_{(C-F)} = 244.5$ Hz), 159.7, 151.8, 152.5, 151.3, 149.7, 146.1, 145.1, 141.3 (d, $^{3}J_{(C-F)} = 7.3$ Hz), 138.1, 136.7, 130.2, 130.0 (d, $^{3}J_{(C-F)} = 8.3$ Hz), 129.9, 126.2, 124.5, 122.9, 117.3, 115.6 (d, $^{2}J_{(C-F)} = 20.9$ Hz), 113.4 (d, $^{2}J_{(C-F)} = 21.0$ Hz), 111.3, 63.9, 40.8, 35.3, 34.7, 31.3.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{30}$H$_{30}$FN$_{3}$O$_{3}$Na 522.2163; Found 522.2192.

Diastereomer A

$\text{H NMR}$ (500 MHz, CDCl$_3$): $\delta$ 8.45 (d, $J = 5.0$ Hz, 1H), 8.27 (s, 1H), 7.37 (br s, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.24–7.18 (m, 1H), 7.13 (br s, 1H), 7.03–6.99 (m, 1H), 6.92–6.80 (m, 3H), 6.50 (br s, 1H), 6.23 (br d, $J = 5.0$ Hz, 1H), 6.09 (d, $J_{(H-F)} = 50.5$ Hz, 1H), 5.87 (s, 1H), 3.66–3.52 (m, 2H), 2.83 (t, $J = 7.0$ Hz, 2H), 1.27 (s, 9H).

$^{13}$C NMR (125 MHz, CD$_3$OD): $\delta$ 167.9, 164.5 (d, $^{2}J_{(C-F)} = 25.8$ Hz), 163.0 (d, $^{1}J_{(C-F)} = 244.6$ Hz), 153.3, 151.4, 150.3, 141.2 (d, $^{3}J_{(C-F)} = 7.0$ Hz), 138.0, 133.4, 130.4 (br s), 130.2 (d, $^{3}J_{(C-F)} = 8.1$ Hz), 129.4, 126.7 (br s), 124.6 (d, $^{4}J_{(C-F)} = 2.6$ Hz), 123.1, 115.8 (d, $^{5}J_{(C-F)} = 20.9$ Hz), 113.6 (d, $^{2}J_{(C-F)} = 20.8$ Hz), 90.5 (d, $^{1}J_{(C-F)} = 246.3$ Hz), 63.4, 40.9, 35.4, 34.9, 31.3.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{27}$H$_{28}$ClF$_{2}$N$_{3}$O$_{3}$Na 522.1730; Found 522.1756.

Diastereomer A

$\text{N-[4-(tert-Butyl)phenyl]-2-chloro-2-fluoro-N-(2-[(3-fluoro-phenethyl)amino]-2-oxo-1-(pyridin-3-yl)ethyl]acetamide (3)}$

Diastereomer A: a white solid; diastereomer B: a white solid.

69% yield.
2-{N-[4-(tert-Butyl)phenyl]acetamido}-N-(3-fluoro-phenethyl)-2-(pyridin-3-yl)acetamide (4)
A white solid. 78% yield.

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3\text{): } & \delta 8.45 \text{ (d, } J = 4.0 \text{ Hz, 1H), } 8.38 \text{ (s, 1H), } 7.37 \text{ (d, } J = 8.0 \text{ Hz, 1H), } 7.26-7.20 \text{ (m, 3H), } 7.05-7.00 \text{ (m, 1H), } 6.96-6.78 \text{ (m, 5H), } 6.20 \text{ (br s, 1H), } 5.93 \text{ (s, 1H), } 3.62-3.53 \text{ (m, 2H), } 2.90-2.80 \text{ (m, 2H), } 1.86 \text{ (s, 3H), } 1.26 \text{ (s, 9H).}
\end{align*}
\]

\[
\begin{align*}
\text{C NMR (125 MHz, CDCl}_3\text{): } & \delta 171.7, 169.1, 163.9, 151.9, 151.1, 149.6, 141.3 \text{ (d, } 3\text{J(C-F) = 7.4 Hz), } 137.9, 137.4, 130.5, 130.1 \text{ (d, } 3\text{J(C-F) = 8.1 Hz), } 129.2, 126.2, 124.5 \text{ (d, } 4\text{J(C-F) = 2.8 Hz), } 122.8, 115.7 \text{ (d, } 2\text{J(C-F) = 20.9 Hz), } 113.4 \text{ (d, } 2\text{J(C-F) = 20.6 Hz), } 62.7, 40.7, 35.3, 34.6, 31.2, 23.2.
\end{align*}
\]

LRMS (ESI) \text{m/z [M+H]}^+ \text{ calcd for } C_{27}H_{31}FN_3O_2 448.24; \text{ Found 448.23.}

N-[4-(tert-Butylphenyl]-2,2-difluoro-N-[2-[(3-fluorophenethyl)-amino]-2-oxo-1-(pyridin-3-yl)ethyl]acetamide (5)
A white solid. 83% yield.

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3\text{): } & \delta 8.42 \text{ (dd, } J = 5.0, 2.0 \text{ Hz, 1H), } 8.18 \text{ (d, } J = 2.0 \text{ Hz, 1H), } 7.33-7.15 \text{ (m, 6H), } 7.01 \text{ (dd, } J = 8.0, 5.0 \text{ Hz, 1H), } 6.92-6.80 \text{ (m, 3H), } 6.52 \text{ (br s, 1H), } 5.71 \text{ (t, } J_{\text{H-F}} = 53.0 \text{ Hz, 1H), } 5.93 \text{ (s, 1H), } 3.67-3.58 \text{ (m, 1H), } 3.56-3.45 \text{ (m, 1H), } 2.83 \text{ (t, } J = 7.0 \text{ Hz, 2H), } 1.26 \text{ (s, 9H).}
\end{align*}
\]

\[
\begin{align*}
\text{C NMR (125 MHz, CDCl}_3\text{): } & \delta 167.9, 163.0 \text{ (d, } 1\text{J(C-F) = 244.6 Hz), } 162.6 \text{ (t, } 2\text{J(C-F) = 26.6 Hz), } 153.2, 151.3, 150.1, 141.3 \text{ (d, } 3\text{J(C-F) = 7.1 Hz), } 138.0, 133.1, 130.2, 130.1 \text{ (d, } 3\text{J(C-F) = 8.3 Hz), } 129.4, 126.4 \text{ (br s), } 124.6 \text{ (d, } 4\text{J(C-F) = 2.6 Hz), } 123.2, 115.7 \text{ (d, } 2\text{J(C-F) = 20.8 Hz), } 113.5 \text{ (d, } 2\text{J(C-F) = 20.9 Hz), } 105.7 \text{ (t, } 1\text{J(C-F) = 244.3 Hz), } 63.1, 40.9, 35.3, 34.8, 31.3.
\end{align*}
\]

LRMS (ESI) \text{m/z [M+H]}^+ \text{ calcd for } C_{22}H_{29}F_3N_3O_2 484.22; \text{ Found 484.21.}
2-Chloro-2-fluoro-N-[2-[(3-fluorophenethyl)amino]-2-oxo-1-(pyridin-3-yl)ethyl]-N-(4-isopropylphenyl)acetamide (6)

Diastereomer A: a white solid; diastereomer B: colorless oil.
24% yield.

**1H NMR** (500 MHz, CDCl₃): δ 8.48 (dd, J = 5.0, 1.5 Hz, 1H), 8.36 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.24–7.19 (m, 2H), 7.06 (dd, J = 8.0, 5.0 Hz, 1H), 6.99 (br s, 1H), 6.92–6.83 (m, 3H), 6.51 (br s, 1H), 6.06 (d, J(F-H) = 50.5 Hz, 1H), 6.05 (br s, 1H), 5.89 (s, 1H), 3.63–3.54 (m, 2H), 2.89–2.81 (m, 3H), 1.20 (dd, J = 7.0, 2.0 Hz, 6H).

**13C NMR** (125 MHz, CDCl₃): δ 169.0, 164.6 (d, J(C-F) = 25.4 Hz), 162.8 (d, J(C-F) = 242.8 Hz), 150.6, 150.5, 148.7, 141.8 (d, J(C-F) = 7.3 Hz), 138.6, 133.5, 131.2 (br s), 130.2, 129.7 (d, J(C-F) = 8.3 Hz), 126.9 (br s), 124.4, 123.4, 115.1 (d, J(C-F) = 21.3 Hz), 112.6 (d, J(C-F) = 20.9 Hz), 90.6 (d, J(C-F) = 244.9 Hz), 63.1, 40.4, 34.6, 33.6, 22.7.

**HRMS** (ESI) m/z [M+Na]+ calcd for C₂₆H₂₆ClF₂N₃O₂Na 508.1574; Found 508.1603.

Diastereomer B

**1H NMR** (500 MHz, CDCl₃): δ 8.44 (dd, J = 5.0, 1.5 Hz, 1H), 8.27 (s, 1H), 7.28 (br s, 2H), 7.27–7.26

**13C NMR** (125 MHz, CDCl₃): δ 169.8, 164.3 (d, J(C-F) = 25.4 Hz), 162.8 (d, J(C-F) = 242.8 Hz), 150.6, 150.5, 148.6, 141.8 (d, J(C-F) = 7.3 Hz), 138.6, 133.6, 130.2, 129.7 (d, J(C-F) = 8.4 Hz), 126.9, 124.4, 123.3, 115.1 (d, J(C-F) = 21.1 Hz), 112.6 (d, J(C-F) = 20.9 Hz), 90.6 (d, J(C-F) = 244.1 Hz), 62.9, 40.4, 34.6, 33.6, 22.7.

**HRMS** (ESI) m/z [M+Na]+ calcd for C₂₆H₂₆ClF₂N₃O₂Na 508.1574; Found 508.1585.

2-Chloro-2-fluoro-N-[2-[(3-fluorophenethyl)amino]-2-oxo-1-(pyridin-3-yl)ethyl]-N-[4-(1-methylcyclohexyl)phenyl]acetamide (7)

Diastereomer A: yellow oil; diastereomer B: colorless oil.
39% yield.

**1H NMR** (500 MHz, CDCl₃): δ 8.44 (dd, J = 5.0, 1.5 Hz, 1H), 8.27 (s, 1H), 7.28 (br s, 2H), 7.27–7.26
(m, 1H), 7.22–7.18 (m, 1H), 6.99 (dd, J = 8.0, 5.0 Hz, 1H), 6.91–6.86 (m, 2H), 6.83 (tt, J = 9.5, 2.0 Hz, 1H), 6.50 (br s, 1H), 6.30 (br s, 1H), 6.11 (d, J_{\text{H}-F} = 50.0 Hz, 1H), 5.89 (s, 1H), 3.65–3.51 (m, 2H), 2.83 (t, J = 7.0 Hz, 1H), 1.89 (br s, 2H), 1.56–1.50 (m, 4H), 1.46–1.24 (m, 4H), 1.12 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.8, 164.4 (d, $^2$J$_{\text{C}-\text{F}} = 25.4$ Hz), 162.9 (d, $^1$J$_{\text{C}-\text{F}} = 244.8$ Hz), 152.1, 151.2, 150.0, 141.1 (d, $^3$J$_{\text{C}-\text{F}} = 7.1$ Hz), 138.0, 133.0, 130.7 (br s), 130.1 (d, $^3$J$_{\text{C}-\text{F}} = 8.4$ Hz), 129.3, 127.2 (br s), 124.5, 123.0, 115.6 (d, $^2$J$_{\text{C}-\text{F}} = 21.0$ Hz), 113.5 (d, $^2$J$_{\text{C}-\text{F}} = 21.0$ Hz), 90.4 (d, $^1$J$_{\text{C}-\text{F}} = 246.1$ Hz), 63.1, 40.8, 38.0, 37.8, 37.7, 35.2, 30.3 26.2, 22.5.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{30}$H$_{32}$ClF$_2$N$_2$O$_3$Na 562.2043; Found 562.2020.

**Diastereomer B**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.46 (dd, J = 5.0, 1.5 Hz, 1H), 8.34 (d, J = 2.0 Hz, 1H), 7.28 (br s, 2H), 7.32–7.28 (m, 1H), 7.24–7.18 (m, 1H), 7.02 (dd, J = 8.0, 4.5 Hz, 1H), 6.93–6.83 (m, 3H), 6.52 (br s, 1H), 6.15 (br s, 1H), 6.10 (d, J$_{\text{H}-\text{F}} = 50.5$ Hz, 1H), 5.91 (s, 1H), 3.68–3.51 (m, 2H), 2.84 (t, J = 7.0 Hz, 1H), 1.89 (br s, 2H), 1.56–1.50 (m, 4H), 1.47–1.26 (m, 4H), 1.13 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.7, 164.2 (d, $^2$J$_{\text{C}-\text{F}} = 25.3$ Hz), 162.9 (d, $^1$J$_{\text{C}-\text{F}} = 244.6$ Hz), 152.2, 151.0, 149.9, 141.0 (d, $^3$J$_{\text{C}-\text{F}} = 7.0$ Hz), 137.9, 133.3, 130.1 (d, $^3$J$_{\text{C}-\text{F}} = 8.1$ Hz), 130.0 (br s), 129.3, 127.2 (br s), 124.5, 123.0, 115.7 (d, $^2$J$_{\text{C}-\text{F}} = 20.9$ Hz), 113.5 (d, $^2$J$_{\text{C}-\text{F}} = 20.8$ Hz), 90.4 (d, $^1$J$_{\text{C}-\text{F}} = 246.0$ Hz), 63.4, 40.8, 38.0, 37.8, 37.7, 35.2, 30.3, 26.2, 22.5.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{30}$H$_{32}$ClF$_2$N$_2$O$_3$Na 562.2043; Found 562.2028.

**2-Chloro-2-fluoro-N-[2-[(3-fluorophenethyl)amino]-2-oxo-1-(pyridin-3-yl)ethyl]-N-[4-(trifluoromethyl)phenyl]acetamide (8)**

Diastereomer A: a yellow solid; diastereomer B: a pale-yellow oil. 35% yield.

**Diastereomer A**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.57 (br s, 1H), 8.52 (d, J = 4.5 Hz, 1H), 7.54 (br s, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.21 (q, J = 8.0 Hz, 1H), 7.16 (dd, J = 7.5, 4.5 Hz, 1H), 6.92–6.87 (m, 2H), 6.83 (d, J = 9.5 Hz, 1H), 6.16 (br s, 1H), 6.04 (s, 1H), 6.02 (d, J$_{\text{H}-\text{F}} = 50.0$ Hz, 1H), 3.65–3.53 (m, 2H), 2.83 (t, J = 6.8 Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.6, 163.8 (d, $^2$J$_{\text{C}-\text{F}} = 25.3$ Hz), 162.9 (d, $^1$J$_{\text{C}-\text{F}} = 244.8$ Hz), 151.3, 150.6, 140.9 (d, $^3$J$_{\text{C}-\text{F}} = 7.1$ Hz), 139.3, 137.6, 132.3–131.5 (m), 130.1 (d, $^3$J$_{\text{C}-\text{F}} = 8.1$ Hz), 128.7, 126.5 (br s), 124.5, 123.4 (q, $^1$J$_{\text{C}-\text{F}} = 135.5$ Hz), 115.6 (d, $^2$J$_{\text{C}-\text{F}} = 21.0$ Hz), 113.6 (d, $^2$J$_{\text{C}-\text{F}} = 20.9$ Hz), 90.4 (d, $^1$J$_{\text{C}-\text{F}} = 248.9$ Hz), 63.0, 40.8, 32.2.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{24}$H$_{15}$ClF$_3$N$_2$O$_3$Na 534.0978; Found 534.0976.
Diastereomer B

$^1$H NMR (500 MHz, MeOD): $\delta$ 8.24 (d, $J = 4.0$ Hz, 1H), 8.20 (s, 1H), 7.47 (br s, 3H), 7.30 (d, $J = 7.5$ Hz, 1H), 7.10–7.05 (m, 3H), 6.84 (d, $J = 7.5$ Hz, 1H), 6.78–6.75 (m, 2H), 6.19 (d, $J_{\text{H-F}} = 49.0$ Hz, 1H), 6.04 (s, 1H), 3.55–3.49 (m, 1H), 3.35–3.30 (m, 1H), 2.76–2.65 (m, 3H).

$^{13}$C NMR (125 MHz, MeOD): $\delta$ 168.6, 163.8 (d, $^2J_{\text{C-F}} = 25.1$ Hz), 162.8 (d, $^1J_{\text{C-F}} = 242.6$ Hz), 150.7, 148.9, 141.7 (d, $^3J_{\text{C-F}} = 7.3$ Hz), 139.7, 138.6, 132.2 (br s), 130.9 (q, $^2J_{\text{C-F}} = 32.5$ Hz), 129.8, 129.7 (d, $^3J_{\text{C-F}} = 8.5$ Hz), 125.9, 124.4, 123.5 (q, $^1J_{\text{C-F}} = 140.8$ Hz), 115.2 (d, $^2J_{\text{C-F}} = 21.0$ Hz), 112.6 (d, $^2J_{\text{C-F}} = 21.3$ Hz), 90.8 (d, $^1J_{\text{C-F}} = 245.9$ Hz), 62.7, 40.4, 34.6.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{24}$H$_{15}$ClF$_5$N$_2$O$_2$Na 534.0978; Found 535.1282.

[**Figure**]

2-Chloro-2-fluoro-N-[2-[(3-fluorophenethyl)amino]-2-oxo-1-(pyridin-3-yl)ethyl]-N-(4-(pentafluoro-1$^\delta$-sulfaneyl)phenyl)-acetamide (9)

Diastereomer A: a white solid; diastereomer B: a white solid.

37% yield.

Diastereomer A

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.50 (dd, $J = 5.0$, 1.5 Hz, 1H), 8.31 (d, $J = 2.0$ Hz, 1H), 7.66 (br s, 3H), 7.29–7.26 (m, 1H), 7.23–7.19 (m, 1H), 7.09 (dd, $J = 7.3$, 4.8 Hz, 1H), 6.91–6.87 (m, 2H), 6.82 (tt, $J = 9.5$, 2.0 Hz, 1H), 6.04 (d, $J_{\text{H-F}} = 50.0$ Hz, 1H), 5.94 (br s, 1H), 5.93 (s, 1H), 3.69–3.63 (m, 1H), 3.56–3.50 (m, 1H), 2.83 (t, $J = 6.8$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.7, 163.7 (d, $^2J_{\text{C-F}} = 25.3$ Hz), 162.9 (d, $^1J_{\text{C-F}} = 244.6$ Hz), 151.2, 150.7, 140.9 (d, $^3J_{\text{C-F}} = 7.0$ Hz), 138.9, 137.5, 131.8, 130.1 (d, $^2J_{\text{C-F}} = 8.4$ Hz), 128.7, 127.1 (br s), 124.5, 123.5, 115.6 (d, $^2J_{\text{C-F}} = 21.0$ Hz), 113.6 (d, $^2J_{\text{C-F}} = 20.9$ Hz), 90.5 (d, $^1J_{\text{C-F}} = 248.8$ Hz), 63.0, 40.8, 35.2.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{23}$H$_{19}$ClF$_7$N$_2$O$_2$SNa 592.0667; Found 592.0671.

Diastereomer B

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.48 (d, $J = 9.5$ Hz, 1H), 8.26 (s, 1H), 7.66 (br s, 3H), 7.24–7.17 (m, 2H), 7.07 (dd, $J = 8.0$, 5.0 Hz, 1H), 6.90–6.86 (m, 2H), 6.81 (d, $J = 10.0$ Hz, 1H), 6.19 (br s, 1H), 6.04 (d, $J_{\text{H-F}} = 49.5$ Hz, 1H), 5.91 (s, 1H), 3.66–3.60 (m, 1H), 3.57–3.50 (m, 1H), 2.82 (t, $J = 6.8$ Hz, 2H).

$^{13}$C NMR (125 MHz, MeOD): $\delta$ 167.3, 163.4 (d, $^2J_{\text{C-F}} = 25.0$ Hz), 162.9 (d, $^1J_{\text{C-F}} = 244.9$ Hz), 151.2, 150.7, 140.9 (d, $^3J_{\text{C-F}} = 7.0$ Hz), 139.2, 137.4, 131.8 (br s), 130.2 (d, $^3J_{\text{C-F}} = 8.1$ Hz), 128.6, 127.2 (br s), 124.5, 123.5, 115.6 (d, $^2J_{\text{C-F}} = 20.9$ Hz), 113.6 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 90.8 (d, $^1J_{\text{C-F}} = 249.0$ Hz), 63.2, 40.9, 35.2.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{23}$H$_{19}$ClF$_7$N$_2$O$_2$SNa 592.0667; Found 592.0688.
A mixture of diastereomers. Yellow amorphous. 65% yield.

**LRMS (ESI)** m/z [M+Na]+ calcd for C_{28}H_{27}ClF_{2}N_{4}O_{2}Na 523.17; Found 523.17.

A mixture of diastereomers. Yellow amorphous. 75% yield.

**LRMS (ESI)** m/z [M+Na]+ calcd for C_{28}H_{27}ClF_{2}N_{4}O_{2}Na 523.17; Found 523.17.
N-[4-(tert-Butyl)phenyl]-2-chloro-2-fluoro-N-(2-((3-fluorophenethyl)amino)-2-oxo-1-(pyrimidin-5-yl)ethyl)acetamide (12)

Diastereomer A: white solid; diastereomer B: white solid.
67% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.06 (s, 1H), 8.42 (s, 2H), 7.43–7.14 (m, 5H), 7.00–6.88 (m, 3H), 6.48 (t, $J = 5.5$ Hz, 1H), 6.02 (d, $J_{HF} = 50.0$ Hz, 1H), 5.99 (s, 1H), 3.71–3.54 (m, 2H), 2.93–2.83 (m, 2H), 1.28 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.0, 164.9 (d, $^2J_{CF} = 25.6$ Hz), 163.1 (d, $^1J_{CF} = 245.3$ Hz), 158.8, 158.6, 154.1, 141.0 (d, $^3J_{CF} = 7.0$ Hz), 132.5, 130.3 (d, $^3J_{CF} = 8.3$ Hz), 129.8 (br s), 127.4, 127.1 (br s), 124.6 (d, $^4J_{CF} = 2.6$ Hz), 115.7 (d, $^2J_{CF} = 21.0$ Hz), 113.8 (d, $^2J_{CF} = 20.3$ Hz), 90.3 (d, $^1J_{CF} = 246.6$ Hz), 61.1, 41.0, 35.3, 35.0, 31.3.

LRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{26}$H$_{27}$ClF$_2$N$_4$O$_2$Na 523.17; Found 523.18.

Diastereomer B

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.07 (s, 1H), 8.43 (s, 2H), 7.43–7.14 (m, 5H), 7.00–6.89 (m, 3H), 6.23 (br s, 1H), 6.06 (d, $J_{HF} = 50.5$ Hz, 1H), 6.01 (s, 1H), 3.70–3.58 (m, 2H), 2.89 (t, $J = 7.0$ Hz, 2H), 1.29 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.8, 164.5 (d, $^2J_{CF} = 25.5$ Hz), 163.0 (d, $^1J_{CF} = 245.3$ Hz), 158.7, 158.3, 154.0, 140.8 (d, $^3J_{CF} = 7.3$ Hz), 132.6, 130.2 (d, $^3J_{CF} = 8.1$ Hz), 129.7 (br s), 127.2, 127.0 (br s), 124.4 (d, $^4J_{CF} = 2.8$ Hz), 115.7 (d, $^2J_{CF} = 21.0$ Hz), 113.7 (d, $^2J_{CF} = 20.9$ Hz), 90.2 (d, $^1J_{CF} = 246.9$ Hz), 61.1, 40.9, 35.2, 34.9, 31.1.

LRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{26}$H$_{27}$ClF$_2$N$_4$O$_2$Na 523.17; Found 523.17.

N-[4-(tert-Butyl)phenyl]-2-chloro-2-fluoro-N-(2-((3-fluorophenethyl)amino)-2-oxo-1-(pyrazin-2-yl)ethyl)acetamide (13)

A mixture of diastereomers. A white solid. 83% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.74 (d, $J = 1.5$ Hz, 0.5H), 8.66 (d, $J = 1.5$ Hz, 0.5H), 8.53–8.49 (m, 1H), 8.40–8.37 (m, 1H), 7.53–7.05 (m, 5H), 6.95–6.88 (m, 2H), 6.85–6.78 (m, 1H), 6.17 (d, $J_{HF} = 50.5$ Hz, 1H), 6.14 (d, $J_{HF} = 50.0$ Hz, 1H), 5.84 (s, 0.5H), 5.67 (s, 0.5H), 6.01 (s, 1H), 3.69–3.59 (m, 1H), 3.55–3.45 (m, 1H), 2.84–2.68 (m, 2H), 1.30 (s × 2, 9H).
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 165.9, 165.8, 164.2 (d $\times$ 2, $^2J_{(C-F)} = 25.5$ Hz), 162.9 (d, $^1J_{(C-F)} = 244.3$ Hz), 153.3, 150.1, 150.0, 145.7, 145.0, 144.1, 144.0, 143.1, 142.9, 141.3 (d, $^3J_{(C-F)} = 7.8$ Hz), 141.2 (d, $^3J_{(C-F)} = 7.8$ Hz), 135.7, 135.0, 130.1 (d, $^3J_{(C-F)} = 8.3$ Hz), 141.2 (d, $^3J_{(C-F)} = 7.8$ Hz), 129.1 (br s), 128.7 (br s), 126.9, 126.8, 124.5, 115.8 (d $\times$ 2, $^2J_{(C-F)} = 20.9$ Hz), 113.4 (d $\times$ 2, $^2J_{(C-F)} = 20.9$ Hz), 90.4 (d, $^1J_{(C-F)} = 246.4$ Hz), 90.1 (d, $^1J_{(C-F)} = 246.6$ Hz), 66.8, 66.2, 40.9, 40.8, 35.2, 34.82, 34.81, 31.2.

LRMS (ESI) $m/z$ [M+Na]$^+$ calcd for C$_{26}$H$_{27}$ClF$_2$N$_4$O$_2$Na 523.17; Found 523.17.

$N$-[4-(tert-Butyl)phenyl]-$N$-[2-(tert-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl]-2-chloro-2-fluoroacetamide (14)

Diastereomer A: a white solid; diastereomer B: colorless amorphous. 61% yield.

Diastereomer A

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.47 (dd, $J = 4.5$, 1.5 Hz, 1H), 8.42 (d, $J = 1.5$ Hz, 1H), 7.55 (br s, 1H), 7.41 (tt, $J = 8.0$, 1.8 Hz, 1H), 7.38 (br s, 1H), 7.12 (br s, 1H), 7.05 (dd, $J = 8.0$, 5.0 Hz, 1H), 6.52 (br s, 1H), 6.08 (d, $J_{(H-F)} = 50.5$ Hz, 1H), 5.85 (s, 1H), 5.79 (br s, 1H), 1.36 (s, 9H), 1.26 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.8, 164.3 (d, $^2J_{(C-F)} = 25.5$ Hz), 153.1, 151.4, 150.1, 137.8, 133.4, 130.0 (br s), 129.5, 126.2 (br s), 123.0, 90.4 (d, $^1J_{(C-F)} = 246.4$ Hz), 63.6, 52.1, 34.7, 31.2, 28.6.

HRMS (ESI) $m/z$ [M+Na]$^+$ calcd for C$_{29}$H$_{29}$ClF$_2$N$_3$O$_2$Na 456.1825; Found 456.1853.

Diastereomer B

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.47 (dd, $J = 4.8$, 1.8 Hz, 1H), 8.42 (d, $J = 2.0$ Hz, 1H), 7.51 (br s, 1H), 7.39 (tt, $J = 8.0$, 2.0 Hz, 1H), 7.38 (br s, 1H), 7.16 (br s, 1H), 7.04 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.48 (br s, 1H), 6.08 (d, $J_{(H-F)} = 50.5$ Hz, 1H), 5.98 (s, 1H), 5.94 (br s, 1H), 1.39 (s, 9H), 1.27 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.6, 164.3 (d, $^2J_{(C-F)} = 25.4$ Hz), 153.3, 151.5, 150.0, 138.0, 133.2, 129.8 (br s), 129.2, 126.5 (br s), 122.9, 90.3 (d, $^1J_{(C-F)} = 246.3$ Hz), 63.0, 52.0, 34.8, 31.2, 28.6.

HRMS (ESI) $m/z$ [M+Na]$^+$ calcd for C$_{29}$H$_{29}$ClF$_2$N$_3$O$_2$Na 456.1825; Found 456.1846.
N-[4-(tert-Butyl)phenyl]-2-chloro-2-fluoro-N-(2-oxo-2-[[2-(pyridin-2-yl)ethyl]amino]-1-(pyridin-3-yl)ethyl)acetamide (15)

A mixture of diastereomers. A white solid. 7% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.48 (t, $J = 5.0$ Hz, 1H), 8.37 (d, $J = 4.0$ Hz, 1H), 8.32 (br s, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.50 (br s, 2H), 7.40 (q, $J = 8.0$ Hz, 1H), 7.23 (br s, 2H), 7.15–7.03 (m, 3H), 6.62 (br s, 1H), 6.07 (d x 2, $J = 50.5$ Hz, 1H), 5.92 (s, 0.5H), 5.91 (s, 0.5H), 3.77–3.68 (m, 2H), 3.03–2.94 (m, 2H), 1.27 (s x 2, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.3, 167.2, 164.1 (d, $^2J_{(C-F)} = 25.4$ Hz), 164.0 (d, $^2J_{(C-F)} = 25.3$ Hz), 159.3, 153.0, 151.5, 151.4, 150.0, 149.9, 148.9, 138.0, 137.8, 136.8, 134.1, 133.8, 129.8 (br s), 129.7, 126.5 (br s), 123.6, 123.1, 123.0, 121.6, 90.4 (d, $^1J_{(C-F)} = 245.9$ Hz), 64.1, 63.8, 39.1, 36.2, 34.7, 31.2.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{26}$H$_{28}$ClFN$_4$O$_2$Na 505.1777; Found 505.1800.

N-[4-(tert-Butyl)phenyl]-2-chloro-2-fluoro-N-(2-oxo-2-[[2-(pyridin-3-yl)ethyl]amino]-1-(pyridin-3-yl)ethyl)acetamide (16)

A mixture of diastereomers. Colorless amorphous. 75% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.48–8.27 (m, 4H), 7.56–6.98 (m, 7H), 6.61–6.44 (m, 2H), 8.37 (d, $J = 4.0$ Hz, 1H), 6.08 (d x 2, $J = 50.0$ Hz, 1H), 5.91 (s, 0.5H), 5.89 (s, 0.5H), 3.65–3.53 (m, 2H), 2.90–2.81 (m, 2H), 1.27 (s x 2, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.2, 168.1, 164.5 (d, $^2J_{(C-F)} = 26.8$ Hz), 164.0 (d, $^2J_{(C-F)} = 25.6$ Hz), 153.35, 153.32, 151.4, 151.3, 150.26, 150.23, 150.22, 137.9, 137.7, 136.61, 136.56, 134.25, 134.23, 133.7, 133.4, 130.5 (br s), 129.33, 129.31, 126.65, 126.48 (br s), 123.6, 123.22, 123.16, 90.5 (d x 2, $^1J_{(C-F)} = 245.6$ Hz), 40.93, 40.90, 34.9, 32.9, 31.3.

HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_{26}$H$_{28}$ClFN$_4$O$_2$Na 505.1777; Found 505.1783.
**Diastereomer A**

1H NMR (500 MHz, CDCl3): δ 9.03 (s, 1H), 9.01 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.50 (dd, J = 4.8, 1.8 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.30 (br s, 1H), 7.79 (br s, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.47–7.44 (m, 3H), 7.40 (d, J = 5.5 Hz, 1H), 7.14 (br s, 1H), 7.04 (dd, J = 8.3, 4.8 Hz, 1H), 6.57 (br s, 1H), 6.38 (s, 1H), 6.22 (d, J(H-F) = 50.5 Hz, 1H), 1.28 (s, 9H).

13C NMR (125 MHz, CDCl3): δ 166.8, 165.2 (d, 2J(C-F) = 26.0 Hz), 153.6, 152.0, 151.6, 150.5, 142.3, 136.1, 132.7, 128.7, 128.3, 127.2 (br s), 124.0 (br s), 123.1, 119.9, 34.8, 31.2.

HRMS (ESI) m/z [M+Na]+ calcld for C28H26ClFN4O2Na 527.1621; Found 527.1612.

**Diastereomer B**

1H NMR (500 MHz, CDCl3): δ 9.40 (s, 1H), 8.93 (s, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.47 (dd, J = 4.5, 1.5 Hz, 1H), 8.33 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 1.5 Hz, 1H), 7.88 (br s, 1H), 7.13 (br s, 1H), 7.03 (dd, J = 8.0, 5.0 Hz, 1H), 6.52 (br s, 1H), 6.51 (s, 1H), 6.19 (d, J(H-F) = 50.5 Hz, 1H), 1.28 (s, 9H).

13C NMR (125 MHz, CDCl3): δ 166.9, 164.9 (d, 2J(C-F) = 25.6 Hz), 153.5, 151.9, 151.5, 150.3, 142.1, 137.8, 136.3, 132.7, 132.6, 128.7, 128.3, 127.1 (br s), 126.4 (br s), 123.9, 123.1, 119.9, 115.7, 90.7 (d, 1J(C-F) = 259 Hz), 63.7, 34.8, 31.2.

HRMS (ESI) m/z [M+Na]+ calcld for C28H26ClFN4O2Na 527.1621; Found 527.1588.
124.6 (d, $^4J_{(C-F)} = 2.6$ Hz), 115.7 (d, $^2J_{(C-F)} = 20.9$ Hz), 113.9 (d, $^2J_{(C-F)} = 20.8$ Hz), 90.5 (d, $^1J_{(C-F)} = 249.8$ Hz), 61.2, 41.0, 35.3.

**HRMS (ESI) m/z [M+Na]$^+$ calcld for C$_{22}$H$_{18}$ClF$_7$N$_4$O$_2$SNa 593.0619; Found 593.0638.**

![Chemical Structure](image)

(R)-2-Chloro-2-fluoro-N-[[R]-2-[[3-fluorophenethyl]amino]-2-oxo-1-(pyrimidin-5-yl)ethyl]-N-[4-(pentafluoro-$\lambda^6$-sulfaneyl)phenyl]acetamide ((R,R)-18)

Colorless form. 30% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.10 (s, 1H), 8.48 (s, 2H), 7.70 (br s, 4H), 7.26–7.21 (m, 1H), 6.94–6.84 (m, 3H), 6.15 (t, $J = 5.5$ Hz, 1H), 6.04 (d, $J_{(H-F)} = 50.0$ Hz, 1H), 5.98 (s, 1H), 3.67–3.57 (m, 2H), 2.85 (t, $J = 7.0$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.7, 164.2 (d, $^2J_{(C-F)} = 25.3$ Hz), 163.1 (d, $^1J_{(C-F)} = 245.1$ Hz), 159.3, 158.4, 154.7, 140.8 (d, $^3J_{(C-F)} = 7.3$ Hz), 138.4, 131.6, 130.4 (d, $^3J_{(C-F)} = 8.3$ Hz), 127.7 (br s), 126.9, 124.6 (d, $^4J_{(C-F)} = 2.6$ Hz), 115.7 (d, $^2J_{(C-F)} = 20.9$ Hz), 113.9 (d, $^2J_{(C-F)} = 20.8$ Hz), 90.5 (d, $^1J_{(C-F)} = 249.8$ Hz), 61.2, 41.0, 35.3.

**HRMS (ESI) m/z [M+Na]$^+$ calcld for C$_{22}$H$_{18}$ClF$_7$N$_4$O$_2$SNa 593.0619; Found 593.0638.**

![Chemical Structure](image)

(S)-2-Chloro-2-fluoro-N-[[R]-2-[[3-fluorophenethyl]amino]-2-oxo-1-(pyrimidin-5-yl)ethyl]-N-[4-(pentafluoro-$\lambda^6$-sulfaneyl)phenyl]acetamide ((R,S)-18)

Colorless form. 25% yield.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.10 (s, 1H), 8.46 (s, 2H), 7.70 (br s, 4H), 7.25–7.21 (m, 2H), 6.94–6.84 (m, 3H), 6.14 (t, $J = 5.5$ Hz, 1H), 6.01 (d, $J_{(H-F)} = 50.0$ Hz, 1H), 5.96 (s, 1H), 3.66–3.57 (m, 2H), 2.90–2.80 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.7, 164.2 (d, $^2J_{(C-F)} = 25.3$ Hz), 163.1 (d, $^1J_{(C-F)} = 245.1$ Hz), 159.3, 158.4, 154.7, 140.8 (d, $^3J_{(C-F)} = 7.3$ Hz), 138.4, 131.6, 130.4 (d, $^3J_{(C-F)} = 8.3$ Hz), 127.7 (br s), 126.9, 124.6 (d, $^4J_{(C-F)} = 2.6$ Hz), 115.7 (d, $^2J_{(C-F)} = 20.9$ Hz), 113.9 (d, $^2J_{(C-F)} = 20.8$ Hz), 90.5 (d, $^1J_{(C-F)} = 249.8$ Hz), 61.2, 41.0, 35.3.

**HRMS (ESI) m/z [M+Na]$^+$ calcld for C$_{22}$H$_{18}$ClF$_7$N$_4$O$_2$SNa 593.0619; Found 593.0641.
(S)-2-Chloro-2-fluoro-N-[(S)-2-[(3-fluorophenethyl)amino]-2-oxo-1-(pyrimidin-5-yl)ethyl]-N-[4-(pentafluoro-λ6-sulfaneyl)phenyl]acetamide ((S,S)-18)

Colorless form. 25% yield.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 9.10 (s, 1H), 8.48 (s, 2H), 7.70 (br s, 4H), 7.26–7.21 (m, 1H), 6.94–6.84 (m, 3H), 6.15 (t, \(J = 5.5\) Hz, 1H), 6.04 (d, \(J_{(H\text{-}F)} = 50.0\) Hz, 1H), 5.98 (s, 1H), 3.67–3.57 (m, 2H), 2.85 (t, \(J = 7.0\) Hz, 2H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 166.6, 163.9 (d, \(^3\)J\(_{C\text{-}F}\) = 25.1 Hz), 163.0 (d, \(^1\)J\(_{C\text{-}F}\) = 244.9 Hz), 159.3, 158.3, 154.7, 140.7 (d, \(^3\)J\(_{C\text{-}F}\) = 7.3 Hz), 138.8, 131.4 (br s), 130.4 (d, \(^3\)J\(_{C\text{-}F}\) = 8.3 Hz), 127.8 (br s), 127.0, 124.5 (d, \(^4\)J\(_{C\text{-}F}\) = 2.8 Hz), 115.7 (d, \(^2\)J\(_{C\text{-}F}\) = 21.1 Hz), 113.9 (d, \(^2\)J\(_{C\text{-}F}\) = 20.9 Hz), 90.7 (d, \(^1\)J\(_{C\text{-}F}\) = 249.0 Hz), 61.4, 41.1, 35.2.

HRMS (ESI) \(m/z\) [M+Na]\(^{+}\) calcd for C\(_{22}\)H\(_{18}\)ClF\(_7\)N\(_4\)O\(_2\)SNa 593.0619; Found 593.0616.

(R)-2-Chloro-2-fluoro-N-[(R)-2-[(3-ethynylphenethyl)amino]-2-oxo-1-(pyrimidin-5-yl)ethyl]-2-fluoro-N-[4-(pentafluoro-λ6-sulfaneyl)phenyl]acetamide (22)

Colorless form. 25% yield.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 9.09 (s, 1H), 8.47 (s, 2H), 7.72 (br s, 4H), 7.45 (d, \(J = 7.5\) Hz, 1H), 7.27 (s, 1H), 7.24 (t, \(J = 7.5\) Hz, 1H), 7.15 (d, \(J = 7.5\) Hz, 1H), 6.27 (t, \(J = 5.5\) Hz, 1H), 6.03 (d, \(J_{(H\text{-}F)} = 50.0\) Hz, 1H), 5.99 (s, 1H), 3.69–3.55 (m, 2H), 3.07 (s, 1H), 2.83 (t, \(J = 7.0\) Hz, 2H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 166.6, 163.9 (d, \(^2\)J\(_{C\text{-}F}\) = 25.1 Hz), 159.2, 158.3, 154.6 (m), 138.7, 138.5, 132.4, 131.4 (br s), 130.7, 129.5, 128.9, 127.9 (br s), 127.0, 122.6, 90.7 (d, \(^1\)J\(_{C\text{-}F}\) = 248.8 Hz), 83.4, 77.8, 61.3, 41.1, 35.2.

HRMS (ESI) \(m/z\) [M+Na]\(^{+}\) calcd for C\(_{24}\)H\(_{19}\)ClF\(_6\)N\(_4\)O\(_2\)SNa 599.0714; Found 599.0704.
**N-[4-(tert-Butyl)phenyl]-N-\{2-[(3-ethynylphenethyl)-amino]-2-oxo-1-(pyridin-3-yl)ethyl\}acrylamide (23)**

A white solid. 66% yield.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta \) 8.44 (dd, \(J = 4.5, 2.0 \text{ Hz}, 1\text{H}\)), 8.33 (d, \(J = 2.0 \text{ Hz}, 1\text{H}\)), 7.36 (d, \(J = 8.0 \text{ Hz}, 1\text{H}\)), 7.32 (d, \(J = 7.5 \text{ Hz}, 1\text{H}\)), 7.29 (s, 1H), 7.23 (d, \(J = 8.5 \text{ Hz}, 2\text{H}\)), 7.20 (t, \(J = 7.5 \text{ Hz}, 1\text{H}\)), 7.14 (d, \(J = 7.5 \text{ Hz}, 1\text{H}\)), 6.83 (br s, 2H), 6.58 (t, \(J = 5.0 \text{ Hz}, 1\text{H}\)), 6.39 (dd, \(J = 17.0, 2.0 \text{ Hz}, 1\text{H}\)), 6.01 (s, 1H), 5.95 (dd, \(J = 17.0, 10.5 \text{ Hz}, 1\text{H}\)), 5.55 (dd, \(J = 10.5, 2.0 \text{ Hz}, 1\text{H}\)), 3.68−3.51 (m, 2H), 3.05 (s, 1H), 2.82 (t, \(J = 7.0 \text{ Hz}, 2\text{H}\)), 1.27 (s, 9H).

\(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta \) 169.1, 166.6, 152.0, 151.3, 149.7, 139.1, 138.0, 136.3, 132.5, 130.5, 130.4, 129.7, 129.5, 128.9, 128.7, 128.4, 126.3, 123.0, 122.5, 83.6, 77.4, 63.2, 40.8, 35.3, 34.7, 31.3.

HRMS (ESI) m/z [M+Na]\(^+\) calcd for C\(_{30}\)H\(_{31}\)N\(_3\)O\(_2\)Na 488.2308; Found 488.2313.
Optical resolution of chlorofluoroacetic acid

(S)-2-Chloro-2-fluoro-N-[(R)-2-hydroxy-1-phenylethyl]acetamide (21A) and (R)-2-Chloro-2-fluoro-N-[(R)-2-hydroxy-1-phenylethyl]acetamide (21B)

A 200 mL round-bottom flask was charged with (R)-(−)-2-Phenylglycinol (20) (12.4 g, 90.1 mmol). Ethyl chlorofluoroacetate (15.0 mL, 129 mmol) was slowly added at 0 °C with stirring. The suspension became clear in a few moments and then solidified. The solid was dissolved in AcOEt and added SiO₂ (~160 mL). Solvents were removed under reduced pressure and the residue was purified by flash column chromatography (hexane/AcOEt = 5:1 to 1:2) to give pure 21A (dr >99:1, 7.22 g), a mixture of 21A and 21B (dr = 28:72, 3.47 g), and pure 21B (dr <1:99, 5.69 g) as white solids. Total 16.4 g, 78% yield (dr = 1:1).

21A

\(^{1}H\) NMR (500 MHz, CDCl₃): ð 7.41–7.30 (m, 5H), 7.07 (br s, 1H), 6.32 (d, \(J_{H-F} = 51.0 \text{ Hz}, 1\text{H})\), 5.10 (p, \(J = 4.5 \text{ Hz, } 1\text{H})\), 3.97–3.94 (m, 2H).

\(^{13}C\) NMR (125 MHz, CDCl₃): ð 164.3 (d, \(2J_{C-F} = 22.0 \text{ Hz})\), 137.9, 129.2, 128.4, 126.7, 94.2 (d, \(1J_{C-F} = 254.4 \text{ Hz})\), 65.7, 55.6.

HRMS (ESI) m/z [M+Na]⁺ calcd for C₁₀H₁₁ClFNO₂Na 254.0355; Found 254.0384.

21B

\(^{1}H\) NMR (500 MHz, CDCl₃): ð 7.42–7.31 (m, 5H), 7.05 (br s, 1H), 6.35 (d, \(J_{H-F} = 51.0 \text{ Hz}, 1\text{H})\), 5.11 (p, \(J = 4.5 \text{ Hz, } 1\text{H})\), 3.97–3.94 (m, 2H).

\(^{13}C\) NMR (125 MHz, CDCl₃): ð 164.2 (d, \(2J_{C-F} = 21.8 \text{ Hz})\), 137.7, 129.2, 128.4, 126.6, 94.3 (d, \(1J_{C-F} = 255.0 \text{ Hz})\), 65.9, 55.5.

HRMS (ESI) m/z [M+Na]⁺ calcd for C₁₀H₁₁ClFNO₂Na 254.0355; Found 254.0393.
(S)-Chlorofluoroacetic acid
To a stirred solution of 21A (4.21 g, 18.2 mmol) in 1,4-dioxane (30 mL) was added 3M H$_2$SO$_4$ (30 mL) at ambient temperature. After heated at reflux for 7.5 h, the reaction mixture was cooled to ambient temperature. The mixture was diluted with water (250 mL) and extracted with diethyl ether (60 mL × 4). The combined organic layers were washed sequentially with water (100 mL × 2) and brine, dried over MgSO$_4$, and evaporated (the water bath temperature was kept below 30 °C). In a round-bottom flask, the residue was heated at 110 °C for 10 min under atmospheric pressure to remove solvents. The flask was equipped with a distillation apparatus and the receiver flask was cooled in liquid nitrogen. The pressure of the system was reduced to ~10 mmHg and (S)-chlorofluoroacetic acid was trapped in the receiver flask. The product was obtained as a 36% solution in 1,4-dioxane (1.76 g, ca. 32% yield). Colorless liquid. (R)-Chlorofluoroacetic acid was prepared from 21B in a similar manner. Amide coupling with 20 using propylphosphonic anhydride as the condensation agent gave stereochemically pure 21A and 21B from (S)- and (R)-chlorofluoroacetic acid, respectively, indicating high enantiopurity of the obtained material.

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.31 (d, $J_{(H-F)}$ = 50.5 Hz, 1H).
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