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Supplemental information

Potent and biostable inhibitors of the main protease of SARS-CoV-2

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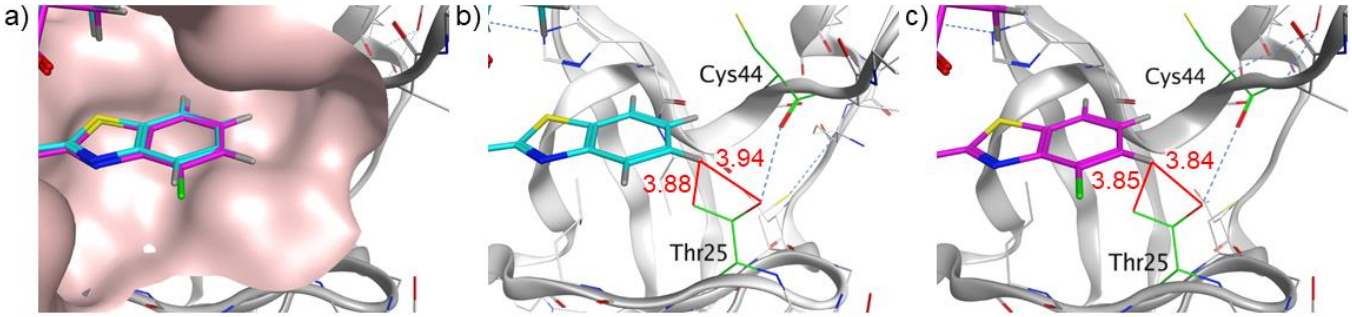


Figure S1. The superimposed structure of SARS-CoV-2 M^{pro} and 5h (PDB: 7JKV) or **3** (overlay images PDB: 8DOY), Related to Figure 7.

The binding pocket of M^{pro} is shown in stick (green)/ribbon (gray)/surface (pink) presentation, and 5h/**3** is shown in overlay images of cyan/magenta sticks, respectively. Hydrogen, nitrogen, oxygen, fluorine and sulfur atoms are shown in gray, blue, red, green and yellow, respectively. a) Benzothiazole moieties of 5h/**3** in the binding pocket of M^{pro} is shown in the center. b) The formation of a hydrogen bond between the M^{pro} Thr25 sidechain hydroxyl group and Cys44 mainchain carbonyl group is shown in light blue dotted line, and the distance between hydrogen atom in benzothiazole 5-position of 5h bound to M^{pro} and Thr25 sidechain is shown in red solid line with the distance (Å). c) The formation of a hydrogen bond between the M^{pro} Thr25 sidechain hydroxyl group and Cys44 mainchain carbonyl group is shown in light blue dotted line, and the distance between hydrogen atom in benzothiazole 5-position of **3** bound to M^{pro} and Thr25 sidechain is shown in red solid line with the distance (Å).

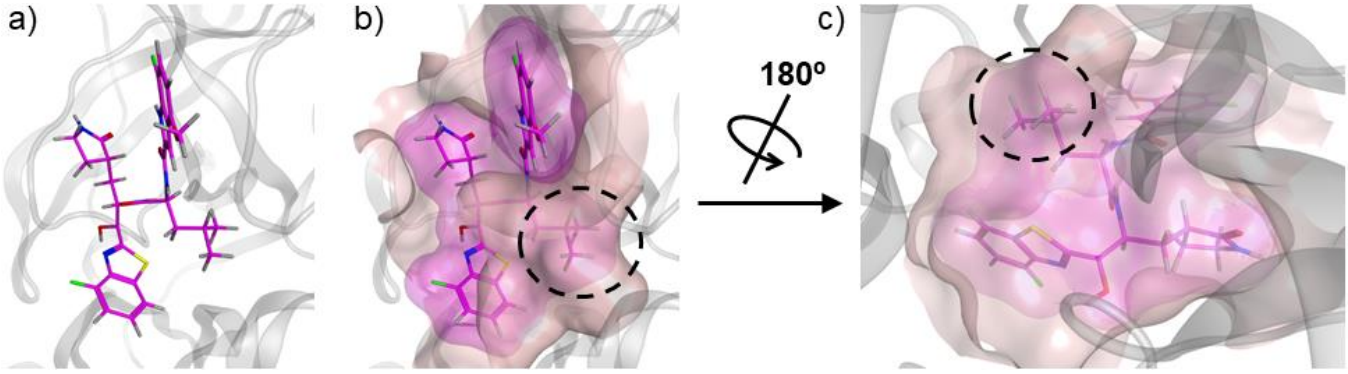


Figure S2. The X-ray co-crystal structure of SARS-CoV-2 M^{pro} and **3** (PDB: 8DOY), Related to Figure 11.
The binding pocket of M^{pro} is shown in ribbon (gray)/surface (pink) presentation, and **3** is shown in magenta as sticks and surface representation. Hydrogen, nitrogen, oxygen, fluorine and sulfur atoms are shown in gray, blue, red, green and yellow, respectively. a) **3** bound in the binding pocket of M^{pro} is shown in the center. b) Representation of M^{pro} binding surface (pink) and **3** surface (magenta). The P2 leucine sidechain is highlighted with dotted circle. c) Rotated views of b).

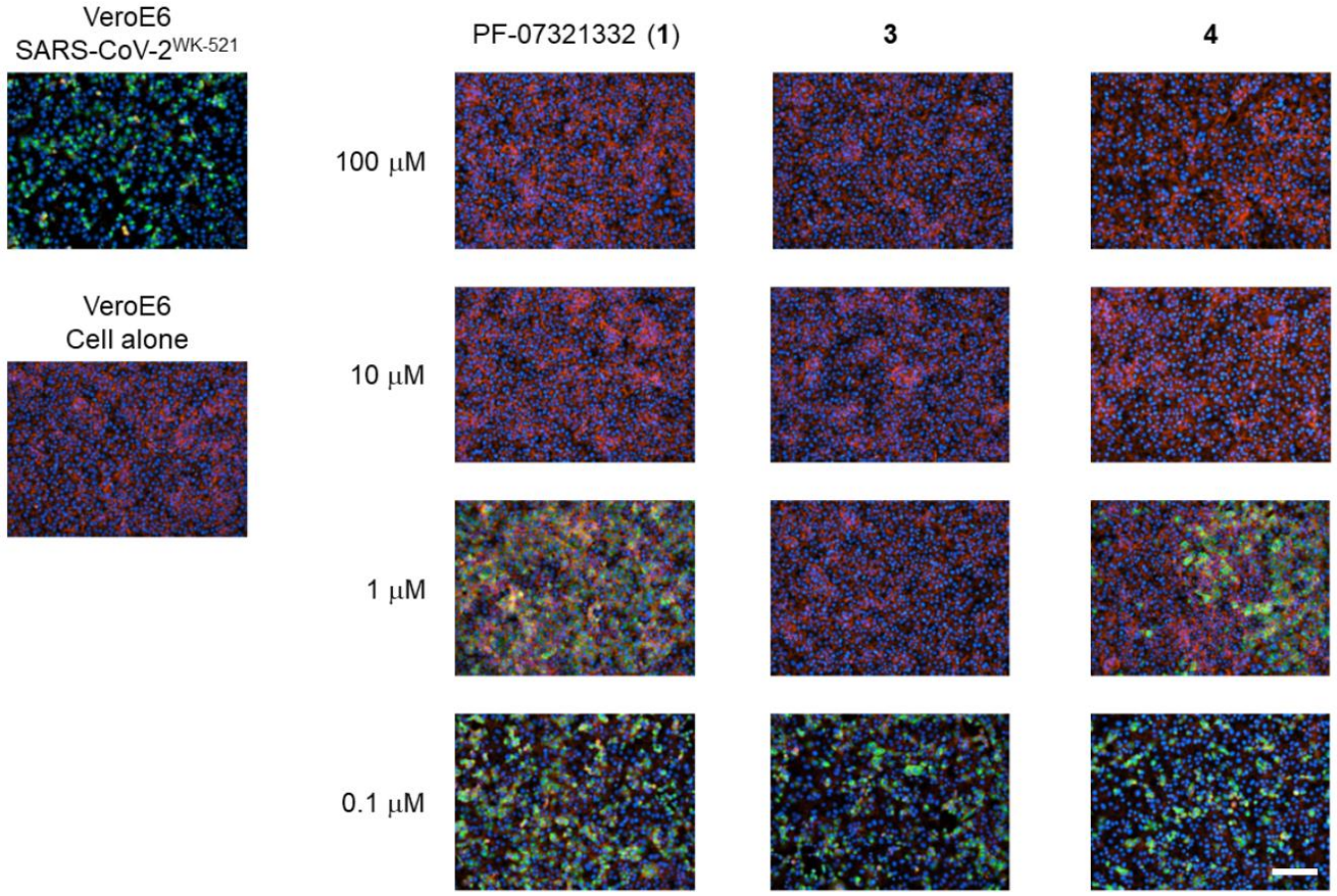


Figure S3. Immunostaining experiments of SARS-CoV-2^{WK-521} infected VeroE6 cells treated with PF-07321332 (**1**), **3**, and **4**, Related to Table 1.

The experiments were performed using a procedure reported previously.[S1] In brief, VeroE6 cells were exposed to SARS-CoV-2^{WK-521} for 1 h, the viruses were washed out, and the virus exposed cells were cultured in the presence or absence of various concentrations of each test compound for 3 days. Cells in 96-well microtiter culture plate were fixed with 4% paraformaldehyde in PBS for 15 min, washed with PBS (300 μL/well) three times for 5 min each, and were then blocked with a blocking buffer (10% goat serum, 1% BSA, 0.3% Triton X-100, and PBS 1X) for 1 h. After removing the blocking buffer, the cells were immediately stained with primary antibodies: convalescent IgG fraction (1/500 dilution), which was isolated from serum of a convalescent COVID-19 individual using spin column-based antibody purification kit (Cosmo Bio, Tokyo, Japan), overnight at 4 °C. The stained cells were washed with PBS (300 μL/well) three times for 5 min each, and the cells were incubated with the secondary antibody: goat polyclonal anti-human-IgG-Alexa Fluor 488 Fab fragment antibody (1/200 dilution)(Jackson ImmunoResearch Laboratories, Inc, West Grove, PA, USA), together with Texas Red™-X dye conjugated Phalloidin (Thermo Fisher Scientific, Waltham, MA, USA) for F-actin visualization for 2 h. After washing the cells with PBS (300 μL/well) three times for 5 min each, DAPI solution (Thermo Fisher Scientific) in PBS (50 μL/well) was added to stain nuclei. Signals were acquired with a Cytation 5 Cell Imaging Multi-Mode Reader and Gen 5 (v3.05) software (BioTek). Numerous positive signals were observed in the cells cultured in the presence of PF-07321332 (**1**) and compound **4** at 1 μM, while in the cells cultured with 1 μM of compound **3**, no such virus positive signals were found. SARS-CoV-2 antigens, F-actin, and nuclei are stained in green, red, and blue, respectively.

Representative images from two or three independently conducted experiments are shown. Scale bar = 100 μm.

Table S1. Data collection, phasing, and refinement statistics (molecular replacement) of a co-crystal structure of SARS-CoV-2 M^{pro} and **3**, Related to Figure 8.

	M^{pro}/**3** (PDB: 8DOY)
Data collection	
Space group	P 1 21 1
Cell dimensions	
a, *b*, *c* (Å)	54.045, 98.942, 57.723,
α, β, γ (°)	90, 106.28, 90,
Resolution (Å)	55.41 - 1.591 (1.648 - 1.591)*
R_{sym} or R_{merge}	0.2074 (2.399)
I / σI	5.59 (0.21)
Completeness (%)	98.4 (96.1)
Redundancy	8.3 (7.9)
Refinement	
Resolution (Å)	
No. reflections	70929 (2761)
R_{work} / R_{free}	*0.197 / 0.245*
No. atoms	4955
Protein	4685
Ligand/ion	129
Water	141
B-factors	33.12
Protein	33.00
Ligand/ion	36.46
Water	33.91
R.m.s deviations	
Bond lengths (Å)	0.011
Bond angles (°)	1.71

One crystal was used.

*Values in parentheses are for highest-resolution shell.

Table S2. PK profiles of compounds **3, 4** and **28**, Related to Figure 13.

Compound **3** (i.v. administration), average injection amount (50 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.22	0.03
Half-life	hr	0.584	0.05
Clearance	mL/hr/kg	231.74	29.22
Volume of distribution	mL/kg	145.22	31.13

Compound **3** (p.o. administration), average injection amount (500 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.04	0.01
Half-life	hr	4.33	0.51
Clearance	mL/hr/kg	11529.06	2037.38
Volume of distribution	mL/kg	72026.55	20504.56

Compound **3** (i.p. administration), average injection amount (500 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	6.57	0.38
Half-life	hr	2.72	0.18
Clearance	mL/hr/kg	76.10	4.35
Volume of distribution	mL/kg	298.36	19.81

Compound **4** (i.v. administration), average injection amount (50 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.22	0.00
Half-life	hr	0.54	0.02
Clearance	mL/hr/kg	230.22	3.73
Volume of distribution	mL/kg	179.91	5.36

Compound **4** (p.o. administration), average injection amount (537.5 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.53	0.07
Half-life	hr	2.85	0.24
Clearance	mL/hr/kg	1014.07	133.29
Volume of distribution	mL/kg	4165.24	878.52

Compound **4** (i.p. administration), average injection amount (525 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	29.21	1.09
Half-life	hr	3.84	0.07
Clearance	mL/hr/kg	17.97	0.67
Volume of distribution	mL/kg	99.58	2.50

Compound **28** (i.v. administration), average injection amount (50 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.22	0.01
Half-life	hr	0.82	0.04
Clearance	mL/hr/kg	227.25	10.59
Volume of distribution	mL/kg	268.04	15.08

Compound **28** (p.o. administration), average injection amount (500 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	0.12	0.02
Half-life	hr	1.57	0.17
Clearance	mL/hr/kg	4259.19	722.87
Volume of distribution	mL/kg	9649.86	2038.39

Compound **28** (i.p. administration), average injection amount (500 μg, n = 2)

	unit	estimated amount	SE
AUC to infinity	μg/mL·hr	11.89	0.72
Half-life	hr	1.56	0.05
Clearance	mL/hr/kg	42.07	2.54
Volume of distribution	mL/kg	94.81	4.74

Data S1. Experimental procedures including characterization data, Related to STAR Methods.

Table of contents

I. General methods for synthesis and characterization of compounds

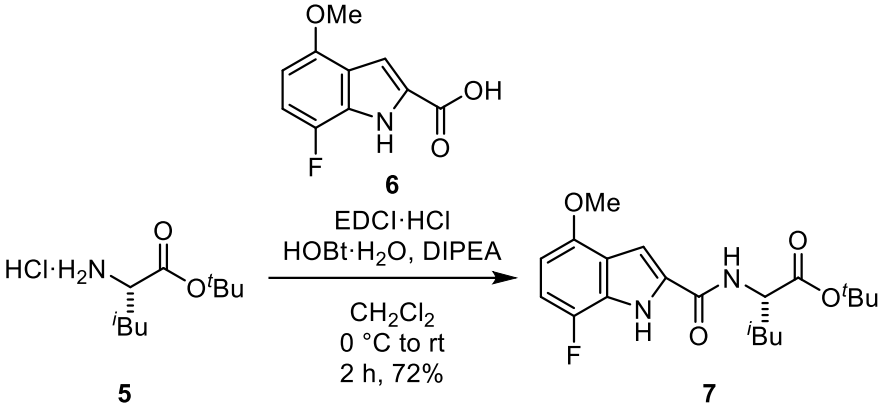
I-I. General methods for synthesis

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of nitrogen or argon (Ar), using commercially supplied solvents and reagents purchased from Sigma-Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Chemical Corporation, KANTO CHEMICAL CO.,INC., NACALAI TESQUE, INC., WATANABE CHEMICAL INDUSTRIES, LTD., KOKUSAN CHEMICAL Co.,Ltd., BLDpharm, Ambeed, Combi-Blocks, PharmaBlock Sciences (Nanjing), Inc., Enamine Ltd., 1ClickChemistry Inc., 1PlusChem, Chemspace LLC, CHEM-IMPEX INT'L INC., Matrix Scientific, and Absolute Chiral without further purification unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.) or automatic silica gel flash column chromatography system (Isolera One (Biotage, Sweden) and Pure C-815 (Buchi, Switzerland)). Preparative RP-HPLC was performed using a Cosmosil $5C_{18}$-ARII column (20 × 250 mm, Nacalai Tesque, Inc., Japan) on a JASCO PU-2086 plus, PU-2087 plus, and PU-4086-Binary (JASCO Corporation, Ltd., Japan) in a linear gradient of MeCN containing 0.1% TFA (Solvent B) in H_2O containing 0.1% (v/v) TFA (Solvent A) at a flow rate of 10 cm^3 min^{-1}, and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus and UV-4075 (JASCO Corporation, Ltd., Japan). For NP-HPLC, a CHIRALPAK IC semi-preparative column (10 x 250 mm, Daicel Corporation, Japan) were used on a JASCO PU-2086 plus in a linear gradient of isopropanol in *n*-hexane at a flow rate of 3.0 cm^3 min^{-1}, and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus.

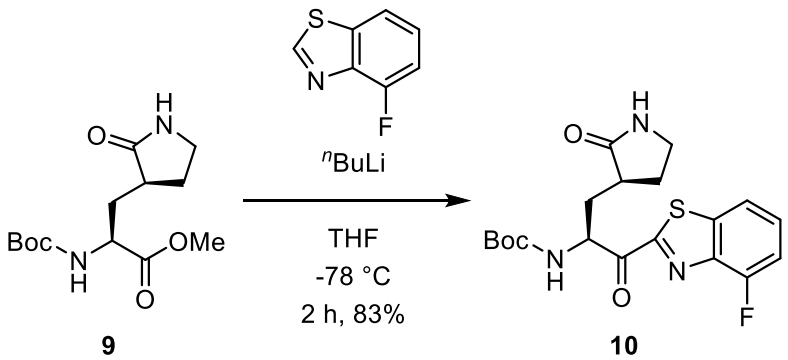
I-II. Characterization methods

^1H NMR(400 MHz or 500 MHz) and ^{13}C NMR(100 MHz or 125 MHz) spectra were recorded using a Bruker AVANCE III 400 spectrometer, Bruker AVANCE 500 spectrometer (Bruker, USA), and JNM-ECA500 (JEOL, Japan). Coupling constants are reported in Hertz, and peak shifts are reported in d (ppm) relative to $CDCl_3$ (^1H 7.26 ppm, ^{13}C 77.16 ppm), MeOD (^1H 3.31 ppm, ^{13}C 49.00 ppm), dimethyl sulfoxide (DMSO)-d_6 (^1H 2.50 ppm, ^{13}C 39.52 ppm). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF focus in the positive and negative detection mode. For analytical HPLC, a Cosmosil $5C_{18}$-ARII column (4.6 × 250 mm, Nacalai Tesque, Inc.) was employed with a linear gradient of MeCN containing 0.1% (v/v) trifluoroacetic acid (TFA) (Solvent B) in H_2O containing 0.1% (v/v) TFA (Solvent A) at a flow rate of 1.0 cm^3 min^{-1} on a PU-2089 plus (JASCO Corporation, Ltd.), and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus. For NP-HPLC, a CHIRALPAK IC analytical column (4.6 x 250 mm, Daicel Corporation) was employed with a linear gradient of isopropanol in *n*-hexane at a flow rate of 1.0 cm^3 min^{-1} on a PU-2089 plus (JASCO Corporation, Ltd.), and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus.

II. Synthetic procedures and characterization data of compounds

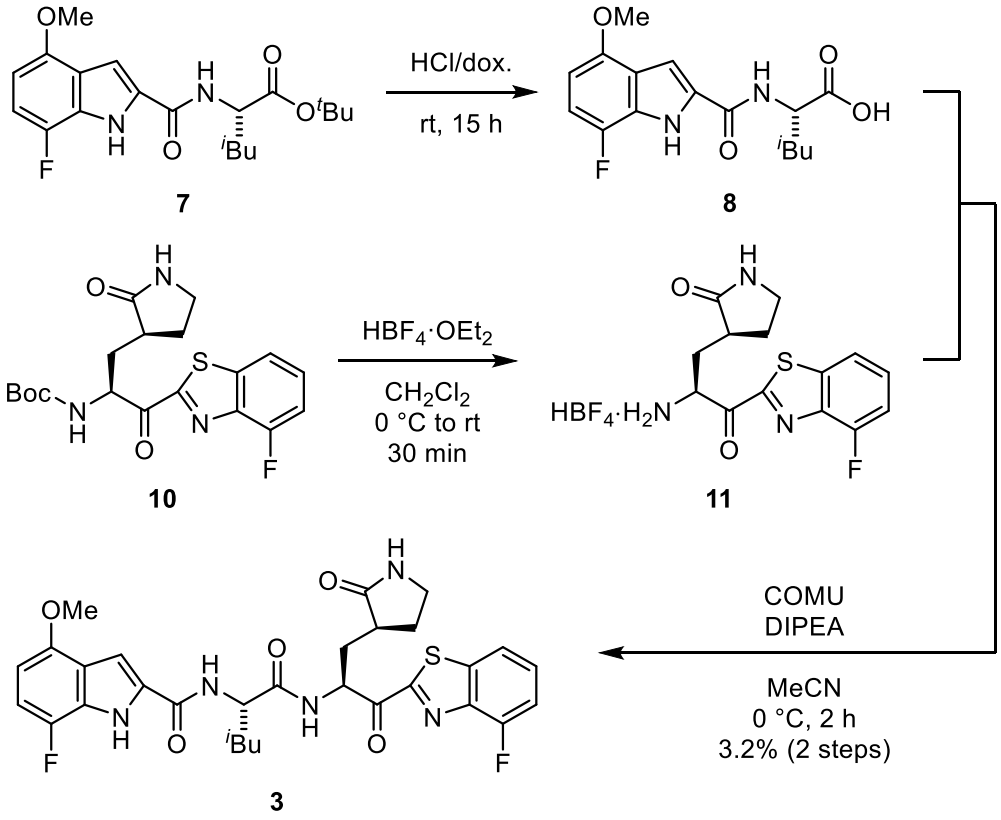


***tert*-Butyl (7-fluoro-4-methoxy-1*H*-indole-2-carbonyl)-L-leucinate (7)**: To a solution of 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (2.09 g, 10.0 mmol) in CH_2Cl_2 (100 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (2.46 g, 11.0 mmol), 1-hydroxybenzotriazole (HOBt)·H_2O (1.62 g, 12.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)·HCl (2.30 g, 12.0 mmol), and *N*,*N*-diisopropylethylamine (DIPEA, 5.90 mL, 35.0 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash chromatography over silica gel with *n*-hexane/EtOAc (5:1 to 3:1) to obtain **7** as a yellow solid (2.74 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (brs, 1H), 7.04-7.03 (m, 1H), 6.87 (dd, *J* = 10.5 Hz and 8.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.33 (dd, *J* =8.5 Hz and 2.9 Hz, 1H), 4.75-4.70 (m, 1H), 3.92 (s, 3H), 1.78-1.70 (m, 2H), 1.65-1.62 (m, 1H), 1.49 (s, 9H), 1.00-0.97 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.3, 160.7, 150.3 (d, *J* = 1.9 Hz), 144.7 (d, *J* = 238.3 Hz), 130.1, 126.1 (d, *J* = 16.3 Hz), 121.6 (d, *J* = 4.6 Hz), 109.0 (d, *J* = 17.7 Hz), 101.0, 98.9 (d, *J* = 6.2 Hz), 82.5, 55.8, 51.6, 42.3, 28.2 (3C), 25.2, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{28}FN_2O_4$ $[M+H]^+$ 379.2028, found 379.2031.



***tert*-Butyl ((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (10)**: To a solution of 4-fluorobenzo[*d*]thiazole (766 mg, 5.00 mmol) in THF (9 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 2.81 mL, 4.50 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (286 mg, 1.00 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 2 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was evaporated and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **10** as a pale yellow solid (338 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.51

(ddd, J = 8.1 Hz, 8.1 Hz, and 4.6 Hz, 1H), 7.30-7.24 (m, 1H), 5.88 (s, 1H), 5.80 (br, 1H), 5.61 (br, 1H), 3.44-3.40 (m, 2H), 2.73-2.61 (m, 2H), 2.26-2.07 (m, 3H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 193.1, 179.7, 164.3, 157.4 (d, J = 261.1 Hz), 155.9, 142.9 (d, J = 14.0 Hz), 139.8 (d, J = 2.3 Hz), 129.1 (d, J = 7.1 Hz), 118.3 (d, J = 4.5 Hz), 112.6 (d, J = 17.5 Hz), 80.2, 55.6, 40.6, 38.7, 34.7, 28.4 (3C), 28.0; HRMS (ESI), m/z calcd for $C_{19}H_{23}FN_3O_4S$ $[M+H]^+$ 408.1388, found 408.1384.

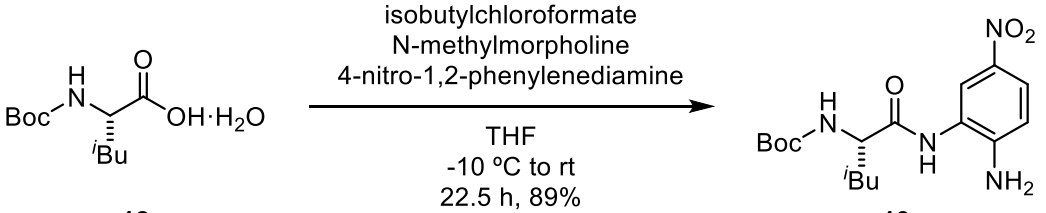


7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (3): The *tert*-butyl ester **7** (75.7 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (dox., 2.0 mL) at room temperature. The solution was stirred for 15 h at room temperature, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 **11** salt was used immediately in next step without purification.

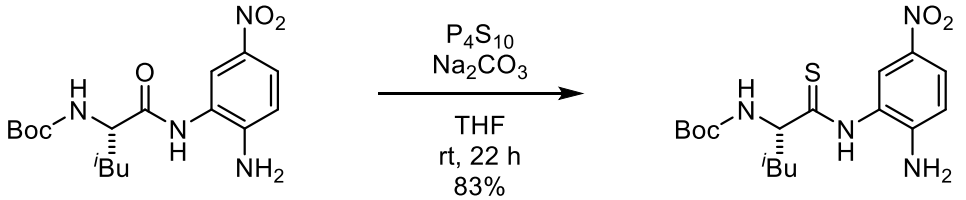
The crude amine **11** (0.200 mmol) was treated with the crude carboxylic acid **8** (0.200 mmol), 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholino)] uronium hexafluorophosphate (COMU, 85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the solution was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to afford the title compound **3**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC

semi-preparative NP-HPLC to give the title compound **3** as a yellow solid (3.93 mg, 3.2% (2 steps)): t_R = 19.9 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.72-8.71 (m, 1H), 7.73-7.72 (m, 1H), 7.50-7.46 (m, 1H), 7.23-7.19 (m, 1H), 7.12-7.07 (m, 2H), 6.83-6.79 (m, 1H), 6.56 (s, 1H), 6.28-6.25 (m, 1H), 5.73-5.71 (m, 1H), 5.01-4.97 (m, 1H), 3.87 (s, 3H), 3.38-3.37 (m, 2H), 2.69 (s, 1H), 2.52 (s, 1H), 2.29-2.23 (m, 2H), 2.11-2.04 (m, 1H), 1.85-1.66 (m, 4H), 0.98 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8, 180.1, 172.9, 164.6, 161.0, 157.3 (d, J = 260.46 Hz), 150.3 (d, J = 2.0 Hz), 144.8 (d, J = 237.7 Hz), 142.8 (d, J = 13.7 Hz), 139.8 (d, J = 2.2 Hz), 130.2, 129.0 (d, J = 6.9 Hz), 126.2 (d, J = 15.8 Hz), 121.5 (d, J = 5.7 Hz), 118.2 (d, J = 4.3 Hz), 112.5 (d, J = 17.6 Hz), 108.8 (d, J = 17.9 Hz), 102.3, 98.7 (d, J = 6.1 Hz), 55.8, 55.3, 51.7, 42.7, 40.9, 39.4, 32.9, 28.5, 25.0, 23.0, 22.3; HRMS (ESI), *m/z* calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$ 612.2087, found 612.2090.



12 **13**

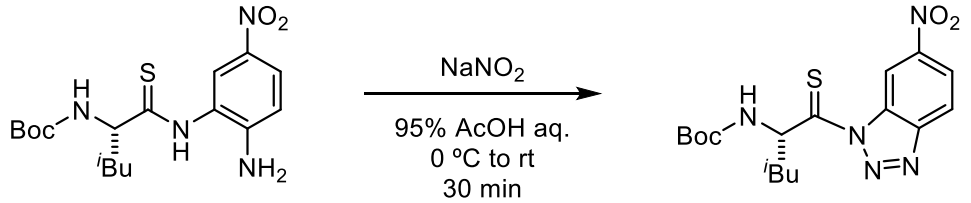
***tert*-Butyl (*S*)-(1-((2-amino-5-nitrophenyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (13)**: To a solution of *N*-Boc-L-leucine hydrate **12** (499 mg, 2.00 mmol) in THF (20 mL) were added *N*-methylmorpholine (440 μL, 4.00 mmol), isobutylchloroformate (289 μL, 2.20 mmol) at -10 °C under Ar. The reaction mixture was stirred for 20 min and was added 4-nitro-1,2-phenylenediamine (337 mg, 2.20 mmol) at the same temperature. The reaction was allowed to proceed at -10 °C for 2 h, and then stirred at room temperature for 22.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by automated silica gel flush column chromatography system (Isolera One) with $CHCl_3$/MeOH (100:0 to 47:3) to afford **13** (650 mg, 89%) as a yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.01–7.89 (m, 2H), 6.71 (d, J = 8.8 Hz, 1H), 5.04 (d, J = 5.6 Hz, 1H), 4.22-4.11 (m, 1H), 3.05 (brs, 2H), 1.87-1.70 (m, 2H), 1.68-1.55 (m, 1H), 1.46 (s, 9H), 1.01 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 157.0, 148.0, 139.0, 124.3, 123.5, 121.5, 115.2, 81.5, 54.3, 40.2, 28.5 (3C), 25.1, 23.1, 22.3; HRMS (ESI), *m/z* calcd for $C_{17}H_{27}N_4O_5$ $[M+H]^+$ 367.1976, found 367.1972.



13 **14**

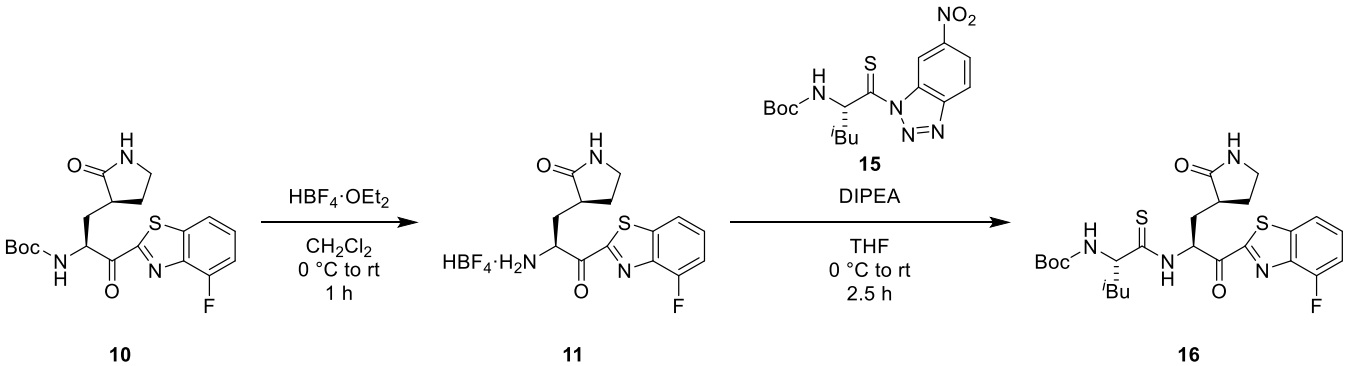
***tert*-Butyl (*S*)-(1-((2-amino-5-nitrophenyl)amino)-4-methyl-1-thioxopentan-2-yl)carbamate (14)**: To a suspension of anhydrous Na_2CO_3 (144 mg, 1.36 mmol) in THF (14 mL) were added P_4S_{10} (302 mg, 1.36 mmol) at

room temperature under Ar and the mixture was stirred for 1 h until the mixture turned into a clear pale yellow solution. To the reaction mixture was then added **13** (500 mg, 1.37 mmol) and was stirred for 22 h. After the reaction completion, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with $CHCl_3$ to afford **14** (432 mg, 83%) as a yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.10 (d, *J* = 2.6 Hz, 1H), 8.06 (dd, *J* = 9.0 and Hz 2.6 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.19 (d, *J* = 6.4 Hz, 1H), 4.52-4.43 (m, 1H), 3.49 (brs, 2H), 1.95-1.85 (m, 1H), 1.85-1.66 (m, 2H), 1.43 (s, 9H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 157.1, 148.9, 138.5, 125.8, 125.3, 122.3, 115.2, 81.6, 61.1, 43.8, 28.5 (3C), 25.2, 23.1, 22.4; HRMS (ESI), *m*/*z* calcd for $C_{17}H_{27}N_4O_4S[M+H]^+$ 383.1748, found 383.1743.



14 **15**

***tert*-Butyl (*S*)-(4-methyl-1-(6-nitro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1-thioxopentan-2-yl)carbamate (15)**: To a solution of **14** (154 mg, 0.402 mmol) in glacial acetic acid (diluted with 5% water, 4.0 mL) was dissolved at 40 ºC and then cooled to 0 ºC. The mixture was added $NaNO_2$ (42.1 mg, 0.610 mmol) portionwise with stirring. The reaction was allowed to proceed at room temperature for 30 min. Ice and water (~40 mL) were then added and the resulting precipitate was corrected by filtration and washed with ice-cooled water. The residue was dried *in vacuo* at room temperature overnight to afford **15** as an orange solid, which was used in the next step without further purification.

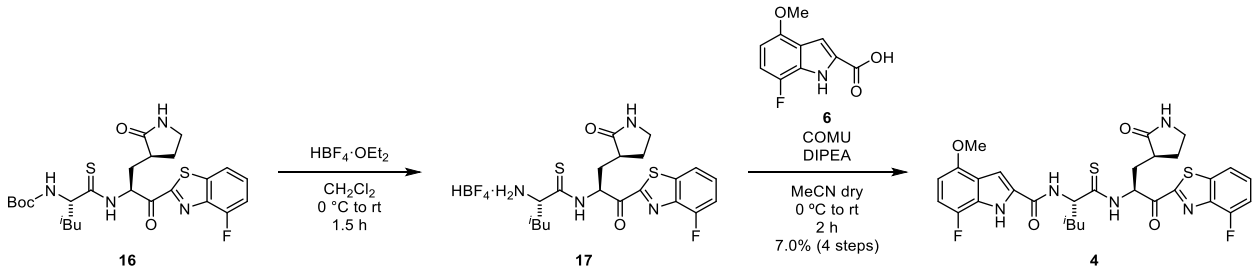


10 **11** **16**

***tert*-butyl ((*S*)-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)carbamate (16)**: To a solution of Boc protected amine **10** (81.4 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added HBF_4·OEt_2 (96.1 μL, 0.700 mmol) dropwise at 0 °C under Ar and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH. The obtained crude amine HBF_4 salt **11** was used immediately in next step without purification.

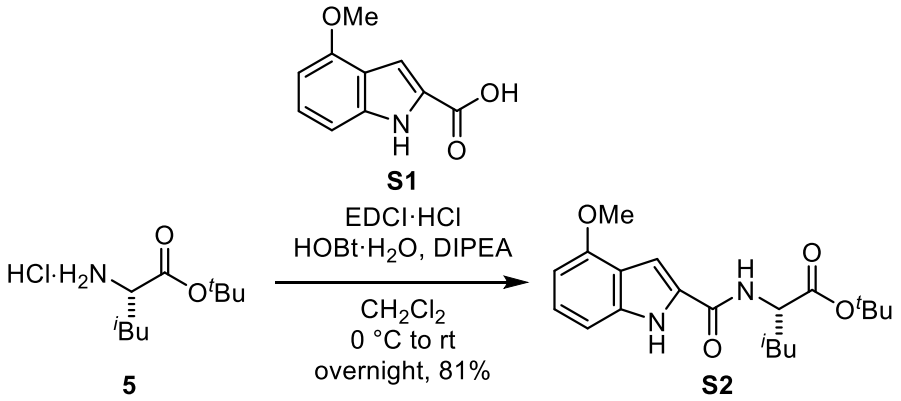
To a solution of the corresponding amine HBF_4 salt **11** (0.200 mmol) in THF (2.0 mL) was added DIPEA (34.0 μL, 0.202 mmol) at room temperature under Ar. To the solution was added triazole **15** (78.8 mg, 0.200 mmol)

dissolved in THF (2.0 mL) and DIPEA (102 μL, 0.605 mmol) at 0 °C and the mixture was stirred for 2.5 h at room temperature. After the reaction completion, the volatile was removed *in vacuo*, and the residue was roughly purified by automated silica gel flush column chromatography system (Isolera One) with $CHCl_3$/MeOH (100:0 to 47:3) to afford crude **16**.

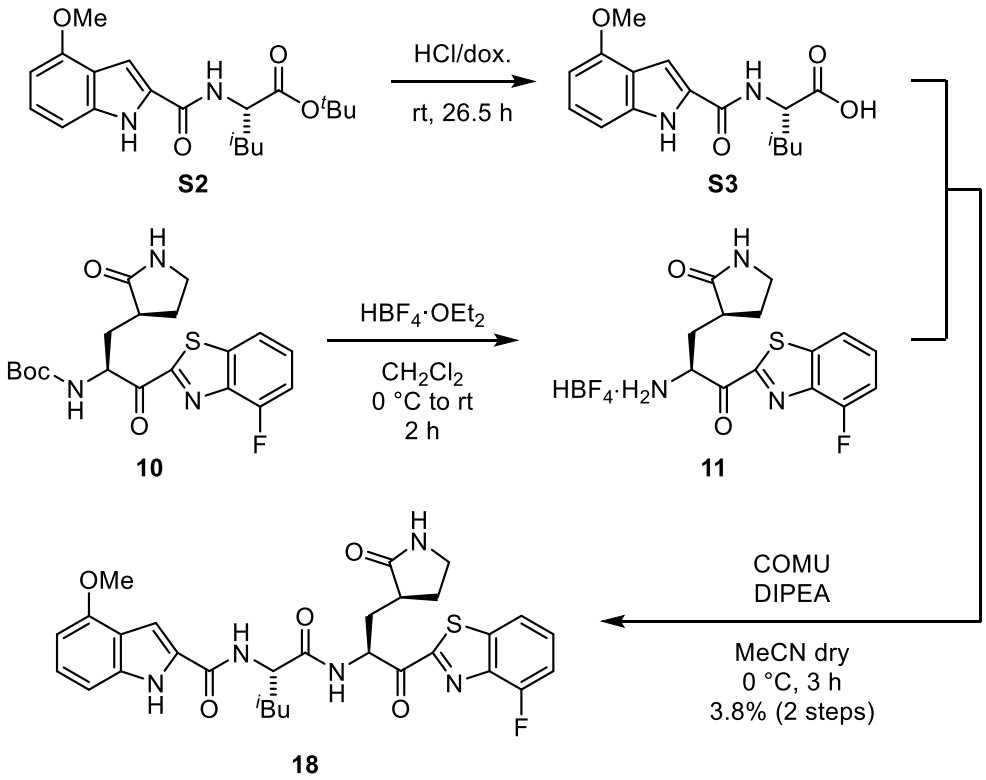


7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (4): To a solution of the crude thioamide **16** (0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 °C under Ar, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH. The crude amine HBF_4 salt **17** was used immediately in next step without purification.

To a solution of the crude amine HBF_4 salt **17** (0.200 mmol) in MeCN (2.0 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (42.1 mg, 0.201 mmol), COMU (85.8 mg, 0.200 mmol), and DIPEA (136 μL, 0.806 mmol) at 0 °C under Ar. The reaction was allowed to proceed at room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, then the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was roughly purified by automated silica gel flush column chromatography system (Isolera One) with $CHCl_3$/MeOH (100:0 to 47:3) to afford **4** as a crude product. Further purification was performed by CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **4** as a pale yellow powder (8.8 mg, 7.0% (4 steps)): t_R = 16.8 min (linear gradient of B in A, 50 to 90% over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.95 (s, 1H), 9.56 (s, 1H), 7.78-7.75 (m, 1H), 7.53-7.48 (m, 1H), 7.28-7.21 (m, 2H), 7.12-7.10 (m, 2H), 6.88-6.83 (m, 1H), 6.33-6.30 (m, 1H), 6.06 (d, *J* = 10.9 Hz, 1H), 5.50-5.45 (m, 1H), 3.90 (s, 3H), 3.49-3.40 (m, 2H), 2.71 (br, 1H), 2.59-2.50 (m, 2H), 2.29-2.24 (m, 1H), 2.19-2.11 (m, 1H), 1.83-1.73 (m, 3H), 1.03-1.01 (m, 3H), 0.98-0.97 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 206.0, 189.6, 180.0, 164.8, 160.4, 157.3 (d, *J* = 262.1 Hz), 150.3, 144.7 (d, *J* = 239.3 Hz), 142.8 (d, *J* = 13.2 Hz), 139.8, 130.2, 128.9 (d, *J* = 6.0 Hz), 126.1 (d, *J* = 16.8 Hz), 121.6 (d, *J* = 3.7 Hz), 118.3 (d, *J* = 3.7 Hz), 112.5 (d, *J* = 18.0 Hz), 109.0 (d, *J* = 18.0 Hz), 101.7, 98.8 (d, *J* = 4.8 Hz), 60.8, 56.2, 55.8, 46.9, 41.1, 39.8, 32.3, 28.4, 24.9, 23.0, 22.5; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}F_2N_5O_4S_2$ $[M+H]^+$ 628.1858, found 628.1858.



***tert*-Butyl (4-methoxy-1*H*-indole-2-carbonyl)-L-leucinate (S2)**: To a solution of 4-methoxy-1*H*-indole-2-carboxylic acid **S1** (956 mg, 5.00 mmol) in CH_2Cl_2 (50 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (1.23 g, 5.50 mmol), $HOBt·H_2O$ (811 mg, 6.00 mmol), EDCI·HCl (1.15 g, 6.00 mmol), and DIPEA (2.95 mL, 17.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for overnight. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (5:1 to 3:1) to obtain **S2** as a yellow foam (1.47 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (brs, 1H), 7.22-7.18 (m, 1H), 7.05-7.01 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 4.75-4.70 (m, 1H), 3.95 (s, 3H), 1.80-1.70 (m, 2H), 1.68-1.64 (m,1H), 1.49 (s, 9H), 1.00-0.97 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.3, 161.3, 154.3, 137.8, 129.2, 125.7, 119.0, 105.1, 100.4, 99.8, 82.3, 55.4, 51.6, 42.3, 28.2 (3C), 25.2, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{28}N_2NaO_4$ $[M+Na]^+$ 383.1941, found 383.1946.

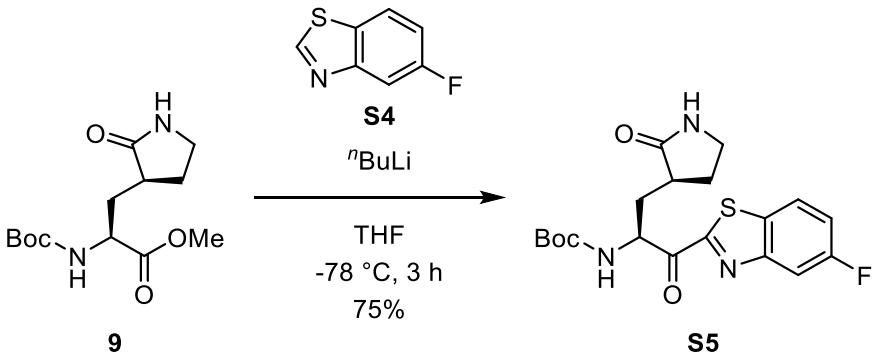


***N*-((*S*)-1-(((*S*)-1-(4-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (18)**: The *tert*-butyl ester **S2** (72.1mg, 0.200

mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred for 26.5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

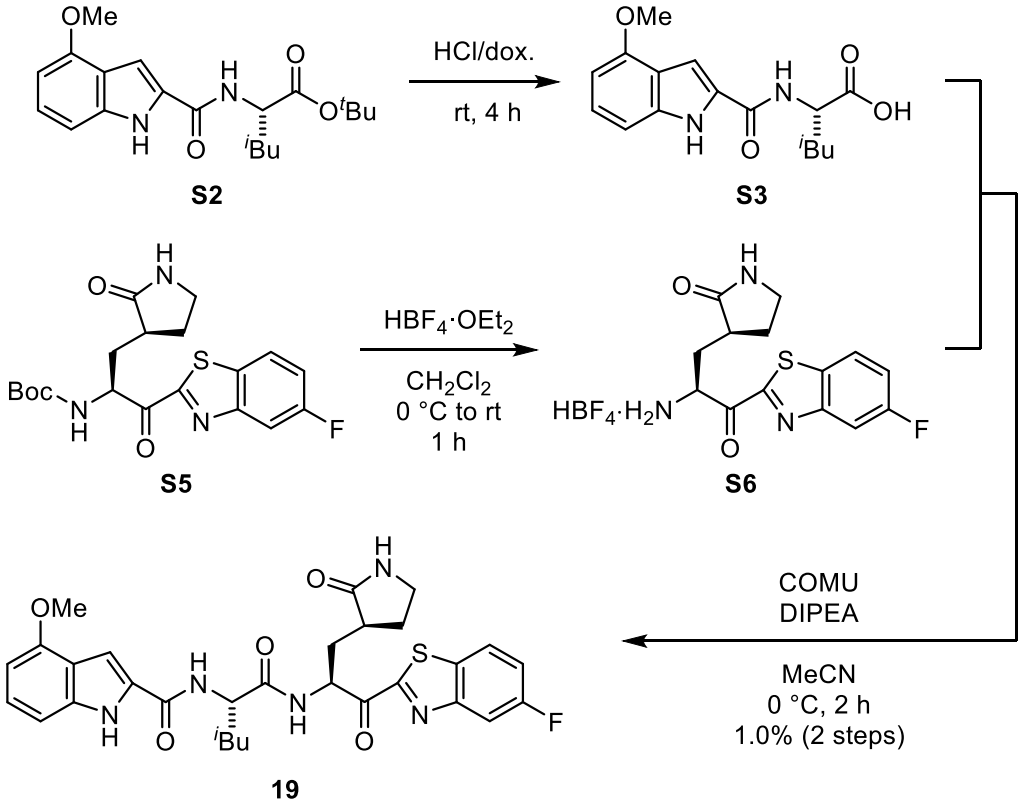
To a solution of Boc protected amine **10** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.200 mmol) was coupled to the crude carboxylic acid **S3** (0.200 mmol) using COMU (85.7 mg, 0.200 mmol) in the presence of DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the solution was allowed to stir for 3 h at 0 ºC. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **18**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **18** as a yellow solid (4.46 mg, 3.8% (2 steps)): t_R = 18.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.48 (ddd, *J* = 8.1 Hz, 8.0 Hz, and 4.6 Hz, 1H), 7.23-7.20 (m, 1H), 7.12-7.09 (m, 3H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.70 (s, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 5.75-5.71 (m, 1H), 5.00-4.95 (m, 1H), 3.90 (s, 3H), 3.31-3.22 (m, 2H), 3.30-3.22 (m, 2H), 2.67 2.61 (m, 1H), 2.46-2.41 (m, 1H), 2.28-2.22 (m, 1H), 2.19-2.14 (m, 1H), 2.06-1.98 (m, 1H), 1.84-1.75 (m, 2H), 1.71-1.66 (m, 1H), 0.96 (d, *J* = 6.1 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 180.1, 172.9, 164.6, 161.7, 157.3 (d, *J* = 260.7 Hz), 154.3, 142.8 (d, *J* = 14.1 Hz), 139.8 (d, *J* = 2.2 Hz), 138.1, 129.1, 129.0 (d, *J* = 7.1 Hz), 125.5, 119.0, 118.2 (d, *J* = 4.4 Hz), 112.5 (d, *J* = 17.5 Hz), 105.3, 101.1, 99.7, 55.4, 55.1, 51.7, 42.4, 40.8, 39.2, 32.9, 28.3, 24.9, 23.0, 22.4; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{33}FN_5O_5S$ $[M+H]^+$ 594.2181, found 594.2182.



***tert*-Butyl ((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S5)**: To a solution of 5-fluorobenzo[*d*]thiazole **S4** (322 mg, 2.10 mmol) in THF (3.2 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 1.20 mL, 1.92 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (121 mg, 0.423 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 3 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was evaporated and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was purified by flash chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **S5** as a pale yellow solid (129 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.9 Hz

and 5.0 Hz, 1H), 7.84 (dd, J = 9.0 Hz and 2.3 Hz, 1H), 7.33 (ddd, J = 8.8 Hz, 8.8 Hz, and 2.5 Hz, 1H), 5.86-5.66 (m, 2H), 5.56 (br, 1H), 3.42-3.39 (m, 2H), 2.70-2.62 (m, 2H), 2.17-2.05 (m, 3H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 193.2, 179.6, 166.3, 162.3 (d, J = 245.8 Hz), 155.9, 154.4 (d, J = 12.0 Hz), 133.0, 123.5 (d, J = 9.8 Hz), 117.4 (d, J = 25.6 Hz), 111.3 (d, J = 23.4 Hz), 80.2, 55.5, 40.6, 38.5, 34.6, 28.4 (3C), 28.2; HRMS (ESI), m/z calcd for $C_{19}H_{22}FN_3NaO_4S$ $[M+Na]^+$ 430.1207, found 430.1212.

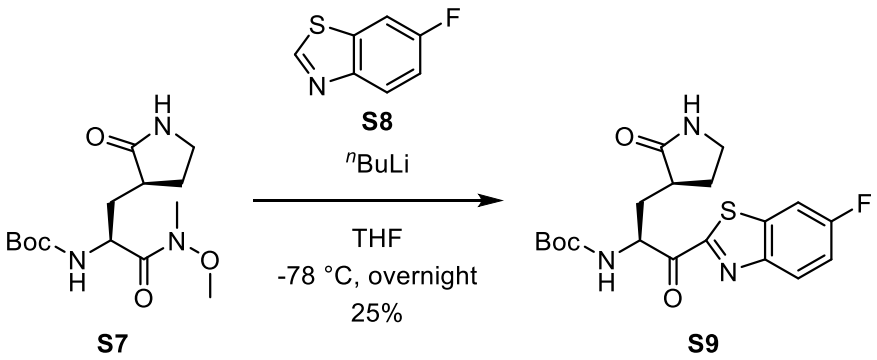


***N*-((*S*)-1-(((*S*)-1-(5-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (19)**: The *tert*-butyl ester **S2** (360 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (19 mL) at room temperature. The solution was stirred at room temperature for 4 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

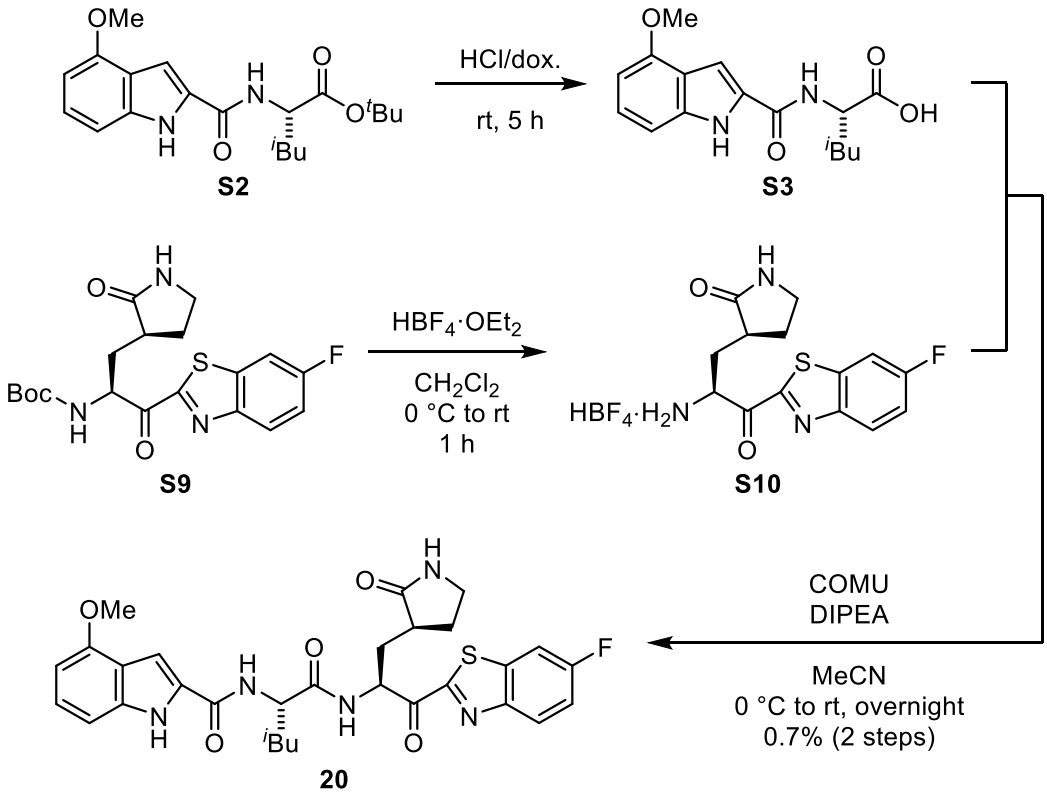
To a solution of Boc protected amine **S5** (407 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added $HBF_4{\cdot}OEt_2$ (480 μL, 3.50 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

The crude amine **S6** (1.00 mmol) was treated with the crude carboxylic acid **S3** (1.00 mmol), COMU (428 mg, 1.00 mmol), and DOPEA (337 μL, 2.00 mmol) in MeCN (10 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **19**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **19** as a yellow solid (6.19 mg, 1.0% (2 steps)): t_R = 18.6 min (linear gradient of B in A, 40 to 70% over 30 min); ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.70 (d, J = 6.1 Hz,

1H), 7.90 (dd, J = 8.9 Hz and 5.0 Hz, 1H), 7.75 (dd, J = 9.0 Hz and 2.4 Hz, 1H), 7.30 (ddd, J = 8.8 Hz, 8.8 Hz, and 2.5 Hz, 1H), 7.15-7.11 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.47-6.45 (m, 2H), 5.70-5.67 (m, 1H), 4.95-4.91 (m, 1H), 3.91 (s, 3H), 3.32-3.24 (m, 2H), 2.68-2.61 (m, 1H), 2.49-2.44 (m, 1H), 2.27-2.20 (m, 1H), 2.16-2.11 (m, 1H), 2.02-1.93 (m, 1H), 1.84-1.75 (m, 2H), 1.71-1.65 (m, 1H), 0.97 (d, J = 6.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 192.0, 180.1, 172.8, 166.5, 162.2 (d, J = 245.7 Hz), 161.6, 154.4 (d, J = 12.1 Hz), 154.3, 138.0, 132.9, 129.1, 125.6, 123.4 (d, J = 9.6 Hz), 119.0, 117.3 (d, J = 25.5 Hz), 111.2 (d, J = 23.2 Hz), 105.3, 101.1, 99.7, 55.4, 55.2, 51.7, 42.3, 40.8, 39.2, 32.9, 28.6, 25.0, 23.0, 22.4; HRMS (ESI), m/z calcd for $C_{30}H_{33}FN_5O_5S$ $[M+H]^+$ 594.2181, found 594.2185.



***tert*-Butyl ((*S*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S9)**: To a solution of 6-fluorobenzo[*d*]thiazole **S8** (766 mg, 5.00 mmol) in THF (9.0 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 2.81 mL, 4.50 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the Weinreb amide **S7** (315 mg, 1.00 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred overnight at -78 °C. The reaction mixture was added saturated aqueous NH_4Cl. The mixture was evaporated and extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by flash chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **S9** as a reddish brown solid (99.9 mg, 25%); ^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J = 9.1 Hz and 4.8 Hz, 1H), 7.65 (dd, J = 7.9 Hz and 2.4 Hz, 1H), 7.33 (ddd, J = 8.9 Hz, 8.9 Hz, and 2.4 Hz, 1H), 5.86-5.84 (m, 1H), 5.68 (brs, 1H), 5.57-5.54 (m, 1H), 3.41-3.39 (m, 2H), 2.68-2.62 (m, 2H), 2.18-2.05 (m, 3H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 193.0, 179.6, 163.8 (d, J = 2.0 Hz), 162.3 (d, J = 250.8 Hz), 155.9, 150.3, 138.7 (d, J = 11.4 Hz), 127.2 (d, J = 9.9 Hz), 116.7 (d, J = 25.4 Hz), 108.5 (d, J = 26.7 Hz), 80.2, 55.5, 40.5, 38.5, 34.6, 28.4 (3C), 28.3; HRMS (ESI), m/z calcd for $C_{19}H_{22}FN_3NaO_4S$ $[M+Na]^+$ 430.1207, found 430.1206.

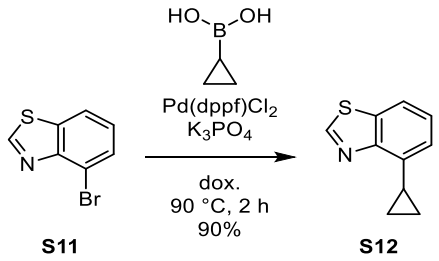


***N*-((*S*)-1-(((*S*)-1-(6-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (20)**: The *tert*-butyl ester **S2** (72.1 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (4.0 mL) at room temperature. The solution was stirred at room temperature for 5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S9** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S10** was used immediately in next step without purification.

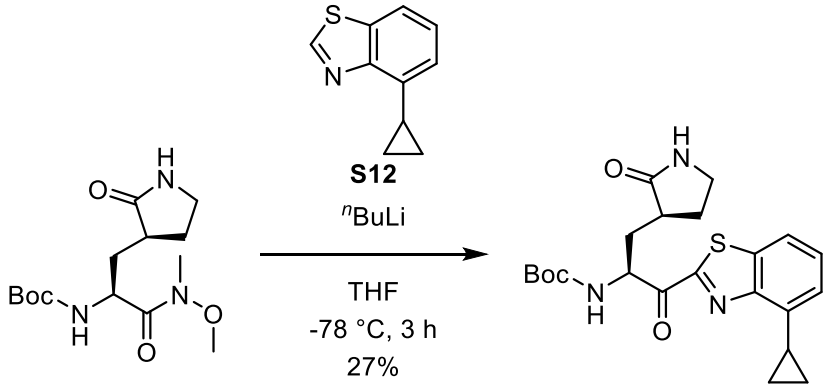
The crude amine **S10** (0.200 mmol) was treated with the crude carboxylic acid **S3** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **20**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **20** as a yellow solid (4.09 mg, 0.7% (2 steps)): t_R = 23.3 min (linear gradient of B in A, 35 to 65 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.65 (d, *J* = 5.3 Hz, 1H), 8.00 (dd, *J* = 9.0 Hz and 4.8 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz and 2.4 Hz, 1H), 7.22 (ddd, *J* = 8.9 Hz, 8.0 Hz, and 2.5 Hz, 1H), 7.16 (dd, *J* = 8.1 Hz and 8.0 Hz, 1H), 7.10 (s, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 6.18 (s, 1H), 5.67-5.64 (m, 1H), 4.89-4.84 (m, 1H), 3.93 (s, 3H), 3.32-3.30 (m, 2H), 2.64-2.63 (m, 1H), 2.49-2.47 (m, 1H), 2.26-2.19 (m, 1H), 2.15-2.11 (m, 1H), 1.99-1.93 (m, 1H), 1.87-1.74 (m, 3H), 0.968 (d, *J* = 6.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8, 180.1, 172.6, 164.1 (d, *J* = 3.8 Hz), 162.2 (d, *J* = 251.2 Hz), 161.5, 154.3, 150.2, 138.7 (d, *J* = 11.3 Hz), 137.9, 129.0, 127.1 (d, *J* = 9.8 Hz), 125.7, 119.0, 116.6 (d, *J* = 25.3 Hz), 108.5 (d, *J* = 26.6 Hz), 105.2, 101.0, 99.8, 55.5, 55.4, 51.8, 42.2, 40.7, 39.2,

33.1, 28.8, 25.0, 23.1, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{33}FN_5O_5S$ $[M+H]^+$ 594.2181, found 594.2177.



S11 **S12**

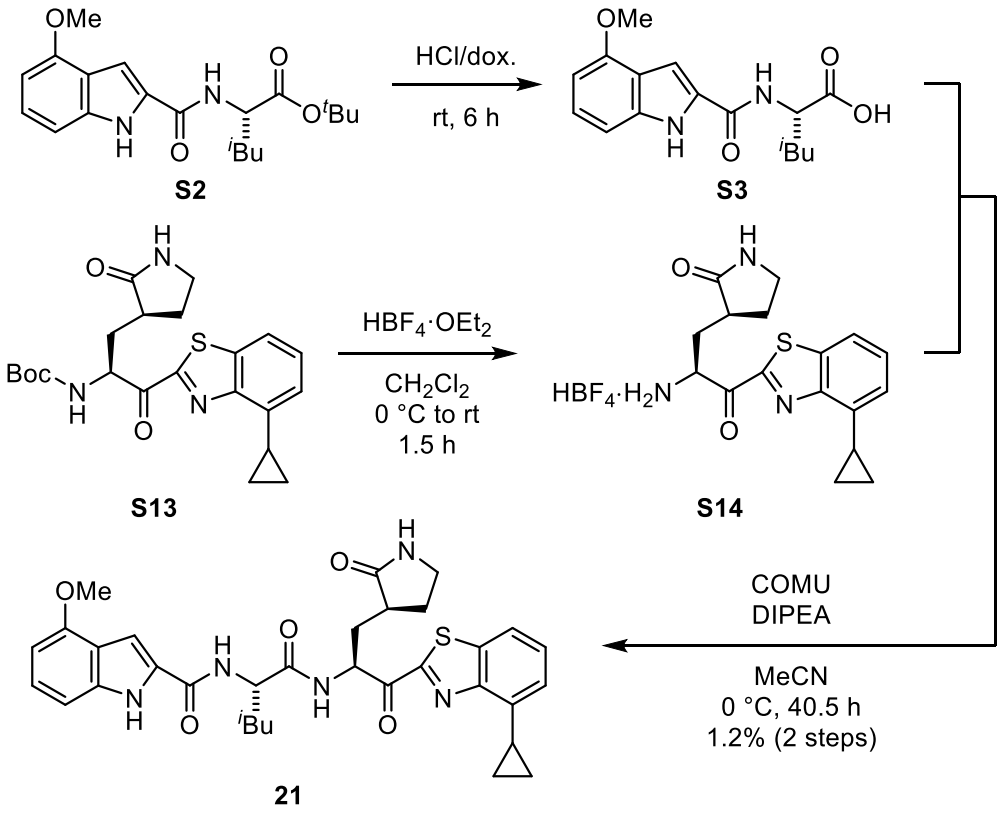
4-Cyclopropylbenzo[*d*]thiazole (S12): To a solution of 4-bromo-1,3-benzothiazole **S11** (2.14 g, 10.0 mmol) in 1,4-dioxane (100 mL) was added potassium phosphate tribasic (6.37 g, 30.0 mmol), cyclopropylboronic acid (1.72 g, 20.0 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (731 mg, 0.999 mmol) at room temperature. The reaction mixture was heated at 90 °C and was stirred at 90 °C for 2 h. The mixture was cooled to room temperature, added water, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with *n*-hexane/EtOAc (7:1) to afford the compound **S12** as a yellow oil (1.57 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.75 (dd, *J* = 8.0 Hz and 0.9 Hz, 1H), 7.34 (dd, *J* = 7.8 Hz and 7.8 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 2.88-2.81 (m, 1H), 1.17-1.13 (m, 2H), 0.95-0.91 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.9, 152.7, 139.6, 133.7, 125.8, 120.6, 118.7, 12.4, 9.4 (2C); HRMS (ESI), *m*/*z* calcd for $C_{10}H_{10}NS$ $[M+H]^+$ 176.0528, found 176.0529.



S7 **S13**

***tert*-Butyl ((*S*)-1-(4-cyclopropylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S13)**: To a solution of 4-cyclopropylbenzo[*d*]thiazole **S12** (876 mg, 5.00 mmol) in THF (9.0 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 2.81 mL, 4.50 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the Weinreb amide **S7** (315 mg, 1.00 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 3 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **S13** as a reddish brown solid (116 mg, 27%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.43 (dd, *J* = 7.8 Hz and 7.8 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 5.73-5.71 (m, 1H), 5.68-5.63 (m, 1H), 5.59 (s, 1H), 3.41-3.38 (m, 2H), 2.80-2.75 (m, 1H), 2.70-2.63 (m, 2H), 2.22-2.11 (m, 3H),

1.45 (s, 9H), 1.19-1.10 (m, 2H), 1.07-1.00 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 193.2, 179.5, 162.4, 156.0, 152.6, 142.2, 137.6, 128.4, 121.6, 119.1, 80.2, 55.4, 40.4, 38.5, 35.4, 28.5 (3C), 28.0, 12.8, 10.3, 10.2; HRMS (ESI), *m*/*z* calcd for $C_{22}H_{28}N_3O_4S$ $[M+H]^+$ 430.1795, found 430.1791.

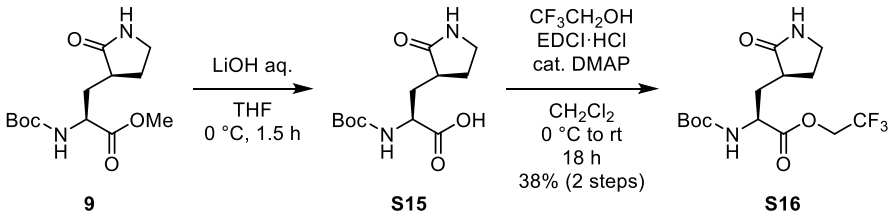


***N*-((*S*)-1-(((*S*)-1-(4-Cyclopropylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (21)**: The *tert*-butyl ester **S2** (90.1 mg, 0.250 mmol) was treated with 4 M HCl in dioxane (2.5 mL) at room temperature. The solution was stirred at room temperature for 6 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S13** (107 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (120 μL, 0.880 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S14** was used immediately in next step without purification.

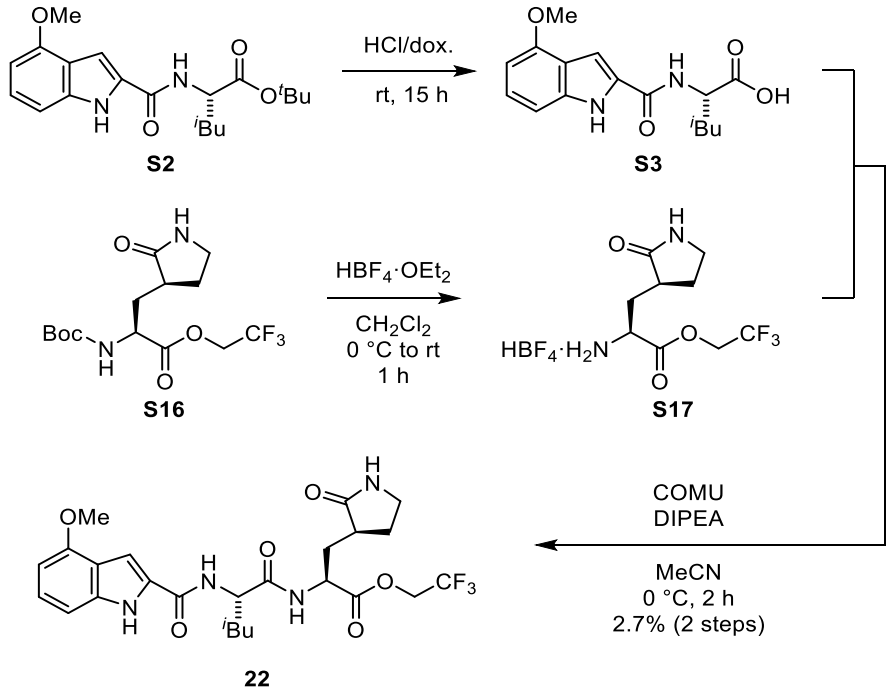
The crude amine **S14** (0.250 mmol) was treated with the crude carboxylic acid **S3** (0.250 mmol), COMU (107 mg, 0.250 mmol), and DIPEA (84.3 μL, 0.500 mmol) in MeCN (2.5 mL) at 0 °C, and the mixture was allowed to stir for 40.5 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **21**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **21** as a yellow solid (7.20 mg, 1.2% (2 steps)): t_R = 15.6 min (linear gradient of B in A, 53 to 63 % over 30 min); ^1H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.45 (d, *J* = 6.6 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 7.8 Hz and 7.8 Hz, 1H), 7.13-7.08 (m, 3H),

7.01 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.62 (s, 1H), 6.44 (d, J = 7.8 Hz, 1H), 5.83-5.79 (m, 1H), 5.02-4.98 (m, 1H), 3.91 (s, 3H) 3.18-3.17 (m, 2H), 2.78-2.73 (m, 1H), 2.65-2.58 (m, 1H), 2.45-2.44 (m, 1H), 2.29-2.23 (m, 1H), 2.18-2.14 (m, 1H), 2.05-1.97 (m, 1H), 1.84-1.75 (m, 2H), 1.70-1.66 (m, 1H), 1.14-1.05 (m, 2H), 1.01-0.95 (m, 8H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 192.3, 180.0, 172.9, 162.6, 161.7, 154.3, 152.6, 142.2, 138.1, 137.6, 129.1, 128.3, 125.6, 121.4, 119.0, 119.0, 105.3, 101.1, 99.7, 55.4, 54.9, 51.8, 42.4, 40.6, 39.0, 33.5, 28.2, 25.0, 23.0, 22.5, 12.7, 10.4, 10.2; HRMS (ESI), m/z calcd for $C_{33}H_{38}N_5O_5S$ $[M+H]^+$ 616.2588, found 616.2590.



2,2,2-Trifluoroethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (S16): Methyl ester **9** (143 mg, 0.500 mmol) in THF (5.0 mL) was treated with $LiOH·H_2O$ (2.0 M in H_2O, 0.500 mL, 1.00 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was acidified with 2.0 M HCl aq., and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain the corresponding carboxylic acid **S15**, which was used in next step without purification.

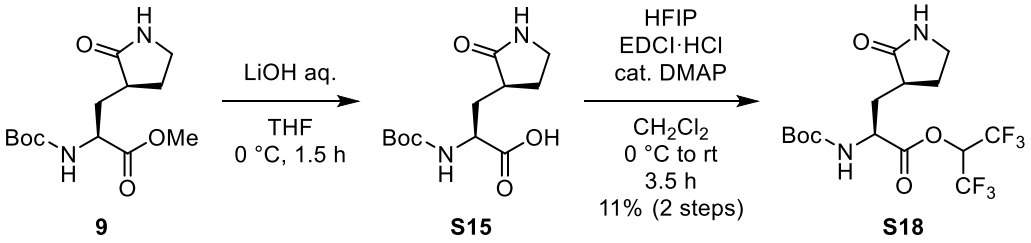
To a solution of the crude carboxylic acid **S15** (0.500 mmol) in CH_2Cl_2 (5.0 mL) were added trifluoroethanol (39.3 μL, 0.550 mmol), EDCI·HCl (105 mg, 0.550 mmol), and 4-dimethylaminopyridine (DMAP, 6.12 mg, 50.1 μmol) at 0 °C. After the mixture was stirred for 18 h at room temperature, the reaction was quenched by the addition of sat. NH_4Cl aq., and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with EtOAc/MeOH (40:1) to obtain the compound **S16** as a yellow oil (68.2 mg, 38% (2 steps)); ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H), 5.96 (d, J = 7.4 Hz, 1H), 4.60-4.53 (m, 1H), 4.45-4.37 (m, 1H), 4.35-4.32 (m, 1H), 3.37-3.30 (m, 2H), 2.53-2.47 (m, 1H), 2.44-2.39 (m, 1H), 2.15-2.09 (m, 1H), 1.87-1.79 (m, 2H), 1.41 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 179.9, 171.3, 155.9, 122.8 (q, J = 277.3 Hz), 80.2, 61.0 (q, J = 36.8 Hz), 52.6, 40.6, 38.4, 33.3, 30.4, 28.3 (3C); HRMS (ESI), m/z calcd for $C_{14}H_{21}F_3N_2NaO_5$ $[M+Na]^+$ 377.1295, found 377.1297.



2,2,2-Trifluoroethyl (*S*)-2-((*S*)-2-(4-methoxy-1*H*-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (22): The *tert*-butyl ester **S2** (108 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred for 15 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

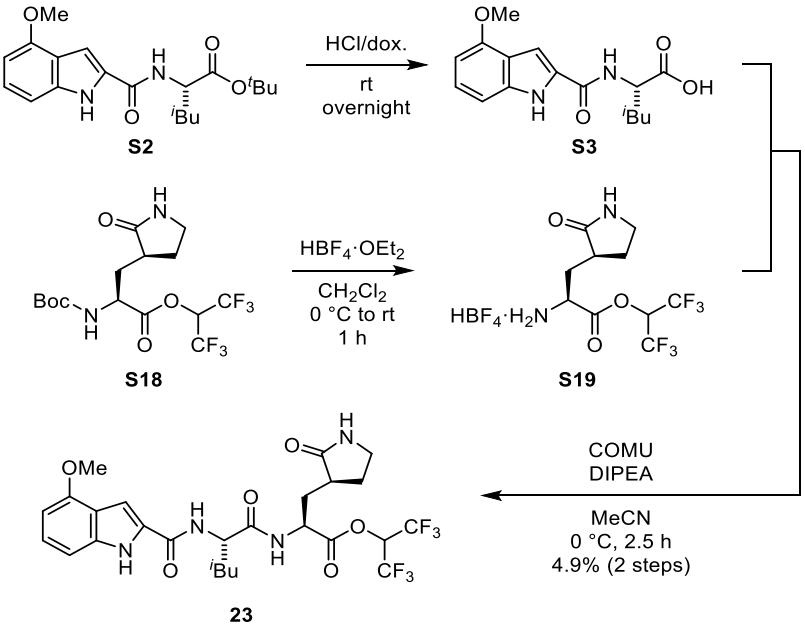
To a solution of Boc protected amine **S16** (106 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S17** was used immediately in next step without purification.

The crude amine **S17** (0.300 mmol) was coupled to the crude carboxylic acid **S3** (0.300 mmol) using COMU (129 mg, 0.300 mmol) in the presence of DIPEA (101 µL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C and the solution was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **22**. Further purification was performed by preparative RP-HPLC to give the title compound **22** as a white solid (4.37 mg, 2.7% (2 steps)): t_R = 13.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.62 (d, J = 5.9 Hz, 1H), 7.18-7.14 (m, 2H), 7.06-7.05 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.65 (s, 1H), 6.48 (d, J = 7.8 Hz, 1H), 4.89-4.85 (m, 1H), 4.61-4.39 (m, 3H), 3.91 (s, 3H), 3.27-3.16 (m, 2H), 2.51-2.45 (m, 1H), 2.32-2.27 (m, 1H), 2.25-2.18 (m, 1H), 1.93-1.88 (m, 1H), 1.80-1.75 (m, 3H), 1.73-1.65 (m, 1H), 0.98-0.97 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.2, 173.2, 170.4, 161.8, 154.3, 138.1, 128.9, 125.8, 122.9 (q, J = 277.2 Hz), 119.0, 105.2, 101.3, 99.8, 61.1 (q, J = 36.8 Hz), 55.5, 51.8 (2C), 42.1, 40.8, 38.7, 32.3, 28.4, 24.9, 22.9, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{25}H_{32}F_3N_4O_6$ $[M+H]^+$ 541.2268, found 541.2265.



1,1,1,3,3,3-Hexafluoropropan-2-yl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (S18): Methyl ester **9** (143 mg, 0.500 mmol) in THF (5.0 mL) was treated with LiOH·H_2O (2.0 M in H_2O, 0.500 mL, 1.00 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was acidified with 2.0 M HCl aq., and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain the corresponding carboxylic acid **S15**, which was used in next step without purification.

To a solution of the crude carboxylic acid **S15** (0.500 mmol) in CH_2Cl_2 (5.0 mL) were added 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 57.9 μL, 0.550 mmol), EDCI·HCl (105 mg, 0.550 mmol), and DMAP (6.12 mg, 50.1 μmol) at 0 °C. After the mixture was stirred for 3.5 h at room temperature, the reaction was quenched by the addition of sat. NH_4Cl aq., and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$/MeOH (20:1) to obtain the compound **S18** as a white solid (23.2 mg, 11% in 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.19 (d, J = 6.8 Hz, 1H), 5.76 (hept, J = 6.0 Hz, 1H), 4.43-4.39 (m, 1H), 3.40-3.33 (m, 2H), 2.57-2.51 (m, 1H), 2.48-2.43 (m, 1H), 2.17-2.10 (m, 1H), 1.91-1.83 (m, 2H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.5, 169.9, 155.8, 120.4 (q, J = 282.1 Hz, 2C), 80.5, 67.1 (hept, J = 34.9 Hz), 53.0, 40.6, 38.5, 32.8, 28.6, 28.3 (3C); HRMS (ESI), m/z calcd for $C_{15}H_{21}F_6N_2O_5$ $[M+H]^+$ 423.1349, found 423.1348.

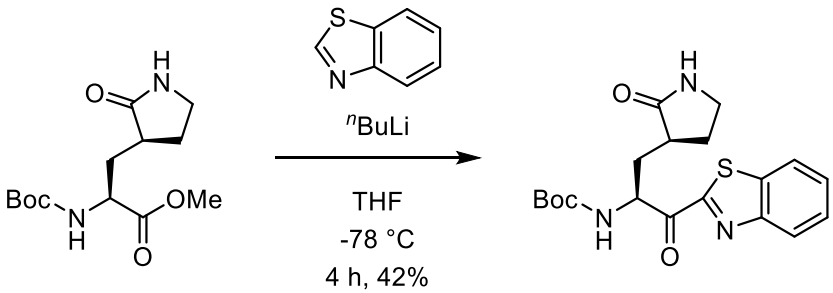


1,1,1,3,3,3-Hexafluoropropan-2-yl (*S*)-2-((*S*)-2-(4-methoxy-1*H*-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (23): The *tert*-butyl ester **S2** (44.3 mg, 0.120 mmol) was treated with 4 M HCl in dioxane (1.2 mL) at room temperature. The solution was stirred overnight at

room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

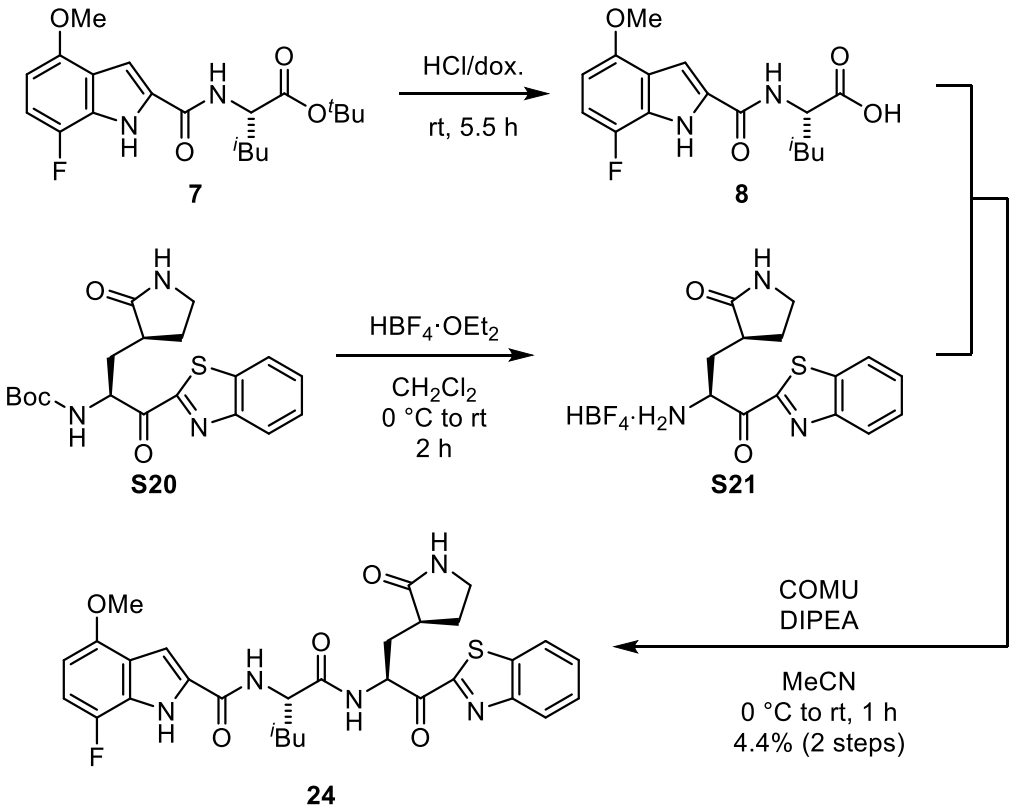
To a solution of Boc protected amine **S18** (52.0 mg, 0.120 mmol) in CH_2Cl_2 (1.2 mL) was added $HBF_4{\cdot}OEt_2$ (59.1 μL, 0.430 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S19** was used immediately in next step without purification.

The crude amine **S19** (0.120 mmol) was coupled to the crude carboxylic acid **S3** (0.12 mmol) using COMU (52.7 mg, 0.120 mmol) in the presence of DIPEA (41.5 μL, 0.250 mmol) in MeCN (1.2 mL) at 0 °C and the solution was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **23**. Further purification was performed by preparative RP-HPLC to give the title compound **23** as a white solid (3.69 mg, 4.9% (2 steps)): t_R = 19.9 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, MeOD) δ 7.28-7.27 (m, 1H), 7.16-7.12 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 6.39 (hept, J = 6.1 Hz, 1H), 4.75-4.71 (m, 1H), 4.66-4.63 (m, 1H), 3.92 (s, 3H), 3.29-3.23 (m, 2H), 2.72-2.65 (m, 1H), 2.32-2.26 (m, 2H), 1.89-1.67 (m, 5H), 1.02 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, MeOD) δ 181.5, 175.7, 170.1, 164.0, 155.7, 139.8, 130.2, 126.3, 122.1 (q, J = 280.8 Hz), 120.1, 106.1, 103.1, 100.3, 68.2 (hept, J = 34.7 Hz), 55.7, 53.3, 51.6, 41.7, 41.4, 39.4, 33.1, 28.6, 26.0, 23.3, 22.1; HRMS (ESI), m/z calcd for $C_{26}H_{31}F_6N_4O_6$ $[M+H]^+$ 609.2142, found 609.2141.



9 **S20**

***tert*-Butyl ((*S*)-1-(benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (12a)**: To a solution of benzo[*d*]thiazole (0.540 mL, 5.00 mmol) in THF (9.0 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 2.81 mL, 4.50 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (286 mg, 1.00 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 4 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was evaporated and extracted with EtOAc. The organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was purified by flash column chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **S21** as a reddish brown solid (164 mg, 42%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 7.9 Hz, 1H), 7.99-7.98 (m, 1H), 7.59-7.53 (m, 2H), 5.85-5.84 (m, 2H), 5.61-5.58 (m, 1H), 3.41-3.39 (m, 2H), 2.69-2.63 (m, 2H), 2.18-2.05 (m, 3H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.4, 179.7, 163.9, 155.9, 153.6, 137.4, 128.1, 127.2, 125.8, 122.7, 80.1, 55.5, 40.5, 38.6, 34.8, 28.4 (3C), 28.2; HRMS (ESI), m/z calcd for $C_{19}H_{24}N_3O_4S$ $[M+H]^+$ 390.1482, found 390.1484.

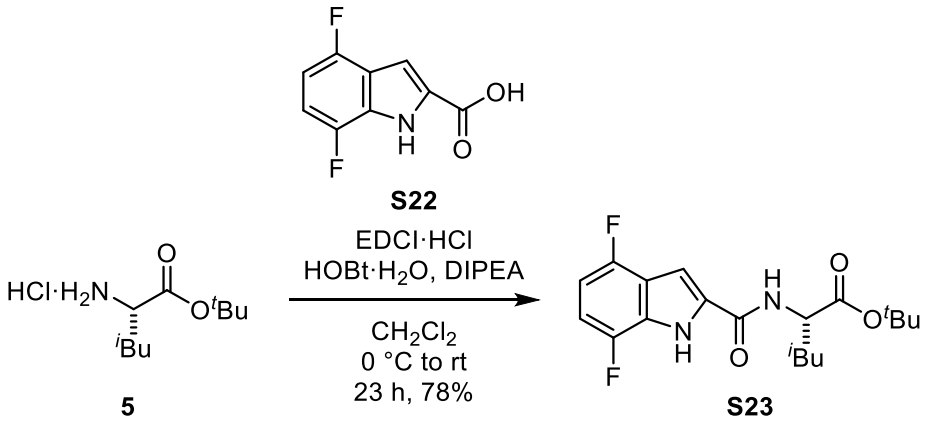


***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (24)**: The *tert*-butyl ester **7** (94.6 mg, 0.250 mmol) was treated with 4 M HCl in dioxane (2.5 mL) at room temperature. The solution was stirred at room temperature for 5.5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

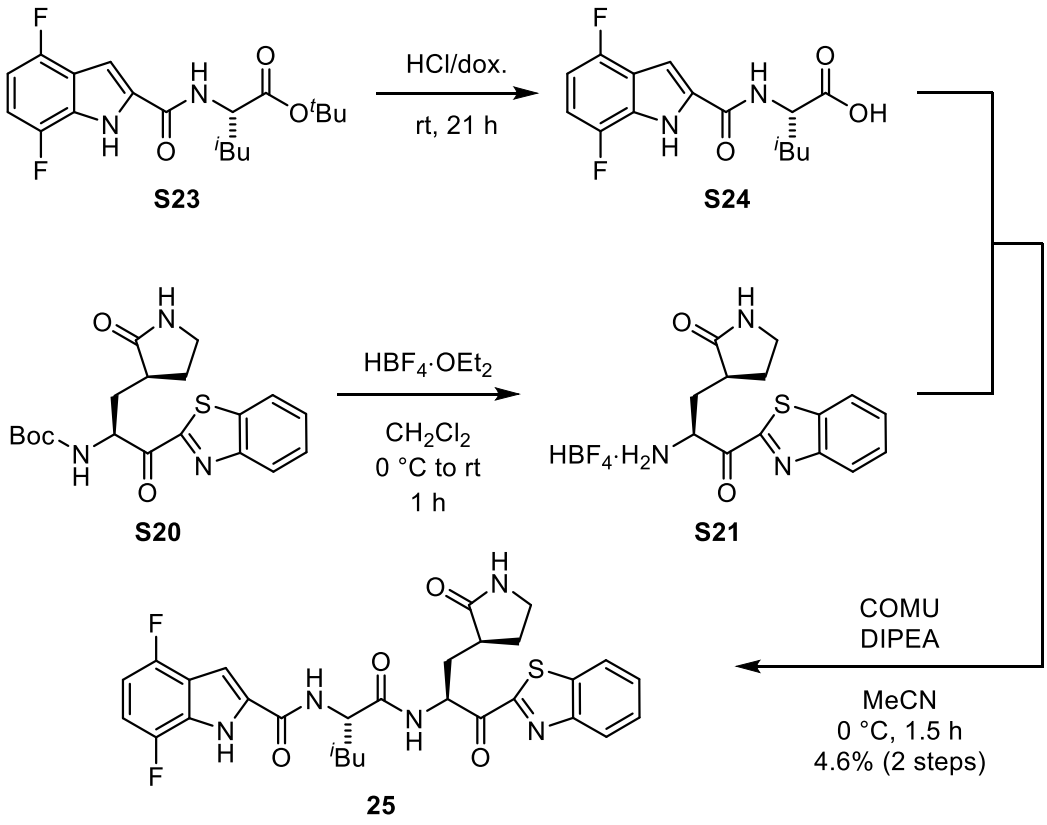
To a solution of Boc protected amine **S20** (97.4 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (120 μL, 0.880 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.250 mmol) was treated with the crude carboxylic acid **8** (0.250 mmol), COMU (107 mg, 0.250 mmol), and DIPEA (84.3 μL, 0.500 mmol) in MeCN (2.5 mL) at 0 °C, and the mixture was allowed to stir for 1 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **24**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **24** as a pale yellow solid (6.54 mg, 4.4% (2 steps)): t_R = 19.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.66 (d, *J* = 6.3 Hz, 1H), 8.06-8.04 (m, 1H), 7.96-7.94 (m, 1H), 7.52-7.48 (m, 2H), 7.23 (s, 1H), 7.09-7.08 (m, 1H), 6.82-6.79 (m, 1H), 6.63 (brs, 1H), 6.28-6.26 (m, 1H), 5.74-5.70 (m, 1H), 4.99-4.95 (m, 1H), 3.87 (s, 3H), 3.35-3.34 (m, 2H), 2.71-2.65 (m, 1H), 2.52-2.51 (m, 1H), 2.30-2.24 (m, 1H), 2.19-2.14 (m, 1H), 2.06-1.98 (m, 1H), 1.85-1.74 (m, 2H), 1.70-1.64 (m, 1H), 0.97-0.94 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.1, 180.2, 172.9, 164.1,

161.0, 153.5, 150.3 (d, J = 2.0 Hz), 144.8 (d, J = 237.9 Hz), 137.3, 130.2, 128.0, 127.1, 126.2 (d, J = 15.9 Hz), 125.7, 122.5, 121.5 (d, J = 4.7 Hz), 108.8 (d, J = 17.9 Hz), 102.3, 98.7 (d, J = 6.1 Hz), 55.8, 55.3, 51.8, 42.5, 40.9, 39.3, 33.1, 28.5, 25.0, 23.0, 22.3; HRMS (ESI), m/z calcd for $C_{30}H_{33}FN_5O_5S$ $[M+H]^+$ 594.2181, found 594.2176.



***tert*-Butyl (4,7-difluoro-1*H*-indole-2-carbonyl)-L-leucinate (S23)**: To a solution of 4,7-difluoro-1*H*-indole-2-carboxylic acid **S22** (591 mg, 3.00 mmol) in CH_2Cl_2 (30 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (738 mg, 3.30 mmol), HOBt·H_2O (486 mg, 3.60 mmol), EDCI·HCl (690 mg, 3.60 mmol), and DIPEA (1.77 mL, 10.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 23 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (10:1 to 5:1) to obtain **S23** as a white solid (860 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (brs, 1H), 6.98-6.97 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.86 (ddd, J = 10.1 Hz, 8.5 Hz, and 3.5 Hz, 1H), 6.69-6.64 (m, 1H), 4.79-4.74 (m, 1H), 1.82-1.71 (m, 2H), 1.70-1.64 (m, 1H), 1.51 (s, 9H), 1.00-0.98 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.7, 160.4, 152.8 (dd, J = 245.0 Hz and 2.6 Hz), 146.0 (dd, J =241.8 Hz and 3.4 Hz), 131.4, 126.6 (dd, J = 16.4 Hz and 10.5 Hz), 119.9 (dd, J = 24.8 Hz and 5.3 Hz), 108.8 (dd, J = 19.0 Hz and 8.3 Hz), 104.5 (dd, J = 21.9 Hz and 6.5 Hz), 99.6, 82.7, 51.7, 42.0, 28.2 (3C), 25.2, 23.0, 22.2; HRMS (ESI), m/z calcd for $C_{19}H_{25}F_2N_2O_3$ $[M+H]^+$ 367.1828, found 367.1831.

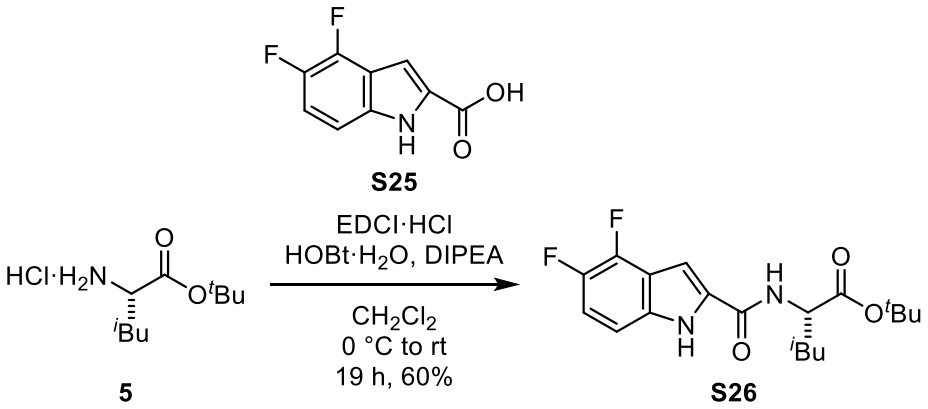


***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (25)**: The *tert*-butyl ester **S23** (75.0 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 21 h, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

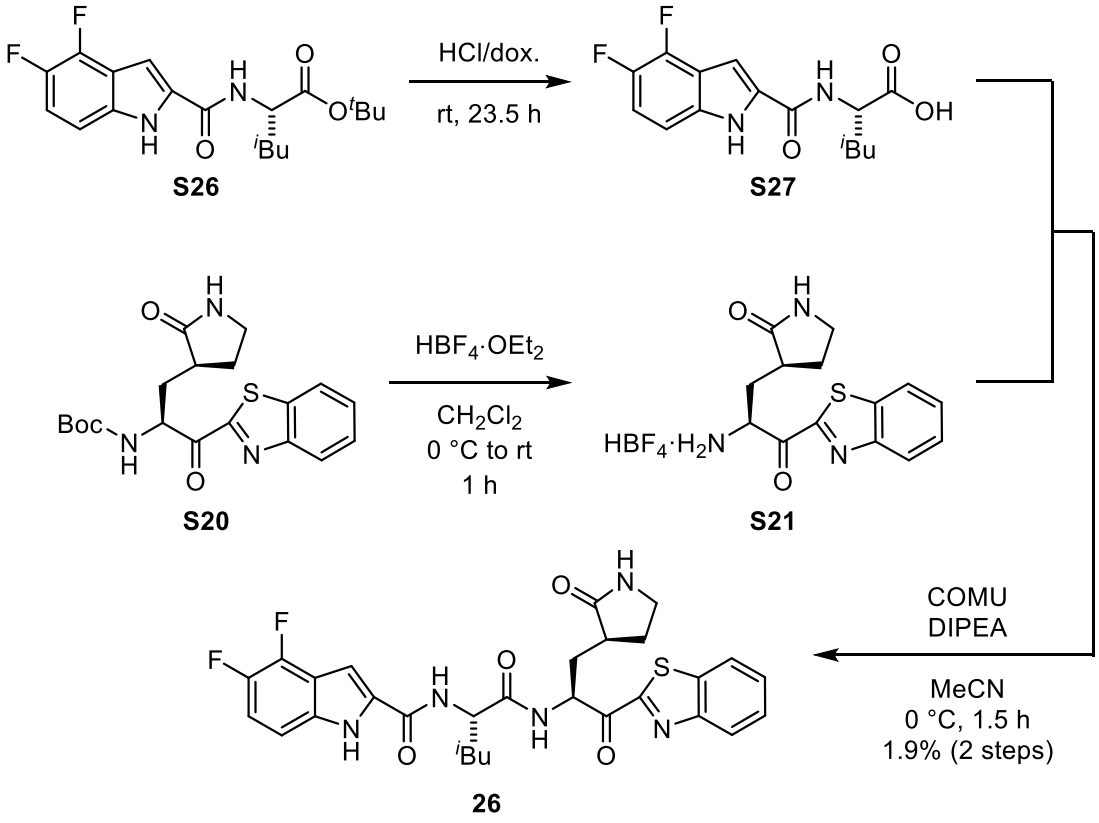
To a solution of Boc protected amine **S20** (77.8 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.200 mmol) was treated with the crude carboxylic acid **S24** (0.200 mmol), COMU (94.2 mg, 0.220 mmol), and DIPEA (68.0 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **25**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **25** as a yellow solid (5.37 mg, 4.6% (2 steps)): t_R = 20.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.85 (s, 1H), 8.03-8.01 (m, 1H), 7.96-7.95 (m, 1H), 7.52-7.48 (m, 2H), 7.41 (br, 1H), 7.00 (s, 1H), 6.83-6.80 (m, 1H), 6.63-6.60 (m, 1H), 6.41 (brs, 1H), 5.74 (br, 1H), 4.95 (br, 1H), 3.41 (br, 2H), 2.74 (br, 1H), 2.57 (br, 1H), 2.22 (br, 2H), 2.03 (br, 1H), 1.82-1.69 (m, 3H), 0.97 (d, J = 5.9 Hz, 3H), 0.95 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 180.4, 173.1, 164.1, 160.6, 153.5, 152.8 (dd, J = 245.0 Hz and 1.4 Hz), 146.0 (dd, J = 241.5 Hz and 2.8 Hz), 137.4, 131.6, 128.0, 127.1, 126.7 (dd, J = 16.5 Hz and 10.9 Hz), 125.7, 122.5, 119.8 (dd, J = 24.9 Hz and 4.5 Hz), 108.6 (dd, J = 18.7 Hz and 7.9 Hz), 104.3 (dd, J = 21.4 Hz and 5.9 Hz), 100.9, 55.6, 51.9, 42.4, 41.0, 39.7, 32.8,

29.0, 25.0, 23.1, 22.2; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{30}F_2N_5O_4S$ $[M+H]^+$ 582.1981, found 582.1983.



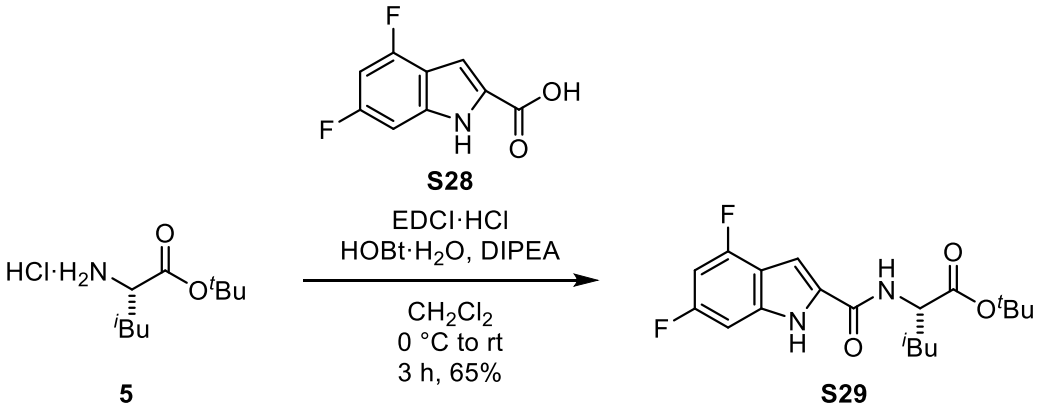
***tert*-Butyl (4,5-difluoro-1*H*-indole-2-carbonyl)-L-leucinate (S26)**: To a solution of 4,5-difluoro-1*H*-indole-2-carboxylic acid **S25** (591 mg, 3.00 mmol) in CH_2Cl_2 (30 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (738 mg, 3.30 mmol), HOBt·H_2O (486 mg, 3.60 mmol), EDCI·HCl (690 mg, 3.60 mmol), and DIPEA (1.77 mL, 10.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 19 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (10:1 to 5:1) to obtain **S26** as a white foam (656 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (brs, 1H), 7.11-7.09 (m, 2H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.76-4.71 (m, 1H), 1.82-1.72 (m, 2H), 1.71-1.64 (m, 1H), 1.51 (s, 9H), 1.00 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.4, 160.7, 144.4 (dd, *J* = 236.4 Hz and 10.9 Hz), 143.4 (dd, *J* = 250.5 Hz and 14.2 Hz), 134.2 (d, *J* = 8.5 Hz), 132.0, 118.5 (dd, *J* = 18.3 Hz and 1.8 Hz), 114.8 (d, *J* = 22.1 Hz), 107.7 (dd, *J* = 7.4 Hz and 4.6 Hz), 99.0 (d, *J* = 6.0 Hz), 82.7, 51.8, 42.0, 28.2 (3C), 25.2, 23.0, 22.2; HRMS (ESI), *m*/*z* calcd for $C_{19}H_{25}F_2N_2O_3$ $[M+H]^+$ 367.1828, found 367.1825.



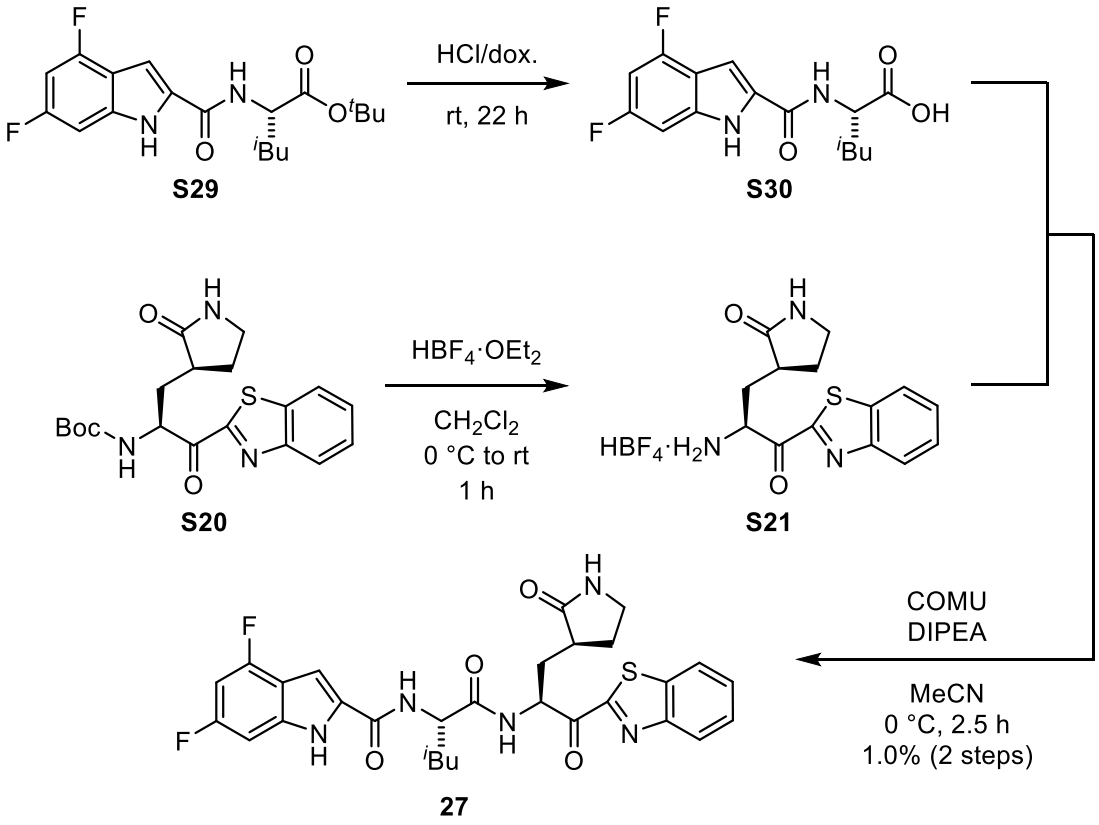
***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,5-difluoro-1*H*-indole-2-carboxamide (26)**: The *tert*-butyl ester **S26** (73.1 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 23.5 h, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S27**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S20** (77.8 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.200 mmol) was treated with the crude carboxylic acid **S27** (0.200 mmol), COMU (94.2 mg, 0.220 mmol), and DIPEA (68.0 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **26**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **26** as a yellow solid (2.18 mg, 1.9% (2 steps)): t_R = 21.5 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.82 (brs, 1H), 8.08-8.06 (m, 1H), 7.97-7.95 (m, 1H), 7.53-7.51 (m, 2H), 7.39 (br, 1H), 7.05-6.97 (m, 3H), 6.44 (s, 1H), 5.75 (br, 1H), 4.91 (br, 1H), 3.35 (br, 2H), 2.70 (br, 1H), 2.53-2.52 (m, 1H), 2.20 (br, 2H), 2.01 (br, 1H), 1.84-1.70 (m, 3H), 0.96 (br, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.2, 180.5, 172.9, 164.0, 161.1, 153.5, 144.3 (dd, J =235.8 Hz and 10.6 Hz), 143.3 (dd, J =250.3 Hz and 13.8 Hz), 137.4, 134.4 (d, J = 8.7 Hz), 132.1, 128.1, 127.2, 125.7, 122.5, 118.4 (d, J = 18.1 Hz), 114.6 (d, J = 22.0 Hz), 107.9-107.8 (m), 99.8-99.7 (m), 55.5, 52.0, 42.2, 40.9, 39.5, 32.9, 28.8, 25.0, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{30}F_2N_5O_4S$ $[M+H]^+$ 582.1981, found 582.1986.



***tert*-Butyl (4,6-difluoro-1*H*-indole-2-carbonyl)-L-leucinate (S29)**: To a solution of 4,6-difluoro-1*H*-indole-2-carboxylic acid **S28** (1.97 g, 10.0 mmol) in CH_2Cl_2 (100 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (2.46 g, 11.0 mmol), HOBt·H_2O (1.62 g, 12.0 mmol), EDCI·HCl (2.30 g, 12.0 mmol), and DIPEA (5.90 mL, 35.0 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (5:1) to obtain **S29** as a pale yellow solid (2.39 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61-10.59 (m, 1H), 7.45-7.37 (m, 1H), 6.96 (d, J = 1.9 Hz, 1H), 6.92 (dd, J = 9.1 Hz and 1.7 Hz, 1H), 6.56-6.52 (m, 1H), 4.81-4.77 (m, 1H), 1.86-1.79 (m, 1H), 1.77-1.71 (m, 2H), 1.56 (s, 9H), 1.01 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.4, 161.3, 160.7 (dd, J = 241.4 Hz and 11.6 Hz), 156.6 (dd, J = 251.8 Hz and 15.1 Hz), 138.1 (dd, J = 15.2 Hz and 12.4 Hz), 130.8 (d, J = 3.3 Hz), 113.9 (d, J = 22.0 Hz), 99.3, 96.0 (dd, J =29.9 Hz and 23.0 Hz), 94.5 (dd, J = 26.2 Hz and 4.5 Hz), 82.9, 51.9, 41.6, 28.2 (3C), 25.2, 22.9, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{19}H_{25}F_2N_2O_3$ $[M+H]^+$ 367.1828, found 367.1823.

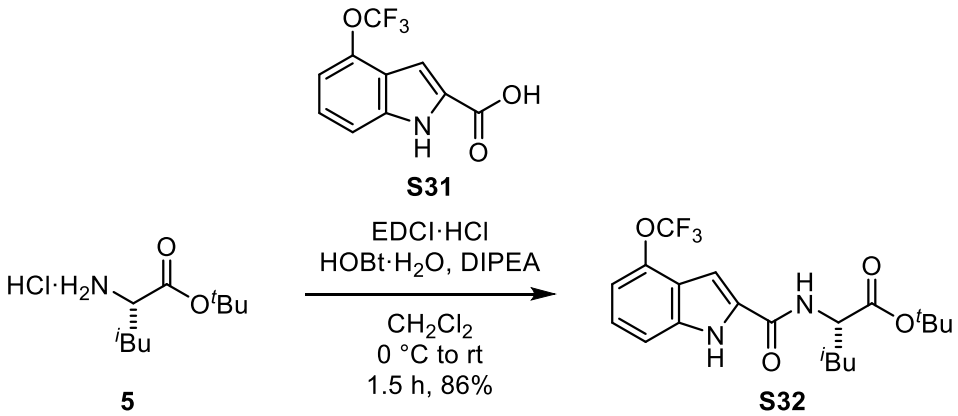


***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,6-difluoro-1*H*-indole-2-carboxamide (27)**: The *tert*-butyl ester **S29** (183 mg, 0.500 mmol) was treated with 4 M HCl in dioxane (5.0 mL) at room temperature. The solution was stirred at room temperature for 22 h, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S30**, which was used immediately in next step without purification.

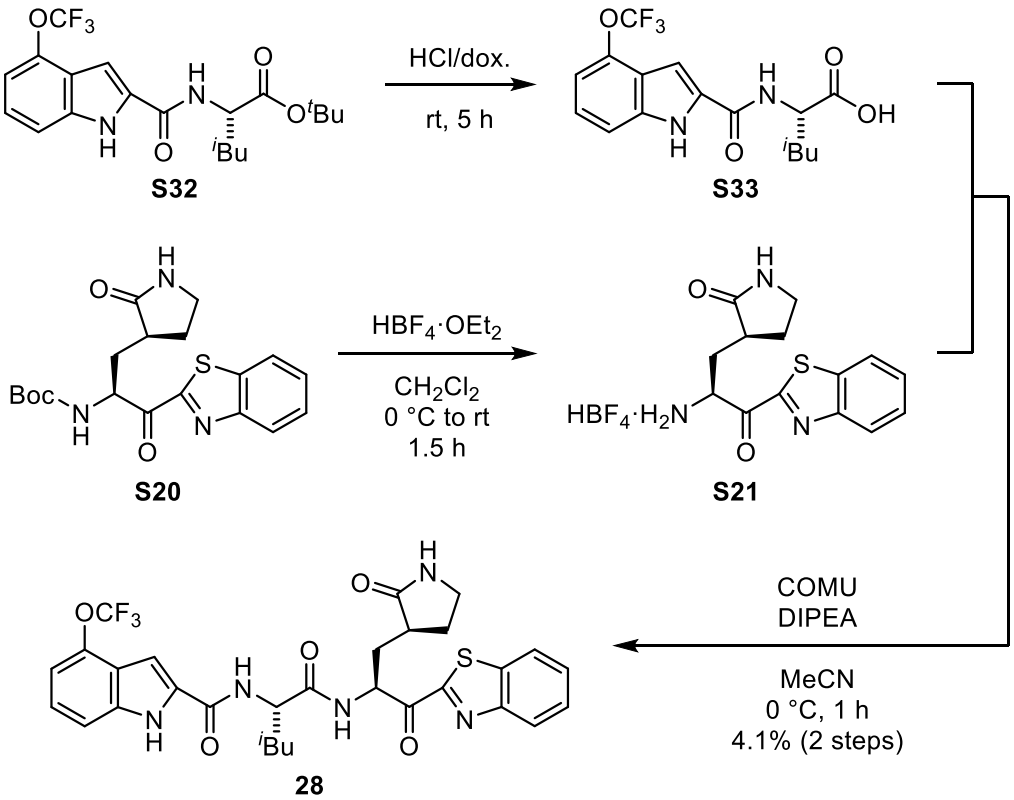
To a solution of Boc protected amine **S20** (195 mg, 0.500 mmol) in CH_2Cl_2 (5.0 mL) was added $HBF_4{\cdot}OEt_2$ (240 μL, 1.75 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.500 mmol) was treated with the crude carboxylic acid **S30** (0.500 mmol), COMU (278 mg, 0.650 mmol), and DIPEA (170 μL, 1.00 mmol) in MeCN (5.0 mL) at 0 °C, and the mixture was allowed to stir for 2.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **27**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **27** as a yellow solid (2.83 mg, 1.0% (2 steps)): t_R = 21.5 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.88-8.87 (m, 1H), 8.08-8.05 (m, 1H), 7.96-7.94 (m,1H), 7.53-7.47 (m, 3H), 7.01-7.01 (m, 1H), 6.82-6.80 (m, 2H), 6.55-6.51 (m, 1H), 5.78-5.74 (m, 1H), 4.98-4.94 (m, 1H), 3.32-3.30 (m, 2H), 2.71-2.65 (m, 1H), 2.51-2.45 (m, 1H), 2.26-2.16 (m, 2H), 2.02-1.94 (m, 1H), 1.84-1.67 (m, 3H), 0.96 (d, J = 5.6 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.2, 180.4, 172.9, 164.0, 161.2, 160.7 (dd, J = 241.9 Hz and 12.0 Hz), 156.6 (dd, J = 251.6 Hz and 15.2 Hz), 153.5, 137.9 (dd, J = 15.2 Hz and 13.0 Hz), 137.4, 131.0 (d, J = 2.7 Hz), 128.1, 127.2, 125.7, 122.5, 113.9 (d, J = 22.9 Hz), 99.8, 96.1 (dd, J = 30.0 Hz and 23.3 Hz), 94.4 (dd, J = 25.6 Hz and 4.6 Hz), 55.4, 51.9, 42.3, 40.9, 39.4, 32.9, 28.7, 25.0, 22.9,

22.3; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{30}F_2N_5O_4S$ $[M+H]^+$ 582.1981, found 582.1981.



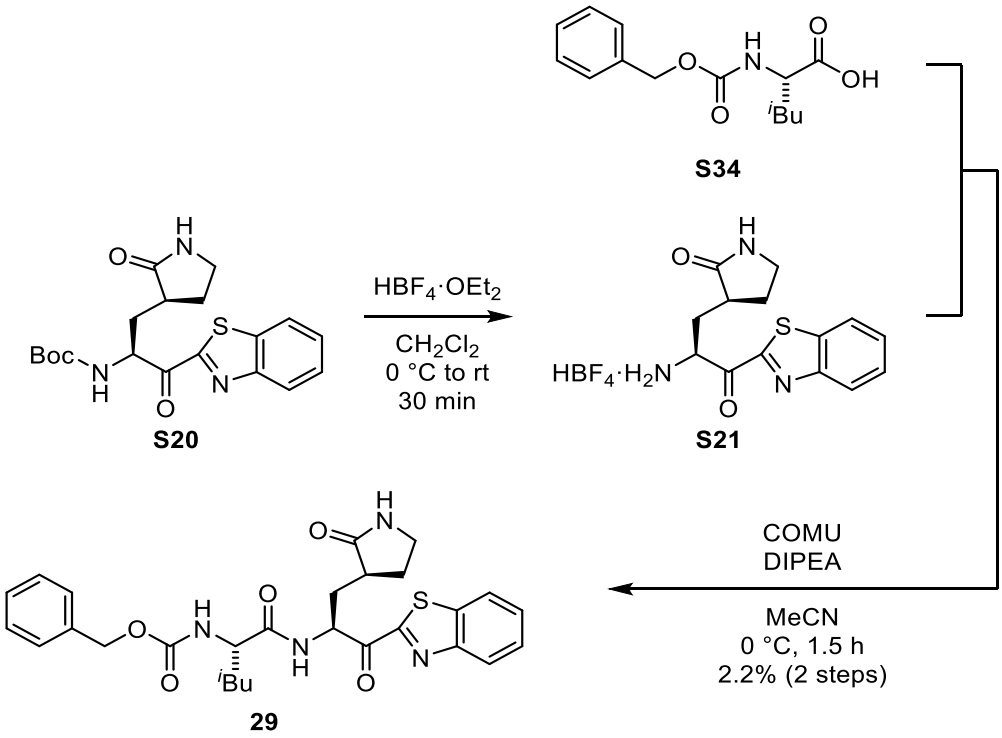
***tert*-Butyl (4-(trifluoromethoxy)-1*H*-indole-2-carbonyl)-L-leucinate (S32)**: To a solution of 4-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid **S31** (2.45 g, 10.0 mmol) in CH_2Cl_2 (100 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (2.46 g, 11.0 mmol), HOBt·H_2O (1.62 g, 12.0 mmol), EDCI·HCl (2.30 g, 12.0 mmol), and DIPEA (5.90 mL, 35.0 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (5:1 to 3:1) to obtain **S32** as a white solid (3.55 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (brs, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.25-7.22 (m, 1H), 7.01-7.00 (m, 2H), 6.85-6.84 (m, 1H), 4.77-4.73 (m, 1H), 1.81-1.72 (m, 2H), 1.71-1.66 (m,1H), 1.51 (s, 9H), 1.00 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.5, 160.9, 143.0, 138.1, 131.2, 124.7, 121.6, 121.0 (q, *J* = 257.6 Hz), 111.8, 111.0, 99.4, 82.6, 51.8, 42.1, 28.2 (3C), 25.2, 23.0, 22.2; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{26}F_3N_2O_4$ $[M+H]^+$ 415.1839, found 415.1837.



***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-(trifluoromethoxy)-1*H*-indole-2-carboxamide (28)**: The *tert*-butyl ester **S32** (87.0 mg, 0.210 mmol) was treated with 4 M HCl in dioxane (2.1 mL) at room temperature and the solution was stirred at room temperature for 5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S33**, which was used immediately in next step without purification

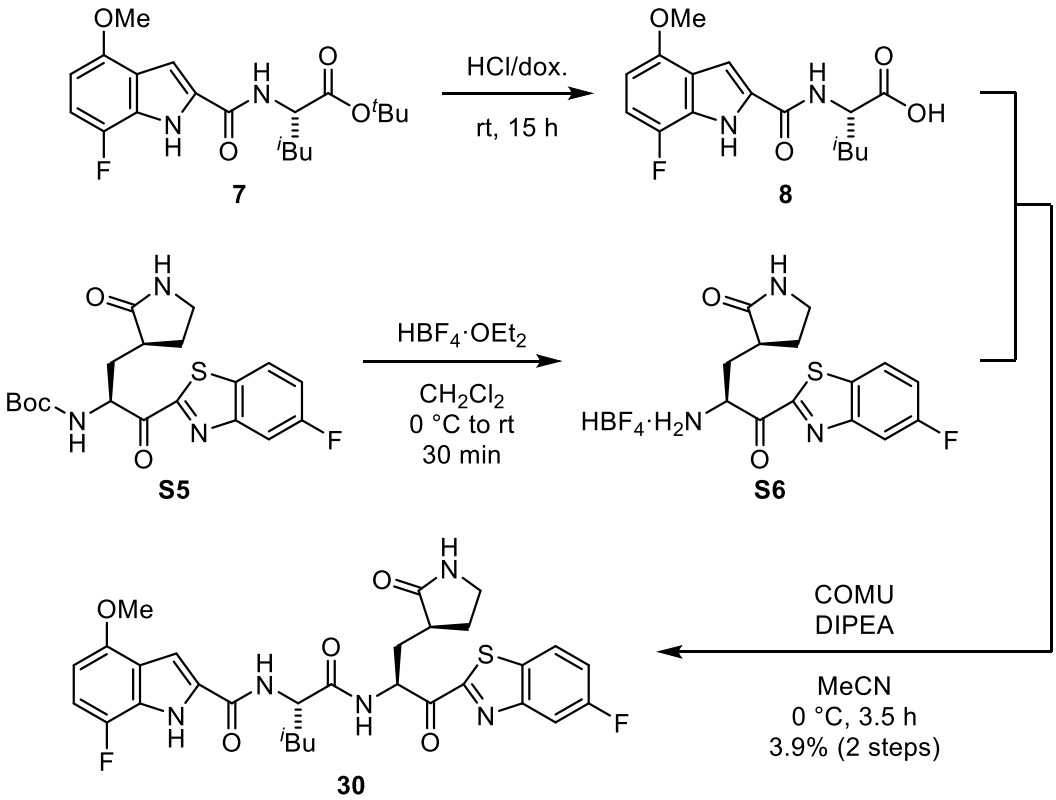
To a solution of Boc protected amine **S20** (80.4 mg, 0.210 mmol) in CH_2Cl_2 (2.1 mL) was added $HBF_4{\cdot}OEt_2$ (102 µL, 0.740 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.210 mmol) was treated with the crude carboxylic acid **S33** (0.210 mmol), COMU (89.9 mg, 0.210 mmol), and DIPEA (70.9 µL, 0.420 mmol) in MeCN (2.1 mL) at 0 °C, and the mixture was allowed to stir for 1 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **28**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **28** as a pale yellow solid (5.45 mg, 4.1% (2 steps)): t_R = 25.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.2 (s, 1H), 8.81-8.80 (m, 1H), 8.08-8.06 (m, 1H), 7.96-7.94 (m, 1H), 7.52-7.50 (m, 2H), 7.30-7.28 (m, 1H), 7.25-7.11 (m, 2H), 7.05 (s, 1H), 6.93-6.92 (m, 1H), 6.54 (brs, 1H), 5.76-5.72 (m, 1H), 4.95-4.92 (m, 1H), 3.32-3.31 (m, 2H), 2.72-2.65 (m, 1H), 2.51-2.48 (m, 1H), 2.26-2.14 (m, 2H), 2.04-1.96 (m, 1H), 1.86-1.75 (m, 2H), 1.73-1.67 (m, 1H), 0.97-0.96 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.3, 180.3, 172.7, 164.0, 161.2, 153.5, 142.9, 138.3, 137.4, 131.2, 128.1, 127.2, 125.8, 124.5, 122.5, 121.5, 121.0 (q, J = 257.5 Hz), 111.7, 111.2, 100.2, 55.3, 52.0, 42.4, 40.9, 39.4, 33.0, 28.6, 25.0, 23.0, 22.4; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{31}F_3N_5O_5S$ $[M+H]^+$ 630.1993, found 630.1995.



Benzyl ((*S*)-1-(((*S*)-1-(benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (29): To a solution of Boc protected amine **S20** (117 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise a solution of $HBF_4{\cdot}OEt_2$ (144 μL, 1.05 mmol) at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.300 mmol) was coupled to N^{α}-Cbz-L-Leu-OH **S34** (79.6 mg, 0.300 mmol) using COMU (129 mg, 0.300 mmol) in the presence of DIPEA (101 μL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C and the solution was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **29**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **29** as a white solid (3.66 mg, 2.2% (2 steps)): t_R = 18.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6.2 Hz, 1H), 8.18-8.16 (m, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.58-7.52 (m, 2H), 7.34-7.30 (m, 5H), 6.27 (s, 1H), 5.72-5.68 (m, 1H), 5.43 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 4.42-4.38 (m, 1H), 3.36-3.33 (m, 2H), 2.66-2.61 (m, 1H), 2.54-2.51 (m, 1H), 2.25-2.15 (m, 2H), 2.07-1.99 (m, 1H), 1.76-1.66 (m, 2H), 1.55-1.49 (m, 1H), 0.96-0.94 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.2, 180.0, 172.9, 164.2, 156.2, 153.6, 137.4, 136.5, 128.6, 128.2, 128.1, 127.2, 125.8, 122.5, 67.0, 55.1, 53.4, 42.6, 40.7, 39.1, 33.3, 28.7, 24.8, 23.1, 22.2; HRMS (ESI), *m*/*z* calcd for $C_{28}H_{33}N_4O_5S$ $[M+H]^+$ 537.2166, found 537.2171.

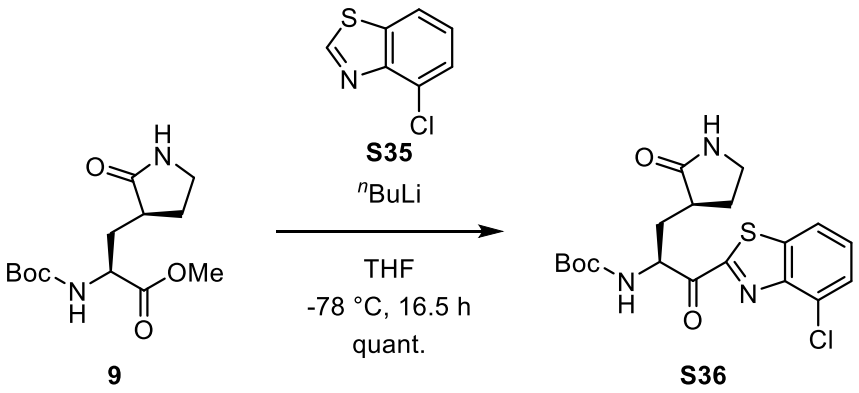


7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (30): The *tert*-butyl ester **7** (75.7 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 15 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

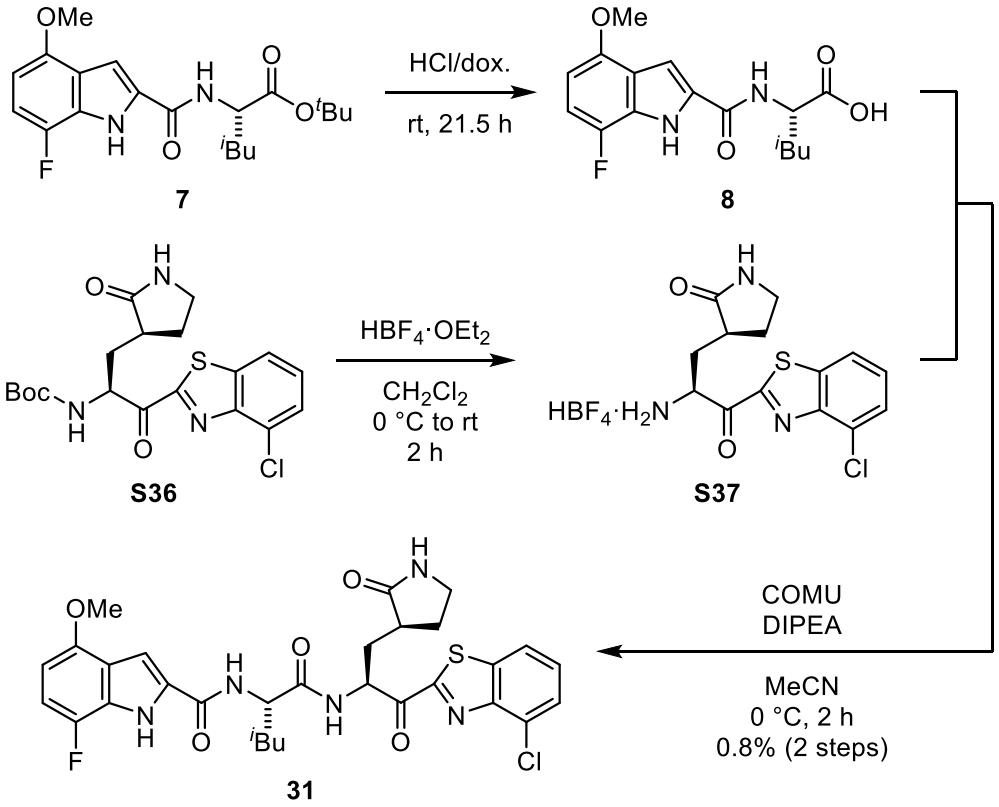
To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

The crude amine **S6** (0.200 mmol) was treated with the crude carboxylic acid **8** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 3.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **30**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **30** as a pale yellow solid (4.72 mg, 3.9% (2 steps)): t_R = 19.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.84 (d, *J* = 5.5 Hz, 1H), 7.89 (dd, *J* = 8.9 Hz and 5.0 Hz, 1H), 7.69 (dd, *J* = 9.1 Hz and 2.3 Hz, 1H), 7.23 (ddd, 8.8 Hz, 8.8 Hz, and 2.5 Hz, 1H), 7.07-7.07 (m, 1H), 7.04-7.02 (d, *J* = 8.5 Hz, 1H), 6.84 (dd, *J* = 10.5 Hz and 8.5 Hz, 1H), 6.29 (dd, *J* = 8.5 Hz and 2.9 Hz, 1H), 6.27 (s, 1H), 5.69-5.65 (m, 1H), 4.97-4.92 (m, 1H), 3.88 (s, 3H), 3.40-3.38 (m, 2H), 2.73-2.67 (m, 1H), 2.56-2.52 (m, 1H), 2.26-2.16 (m, 2H), 2.05-1.96 (m, 1H), 1.88-1.74 (m, 2H), 1.67-1.64 (m, 1H), 1.00-0.98 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8, 180.1, 172.8, 166.5, 162.1 (d, *J* = 245.3 Hz), 160.9, 154.3 (d, *J* = 12.0 Hz), 150.3 (d, *J* = 2.3 Hz), 144.8 (d, *J* = 237.7 Hz), 132.9 (d, *J* = 1.2 Hz), 130.2, 126.2 (d, *J* = 16.2 Hz), 123.4 (d, *J* = 9.7 Hz), 121.5 (d, *J* = 4.6 Hz), 117.3 (d, *J* = 25.5 Hz), 111.2 (d, *J* = 23.3 Hz), 108.8

(d, J = 17.6 Hz), 102.3, 98.7 (d, J = 6.2 Hz), 55.8, 55.5, 51.6, 42.7, 40.9, 39.5, 32.7, 28.9, 25.0, 23.1, 22.3; HRMS (ESI), m/z calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$ 612.2087, found 612.2084.



***tert*-Butyl ((*S*)-1-(4-chlorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S36):** To a solution of 4-chlorobenzo[*d*]thiazole **S35** (424 mg, 2.50 mmol) in THF (4.0 mL) was added ^{n}BuLi (1.59 M in *n*-hexane, 1.41 mL, 2.25 mmol) dropwise over 10 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (143 mg, 0.500 mmol) in THF (1.0 mL) was added dropwise over 5 min and the solution was stirred for 16.5 h at -78 °C. The reaction mixture was added saturated aqueous NH_4Cl and the mixture was allowed to stir at 0 °C. The mixture was evaporated and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$/MeOH (90:1) to obtain the compound **S36** as an yellow solid (214 mg, quant); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.82 (m, 1H), 7.56-7.54 (m, 1H), 7.44-7.40 (m, 1H), 6.90 (s, 1H), 5.81 (d, J = 8.5 Hz, 1H), 5.63-5.59 (m, 1H), 3.43-3.34 (m, 2H), 2.72-2.60 (m, 2H), 2.34-2.24 (m, 1H), 2.18-2.02 (m, 2H), 1.42 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 193.0, 179.8, 164.1, 156.0, 150.6, 138.8, 130.8, 128.6, 127.5, 121.1, 80.2, 55.6, 40.6, 38.8, 35.1, 28.4 (3C), 28.1; HRMS (ESI), m/z calcd for $C_{19}H_{23}ClN_3O_4S$ $[M+H]^+$ 424.1092, found 424.1092.

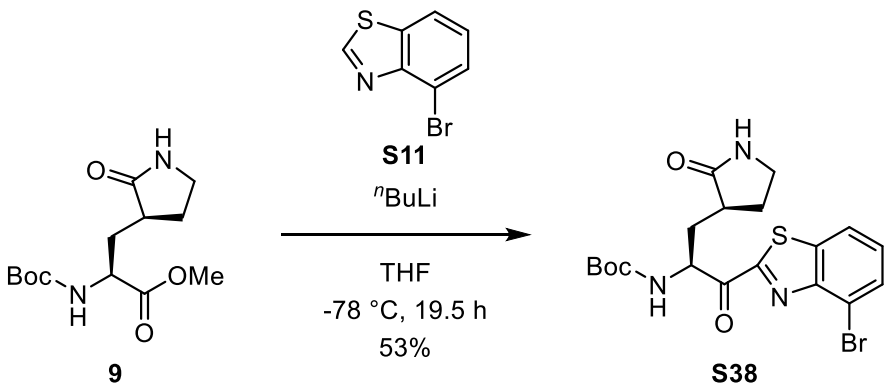


***N*-((*S*)-1-(((*S*)-1-(4-Chlorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (31)**: The *tert*-butyl ester **7** (144 mg, 0.380 mmol) was treated with 4 M HCl in dioxane (4.0 mL) at room temperature. The solution was stirred for 21.5 h at room temperature, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

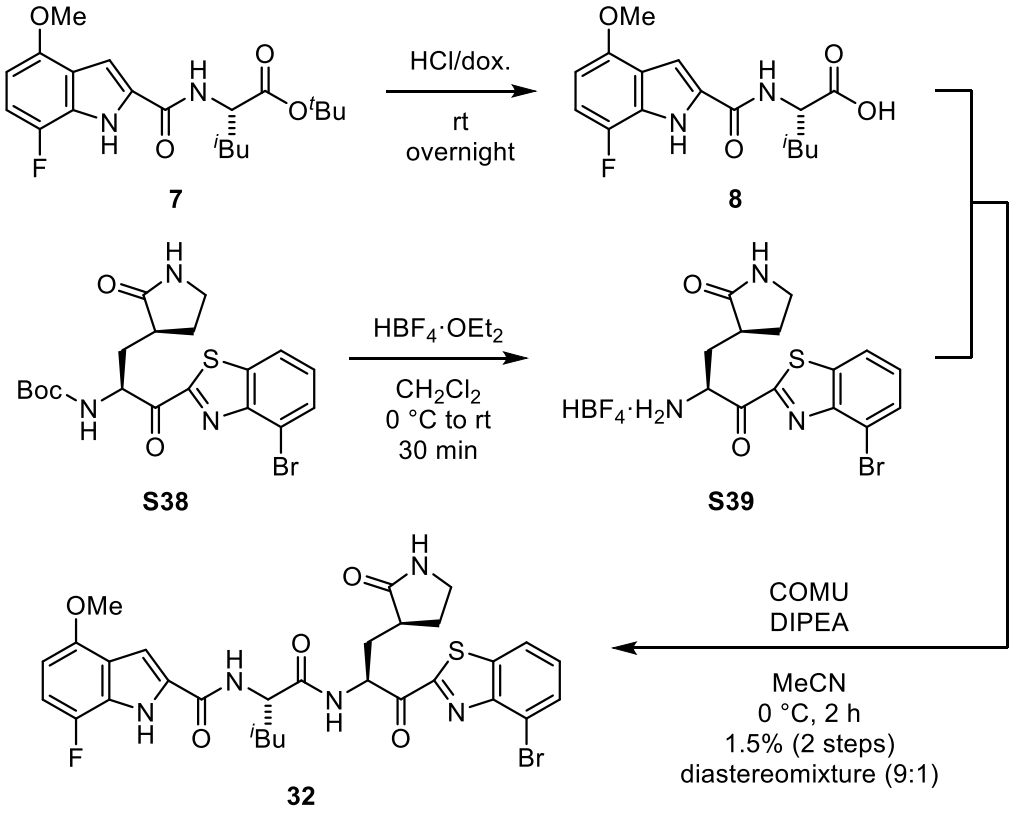
To a solution of Boc protected amine **S36** (86.8 mg, 0.250 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4 \cdot OEt_2$ (120 μL, 0.875 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S37** was used immediately in next step without purification.

The crude amine **S37** (0.250 mmol) was treated with the crude carboxylic acid **8** (0.380 mmol), COMU (118 mg, 0.280 mmol), and DIPEA (85.0 μL, 0.500 mmol) in MeCN (3.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to give the title compound **31**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **31** as a pale yellow solid (1.24 mg, 0.8% (2 steps)): t_R = 21.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.46 (d, *J* = 6.1 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.59-7.57 (m, 1H), 7.47-7.44 (m, 1H), 7.09-7.08 (m, 1H), 6.86 (dd, *J* = 10.5 Hz and 8.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.32 (dd, *J* = 8.4 Hz and 2.9 Hz, 1H), 6.15 (brs, 1H), 5.76-5.72 (m, 1H), 4.90-4.85 (m, 1H), 3.90 (s, 3H), 3.43-3.41 (m, 2H), 2.75-2.69 (m, 1H), 2.61-2.56 (m, 1H), 2.35-2.29 (m, 1H), 2.23-2.14 (m, 2H), 1.87-1.73 (m, 3H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.7, 180.1, 172.6, 164.5, 160.9, 150.6, 150.4 (d, *J* = 2.3 Hz), 144.8 (d, *J* = 238.1 Hz), 138.8, 130.7, 130.1, 128.6, 127.4, 126.2 (d, *J* = 15.5 Hz), 121.6 (d, *J* = 4.2 Hz), 121.1, 109.0 (d, *J* = 17.9 Hz), 101.9, 98.8 (d, *J* = 6.1 Hz), 55.8, 55.7, 51.8, 42.5, 40.9, 39.5, 33.3, 28.7, 25.0, 23.1, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}ClFN_5O_5S$ $[M+H]^+$

628.1791, found 628.1795.



***tert*-Butyl ((*S*)-1-(4-bromobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S39):** To a solution of 4-bromobenzo[*d*]thiazole **S11** (2.14 g, 10.0 mmol) in THF (18 mL) was added ^{n}BuLi (1.59 M in *n*-hexane, 5.70 mL, 9.06 mmol) dropwise over 10 min at -78 °C. After 3 h stirring at -78 °C, the methyl ester **9** (572 mg, 2.00 mmol) in THF (2.0 mL) was added dropwise over 5 min at -78 °C and the solution was stirred for 19.5 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to stir at 0 °C for 20 min. The aqueous layer was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by flash column chromatography over silica gel with *n*-hexane/EtOAc (1:2 to 1:3) to obtain the compound **S38** as a yellow solid (500 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.1 Hz and 0.9 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz and 0.8 Hz, 1H), 7.40 (dd, *J* = 7.9 Hz and 7.9 Hz, 1H), 5.69-5.62 (m, 3H), 3.49-3.40 (m, 2H), 2.77-2.66 (m, 2H), 2.48-2.40 (m, 1H), 2.25-2.19 (m, 1H), 2.10-2.04 (m, 1H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.0, 179.8, 163.9, 156.0, 151.8, 138.2, 130.8, 129.0, 121.8, 119.6, 80.3, 55.6, 40.8, 38.8, 35.3, 28.4 (3C), 27.6; HRMS (ESI), *m*/*z* calcd for $C_{19}H_{23}BrN_3O_4S$ $[M+H]^+$ 468.0587, found 468.0586.

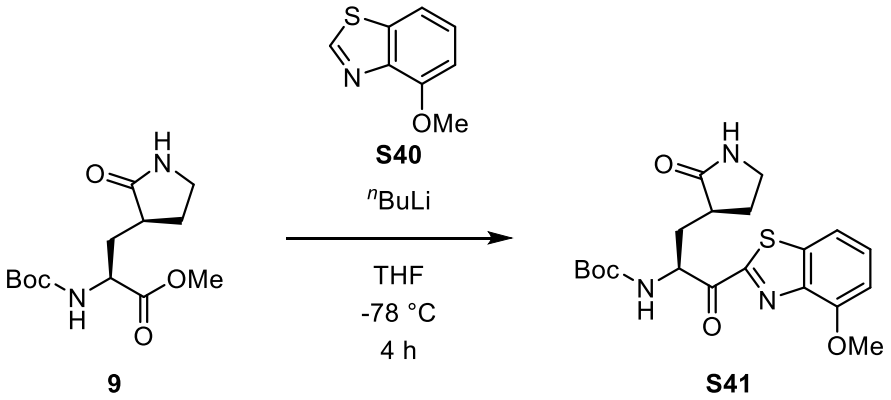


***N*-((*S*)-1-(((*S*)-1-(4-Bromobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (32)**: The *tert*-butyl ester **7** (366 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (10 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

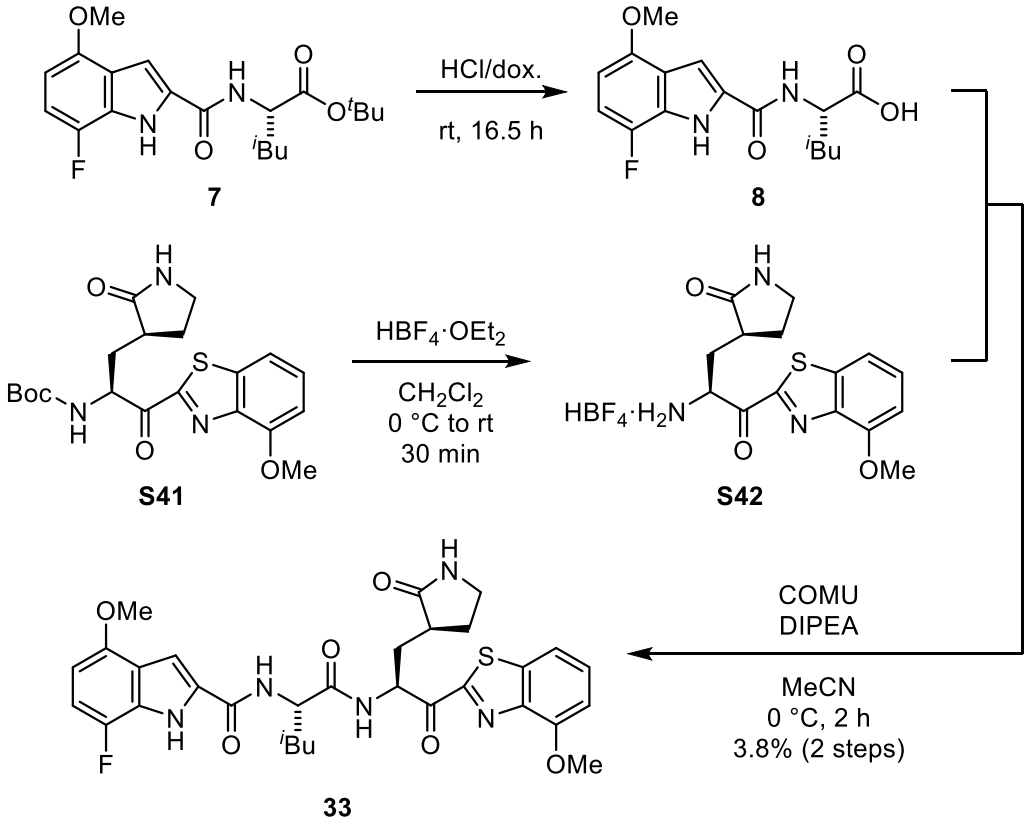
To a solution of Boc protected amine **S38** (423 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added $HBF_4{\cdot}OEt_2$ (480 μL, 3.50 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S39** was used immediately in next step without purification.

The crude amine **S39** (1.00 mmol) was treated with the crude carboxylic acid **8** (1.00 mmol), COMU (471 mg, 1.10 mmol), and DIPEA (340 μL, 2.00 mmol) in MeCN (10 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **32**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **32** as a pale yellow powder (10.1 mg, 1.5% (2 steps) as diastereomixture (9:1)): t_R = 22.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (brs, 1H), 9.03 (d, J = 5.7 Hz, 0.1H), 8.90 (d, J = 6.9 Hz, 0.9H), 8.45 (d, J = 8.0 Hz, 0.9H), 8.40 (d, J = 8.0 Hz, 0.1H), 8.32-8.26 (m, 1H), 7.94-7.93 (m, 1H), 7.69 (br, 1H), 7.57-7.54 (m, 1H), 7.35 (brs, 0.9H), 7.32 (brs, 0.1H), 6.94-6.90 (m, 1H), 6.42-6.40 (m, 1H), 5.57-5.48 (m, 1H), 4.66-4.59 (m, 1H), 3.86 (brs, 3H), 3.26-3.17 (m, 1.8H), 3.14-3.07 (m, 0.2H), 2.65-2.52 (m, 1H), 2.40-2.28 (m, 1H), 2.16-2.05 (m, 2H), 1.99-1.92 (m, 1H), 1.81-1.48 (m, 3H), 0.93-0.85 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 193.1, 192.6, 178.0, 177.9, 172.9, 172.3, 165.6, 164.8, 160.3, 160.2, 150.8, 149.7, 144.2 (d, J = 238.0 Hz), 137.5, 131.5, 130.7, 129.3, 129.2, 125.6 (d, J =

15.6 Hz), 123.0, 122.9, 120.8 (d, J = 4.8 Hz), 118.0, 108.0 (d, J = 18.0 Hz), 102.7, 102.7, 98.4 (d, J = 4.8 Hz), 55.5, 53.9, 53.8, 51.1, 51.0, 40.6, 38.3, 38.1, 32.3, 32.2, 28.1, 27.0, 24.4, 23.1, 23.0, 21.4, 21.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}BrFN_5O_5S$ $[M+H]^+$ 672.1286, found 672.1286.



***tert*-Butyl ((*S*)-1-(4-methoxybenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S41)**: To a solution of 4-methoxybenzo[*d*]thiazole **S40** (248 mg, 1.50 mmol) in THF (2.0 mL) was added ^{n}BuLi (0.5 M in *n*-hexane, 2.70 mL, 1.35 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (85.9 mg, 0.300 mmol) in THF (1.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 4 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was evaporated and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was roughly purified by flash chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the crude compound **S41** (71.5 mg) as a yellow solid, which was used for next step without further purification; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{25}N_3NaO_5S$ $[M+H]^+$ 442.1407, found 442.1406.

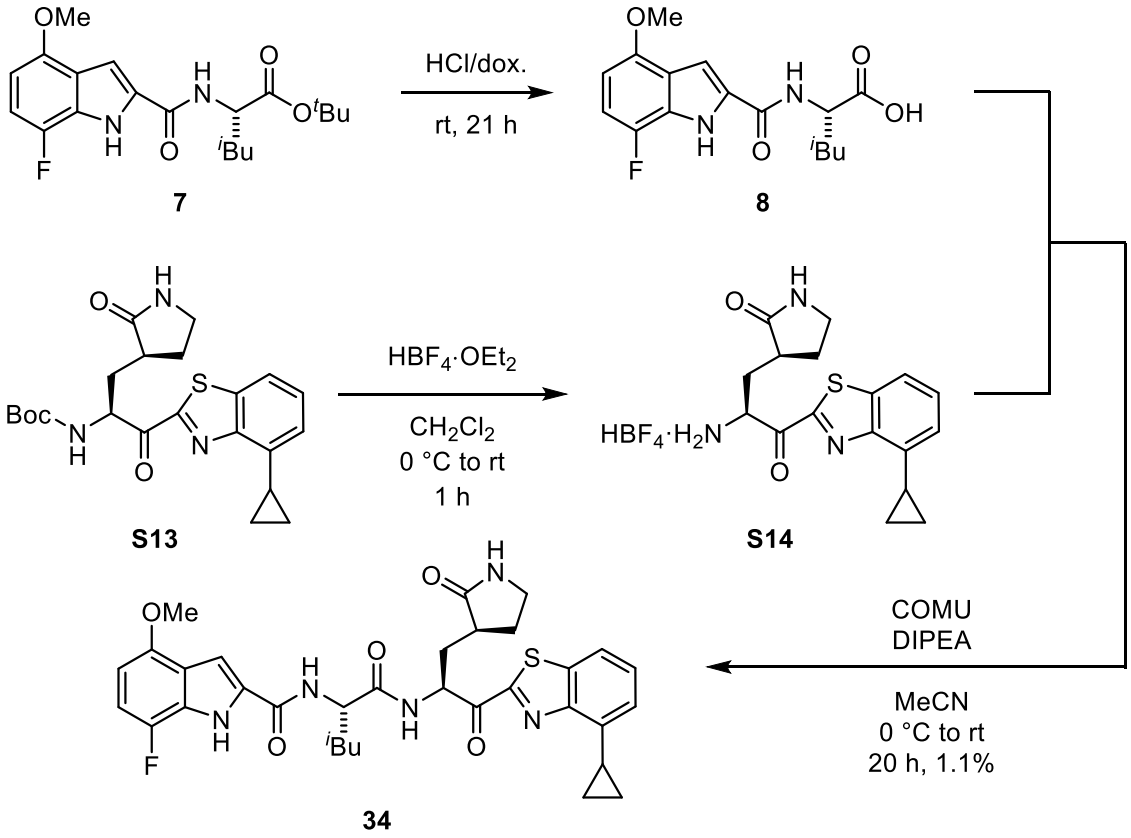


7-Fluoro-4-methoxy-*N*-((*S*)-1-(((*S*)-1-(4-methoxybenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (33): The *tert*-butyl ester **7** (64.3 mg, 0.170 mmol) was treated with 4 M HCl in dioxane (1.7 mL) at room temperature. The solution was stirred at room temperature for 16.5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S41** (71.3 mg, 0.170 mmol) in CH_2Cl_2 (1.7 mL) was added $HBF_4{\cdot}OEt_2$ (82.3 μL, 0.600 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S42** was used immediately in next step without purification.

The crude amine **S42** (0.170 mmol) was treated with the crude carboxylic acid **8** (0.170 mmol), COMU (72.8 mg, 0.170 mmol), and DIPEA (57.4 μL, 0.340 mmol) in MeCN (1.7 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **33**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **33** as a white solid (3.98 mg, 3.8% (2 steps)): t_R = 18.4 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, MeOD) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.24 (d, *J* = 2.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 10.9 Hz and 8.6 Hz, 1H), 6.37 (dd, *J* = 8.6 Hz and 2.9 Hz, 1H), 5.64 (dd, *J* = 11.5 Hz and 3.4 Hz, 1H), 4.67 (dd, *J* = 8.6 Hz and 6.3 Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 3.38-3.33 (m, 2H), 2.79-2.73 (m, 1H), 2.48-2.41 (m, 1H), 2.31-2.25 (m, 1H), 2.14-2.09 (m, 2H), 1.79-1.71 (m, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, MeOD) δ 193.3, 181.9, 175.4, 163.5, 163.4, 156.6, 151.7, 146.1 (d, *J* = 238.0 Hz), 145.1, 140.1, 131.5, 130.7, 127.7 (d, *J* = 15.6 Hz), 122.7 (d, *J* = 4.8 Hz), 115.1, 109.4 (d, *J* = 18.0 Hz), 108.6, 104.2, 99.3 (d, *J* = 5.9 Hz), 56.7, 56.1, 55.9, 53.6, 41.8, 41.6, 40.2,

34.0, 28.6, 26.1, 23.3, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{35}FN_5O_6S$ $[M+H]^+$ 624.2287, found 624.2287.

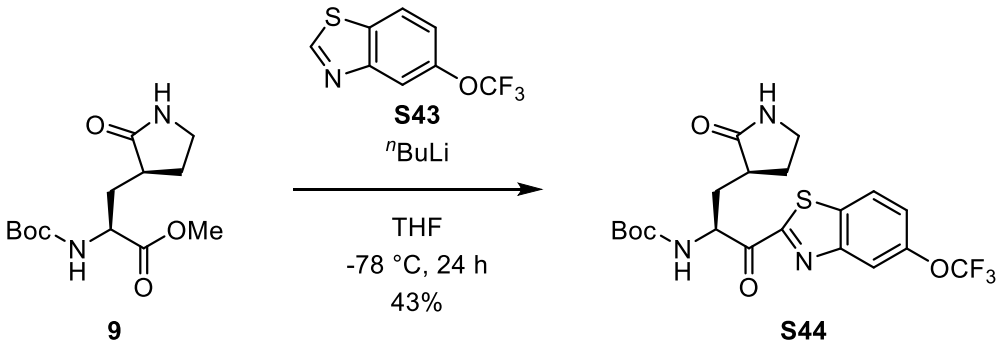


***N*-((*S*)-1-(((*S*)-1-(4-Cyclopropylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (34)**: The *tert*-butyl ester **7** (280 mg, 0.740 mmol) was treated with 4 M HCl in dioxane (7.4 mL) at room temperature. The solution was stirred at room temperature for 21 h, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

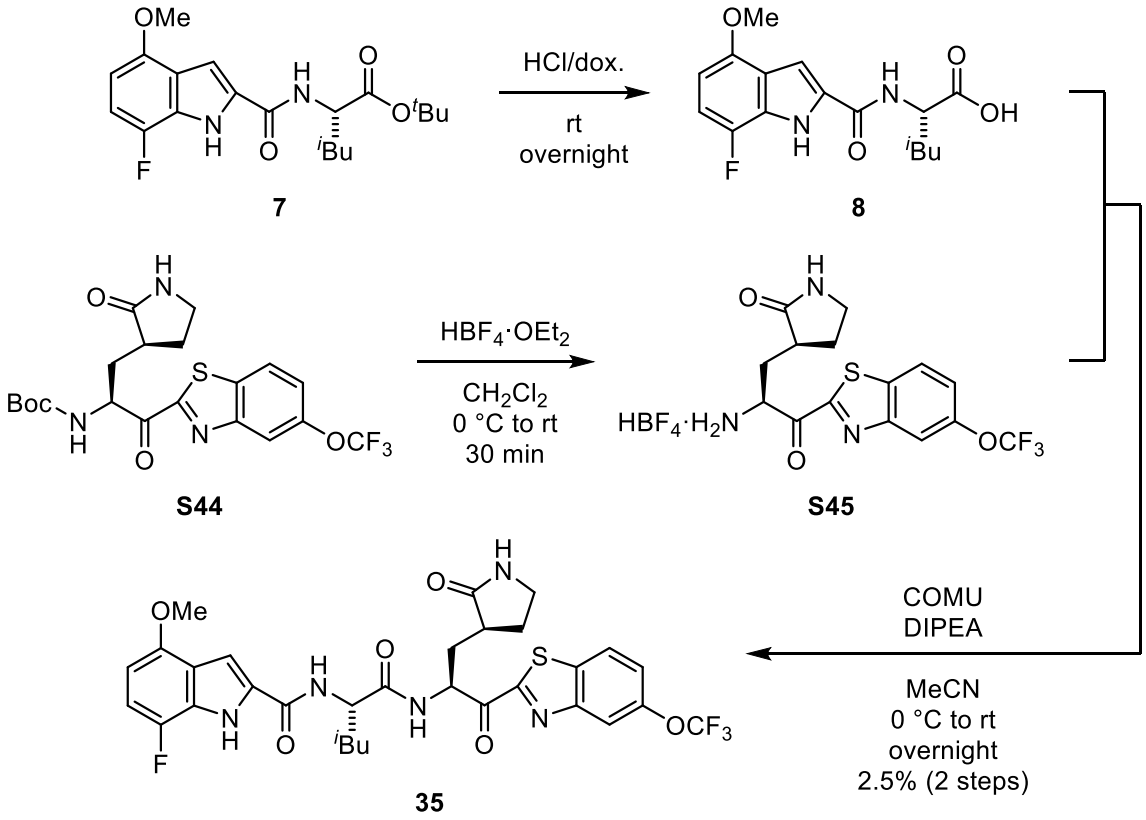
To a solution of Boc protected amine **S13** (317 mg, 0.740 mmol) in CH_2Cl_2 (7.4 mL) was added $HBF_4{\cdot}OEt_2$ (357 μL, 2.60 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S14** was used immediately in next step without purification.

The crude amine **S14** (0.740 mmol) was treated with the crude carboxylic acid **8** (0.740 mmol), COMU (385 mg, 0.890 mmol), and DIPEA (251 μL, 1.48 mmol) in MeCN (7.4 mL) at 0 °C, and the mixture was allowed to stir for 20 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **34**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **34** as a pale yellow solid (5.16 mg, 1.1%): t_R = 25.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.05-12.05 (m, 1H), 8.88 (d, *J* = 6.6 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.53-7.50 (m, 1H), 7.35-7.34 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 10.9 Hz and 8.6 Hz, 1H), 6.40 (dd, *J* = 8.6 Hz and 2.9 Hz, 1H), 5.61-5.56 (m, 1H), 4.64-4.59 (m, 1H), 3.86 (s, 3H), 3.21-3.14 (m, 2H), 2.81-2.75 (m, 1H), 2.58-2.51 (m, 1H),

2.31-2.25 (m, 1H), 2.18-2.13 (m, 1H), 1.95-1.86 (m, 2H), 1.71-1.61 (m, 2H), 1.56-1.51 (m, 1H), 1.19-1.10 (m, 2H), 1.05-0.97 (m, 2H), 0.90 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 192.9, 178.1, 172.8, 163.0, 160.3, 151.8, 149.7, 144.2 (d, J = 238.0 Hz), 141.4, 136.5, 131.5, 128.5, 125.7 (d, J = 15.6 Hz), 121.5, 120.8 (d, J = 4.8 Hz), 119.6, 108.1 (d, J = 18.0 Hz), 102.7, 98.4 (d, J = 5.9 Hz), 55.5, 53.6, 51.2, 40.5, 38.2, 32.3, 27.3, 24.4, 23.1, 21.4, 12.3, 10.3 (2C); HRMS (ESI), m/z calcd for $C_{33}H_{37}FN_5O_5S$ $[M+H]^+$ 634.2494, found 634.2494.



***tert*-Butyl ((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)-1-(5-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)propan-2-yl)carbamate (S44):** To a solution of 5-(trifluoromethoxy)benzo[*d*]thiazole **S43** (239 mg, 1.09 mmol) in THF (8.0 mL) was added ^{n}BuLi (1.57 M in *n*-hexane, 0.578 mL, 0.908 mmol) dropwise at -78 °C. After 1 h stirring at -78 °C, to the mixture was added methyl ester **9** (104 mg, 0.363 mmol) portionwise and the solution was stirred for 24 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl at -78 ºC and the mixture was allowed to reach ambient temperature. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was purified by silica gel flash column chromatography with *n*-hexane/EtOAc (1:2 to 1:4) to afford the compound **S44** as a pale yellow solid (73.9 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (brs, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.44 (dd, J = 8.9 Hz and 1.8 Hz, 1H), 5.87 (br, 1H), 5.72 (br, 1H), 5.56 (br, 1H), 3.43-3.40 (m, 2H), 2.71-2.63 (m, 2H), 2.21-2.06 (m, 3H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 193.1, 179.6, 166.5, 155.9, 154.1, 148.5, 135.6, 123.6, 122.0, 120.6 (q, J = 258.3 Hz), 117.6, 80.3, 55.6, 40.6, 38.5, 34.4, 28.4 (3C), 28.3; HRMS (ESI), m/z calcd for $C_{20}H_{23}F_3N_3O_5S$ $[M+H]^+$ 474.1305, found 474.1303.

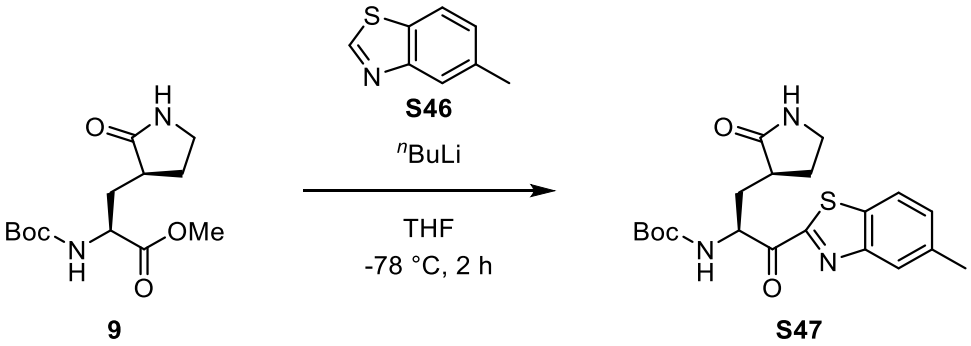


7-Fluoro-4-methoxy-*N*-((*S*)-4-methyl-1-oxo-1-(((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)-1-(5-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)propan-2-yl)amino)pentan-2-yl)-1*H*-indole-2-carboxamide (35): The *tert*-butyl ester **7** (110 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

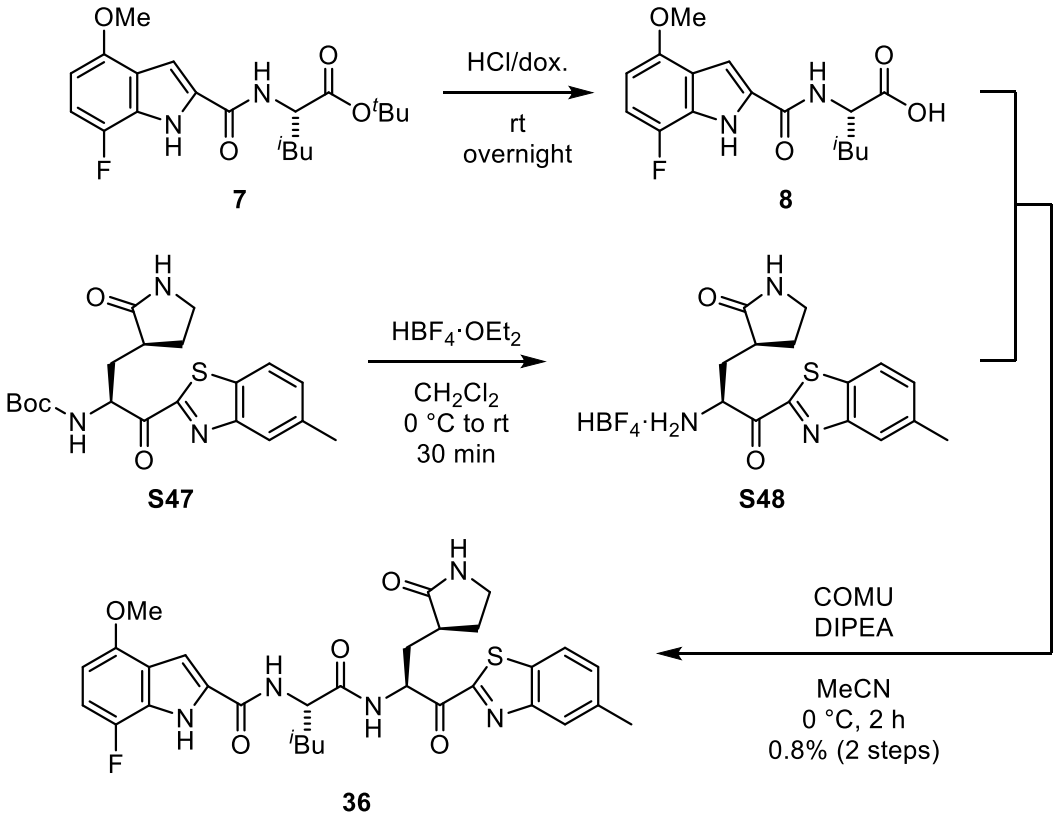
To a solution of Boc protected amine **S44** (128 mg, 0.270 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (144 μL, 1.05 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S45** was used immediately in next step without purification.

The crude amine **S45** (0.270 mmol) was treated with the crude carboxylic acid **8** (0.300 mmol), COMU (129 mg, 0.330 mmol), and DIPEA (102 μL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **35**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **35** as a pale yellow solid (4.53 mg, 2.5% (2 steps)): t_R = 16.0 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.91 (d, *J* = 5.7 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 7.38 (dd, *J* = 9.2 Hz and 1.7 Hz, 1H), 7.24 (s, 1H), 7.07-7.06 (m, 1H), 6.81 (dd, *J* = 10.6 Hz and 8.3 Hz, 1H), 6.63 (s, 1H), 6.26 (dd, *J* = 8.6 Hz and 2.9 Hz, 1H), 5.70-5.65 (m, 1H), 5.01-4.97 (m, 1H), 3.86 (s, 3H), 3.40-3.34 (m, 2H), 2.73-2.67 (m, 1H), 2.55-2.49 (m, 1H), 2.28-2.21 (m, 1H), 2.19-2.14 (m, 1H), 2.04-1.96 (m, 1H), 1.84-1.74 (m, 2H), 1.71-1.66 (m, 1H), 0.99-0.97 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.8, 180.2, 173.1, 166.6, 161.0, 153.9, 150.2, 148.4, 144.8 (d, *J* = 237.9 Hz), 135.5, 130.2, 126.2 (d, *J* = 237.9 Hz), 123.4, 121.8, 121.4 (d, *J* = 4.8 Hz), 120.6 (q, *J* = 258.4 Hz), 117.4, 108.8 (d,

J = 16.9 Hz), 102.5, 98.6 (d, J = 5.9 Hz), 55.7, 55.4, 51.6, 42.6, 40.9, 39.4, 32.6, 28.7, 25.0, 23.0, 22.2; HRMS (ESI), m/z calcd for $C_{31}H_{32}F_4N_5O_6S$ $[M+H]^+$ 678.2004, found 678.2001.



***tert*-Butyl ((*S*)-1-(5-methylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S47):** To a solution of 5-methylbenzo[*d*]thiazole **S46** (124 mg, 0.832 mmol) in THF (3.3 mL) was added ^{n}BuLi (1.56 M in *n*-hexane, 0.478 mL, 0.747 mmol) dropwise over 10 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **9** (47.5 mg, 0.166 mmol) in THF (0.83 mL) was added dropwise over 5 min at -78 °C and the solution was stirred for 2 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to stir at -78 °C. The aqueous layer was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was roughly purified by flash column chromatography over silica gel with $CHCl_3$/MeOH (40:1) to obtain the compound **S47** (47.1 mg) as a yellow solid, which was used for next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.36-7.34 (m, 1H), 6.64 (brs, 1H), 5.87-5.85 (m, 1H), 5.57 (br, 1H), 3.39-3.37 (m, 2H), 2.69-2.59 (m, 2H), 2.51 (s, 3H), 2.15-2.04 (m, 3H), 1.43 (s, 9H); HRMS (ESI), m/z calcd for $C_{20}H_{26}N_3O_4S$ $[M+H]^+$ 404.1639, found 404.1642.

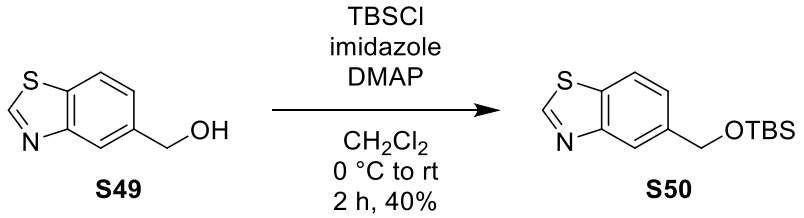


7-Fluoro-4-methoxy-*N*-((*S*)-4-methyl-1-(((*S*)-1-(5-methylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (36): The *tert*-butyl ester **7** (397 mg, 1.05 mmol) was treated with 4 M HCl in dioxane (11 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

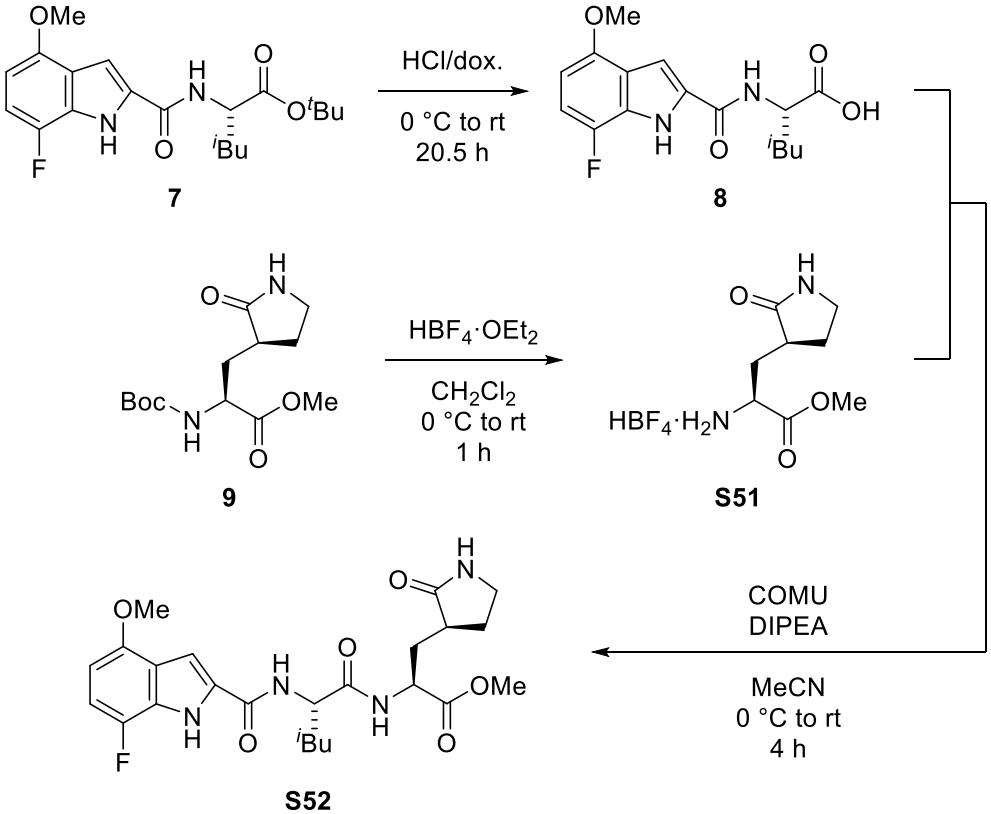
To a solution of Boc protected amine **S47** (425 mg, 1.05 mmol) in CH_2Cl_2 (10.5 mL) was added $HBF_4{\cdot}OEt_2$ (505 μL, 3.68 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S48** was used immediately in next step without purification.

The crude amine **S48** (1.05 mmol) was treated with the crude carboxylic acid **8** (1.05 mmol), COMU (495 mg, 1.16 mmol), and DIPEA (357 μL, 2.10 mmol) in MeCN (10.5 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **36**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **36** as a pale yellow solid (4.80 mg, 0.8% (2 steps)): t_R = 21.3 min (linear gradient of B in A, 40 to 70 % over 30 min) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.64 (d, *J* = 6.3 Hz, 1H), 7.80-7.78 (m, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.31 (dd, *J* = 8.0 Hz and 1.1 Hz, 1H), 7.10-7.09 (m, 1H), 6.80 (dd, *J* = 10.3 Hz and 8.6 Hz, 1H), 6.75 (brs, 1H), 6.26 (dd, *J* = 8.6 Hz and 2.9 Hz, 1H), 5.73-5.69 (m, 1H), 5.01-4.97 (m, 1H), 3.87 (s, 3H), 3.35-3.30 (m, 2H), 2.71-2.64 (m, 1H), 2.53-2.47 (m, 1H), 2.44 (s, 3H), 2.31-2.25 (m, 1H), 2.17-2.12 (m, 1H), 2.06-1.98 (m, 1H), 1.84-1.65 (m, 3H), 0.96-0.94 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.1, 180.2, 173.0, 164.0, 161.0, 153.9, 150.3, 144.8 (d, *J* = 239.1 Hz), 137.4, 134.4, 130.2, 129.9, 126.3 (d, *J* = 15.6 Hz), 125.3, 121.9, 121.5 (d, *J* = 4.8 Hz), 108.7 (d, *J* = 18.0 Hz), 102.4, 98.6 (d, *J* =

5.9 Hz), 55.8, 55.3, 51.7, 42.5, 40.9, 39.3, 33.2, 28.4, 25.0, 23.0, 22.3, 21.5; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{35}FN_5O_5S$ $[M+H]^+$ 608.2337, found 608.2333.



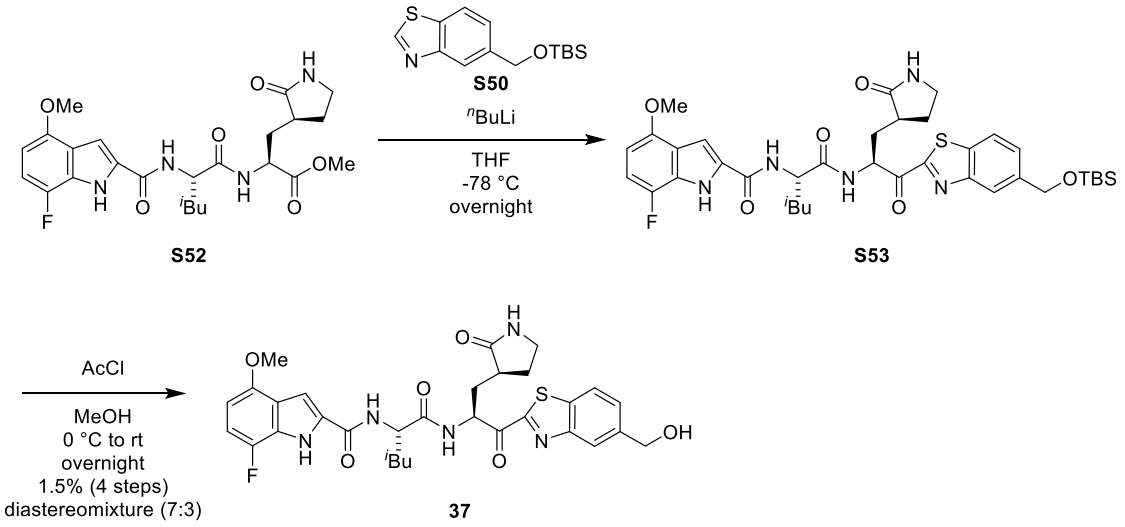
5-(((*tert*-Butyldimethylsilyl)oxy)methyl)benzo[*d*]thiazole (S50): To a solution of benzo[*d*]thiazol-5-ylmethanol **S49** (60.1 mg, 0.364 mmol) in CH_2Cl_2 (4.0 mL) was added *tert*-butyldimethylsilyl (TBS) chloride (112 mg, 0.743 mmol), imidazole (99.2 mg, 1.46 mmol), and DMAP (3.70 mg, 30.3 μmol) at 0 ºC under Ar. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, and the reaction was quenched by the addition of H_2O at 0 ºC. The mixture was allowed to reach ambient temperature. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by automated flush column chromatography system with *n*-hexane/EtOAc (Isolera One, 100:0 to 24:1) to afford **S50** (41.1 mg, 40%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.11-8.11 (m, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.42 (dd, *J* = 8.3 Hz and 1.0 Hz, 1H), 4.91 (s, 2H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.3, 153.6, 140.4, 132.3, 124.2, 121.7, 121.0, 64.9, 26.1 (3C), 18.6, -5.1 (2C); HRMS (ESI), *m*/*z* calcd for $C_{14}H_{22}NOSSi$ $[M+H]^+$ 280.1186, found 280.1188.



Methyl (*S*)-2-((*S*)-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoatea (S52): The *tert*-butyl ester **7** (300 mg, 0.793 mmol) was treated with 4 M HCl in dioxane (7.9 mL) at 0 °C. The solution was stirred at room temperature for 20.5 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **9** (227 mg, 0.793 mmol) in CH_2Cl_2 (7.9 mL) was added $HBF_4 \cdot OEt_2$ (327 μL, 2.38 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S51** was used immediately in next step without purification.

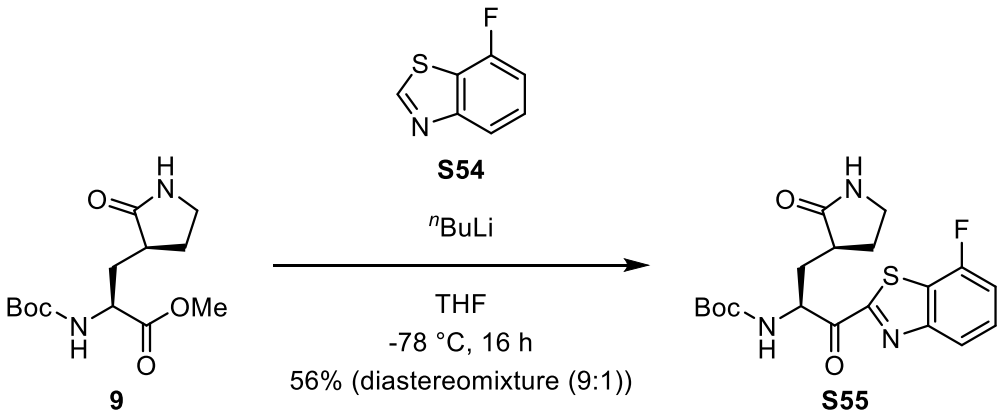
To a solution of the crude amine **S51** (0.793 mmol) in MeCN (4.0 mL) was added a solution of the crude carboxylic acid **8** (0.793 mmol) in MeCN (4.0 mL) at room temperature. To the solution was added COMU (340 mg, 0.794 mmol), and DIPEA (276 μL, 1.59 mmol) at 0 °C, and the mixture was allowed to stir for 4 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 19:1) to obtain the title compound **S52** (167 mg), which was used immediately in next step without further purification.



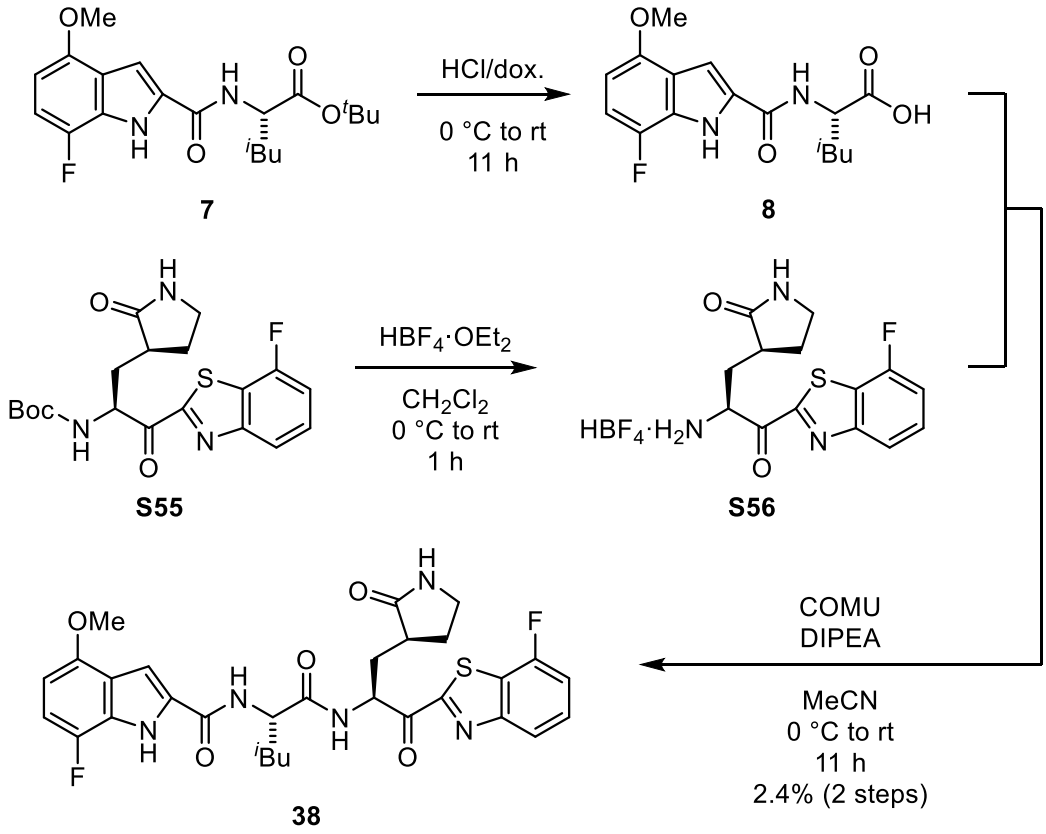
7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(5-(hydroxymethyl)benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (37): To a solution of benzo[*d*]thiazole **S50** (408 mg, 1.46 mmol) in THF (2.9 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 0.82 mL, 1.31 mmol) at -78 °C, and the mixture was stirred at -78 °C for 1.5 h. The mixture was then added the crude methyl ester **S52** (143 mg, 0.29 mmol) in THF (1.5 mL) at -78 °C. The reaction mixture was stirred overnight at -78 °C and then was added saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was roughly purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 20:1) to obtain **S53** (124.3 mg).

A portion of the obtained **S53** (89.0 mg, 0.120 mmol) in MeOH (1.0 mL) was treated with AcCl (4 μL, 0.0560 mmol) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was then cooled to 0 °C and added saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography

system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **37**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **37** as a pale yellow solid (7.2 mg, 1.5% (4 steps) as diastereomixture (7:3)): t_R = 12.1 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (br, 1H), 8.99-8.97 (m, 0.3H), 8.93-8.91 (m, 0.7H), 8.48-8.45 (m, 1H), 8.20 (d, J = 2.9 Hz, 0.3H), 8.18 (d, J = 4.0 Hz, 0.7H), 8.14 (br, 1H), 7.71-7.71 (m, 0.7H), 7.68 (br, 0.3H), 7.60-7.58 (m, 1H), 7.33-7.31 (m, 1H), 6.93-6.89 (m, 1H), 6.42-6.39 (m, 1H), 5.59-5.56 (m, 0.3H), 5.52-5.48 (m, 0.7H), 5.45 (brs, 1H), 4.67 (s, 2H), 4.63-4.57 (m, 1H), 3.86-3.86 (m, 3H), 3.22-3.16 (m, 1.4H), 3.08-3.06 (m, 0.6H), 2.57-2.53 (m, 1H), 2.40-2.12 (m, 2H), 1.89-1.48 (m, 5H), 0.91-0.85 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 193.4, 192.9, 178.1, 177.9, 172.7, 172.4, 164.8, 164.5, 160.3, 160.2, 153.1, 149.7, 144.2 (d, J = 236.8 Hz), 142.7, 134.7, 134.6, 131.5, 127.1, 125.6 (d, J = 16.9 Hz), 122.7, 122.2, 120.8 (d, J = 6.0 Hz), 108.0 (d, J = 16.9 Hz), 102.7, 102.6, 98.4 (d, J = 6.0 Hz), 62.4, 55.5, 54.1, 53.7, 51.1, 40.7, 40.5, 38.3, 38.1, 32.2, 32.1, 28.2, 27.4, 24.4, 24.3, 23.1, 23.0, 21.4, 21.4; HRMS (ESI), m/z calcd for $C_{31}H_{35}FN_5O_6S$ $[M+H]^+$ 624.2287, found 624.2285.



***tert*-Butyl ((*S*)-1-(7-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S55):** To a solution of 7-fluorobenzo[*d*]thiazole **S54** (1.00 g, 6.53 mmol) in THF (10 mL) was added ^{n}BuLi (1.59 M in *n*-hexane, 3.71 mL, 5.90 mmol) dropwise over 10 min at -78 °C. After 2 h stirring at -78 °C, the methyl ester **9** (374 mg, 1.31 mmol) in THF (3.1 mL) was added dropwise over 5 min at -78 °C and the solution was stirred for 16 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to stir at 0 °C for 20 min. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was purified by silica gel flash column chromatography with *n*-hexane/EtOAc (1:2 to 1:3) to obtain the title compound **S55** as a pale yellow solid (297 mg, 56% as diastereomixture (9:1)); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.97 (m, 1H), 7.57-7.52 (m, 1H), 7.28-7.23 (m, 1H), 6.38 (br, 0.1H), 6.05 (s, 1H), 5.90-5.88 (m, 0.9H), 5.65 (br, 0.1H), 5.56 (br, 0.9H), 3.41-3.38 (m, 1.8H), 3.33-3.29 (m, 0.2H), 2.70-2.50 (m, 2H), 2.38-2.31 (m, 0.2H), 2.19-2.03 (m, 2.7H), 1.94-1.88 (m, 0.1H), 1.44 (brs, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.7, 193.1, 179.7, 165.3, 165.1, 157.3 (d, J = 251.9 Hz), 156.2 (d, J = 1.5 Hz), 155.9, 128.1 (d, J = 6.7 Hz), 125.0 (d, J = 16.8 Hz), 124.9 (d, J = 15.1 Hz), 121.8 (d, J = 2.8 Hz), 121.7 (d, J = 3.2 Hz), 113.1 (d, J = 18.3 Hz), 113.0 (d, J = 17.6 Hz), 80.2, 80.1 55.6, 55.4, 40.6, 38.6, 38.3, 34.4, 32.9, 28.4 (3C), 28.2; HRMS (ESI), m/z calcd for $C_{19}H_{22}FN_3NaO_4S$ $[M+H]^+$ 430.1207, found 430.1202.

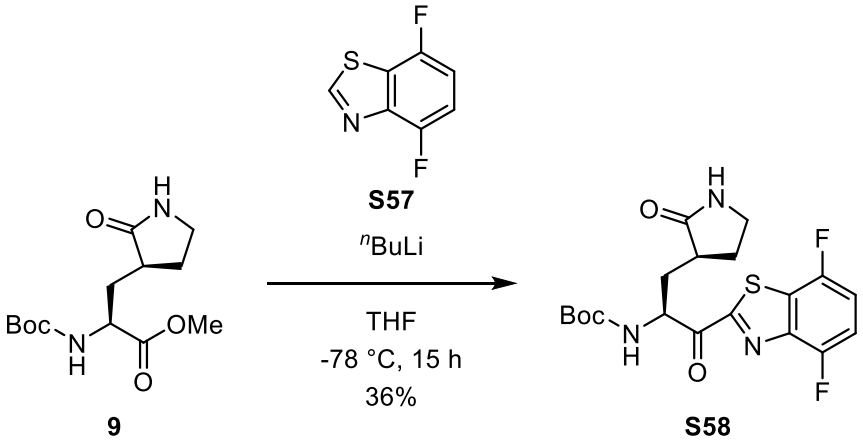


7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(7-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (38): The *tert*-butyl ester **7** (189 mg, 0.500 mmol) was treated with 4 M HCl in dioxane (10 mL) at 0 °C. The solution was stirred for 11 h at room temperature, and then concentrated under reduced pressure to obtain a corresponding carboxylic acid **8**, which was used immediately in next step without purification.

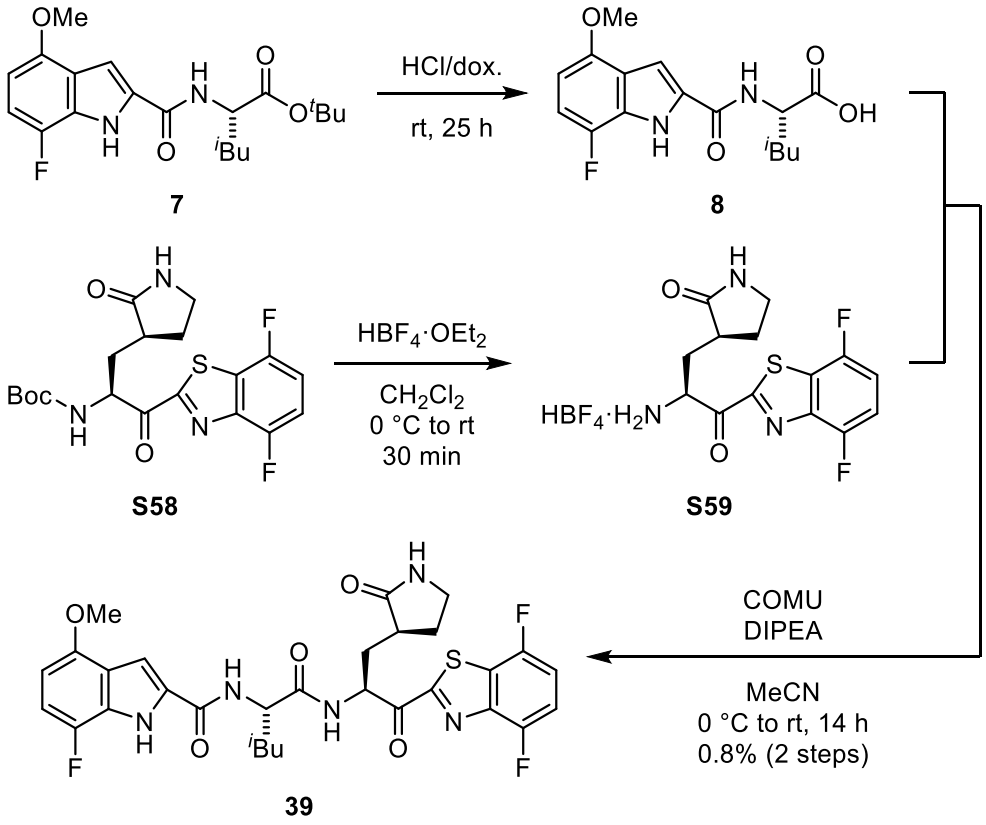
To a solution of Boc protected amine **S55** (102 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (68.6 μL, 0.500 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S56** was used immediately in next step without purification.

The crude amine **S56** (0.250 mmol) was treated with the crude carboxylic acid **8** (0.250 mmol), COMU (128 mg, 0.300 mmol), and DIPEA (128 μL, 0.750 mmol) in MeCN (2.5 mL) at 0 °C, and the mixture was allowed to stir for 11 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **38**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **38** as a yellow solid (3.68 mg, 2.4% (2 steps)): t_R = 20.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.79 (d, *J* = 6.3 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.47-7.41 (m, 2H), 7.22-7.19 (m, 1H), 7.10-7.09 (m, 1H), 6.89 (s, 1H), 6.78 (dd, *J* = 10.3 Hz and 8.6 Hz, 1H), 6.24 (dd, *J* = 8.6 Hz and 2.9 Hz, 1H), 5.70-5.66 (m, 1H), 5.00-4.96 (m, 1H), 3.85 (s, 3H), 3.34-3.26 (m, 2H), 2.71-2.65 (m, 1H), 2.49-2.44 (m, 1H), 2.31-2.25 (m, 1H), 2.16-2.11 (m, 1H), 2.02-1.94 (m, 1H), 1.82-1.72 (m, 2H), 1.70-1.65 (m, 1H), 0.94 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.8, 180.2, 173.2, 165.2, 161.1, 157.2 (d, *J* = 252.4 Hz), 156.1, 150.2, 144.7 (d, *J* = 238.0 Hz), 130.2, 127.9 (d, *J* = 6.0 Hz), 126.3 (d, *J* = 16.8 Hz), 124.9 (d, *J* = 16.8 Hz), 121.5 (d, *J* = 3.5 Hz), 121.4 (d, *J* = 4.8

Hz), 113.0 (d, J = 18.0 Hz), 108.7 (d, J = 16.9 Hz), 102.5, 98.6 (d, J = 6.0 Hz), 55.7, 55.3, 51.7, 42.3, 40.8, 39.2, 32.8, 28.4, 24.9, 23.0, 22.3; HRMS (ESI), m/z calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$ 612.2087, found 612.2084.



***tert*-Butyl ((*S*)-1-(4,7-difluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (S58):** To a solution of 4,7-difluorobenzo[*d*]thiazole **S57** (500 mg, 2.92 mmol) in THF (4.0 mL) was added ^{n}BuLi (1.57 M in *n*-hexane, 1.67 mL, 2.63 mmol) dropwise over 10 min at -78 °C. After 2 h stirring at -78 °C, the methyl ester **9** (167.2 mg, 0.584 mmol) in THF (1.8 mL) was added dropwise over 5 min at -78 °C and the solution was stirred for 15 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to stir at 0 °C for 20 min. The mixture was evaporated and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure followed by flash column chromatography over silica gel with EtOAc to obtain the compound **S58** as a yellow solid (90.0 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.21 (m, 2H), 5.87-5.84 (m, 1H), 5.61-5.56 (m, 2H), 3.43-3.41 (m, 2H), 2.72-2.62 (m, 2H), 2.20-2.13 (m, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.9, 179.8, 165.5, 155.9, 153.5 (dd, J = 257.2 Hz and 3.6 Hz), 153.1 (dd, J = 247.5 Hz and 3.6 Hz), 144.1 (d, J = 15.6 Hz), 126.8 (dd, J = 19.3 Hz and 2.4 Hz), 113.6 (dd, J = 20.4 Hz and 7.2 Hz), 113.1 (dd, J = 20.4 Hz and 7.2 Hz), 80.4, 55.7, 40.6, 38.7, 34.3, 28.4 (3C), 28.1; HRMS (ESI), m/z calcd for $C_{19}H_{22}F_2N_3O_4S$ $[M+H]^+$ 426.1294, found 426.1291.

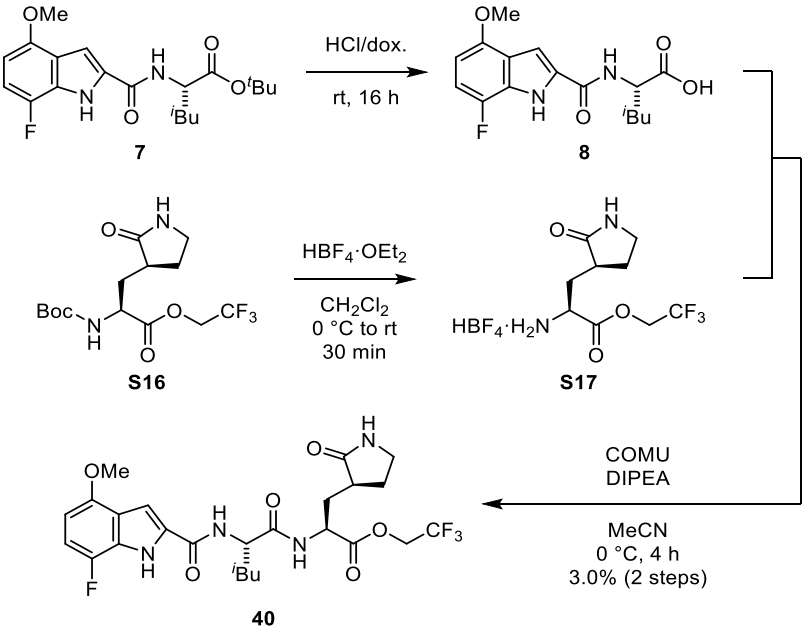


***N*-((*S*)-1-(((*S*)-1-(4,7-Difluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (39)**: The *tert*-butyl ester **7** (128 mg, 0.350 mmol) was treated with 4 M HCl in dioxane (3.5 mL) at room temperature. The solution was stirred at room temperature for 25 h, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S58** (129 mg, 0.302 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (145 μL, 1.06 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S59** was used immediately in next step without purification.

The crude amine **S59** (0.302 mmol) was treated with the crude carboxylic acid **8** (0.350 mmol), COMU (165 mg, 0.385 mmol), and DIPEA (118 μL, 0.700 mmol) in MeCN (3.5 mL) at 0 °C, and the mixture was allowed to stir for 14 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **39**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **39** as a pale yellow solid (1.59 mg, 0.8% (2 steps)): t_R = 22.1 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 7.21-7.16 (m, 2H), 7.09-7.08 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.82 (dd, *J* = 10.6 Hz and 8.4 Hz, 1H), 6.48 (s, 1H), 6.28 (dd, *J* = 8.5 Hz and 2.9 Hz, 1H), 5.69-5.64 (m, 1H), 4.98-4.93 (m, 1H), 3.87 (s, 3H), 3.41-3.33 (m, 2H), 2.75-2.67 (m, 1H), 2.55-2.48 (m, 1H), 2.29-2.16 (m, 2H), 2.09-1.98 (m, 1H), 1.86-1.73 (m, 2H), 1.70-1.64 (m, 1H), 0.99-0.97 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.5, 180.2, 172.9, 165.8, 161.0, 153.5 (dd, *J* = 257.3 Hz and 3.8 Hz), 153.8 (dd, *J* = 248.3 Hz and 3.7 Hz), 150.3 (d, *J* = 1.9 Hz), 144.7 (d, *J* = 238.3 Hz), 144.1 (dd, *J* = 15.8 Hz and 2.6 Hz), 130.2, 126.9 (dd, *J* = 19.5 Hz and 3.0 Hz), 126.2 (d, *J* = 16.0 Hz), 121.5

(d, J = 4.8 Hz), 113.4 (dd, J = 21.5 Hz and 6.8 Hz), 113.0 (dd, J = 20.6 Hz and 7.2 Hz), 108.9 (d, J = 17.7 Hz), 102.2, 98.8 (d, J = 6.2 Hz), 55.8, 55.5, 51.7, 42.5, 40.9, 39.5, 32.6, 28.7, 25.0, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{31}F_3N_5O_5S$ $[M+H]^+$ 630.1993, found 630.1992.

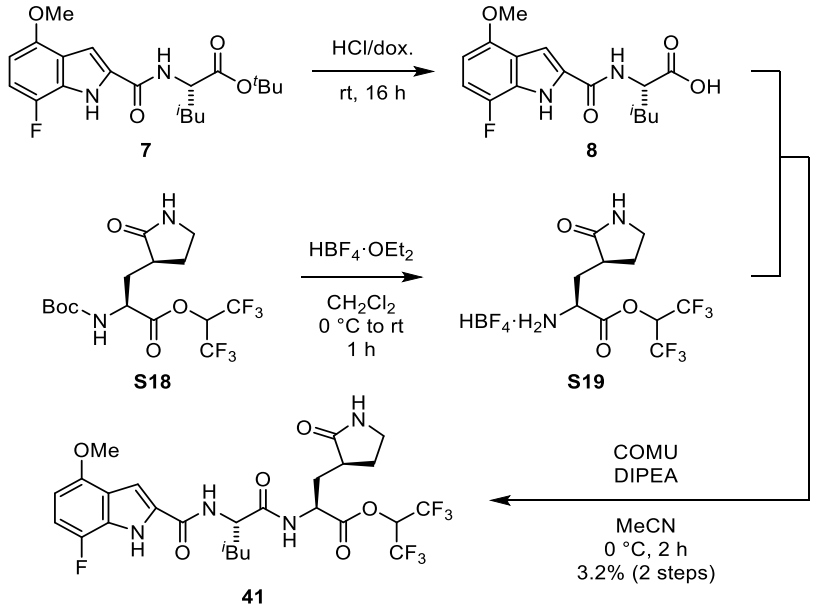


2,2,2-Trifluoroethyl (*S*)-2-((*S*)-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (40): The *tert*-butyl ester **7** (114 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred for 16 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S16** (106 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S17** was used immediately in next step without purification.

The crude amine **S17** (0.300 mmol) was coupled to the crude carboxylic acid **8** (0.300 mmol) using COMU (129 mg, 0.300 mmol) in the presence of DIPEA (101 µL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C and the solution was allowed to stir for 4 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **40**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **40** as a white solid (4.96 mg, 3.0% (2 steps)): t_R = 14.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.67 (d, J = 5.9 Hz, 1H), 7.11-7.10 (m, 1H), 7.05 (d, J = 8.5 Hz), 6.84 (dd, J = 10.6 Hz and 8.5 Hz, 1H), 6.51 (s. 1H), 6.30 (dd, J = 8.5 Hz and 2.8 Hz, 1H), 4.92-4.88 (m, 1H), 4.62-4.41 (m, 3H), 3.89 (s, 3H), 3.36-3.28 (m, 2H), 2.54-2.48 (m, 1H), 2.40-2.35 (m, 1H), 2.26-2.20 (m, 1H), 2.01-1.92 (m, 2H), 1.88-1.74 (m, 2H), 1.69-1.65 (m, 1H), 0.99-0.97 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.0, 173.2, 170.3, 161.1, 150.3 (d, J = 2.2 Hz), 144.8 (d, J = 237.6 Hz), 130.1, 126.2 (d, J = 15.8 Hz), 122.9 (q, J = 277.2 Hz), 121.5 (d, J = 4.6 Hz), 108.9 (d, J = 17.9

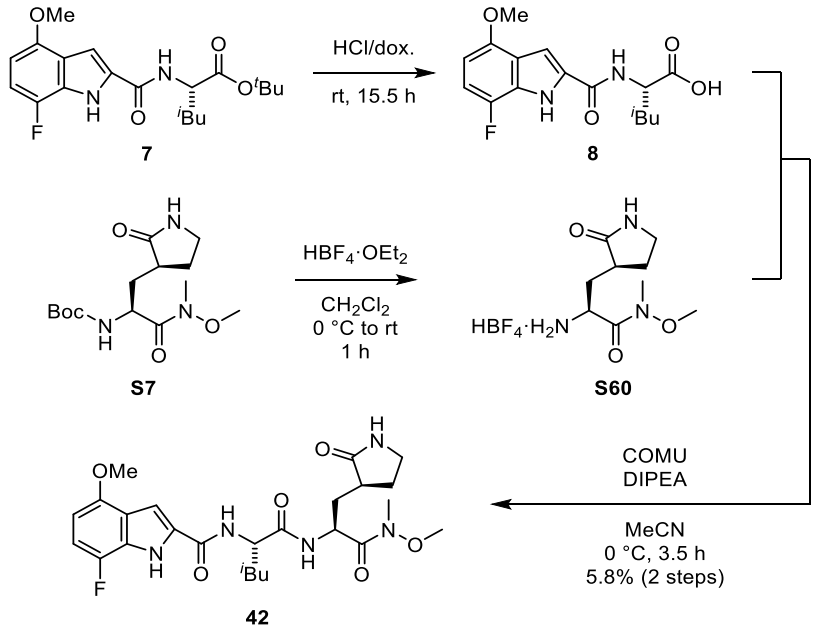
Hz), 102.2, 98.8 (d, J = 6.2 Hz), 61.1 (q, J = 36.9 Hz), 55.8, 52.1, 51.8, 42.4, 40.8, 38.9, 32.3, 28.7, 24.9, 22.9, 22.3; HRMS (ESI), m/z calcd for $C_{25}H_{31}F_4N_4O_6$ $[M+H]^+$ 559.2174, found 559.2173.



1,1,1,3,3,3-Hexafluoropropan-2-yl (*S*)-2-((*S*)-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (41): The *tert*-butyl ester **7** (114 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred for 16 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S18** (127 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S19** was used immediately in next step without purification.

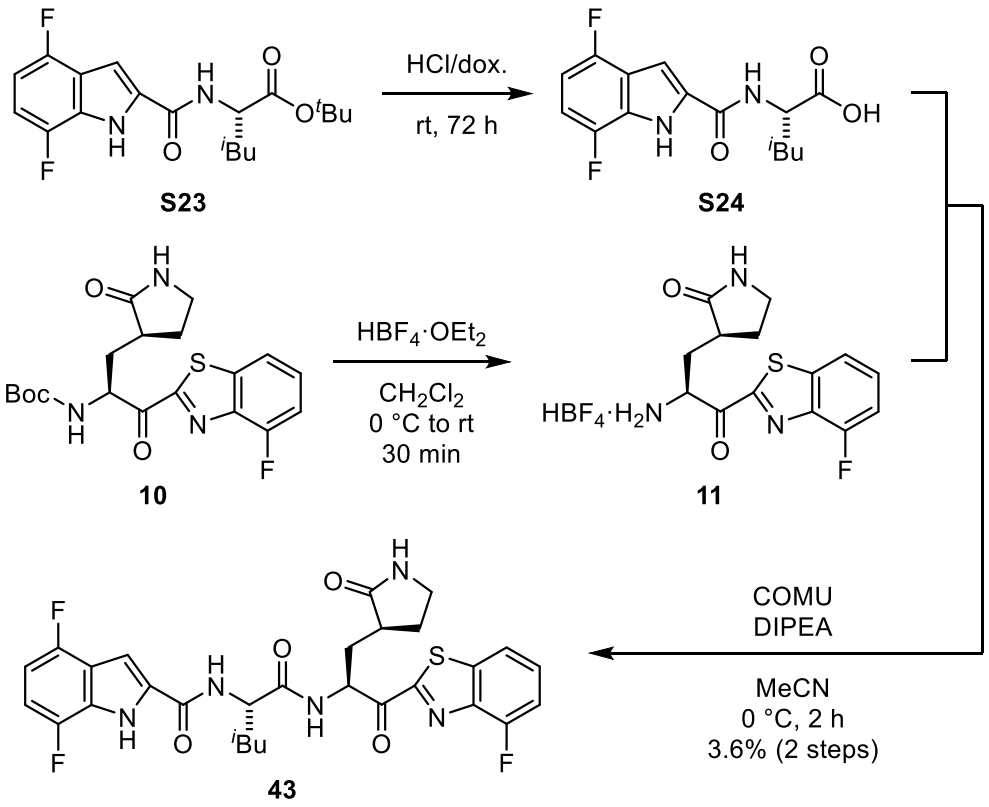
The crude amine **S19** (0.300 mmol) was coupled to the crude carboxylic acid **8** (0.300 mmol) using COMU (129 mg, 0.300 mmol) in the presence of DIPEA (101 µL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C and the solution was allowed to stir for 2 h at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **41**. Further purification was performed by preparative RP-HPLC to give the title compound **41** as a white solid (6.10 mg, 3.2% (2 steps)): t_R = 21.1 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.96 (d, J = 4.9 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.11-7.10 (m, 1H), 6.83 (dd, J = 10.5 Hz and 8.5 Hz, 1H), 6.70 (s, 1H), 6.29 (dd, J = 8.5 Hz and 2.8 Hz, 1H), 5.78 (hept, J = 6.0 Hz, 1H), 4.89-4.85 (m, 1H), 4.60-4.56 (m, 1H), 3.88 (s, 3H), 3.37-3.29 (m, 2H), 2.59-2.53 (m, 1H), 2.42-2.36 (m, 1H), 2.26-2.20 (m, 1H), 1.97-1.93 (m, 1H), 1.89--1.83 (m, 1H), 1.81-1.75 (m, 2H), 1.72-1.65 (m, 1H), 0.98 (d, J = 6.0 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.1, 173.5, 168.8, 161.2, 150.3 (d, J = 1.7 Hz), 144.7 (d, J = 237.7 Hz), 129.9, 126.3 (d, J = 16.2 Hz), 121.5 (d, J = 4.6 Hz), 120.4 (d, J = 282.9 Hz, 2C), 109.0 (d, J = 17.9 Hz), 102.4, 98.8 (d, J = 6.0 Hz), 67.2 (hept, J = 35.0 Hz), 55.8, 52.3, 51.8, 42.2, 41.0, 39.1, 31.8, 28.7, 24.9, 22.9, 22.2; HRMS (ESI), m/z calcd for $C_{26}H_{30}F_7N_4O_6$ $[M+H]^+$ 627.2048, found 627.2049.



7-Fluoro-4-methoxy-*N*-((*S*)-1-(((*S*)-1-(methoxy(methyl)amino)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (42): The *tert*-butyl ester **7** (75.7 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (4.0 mL) at room temperature. The solution was stirred for 15.5 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **8**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S7** (63.1 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 µL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S60** was used immediately in next step without purification.

The crude amine **S60** (0.200 mmol) was coupled to the crude carboxylic acid **8** (0.200 mmol) using COMU (85.7 mg, 0.200 mmol) in the presence of DIPEA (67.5 µL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C and the solution was allowed to stir for 3.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **42**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **42** as a pale yellow solid (6.08 mg, 5.8% (2 steps)): t_R = 20.2 min (linear gradient of B in A, 25 to 55% over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.6 (s, 1H), 8.35-8.34 (m, 1H), 7.08-7.06 (m, 2H), 6.82 (dd, *J* = 10.5 Hz and 8.5 Hz, 1H), 6.48 (brs, 1H), 6.29 (dd, *J* = 8.4 Hz and 2.6 Hz, 1H), 5.05-5.03 (m, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.26 (s, 3H), 3.20-3.18 (m, 2H), 2.47 (br, 1H), 2.39 (br, 1H), 2.17-2.12 (m, 1H), 1.80-1.66 (m, 5H), 0.95-0.93 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.0, 172.7, 172.2, 161.0, 150.2 (d, *J* = 1.6 Hz), 144.9 (d, *J* = 238.7 Hz), 130.4, 126.5 (d, *J* = 15.9 Hz), 121.5 (d, *J* = 5.1 Hz), 108.6 (d, *J* = 17.9 Hz), 101.8, 98.5 (d, *J* = 6.1 Hz), 61.8, 55.8, 52.0, 48.5, 42.5, 40.6, 38.4, 33.6, 32.4, 28.4, 25.0, 23.1, 22.6; HRMS (ESI), *m*/*z* calcd for $C_{25}H_{35}FN_5O_6$ $[M+H]^+$ 520.2566, found 520.2566.

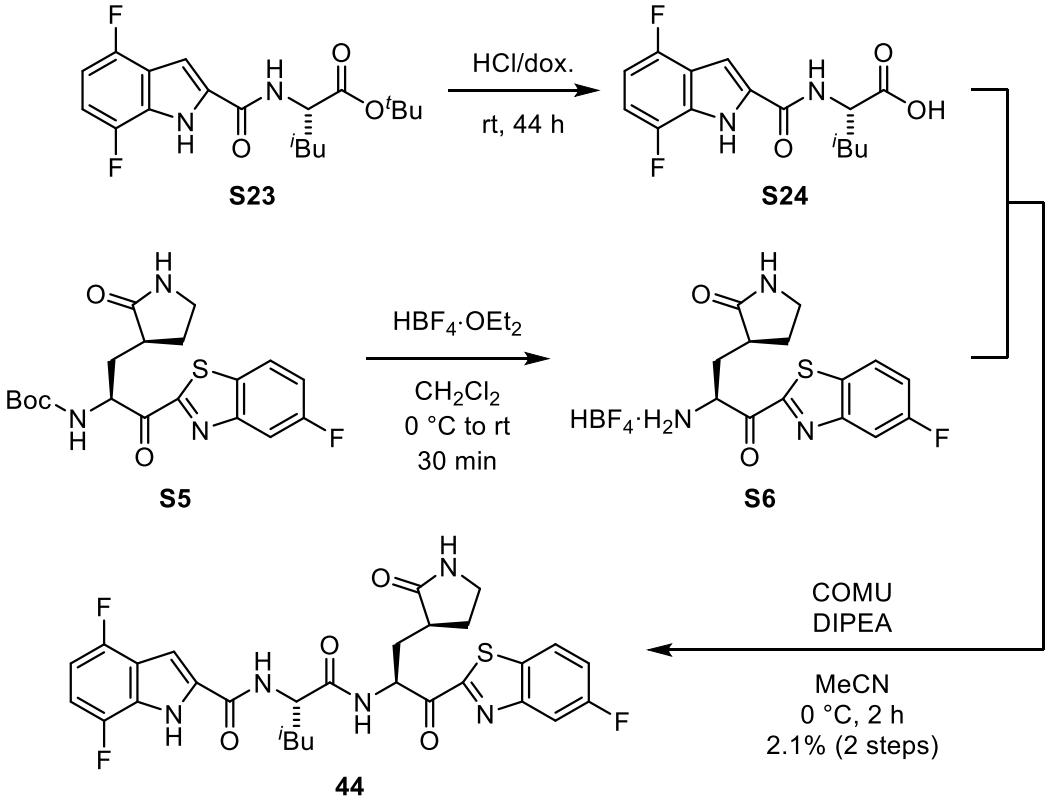


4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (43): The *tert*-butyl ester **S23** (73.3 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 72 h. Concentration under reduced pressure gave a carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.200 mmol) was treated with the crude carboxylic acid **S24** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **43**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **43** as a white solid (4.34 mg, 3.6% (2 steps)): t_R = 21.0 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.4 (s, 1H), 9.00 (d, J = 6.8 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.09-8.08 (m, 1H), 7.70 (s, 1H), 7.65 (dd, J = 8.1 Hz, 8.1 Hz, and 4.8 Hz, 2H), 7.50 (dd, J = 10.7 Hz and 8.2 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.02-6.97 (m, 1H), 6.81-6.77 (m, 1H), 5.47-5.43 (m, 1H), 4.63-4.59 (m, 1H), 3.21-3.13 (m, 2H), 2.57-2.52 (m, 1H), 2.31-2.25 (m, 1H), 2.19-2.13 (m, 1H), 1.91-1.80 (m, 2H), 1.68-1.50 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 192.6, 178.1, 172.5, 165.2, 159.9, 156.2 (d, J = 257.6 Hz), 152.0 (d, J = 242.1 Hz), 145.7 (d, J = 241.4 Hz), 141.7 (d, J = 13.8 Hz), 138.9, 133.1, 129.4 (d, J = 7.4 Hz), 126.4 (dd, J = 16.3 Hz and 11.1 Hz), 119.4 (d, J = 4.3 Hz), 119.0 (dd, J = 24.8 Hz and 5.8 Hz), 112.7 (d, J = 17.2 Hz), 108.0 (dd, J = 19.2 Hz and 8.4 Hz), 103.7 (dd, J =

21.5 Hz and 6.5 Hz), 100.6, 53.8, 51.1, 40.4, 38.1, 32.0, 27.3, 24.3, 23.0, 21.4; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$ 612.2087, found 612.2090.

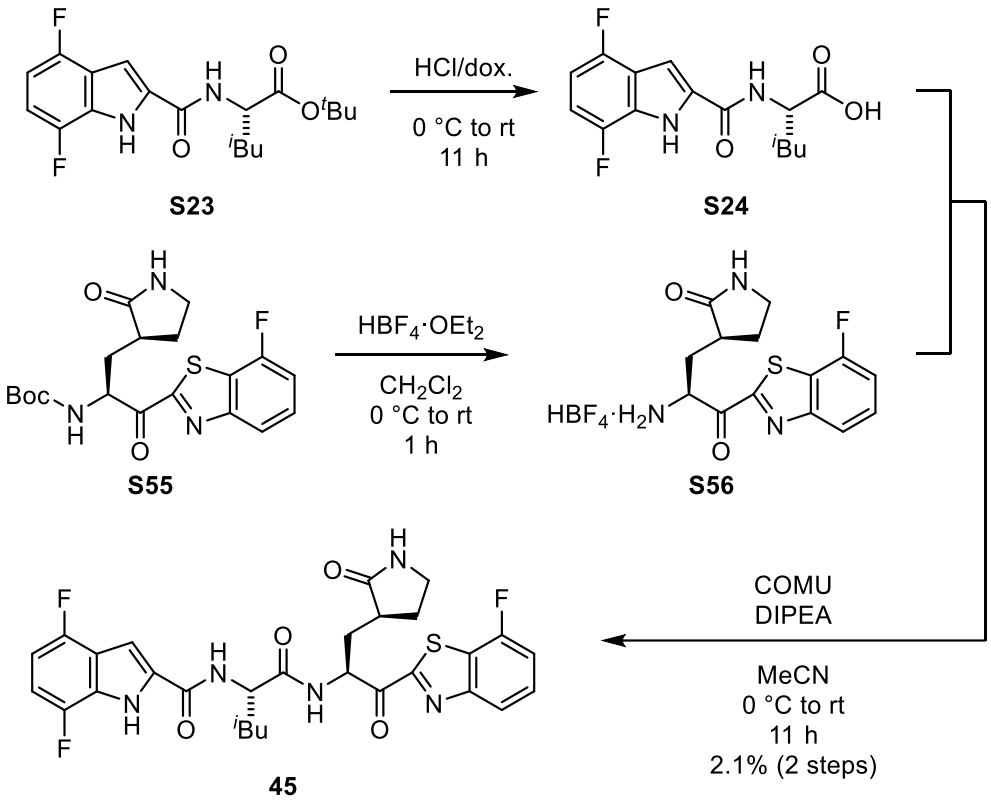


4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (44): The *tert*-butyl ester **S23** (110 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred at room temperature for 44 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (122 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

The crude amine **S6** (0.300 mmol) was treated with the crude carboxylic acid **S24** (0.300 mmol), COMU (129 mg, 0.300 mmol), and DIPEA (101 µL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **44**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **44** as a white solid (3.85 mg, 2.1% (2 steps)): t_R = 21.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.4 (s, 1H), 8.99 (d, J = 6.8 Hz, 1H), 8.54 (d, J = 7.9 Hz, 1H), 8.31 (dd, J = 8.9 Hz and 5.3 Hz, 1H), 8.05 (dd, J = 9.5 Hz and 2.5 Hz, 1H), 7.71 (s, 1H), 7.55 (ddd, J = 9.0 Hz, 9.0 Hz, and 2.5 Hz, 1H), 7.35 (br, 1H), 7.02-6.97 (m, 1H), 6.81-6.77 (m, 1H), 5.47-5.43 (m, 1H), 4.64-4.59 (m, 1H), 3.21-3.13 (m, 2H), 2.56-2.51 (m, 1H), 2.28-2.23 (m, 1H), 2.18-2.12 (m, 1H), 1.90-

1.80 (m, 2H), 1.69-1.51 (m, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ 192.7, 178.1, 172.5, 167.0, 161.6 (d, J = 243.0 Hz), 159.9, 153.7 (d, J = 12.5 Hz), 152.0 (dd, J = 241.9 Hz and 1.9 Hz), 145.7 (d, J = 242.8 Hz), 133.1, 132.3, 126.5-126.3 (m), 124.8 (d, J = 9.9 Hz), 119.0 (dd, J = 25.5 Hz and 5.5 Hz), 117.0 (d, J = 25.3 Hz), 110.6 (d, J = 23.7 Hz), 108.0 (dd, J = 20.0 Hz and 8.5 Hz), 103.7 (dd, J = 20.7 Hz and 4.9 Hz), 100.6, 53.8, 51.3, 40.5, 38.0, 32.0, 27.4, 24.3, 23.0, 21.4; HRMS (ESI), m/z calcd for $C_{29}H_{29}F_3N_5O_4S$ $[M+H]^+$ 600.1887, found 600.1888.

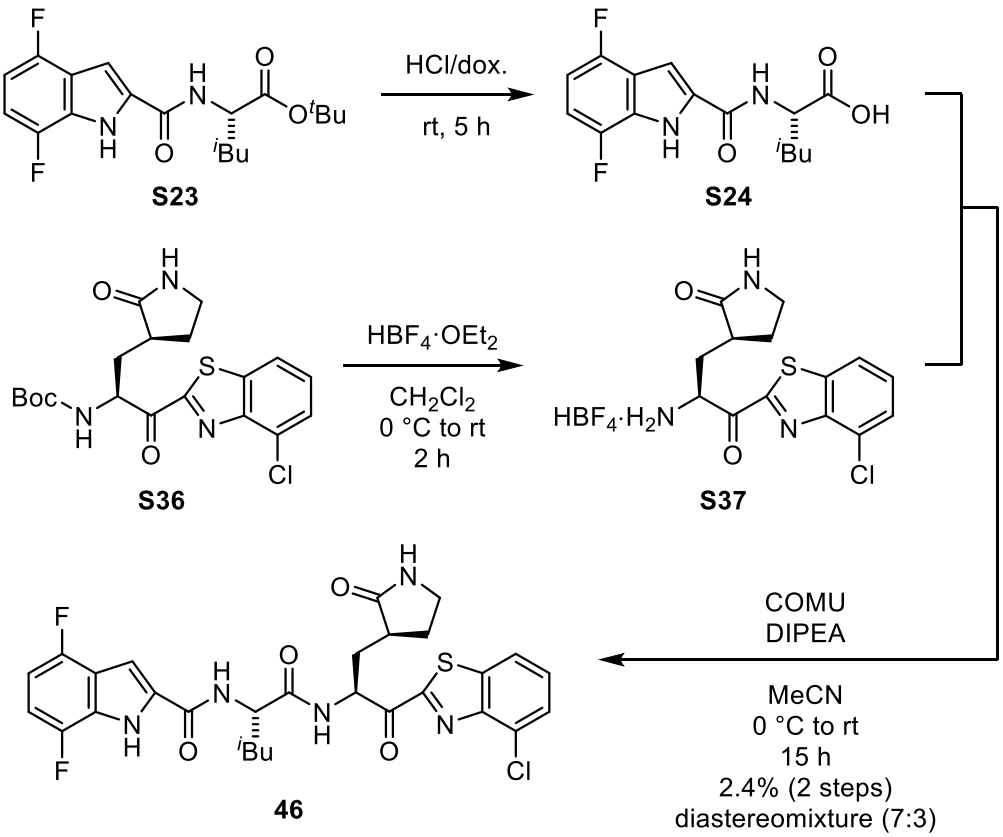


4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(7-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (45): The *tert*-butyl ester **S23** (183 mg, 0.500 mmol) was treated with 4 M HCl in dioxane (10 mL) at 0 °C. The solution was stirred for 11 h at room temperature, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S55** (102 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (68.6 μL, 0.500 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S56** was used immediately in next step without purification.

The crude amine **S56** (0.250 mmol) was treated with the crude carboxylic acid **S24** (0.250 mmol), COMU (128 mg, 0.300 mmol), and DIPEA (128 μL, 0.750 mmol) in MeCN (2.5 mL) at 0 °C, and the mixture was allowed to stir for 11 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic solvent was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **45**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **45** as a yellow solid (3.11 mg, 2.1% (2

steps)): t_R = 22.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.39 (s, 1H), 9.05 (d, J = 6.9 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.70-7.66 (m, 1H), 7.56-7.53 (m, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.02-6.97 (m, 1H), 6.81-6.77 (m, 1H), 5.45-5.40 (m, 1H), 4.64-4.59 (m, 1H), 3.22-3.13 (m, 2H), 2.57-2.51 (m, 1H), 2.30-2.24 (m, 1H), 2.20-2.14 (m, 1H), 1.91-1.79 (m, 2H), 1.68-1.58 (m, 2H), 1.56-1.50 (m, 1H), 0.88 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.4, 178.1, 172.5, 165.3, 159.9, 156.4 (d, J = 248.9 Hz), 155.5, 152.0 (d, J = 240.3 Hz), 145.7 (dd, J = 241.5 Hz and 2.4 Hz), 133.1, 128.9 (d, J = 7.3 Hz), 126.4 (dd, J = 16.8 Hz and 10.8 Hz), 123.4 (d, J = 16.9 Hz), 121.7 (d, J = 3.7 Hz), 119.0 (dd, J = 24.1 Hz and 6.0 Hz), 113.4 (d, J = 18.0 Hz), 108.0 (dd, J = 19.2 Hz and 8.4 Hz), 103.7 (dd, J = 21.7 Hz and 7.2 Hz), 100.6, 53.9, 51.1, 40.4, 38.0, 31.9, 27.4, 24.3, 23.0, 21.4; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{29}F_3N_5O_4S$ $[M+H]^+$ 600.1887, found 600.1887.

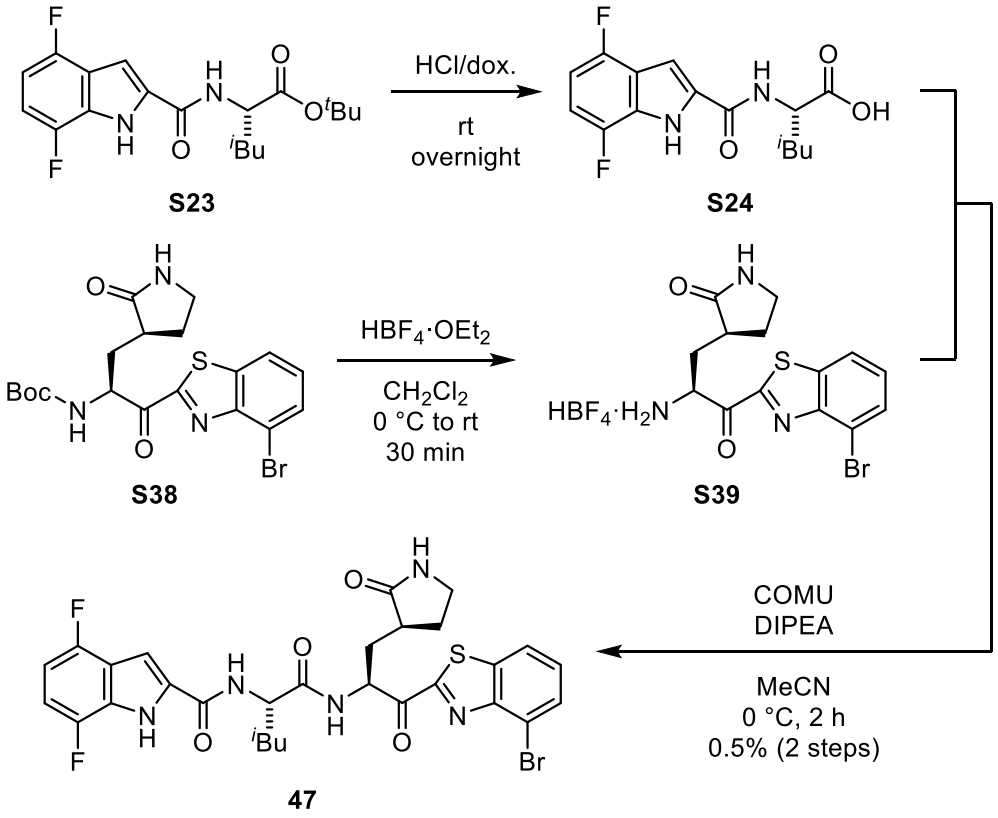


***N*-((*S*)-1-(((*S*)-1-(4-chlorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (46)**: The *tert*-butyl ester **S23** (366 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (10 mL) at room temperature. The solution was stirred for 5 h at room temperature, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S36** (200 mg, 0.470 mmol) in CH_2Cl_2 (5.0 mL) was added $HBF_4{\cdot}OEt_2$ (225 µL, 1.64 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S37** was used immediately in next step without purification.

The crude amine **S37** (0.470 mmol) was treated with the crude carboxylic acid **S24** (1.00 mmol), COMU (222 mg, 0.520 mmol), and DIPEA (159 µL, 0.940 mmol) in MeCN (5.0 mL) at 0 °C, and the mixture was allowed

to stir for 15 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **46**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **46** as a pale yellow powder (6.9 mg, 2.4% (2 steps) as diastereomixture (7:3)): t_R = 27.0 min (linear gradient of B in A, 20 to 80% over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (br, 1H), 9.11-9.09 (m, 0.3H), 8.96 (d, J = 6.9 Hz, 0.7H), 8.59-8.56 (m, 0.7H), 8.53-8.51 (m, 0.3H), 8.26-8.23 (m, 1H), 7.79-7.76 (m, 1H), 7.69-7.68 (m, 1H), 7.65-7.61 (m, 1H), 7.37 (s, 0.7H), 7.35 (s, 0.3H), 7.02-6.97 (m, 1H), 6.81-6.77 (m, 1H), 5.55-5.47 (m, 1H), 4.67-4.60 (m, 1H), 3.24-3.16 (m, 1.4H), 3.12-3.09 (m, 0.6H), 2.57-2.52 (m, 1H), 2.40-2.27 (m, 1.4H), 2.16-2.11 (m, 0.6H), 2.04-1.89 (m, 1.4H), 1.81-1.51 (m, 3.6H), 0.92-0.84 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 193.0, 192.6, 178.0, 177.9, 172.7, 172.1, 165.8, 165.2, 159.9, 159.9, 152.0 (d, J = 243.9 Hz), 149.6, 145.7 (d, J = 244.1 Hz), 138.1, 133.2, 129.0, 128.9, 128.7, 127.5, 127.5, 126.5-126.4 (m), 122.4, 122.3, 119.1-118.9 (m), 108.1-107.9 (m), 103.8-103.6 (m), 100.7 (br), 54.0, 53.9, 51.2, 51.0, 40.5, 40.4, 38.3, 38.1, 32.2, 32.1, 28.1, 27.1, 24.3, 23.1, 23.0, 21.4, 21.2; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{29}ClF_2N_5O_4S$ $[M+H]^+$ 616.1591, found 616.1586.

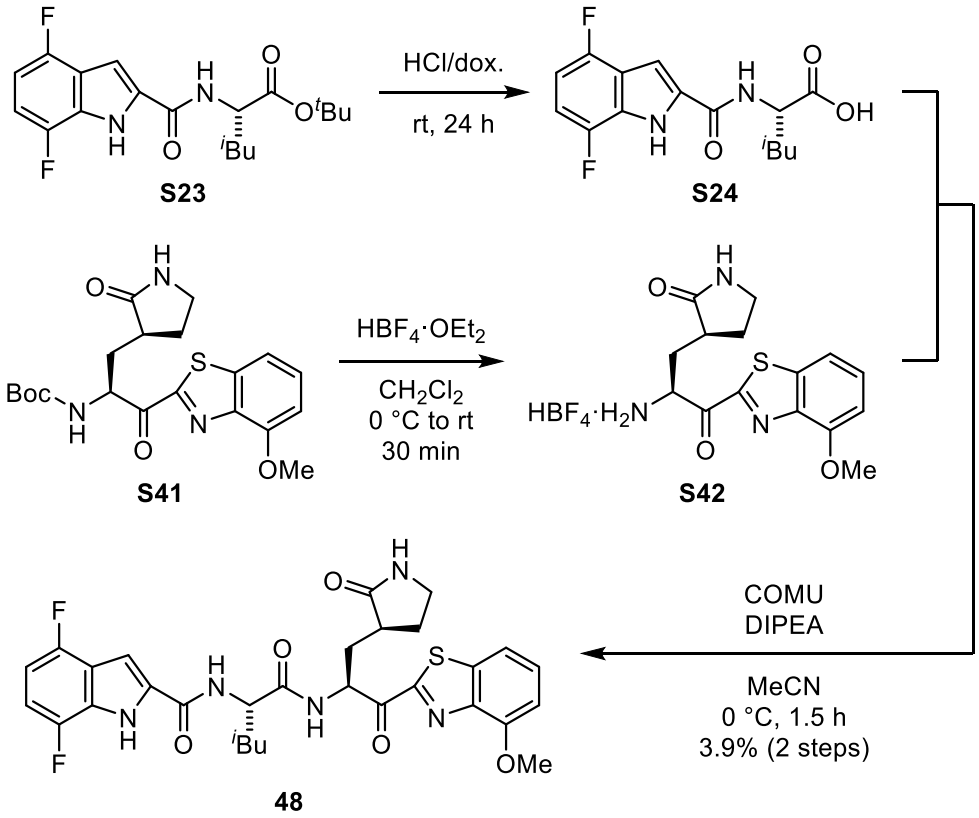


***N*-((*S*)-1-(((*S*)-1-(4-Bromobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (47)**: The *tert*-butyl ester **S23** (366 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (10 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S38** (468 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added HBF_4·OEt_2

(480 μL, 3.50 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S39** was used immediately in next step without purification.

The crude amine **S39** (1.00 mmol) was treated with the crude carboxylic acid **S24** (1.00 mmol), COMU (471 mg, 1.10 mmol), and DIPEA (340 μL, 2.00 mmol) in MeCN (10 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **47**. Further purification was performed by preparative RP-HPLC to give the title compound **47** as a pale yellow solid (3.01 mg, 0.5% (2 steps)): t_R = 23.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.94 (d, J = 6.3 Hz, 1H), 8.57 (d, J = 7.4 Hz, 1H), 8.29-8.27 (m, 1H), 7.94-7.92 (m, 1H), 7.70 (s, 1H), 7.57-7.53 (m, 1H), 7.38 (br, 1H), 7.02-6.97 (m, 1H), 6.81-6.77 (m, 1H), 5.57-5.52 (m, 1H), 4.68-4.63 (m, 1H), 3.26-3.16 (m, 2H), 2.58-2.52 (m, 1H), 2.33-2.28 (m, 1H), 2.15-2.05 (m, 2H), 1.97-1.91 (m, 1H), 1.73-1.56 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.6, 178.0, 172.8, 164.8, 160.0, 152.0 (d, J = 242.8 Hz), 150.8, 145.7 (dd, J = 242.2 Hz and 3.0 Hz), 137.5, 133.2, 130.8, 129.3, 126.4 (dd, J = 16.2 Hz and 11.4 Hz), 123.0, 119.0 (dd, J = 24.6 Hz and 5.4 Hz), 118.0, 108.0 (dd, J = 18.0 Hz and 8.4 Hz), 103.8 (dd, J = 21.6 Hz and 6.0 Hz), 100.7, 53.9, 51.2, 40.6, 38.3, 32.3, 27.0, 24.4, 23.1, 21.4; HRMS (ESI), m/z calcd for $C_{29}H_{29}BrF_2N_5O_4S$ $[M+H]^+$ 660.1086, found 660.1085.

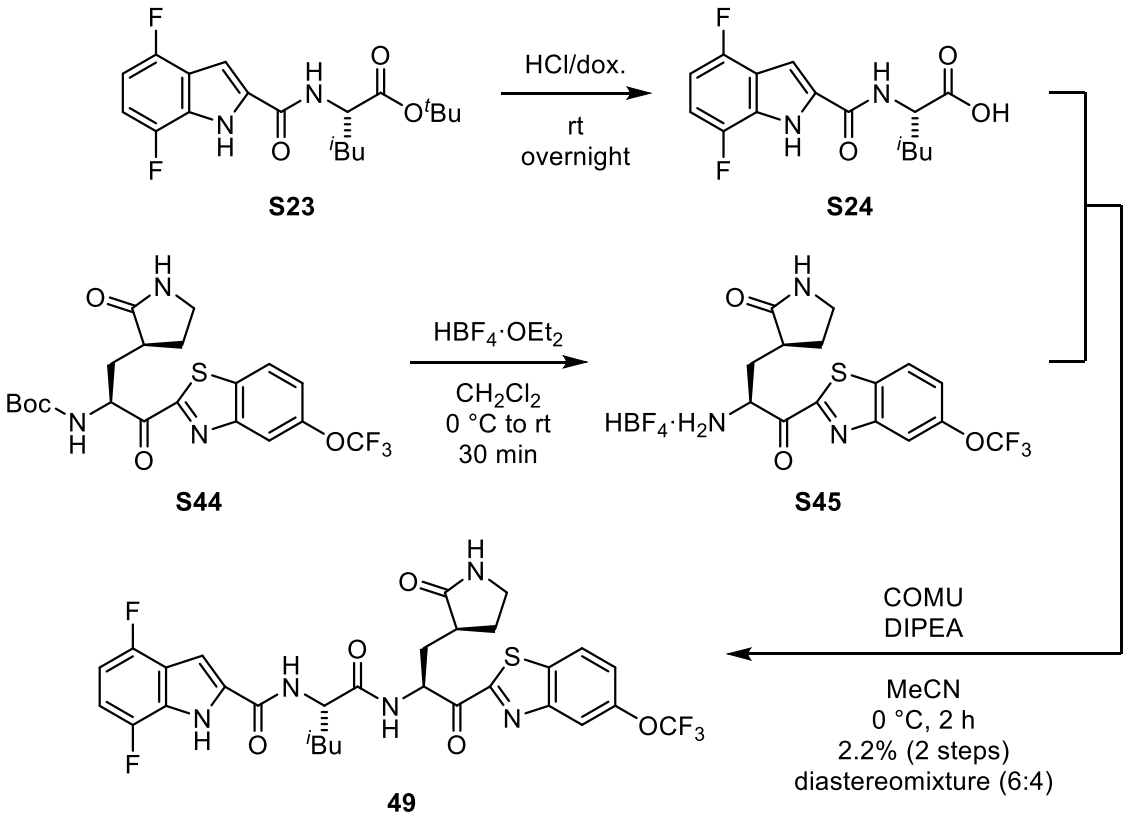


4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(4-methoxybenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (48): The *tert*-butyl ester **S23** (73.3 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room

temperature for 24 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S41** (83.9 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S42** was used immediately in next step without purification.

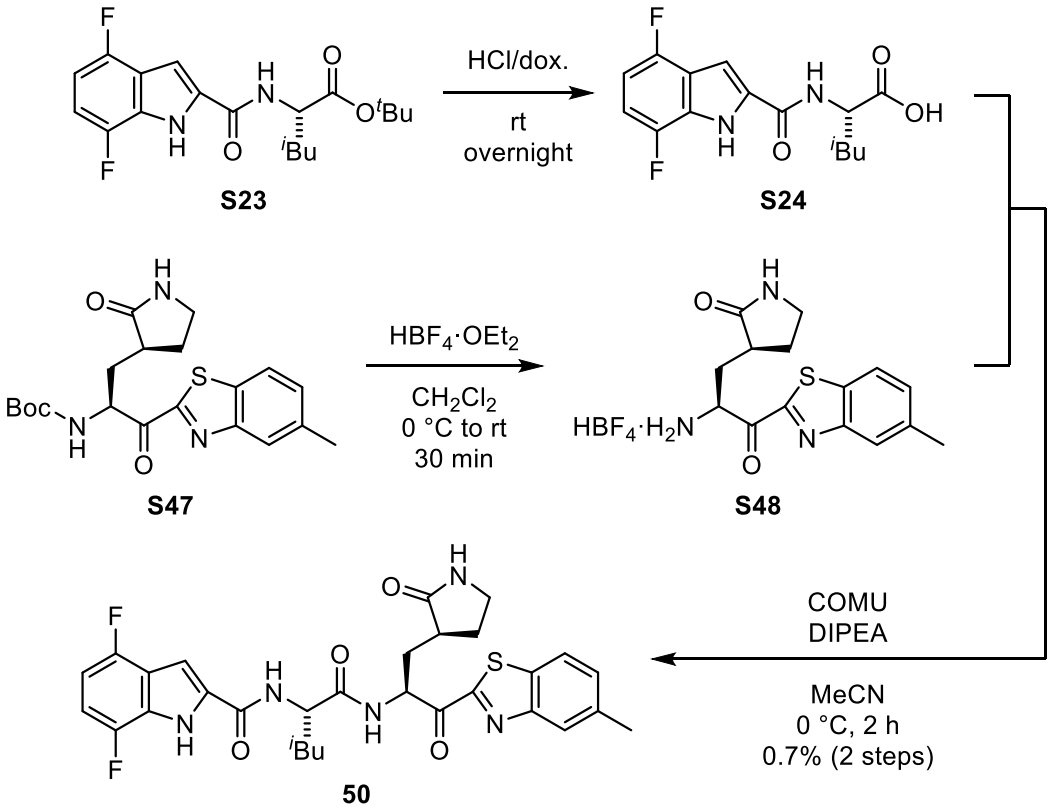
The crude amine **S42** (0.200 mmol) was treated with the crude carboxylic acid **S24** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to give the title compound **48**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **48** as a white solid (4.4 mg, 3.9% (2 steps)): t_R = 19.5 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, MeOD) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 1H), 7.25 (d, *J* = 2.9 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.92-6.87 (m, 1H), 6.70-6.66 (m, 1H), 5.65 (dd, *J* = 11.2 Hz and 3.7 Hz, 1H), 4.68 (dd, *J* = 8.6 Hz and 6.3 Hz, 1H), 4.03 (s, 3H), 3.39-3.33 (m, 2H), 2.80-2.74 (m, 1H), 2.49-2.43 (m, 1H), 2.30-2.25 (m, 1H), 2.16-2.08 (m, 2H), 1.80-1.70 (m, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 5.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, MeOD) δ 193.3, 181.9, 175.3, 163.5, 162.9, 156.6, 154.1 (dd, *J* = 243.9 Hz and 2.4 Hz), 147.5 (dd, *J* = 241.5 Hz and 3.5 Hz), 145.1, 140.1, 133.4, 130.8, 128.3 (dd, *J* = 16.2 Hz and 11.4 Hz), 120.9 (dd, *J* = 25.3 Hz and 4.9 Hz), 115.1, 109.2 (dd, *J* = 19.2 Hz and 8.4 Hz), 108.6, 104.7 (dd, *J* = 21.6 Hz and 7.2 Hz), 101.9, 56.8, 55.9, 53.7, 41.7, 41.6, 40.2, 34.0, 28.6, 26.1, 23.3, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$ 612.2087, found 612.2087.



4,7-Difluoro-*N*-((*S*)-4-methyl-1-oxo-1-(((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)-1-(5-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)propan-2-yl)amino)pentan-2-yl)-1*H*-indole-2-carboxamide (49): The *tert*-butyl ester **S23** (73.3 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S44** (94.9 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S45** was used immediately in next step without purification.

The crude amine **S45** (0.200 mmol) was treated with the crude carboxylic acid **S24** (0.200 mmol), COMU (94.2 mg, 0.220 mmol), and DIPEA (68.0 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **49**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **49** as a yellow solid (2.88 mg, 2.2% (2 steps) as diastereomixture (6:4)): t_R = 26.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 0.4H), 10.14 (s, 0.6H), 9.19 (d, *J* = 5.2 Hz, 0.4H), 9.00 (d, *J* = 4.6 Hz, 0.6H), 8.01 (s, 0.4H), 7.97-7.94 (m, 1H), 7.85 (s, 0.6H), 7.66 (br, 0.6H), 7.41-7.38 (m, 1H), 7.23-7.21 (m, 0.4H), 7.10 (s, 0.4H), 6.99 (s, 0.6H), 6.81-6.77 (m, 1H), 6.74 (br, 0.6H), 6.62-6.57 (m, 1H), 6.47 (s, 0.4H), 5.85-5.81 (m, 0.4H), 5.74-5.69 (m, 0.6H), 4.98-4.89 (m, 1H), 3.40-3.30 (m, 2H), 2.80-2.74 (m, 1H), 2.67-2.53 (m, 1H), 2.46-2.20 (m, 2H), 2.08-1.90 (m, 1H), 1.85-1.67 (m, 3H), 0.97-0.92 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.3, 191.6, 180.7, 173.4, 172.8, 166.6, 166.5, 161.0, 160.7, 154.1, 153.9, 152.8 (d, *J* = 246.3 Hz), 152.7 (d, *J* = 246.3 Hz), 148.5, 148.4, 146.1 (dd, *J* = 241.0 Hz and 3.0 Hz), 146.0 (dd, *J* = 240.9 Hz and 3.0 Hz), 135.6, 135.5, 131.9, 131.4, 126.9-126.6 (m), 123.5, 123.5, 121.9, 121.9, 120.6 (q, *J* = 259.6 Hz), 120.6 (q, *J* = 258.4 Hz), 119.9-119.7 (m), 117.5, 117.4, 108.7-108.5 (m), 104.4-104.1 (m), 101.3, 101.1, 55.6, 54.1, 52.2, 51.9, 42.2, 41.9, 41.2, 41.1, 39.6, 38.1, 32.5, 30.9, 28.8, 28.2, 25.1, 25.0, 23.2, 23.0, 22.1, 21.9; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{29}F_5N_5O_5S$ $[M+H]^+$ 666.1804, found 666.1808.

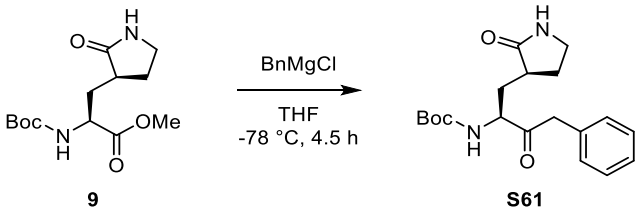


4,7-Difluoro-*N*-((*S*)-4-methyl-1-(((*S*)-1-(5-methylbenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (50): The *tert*-butyl ester **S23** (311 mg, 0.850 mmol) was treated with 4 M HCl in dioxane (8.5 mL) at room temperature. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

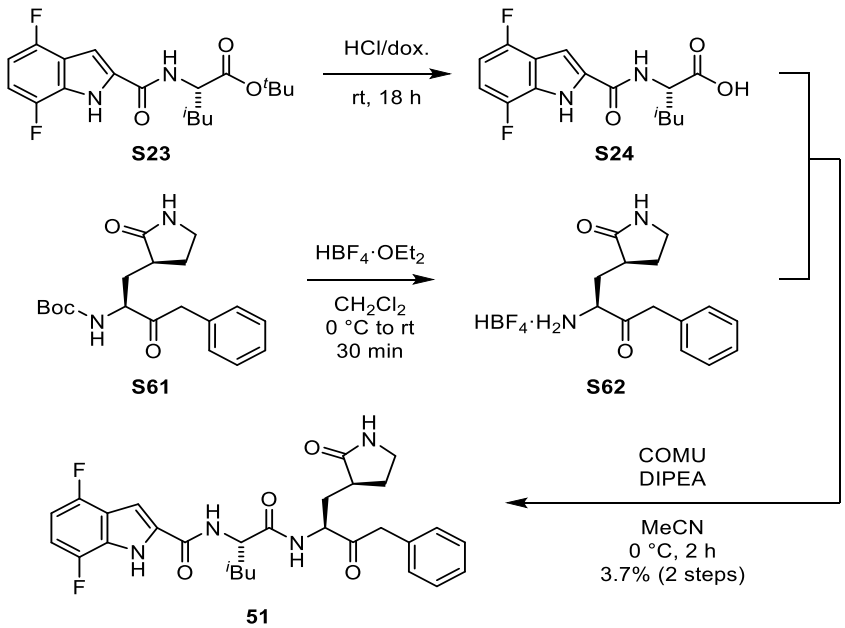
To a solution of Boc protected amine **S47** (342 mg, 0.850 mmol) in CH_2Cl_2 (8.5 mL) was added $HBF_4{\cdot}OEt_2$ (408 μL, 2.97 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **S48** was used immediately in next step without purification.

The crude amine **S48** (0.850 mmol) was treated with the crude carboxylic acid **S24** (0.850 mmol), COMU (400 mg, 0.930 mmol), and DIPEA (340 μL, 1.70 mmol) in MeCN (8.5 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **50**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **50** as a pale yellow solid (3.50 mg, 0.7% (2 steps)): t_R = 25.8 min (linear gradient of B in A, 40 to 70 % over 30 min)); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.41 (brs, 1H), 8.95 (d, J = 6.9 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 7.46 (dd, J = 8.6 Hz and 1.1 Hz, 1H), 7.37-7.37 (m, 1H), 7.00 (ddd, J = 11.2 Hz, 7.7 Hz, and 2.6 Hz, 1H), 6.81-6.77 (m, 1H), 5.49-5.45 (m, 1H), 4.65-4.60 (m, 1H), 3.22-3.14 (m, 2H), 2.57-2.51 (m, 1H), 2.46 (s, 3H), 2.30-2.24 (m, 1H), 2.19-2.11 (m, 1H), 1.91-1.81 (m, 2H), 1.72-1.53 (m, 3H), 0.90 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.9, 178.1, 172.5, 164.4, 159.9, 153.3, 152.0 (d, J = 243.9 Hz), 145.7 (dd, J = 241.5 Hz and 2.4 Hz), 137.4, 133.5, 133.1, 129.9, 126.4 (dd, J = 16.8 Hz and 10.8 Hz), 124.8, 122.6, 119.0 (dd, J = 24.6 Hz

and 5.4 Hz), 108.0 (dd, J = 19.2 Hz and 8.4 Hz), 103.7 (dd, J = 21.0 Hz and 6.7 Hz), 100.6, 53.8, 51.2, 40.5, 38.1, 32.2, 27.3, 24.3, 23.0, 21.4, 20.9; HRMS (ESI), m/z calcd for $C_{30}H_{32}F_2N_5O_4S$ $[M+H]^+$ 596.2138, found 596.2135.



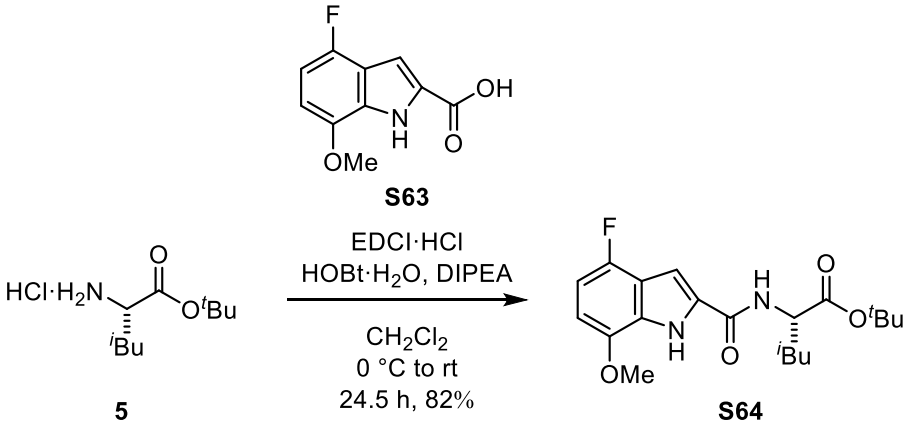
***tert*-Butyl ((*S*)-3-oxo-1-((*S*)-2-oxopyrrolidin-3-yl)-4-phenylbutan-2-yl)carbamate (S61)**: To a solution of methyl ester **9** (143 mg, 0.500 mmol) in THF (5.0 mL) was added benzyl magnesium chloride in THF (0.8 M, 2.81 mL, 2.25 mmol) dropwise at -78 °C. After the mixture was stirred for 4.5 h at -78 °C, the reaction was quenched by the addition of sat. NH_4Cl aq., and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was roughly purified with flash column chromatography over silica gel with EtOAc. The obtained crude **S61** (white foam, 91.0 mg) was used for next step without further purification. HRMS (ESI), m/z calcd for $C_{19}H_{26}N_2NaO_4$ $[M+Na]^+$ 369.1785, found 369.1781.



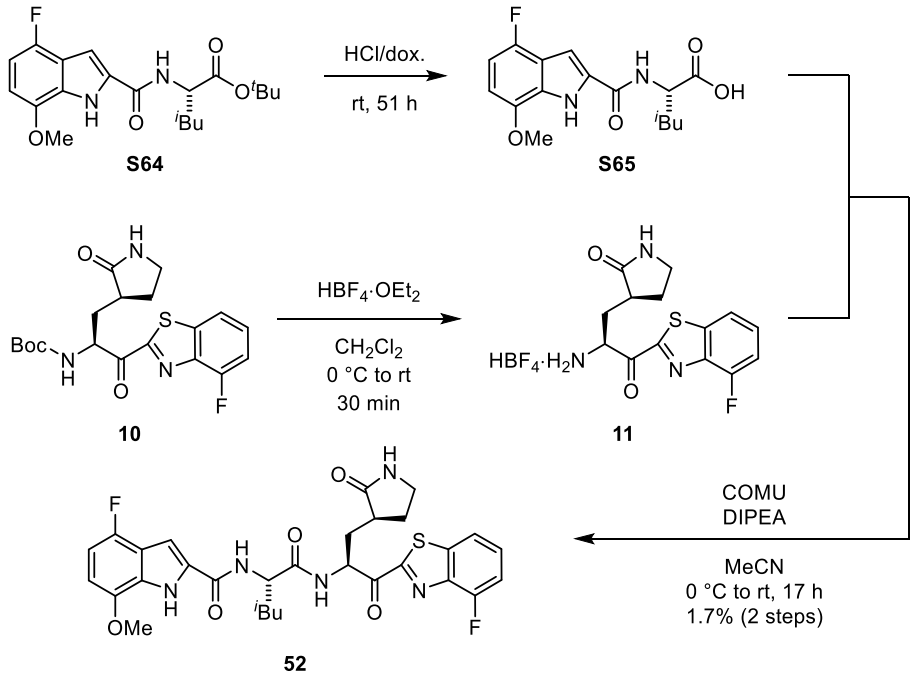
4,7-Difluoro-*N*-((*S*)-4-methyl-1-oxo-1-(((*S*)-3-oxo-1-((*S*)-2-oxopyrrolidin-3-yl)-4-phenylbutan-2-yl)amino)pentan-2-yl)-1*H*-indole-2-carboxamide (51): The *tert*-butyl ester **S23** (73.3 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred for 18 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S61** (69.3 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S62** was used immediately in next step without purification.

The crude amine **S62** (0.200 mmol) was coupled to the crude carboxylic acid **S24** (0.200 mmol) using COMU (85.7 mg, 0.200 mmol) in the presence of DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the solution was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **51**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **51** as a white solid (3.97 mg, 3.7% (2 steps)): t_R = 19.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.2 (s, 1H), 8.61 (d, *J* = 5.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.28-7.25 (m, 2H), 7.23-7.21 (m, 1H), 7.19-7.17 (m, 1H), 7.02 (br, 1H), 6.83-6.79 (m, 1H), 6.62 (ddd, *J* = 8.9 Hz, 8.9 Hz, and 2.7 Hz, 1H), 6.51 (s, 1H), 4.91-4.87 (m, 1H), 4.60-4.56 (m, 1H), 3.85 (s, 2H), 3.28-3.26 (m, 2H), 2.49-2.42 (m, 1H), 2.31 (br, 1H), 2.09-2.02 (m, 1H), 1.81-1.66 (m, 5H), 0.97-0.95 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 206.2, 180.4, 173.6, 160.8, 152.8 (dd, *J* = 244.9 Hz and 2.2 Hz), 146.0 (dd, *J* = 241.1 Hz and 2.8 Hz), 133.6, 131.6, 129.9 (2C), 128.8 (2C), 127.3, 126.7 (dd, *J* = 16.2 Hz and 10.6 Hz), 119.8 (dd, *J* = 24.9 Hz and 5.2 Hz), 108.6 (dd, *J* = 19.1 Hz and 8.3 Hz), 104.3 (dd, *J* = 21.9 Hz and 6.6 Hz), 100.9, 58.1, 52.2, 46.5, 41.9, 40.9, 39.0, 31.7, 28.9, 25.1, 23.1, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{33}F_2N_4O_4$ $[M+H]^+$ 539.2464, found 539.2463.



***tert*-Butyl (4-fluoro-7-methoxy-1*H*-indole-2-carbonyl)-L-leucinate (S64)**: To a solution of 4-fluoro-7-methoxy-1*H*-indole-2-carboxylic acid (500 mg, 2.39 mmol) in CH_2Cl_2 (25 mL) was added L-leucine *tert*-butyl ester hydrochloride **5** (534 mg, 2.39 mmol), $HOBt·H_2O$ (440 mg, 2.87 mmol), EDCI·HCl (550 mg, 2.87 mmol), and DIPEA (1.40 mL, 8.37 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 24.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (5:1) to obtain **S64** as a light brown solid (738 mg, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.04-7.01 (m, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.64 (dd, *J* = 9.7 Hz and 8.6 Hz, 1H), 6.48 (dd, *J* = 8.3 Hz and 3.4 Hz, 1H), 4.78-4.74 (m, 1H), 3.88 (s, 3H), 1.81-1.63 (m, 3H), 1.51 (s, 9H), 0.98-0.96 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.8, 160.8, 151.3 (d, *J* = 241.1 Hz), 143.0 (d, *J* = 2.4 Hz), 130.3, 128.8 (d, *J* = 10.8 Hz), 118.2 (d, *J* = 24.0 Hz), 104.1 (d, *J* = 20.4 Hz), 103.0 (d, *J* = 7.2 Hz), 99.4, 82.5, 55.8, 51.6, 42.0, 28.1 (3C), 25.1, 23.0, 22.2; HRMS (ESI), *m*/*z* calcd for $C_{20}H_{28}FN_2O_4$ $[M+H]^+$ 379.2028, found 379.2029.

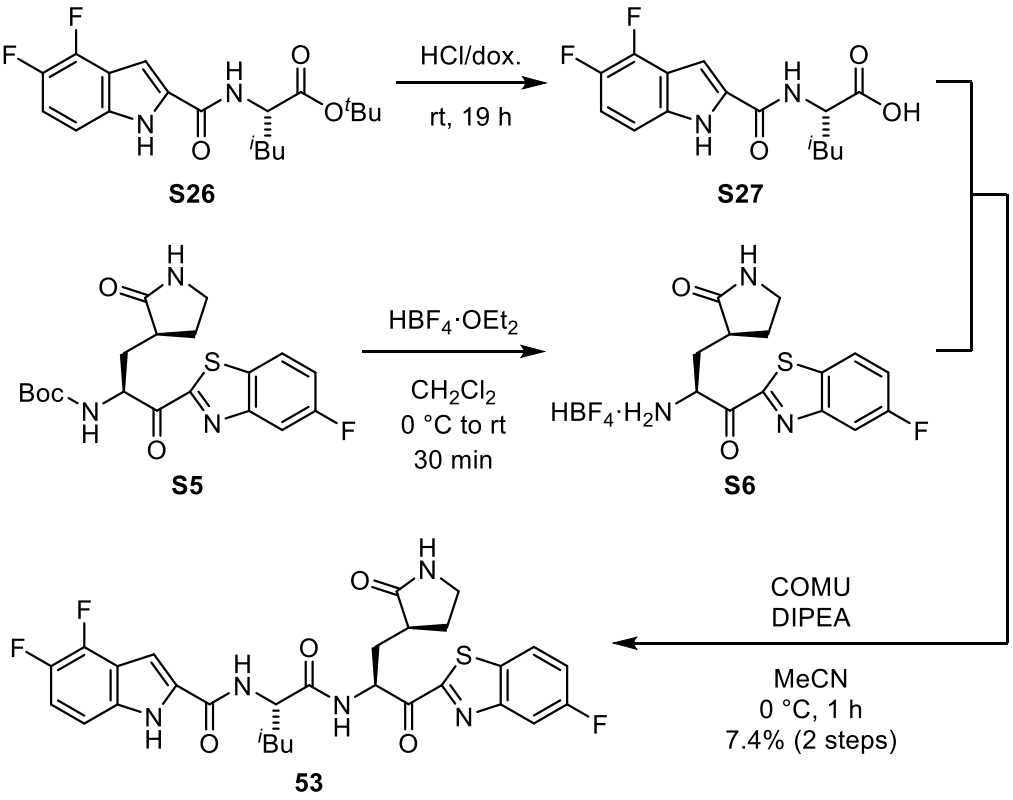


4-Fluoro-*N*-((*S*)-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-methoxy-1*H*-indole-2-carboxamide (52): The *tert*-butyl ester **S64** (110 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred for 51 h at room temperature, and then concentrated under reduced pressure to obtain the corresponding carboxylic acid **S65**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (134 mg, 0.330 mmol) in CH_2Cl_2 (3.3 mL) was added $HBF_4{\cdot}OEt_2$ (144 μL, 1.05 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.330 mmol) was treated with the crude carboxylic acid **S65** (0.300 mmol), COMU (141 mg, 0.330 mmol), and DIPEA (374 μL, 0.660 mmol) in MeCN (3.0 mL) at 0 °C, and the mixture was allowed to stir for 17 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **52**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **52** as a yellow solid (3.12 mg, 1.7% (2 steps)): t_R = 20.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.85 (br, 1H), 9.04 (d, J = 6.9 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.67-7.63 (m, 1H), 7.52-7.48 (m, 1H), 7.13-7.12 (m, 1H), 6.75-6.71 (m, 1H), 6.67-6.65 (m, 1H), 5.46-5.42 (m, 1H), 4.63-4.59 (m, 1H), 3.90 (s, 3H), 3.21-3.13 (m, 2H), 2.57-2.51 (m, 1H), 2.30-2.24 (m, 1H), 2.19-2.13 (m, 1H), 1.91-1.80 (m, 2H), 1.68-1.60 (m, 1H), 1.59-1.50 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.7, 178.1, 172.7, 165.2, 159.7, 156.2 (d, J = 257.2 Hz), 150.4 (d, J = 239.1 Hz), 143.1 (d, J = 2.4 Hz), 141.8 (d, J = 14.4 Hz), 138.9 (d, J = 2.4 Hz), 132.0, 129.4 (d, J = 7.2 Hz), 128.7 (d, J = 10.8 Hz), 119.4 (d, J = 3.7 Hz), 117.1 (d, J = 25.2 Hz), 112.8 (d, J = 16.9 Hz), 103.6 (d, J = 20.4 Hz), 103.0 (d, J = 8.4 Hz), 101.5, 55.8, 53.9, 51.0, 48.7, 40.7, 38.1, 31.9, 27.4, 24.3, 23.0, 21.5; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{32}F_2N_5O_5S$ $[M+H]^+$

612.2087, found 612.2083.

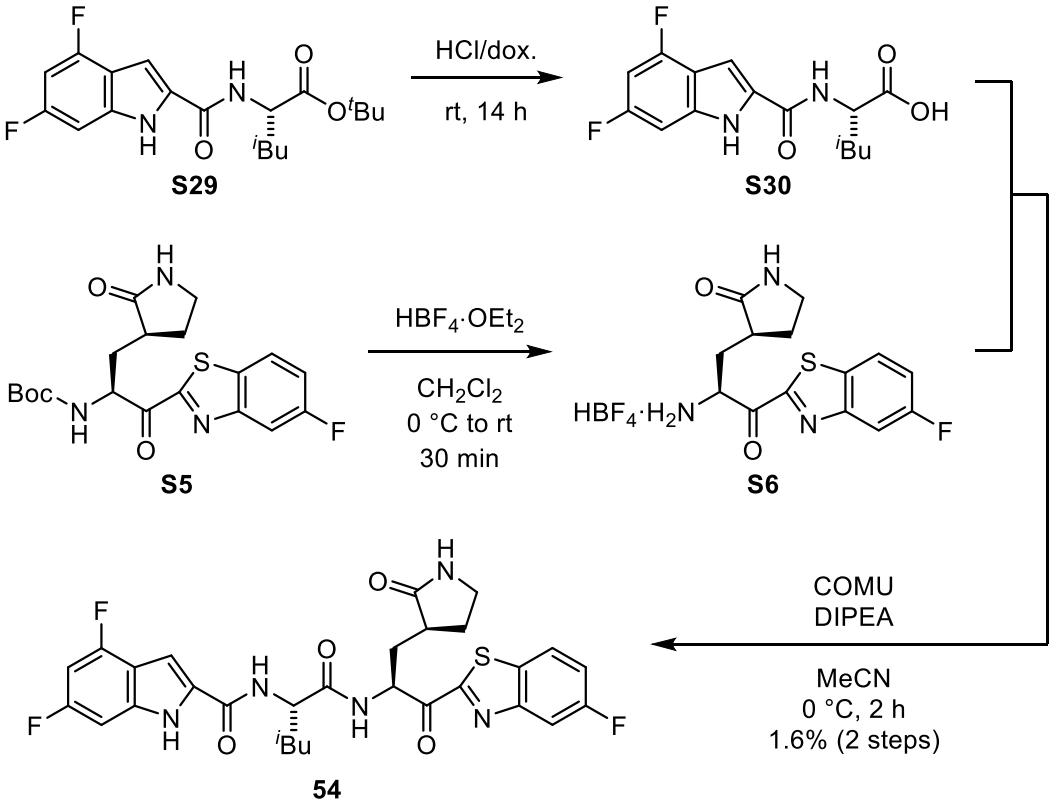


4,5-Difluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (53): The *tert*-butyl ester **S26** (73.3 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 19 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S27**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

The crude amine **S6** (0.200 mmol) was treated with the crude carboxylic acid **S27** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **53**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **53** as a white solid (8.89 mg, 7.4% (2 steps)): t_R = 21.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (s, 1H), 8.95 (d, J = 5.2 Hz, 1H), 7.88 (dd, J = 8.9 Hz and 4.9 Hz, 1H), 7.70 (dd, J = 9.0 Hz and 2.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.29 (ddd, J = 8.8 Hz, 8.8 Hz, and 2.4 Hz, 1H), 7.03 (brs, 1H), 7.00-6.96 (m, 2H), 6.48 (s, 1H), 5.72-5.68 (m, 1H), 4.95-4.90 (m, 1H), 3.35-3.33 (m, 2H), 2.73-2.67 (m, 1H), 2.50 (br, 1H), 2.24-2.16 (m, 2H), 2.03-1.94 (m, 1H), 1.84-1.76 (m, 2H), 1.73-1.69 (m, 1H), 0.97-0.96 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.9, 180.3, 166.4, 162.2 (d, J =

245.7 Hz), 161.0, 154.3 (d, J = 12.1 Hz), 144.3 (dd, J = 236.0 Hz and 10.8 Hz), 143.3 (dd, J = 250.4 Hz and 14.2 Hz), 134.4 (d, J = 8.8 Hz), 132.9, 132.0, 123.4 (d, J = 9.6 Hz), 118.3 (d, J = 17.2 Hz), 117.3 (d, J = 25.5 Hz), 114.5 (d, J = 22.1 Hz), 111.2 (d, J = 23.4 Hz), 107.8 (dd, J = 6.0 Hz and 4.5 Hz), 99.7 (d, J = 5.5 Hz), 55.5, 51.9, 42.3, 40.9, 39.5, 32.6, 28.9, 25.0, 23.0, 22.3; HRMS (ESI), m/z calcd for $C_{29}H_{29}F_3N_5O_4S$ $[M+H]^+$ 600.1887, found 600.1883.

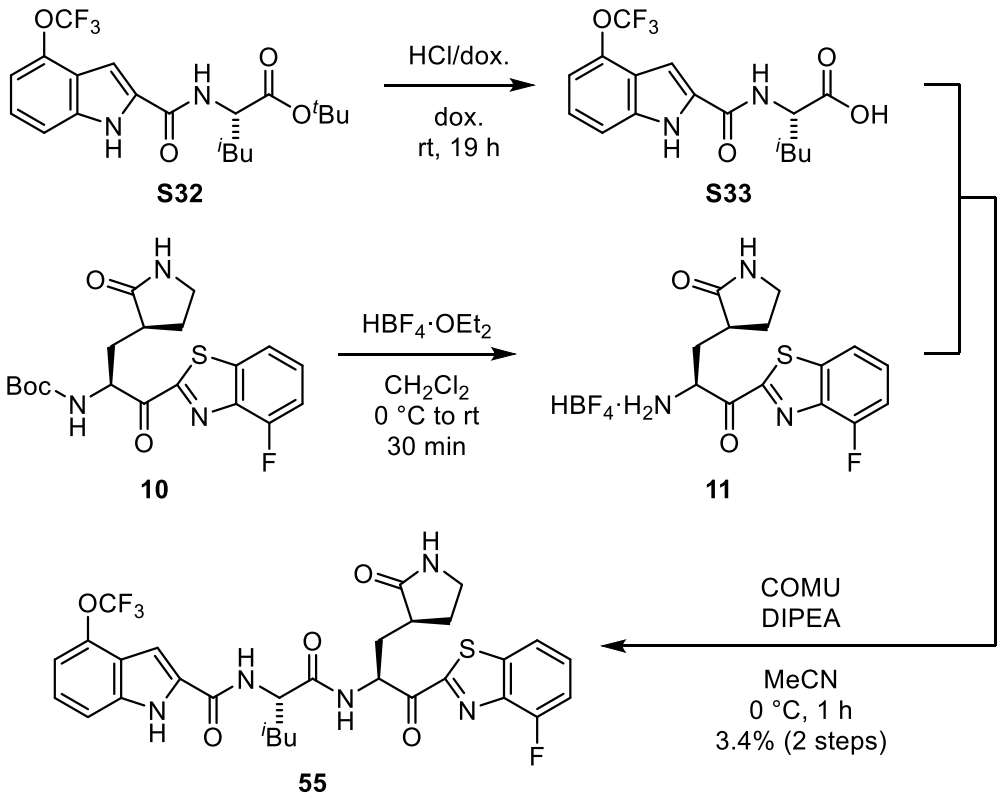


4,6-Difluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (54): The *tert*-butyl ester **S29** (110 mg, 0.300 mmol) was treated with 4 M HCl in dioxane (3.0 mL) at room temperature. The solution was stirred at room temperature for 14 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S30**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (122 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

The crude amine **S6** (0.300 mmol) was treated with the crude carboxylic acid **S30** (0.300 mmol), COMU (129 mg, 0.300 mmol), and DIPEA (101 µL, 0.600 mmol) in MeCN (3.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **54**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **54** as a white solid (2.88 mg, 1.6% (2 steps)): t_R = 22.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.0 (s, 1H), 8.93 (d, J = 6.9

Hz, 1H), 8.52 (d, *J* = 8.1 Hz,, 1H), 8.24 (dd, *J* = 9.1 Hz and 4.9 Hz, 1H), 8.17 (dd, *J* = 8.7 Hz and 2.6 Hz, 1H), 7.70 (s, 1H), 7.52 (ddd, *J* = 9.0 Hz, 9.0 Hz, and 2.7 Hz, 1H), 7.36 (s, 1H), 7.02 (dd, *J* = 9.3 Hz and 1.6 Hz, 1H), 6.88 (ddd, *J* = 10.3 Hz, 10.3 Hz, and 2.0 Hz, 1H), 5.47-5.43 (m, 1H), 4.61-4.57 (m, 1H), 3.21-3.12 (m, 2H), 2.58-2.51 (m, 1H), 2.28-2.22 (m, 1H), 2.18-2.12 (m, 1H), 1.90-1.79 (m, 2H), 1.68-1.60 (m, 2H), 1.56-1.50 (m, 1H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ 192.6, 178.1, 172.5, 164.6 (d, *J* = 3.5 Hz), 161.3 (d, *J* = 247.3 Hz), 160.2, 159.2 (dd, *J* = 238.9 Hz and 12.3 Hz), 155.8 (dd, *J* = 248.9 Hz and 15.7 Hz), 149.8, 137.8 (d, *J* = 12.1 Hz), 137.6 (dd, *J* = 15.7 Hz and 12.8 Hz), 132.3 (d, *J* = 3.3 Hz), 126.9 (d, *J* = 10.1 Hz), 116.6 (d, *J* = 25.5 Hz), 113.1 (d, *J* = 21.9 Hz), 109.3 (d, *J* = 27.3 Hz), 99.1, 95.2 (dd, *J* = 29.8 Hz and 23.2 Hz), 94.6 (dd, *J* = 25.7 Hz and 4.2 Hz), 53.7, 51.1, 40.3, 38.0, 32.1, 27.4, 25.5, 24.3, 23.0, 21.4; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{29}F_3N_5O_4S$ $[M+H]^+$ 600.1887, found 600.1891.

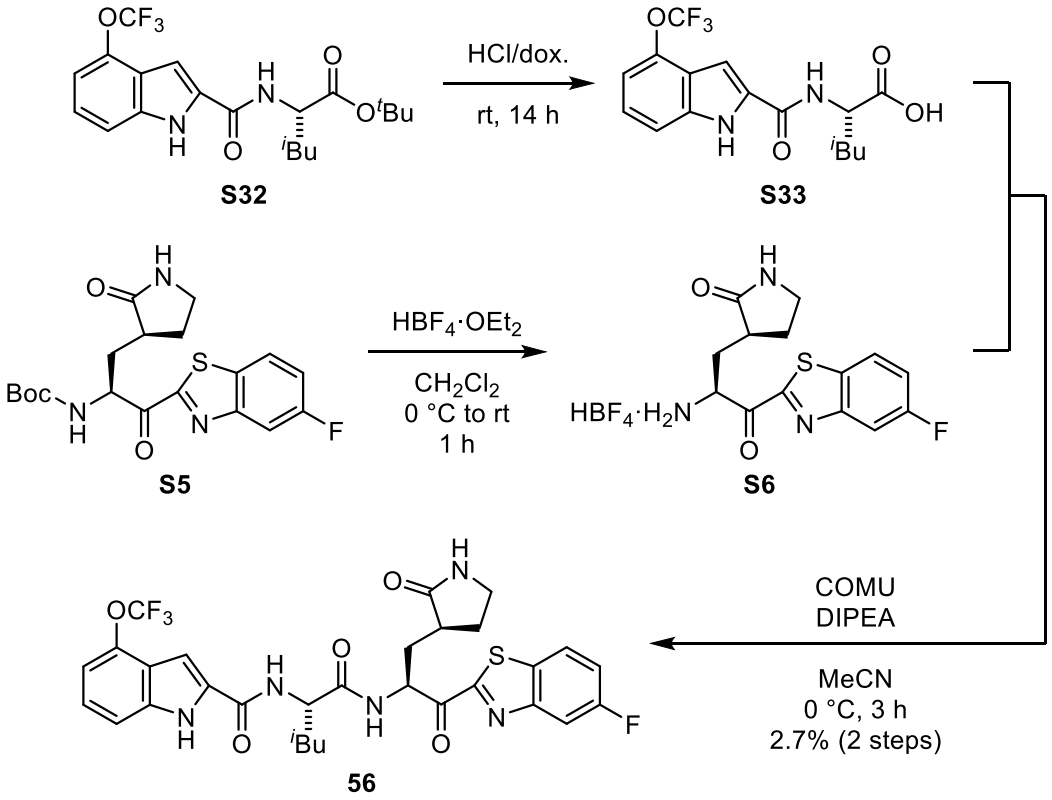


***N*-((*S*)-1-(((*S*)-1-(4-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-(trifluoromethoxy)-1*H*-indole-2-carboxamide (55)**: The *tert*-butyl ester **S32** (67.6 mg, 0.160 mmol) was treated with 4 M HCl in dioxane (1.6 mL) at room temperature. The solution was stirred for 19 h at room temperature. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S33**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (66.5 mg, 0.160 mmol) in CH_2Cl_2 (1.6 mL) was added $HBF_4{\cdot}OEt_2$ (78.4 μL, 0.570 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.160 mmol) was treated with the crude carboxylic acid **S33** (0.160 mmol), COMU (68.8 mg, 0.160 mmol), and DIPEA (55.0 μL, 0.330 mmol) in MeCN (1.6 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The

extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **55**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **55** as a yellow solid (3.62 mg, 3.4% (2 steps)): t_R = 27.1 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.87 (d, *J* = 5.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.50-7.45 (m, 1H), 7.30-7.27 (m, 2H), 7.23-7.19 (m, 1H), 7.14-7.11 (m, 1H), 7.02 (s, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.70 (brs, 1H), 5.76-5.72 (m, 1H), 4.99-4.95 (m, 1H), 3.35-3.27 (m, 2H), 2.72-2.65 (m, 1H), 2.50-2.44 (m, 1H), 2.27-2.17 (m, 2H), 2.09-2.00 (m, 1H), 1.86-1.78 (m, 2H), 1.74-1.68 (m, 1H), 0.97 (d, *J* = 5.7 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.0, 180.3, 172.9, 164.5, 161.3, 157.3 (d, *J* = 262.0 Hz), 142.8, 142.8 (d, *J* = 14.4 Hz), 139.8, 138.3, 131.2, 129.0 (d, *J* = 7.2 Hz), 124.5, 121.4, 120.9 (q, *J* = 258.0 Hz), 118.2 (d, *J* = 3.7 Hz), 112.5 (d, *J* = 18.0 Hz), 111.7, 111.2, 100.2, 55.3, 51.9, 42.3, 40.8, 39.4, 32.8, 28.4, 24.9, 22.9, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{30}F_4N_5O_5S$ $[M+H]^+$ 648.1898, found 648.1898.

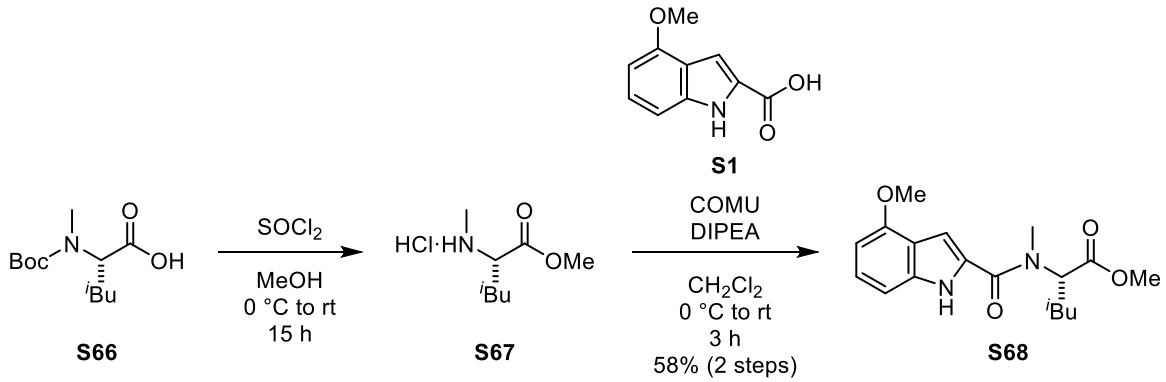


***N*-((*S*)-1-(((*S*)-1-(5-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-(trifluoromethoxy)-1*H*-indole-2-carboxamide (56)**: The *tert*-butyl ester **S32** (82.9 mg, 0.200 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred at room temperature for 14 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S33**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added HBF_4·OEt_2 (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

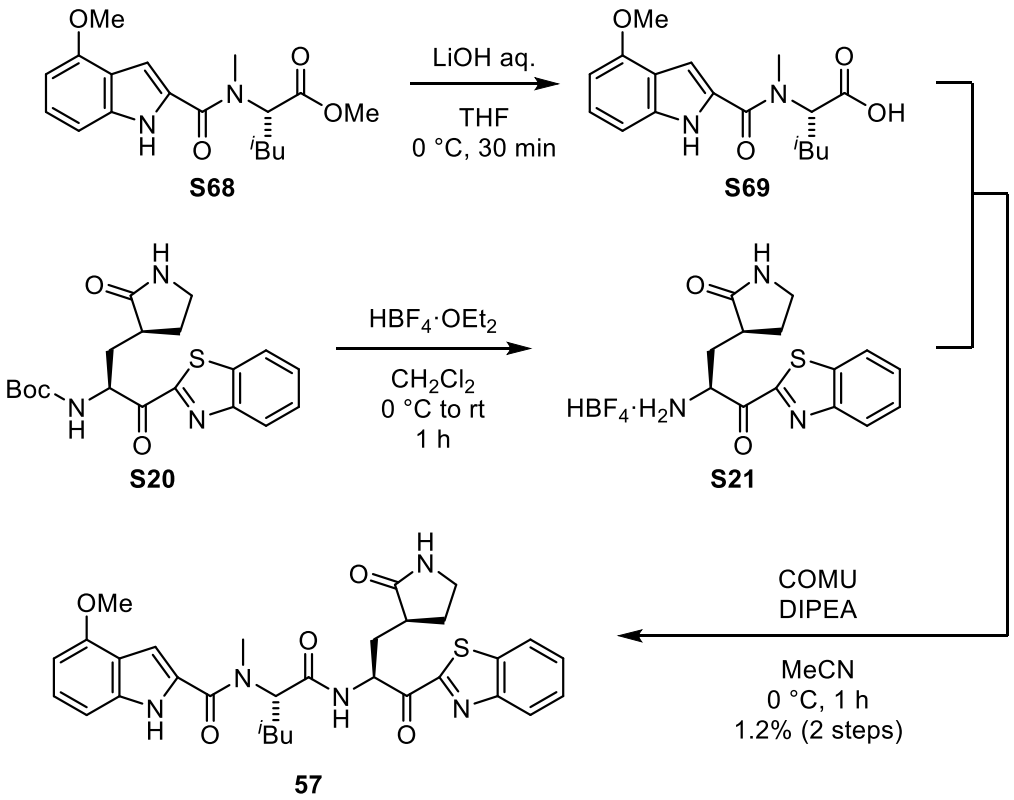
The crude amine **S6** (0.200 mmol) was treated with the crude carboxylic acid **S33** (0.200 mmol), COMU

(85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 3 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **56**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **56** as a pale yellow solid (3.49 mg, 2.7% (2 steps)): t_R = 25.6 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.3 (s, 1H), 8.92 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.9 Hz and 5.0 Hz, 1H), 7.71 (dd, J = 9.0 Hz and 2.2 Hz, 1H), 7.34-7.26 (m, 3H), 7.14-7.11 (m, 1H), 7.04 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 5.71-5.69 (m, 1H), 4.97-4.93 (m, 1H), 3.32-3.31 (m, 2H), 2.72-2.65 (m, 1H), 2.50-2.46 (m, 1H), 2.25-2.13 (m, 2H), 2.02-1.93 (m, 1H), 1.86-1.77 (m, 2H), 1.73-1.69 (m, 1H), 0.97 (d, *J* = 6.1 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 180.3, 172.9, 166.4, 162.2 (d, *J* = 247.3 Hz), 161.3, 154.3 (d, *J* = 12.2 Hz), 142.9, 138.3, 132.9, 131.2, 124.5, 123.4 (d, *J* = 9.7 Hz), 121.4, 121.0 (q, *J* = 257.5 Hz), 117.3 (d, *J* = 25.5 Hz), 111.7, 111.2 (d, *J* = 23.8 Hz), 111.2, 100.3, 55.3, 51.9, 42.3, 40.9, 39.4, 32.7, 28.7, 25.0, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{30}F_4N_5O_5S$ $[M+H]^+$ 648.1898, found 648.1896.



Methyl *N*-(4-methoxy-1*H*-indole-2-carbonyl)-*N*-methyl-L-leucinate (S68): To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucine **S66** (1.23 g, 5.00 mmol) in MeOH (20 mL) was added thionyl chloride (1.09 mL, 15.0 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 15 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S67**, which was used immediately in next step without purification.

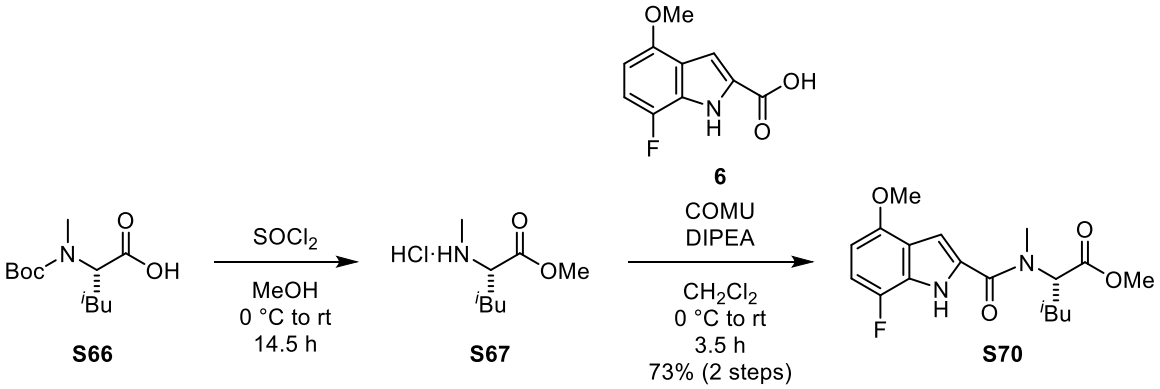
To a solution of the crude methyl ester **S67** (5.00 mmol) in CH_2Cl_2 (20 mL) was added 4-methoxy-1*H*-indole-2-carboxylic acid (956 mg, 5.00 mmol), COMU (2.36 g, 5.50 mmol), and DIPEA (1.83 mL, 10.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to afford **S68** as an orange solid (964 mg, 58% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (brs, 1H), 7.23-7.20 (m, 1H), 7.06 (s, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 5.48-5.45 (m, 1H), 3.96 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H), 1.90-1.84 (m, 2H), 1.64-1.57 (m, 1H), 0.98-0.95 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.4, 163.7, 154.4, 137.1, 128.1, 125.9, 119.2, 104.9, 104.2, 99.6, 55.9, 55.4, 52.4, 37.7, 33.8, 25.3, 23.4, 21.6; HRMS (ESI), *m*/*z* calcd for $C_{18}H_{24}N_2NaO_4$ $[M+Na]^+$ 355.1628, found 355.1626.



***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide (57)**: To a solution of methyl ester **S68** (166 mg, 0.500 mmol) in THF (5.0 mL) was added an aqueous LiOH (2.0 M, 0.500 mL, 1.00 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C, and then the mixture was acidified with HCl (2.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S69**, which was used immediately in next step without purification.

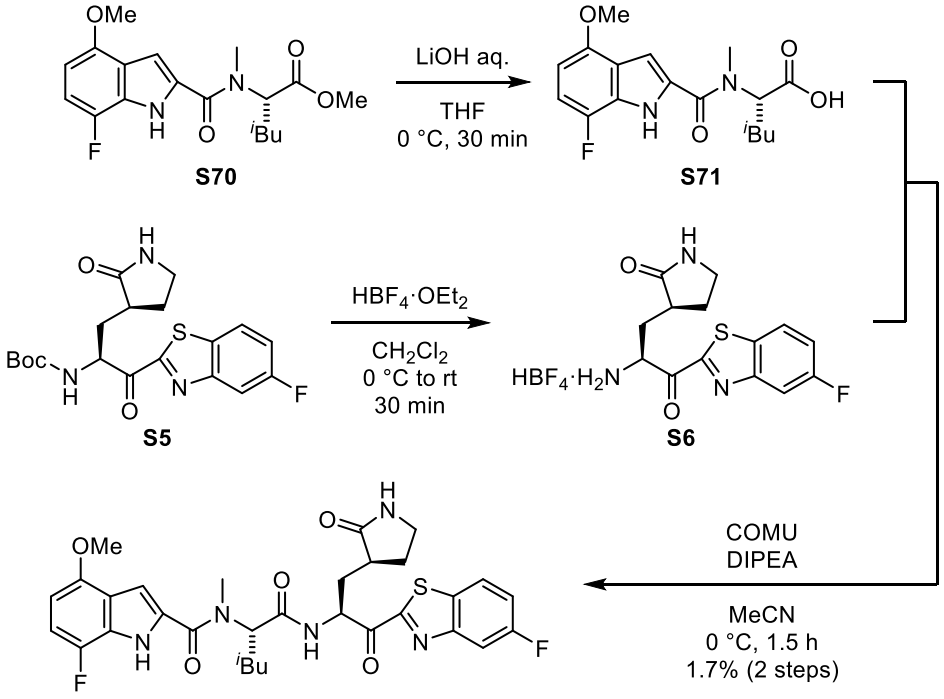
To a solution of Boc protected amine **S20** (195 mg, 0.500 mmol) in CH_2Cl_2 (5.0 mL) was added $HBF_4{\cdot}OEt_2$ (240 µL, 1.75 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S21** was used immediately in next step without purification.

The crude amine **S21** (0.500 mmol) was coupled with the crude carboxylic acid **S69** (0.500 mmol) using COMU (214 mg, 0.500 mmol) in the presence of DIPEA (169 µL, 1.00 mmol) in MeCN (5.0 mL) at 0 °C and the solution was allowed to stir for 1 h at 0 ºC. The reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$. and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **57**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **57** as a yellow solid (3.53 mg, 1.2% (2 steps)): t_R = 21.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.17-8.09 (m, 2H), 7.98-7.96 (m, 1H), 7.53-7.51 (m, 2H), 7.22-7.19 (m, 1H), 7.06-7.03 (m, 2H), 6.49 (d, *J* = 7.4 Hz, 1H), 6.23 (brs, 1H), 5.74 (s, 1H), 5.33 (s, 1H), 3.96 (s, 3H), 3.37-3.30 (m, 5H), 2.53-2.49 (m, 2H), 2.22-2.13 (m, 2H), 2.05-2.00 (m, 1H), 1.86-1.83 (m, 2H), 1.62-1.58 (m, 1H), 0.96-0.93 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.3, 180.2, 171.4, 164.3, 164.1, 154.4, 153.5, 137.4, 137.3, 128.1, 127.2, 126.0, 125.9, 125.8, 122.5, 119.1, 105.1, 104.4, 99.6, 56.4, 55.4, 55.0, 40.9, 36.9, 33.9, 33.5, 29.8, 28.5, 25.1, 23.3, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{36}N_5O_5S$ $[M+H]^+$ 590.2432, found 590.2429.



Methyl *N*-(4-methoxy-1*H*-indole-2-carbonyl)-*N*-methyl-L-leucinate (S70): To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucine **S66** (735 mg, 3.00 mmol) in MeOH (12 mL) was added thionyl chloride (0.653 mL, 9.00 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 14.5 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S67**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S67** (3.00 mmol) in CH_2Cl_2 (12 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (628 mg, 3.00 mmol), COMU (1.41 g, 3.30 mmol), and DIPEA (1.08 mL, 6.20 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to afford **S70** as an orange solid (773 mg, 73% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (br, 1H), 7.05 (br, 1H), 6.88 (dd, J = 10.4 Hz and 8.5 Hz, 1H), 6.33 (dd, J = 8.5 Hz and 2.9 Hz, 1H), 5.49-5.46 (m ,1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.36 (s, 3H), 1.89-1.81 (m, 2H), 1.61-1.50 (m, 1H), 1.00-0.95 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.3, 163.2, 150.3 (d, J = 2.2 Hz), 144.6 (d, J = 238.8 Hz), 129.0, 125.5 (d, J = 16.1 Hz), 121.7 (d, J = 5.0 Hz), 109.1 (d, J = 17.6 Hz), 104.7, 98.6 (d, J = 5.4 Hz), 55.9, 55.7, 52.4, 37.6, 33.8, 25.3, 23.4, 21.6; HRMS (ESI), *m*/*z* calcd for $C_{18}H_{24}FN_2O_4$ $[M+H]^+$ 351.1715, found 351.1715.

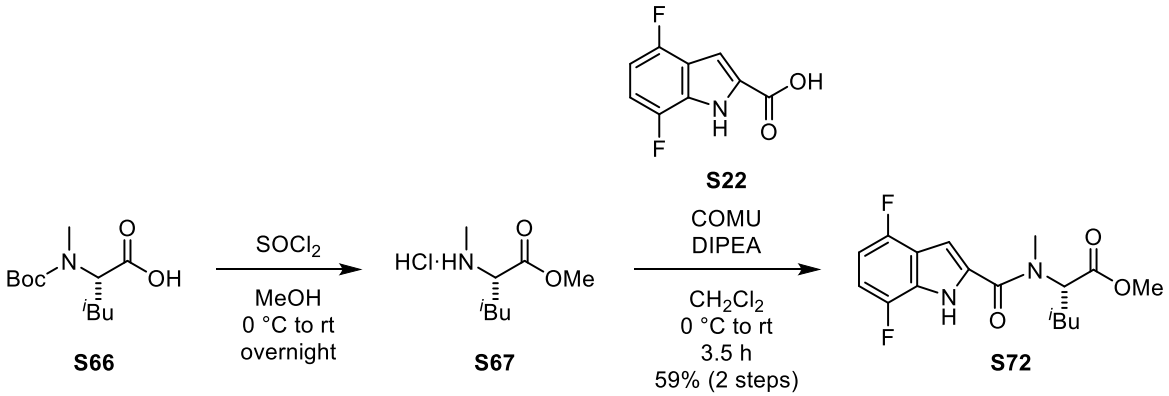


7-Fluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-*N*-methyl-1*H*-indole-2-carboxamide (58): To a solution of methyl ester **S70** (105 mg, 0.300 mmol) in THF (3.0 mL) was added an aqueous solution of LiOH (2.0 M, 0.300 mL, 0.600 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C, and then the mixture was acidified with HCl (2.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S71**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (122 mg, 0.300 mmol) in CH_2Cl_2 (3.0 mL) was added $HBF_4{\cdot}OEt_2$ (144 µL, 1.05 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

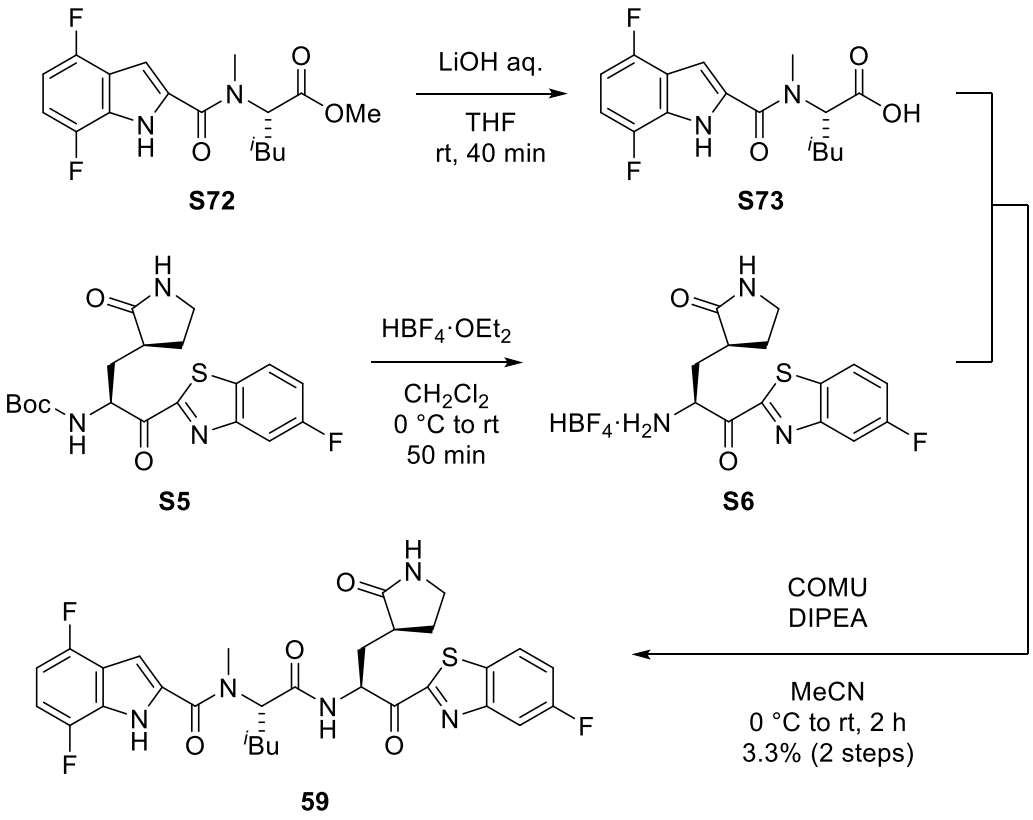
The crude amine **S6** (0.300 mmol) was coupled with the crude carboxylic acid **S71** (0.300 mmol) using COMU (129 mg, 0.300 mmol) in the presence of DIPEA (101 µL, 0.600 mmol) in MeCN (5.0 mL) at 0 °C and the solution was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **58**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **58** as a pale yellow solid (3.13 mg, 1.7% (2 steps)): t_R = 24.1 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.37 (s, 1H), 8.05 (dd, *J* = 8.8 Hz and 4.6 Hz, 1H), 7.62 (dd, *J* = 7.9 Hz and 2.3 Hz, 1H), 7.27-7.24 (m, 1H), 7.00 (s, 1H), 6.86 (dd, *J* = 10.2 Hz and 8.7 Hz, 1H), 6.43 (s, 1H), 6.31 (dd, *J* = 8.4 Hz and 2.4 Hz, 1H), 5.69-5.67 (m, 1H), 5.39 (br, 1H), 3.91 (s, 3H), 3.36-3.31 (m, 5H), 2.62 (br, 1H), 2.49 (br, 1H), 2.19-2.13 (m, 2H), 2.04-1.94 (m, 1H), 1.90-1.78 (m, 1H), 1.56 (br, 1H), 0.96 (br, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8, 180.5, 171.5, 164.1, 164.0, 162.2 (d, *J* = 250.9 Hz), 150.3 (d, *J* = 1.1 Hz), 150.2, 144.7 (d, *J* = 238.2 Hz), 138.7 (d, *J* = 11.6 Hz), 129.2, 127.1 (d, *J* = 9.7 Hz), 125.6 (d, *J* = 16.1 Hz), 121.6 (d, *J* = 4.6 Hz), 116.6 (d, *J* = 25.2 Hz), 108.9 (d, *J* = 17.7 Hz), 108.4 (d, *J* = 26.7 Hz), 104.7, 98.6 (d, *J* = 5.4 Hz), 56.3, 55.8, 55.1, 41.1, 39.4, 37.0, 33.7, 33.0, 28.6, 25.1,

23.3, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{34}F_2N_5O_5S$ $[M+H]^+$ 626.2243, found 626.2245.



Methyl *N*-(4-methoxy-1*H*-indole-2-carbonyl)-*N*-methyl-L-leucinate (S72): To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucine **S66** (491 mg, 2.00 mmol) in MeOH (8.0 mL) was added thionyl chloride (0.435 mL, 6.00 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight, and then concentrated under reduced pressure to obtain the crude methyl ester **S67**, which was used immediately in next step without purification.

To a solution of methyl ester **S67** (2.00 mmol) in CH_2Cl_2 (8.0 mL) was added 4,7-difluoro-1*H*-indole-2-carboxylic acid **S22** (344 mg, 2.00 mmol), COMU (942 mg, 2.20 mmol), and DIPEA (0.732 mL, 4.20 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to afford **S72** as an orange solid (399 mg, 59% (2 steps)): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.7 (brs, 1H), 6.99 (s, 1H), 6.86-6.80 (m, 1H), 6.66-6.61 (m,1H), 5.63-5.59 (m, 1H), 3.67 (s, 3H), 3.37 (s, 3H), 1.89-1.86 (m, 2H), 1.67-1.57 (m, 1H), 1.00-0.96 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.1, 163.2, 152.8 (dd, *J* = 244.8 Hz and 1.9 Hz), 146.0 (dd, *J* = 242.2 Hz and 3.3 Hz), 130.5, 126.3 (dd, *J* = 16.2 Hz and 10.7 Hz), 119.8 (dd, *J* = 24.0 Hz and 4.9 Hz), 108.6 (dd, *J* = 19.0 Hz and 8.1 Hz), 104.0 (dd, *J* = 21.7 Hz and 6.2 Hz), 102.9, 55.8, 52.3, 37.5, 33.8, 25.2, 23.3, 21.4; HRMS (ESI), *m*/*z* calcd for $C_{17}H_{21}F_2N_2O_3$ $[M+H]^+$ 339.1515, found 339.1514.

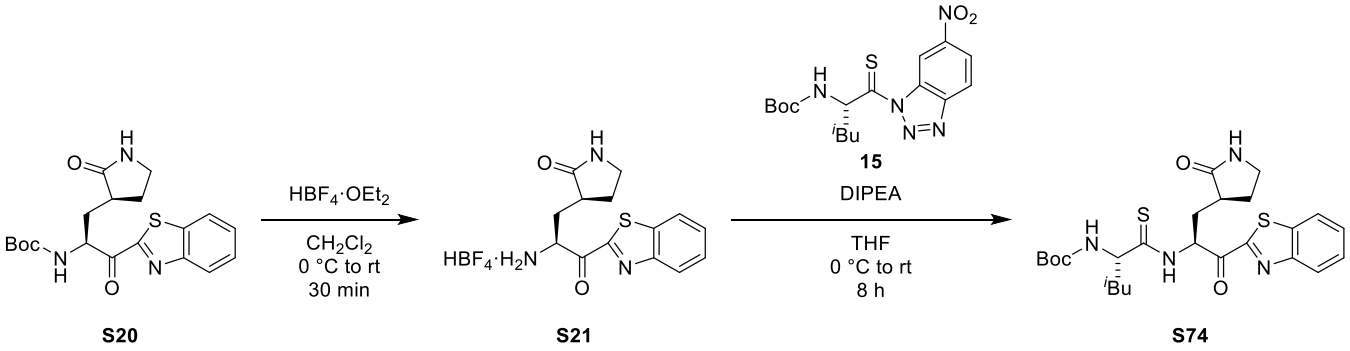


4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-*N*-methyl-1*H*-indole-2-carboxamide (59): To a solution of methyl ester **S72** (67.7 mg, 0.200 mmol) in THF (2.0 mL) was added an 2.0 M LiOH aq. (0.200 mL, 0.400 mmol) at room temperature. The mixture was stirred for 40 min at room temperature, and then the mixture was acidified with HCl (2.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S73**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 50 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH to obtain corresponding amine HBF_4 salt **S6**, which was used immediately in next step without purification.

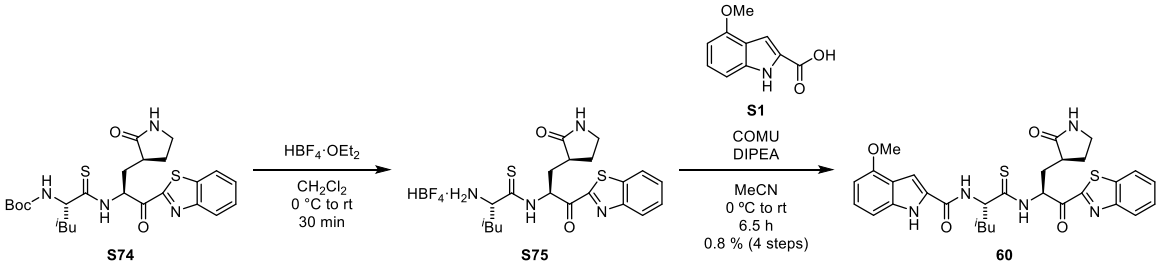
The amine HBF_4 salt **S6** (0.200 mmol) and the crude carboxylic acid **S73** (0.200 mmol) were dissolved in MeCN (2.0 mL) and was added COMU (85.7 mg, 0.200 mmol) and DIPEA (67.5 μL, 0.400 mmol) at 0 °C. The mixture was allowed to stir for 2 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified by silica gel flush column chromatography with $CHCl_3$/MeOH (95:5). Further purification was performed using preparative RP-HPLC to afford the title compound **59** (pale yellow powder, 4.06 mg, 3.3% (2 steps)): t_R = 25.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (brs, 1H), 8.59 (brs, 1H), 7.92 (dd, *J* = 8.8 Hz and 4.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.34–7.30 (m, 1H), 6.95 (brs, 1H), 6.88–6.84 (m, 1H), 6.67–6.64 (m, 1H), 6.21 (brs, 1H), 5.69–5.68 (m, 1H), 5.42 (brs, 1H), 3.39 (br, 2H), 3.25 (br, 2H), 2.67 (br, 1H), 2.52 (br, 1H), 2.14 (br, 2H), 2.01–1.97 (m, 1H), 1.93–1.89 (m, 1H), 1.80 (br, 1H), 1.57 (br, 1H), 0.97 (br, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.9, 180.4, 171.4, 166.6, 164.0, 162.2 (d, *J* = 245.6 Hz), 154.4 (d, *J* = 12.0 Hz), 153.9–151.9 (m), 147.0–145.0 (m), 133.0, 130.9,

126.2, 123.5 (d, J = 9.8 Hz), 120.0–119.8 (m), 117.3 (d, J = 25.5 Hz), 111.2 (23.2 Hz), 108.6 (dd, J = 19.1 Hz and 8.3 Hz), 104.3 (dd, 21.9 Hz and 6.3 Hz), 102.6, 56.2, 55.5, 41.1, 39.8, 36.9, 33.5, 32.6, 29.0, 25.1, 23.3, 22.1; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{30}F_3N_5O_4S$ $[M+H]^+$ 614.2043, found 614.2038.



***tert*-Butyl ((*S*)-1-(((*S*)-1-(benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)carbamate (S74)**: To a solution of **S20** (199 mg, 0.512 mmol) in CH_2Cl_2 (5.1 mL) was added $HBF_4{\cdot}OEt_2$ (246 μL, 1.79 mmol) dropwise at 0 °C under Ar and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid **S21** was used immediately in next step without purification.

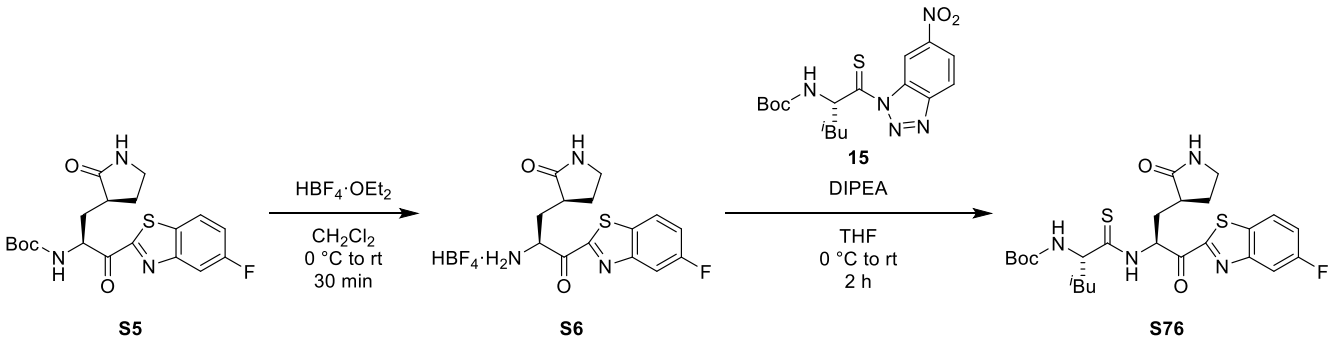
To a solution of **S21** (0.512 mmol) in THF (4.0 mL) was added DIPEA (86.4 μL, 0.512 mmol) at room temperature under Ar. To the solution was added triazole **15** (159 mg, 0.405 mmol) dissolved in THF (6.0 mL) and DIPEA (259 μL, 1.54 mmol) at 0 °C and the mixture was stirred for 8 h at room temperature. After reaction completion, the solvent was removed *in vacuo*, and the residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 47:3)) to afford crude **S74**, which was used in next step without further purification.



***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (60)**: To a solution of the crude Boc protected amine **S74** (0.405 mmol) in CH_2Cl_2 (4.1 mL) was added $HBF_4{\cdot}OEt_2$ (195 μL, 1.42 mmol) dropwise at 0 °C under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH to obtain the crude amine HBF_4 salt **S75**, which was used immediately in next step without purification.

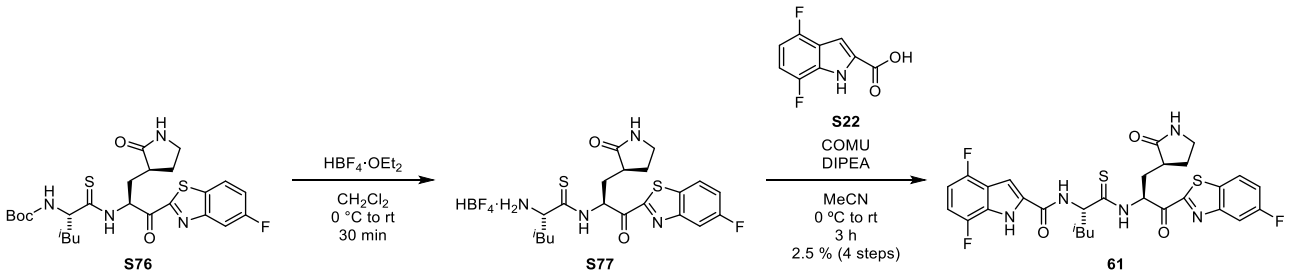
To a solution of the crude amine **S75** (0.405 mmol) in MeCN (4.1 mL) was added 4-methoxy-1*H*-indole-2-carboxylic acid **S1** (77.6 mg, 0.406 mmol), COMU (174 mg, 0.406 mmol), and DIPEA (273 μL, 1.62 mmol) at 0 °C under Ar. The reaction was allowed to proceed at room temperature for 6.5 h. The reaction was quenched by

the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, then the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 19:1)) to obtain the title compound **60**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **60** as an yellow solid (2.38 mg, 0.8% (4 steps)): t_R = 21.6 min (linear gradient of B in A, 45 to 75% over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.57 (d, J = 1.8 Hz, 1H), 11.03 (d, J =6.0 Hz, 1H), 8.44 (d, J = 8.1 Hz, 1H), 8.28–8.22 (m, 2H), 7.83 (s, 1H), 7.67–7.63 (m, 2H), 7.37 (d, J = 1.7 Hz, 1H) 7.11-7.08 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 6.06-6.02 (m, 1H), 5.02-4.98 (m, 1H), 3.88 (s, 3H), 3.24-3.17 (m, 2H), 2.68-2.62 (m, 1H), 2.40-2.34 (m, 1H), 2.30-2.24 (m, 1H), 2.07-1.99 (m, 1H), 1.95-1.87 (m, 1H), 1.78-1.72 (m, 2H), 1.61-1.55 (m, 1H), 0.94 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 207.1, 190.9, 178.1, 164.4, 160.8, 153.6, 152.8, 137.8, 136.3, 130.0, 128.2, 127.5, 125.3, 124.5, 123.2, 118.1, 105.4, 101.3, 99.2, 60.0, 56.9, 55.1, 43.5, 38.4, 31.7, 27.6, 25.5, 24.4, 23.0, 21.7; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{34}N_5O_4S_2$ $[M+H]^+$ 592.2047, found 592.2044.



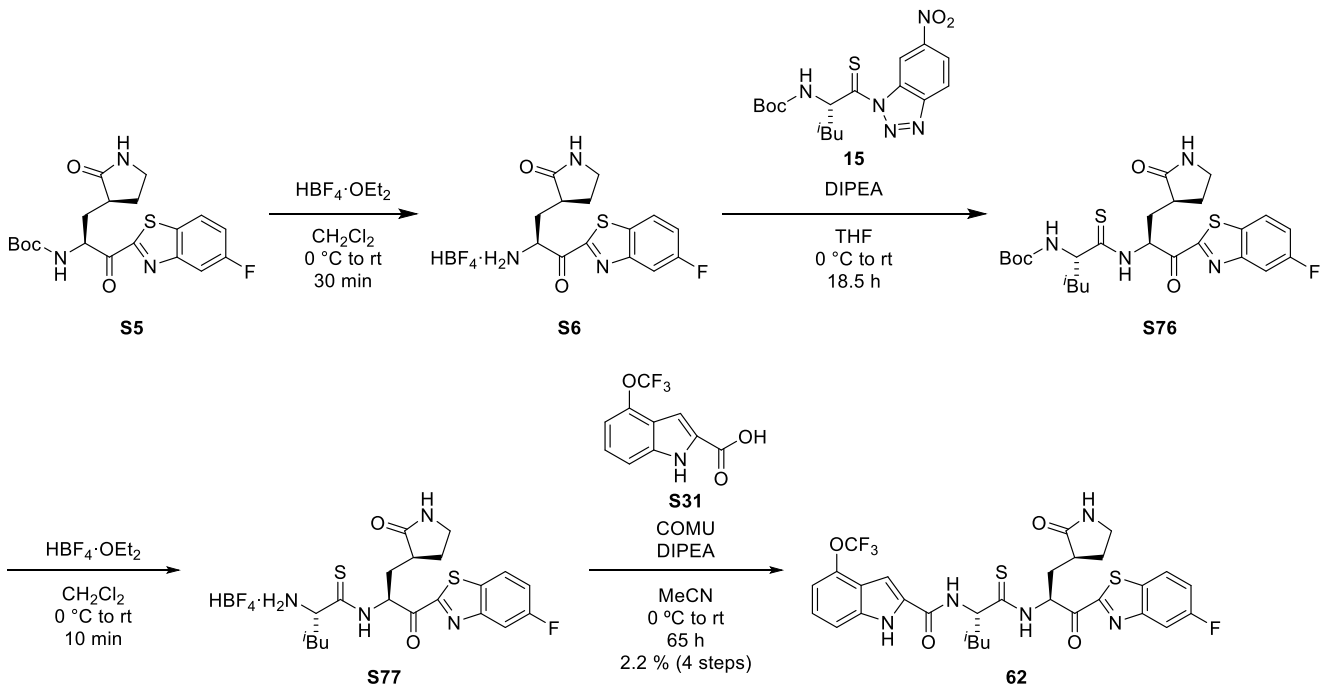
***tert*-Butyl ((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)carbamate** (**S76**): To a solution of Boc protected amine **S5** (83.0 mg, 0.204 mmol) in CH_2Cl_2 (2.0 mL) was added HBF_4·OEt_2 (98.0 μL, 0.714 mmol) dropwise at 0 °C under Ar and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH to obtain the crude amine HBF_4 salt **S6**, which was used immediately in next step without purification.

To a solution of the corresponding amine HBF_4 salt **S6** (0.204 mmol) in THF (2.1 mL) was added DIPEA (34.4 μL, 0.204 mmol) at room temperature under Ar. To the solution was added triazole **15** (80.3 mg, 0.204 mmol) dissolved in THF (2.0 mL) and DIPEA (103 μL, 0.610 mmol) at 0 °C and the mixture was stirred for 2 h at room temperature. After reaction completion, the solvent was removed *in vacuo*, and the residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 19:1)) to afford crude **S76**, which was used in next step without further purification.



4,7-Difluoro-*N*-((*S*)-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)-1*H*-indole-2-carboxamide (**61**): To a solution of the crude thioamide **S76** (0.204 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (98.0 μL, 0.714 mmol) dropwise at 0 °C under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH to obtain the crude amine HBF_4 salt **S77**, which was used immediately in next step without purification.

To a solution of the amine HBF_4 salt **S77** (0.204 mmol) in MeCN (2.0 mL) were added 4,7-difluoro-1*H*-indole-2-carboxylic acid **S22** (40.2 mg, 0.204 mmol), COMU (87.1 mg, 0.203 mmol), and DIPEA (138 μL, 0.818 mmol) at 0 °C under Ar. The reaction was allowed to proceed at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, then the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 20:1)) to obtain the title compound **61**. Further purification was performed by CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **61** as a white solid (3.08 mg, 2.5% (4 steps)): t_R = 20.6 min (linear gradient of B in A, 50 to 80% over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.1 (s, 1H), 9.69 (s, 1H), 7.94 (dd, *J* = 8.9 Hz and 5.0 Hz, 1H), 7.83 (dd, *J* = 9.1 Hz and 2.3 Hz, 1H), 7.32 (ddd, *J* = 8.7 Hz, 8.7 Hz, and 2.3 Hz, 1H), 7.25-7.22 (m, 1H), 7.07 (brs, 1H), 6.88-6.84 (m, 1H), 6.69-6.63 (m, 2H), 6.01-5.99 (m, 1H), 5.37-5.33 (m, 1H), 3.46-3.45 (m, 2H), 2.75 (br, 1H), 2.56 (br, 1H), 2.44-2.37 (m, 1H), 2.30-2.27 (m, 1H), 2.08-2.00 (m, 1H), 1.89-1.72 (m, 3H), 1.04 (d, *J* = 6.1 Hz, 3H), 1.00 (d, *J* = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 205.4, 189.6, 180.4, 166.9, 162.2 (d, *J* = 245.5 Hz), 160.0, 154.3 (d, *J* = 12.0 Hz), 152.9 (d, *J* = 245.6 Hz), 146.0 (dd, *J* = 241.3 Hz and 2.8 Hz), 133.0, 131.7, 126.6 (dd, *J* = 16.4 Hz and 10.4 Hz), 123.5 (d, *J* = 9.8 Hz), 120.0 (dd, *J* = 25.0 Hz and 5.0 Hz), 117.2 (d, *J* = 25.5 Hz), 111.3 (d, *J* = 23.4 Hz), 108.9 (dd, *J* = 19.0 Hz and 8.2 Hz), 104.6 (dd, *J* = 21.9 Hz and 6.6 Hz), 100.2, 61.3, 56.6, 46.7, 41.2, 40.0, 32.1, 29.2, 25.0, 23.0, 22.4; HRMS (ESI), *m*/*z* calcd for $C_{29}H_{29}F_3N_5O_3S_2$ $[M+H]^+$ 616.1658, found 616.1658.



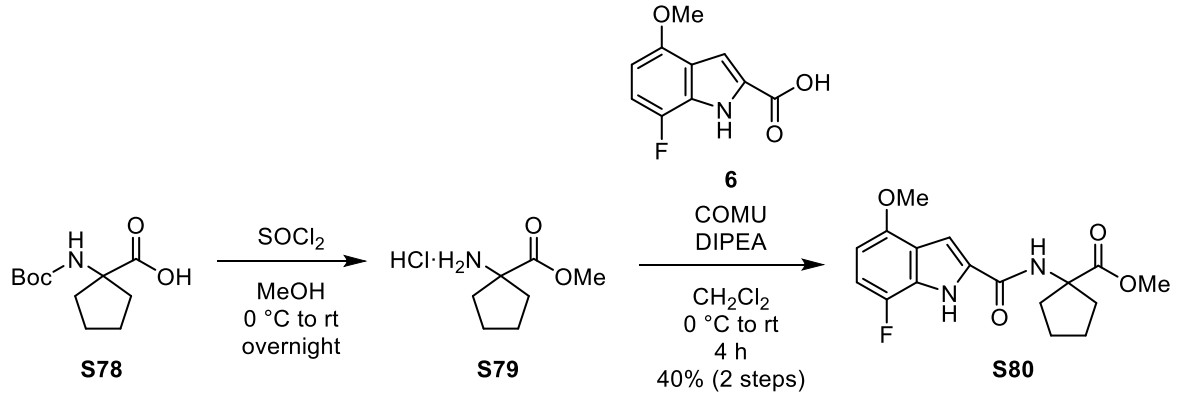
***N*-((*S*)-1-(((*S*)-1-(5-Fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-thioxopentan-2-yl)-4-(trifluoromethoxy)-1*H*-indole-2-carboxamide (62)**: To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 °C under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH to obtain the crude amine HBF_4 salt **S6**, which was used immediately in next step without purification.

To a solution of the crude amine HBF_4 salt **S6** (0.200 mmol) in THF (2.0 mL) was added DIPEA (33.7 μL, 0.200 mmol) at room temperature under Ar. To the solution was added triazole **15** (78.9 mg, 0.201 mmol) dissolved in THF (2.0 mL) and DIPEA (101 μL, 0.599 mmol) at 0 °C, and the mixture was stirred for 18.5 h at room temperature. After reaction completion, the solvent was removed *in vacuo*, and the residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 19:1)) to afford crude **S76**, which was used in next step without further purification.

To a solution of the crude thioamide **S76** (0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 °C under Ar, and the mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed with Et_2O containing 2% (v/v) MeOH to obtain the crude amine HBF_4 salt **S77**, which was used immediately in next step without purification.

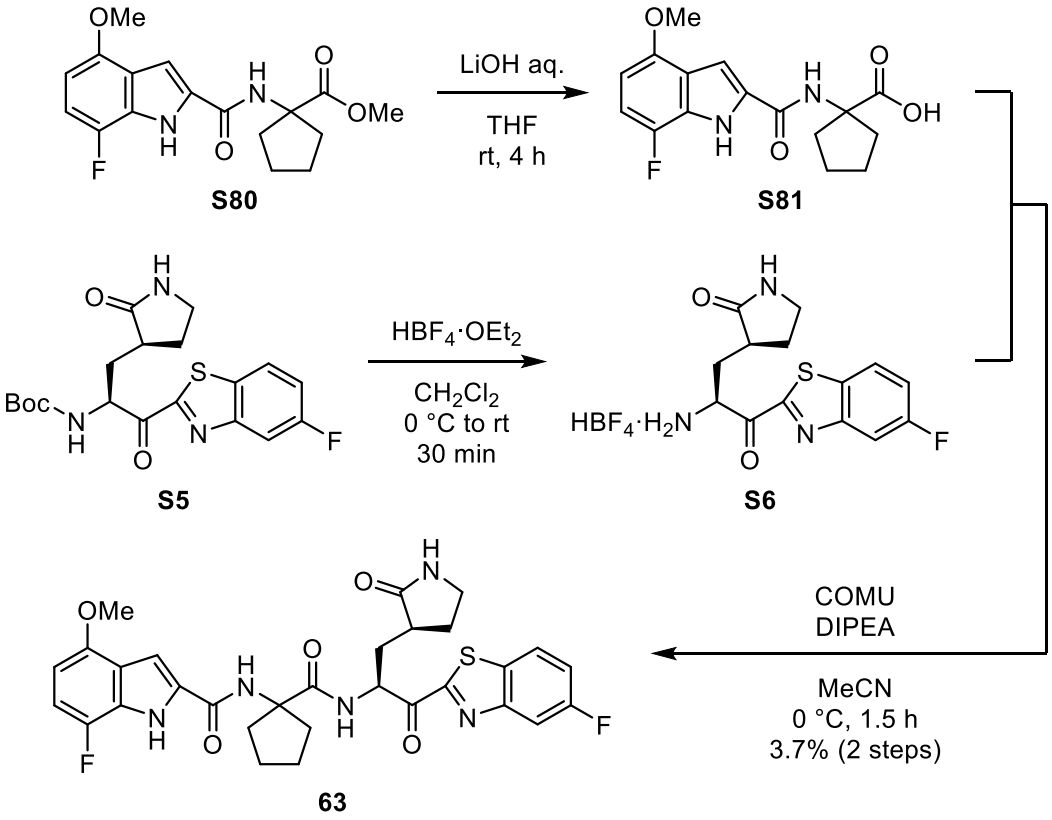
To a solution of the crude amine HBF_4 salt **S77** (0.200 mmol) in MeCN (2.0 mL) was added 4-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid **S31** (49.5 mg, 0.202 mmol), COMU (85.9 mg, 0.201 mmol), and DIPEA (135 μL, 0.800 mmol) at 0 °C under Ar. The reaction was allowed to proceed at room temperature for 65 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, then the organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was roughly purified by automated silica gel flush column chromatography system (Isolera One, $CHCl_3$/MeOH (100:0 to 19:1)) to afford the title compound **62**. Further purification was performed by CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **62** as a white to pale yellow powder (2.94 mg, 2.2% (4 steps)): t_R = 16.1 min (linear gradient of B in A, 60 to 90% over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.39 (s, 1H), 10.17 (s, 1H), 7.92

(dd, J = 9.2 Hz and 5.2 Hz, 1H), 7.84 (dd, J = 8.9 Hz and 2.6 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.32 (ddd, J = 8.7 Hz, 8.7 Hz, and 2.5 Hz, 1H), 7.25-7.23 (m, 1H), 7.17 (br, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.01-6.99 (m, 1H), 6.18-6.16 (m, 1H), 6.02 (br, 1H), 5.30-5.26 (m, 1H), 3.30-3.25 (m, 1H), 3.21-3.18 (m, 1H), 2.74-2.67 (m, 1H), 2.45-2.37 (m, 2H), 2.20-2.15 (m, 1H), 2.01-1.95 (m, 1H), 1.86-1.75 (m, 3H), 1.04 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 204.5, 191.9, 180.6, 167.0, 162.3 (d, J = 245.1 Hz), 160.9, 154.3 (d, J = 12.1 Hz), 142.9, 138.4, 133.0, 131.4, 124.7, 123.5 (d, J = 9.7 Hz), 121.6, 121.1 (q, J = 257.2 Hz), 117.2 (d, J = 25.2 Hz), 111.8, 111.5, 111.3 (d, J = 22.8 Hz), 100.0, 59.5, 58.4, 45.9, 41.2, 37.9, 30.6, 28.8, 25.4, 23.3, 22.0; HRMS (ESI), m/z calcd for $C_{30}H_{30}F_4N_5O_4S_2$ $[M+H]^+$ 664.1670, found 664.1669.



Methyl 1-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)cyclopentane-1-carboxylate (S80): To a solution of *N*-Boc-cycloleucine **S78** (115 mg, 0.500 mmol) in MeOH (2.0 mL) was added thionyl chloride (0.109 mL, 1.50 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight, and then concentrated under reduced pressure to obtain the crude methyl ester **S79**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S79** (0.500 mmol) in CH_2Cl_2 (2.0 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (105 mg, 0.500 mmol), COMU (236 mg, 0.550 mmol), and DIPEA (0.183 mL, 1.05 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to afford **S80** as an orange solid (66.9 mg, 40% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (brs, 1H), 6.99-6.98 (m, 1H), 6.88 (dd, J = 10.5 Hz and 8.5 Hz, 1H), 6.54 (s, 1H), 6.34 (dd, J = 8.5 Hz and 2.9 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 2.37-2.29 (m, 2H), 2.14-2.09 (m, 2H), 1.91-1.84 (m, 4H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 174.8, 160.8, 150.2 (d, J = 1.9 Hz), 144.7 (d, J = 238.6 Hz), 130.2, 126.0 (d, J = 16.3 Hz), 121.5 (d, J = 4.7 Hz), 109.1 (d, J = 17.6 Hz), 100.9, 98.9 (d, J = 6.1 Hz), 66.4, 55.8, 52.9, 37.7 (2C), 25.1 (2C); HRMS (ESI), m/z calcd for $C_{17}H_{20}FN_2O_4$ $[M+H]^+$ 335.1402, found 335.1401.

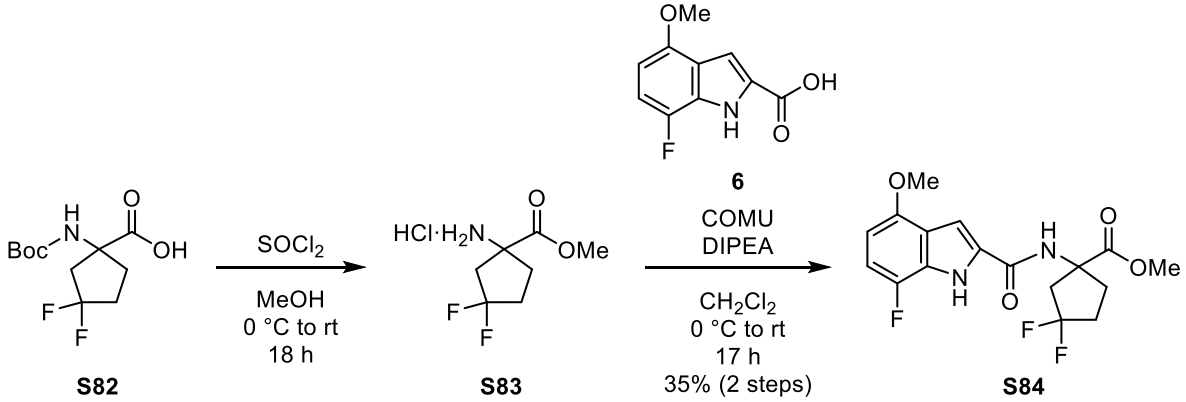


7-Fluoro-*N*-(1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)cyclopentyl)-4-methoxy-1*H*-indole-2-carboxamide (63): To a solution of methyl ester **S80** (60.2 mg, 0.180 mmol) in THF (1.8 mL) was added an aqueous LiOH (2.0 M, 0.180 mL, 0.360 mmol) at room temperature. The mixture was stirred for 4 h at room temperature, and then the mixture was acidified with HCl (2.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S81**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (73.3 mg, 0.180 mmol) in CH_2Cl_2 (1.8 mL) was added $HBF_4{\cdot}OEt_2$ (86.5 μL, 0.630 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

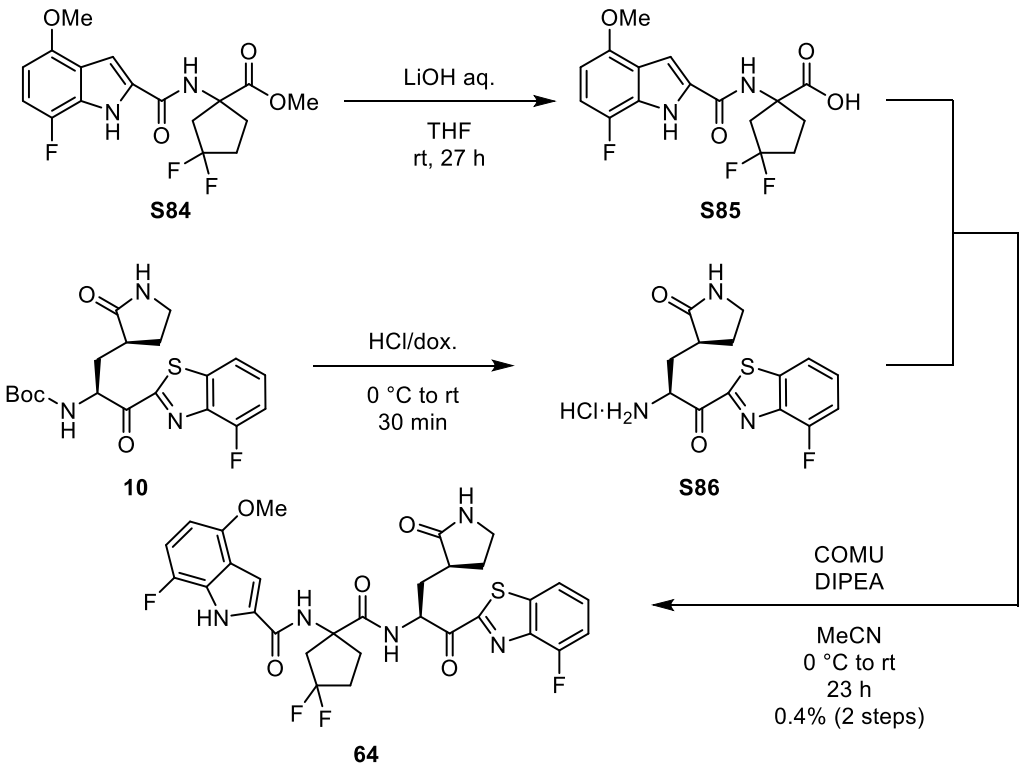
The crude amine **S6** (0.180 mmol) was treated with the crude carboxylic acid **S81** (0.180 mmol), COMU (77.1 mg, 0.180 mmol), and DIPEA (60.7 μL, 0.360 mmol) in MeCN (1.8 mL) at 0 °C, and the mixture was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **63**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **63** as a pale yellow solid (4.04 mg, 3.7% (2 steps)): t_R = 15.7 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (s, 1H), 8.64 (d, *J* = 6.4 Hz, 1H), 7.86 (dd, *J* = 8.8 Hz and 4.9 Hz, 1H), 7.69 (dd, *J* = 8.9 Hz and 1.7 Hz, 1H), 7.24-7.22 (m, 1H), 6.91 (s, 1H), 6.86 (brs, 1H), 6.78 (dd, *J* = 10.3 Hz and 8.5 Hz, 1H), 6.24 (dd, *J* = 8.4 Hz and 2.6 Hz, 1H), 5.89 (s, 1H), 5.76-5.72 (m, 1H), 3.78 (s, 3H), 3.21-3.18 (m, 1H), 3.07-3.06 (m, 1H), 2.70 (br, 1H), 2.60-2.49 (m, 2H), 2.33-2.27 (m, 1H), 2.18-2.04 (m, 4H), 1.86-1.78 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.9, 180.3, 174.4, 166.7, 162.1 (d, *J* = 245.6 Hz), 161.4, 154.3 (d, *J* = 12.3 Hz), 150.1 (d, *J* = 2.0 Hz), 144.7 (d, *J* = 238.7 Hz), 132.8, 130.8, 126.2

(d, J = 16.0 Hz), 123.3 (d, J = 9.7 Hz), 121.3 (d, J = 4.6 Hz), 117.1 (d, J = 25.6 Hz), 111.1 (d, J = 23.2 Hz), 108.8 (d, J = 17.8 Hz), 101.6, 98.6 (d, J = 5.8 Hz), 67.6, 55.6, 55.5, 40.7, 38.7, 38.7, 36.4, 32.9, 28.6, 24.8, 24.7; HRMS (ESI), m/z calcd for $C_{30}H_{30}F_2N_5O_5S$ $[M+H]^+$ 610.1930, found 610.1927.



Methyl 3,3-difluoro-1-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)cyclopentane-1-carboxylate (S84): To a solution of 1-((*tert*-butoxycarbonyl)amino)-3,3-difluorocyclopentane-1-carboxylic acid **S82** (100 mg, 0.378 mmol) in MeOH (3.7 mL) was added thionyl chloride (0.0822 mL, 1.13 mmol) at 0 °C. The mixture was warmed to room temperature and stirred 18 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S83**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S83** (0.378 mmol) in CH_2Cl_2 (3.8 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (79.0 mg, 0.378 mmol), COMU (178 mg, 0.415 mmol), and DIPEA (0.134 mL, 0.793 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 17 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure, and the residue was purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to afford **S84** as a white powder (48.5 mg, 35% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (brs, 1H), 7.04-7.03 (m, 1H), 6.89 (dd, J = 10.4 Hz and 8.5 Hz, 1H), 6.65 (s, 1H), 6.35 (dd, J = 8.5 Hz and 2.9 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.07-2.94 (m, 1H), 2.70-2.62 (m, 1H), 2.56-2.50 (m, 1H), 2.43-2.29 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.6, 161.2, 150.3 (d, J = 2.6 Hz), 144.6 (d, J = 238.4 Hz), 130.9 (dd, J = 251.4 Hz and 247.1 Hz), 129.3, 126.2 (d, J = 16.3 Hz), 121.4 (d, J = 4.6 Hz), 109.4 (d, J = 17.5 Hz), 101.7 (d, J = 1.7 Hz), 99.0 (d, J = 6.0 Hz), 63.4 (dd, J = 6.8 Hz and 2.9 Hz), 55.8, 53.4, 45.8 (t, J = 26.8 Hz), 34.6 (t, J = 25.5 Hz), 34.2-34.1 (m); HRMS (ESI), m/z calcd for $C_{17}H_{17}F_3N_2NaO_4$ $[M+Na]^+$ 393.1033, found 393.1038.

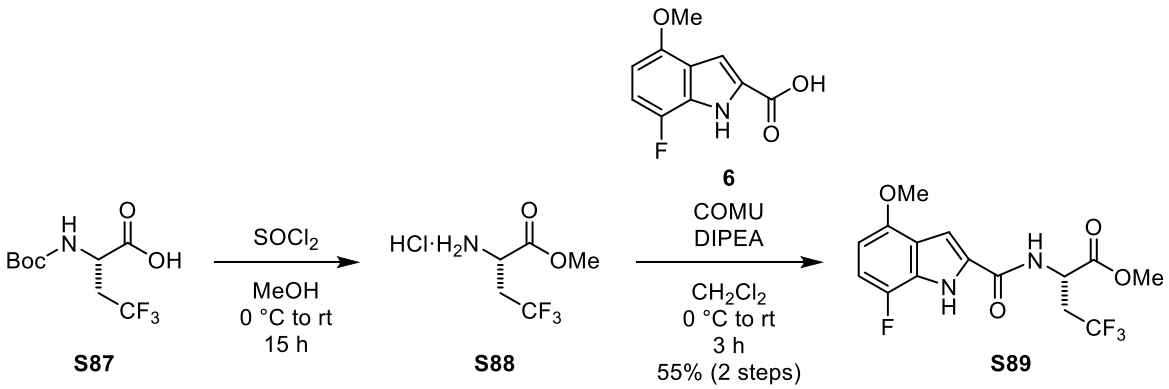


***N*-(3,3-Difluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)cyclopentyl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (64)**: The methyl ester **S84** (559 mg, 1.51 mmol) in THF (15 mL) was treated with LiOH aq. (2.0 M, 2.27 mL, 4.53 mmol) at room temperature and the solution was allowed to stir for 27 h at room temperature. The reaction mixture was acidified with aqueous HCl (1.0 M) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain the corresponding carboxylic acid **S85**, which was used immediately in the next reaction without purification.

The Boc protected amine **10** (291 mg, 0.946 mmol) was treated with 4 M HCl in dioxane (4.7 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude amine HCl salt **S86** was used immediately in next step without purification.

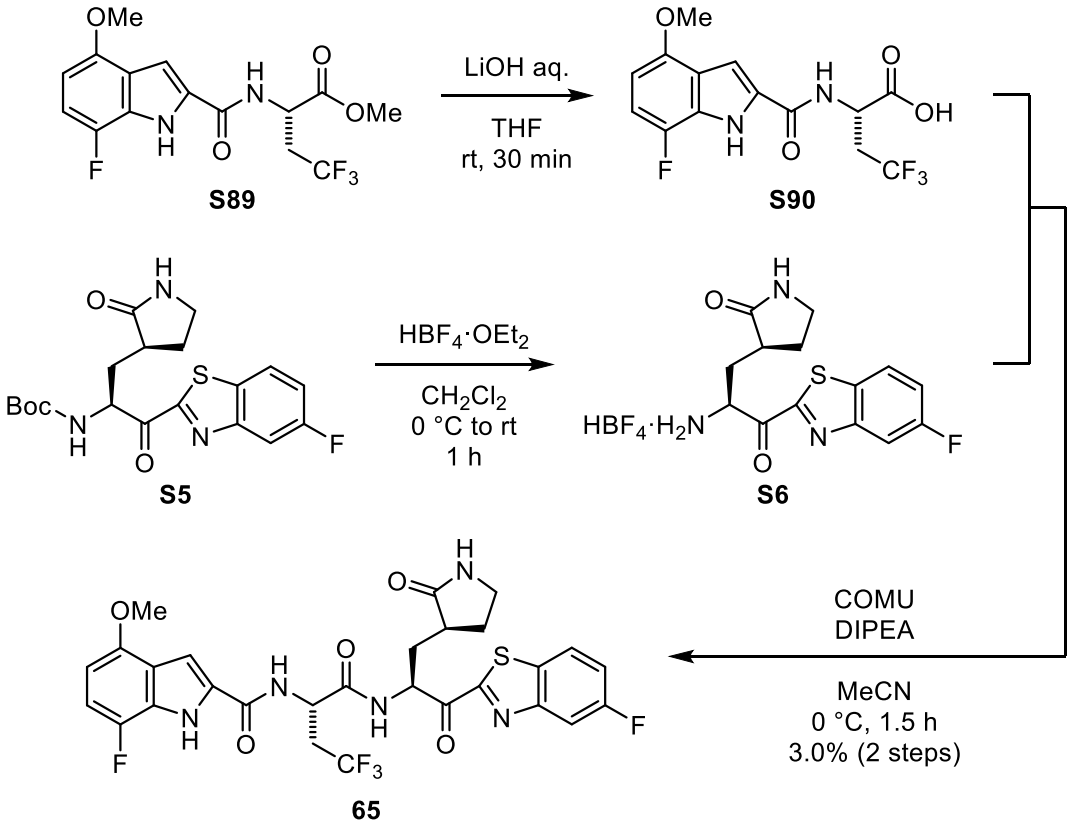
The crude amine **S86** (0.946 mmol) was treated with the crude carboxylic acid **S85** (0.946 mmol), COMU (445 mg, 1.04 mmol), and DIPEA (0.638 mL, 3.78 mmol) in MeCN (9.5 mL) at 0 °C, and the solution was allowed to stir for 23 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Pure C-815, $CHCl_3$/MeOH = 100:0 to 94:6) to afford the title compound **64**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **64** as a pale yellow powder (2.19 mg, 0.4% (2 steps)): t_R = 17.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (br, 1H), 8.97 (d, *J* = 6.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.47-7.43 (m, 1H), 7.19-7.15 (m, 1H), 7.03 (s, 1H), 6.96 (s, 1H), 6.84 (dd, *J* = 10.2 Hz and 8.6 Hz, 1H), 6.28 (dd, *J* = 8.4 Hz and 2.7 Hz, 1H), 5.76-5.72 (m, 1H), 5.50 (s, 1H), 3.82 (s, 3H), 3.36-3.26 (m, 1H), 3.20-3.16 (m, 1H), 3.07-3.01 (m, 1H), 2.69-2.62 (m, 2H), 2.60-2.47 (m, 2H), 2.41-2.29 (m, 3H), 2.24-2.20 (m, 1H), 2.08-2.01 (m, 1H), 1.91-1.83 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.7, 180.5, 172.4, 164.7, 161.7, 157.2 (d, *J* = 260.9 Hz), 150.2 (d, *J* = 2.2 Hz), 144.7 (d, *J* = 238.9 Hz), 142.8 (d, *J* = 13.9 Hz), 139.7 (d, *J* = 2.3 Hz), 131.4 (dd, *J* = 252.0 Hz and 245.3 Hz), 130.1, 129.0 (d, *J* = 7.2 Hz), 126.3 (d, *J* = 16.0

Hz), 121.4 (d, J = 4.7 Hz), 118.2 (d, J = 4.4 Hz), 112.5 (d, J = 17.6 Hz), 109.1 (d, J = 17.8 Hz), 102.3, 98.8 (d, J = 6.0 Hz), 64.3 (dd, J = 7.5 Hz and 1.8 Hz), 55.8, 55.7, 44.5 (t, J = 26.0 Hz), 40.7, 38.9, 35.2-35.2 (m), 34.6 (t, J = 25.6 Hz), 32.3, 28.8; HRMS (ESI), m/z calcd for $C_{30}H_{27}F_4N_5NaO_5S$ $[M+Na]^+$ 668.1561, found 668.1558.



Methyl (*S*)-4,4,4-trifluoro-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)butanoate (S89): To a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,4,4-trifluorobutanoic acid **S87** (900 mg, 3.50 mmol) in MeOH (14 mL) was added thionyl chloride (0.762 mL, 10.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 15 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S88**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S88** (0.350 mmol) in CH_2Cl_2 (14 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (732 mg, 3.50 mmol), COMU (1.65 g, 3.85 mmol), and DIPEA (1.28 mL, 7.35 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to afford **S89** as an orange solid (692 mg, 55% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (brs, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.22-7.21 (m, 1H), 6.85 (dd, J = 10.7 Hz and 8.4 Hz, 1H), 6.26 (dd, J = 8.5 Hz and 2.8 Hz, 1H), 5.29-5.25 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.08-2.99 (m, 1H), 2.93-2.82 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.8, 161.3, 150.2 (d, J = 1.8 Hz), 144.8 (d, J = 238.4 Hz), 129.4, 126.7 (d, J = 15.9 Hz), 125.8 (q, J = 277.6 Hz), 121.4 (d, J = 4.7 Hz), 109.0 (d, J = 18.1 Hz), 102.2, 98.4 (d, J = 6.2 Hz), 55.4, 53.2, 47.6-47.5 (m), 35.4 (q, J = 28.4 Hz); HRMS (ESI), m/z calcd for $C_{15}H_{15}F_4N_2O_4$ $[M+H]^+$ 363.0962, found 363.0965.

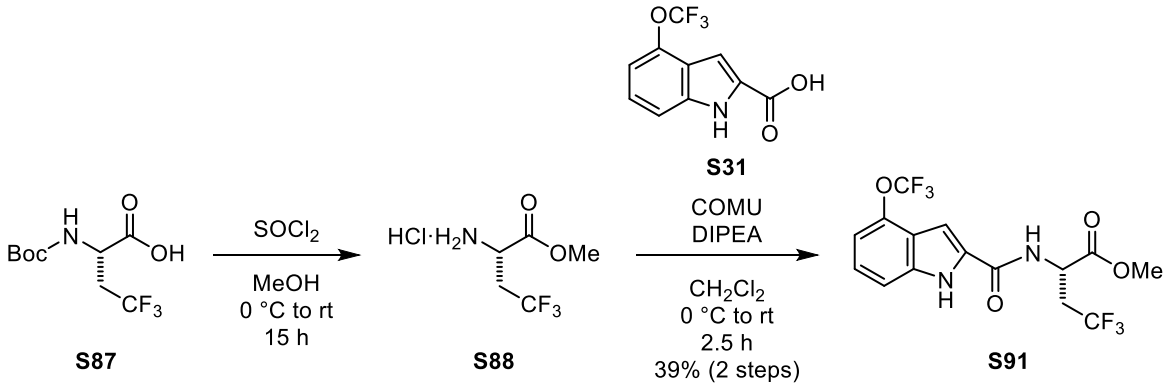


7-Fluoro-4-methoxy-*N*-((*S*)-4,4,4-trifluoro-1-(((*S*)-1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxobutan-2-yl)-1*H*-indole-2-carboxamide (65): To a solution of methyl ester **S89** (72.5 mg, 0.200 mmol) in THF (2.0 mL) was added an aqueous LiOH (2.0 M, 0.200 mL, 0.400 mmol) at room temperature. The mixture was stirred for 30 min at room temperature, and then the mixture was acidified with HCl (2.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S90**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S5** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S6** was used immediately in next step without purification.

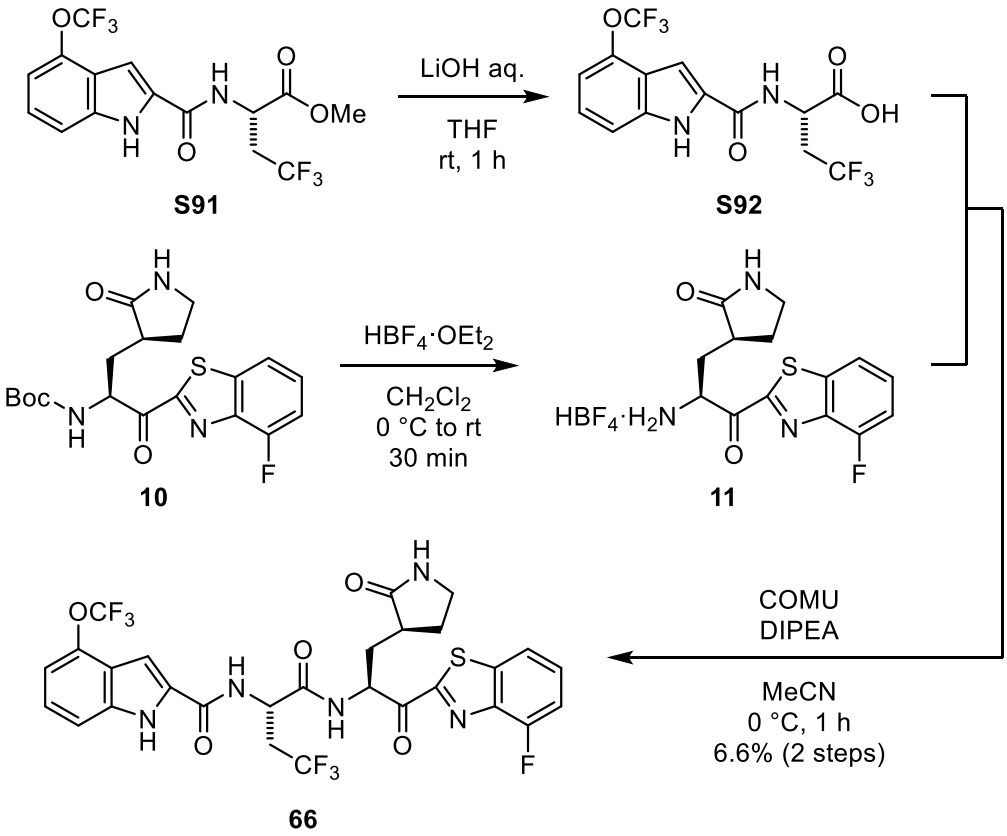
The crude amine **S6** (0.200 mmol) was treated with the crude carboxylic acid **S90** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1.5 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **65**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **65** as a pale yellow solid (3.89 mg, 3.0% (2 steps)): t_R = 18.3 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.1 (s, 1H), 9.17 (d, J = 6.9 Hz, 1H), 8.84 (d, J = 8.5 Hz, 1H), 8.24 (dd, J = 9.1 Hz and 4.9 Hz, 1H), 8.17 (dd, J = 8.7 Hz and 2.6 Hz, 1H), 7.68 (s, 1H), 7.51 (ddd, J = 9.0 Hz, 9.0 Hz, and 2.7 Hz, 1H), 7.29 (br, 1H), 6.93 (dd, J = 11.0 Hz and 8.5 Hz, 1H), 6.42 (dd, J = 8.5 Hz and 2.8 Hz, 1H), 5.48-5.44 (m, 1H), 4.94-4.90 (m, 1H), 3.87 (s, 3H), 3.20-3.12 (m, 2H), 2.85-2.72 (m, 2H), 2.53-2.46 (m, 1H), 2.30-2.24 (m, 1H), 2.17-2.11 (m, 1H), 1.90-1.78 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 192.3, 178.0, 169.9, 164.5 (d, J = 3.5 Hz), 161.4 (d, J = 247.5 Hz), 160.3, 149.8, 149.7 (d, J =

1.6 Hz), 144.2 (d, J = 237.8 Hz), 137.9 (d, J = 12.6 Hz), 131.1, 126.9 (d, J = 10.0 Hz), 126.3 (q, J = 277.4 Hz), 125.7 (d, J = 15.8 Hz), 120.8 (d, J = 5.3 Hz), 116.6 (d, J = 25.5 Hz), 109.3 (d, J = 27.4 Hz), 108.2 (d, J = 17.8 Hz), 102.6, 98.4 (d, J = 5.9 Hz), 55.5, 54.0, 47.2, 37.9, 34.7 (q, J = 27.7 Hz), 31.9, 28.0, 27.4; HRMS (ESI), *m*/*z* calcd for $C_{28}H_{25}F_5N_5O_5S$ $[M+H]^+$ 638.1491, found 638.1493.



Methyl (*S*)-4,4,4-trifluoro-2-(4-(trifluoromethoxy)-1*H*-indole-2-carboxamido)butanoate (S91): To a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,4,4-trifluorobutanoic acid **S87** (514 mg, 2.00 mmol) in MeOH (8.0 mL) was added thionyl chloride (0.435 mL, 6.00 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 15 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S88**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S88** (2.00 mmol) in CH_2Cl_2 (8.0 mL) was added 4-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid **S31** (490 mg, 2.00 mmol), COMU (942 mg, 2.20 mmol), and DIPEA (1.08 mL, 6.20 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. The volatile was removed under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$/MeOH (100:0 to 40:1) to afford **S91** as a pale yellow solid (308 mg, 39% (2 steps)): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (brs, 1H), 7.38-7.36 (m, 1H), 7.30-7.26 (m, 1H), 7.06-7.02 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 5.08-5.04 (m, 1H), 3.86 (s, 3H), 3.03-2.90 (m, 1H), 2.89-2.76 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 161.7, 143.0, 138.7, 130.1, 125.6 (q, J = 277.5 Hz), 125.0, 121.3, 121.0 (q, J = 257.4 Hz), 111.7, 111.2, 100.6, 53.4, 47.8, 35.6 (q, J = 28.8 Hz); HRMS (ESI), *m*/*z* calcd for $C_{15}H_{12}F_6N_2NaO_4$ $[M+Na]^+$ 421.0593, found 421.0593.

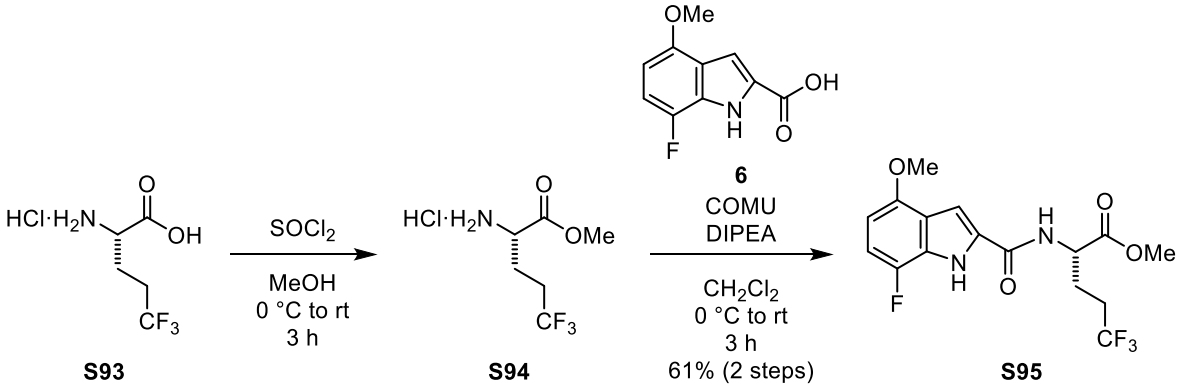


***N*-((*S*)-4,4,4-Trifluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxobutan-2-yl)-4-(trifluoromethoxy)-1*H*-indole-2-carboxamide (66)**: To a solution of methyl ester **S91** (79.7 mg, 0.200 mmol) in THF (2.0 mL) was added an aqueous solution of LiOH (2.0 M, 0.200 mL, 0.400 mmol) at room temperature. The mixture was stirred for 1 h at room temperature, and then the mixture was acidified with HCl (1.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S92**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (81.5 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.1 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

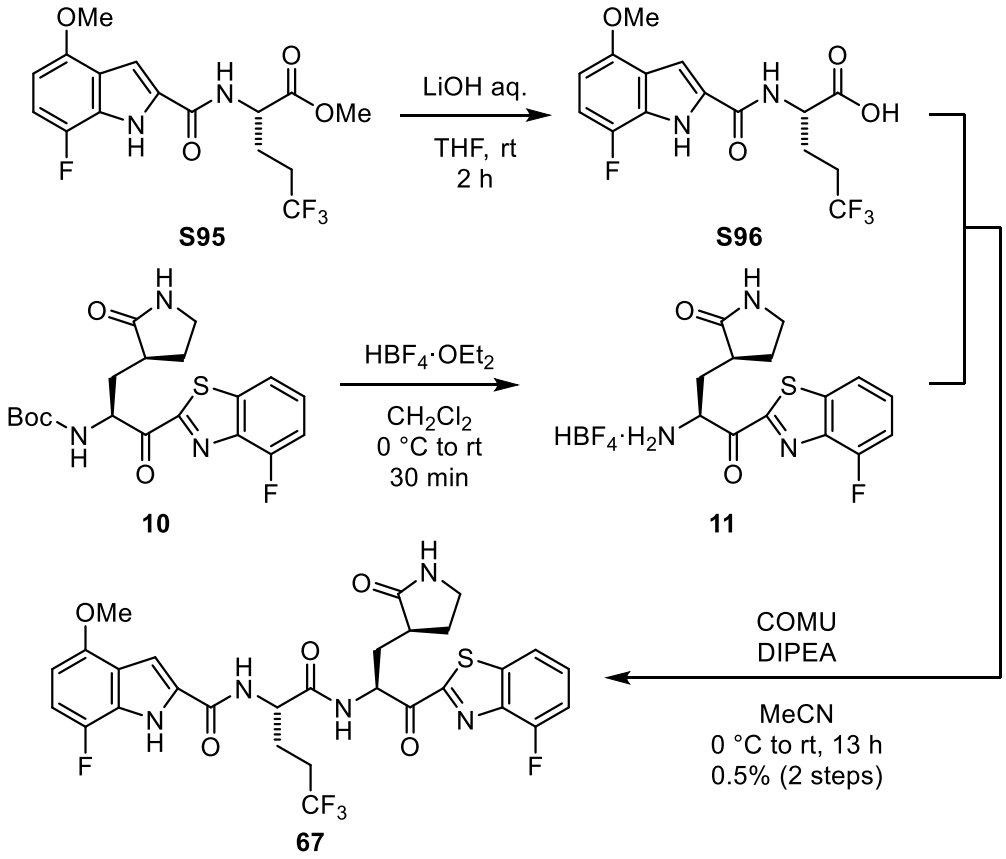
The crude amine **11** (0.200 mmol) was treated with the crude carboxylic acid **S92** (0.200 mmol), COMU (85.7 mg, 0.200 mmol), and DIPEA (67.5 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C, and the mixture was allowed to stir for 1 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **66**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **66** as a pale yellow solid (8.8 mg, 6.6% (2 steps)): t_R = 23.3 min (linear gradient of B in A, 40 to 70 % over 30 min);^{1}H NMR (500 MHz, $CDCl_3$) δ 10.66 (brs, 1H), 9.13 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.59 (brs, 1H), 7.49-7.45 (m, 1H), 7.29-7.28 (m, 1H), 7.22-7.19 (m, 1H), 7.15-7.12 (m, 1H), 7.07 (s, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.43 (brs, 1H), 5.78-5.74 (m, 1H), 5.14 (br, 1H), 3.24 (br, 1H), 3.08-2.95 (m, 2H), 2.88-2.84 (m, 1H), 2.66-2.60 (m, 1H), 2.37 (br, 1H), 2.18-2.15 (m, 2H), 2.00-1.87 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.8, 180.5, 169.7, 164.3, 161.6, 157.3 (d, *J* = 262.1 Hz), 142.8, 142.8 (d, *J* = 14.4 Hz), 139.7, 138.6, 130.7, 129.1 (d, *J* = 7.2 Hz), 126.1 (q, *J* = 278.0 Hz), 124.8, 121.3, 121.0 (q, *J* = 258.0 Hz), 118.2 (d, *J* = 3.7

Hz), 112.6 (d, J = 18.0 Hz), 111.7, 111.3, 100.7, 55.5, 48.6, 40.7, 39.3, 35.7-35.2 (m), 32.8, 28.4; HRMS (ESI), m/z calcd for $C_{28}H_{22}F_7N_5NaO_5S$ $[M+Na]^+$ 696.1122, found 696.1125.



Methyl (*S*)-5,5,5-trifluoro-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)pentanoate (S95): To a solution of (*S*)-2-amino-5,5,5-trifluoropentanoic acid hydrochloride **S93** (104 mg, 0.500 mmol) in MeOH (2.0 mL) was added thionyl chloride (0.0540 mL, 0.750 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S94**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S94** (0.500 mmol) in CH_2Cl_2 (2.0 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (105 mg, 0.500 mmol), COMU (236 mg, 0.550 mmol), and DIPEA (0.218 mL, 1.25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic later was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to obtain **S95** as a reddish brown solid (114 mg, 61% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (brs, 1H), 7.11-7.10 (m, 1H), 6.90 (dd, J = 10.5 Hz and 8.5 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.35 (dd, J = 8.5 Hz and 2.9 Hz, 1H), 4.94-4.90 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 2.35-2.25 (m, 2H), 2.23-2.14 (m, 1H), 2.08-2.00 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.9, 161.1, 150.3 (d, J = 2.5 Hz), 144.7 (d, J = 238.3 Hz), 129.3, 126.7 (q, J = 276.1 Hz), 126.4 (d, J = 15.9 Hz), 121.5 (d, J = 4.6 Hz), 109.4 (d, J = 17.7 Hz), 101.7 (d, J = 1.4 Hz), 98.9 (d, J = 6.1 Hz), 55.8, 53.2, 51.3, 30.3 (q, J = 29.6 Hz), 25.8-25.8 (m); HRMS (ESI), m/z calcd for $C_{16}H_{17}F_4N_2O_4$ $[M+H]^+$ 377.1119, found 377.1120.

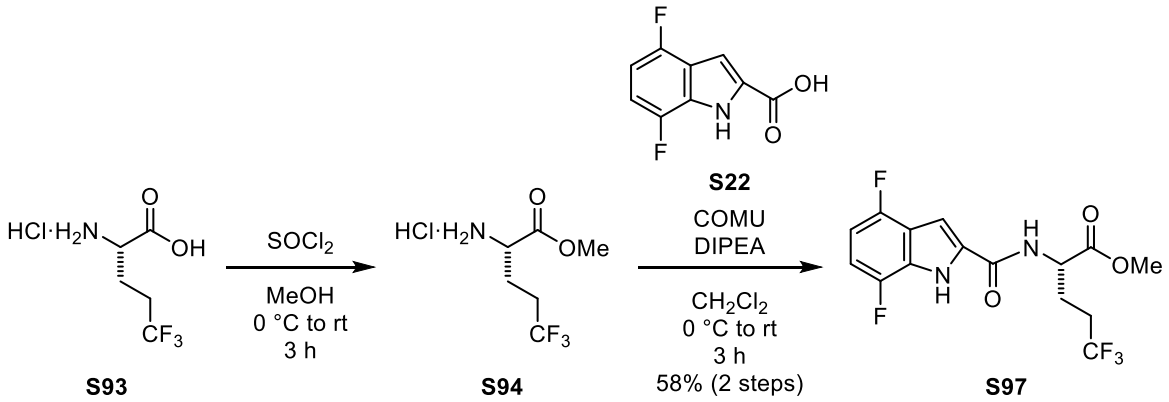


7-Fluoro-4-methoxy-*N*-((*S*)-5,5,5-trifluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (67): To a solution of methyl ester **S95** (331 mg, 0.880 mmol) in THF (8.8 mL) was added an aqueous LiOH (2.0 M, 1.32 mL, 2.64 mmol) at room temperature. The mixture was stirred for 2 h at room temperature, and then the mixture was acidified with HCl (1.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S96**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (367 mg, 0.900 mmol) in CH_2Cl_2 (9.0 mL) was added $HBF_4{\cdot}OEt_2$ (247 μL, 1.80 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

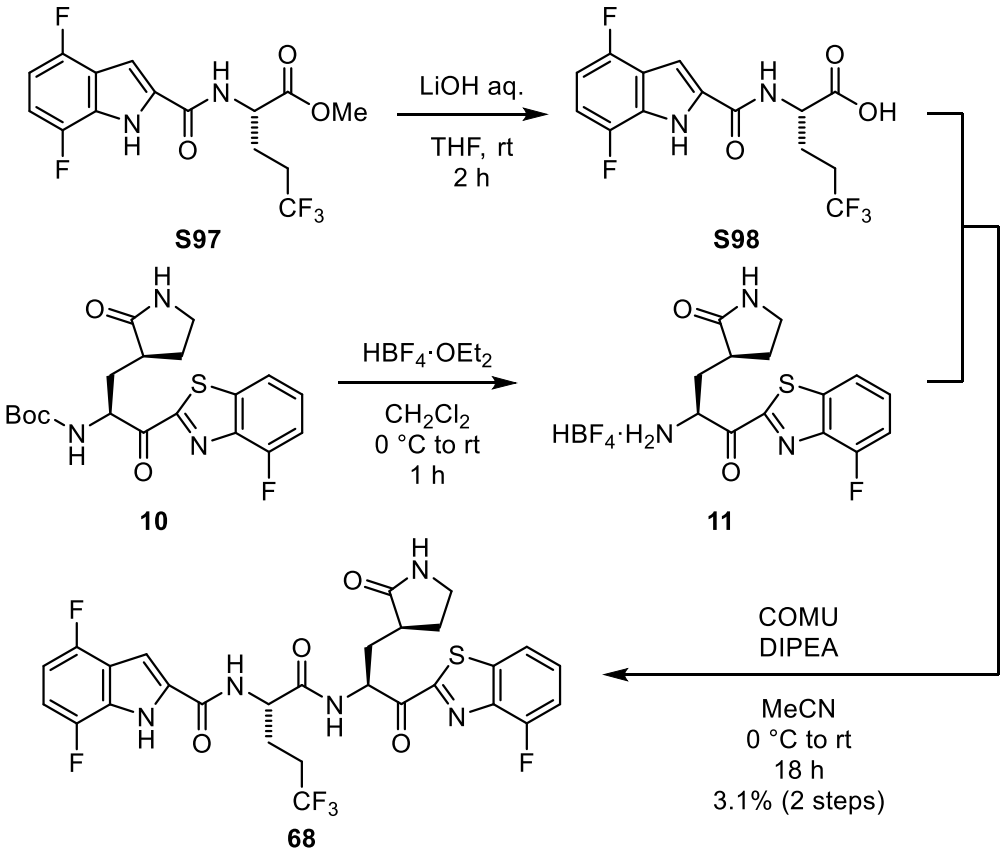
The crude amine **11** (0.500 mmol) was treated with the crude carboxylic acid **S96** (0.500 mmol), COMU (236 mg, 0.550 mmol), and DIPEA (341 μL, 2.00 mmol) in MeCN (5.0 mL) at 0 °C, and the mixture was allowed to stir for 13 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **67**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **67** as a pale yellow solid (1.55 mg, 0.5% (2 steps)): t_R = 20.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s. 1H), 9.24 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.53-7.49 (m, 1H), 7.24-7.21 (m, 2H), 7.12 (brs, 1H), 6.86-6.82 (m, 1H), 6.30-6.27 (m, 2H), 5.73-5.69 (m, 1H), 5.00-4.96 (m, 1H), 3.88 (s, 3H), 3.43-3.41 (m, 2H), 2.78-2.72 (m, 1H), 2.57-2.53 (m, 1H), 2.38-2.26 (m, 4H), 2.20-2.15 (m, 1H), 2.13-2.01 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.5, 180.4, 170.9, 164.5, 161.1, 157.3 (d, J = 260.7 Hz), 150.4 (d, J = 1.7 Hz), 144.7 (d, J = 237.7 Hz),

142.8 (d, J = 13.9 Hz), 139.9 (d, J = 2.4 Hz), 129.8, 129.1 (d, J = 7.2 Hz), 127.0 (q, J = 276.1 Hz), 126.3 (d, J = 16.2 Hz), 121.5 (d, J = 4.9 Hz), 118.3 (d, J = 4.4 Hz), 112.6 (d, J = 17.7 Hz), 109.1 (d, J = 17.7 Hz), 102.6, 98.8 (d, J = 6.2 Hz), 55.9, 55.8, 51.7, 41.0, 39.9, 32.4, 30.0 (q, J = 29.3 Hz), 29.0, 26.3; HRMS (ESI), m/z calcd for $C_{29}H_{27}F_5N_5O_5S$ $[M+H]^+$ 652.1648, found 652.1647.



Methyl (*S*)-2-(4,7-difluoro-1*H*-indole-2-carboxamido)-5,5,5-trifluoropentanoate (S97): To a solution of (*S*)-2-amino-5,5,5-trifluoropentanoic acid hydrochloride **S93** (104 mg, 0.500 mmol) in MeOH (2.0 mL) was added thionyl chloride (0.0540 mL, 0.750 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h, and then concentrated under reduced pressure to obtain the crude methyl ester **S94**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S94** (0.500 mol) in CH_2Cl_2 (2.0 mL) was added 4,7-difluoro-1*H*-indole-2-carboxylic acid **S22** (98.6 mg, 0.500 mmol), COMU (236 mg, 0.550 mmol), and *N*,*N*-diisopropylethylamine (0.218 mL, 1.25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic later was dried over $MgSO_4$ and concentrated under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$ to obtain **S97** as a reddish brown solid (106 mg, 58% (2 steps)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (brs, 1H), 7.07-7.06 (m, 1H), 6.93-6.88 (m, 2H), 6.72-6.68 (m, 1H), 4.96-4.92 (m, 1H), 3.86 (s, 3H), 2.37-2.27 (m, 2H), 2.26-2.16 (m, 1H), 2.10-2.03 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.9, 160.8, 152.8 (dd, J = 245.7 Hz and 2.7 Hz), 146.0 (dd, J = 241.6 Hz and 3.4 Hz), 130.6, 126.9 (dd, J = 16.4 Hz and 10.6 Hz), 126.7 (q, J = 276.2 Hz), 119.9 (dd, J = 24.8 Hz and 5.3 Hz), 109.3 (dd, J = 19.1 Hz and 8.3 Hz), 104.8 (dd, J = 21.9 Hz and 6.5 Hz), 100.2, 53.3, 51.4, 30.4 (q, J = 29.6 Hz), 25.8-25.7 (m); HRMS (ESI), m/z calcd for $C_{15}H_{14}F_5N_2O_3$ $[M+H]^+$ 365.0919, found 365.0915.

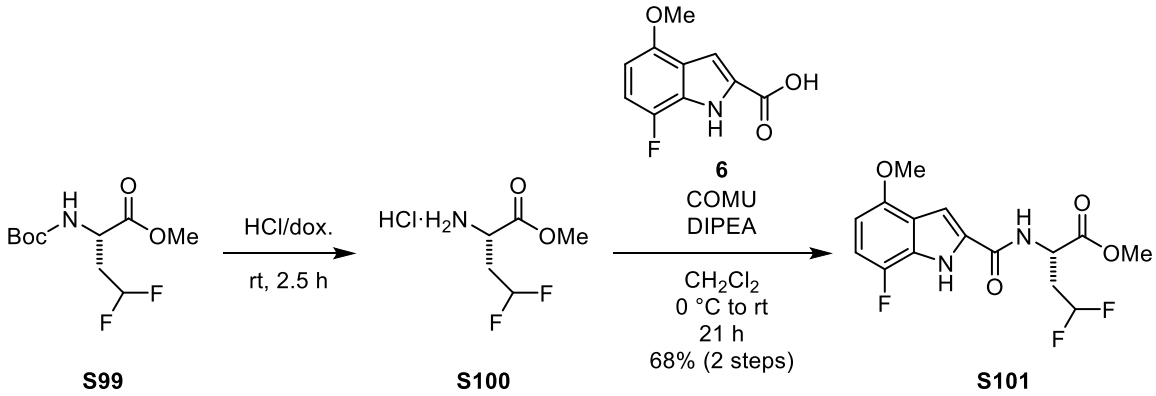


4,7-Difluoro-*N*-((S)-5,5,5-trifluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (68): To a solution of methyl ester **S97** (80.0 mg, 0.220 mmol) in THF (2.2 mL) was added an aqueous LiOH (2.0 M, 330 µL, 0.660 mmol) at room temperature. The mixture was stirred for 2 h at room temperature, and then the mixture was acidified with HCl (1.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S98**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (102 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $HBF_4{\cdot}OEt_2$ (68.6 µL, 0.500 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.250 mmol) was treated with the crude carboxylic acid **S98** (0.220 mmol), COMU (113 mg, 0.260 mmol), and DIPEA (112 µL, 0.660 mmol) in MeCN (2.2 mL) at 0 °C, and the mixture was allowed to stir for 18 h at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to obtain the title compound **68**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **68** as a pale yellow solid (4.38 mg, 3.1% (2 steps)): t_R = 19.4 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.46 (s, 1H), 9.07 (d, J = 6.9 Hz, 1H), 8.70 (d, J = 7.4 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.70 (s, 1H), 7.68-7.64 (m, 1H), 7.50 (dd, J = 10.9 Hz and 8.0 Hz, 1H), 7.39 (d, J = 2.9 Hz, 1H), 7.03-6.98 (m, 1H), 6.82-6.77 (m, 1H), 5.52-5.48 (m, 1H), 4.65-4.61 (m, 1H), 3.22-3.14 (m, 2H), 2.55-2.52 (m, 1H), 2.40-2.27 (m, 3H), 2.18-2.13 (m, 1H), 2.04-1.82 (m, 4H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.5, 178.0, 171.1, 165.1, 160.2, 156.2 (dd, J = 258.4 Hz), 152.0 (d, J = 242.8 Hz), 145.7 (d, J = 243.9 Hz), 141.7 (d, J = 13.2 Hz), 138.9, 132.9, 129.5 (d, J = 7.3 Hz), 127.4 (q, J =

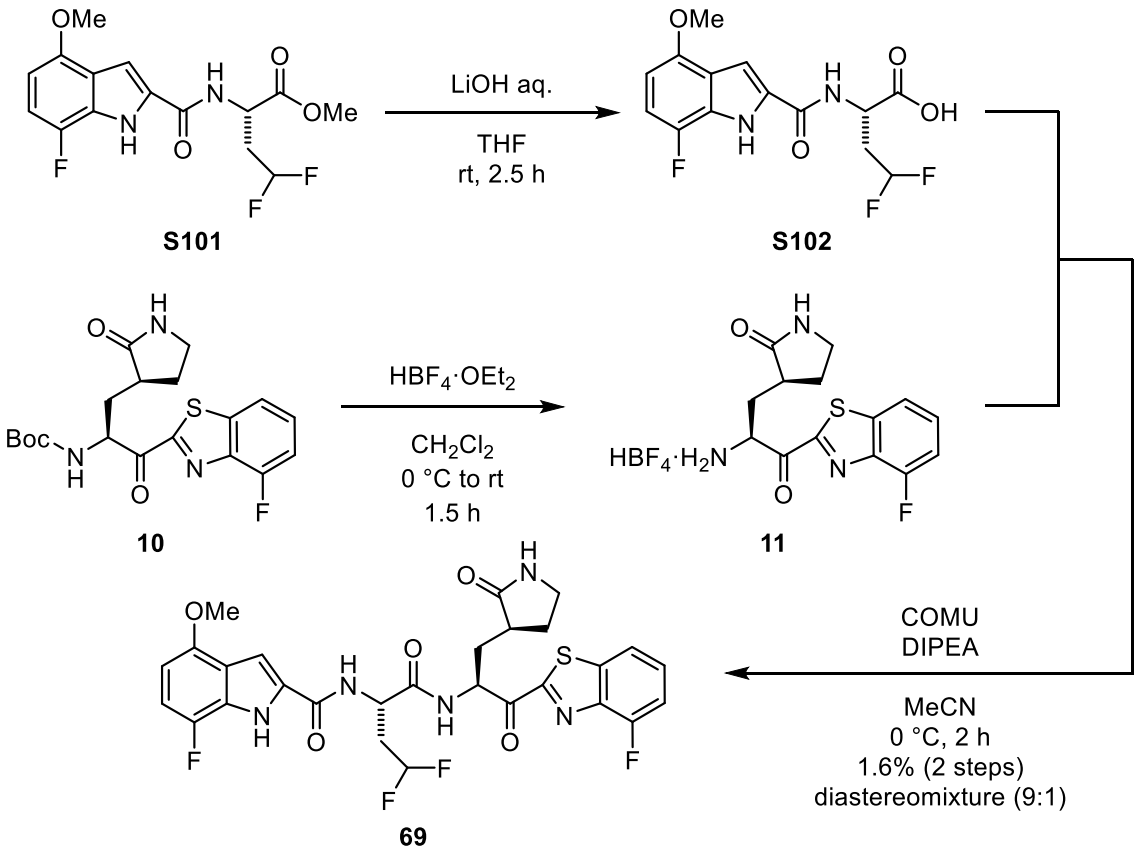
276.8 Hz), 126.6-126.4 (m), 119.4 (d, J = 4.8 Hz), 119.0 (dd, J = 24.6 Hz and 5.5 Hz), 112.8 (d, J = 16.9 Hz), 108.1 (dd, J = 18.6 Hz and 7.8 Hz), 103.8 (dd, J = 21.7 Hz and 4.8 Hz), 100.8, 53.8, 51.6, 38.0, 32.0, 29.6 (q, J = 28.4 Hz), 27.3, 24.3; HRMS (ESI), m/z calcd for $C_{28}H_{24}F_6N_5O_4S$ $[M+H]^+$ 640.1448, found 640.1450.



S99 **S100** **S101**

Methyl (*S*)-4,4-difluoro-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido)butanoate (S101): The methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,4-difluorobutanoate **S99** (253 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (8.0 mL) at room temperature and the solution was stirred for 2.5 h at room temperature. The reaction mixture was concentrated under reduced pressure to obtain the corresponding methyl ester **S100**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S100** (1.00 mmol) in CH_2Cl_2 (10 mL) was added 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid **6** (230 mg, 1.10 mmol), COMU (514 mg, 1.20 mmol), and DIPEA (680 µL, 4.00 mmol) at 0 °C. The mixture was stirred at room temperature for 21 h. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified using automatic flash column chromatography system (Isolera One, *n*-hexane/EtOAc = 84:16 to 0:100) to obtain the title compound **S101** as a green solid (235 mg, 68% (2 steps)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (brs, 1H), 7.11-7.10 (m, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.89 (dd, J = 10.6 Hz and 8.3 Hz, 1H), 6.33 (dd, J = 8.6 Hz and 2.9 Hz, 1H), 6.14-5.89 (m, 1H), 5.07-5.03 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 2.70-2.58 (m, 1H), 2.53-2.41 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 161.1, 150.3 (d, J = 2.4 Hz), 144.7 (d, J = 238.7 Hz), 129.3, 126.4 (d, J = 16.8 Hz), 121.5 (d, J = 4.8 Hz), 115.4 (t, J = 239.9 Hz), 109.3 (d, J = 16.8 Hz), 101.9, 98.8 (d, J = 6.0 Hz), 55.8, 53.3, 48.0 (t, J = 6.0 Hz), 36.6 (t, J = 21.6 Hz); HRMS (ESI), m/z calcd for $C_{15}H_{16}F_3N_2O_4$ $[M+H]^+$ 345.1057, found 345.1061.

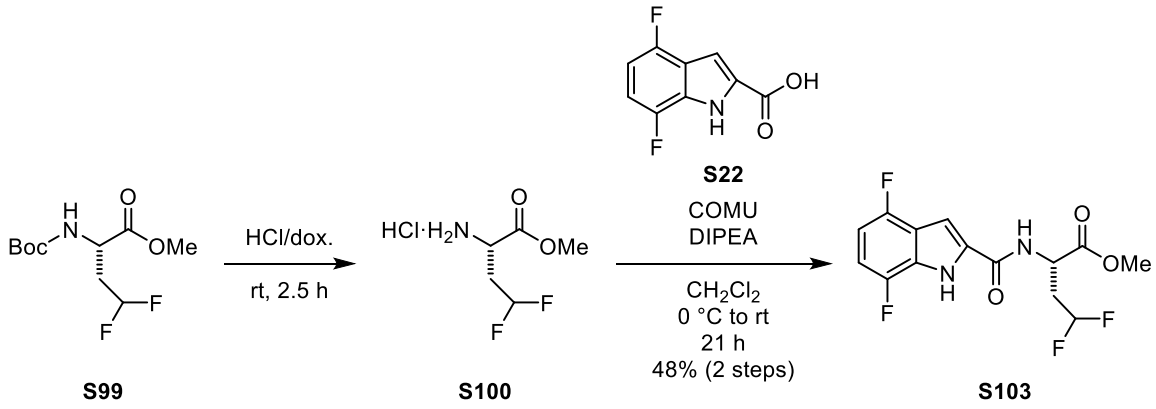


***N*-((*S*)-4,4-Difluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxobutan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (69)**: To a solution of methyl ester **S101** (138 mg, 0.400 mmol) in THF (4.0 mL) was added 2.0 M LiOH aq. (0.400 mL, 0.800 mmol) at room temperature. The mixture was stirred for 2.5 h at room temperature, and then the mixture was acidified with HCl (1.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S102**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (129 mg, 0.320 mmol) in CH_2Cl_2 (4.0 mL) was added $HBF_4{\cdot}OEt_2$ (151 µL, 1.12 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

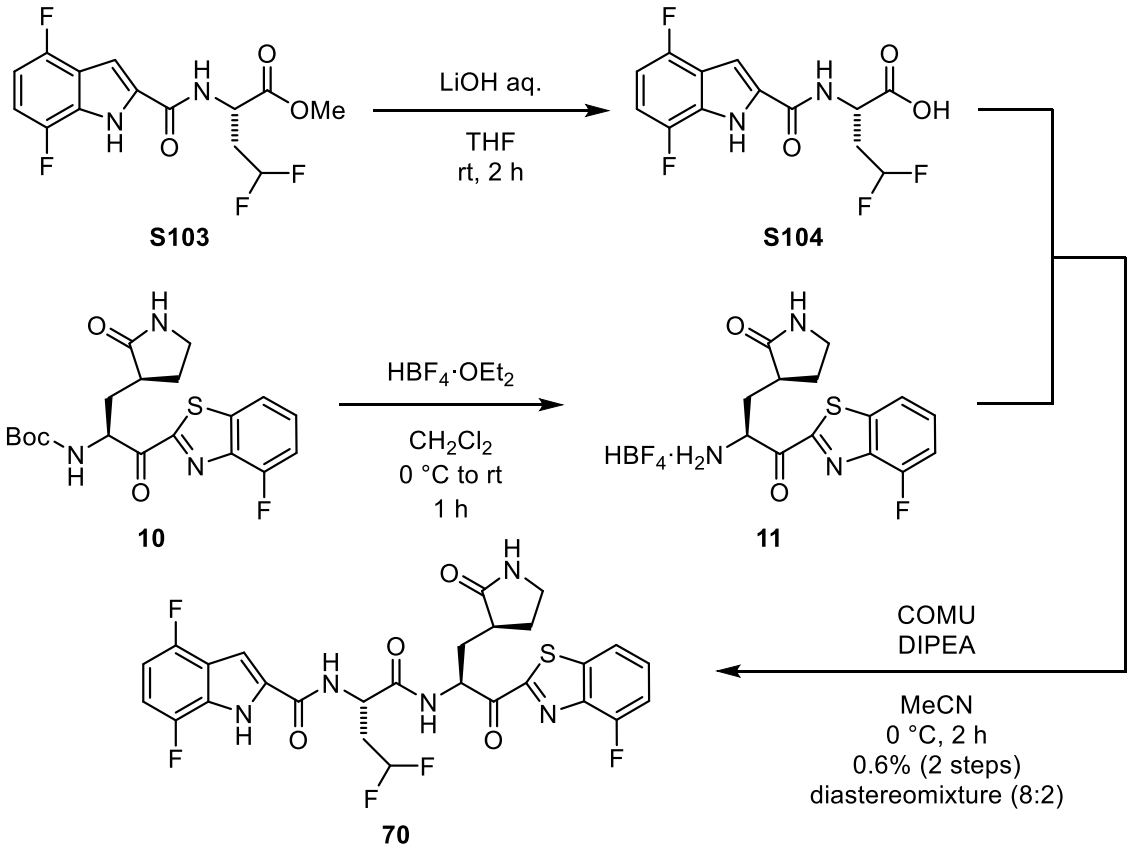
The crude amine **11** (0.320 mmol) was treated with the crude carboxylic acid **S102** (0.400 mmol), COMU (148 mg, 0.350 mmol), and DIPEA (107 µL, 0.630 mmol) in MeCN (4.0 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to give the title compound **69**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **69** as a white to pale yellow solid (3.13 mg, 1.6% (2 steps) as diastereomixture (9:1)): t_R = 16.0 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (s, 0.9H), 12.07 (s, 0.1H), 9.17 (d, J = 6.9 Hz, 0.1H), 9.11 (d, J = 6.9 Hz, 0.9H), 8.71 (d, J = 8.0 Hz, 0.9H), 8.66 (d, J = 8.6 Hz, 0.1H), 8.10-8.08 (m, 1H), 7.69-7.64 (m, 2H), 7.51 (dd, J = 10.3 Hz and 8.0 Hz, 1H), 7.33 (br, 0.9H), 7.31 (br, 0.1H), 6.94-6.90 (m, 1H), 6.43-6.40 (m, 1H), 6.15 (td, J = 56.3 Hz and 4.8 Hz, 0.9H), 6.120.2 (td, J = 56.3 Hz and 4.8 Hz, 0.1H), 5.57-5.54 (m, 0.1H), 5.51-5.47 (m, 0.9H), 4.76-4.69 (m, 1H), 3.87 (s, 2.7H), 3.86 (s, 0.3H), 3.21-3.13 (m, 2H), 2.55-2.52 (m, 1H), 2.39-2.22 (m, 3H), 2.17-2.11 (m, 1H), 1.92-1.69 (m,

2H); $^{13}C\{^{1}H\}$ NMR (126MHz, DMSO-d_6) δ 192.7, 192.4, 178.1, 178.0, 170.8, 170.4, 165.5, 165.1, 160.5, 160.4, 156.2 (d, J = 257.2 Hz), 149.7, 144.2 (d, J = 238.0 Hz), 141.8 (d, J = 13.1 Hz), 138.9 (d, J = 2.4 Hz), 131.2, 129.5 (d, J = 6.0 Hz), 125.7 (d, J = 15.6 Hz), 120.8 (d, J = 4.8 Hz), 119.5 (d, J = 4.8 Hz), 116.2 (t, J = 238.0 Hz), 112.8 (d, J = 16.8 Hz), 108.2 (d, J = 18.0 Hz), 102.8, 102.8, 98.4 (d, J = 6.0 Hz), 55.5, 54.2, 53.9, 48.6, 48.0 (t, J = 6.0 Hz), 47.9-47.8 (m), 38.1, 38.0, 35.7 (t, J = 22.2 Hz), 32.0, 31.9, 28.1, 27.3; HRMS (ESI), m/z calcd for $C_{28}H_{26}F_4N_5O_5S$ $[M+H]^+$ 620.1585, found 620.1589.



Methyl (*S*)-2-(4,7-difluoro-1*H*-indole-2-carboxamido)-4,4-difluorobutanoate (S103): The methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,4-difluorobutanoate **S99** (253 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (8.0 mL) at room temperature and the solution was stirred for 2.5 h at room temperature. The reaction mixture was concentrated under reduced pressure to obtain the corresponding methyl ester **S100**, which was used immediately in next step without purification.

To a solution of the crude methyl ester **S100** (1.00 mmol) in CH_2Cl_2 (10 mL) was added 4,7-difluoro-1*H*-indole-2-carboxylic acid **S22** (216 mg, 1.10 mmol), COMU (514 mg, 1.20 mmol), and DIPEA (680 µL, 4.00 mmol) at 0 °C. The mixture was stirred at room temperature for 21 h. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified using automatic flash column chromatography system (Isolera One, *n*-hexane/EtOAc = 88:12 to 27:73) to obtain the title compound **S103** as a green solid (159 mg, 48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (brs, 1H), 7.25 (d, J = 6.9 Hz, 1H), 7.07-7.06 (m, 1H), 6.89-6.84 (m, 1H), 6.68-6.64 (m, 1H), 6.16-5.92 (m, 1H), 5.14-5.10 (m, 1H), 3.86 (s, 3H), 2.72-2.60 (m, 1H), 2.56-2.45 (m, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 171.5, 161.0, 152.8 (dd, J = 245.9 Hz and 2.4 Hz), 146.1 (dd, J = 241.7 Hz and 3.0 Hz), 130.7, 127.1 (dd, J = 16.2 Hz and 10.2 Hz), 119.8 (dd, J = 25.2 Hz and 6.0 Hz), 115.4 (t, J = 239.9 Hz), 109.1 (dd, J = 19.2 Hz and 8.4 Hz), 104.5 (dd, J = 22.2 Hz and 6.6 Hz), 100.4, 53.4, 48.1 (t, J = 6.0 Hz), 36.5 (t, J = 22.2 Hz); HRMS (ESI), m/z calcd for $C_{14}H_{13}F_4N_2O_3$ $[M+H]^+$ 333.0857, found 333.0853.

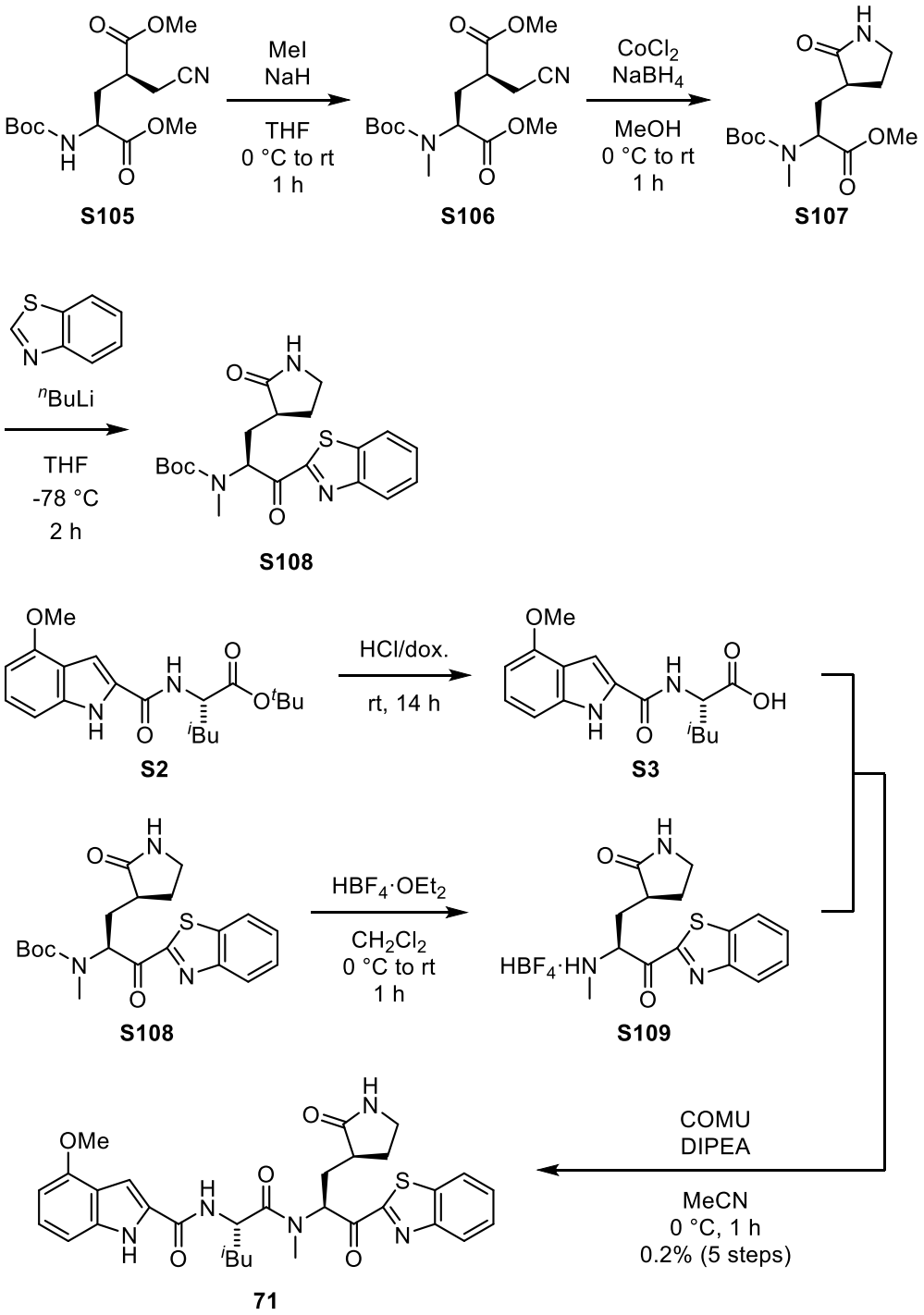


***N*-((*S*)-4,4-Difluoro-1-(((*S*)-1-(4-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxobutan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (70)**: To a solution of methyl ester **S103** (117 mg, 0.350 mmol) in THF (3.5 mL) was added 2.0 M LiOH aq. (350 µL, 0.700 mmol) at room temperature. The mixture was stirred for 2 h at room temperature, and then the mixture was acidified with HCl (1.0 M), extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to obtain the crude carboxylic acid **S104**, which was used immediately in next step without purification.

To a solution of Boc protected amine **10** (142 mg, 0.350 mmol) in CH_2Cl_2 (3.5 mL) was added $HBF_4{\cdot}OEt_2$ (167 µL, 1.22 mmol) dropwise at 0 ºC under Ar, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH. The crude amine HBF_4 salt **11** was used immediately in next step without purification.

The crude amine **11** (0.350 mmol) was treated with the crude carboxylic acid **S104** (0.350 mmol), COMU (165 mg, 0.390 mmol), and DIPEA (119 µL, 0.700 mmol) in MeCN (3.5 mL) at 0 °C, and the mixture was allowed to stir for 2 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 94:6) to give the title compound **70**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **70** as a white powder (1.28 mg, 0.6% (2 steps) as diastereomixture (8:2)): t_R = 16.8 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.46 (s, 1H), 9.20 (br, 0.2H), 9.14 (br, 0.8H), 8.84 (br, 0.8H), 8.81-8.79 (m, 0.2H), 8.11-8.07 (m, 1H), 7.69-7.64 (m, 2H), 7.53-7.48 (m, 1H), 7.34-7.32 (m, 1H), 7.03-6.98 (m, 1H), 6.82-6.78 (m, 1H), 6.28-6.02 (m, 1H), 5.56-5.53 (m, 0.2H), 5.51-5.46 (m, 0.8H), 4.74 (br, 1H), 3.22-3.09 (m, 2H), 2.55-2.52 (m, 1H), 2.41-2.26 (m, 3.2H), 2.18-2.11 (m, 0.8H), 1.93-1.69 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 192.7, 192.4, 178.9, 178.1, 170.7, 170.2, 165.5, 165.1, 160.2, 160.1, 158.9-158.6 (m), 156.2 (d, J = 258.3 Hz), 152.0 (d, J = 242.8 Hz), 145.7 (d, J = 242.8 Hz), 141.8-

141.7 (m), 138.9, 132.9, 129.5-129.5 (m), 126.6-126.4 (m), 119.4, 116.2 (t, J = 238.6 Hz), 112.9-112.7 (m), 108.2-108.0 (m), 103.9-103.7 (m), 100.7, 54.1, 54.0, 48.1, 48.0, 38.1, 38.0, 35.7 (t, J = 21.6 Hz), 32.0, 31.9, 28.1, 27.3; HRMS (ESI), m/z calcd for $C_{27}H_{23}F_5N_5O_4S$ $[M+H]^+$ 608.1385, found 608.1384.



***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)(methyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (71)**: To a solution of the methyl ester **S105** (629 mg, 2.00 mmol) in THF (20 mL) was added NaH (72.0 mg, 3.00 mmol) and MeI (0.187 mL, 3.00 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled 0 °C. The mixture was added saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The obtained crude **S106** was used in the next step without purification.

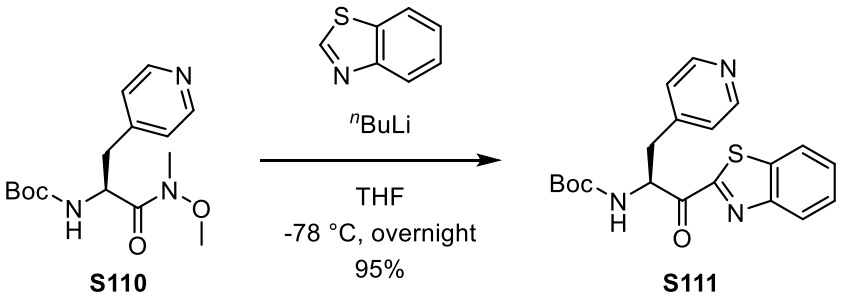
The crude methyl ester **S106** (2.00 mmol) was dissolved in MeOH (10 mL) and the mixture was cooled to 0 °C, and then added $CoCl_2$ (130 mg, 1.00 mmol) and $NaBH_4$ (303 mg, 8.00 mmol) at 0 °C. After stirring the mixture at room temperature for 1 h, the mixture was added saturated aqueous NH_4Cl and continued to stir for 30 min. The mixture was concentrated under reduced pressure and filtered through Celite® 545. The filtrate was concentrated *in vacuo*, and the residue was roughly purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 20:1) to obtain the crude **S107**, which was used in the next reaction without further purification: HRMS (ESI), *m*/*z* calcd for $C_{14}H_{24}N_2NaO_5$ $[M+Na]^+$ 323.1577, found 323.1576.

To a solution of benzo[d]thiazole (1.08 mL, 10.0 mmol) in THF (18 mL) was added ^{n}BuLi (1.6 M in *n*-hexane, 5.63 mL, 4.50 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the methyl ester **S107** (2.00 mmol) in THF (2.0 mL) was added dropwise over 20 min at -78 °C and the solution was stirred for 2 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was evaporated and extracted with EtOAc. The organic layer was dried over $MgSO_4$ followed by concentration *in vacuo*. The residue was roughly purified by silica gel flash column chromatography ($CHCl_3$ to EtOAc) to obtain the crude **S108** (71.4 mg), which was used in the next reaction without further purification: HRMS (ESI), *m*/*z* calcd for $C_{20}H_{26}N_3O_4S$ $[M+H]^+$ 404.1639, found 404.1636.

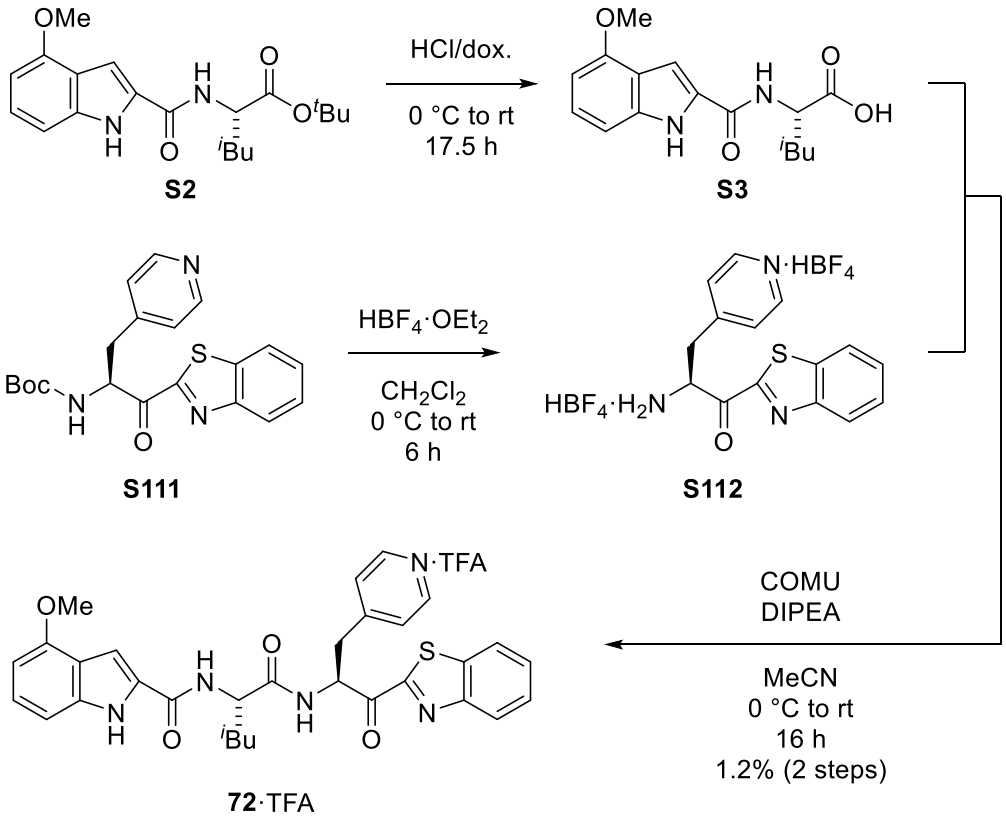
The *tert*-butyl ester **S2** (79.9 mg, 0.222 mmol) was treated with 4 M HCl in dioxane (2.0 mL) at room temperature. The solution was stirred for 14 h. Concentration of the reaction mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

To a solution of the crude Boc protected amine **S108** (71.4 mg, 0.177 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (95.0 μL, 0.690 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentration under reduced pressure, and the crude solid was washed by 2% MeOH in Et_2O. The crude amine HBF_4 salt **S109** was used immediately in next step without purification.

The crude amine **S109** (0.177 mmol) was coupled to the crude carboxylic acid **S3** (0.222 mmol) using COMU (84.8 mg, 0.200 mmol) in the presence of DIPEA (69.0 μL, 0.400 mmol) in MeCN (2.0 mL) at 0 °C and the solution was allowed to stir for 1 h at 0 °C. The reaction mixture was added saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified using automatic flash column chromatography system (Isolera One, $CHCl_3$/MeOH = 100:0 to 95:5) to obtain the title compound **71**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **71** as a yellow solid (2.50 mg, 0.2% (5 steps)): t_R = 20.2 min (linear gradient of B in A, 40 to 70 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (brs, 1H), 8.10-8.09 (m, 1H), 7.98-7.96 (m, 1H), 7.55-7.52 (m, 2H), 7.13-6.96 (m, 5H), 6.46-6.45 (m, 1H), 6.00-5.99 (m, 1H), 4.85 (br, 1H), 3.93 (s, 3H), 3.32 (br, 2H), 2.62-2.61 (m, 1H), 2.20 (br, 2H), 1.97-1.95 (m, 1H), 1.72-1.64 (m, 3H), 0.89-0.88 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.6, 183.0, 172.6, 163.7, 161.9, 154.2, 153.6, 138.2, 137.4, 128.9, 128.2, 127.2, 125.9, 125.6, 122.5, 118.9, 105.4, 101.1, 99.7, 55.4, 53.2, 51.7, 43.0, 41.4, 39.4, 38.0, 31.3, 25.2, 25.0, 23.2, 22.0; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{36}N_5O_5S$ $[M+H]^+$ 590.2432, found 590.2430.



***tert*-Butyl (*S*)-(1-(benzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate (S111)**: To a solution of benzo[*d*]thiazole (1.03 mL, 9.39 mmol) in THF (15 mL) was added ^{n}BuLi (1.58 M in *n*-hexane, 5.35 mL, 8.45 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, the *tert*-butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate **S110** (581 mg, 1.88 mmol) in THF (4.0 mL) was added dropwise at -78 °C and the solution was stirred overnight at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ followed by concentration under reduced pressure. The residue was purified by flash column chromatography over silica gel with $CHCl_3$/MeOH (44:1) to obtain the **S111** as a pale yellow solid (685 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 5.0 Hz, 2H), 8.23 (d, J = 7.7 Hz, 1H), 8.03-8.01 (m, 1H), 7.65-7.57 (m, 2H), 7.16 (br, 2H), 5.92 (br, 1H), 5.39-5.37 (m, 1H), 3.53-3.51 (m, 1H), 3.20-3.15 (m, 1H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.4, 163.4, 155.1, 153.6, 149.3 (2C), 146.3, 137.4, 128.5, 127.5, 126.0, 125.1 (2C), 122.6, 80.5, 56.9, 38.7, 28.4 (3C); HRMS (ESI), *m*/*z* calcd for $C_{20}H_{22}N_3O_3S$ $[M+H]^+$ 384.1376, found 384.1378.

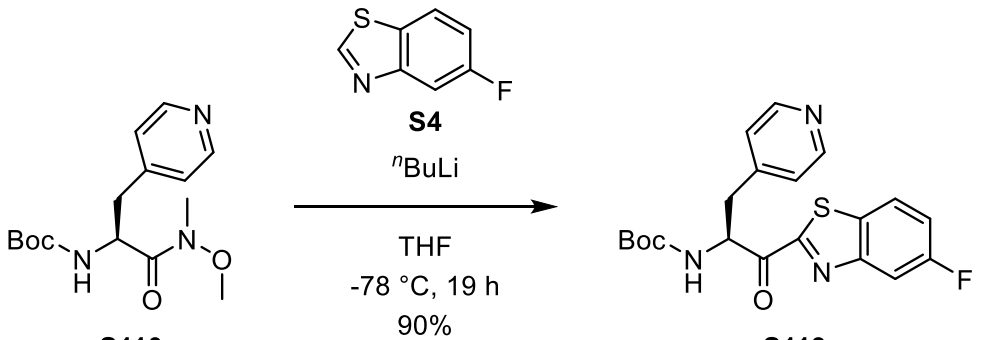


***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-4-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (72)**: The *tert*-butyl ester **S2** (180 mg, 0.500 mmol) was treated with 4

M HCl in dioxane (5.0 mL) at room temperature. The solution was stirred for 17.5 h at room temperature. Concentration of the mixture under reduced pressure gave the corresponding carboxylic acid **S3**, which was used immediately in next step without purification.

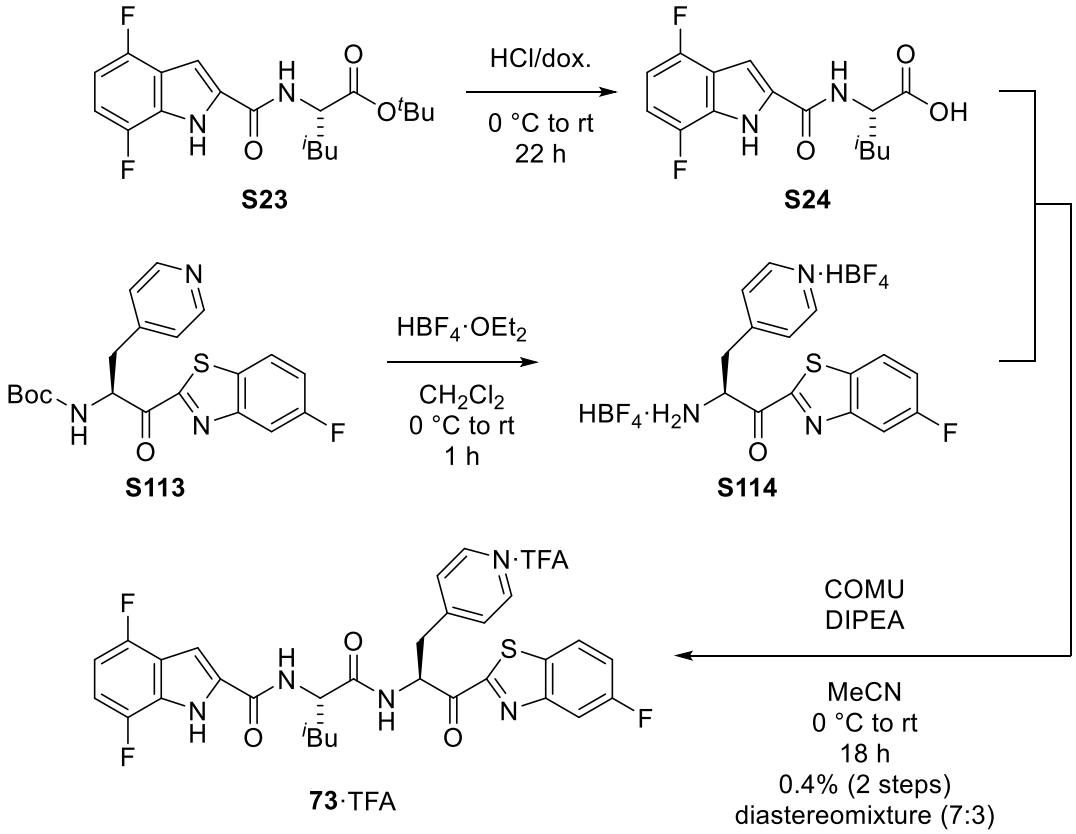
To a solution of Boc protected amine **S111** (192 mg, 0.500 mmol) in CH_2Cl_2 (5.0 mL) was added $HBF_4{\cdot}OEt_2$ (240 µL, 1.75 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH to obtain **S112** as a *bis*-HBF_4 salt, which was used immediately in next step without purification.

The crude carboxylic acid **S3** (0.500 mmol) was dissolved in MeCN (5.0 mL) and was added COMU (278 mg, 0.650 mmol) at 0 °C. To the mixture were then added the crude amine **S112** (0.500 mmol) and DIPEA (170 µL, 1.00 mmol) at 0 °C, and the mixture was allowed to stir for 16 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified by automatic silica gel flush column chromatography system with $CHCl_3$/MeOH (Isolera One, Biotage, 100:0 to 94:6) to obtain the title compound **72**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to obtain the title compound **72** as a TFA salt (**72**·TFA, pale yellow powder, 4.18 mg, 1.2% (2 steps)): t_R = 19.5 min (linear gradient of B in A, 30 to 60 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.27–8.26 (m, 2H), 8.18–8.15 (m, 1H), 8.02–7.98 (m, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.59–7.55 (m, 2H), 7.21 (t, *J* = 16.0 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.01 (d, *J* = 5.2 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.21–6.17 (m, 1H), 4.86–4.81 (m, 1H), 3.93 (s, 3H), 3.48 (dd, *J* = 14.0 Hz and 5.1 Hz, 1H), 3.21 (dd, *J* = 3.23 Hz and 3.19 Hz, 1H), 1.78–1.61 (m, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 172.0, 163.4, 161.8, 154.4, 153.6, 149.5, 145.4, 138.1, 137.4, 128.6, 128.5, 127.5, 126.0, 126.0, 124.9, 122.6, 119.0, 105.3, 101.1, 99.9, 55.9, 55.4, 51.9, 40.9, 38.0, 25.0, 23.0, 22.3; HRMS (ESI), *m*/*z* calcd for $C_{31}H_{32}N_5O_4S$ $[M+H]^+$ 570.2170, found 570.2175.



***tert*-Butyl (*S*)-(1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate (S113)**: To a solution of 5-fluorobenzo[*d*]thiazole **S4** (574 mg, 3.75 mmol) in THF (5.0 mL) was added ^{n}BuLi (1.58 M in *n*-hexane, 2.14 mL, 3.38 mmol) dropwise over 15 min at -78 °C. After 2 h stirring at -78 °C, *tert*-butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-(pyridin-3-yl)propan-2-yl)carbamate **S110** (232 mg, 0.750 mmol) in THF (2.5 mL) was added dropwise at -78 °C and the solution was stirred for 19 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was allowed to stir at room temperature. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure

followed by flash column chromatography over silica gel with $CHCl_3$/MeOH (44:1) to obtain the title compound **S113** as an yellow solid (271 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.96 (dd, *J* = 8.9 Hz and 5.0 Hz, 1H), 7.90 (dd, *J* = 8.9 Hz and 2.3 Hz, 1H), 7.37 (ddd, *J* =8.8 Hz, 8.8 Hz, and 2.4 Hz, 1H), 7.15 (brs, 2H), 5.90-5.89 (m, 1H), 5.34 (d, *J* = 7.4 Hz, 1H), 3.51-3.48 (m, 1H), 3.17-3.12 (m, 1H), 1.40 (s, 9H); ; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.2, 165.8, 162.4 (d, *J* = 246.4 Hz), 155.1, 154.5 (d, *J* = 12.3 Hz), 149.3 (2C), 146.3, 133.0, 125.1 (2C), 123.6 (d, *J* = 9.7 Hz), 117.8 (d, *J* = 25.6 Hz), 111.5 (d, *J* = 23.3 Hz), 80.6, 56.8 38.5, 28.4 (3C); HRMS (ESI), *m*/*z* calcd for $C_{20}H_{21}FN_3O_3S$ $[M+H]^+$ 402.1282, found 402.1277.

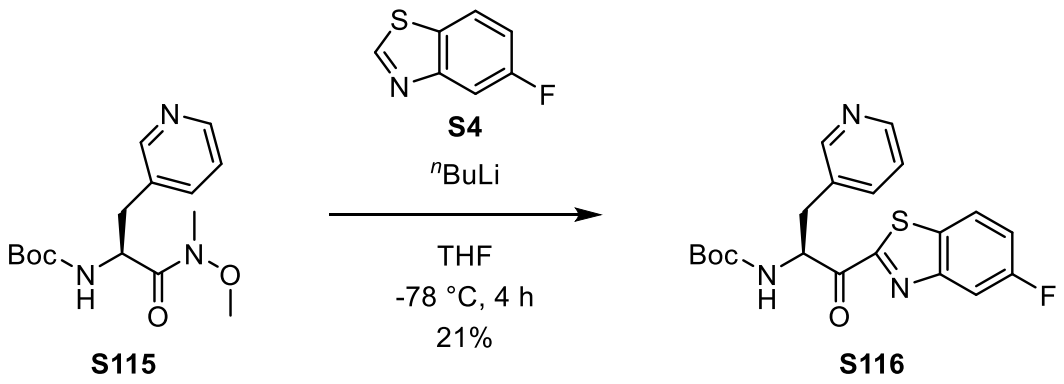


***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-4-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (73)**: The *tert*-butyl ester **S23** (183 mg, 0.500 mmol) was treated with 4 M HCl in dioxane (5.0 mL) at room temperature. The solution was stirred for 22 h at room temperature. Concentration of the mixture under reduced pressure gave the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

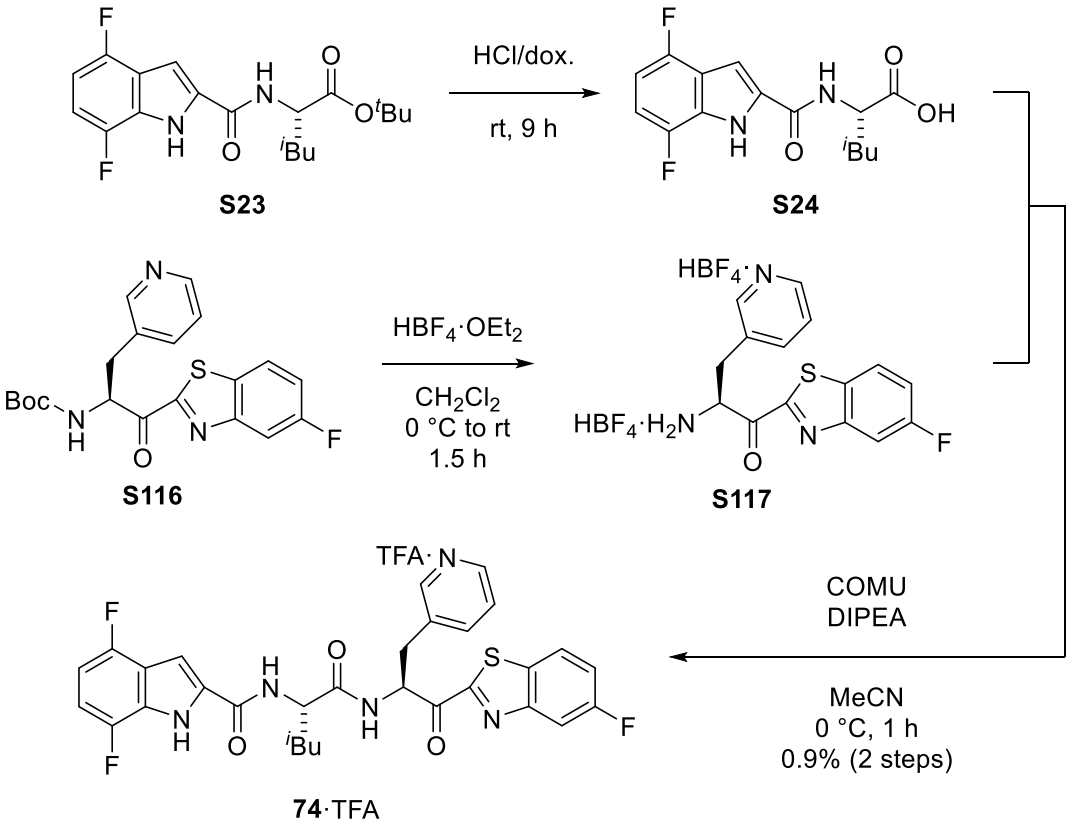
To a solution of Boc protected amine **S113** (201 mg, 0.500 mmol) in CH_2Cl_2 (5.0 mL) was added HBF_4·OEt_2 (240 µL, 1.75 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH to obtain **S114** as a *bis*-HBF_4 salt, which was used immediately in next step without purification.

The crude carboxylic acid **S24** (0.500 mmol) was dissolved in MeCN (5.0 mL) and was added COMU (278 mg, 0.650 mmol) at 0 °C. To the mixture were then added the crude amine **S114** (0.500 mmol) and DIPEA (170 µL, 1.00 mmol) at 0 °C, and the mixture was allowed to stir for 18 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over

$MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified by automatic silica gel flush column chromatography system with $CHCl_3$/MeOH (Isolera One, Biotage, 100:0 to 94:6) to obtain the title compound **73**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **73** as a TFA salt (**73**·TFA, pale yellow powder, 1.55 mg, 0.4% (2 steps) as a diastereomixture (7:3)): t_R = 21.7 min (linear gradient of B in A, 30 to 60 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (s, 0.7H), 10.0 (s, 0.3H), 8.49 (s, 0.6H), 8.34 (s, 1.4H), 7.95 (dd, *J* = 8.9 Hz and 4.9 Hz, 0.7H), 7.89 (dd, *J* = 8.9 Hz and 4.9 Hz, 0.3H), 7.84-7.79 (m, 1H), 7.57 (br, 1H), 7.37-7.29 (m, 1H), 7.19-6.94 (m, 4H), 6.88-6.84 (m, 1H), 6.67-6.63 (m, 1H), 6.19-6.15 (m, 0.7H), 6.12-6.10 (m, 0.3H), 4.85-4.78 (m, 1H), 3.57-3.52 (m, 1H), 3.29-3.21 (m, 1H), 1.76-1.51 (m, 3H), 0.94-0.90 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.5, 172.1, 172.0, 162.4 (d, *J* = 246.8 Hz), 162.3 (d, *J* = 246.1 Hz), 161.0, 160.9, 154.4 (d, *J* = 12.0 Hz), 154.3 (d, *J* = 11.6 Hz), 152.8 (d, *J* = 245.5 Hz), 149.3-149.2 (m), 148.6-148.5 (m), 146.0 (d, *J* = 243.0 Hz), 133.0, 132.9, 131.0, 130.9, 127.0-126.8 (m), 123.6 (d, *J* = 9.2 Hz), 123.5 (d, *J* = 12.6 Hz), 120.0-119.7 (m), 118.0 (d, *J* = 25.7 Hz), 117.8 (d, *J* = 25.4 Hz), 111.4 (d, *J* = 23.6 Hz), 111.4 (d, *J* = 22.5 Hz), 109.2-109.0 (m), 104.7-104.5 (m), 100.4 (d, *J* = 29.0 Hz), 100.2 (d, *J* = 20.9 Hz), 64.6, 56.0, 55.8, 52.2, 52.0, 41.2, 41.0, 38.0, 37.7, 25.5, 25.0, 22.9, 22.3 ; HRMS (ESI), *m*/*z* calcd for $C_{30}H_{27}F_3N_5O_3S$ $[M+H]^+$ 594.1781, found 594.1781.



***tert*-Butyl (*S*)-(1-(5-fluorobenzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-3-yl)propan-2-yl)carbamate (S116)**: To a solution of 5-fluorobenzo[*d*]thiazole **S4** (742 mg, 4.85 mmol) in THF (4.9 mL) was added ^{n}BuLi (1.59 M in *n*-hexane, 2.75 mL, 4.37 mmol) dropwise over 15 min at -78 °C. After 1 h stirring at -78 °C, *tert*-butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-(pyridin-3-yl)propan-2-yl)carbamate **S115** (300 mg, 0.970 mmol) in THF (1.9 mL) was added dropwise at -78 °C and the solution was stirred for 4 h at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and allowed to stir at room temperature for 20 min. The mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$, then was concentrated under reduced pressure followed by flash column chromatography over silica gel with $CHCl_3$/MeOH (40:1) to afford the **S116** as an yellow solid (80.4 mg, 21%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (d, *J* = 4.0 Hz, 1H), 8.36 (s, 1H), 7.94 (dd, *J* = 8.9 Hz and 4.9 Hz, 1H), 7.88 (dd, *J* = 8.9 Hz and 1.9 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.35 (ddd, *J* = 8.8 Hz, 8.8 Hz, and 2.4 Hz, 1H), 7.20 (dd, *J* = 7.6 Hz and 4.9 Hz, 1H), 5.86-5.85 (m, 1H), 5.43-5.41 (m, 1H), 3.46 (dd, *J* = 13.9 Hz and 4.2 Hz, 1H), 3.16 (dd, *J* = 13.7 Hz and 6.8 Hz, 1H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.5, 165.9, 162.3 (d, *J* = 246.3 Hz), 155.1, 154.5 (d, *J* = 12.0 Hz), 150.7, 148.5, 137.1, 132.9, 131.8, 123.5 (d, *J* = 9.0 Hz), 123.5, 117.7 (d, *J* = 25.6 Hz), 111.4 (d, *J* = 23.2 Hz), 80.4, 57.3 36.3, 28.3 (3C); HRMS (ESI), *m*/*z* calcd for $C_{20}H_{21}FN_3O_3S$ $[M+H]^+$ 402.1282, found 402.1281.



***N*-((*S*)-1-(((*S*)-1-(Benzo[*d*]thiazol-2-yl)-1-oxo-3-(pyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4,7-difluoro-1*H*-indole-2-carboxamide (74)**: The *tert*-butyl ester **S23** (366 mg, 1.00 mmol) was treated with 4 M HCl in dioxane (10 mL) at room temperature. The solution was stirred for 9 h at room temperature. Concentration of the mixture under reduced pressure gave the corresponding carboxylic acid **S24**, which was used immediately in next step without purification.

To a solution of Boc protected amine **S116** (80.0 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added $HBF_4{\cdot}OEt_2$ (96.0 μL, 0.700 mmol) dropwise at 0 ºC under nitrogen, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the crude solid was washed by Et_2O containing 2% MeOH to obtain **S117** as a *bis*-HBF_4 salt, which was used immediately in next step without purification.

The crude carboxylic acid **S24** (1.00 mmol) was dissolved in MeCN (2.0 mL) and was added COMU (94.0 mg, 0.220 mmol) at 0 °C. To the mixture were then added the crude amine **S117** (0.200 mmol) and DIPEA (68.0 μL, 0.400 mmol) at 0 °C, and the mixture was allowed to stir 1 h at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was roughly purified by automatic silica gel flush column chromatography system with $CHCl_3$/MeOH (Isolera One, Biotage, 100:0 to 94:6) to obtain the title compound **74**. Further purification was performed by preparative RP-HPLC and CHIRALPAK IC semi-preparative NP-HPLC to give the title compound **74** as a TFA salt (**74**·TFA, pale yellow powder, 1.30 mg, 0.9% (2 steps)): t_R = 22.2 min (linear gradient of B in A, 30 to 60 % over 30 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.55-8.38 (m, 2H), 7.96 (dd, *J* = 8.8 Hz and 4.9 Hz, 1H), 7.86-7.84 (m, 1H), 7.62-7.58 (m, 2H), 7.38-7.34 (m, 1H), 7.23-7.17 (m, 1H), 7.03 (s, 1H), 6.88-6.87 (m, 2H), 6.69-6.66 (m, 1H), 6.10 (br, 1H), 4.77-4.76 (m, 1H), 3.60-3.58 (m, 1H), 3.32-3.27

(m, 1H), 2.02-1.66 (m, 3H), 0.94-0.90 (m, 6H); HRMS (ESI), *m*/*z* calcd for $C_{30}H_{27}F_3N_5O_3S$ $[M+H]^+$ 594.1781, found 594.1786.

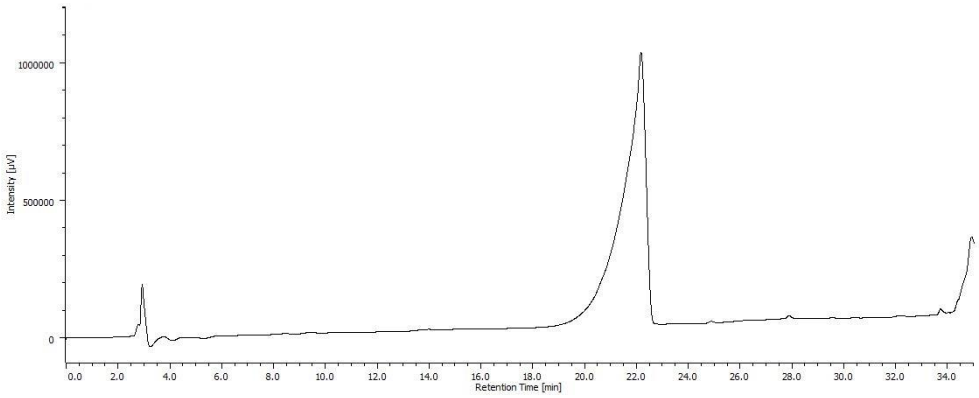


Chart. Purity check of **74** by analytical RP-HPLC (linear gradient of B in A, 30 to 60% over 30 min).

III. References for Supplemental information section

[S1] Hattori, S., Higashi-Kuwata, N., Hayashi, H., Allu, S. R., Raghavaiah, J., Bulut, H., Das, D., Anson, B. J., Lendy, E. K., Takamatsu, Y., et al. (2021). A small compound with an indole moiety inhibits the main protease of SARS-CoV-2 and blocks virus replication. Nat. Commun. 12, 668. 10.1038/s41467-021-20900-6.