SUPPORTING INFORMATION

Development of matrix metalloproteinase-13 inhibitors – A structure-activity/structure-property relationship study

Rita Fuerst[a,c], Jun Yong Choi[a,d], Anna M. Knapinska[b], Lyndsay Smith[b], Michael D. Cameron[a], Claudia Ruiz[a], Gregg B. Fields[*,b] and William R. Roush[*,a]

[a]*Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States*
[b]*Department of Chemistry & Biochemistry, Florida Atlantic University, Jupiter, Florida 33458, United States*
[c]*Institute of Organic Chemistry, Graz University of Technology, 8010 Graz, Austria*
[d]Department of Chemistry and Biochemistry, Queens College and the Graduate Center of the City University of New York, New York 11367, United States

Table of Contents	**Page Nr.**

I. Supplemental Methods for Enzyme Assays

MMP-13 enzyme activation. Full-length recombinant human proMMP-13 (rhMMP-13) was purchased from R&D Systems (catalog no. 511-MM; Minneapolis, MN). MMP-13 was activated by incubating proMMP-13 diluted in 100 µL enzyme assay buffer (EAB; 50 mM Tris•HCl, pH 7.5, 100 mM NaCl, 10 mM $CaCl_2$, 0.05% Brij-35) with 1 mM (p-aminophenyl)mercuric acid (APMA) for 2 h at 37 °C.[2] The stock of active MMP-13 was diluted to 384.6 nM and stored at -80 °C.

Inhibitor kinetics. Inhibition experiments were conducted as described previously.[1] Briefly, fTHP-15 [sequence (Gly-Pro-Hyp)$_5$-Gly-Pro-Lys(Mca)-Gly-Pro-Gln-Gly-Leu-Arg-Gly-Gln-Lys(Dnp)-Gly-Val-Arg-Gly-Pro-Hyp-(Gly-Pro-Hyp)$_4$-NH_2], MMP-13, and inhibitor working solutions were prepared in EAB. All reactions were conducted in 384-well black polystyrene plates (Greiner, North Carolina, catalog no. 784076). Fluorescence was measured on a BioTek H1 microplate reader using $\lambda_{excitation}$ = 324 nm and $\lambda_{emission}$ = 393 nm. Rates of hydrolysis were obtained from plots of fluorescence versus time using data points from only the linear portion of the hydrolysis curve. To determine the IC_{50} of each inhibitor, the compounds were screened in 10-point 3-fold dilution dose-response curve format in triplicates.
The assay began by dispensing 5 µL of test compounds in assay buffer followed by 5 µL of MMP-13. The enzyme was allowed to incubate with the test compounds for 30 min at 25 °C. The assays were initiated by addition of 5 µL of fTHP-15 and immediately placed in the microplate reader to record fluorescence.
To determine IC_{50} values of each compound, the relative fluorescence units (RFU) from wells containing MMP-13, fTHP-15, and inhibitors were plotted vs. no enzyme and untreated controls. For each compound, RFUs from the linear part of the curve were fitted with a four parameter equation describing a sigmoidal dose-response curve with adjustable baseline using GraphPad Prism® version 11 suite of programs. The IC_{50} values of the compounds were determined as the concentrations that resulted in 50% enzyme activity when compared to the activity of the control samples (without a compound). These values were generated from fitted curves by solving for the X-intercept at the 50% inhibition level of Y-intercept using the built-in dose-response model algorithm of GraphPad Prism (LaJolla, CA). Hill slopes were also determined.

Selectivity assay. To determine the selectivity of each inhibitor, the compounds were tested against a selected protease panel consisting of MMP-1, MMP-2, MMP-8, MMP-9, and MT1-MMP. All enzymes were purchased from R&D Systems and activated according to manufacturer's instructions. Upon activation, each enzyme was diluted in EAB to 200 µM and stored at -80°C until further use. The compounds were screened as described above in 10-point 3-fold dilution dose-response curve format in triplicate utilizing fTHP-15 as substrate except for MMP-1, for which Knight substrate was used.[2]

Type II collagen assay. To assess the potency of probes using a physiologically relevant substrate we tested compounds in an assay utilizing type II collagen (Sigma-Aldrich, St. Louis, MO, Cat# 234184). All experiments were performed in 384-well white microtiter plates. The assay was initiated by dispensing 9 µL of 333 nM type II collagen in EAB. 2 µL of test compounds in EAB were added. Reactions were initiated by addition of 9 µL of 4 nM MMP-13 in EAB. After 22 h of incubation at 37 °C, the samples were resolved by electrophoresis on a 8% SDS-PAGE gel. The gel was stained with Coomassie Blue and band intensities quantified vs. no-enzyme and untreated controls. For each compound, band intensity data were fitted with a four parameter equation describing a sigmoidal dose-response curve with adjustable baseline using GraphPad Prism® version 11 suite of programs. The IC_{50} values were generated from fitted curves by solving for X-intercept at the 50% inhibition level of Y-intercept.

II. Methods for In Vitro and In Vivo PK Studies.

Solubility. Compounds from 10 mM DMSO stock solutions were introduced to pre-warmed pH 7.4 phosphate buffered saline in a 96-well plate. The final DMSO concentration was 1% and the plate was maintained at 37ºC for 24 hours on an orbital shaker. The samples were centrifuged through a Millipore

Multiscreen Solvinter 0.45 micron low binding PTFE hydrophilic filter plate and analyzed by HPLC with peak area compared to standards of known concentration.

Permeability. An assessment of permeability was done using a commercial PAMPA (Parallel Artificial Membrane Permeability Assay) kit from BD Biosciences (Cat# 353015).[3] Compound (5 μM) was added to 300 μL PBS in the bottom donor plate and 200 μL of blank PBS was added to the top receiver plate. The plates were incubated in an orbital shaker temperature at 37 ºC for 5 h, aliquots were taken from the donor and receiver plates and the concentration of drug was determined by HPLC-MS analysis. As the initial concentration of the donor solution is known the overall recovery in the system can be calculated. Anything below 100% represents the amount of membrane retention of the corresponding compound. Compound permeability was calculated using the equation

$$P_e = -\frac{\ln\left[1 - \frac{C_A(t)}{C_{eq}}\right]}{\left(A * \left(\frac{1}{V_D} + \frac{1}{V_A}\right) * t\right)}$$

where P_e is expressed in units of cm/s, $C_A(t)$ is drug concentration in the acceptor at time t, V_D is donor well volume, V_A is acceptor well volume, A is the area of the filter (0.3 cm^2), t is time in seconds, and $C_{eq} = [C_D(t) * V_D + C_A(t) * V_A]/(V_D + V_A)$.

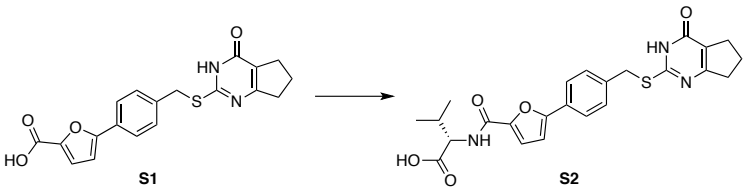
Hepatic microsomal stability. Microsome stability was evaluated by incubating 1 μM compound with 1 mg/mL hepatic microsomes (human, rat, or mouse) in 100 mM potassium phosphate buffer, pH 7.4. The reactions were held at 37 °C with continuous shaking. The reaction was initiated by adding NADPH, 1 mM final concentration. The final incubation volume was 300 μL and 40 μL aliquots were removed at 0, 5, 10, 20, 40, and 60 min. The removed aliquot was added to 160 μL acetonitrile to stop the reaction and precipitate the protein. NADPH dependence of the reaction was evaluated in parallel incubations without NADPH. At the end of the assay, the samples are centrifuged through a 0.45 micron filter plate (Millipore Solventer low binding hydrophilic plates, cat# MSRLN0450) and analyzed by LC-MS/MS. The data was log transformed and results are reported as half-life.

Pharmacokinetics. All procedures described are covered under existing protocols and have been approved by the Scripps Florida IACUC to be conducted in the Scripps vivarium, which is fully AAALAC accredited. Pharmacokinetics were determined in n=3 male Sprague-Dawley rats. Compounds were dosed as indicated in the text via intravenous tail vein injection or by oral gavage. Time points for determination of pharmacokinetic parameters were 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, and 8 h. Plasma concentrations were determined via LC-MS/MS using a nine point standard curve between 0.4 and 2000 ng/mL prepared in rat plasma. Pharmacokinetic analysis was done with WinNonlin, Centara inc. using a noncompartmental model. Synovial fluid was sampled from the rear knee by loading 40 μl saline in a 28 gauge insulin syringe and injecting it into synovial capsule to create positive pressure and then removing a similar volume. Failure to inject saline into the capsule resulted in minimal volume and an increased tendency to get blood contamination in the sample. The concentration of the withdrawn solution was determined by LC-MS/MS. Dilution caused by the addition of saline was not accounted for and the in vivo concentration is assumed to be slightly higher than the measured value.

CYP Inhibition. Cytochrome P450 inhibition was evaluated in human liver microsomes using four selective marker substrates (CYP1A2, phenaceten demethylation to acetaminophen; CYP2C9, tolbutamide hydroxylation to hydroxytolbutamide; CYP2D6, bufuralol hydroxylation to 40 -Hydroxybufuralol; and CYP3A4, midazolam hydroxylation to 10 -hydroxymidazolam) in the presence or absence of 10 mM test compound. The reaction is initiated by the addition of 1 mM NADPH and stopped after ten min by the addition of 2-times volume of acetonitrile containing dextrorphan as an internal standard. The concentration of each marker substrate is approximately its K_m. Furafylline, sulfaphenazole, quinidine, and ketoconazole were included to each run to validate that the assay could identify selective inhibitors of each isoform.

III. Procedures for the Synthesis of Inhibitors and Spectroscopic Analyses

General experimental details. All non-aqueous reactions were carried out under argon atmosphere using flame-dried glassware. Dichloromethane, diethyl ether, *N,N*-dimethylformamide, toluene, and tetrahydrofuran were dried by being passed through a column of desiccant (activated A-1 alumina). Triethylamine was distilled from calcium hydride under an argon atmosphere prior to use. All other commercially available reagents were used without further purification. Reactions were either monitored by thin layer chromatography or analytical LC-MS. Thin layer chromatography was performed on Kieselgel 60 F254 glass plates pre-coated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light and/or by staining with Hanessian solution [H_2SO_4 (conc., 22 mL), phosphormolybdic acid (20 g), $Ce(SO_4)_2$ (0.5 g), 378 mL H_2O)].
Column chromatography was performed on a Biotage Isolera automated flash system. Compound was loaded onto pre-filled cartridges filled with KP-Sil 50 µm irregular silica.
NMR spectra were recorded on a 400 MHz spectrometer and measured in $CDCl_3$, MeOD, or DMSO ($CHCl_3$: ^1H, δ = 7.26, ^{13}C, δ = 77.16, MeOH: ^1H, δ = 3.31, ^{13}C, δ = 49.00, DMSO: ^1H, δ = 2.50, ^{13}C, δ = 39.50). All ^1H and ^{13}C shifts are given in ppm and coupling constants *J* are given in Hz.
High-resolution mass spectra were recorded on a spectrometer (ESI) at the University of Illinois Urbana-Champaign Mass Spectrometry Laboratory.
The structures of all compounds were determined by ^1H-, ^{13}C-, ^{19}F NMR and HPLC/HRMS. The purity of isolated products was determined using an LC-MS instrument (Agilent 1260 Infinity series LC with 500 Ion Trap MS) equipped with Kinetex® 5 µm EVO C18 100 Å LC Column 100 × 4.6 mm (Phenomenex) column. Elution was performed using the following conditions: 2% (v/v) acetonitrile (+0.1% FA) in 98% (v/v) H_2O (+0.1% FA), ramped to 98% acetonitrile over 8 min, and holding at 98% acetonitrile for 1 min with a flow rate of 1.75 mL/min; UV absorption was detected from 200 to 950 nm using a diode array detector. The purity of each compound was ≥95% based on this analysis.

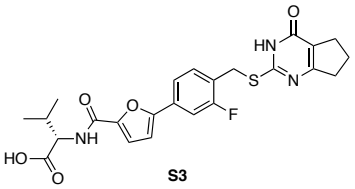


(5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carbonyl)-*L*-valine (**S2**). To a solution of **S1**[4] (546 mg, 1.48 mmol, 1.0 eq), L-valine methyl ester hydrochloride (298 mg, 1.78 mmol, 1.2 eq) and HOBt (220 mg, 1.63 mmol, 1.1 eq) in DMF (7 mL) was added NEt_3 (452 µL, 3.26 mmol, 2.2 eq). The reaction mixture was stirred at room temperature for 5 min and after cooling to 0 °C EDCI•HCl (312 mg, 1.63 mmol, 1.1 eq) was added. The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 hours. After dilution with EtOAc (ca. 10 mL) and washing with 0.1 M HCl (2x 15 mL) the aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x 25 mL) and brine (1x 25 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude L-valine methyl ester (597 mg, 84%) was used for the next step without any further purification.
An aqueous 1 M solution of NaOH (4.74 mL, 4.74 mmol, 3.2 eq) was added to a solution of the methyl ester (597 mg, 1.56 mmol, 1.0 eq) in 14.8 mL of THF/methanol 2:1 and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature the mixture was diluted with 3 mL water and acidified with 1 M HCl (pH~2). The precipitated product was filtered and washed with water providing **S2** (529 mg, 97%) as a white solid.

^1H NMR (400 MHz, DMSO) δ 12.63 (bs, 2H), 8.41 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.09 (d, *J* = 3.6 Hz, 1H), 4.43 (s, 2H), 4.29 (dd, *J* = 7.1, 8.5 Hz,

1H), 2.84 – 2.74 (m, 2H), 2.65 – 2.55 (m, 2H), 2.28 – 2.13 (m, 1H), 2.04 – 1.89 (m, 2H), 0.98 (d, *J* = 5.3 Hz, 3H), 0.96 (d, *J* = 5.4 Hz, 3H).

MS (ESI) calcd. for $C_{24}H_{25}N_3O_5S$ $[M+H]^+$ 468.2; found 468.1.

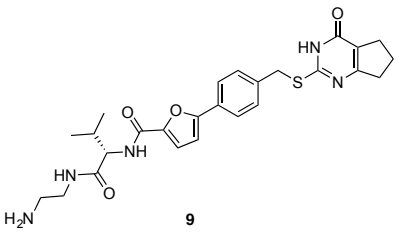


S3

(5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)-phenyl)furan-2-carbonyl)-*L*-valine (**S3**). Compound **S3** was synthesized according to the procedure described for **S2.** 5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]-pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxylic acid[4] and L-valine methyl ester hydrochloride were used as starting materials for the peptide coupling reaction. Hydrolysis of the methyl ester gave compound **S3** in 85% yield over two steps.

^{1}H NMR (400 MHz, DMSO) δ 12.63 (s, 2H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.72 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.43 (s, 2H), 4.29 (dd, *J* = 7.2, 8.5 Hz, 1H), 2.85 – 2.73 (m, 2H), 2.64 – 2.53 (m, 2H), 2.27 – 2.14 (m, 1H), 2.03 – 1.88 (m, 2H), 0.97 (d, *J* = 5.0 Hz, 3H), 0.96 (d, *J* = 5.0 Hz, 3H).

MS (ESI) calcd. for $C_{24}H_{24}FN_3O_5S$ $[M+H]^+$ 486.1; found 486.3.



9

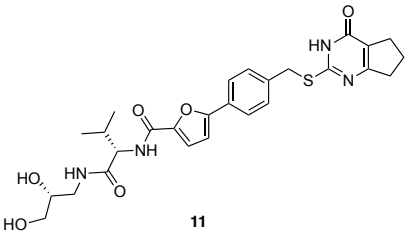
(*S*)-*N*-(1-((2-aminoethyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**9**). Compound **S2** (53 mg, 0.113 mmol, 1.0 eq) was dissolved in DMF (1 mL) before PyBOP (59 mg, 0.113 mmol, 1.0 eq), NEt_3 (31 μL, 0.226 mmol, 2.0 eq) and ethylenediamine (151 μL, 2.26 mmol, 20.0 eq) were added sequentially at room temperature. The reaction mixture was stirred for 16 h, the solvent was evaporated and the crude product was purified by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min). Lyophilization gave 33 mg (53%) of **9** as a white powder.

^{1}H NMR (400 MHz, DMSO) δ 12.58 (bs, 1H), 8.42 – 8.25 (m, 2H), 7.93 – 7.83 (m, 2H), 7.80 (s, 2H), 7.58 – 7.48 (m, 2H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.10 (d, *J* = 3.6 Hz, 1H), 4.43 (s, 2H), 4.23 (t, *J* = 8.3 Hz, 1H), 3.43 – 3.24 (m, 2H), 2.95 – 2.82 (m, 2H), 2.82 – 2.72 (m, 2H), 2.64 – 2.57 (m, 2H), 2.26 – 2.09 (m, 1H), 2.03 – 1.89 (m, 2H), 0.93 (d, *J* = 4.1 Hz, 3H), 0.91 (d, *J* = 4.1 Hz, 3H).

HRMS (ESI) calcd. for $C_{26}H_{31}N_5O_4S$ $[M+H]^+$ 510.2097; found 510.2094.

General procedure for amide coupling. To a solution of the corresponding acid (1.0 eq), EDCI•HCl (1.5 eq), HOBt (1.5 eq) and DIPEA (1.5 eq) in DMF (0.15 M) was added the amine (2.0 eq). The reaction mixture was stirred for 4-16 h at room temperature before it was diluted with EtOAc and washed with 0.1 M HCl (2x). The aqueous phase was extracted with EtOAc (3x) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x) and brine (1x). The organic phase was dried over Na_2SO_4 and the solvent

was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) and/or preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing the desired coupling product.

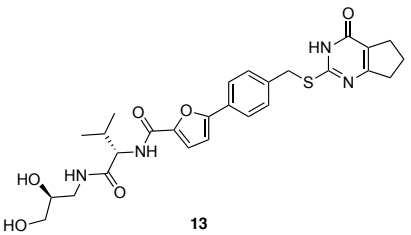


11

N-((*S*)-1-(((*R*)-2,3-dihydroxypropyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**11**). Compound **11** was synthesized according to the general procedure for amide coupling and isolated in 84% yield (58 mg).

^{1}H NMR (400 MHz, MeOD) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 3.7 Hz, 1H), 6.91 (d, *J* = 3.7 Hz, 1H), 4.48 (s, 2H), 4.38 (dd, *J* = 0.9, 8.0 Hz, 1H), 3.98 (s, 1H), 3.80 – 3.67 (m, 1H), 3.56 – 3.46 (m, 2H), 3.45 – 3.37 (m, 1H), 3.29 – 3.21 (m, 1H), 2.97 – 2.81 (m, 2H), 2.79 – 2.64 (m, 2H), 2.29 – 2.15 (m, 1H), 2.16 – 1.99 (m, 2H), 1.03 (d, *J* = 2.2 Hz, 3H), 1.02 (d, *J* = 2.2 Hz, 3H).

HRMS (ESI) calcd. for $C_{27}H_{32}N_4O_6S$ $[M+H]^+$ 541.2121; found 541.2123.

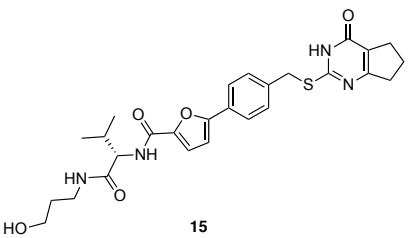


13

N-((*S*)-1-(((*S*)-2,3-dihydroxypropyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**13**). Compound **13** was synthesized according to the general procedure for amide coupling and isolated in 62% yield (45 mg).

^{1}H NMR (400 MHz, MeOD) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 3.6 Hz, 1H), 6.92 (d, *J* = 3.6 Hz, 1H), 4.49 (s, 2H), 4.38 (dd, *J* = 0.9, 8.0 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.57 – 3.46 (m, 2H), 3.45 – 3.37 (m, 1H), 3.29 – 3.21 (m, 1H), 2.93 – 2.84 (m, 3H), 2.77 – 2.67 (m, 2H), 1.42 – 1.34 (m, 1H), 1.04 (d, *J* = 2.3 Hz, 3H), 1.02 (d, *J* = 2.3 Hz, 3H).

HRMS (ESI) calcd. for $C_{27}H_{32}N_4O_6S$ $[M+H]^+$ 541.2121; found 541.2118.



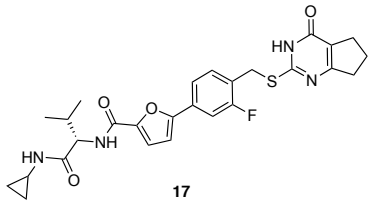
15

(*S*)-*N*-(1-((3-hydroxypropyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**15**). Compound **15** was

synthesized according to the general procedure for amide coupling and isolated in 67% yield (46 mg).

^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 1H), 4.36 (s, 2H), 4.28 – 4.18 (m, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 3.29 – 3.22 (m, 2H), 2.82 – 2.65 (m, 2H), 2.67 – 2.52 (m, 2H), 2.18 – 2.02 (m, 1H), 2.03 – 1.89 (m, 2H), 1.73 – 1.57 (m, 2H), 0.92 (d, *J* = 5.6 Hz, 4H), 0.91 (d, *J* = 5.6 Hz, 4H).

HRMS (ESI) calcd. for $C_{27}H_{32}N_4O_5S$ $[M+H]^+$ 525.2176; found 525.2176.

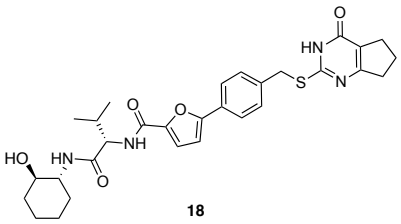


17

(*S*)-*N*-(1-(cyclopropylamino)-3-methyl-1-oxobutan-2-yl)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**17**). Compound **17** was synthesized according to the general procedure for amide coupling and isolated in 69% yield (45 mg).

^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.65 (m, 1H), 7.66 – 7.57 (m, 2H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.00 (d, *J* = 3.7 Hz, 1H), 4.51 (s, 2H), 4.29 (d, *J* = 8.3 Hz, 1H), 3.01 – 2.79 (m, 2H), 2.82 – 2.62 (m, 3H), 2.24 – 2.13 (m, 1H), 2.13 – 2.03 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.73 (m, 2H), 0.58 – 0.52 (m, 2H).

HRMS (ESI) calcd. for $C_{27}H_{29}FN_4O_4S$ $[M+H]^+$ 525.1972; found 525.1977.

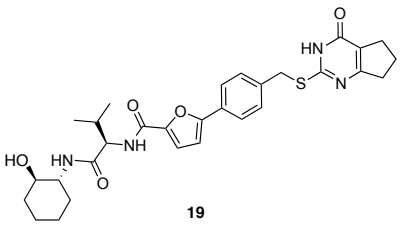


18

N-((*S*)-1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**18**). Compound **18** was synthesized according to the general procedure for amide coupling and isolated in 35% yield (32 mg).

^{1}H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 4.46 (d, *J* = 5.0 Hz, 1H), 4.43 (s, 2H), 4.32 (t, *J* = 8.4 Hz, 1H), 3.52 – 3.38 (m, 1H), 3.31 – 3.17 (m, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.20 – 2.04 (m, 1H), 2.04 – 1.92 (m, 2H), 1.92 – 1.74 (m, 2H), 1.68 – 1.53 (m, 2H), 1.28 – 1.02 (m, 4H), 0.92 (d, *J* = 3.8 Hz, 3H), 0.90 (d, *J* = 3.8 Hz, 3H).

HRMS (ESI) calcd. for $C_{30}H_{36}N_4O_5S$ $[M+H]^+$ 565.2485; found 565.2486.

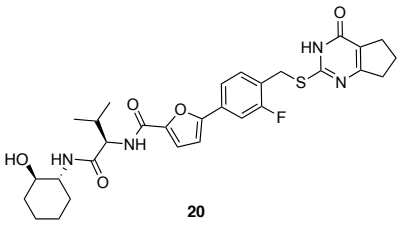


19

N-((*R*)-1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)-5-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**19**). Compound **19** was synthesized according to the general procedure for amide coupling and isolated in 37% yield (34 mg).

^{1}H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 4.43 (s, 2H), 4.28 (t, *J* = 8.5 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.30 – 3.22 (m, 1H), 2.78 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.20 – 2.03 (m, 1H), 2.04 – 1.90 (m, 2H), 1.67 – 1.55 (m, 2H), 1.27 – 1.11 (m, 4H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{30}H_{36}N_4O_5S$ $[M+H]^+$ 565.2485; found 565.2486.

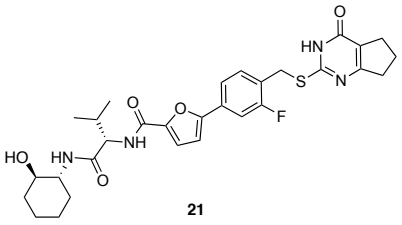


20

5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-((*R*)-1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)furan-2-carboxamide (**20**). Compound **20** was synthesized according to the general procedure for amide coupling and isolated in 69% yield (52 mg).

^{1}H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 8.30 (d, *J* = 8.9 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.86 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.71 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 4.44 (s, 2H), 4.27 (t, *J* = 8.7 Hz, 1H), 3.51 – 3.39 (m, 1H), 3.32 – 3.17 (m, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.64 – 2.55 (m, 2H), 2.21 – 2.04 (m, 1H), 2.07 – 1.91 (m, 2H), 1.91 – 1.73 (m, 2H), 1.60 (s, 2H), 1.18 (s, 4H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{30}H_{36}N_4O_5S$ $[M+H]^+$ 565.2485; found 565.2479.



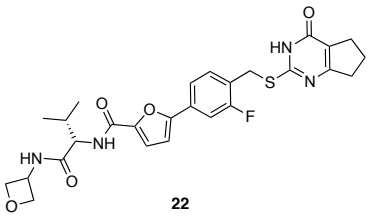
21

5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-((*S*)-1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)furan-2-carboxamide (**21**). Compound **21** was synthesized according to the general procedure for amide coupling and isolated in 57% yield (44 mg).

^{1}H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 8.29 (d, *J* = 8.9 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.85 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.70 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.45 (d, *J* = 5.1 Hz, 1H), 4.44 (s, 2H), 4.31 (t, *J* = 8.6 Hz, 1H), 3.52 – 3.38 (m, 1H), 3.32 – 3.23 (m, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.19 – 2.02 (m, 1H), 2.04 – 1.92 (m, 2H), 1.92 – 1.74 (m, 2H), 1.69 – 1.51 (m, 2H), 1.28 – 1.02 (m, 4H), 0.92 (d, *J* = 3.1 Hz, 3H), 0.90 (d, *J* = 3.1 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 170.42, 168.38, 160.81 (d, *J* = 246.0 Hz), 160.64, 158.96, 157.28, 153.10 (d, *J* = 2.1 Hz), 147.19, 132.08 (d, *J* = 3.4 Hz), 130.78 (d, *J* = 8.9 Hz), 124.37 (d, *J* = 16.3 Hz), 120.29, 119.66, 116.22, 111.17 (d, *J* = 24.0 Hz), 108.98, 70.90, 58.20, 54.35, 34.23, 34.03, 30.82, 30.57, 27.18, 26.72, 24.01, 23.72, 20.59, 19.22, 18.98.

HRMS (ESI) calcd. for $C_{30}H_{36}N_4O_5S$ $[M+H]^+$ 565.2485; found 565.2480.



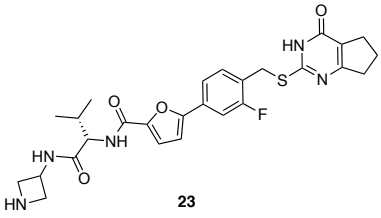
22

(*R*)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(oxetan-3-ylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**22**). Compound **22** was synthesized according to the general procedure for amide coupling and isolated in 84% yield (47 mg).

^{1}H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.95 (d, *J* = 6.4 Hz, 1H), 8.44 (d, *J* = 8.8 Hz, 1H), 7.87 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.71 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.76 – 4.67 (m, 2H), 4.48 – 4.38 (m, 4H), 4.25 (t, *J* = 8.7 Hz, 1H), 2.83 – 2.71 (m, 2H), 2.65 – 2.54 (m, 2H), 2.20 – 2.05 (m, 1H), 2.04 – 1.87 (m, 2H), 0.94 (d, *J* = 4.8 Hz, 3H), 0.92 (d, *J* = 4.8 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 170.62, 168.65, 161.31, 160.70 (d, *J* = 245.80 Hz), 159.86, 157.41, 153.16 (d, *J* = 2.6 Hz), 147.05, 132.03 (d, *J* = 4.0 Hz), 130.72 (d, *J* = 8.9 Hz), 124.48 (d, *J* = 15.0 Hz), 120.31, 119.27, 116.31, 111.18 (d, *J* = 24.0 Hz), 108.89, 76.99, 76.88, 58.32, 43.99, 34.17, 29.93, 27.15, 26.73, 20.60, 19.31, 19.11.

HRMS (ESI) calcd. for $C_{27}H_{29}FN_4O_5S$ $[M+H]^+$ 541.1921; found 541.1927.



23

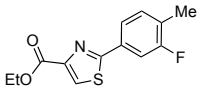
(*R*)-*N*-(1-(azetidin-3-ylamino)-3-methyl-1-oxobutan-2-yl)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**23**). The amide coupling reaction of **S3** with 3-Amino-N-Boc-azetidine following the general procedure described above gave Boc-protected **23** in 92% yield. A solution of the Boc-protected azetidine (60 mg, 0.094 mmol, 1.0 eq) in DCM (2 mL) was treated with TFA (300 μL) and stirred at room temperature for 4 h. The reaction mixture was concentrated to dryness and purified by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH =

1:1, 0.1% TFA, 10 min) providing **23** in 90% yield.

^{1}H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.94 (d, *J* = 6.6 Hz, 1H), 8.70 (s, 2H), 8.53 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.71 – 4.54 (m, 1H), 4.44 (s, 2H), 4.26 – 4.06 (m, 3H), 4.02 – 3.89 (m, 2H), 2.85 – 2.71 (m, 2H), 2.59 (s, 2H), 2.23 – 2.09 (m, 1H), 2.09 – 1.80 (m, 2H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 171.20, 168.57, 160.88, 160.85 (d, *J* = 246.1 Hz), 159.35, 157.59, 153.28 (d, *J* = 2.05 Hz), 147.00, 132.09 (d, *J* = 3.5 Hz), 130.79 (d, *J* = 8.9 Hz), 124.46 (d, *J* = 14.4 Hz), 120.39, 119.61, 116.48, 111.24 (d, *J* = 24.0 Hz), 108.97, 58.57, 52.07, 41.05, 34.24, 29.80, 27.22, 26.75, 20.62, 19.38, 19.11.

HRMS (ESI) calcd. for $C_{27}H_{30}FN_5O_4S$ $[M+H]^+$ 540.2081; found 540.2085.

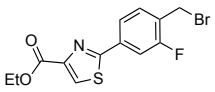


36

Ethyl 2-(3-fluoro-4-methylphenyl)thiazole-4-carboxylate (**36**). To a solution of ethyl-2-bromo-1,3-thiazole-4-carboxylate (250 mg, 1.06 mmol, 1.0 eq) in toluene (4.4 mL) were added 3-fluoro-4-methylbenzeneboronic acid (196 mg, 1.27 mmol, 1.2 eq) in 0.4 mL methanol, Na_2CO_3 (2 M in H_2O, 615 µL) and $Pd(PPh_3)_4$ (43 mg, 0.037 mmol, 0.035 eq). The reaction mixture was heated to 80 °C and stirred for 16 h. The reaction was diluted with water and the product was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-70% EtOAc linear gradient in hexanes) providing **36** in 51% (144 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.73 – 7.61 (m, 2H), 7.29 – 7.22 (m, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.32 (d, *J* = 1.9 Hz, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{13}H_{12}FNO_2S$ $[M+H]^+$ 266.3; found 266.5.

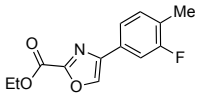


37

Ethyl 2-(4-(bromomethyl)-3-fluorophenyl)thiazole-4-carboxylate (**37**). Benzoyl peroxide (23 mg, 0.0942 mmol, 0.1 eq) and N-bromosuccinimide (201 mg, 1.13 mmol, 1.2 eq) were added to a solution of **36** (250 mg, 0.942 mmol, 1.0 eq) in 4.7 mL CCl_4 and the reaction mixture was stirred for 10 h at 100 °C. The yellow suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (6-36% EtOAc linear gradient in hexanes) providing **37** (199 mg, 61%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.84 – 7.68 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 4.56 – 4.50 (m, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 4H).

MS (ESI) calcd. for $C_{13}H_{11}BrFNO_2S$ $[M+H]^+$ 344.0; found 343.8.

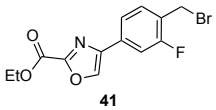


40

Ethyl 4-(3-fluoro-4-methylphenyl)oxazole-2-carboxylate (**40**). To a solution of ethyl-2-bromo-1,3-oxazole-4-carboxylate (150 mg, 0.682 mmol, 1.0 eq) in toluene (2.8 mL) were added 3-fluoro-4-methylbenzeneboronic acid (126 mg, 0.818 mmol, 1.2 eq) in 0.25 mL methanol, Na_2CO_3 (2 M in H_2O, 420 μL) and $Pd(PPh_3)_4$ (28 mg, 0.024 mmol, 0.035 eq). The reaction mixture was heated to 80 °C and stirred for 16 h. The reaction was diluted with water and the product was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-50% EtOAc linear gradient in hexanes) providing **40** in 59% (100 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.86 – 7.67 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{13}H_{12}FNO_3$ $[M+H]^+$ 250.1; found 250.1.

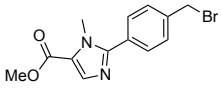


41

Ethyl 4-(4-(bromomethyl)-3-fluorophenyl)oxazole-2-carboxylate (**41**). Benzoyl peroxide (8 mg, 0.0318 mmol, 0.1 eq) and N-bromosuccinimide (68 mg, 0.382 mmol, 1.2 eq) were added to a solution of **40** (100 mg, 0.318 mmol, 1.0 eq) in 3 mL CCl_4 and the reaction mixture was stirred for 10 h at 100 °C. The yellow suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-70% EtOAc linear gradient in hexanes) providing **41** (17 mg, 16%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.77 – 7.70 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 4.54 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{13}H_{11}BrFNO_3$ $[M+H]^+$ 328.0; found 328.1.



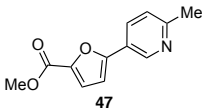
44

Methyl 2-(4-(hydroxymethyl)phenyl)-1-methyl-1*H*-imidazole-5-carboxylate (**44**). To a solution of methyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate[5] (515 mg, 2.35 mmol, 1.0 eq) in dioxane (72 mL) was added $Pd(PPh_3)_4$ (133 mg, 0.115 mmol, 0.049 eq). The mixture was stirred for 15 min at room temperature before 4-hydroxymethylbenzeneboronic acid (357 mg, 2.35 mmol, 1.0 eq) in 22 mL H_2O and K_2CO_3 (390 mg, 2.82 mmol, 1.2 eq) were added. The reaction mixture was heated to 60 °C and stirred for 16 h. The solvent was evaporated and the residue was diluted with EtOAc and H_2O. The phases were separated and the product was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing the corresponding benzylic alcohol in 81% (470 mg) yield.
To a solution of the benzylic alcohol (470 mg, 1.91 mmol, 1.0 eq) in DCM (6.4 mL) were added tetrabromomethane (822 mg, 2.48 mmol, 1.3 eq) and triphenylphosphine (650 mg, 2.48 mmol, 1.3 eq) at 0

°C. The reaction mixture was stirred at 0 °C for 30 min and further 60 min at room temperature before it was quenched by the addition of water. The product was extracted with DCM, the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) giving compound **44** in 50% yield (295 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.63 – 7.59 (m, 2H), 7.55 – 7.49 (m, 2H), 4.54 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H).

MS (ESI) calcd. for $C_{13}H_{13}BrN_2O_2$ $[M+H]^+$ 309.0; found 308.9.

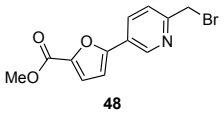


47

Methyl 5-(6-methylpyridin-3-yl)furan-2-carboxylate (**47**).
Synthesis of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine: 5-bromo-2-methylpyridine (250 mg, 1.46 mmol, 1.0 eq), bis(pinacolato)diboron (408 mg, 1.61 mmol, 1.1 eq), potassium acetate (430 mg, 4.38 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (53 mg, 0.073 mmol, 0.05 eq) were mixed in DMF (7.3 mL) in a round bottom flask and heated to 80 °C for 16 h. The solvent was evaporated and the crude product was used without any further purification.
To a solution of methyl-2-bromo-5-furanocarboxylate (248 mg, 1.21 mmol, 0.83 eq) in DME (18 mL) were added the crude boronic ester (1.46 mmol, 1.0 eq) in ethanol (5.25 mL) followed by Na_2CO_3 (2M in H_2O, 1.26 mL) and $Pd(PPh_3)_4$ (168 mg, 0.146 mmol, 0.1 eq). The reaction mixture was stirred for 16 hours at 85 °C. After cooling to room temperature the brown suspension was filtered and the filtrated was concentrated. The residue was dissolved in EtOAc (30 mL), washed with water (1x 30 mL) and brine (1x 30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing compound **47** in 64% yield (203 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (dd, J = 0.8, 2.4 Hz, 1H), 7.97 (dd, J = 2.4, 8.1 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 3.6 Hz, 1H), 3.91 (s, 3H), 2.59 (s, 3H).

MS (ESI) calcd. for $C_{12}H_{11}NO_3$ $[M+H]^+$ 218.1; found 218.2.

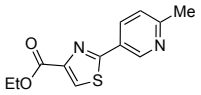


48

Methyl 5-(6-(bromomethyl)pyridin-3-yl)furan-2-carboxylate (**48**). Benzoyl peroxide (11 mg, 0.0465 mmol, 0.1 eq) and N-bromosuccinimide (99 mg, 0.558 mmol, 1.2 eq) were added to a solution of **47** (126 mg, 0.465 mmol, 1.0 eq) in 2.3 mL CCl_4 and the reaction mixture was stirred for 10 h at 100 °C. The yellow suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing **48** (32 mg, 23%) as a light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, J = 1.0, 2.2 Hz, 1H), 8.07 (dd, J = 2.2, 8.2 Hz, 1H), 7.49 (dd, J = 1.0, 8.2 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 6.85 (d, J = 3.6 Hz, 1H), 4.57 (s, 2H), 3.92 (s, 3H).

MS (ESI) calcd. for $C_{12}H_{10}BrNO_3$ $[M+H]^+$ 296.0; found 296.0.

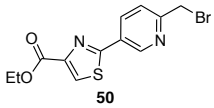


49

Methyl 2-(6-methylpyridin-3-yl)thiazole-4-carboxylate (**49**).
Synthesis of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine: 5-bromo-2-methylpyridine (500 mg, 2.92 mmol, 1.0 eq), bis(pinacolato)diboron (815 mg, 3.21 mmol, 1.1 eq), potassium acetate (860 mg, 8.76 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (107 mg, 0.146 mmol, 0.05 eq) were mixed in DMF (15 mL) in a round bottom flask and heated to 80 °C for 16 h. The solvent was evaporated and the crude product was used without any further purification.
To a solution of ethyl-2-bromo-1,3-thiazole-4-carboxylate (571 mg, 2.42 mmol, 0.83 eq) in DME (36 mL) were added the crude boronic ester (2.92 mmol, 1.0 eq) in ethanol (10 mL) followed by Na_2CO_3 (2 M in H_2O, 2.52 mL) and $Pd(PPh_3)_4$ (337 mg, 0.292 mmol, 0.1 eq). The reaction mixture was stirred for 16 h at 75 °C. After cooling to room temperature the brown suspension was filtered and concentrated. The residue was dissolved in EtOAc (50 mL), washed with water (1x 50 mL) and brine (1x 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing compound **49** in 34% yield (246 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (dd, J = 0.8, 2.4 Hz, 1H), 8.24 (dd, J = 2.4, 8.1 Hz, 1H), 8.18 (s, 1H), 7.27 (d, J = 8.1 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{12}H_{12}N_2O_2S$ $[M+H]^+$ 249.1; found 249.3.

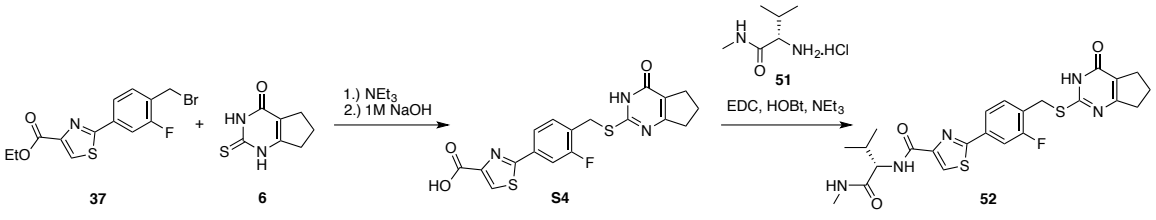


50

Methyl 2-(6-(bromomethyl)pyridin-3-yl)thiazole-4-carboxylate (**50**). Benzoyl peroxide (23 mg, 0.0958 mmol, 0.1 eq) and N-bromosuccinimide (171 mg, 0.958 mmol, 1.0 eq) were added to a solution of **49** (236 mg, 0.958 mmol, 1.0 eq) in 4.8 mL CCl_4 and the reaction mixture was stirred for 10 h at 100 °C. The yellow suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing **50** (61 mg, 19%) as a light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 4.58 (s, 2H), 4.45 (q, J = 7.2 Hz, 1H), 1.42 (t, J = 7.2 Hz, 3H).

MS (ESI) calcd. for $C_{12}H_{11}BrN_2O_2S$ $[M+H]^+$ 327.0; found 327.3.



37 **6** **S4** **51** **52**

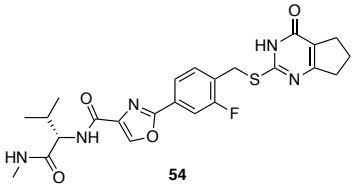
(*S*)-2-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)thiazole-4-carboxamide (**51**). A suspension of **6**[4] (81 mg, 0.48 mmol, 1.0 eq) and triethylamine (80 μL, 0.58 mmol, 1.2 eq) in 0.7 mL DMF was stirred for 15 min at room temperature before **37** (199 mg, 0.58 mmol, 1.2 eq) was added and the reaction mixture was stirred

for 16 h at room temperature. The solids were filtered, washed with small amounts of water, methanol and diethyl ether, and the product was dried under vacuum to give the corresponding methyl ester (156 mg, 66%) as a white solid, which was subsequently hydrolyzed.
To the methyl ester (130 mg, 0.301 mmol, 1.0 eq) dissolved in 1.5 mL THF/methanol 2:1 was added NaOH (1 M in water, 963 μL, 0.963 mmol, 3.2 eq) and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature the mixture was diluted with 1 mL water and acidified with 1 M HCl (pH~2, ca. 1 mL). The precipitated product was filtered and washed with water providing **S4** (108 mg, 89%) as a white solid.
To a solution of **S4** (80 mg, 0.198 mmol, 1.0 eq), EDCI•HCl (57 mg, 0.297 mmol, 1.5 eq), HOBt (40 mg, 0.297 mmol, 1.5 eq) and DIPEA (50 μL, 0.297 mmol, 1.5 eq) in 1 mL DMF was added (*S*)-2-amino-*N*,3-dimethylbutanamide hydrochloride (**51**)[4] (97 mg, 0.396 mmol, 2.0 eq). The reaction mixture was stirred for 4 h at room temperature before it was diluted with EtOAc (ca. 5 mL) and washed with 0.1 M HCl (2x 10 mL). The aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x 10 mL) and brine (1x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) followed by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing compound **52** (67 mg, 66%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 8.39 (s, 1H), 8.20 – 8.07 (m, 2H), 7.93 (dd, *J* = 1.7, 10.7 Hz, 1H), 7.82 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 4.47 (s, 2H), 4.31 (dd, *J* = 7.3, 9.2 Hz, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.63 (d, *J* = 4.6 Hz, 3H), 2.61 – 2.52 (m, 2H), 2.15 – 2.04 (m, 1H), 2.03 – 1.90 (m, 2H), 0.91 (d, *J* = 2.3 Hz, 3H), 0.90 (d, *J* = 2.3 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 170.89, 168.30, 165.57, 160.65 (d, *J* = 247.4 Hz), 160.58, 159.77, 158.73, 150.10, 133.52 (d, *J* = 8.3 Hz), 132.40 (d, *J* = 3.4 Hz), 127.09 (d, *J* = 13.8 Hz), 125.26, 122.52, 119.77, 113.01 (d, *J* = 23.9 Hz), 57.85, 34.20, 30.91, 27.05, 26.69, 25.42, 20.56, 19.27, 18.44.

MS (ESI) calcd. for $C_{24}H_{26}FN_5O_3S_2$ $[M+H]^+$ 516.1539; found 516.1544.

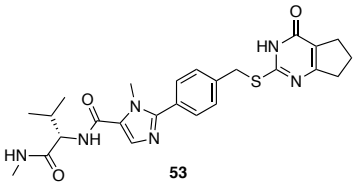


54

(*S*)-4-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)oxazole-2-carboxamide (**54**). Compound **54** was synthesized following the same procedure as described above for **52** and was isolated in 30% (42 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.81 (s, 1H), 8.22 – 8.10 (m, 1H), 7.89 – 7.78 (m, 3H), 7.73 (t, *J* = 7.8 Hz, 1H), 4.48 (s, 2H), 4.31 (dd, *J* = 7.2, 9.1 Hz, 1H), 2.86 – 2.74 (m, 2H), 2.63 (d, *J* = 4.6 Hz, 3H), 2.61 – 2.54 (m, 2H), 2.13 – 2.01 (m, 1H), 2.02 – 1.87 (m, 2H), 0.90 (d, *J* = 3.1 Hz, 3H), 0.88 (d, *J* = 3.1 Hz, 3H).

HRMS (ESI) calcd. for $C_{24}H_{26}FN_5O_4S$ $[M+H]^+$ 500.1765; found 500.1772.

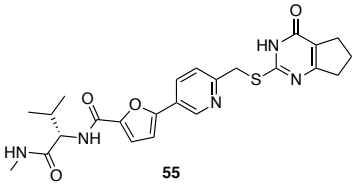


53

(*S*)-1-methyl-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)-2-(4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-1*H*-imidazole-5-carboxamide (**53**). Compound **53** was synthesized following the same procedure as described above for **52** and was isolated in 26% (35 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.84 (s, 1H), 7.66 – 7.59 (m, 2H), 7.57 – 7.50 (m, 2H), 4.46 (s, 2H), 4.21 (t, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 2.78 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.57 (m, 5H), 2.18 – 2.03 (m, 1H), 2.04 – 1.88 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{25}H_{30}N_6O_3S$ $[M+H]^+$ 495.2176; found 495.2177.

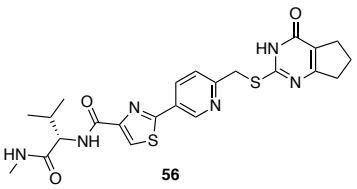


55

(*S*)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)-5-(6-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)pyridin-3-yl)furan-2-carboxamide (**55**). Compound **55** was synthesized following the same procedure as described above for **52** and was isolated in 24% (33 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 9.10 (dd, *J* = 0.8, 2.3 Hz, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.28 (dd, *J* = 2.3, 8.1 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.61 (dd, *J* = 0.8, 8.1 Hz, 1H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 4.55 (s, 2H), 4.21 (t, *J* = 8.7 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.67 – 2.54 (m, 5H), 2.22 – 2.04 (m, 1H), 2.04 – 1.83 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{24}H_{27}N_5O_4S$ $[M+H]^+$ 482.1862; found 482.1864.



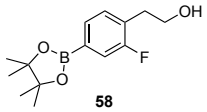
56

(*S*)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)-2-(6-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)pyridin-3-yl)thiazole-4-carboxamide (**56**). Compound **56** was synthesized following the same procedurs as described above for **52** and was isolated in 21% (34 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 9.16 (dd, *J* = 0.8, 2.4 Hz, 1H), 8.42 (s, 1H), 8.38 (dd, *J* = 2.4, 8.2 Hz, 1H), 8.21 – 8.04 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 4.59 (s, 2H), 4.32 (dd, *J* = 7.1, 9.2 Hz,

1H), 2.76 (t, *J* = 7.7 Hz, 2H), 2.69 – 2.56 (m, 5H), 2.19 – 2.03 (m, 1H), 2.04 – 1.86 (m, 2H), 0.91 (d, *J* = 2.7 Hz, 3H), 0.90 (d, *J* = 2.7 Hz, 3H).

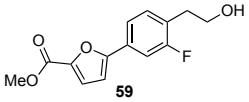
HRMS (ESI) calcd. for $C_{23}H_{26}N_6O_3S_2$ $[M+H]^+$ 499.1586; found 499.1586.



58

2-(2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol (**58**). 2-(4-bromo-2-fluorophenyl)ethan-1-ol (1.5 g, 6.85 mmol, 1.0 eq), bis(pinacolato)diboron (2.09 g, 8.22 mmol, 1.2 eq) and potassium acetate (2.02 g, 20.55 mmol, 3.0 eq) were mixed in 18 mL dioxane. A stream of argon was bubbled through the reaction mixture for 10 min before $Pd(dppf)_2Cl_2.CH_2Cl_2$ (280 mg, 0.343 mmol, 0.05 eq) was added. After stirring at 100 °C for 16 h the reaction mixture was filtered and the solvent was evaporated. The crude product was purified by flash chromatography (5-70% EtOAc linear gradient in hexanes) to provide **58** (1.67 g) in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.39 (dd, *J* = 1.2, 10.3 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 2.87 (t, *J* = 6.6 Hz, 2H), 1.27 (s, 12H).

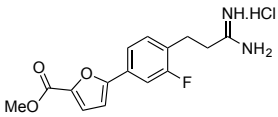


59

Methyl 5-(3-fluoro-4-(2-hydroxyethyl)phenyl)furan-2-carboxylate (**59**). To a solution of methyl-2-bromo-5-furanocarboxylate (154 mg, 0.752 mmol, 1.0 eq) in dioxane (25 mL) was added $Pd(PPh_3)_4$ (43 mg, 0.0376 mmol, 0.05 eq) and the mixture was stirred for 15 min at room temperature before **58** (200 mg, 0.752 mmol, 1.0 eq) and a solution of K_2CO_3 (208 mg, 1.504 mmol, 2.0 eq) in 11.3 mL H_2O were added. The reaction mixture was stirred for 4 h at 55 °C. After cooling to room temperature the brown suspension was concentrated to dryness, the residue was redissolved in EtOAc (50 mL), washed with water (1x 50 mL) and brine (1x 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-70% EtOAc linear gradient in hexanes) providing compound **59** in 95% yield (189 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.45 (dd, *J* = 1.8, 10.7 Hz, 1H), 7.29 (dd, *J* = 7.9, 10.7 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.72 (d, *J* = 3.6 Hz, 1H), 3.91 (s, 3H), 3.89 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 1.23 (s, 3H).

MS (ESI) calcd. for $C_{14}H_{13}FO_4$ $[M+H]^+$ 265.1; found 264.9.



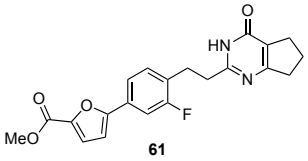
60

Methyl 5-(3-fluoro-4-(2-((methylsulfonyl)oxy)ethyl)phenyl)furan-2-carboxylate (**60**). A solution of **59** (199 mg, 0.753 mmol, 1.0 eq) and NEt_3 (109 μL, 0.783 mmol, 1.04 eq) in THF (1.3 mL) was treated with methanesulfonyl chloride (61 μL, 0.783 mmol, 1.04 eq) at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature before it was diluted with EtOAc and washed with 1 M HCl (2x 20 mL), H_2O (1x 10 mL), sat. $NaHCO_3$ (1x 10 mL), and brine (1x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude mesylated

primary alcohol (207 mg, 85%) was used for the next step without further purification.
A mixture of the methanesulfonate ester (207 mg, 0.683 mmol, 1.0 eq) and KCN (166 mg, 2.55 mmol, 4.0 eq) in DMF (2 mL) was stirred at 60 °C for 12 h. The reaction was quenched by the addition of water (15 mL) and the product was extracted with diethyl ether (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure giving the corresponding nitrile (148 mg) in 91% yield.
To a solution of the nitrile (148 mg, 0.58 mmol, 1.0 eq) in methanol/toluene 1:5 (1.5 mL) was added acetyl chloride (207 μL, 2.9 mmol, 5.0 eq) at 0 °C. The reaction mixture was stirred for 2 h at room temperature before it was recooled to 0 °C and a solution of NH_3 in methanol (7M, 830 μL, 5.8 mmol, 10 eq) was added. After stirring for 12 h at room temperature the suspension was filtered and the solids were washed with methanol (5 mL) and toluene (5 mL). The filtrate was concentrated to dryness providing amidine **60** (165 mg) in 98% yield.

^{1}H NMR (400 MHz, MeOD) δ 7.64 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.60 (dd, *J* = 1.7, 11.0 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 3.93 (s, 3H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H).

MS (ESI) calcd. for $C_{15}H_{15}FN_2O_3$ $[M+H]^+$ 291.1; found 290.1.

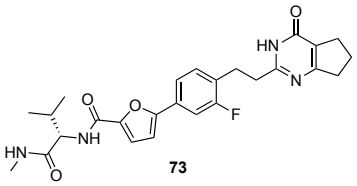


61

Methyl 5-(3-fluoro-4-(2-(4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)ethyl)-phenyl)furan-2-carboxylate (**61**). Amidine **60** (150 mg, 0.459 mmol, 1.0 eq) was added to a solution of sodium (13 mg, 0.551 mmol, 1.2 eq) in ethanol (2.3 mL). The mixture was stirred for 1 h at room temperature before ethyl-2-oxocyclopentylcarboxylate (82 μL, 0.551 mmol, 1.2 eq) was added. After stirring for 16 h at 100 °C the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (1-10% methanol linear gradient in dichloromethane) giving compound **61** (130 mg) in 57% yield.

^{1}H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 7.64 – 7.56 (m, 2H), 7.45 – 7.38 (m, 2H), 7.24 (d, *J* = 3.5 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 7.8 Hz, 2H), 2.91 – 2.78 (m, 2H), 2.77 – 2.67 (m, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{22}H_{21}FN_2O_4$ $[M+H]^+$ 397.2; found 397.5.



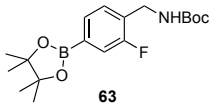
73

(*S*)-5-(3-Fluoro-4-(2-(4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)ethyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**73**). NaOH (1M in water, 1.7 mL, 1.699 mmol, 3.2 eq) was added to compound **61** (250 mg, 0.631 mmol, 1.0 eq) dissolved in THF/methanol 2:1 (3.3 mL) and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature the mixture was diluted with 1 mL water and acidified with 2M HCl (pH~2, ca. 0.9 mL). The precipitated

product was filtered and washed with water providing the corresponding acid (167 mg, 72%) as a white solid.
To a solution of the acid (50 mg, 0.136 mmol, 1.0 eq), EDCI•HCl (39 mg, 0.204 mmol, 1.5 eq), HOBt (28 mg, 0.204 mmol, 1.5 eq) and DIPEA (34 μL, 0.204 mmol, 1.5 eq) in 1 mL DMF was added (*S*)-2-amino-*N*,3-dimethylbutanamide hydrochloride[4] (66 mg, 0.272 mmol, 2.0 eq). The reaction mixture was stirred for 4 h at room temperature before it was diluted with EtOAc (ca. 5 mL) and washed with 0.1M HCl (2x10 mL). The aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x 10 mL) and brine (1x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) followed by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing compound **72** (20 mg, 30%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 4.7 Hz, 1H), 7.82 (dd, *J* = 1.7, 11.1 Hz, 1H), 7.69 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 4.21 (t, *J* = 8.7 Hz, 1H), 3.04 (t, *J* = 7.7 Hz, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.69 – 2.57 (m, 5H), 2.21 – 2.06 (m, 1H), 2.04 – 1.83 (m, 2H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

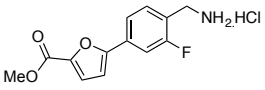
HRMS (ESI) calcd. for: $C_{26}H_{29}FN_4O_4$ $[M+H]^+$ 481.2251; found 481.2256.



63

Tert-butyl (2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (**63**). 2-*Tert*-butyl (4-bromo-2-fluorobenzyl)carbamate (400 mg, 1.32 mmol, 1.0 eq), bis(pinacolato)diboron (401 mg, 1.58 mmol, 1.2 eq) and potassium acetate (389 mg, 3.96 mmol, 3.0 eq) were mixed in 4 mL dioxane. A stream of argon was bubbled through the reaction mixture for 10 min before $Pd(dppf)_2Cl_2.CH_2Cl_2$ (54 mg, 0.066 mmol, 0.05 eq) was added. After stirring at 100 °C for 16 h the reaction mixture was filtered through a plug of Celite and the solvent was evaporated. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) to provide **63** (363 mg) in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.1, 7.4 Hz, 1H), 7.44 (dd, *J* = 1.1, 10.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 4.90 (bs, 1H), 4.37 (d, *J* = 6.1 Hz, 2H), 1.44 (s, 9H), 1.33 (s, 12H).



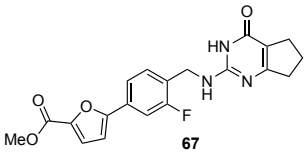
65

Methyl 5-(4-(aminomethyl)-3-fluorophenyl)furan-2-carboxylate hydrochloride (**65**). To a solution of methyl-2-bromo-5-furanocarboxylate (1.05 g, 5.12 mmol, 1.0 eq) in dioxane (171 mL) was added $Pd(PPh_3)_4$ (296 mg, 0.256 mmol, 0.05 eq) and the mixture was stirred for 15 min at room temperature before **63** (1.8 g, 5.12 mmol, 1.0 eq) and a solution of K_2CO_3 (1.42g, 10.24 mmol, 2.0 eq) in 73 mL H_2O were added. The reaction mixture was stirred for 9 h at 55 °C. After cooling to room temperature the brown suspension was concentrated to dryness, the residue was redissolved in EtOAc (50 mL), washed with water (1x 50 mL) and brine (1x 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-70% EtOAc linear gradient in hexanes) providing the corresponding Boc-protected coupling product in 74% yield (1.33 g).
The Boc-protected coupling product (1.3 g, 3.72 mmol) was treated with HCl in dioxane (4 M, 15 mL) The mixture was stirred for 3 h before it was concentrated under reduced pressure giving compound **65**

(1.06 g) in 97% yield.

^{1}H NMR (400 MHz, DMSO) δ 8.57 (s, 2H), 7.80 – 7.67 (m, 3H), 7.47 (d, *J* = 3.7 Hz, 1H), 7.35 (d, *J* = 3.7 Hz, 1H), 4.10 (s, 2H), 3.86 (s, 3H).

HRMS (ESI) calcd. for: $C_{13}H_{13}ClFNO_3$ $[M+H]^+$ 250.1; found 250.2.

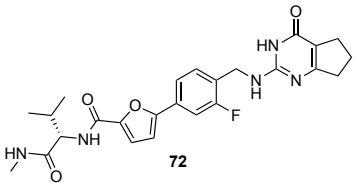


67

Methyl 5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)amino)-methyl)phenyl)furan-2-carboxylate (**67**). 2-chloro-3,5,6,7-tetrahydro-4*H*-cyclopenta[*d*]pyrimidin-4-one[6] (**66**, 149 mg, 0.875 mmol, 1.0 eq) and **65** (250 mg, 0.875 mmol, 1.0 eq) were dissolved in dioxane (4 mL). DIPEA (462 μL, 2.635 mmol, 3.0 eq) was added and the reaction mixture was stirred for 12 h at 90 °C. The reaction mixture was diluted with EtOAc /THF 1:1 (20 mL) and water (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc / THF 1:1 (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was transferred in a frit and washed with diethyl ether/methanol 20:1 (4x5 mL) to provide compound **67** (150 mg) in 45% yield.

^{1}H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 7.71 – 7.60 (m, 2H), 7.52 – 7.39 (m, 2H), 7.26 (d, *J* = 3.7 Hz, 1H), 6.83 (t, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 3.85 (s, 3H), 2.60 – 2.53 (m, 2H), 2.50 – 2.44 (m, 2H), 1.93 – 1.82 (m, 2H).

MS (ESI) calcd. for $C_{20}H_{18}FN_3O_4$ $[M+H]^+$ 384.1; found 384.5.



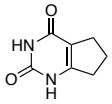
72

(*S*)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)amino)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**72**). Compound **72** was synthesized following the same procedures as described above for **73** and was isolated in 49% (32 mg) yield over two steps.

^{1}H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.12 – 8.03 (m, 1H), 7.86 (dd, *J* = 1.7, 11.3 Hz, 1H), 7.73 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 6.82 (bs, 1H), 4.54 (d, *J* = 5.9 Hz, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.66 – 2.54 (m, 5H), 2.19 – 2.07 (m, 1H), 1.95 – 1.78 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 2H).

^{13}C NMR (176 MHz, DMSO) δ 171.23, 170.40, 160.49 (d, *J* = 245 Hz), 160.30, 157.35, 154.73, 153.24 (d, *J* = 2.2 Hz), 147.00, 130.30 (d, *J* = 8.8 Hz), 129.95 (d, *J* = 4.9 Hz), 126.20 (d, *J* = 15.3 Hz), 120.29, 116.20, 111.56, 111.05 (d, *J* = 24.1 Hz), 108.63, 58.42, 37.67, 34.68, 29.91, 26.51, 25.42, 20.83, 19.36, 19.02.

HRMS (ESI) calcd. for: $C_{25}H_{28}FN_5O_4$ $[M+H]^+$ 482.2204; found 482.2202.

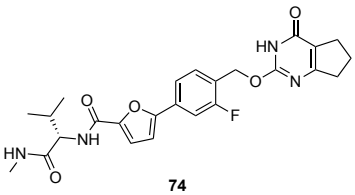


70

1,5,6,7-Tetrahydro-2*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*)-dione (**7**). Ethyl-2-oxo-cyclopentane-carboxylate (5 mL, 33.6 mmol, 1.0 eq) was dissolved in ethanol (10 mL), urea (3 g, 50.5 mmol, 1.5 eq) and conc. HCl (0.5 mL) were added and the reaction mixture was refluxed for 3 h. The solvent was decanted and after the addition of 5% NaOH (12.5 mL) the reaction mixture was refluxed for another 12 h before it was cooled to 0 °C and the product was filtered and dried under vacuum (Yield: 1.58 g, 31%).

^{1}H NMR (400 MHz, DMSO) δ 11.03 (bs, 1H), 10.76 (bs, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.44 (t, *J* = 7.7 Hz, 2H), 1.95 (p, *J* = 7.7 Hz, 2H).

MS (ESI) calcd. for $C_7H_8N_2O_2$ $[M+H]^+$ 153.1; found 153.2.

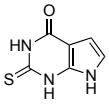


74

(*S*)-5-(3-Fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)oxy)methyl)-phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**74**). Methyl 5-(4-(bromomethyl)-3-fluorophenyl)furan-2-carboxylate[4] (**69**, 167 mg, 0.535 mmol, 1.0 eq), **70** (81 mg, 0.535 mmol, 1.0 eq) and K_2CO_3 (111 mg, 0.803 mmol, 1.5 eq) were dissolved in DMF (3.2 mL) and the reaction mixture was stirred for 14 h at room temperature. After the dilution with EtOAc /THF 1:1 (15 mL) the product was extracted with EtOAc (3x 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10-100% EtOAc linear gradient in hexanes) providing the corresponding methyl ester **71** in 42% yield (87 mg, MS (ESI) $[M+H]^+$ 385.3).
The synthesis of **74** was proceeded following the same procedures as described above for **73** and was isolated in 42% (31 mg) yield over two steps.

^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 8.37 (d, *J* = 8.9 Hz, 1H), 8.11 – 8.03 (m, 1H), 7.89 (dd, *J* = 1.7, 11.5 Hz, 1H), 7.72 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 5.01 (s, 2H), 4.21 (t, *J* = 8.7 Hz, 1H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.64 – 2.53 (m, 5H), 2.21 – 2.05 (m, 1H), 2.03 – 1.86 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

HRMS (ESI) calcd. for: $C_{25}H_{27}FN_4O_5$ $[M+H]^+$ 483.2044; found 483.2044.



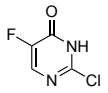
82

2-Thioxo-1,2,3,7-tetrahydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**82**). To a 1 M solution of NaOEt (2.4 mL) were added thiourea (183 mg, 2.40 mmol, 1.0 eq) and 2-cyano-4,4-diethoxybutyrate (500 mg, 2.18 mmol, 0.91 eq) and the reaction mixture was refluxed (108 °C) for 3 h. The solvent was removed *in vacuo* and the residue was portioned between water and diethyl ether. After phase separation the aqueous phase was acidified with acetic acid (140 μL, 2.40 mmol) and the resulting precipitate was filtered and

resuspended in THF (3 mL). After the addition of 6 M HCl (200 μL) the reaction mixture was stirred at room temperature for 14 h before it was diluted with diethyl ether (5 mL) and the precipitated product was filtered and dried under vacuum (Yield: 188 mg, 87%)

^{1}H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 11.87 (s, 1H), 11.26 (s, 1H), 6.72 (dd, *J* = 2.3, 3.3 Hz, 1H), 6.33 (dd, *J* = 2.0, 3.3 Hz, 1H).

MS (ESI) calcd. for $C_6H_5N_3OS$ $[M+H]^+$ 168.0; found 167.9.

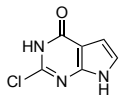


84

2-Chloro-5-fluoropyrimidin-4(3*H*)-one (**84**). To a solution of 5-fluoro-2,4-dichloro-pyrimidine (1 g, 5.99 mmol) in THF (3.3 mL) was added NaOH (1 M in water, 11.7 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was acidified (pH 1) with 1 M HCl. The product was extracted with EtOAc (3x10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure providing crude **84** (638 mg, 72%), which was used for the next step without further purification.

^{1}H NMR (400 MHz, DMSO) δ 8.16 (d, *J* = 3.3 Hz, 1H).

MS (ESI) calcd. for $C_4H_2ClFN_2O$ $[M+H]^+$ 149.0; found 149.3.

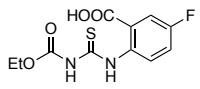


86

2-Chloro-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**86**). A solution of 2,4-dichloro-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine (1 g, 5.32 mmol) in THF (2.9 mL) was treated with NaOH (1 M, 10.4 mL) at 0 °C. After the addition the reaction mixture was heated to 80 °C and the reaction mixture was stirred for 36 h before it was acidified (pH 4) with concentrated acetic acid. The precipitates were filtered and washed with water providing **86** (509 mg, 56%) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 12.77 (s, 1H), 12.02 (s, 1H), 7.07 (dd, *J* = 2.4, 3.4 Hz, 1H), 6.46 (dd, *J* = 2.4, 3.4 Hz, 1H).

MS (ESI) calcd. for $C_6H_4ClN_3O$ $[M+H]^+$ 170.00; found 169.6.

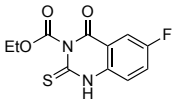


92

2-(3-(Ethoxycarbonyl)thioureido)-5-fluorobenzoic acid (**92**). A solution of 2-amino-5-fluorobenzoic acid (1 g, 6.4 mmol, 1.0 eq) and ethoxycarbonyl-isothiocyanate (844 mg, 6.4 mmol, 1.0 eq) in acetonitrile (10.5 mL) was stirred for 2 h at room temperature. The precipitate was filtered and washed with acetonitrile providing **92** (1.10 g, 60%) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 13.67 (s, 1H), 12.11 (s, 1H), 11.36 (s, 1H), 8.04 (dd, *J* = 5.2, 9.0 Hz, 1H), 7.64 (dd, *J* = 3.1, 9.0 Hz, 1H), 7.48 (ddd, *J* = 3.1, 7.9, 9.0 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{11}H_{11}FN_2O_4S$ $[M+H]^+$ 287.0; found 287.0.

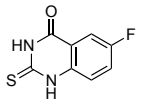


93

Ethyl 6-fluoro-4-oxo-2-thioxo-1,4-dihydroquinazoline-3(2*H*)-carboxylate (**93**). **92** (1.10 g, 3.84 mmol) was treated with acetic anhydride (5.7 mL) and the reaction mixture was stirred at 60 °C for 4 h before the product was filtered, washed with a small amount of acetic anhydride and dried under vacuum (Yield: 1.0 g, 97%).

^{1}H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 7.79 – 7.70 (m, 2H), 7.62 (ddd, *J* = 0.7, 5.1, 8.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

MS (ESI) calcd. for $C_{11}H_9FN_2O_3S$ $[M+H]^+$ 269.0; found 269.2.

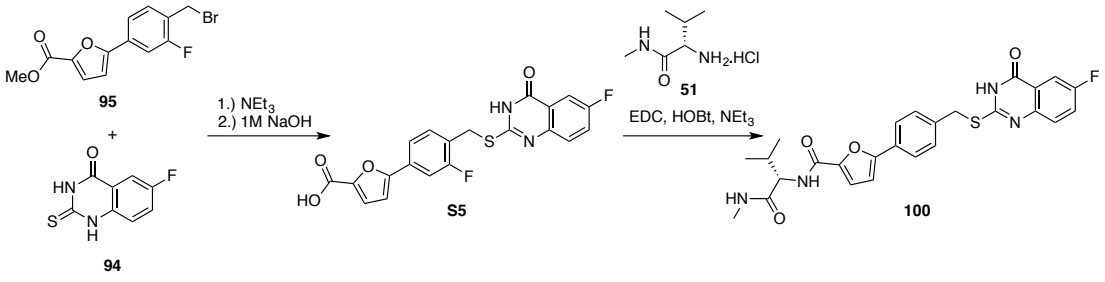


94

6-Fluoro-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**94**). A solution of sodium methoxide (0.5M, 104 mg Na, 4.51 mmol, 1.10 eq in 9 mL MeOH) was added to a solution of **93** (1.10 g, 4.10 mmol, 1.0 eq) in THF (18 mL). The reaction mixture was heated to reflux (87 °C) and stirred for 90 min. After cooling to room temperature concentrated acetic acid (260 μL, 4.51 mmol) was added to precipitate the product. The solvent was removed under reduced pressure and the crude product was refluxed in EtOH/water 2:1 (37.5 mL) for 30 min. The product was filtered and washed with cold ethanol (Yield: 498 mg, 62%).

^{1}H NMR (400 MHz, DMSO) δ 12.68 (s, 2H), 7.75 – 7.56 (m, 2H), 7.41 (dd, *J* = 4.5, 9.8 Hz, 1H).

MS (ESI) calcd. for $C_8H_5FN_2OS$ $[M+H]^+$ 197.0; found 197.4.



(*S*)-5-(3-Fluoro-4-(((6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**100**). A suspension of **94** (78 mg, 0.399 mmol, 1.0 eq) and NEt_3 (66 μL, 0.479 mmol, 1.2 eq) in 1.0 mL DMF was stirred for 15 min at room temperature before **95**[4] (150 mg, 0.479 mmol, 1.2 eq) was added and the reaction mixture was stirred for 16 h at room

temperature. The solids were filtered, washed with small amounts of water, methanol and diethyl ether, and the product was dried under vacuum to give the corresponding methyl ester (131 mg, 77%) as a white solid, which was subsequently hydrolyzed.

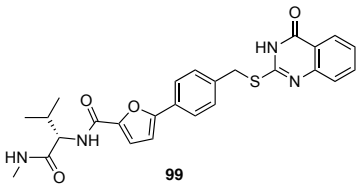
A 1 M solution of NaOH (980 μL, 0.979 mmol, 3.2 eq) was added to the methyl ester (131 mg, 0.306 mmol, 1.0 eq) in THF/MeOH 2:1 (1.5 mL) and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature the mixture was diluted with 1 mL water and acidified with 1M HCl (pH~2, ca. 1 mL). The precipitated product was filtered and washed with water providing **S5** (108 mg, 89%) as a white solid.

To a solution of **S5** (80 mg, 0.193 mmol, 1.0 eq), EDCI•HCl (56 mg, 0.29 mmol, 1.5 eq), HOBt (39 mg, 0.29 mmol, 1.5 eq), and DIPEA (49 μL, 0.29 mmol, 1.5 eq) in 1 mL DMF was added (*S*)-2-amino-*N*,3-dimethylbutanamide hydrochloride[4] (**51**, 94 mg, 0.386 mmol, 2.0 eq). The reaction mixture was stirred for 4 h at room temperature before it was diluted with EtOAc (ca. 5 mL) and washed with 0.1M HCl (2x 10 mL). The aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x 10 mL) and brine (1x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) and preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing compound **100** (62 mg, 61%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 12.77 (s, 1H), 8.40 (d, *J* = 8.9 Hz, 1H), 8.13 – 8.03 (m, 1H), 7.88 (dd, *J* = 1.4, 11.5 Hz, 1H), 7.80 – 7.61 (m, 5H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 4.54 (s, 2H), 4.20 (t, *J* = 8.8 Hz, 1H), 2.60 (d, *J* = 4.6 Hz, 3H), 2.23 – 2.01 (m, 1H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 171.25, 160.87 (d, *J* = 245.94 Hz), 160.61, 159.39 (d, *J* = 244.5 Hz), 157.34, 154.24, 153.10 (d, *J* = 2.10 Hz), 147.13, 145.14, 132.23 (d, *J* = 3.53 Hz), 130.78 (d, *J* = 8.9 Hz), 128.69, 124.46 (d, *J* = 14.9 Hz), 122.98 (d, *J* = 24.0 Hz), 121.17 (d, *J* = 8.0 Hz), 120.28, 116.23, 111.16 (d, *J* = 24.0 Hz), 110.77 (d, *J* = 23.3 Hz), 108.91, 58.43, 29.93, 27.21, 25.43, 19.36, 19.02.

HRMS (ESI) calcd. for: $C_{26}H_{24}F_2N_4O_4S$ $[M+H]^+$ 527.1565; found 527.1568.

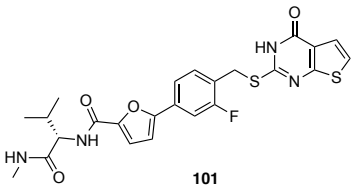


99

(*S*)-5-(3-Fluoro-4-(((4-oxo-3,4-dihydroquinazolin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**99**). Compound **99** was synthesized following the same procedures as described above for **100** and was isolated in 32% (47 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 8.26 (d, *J* = 8.9 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.91 – 7.85 (m, 2H), 7.80 (ddd, *J* = 1.6, 7.1, 8.9 Hz, 1H), 7.67 – 7.57 (m, 3H), 7.44 (ddd, *J* = 1.2, 7.1, 8.1 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 4.54 (s, 2H), 4.20 (t, *J* = 8.7 Hz, 1H), 2.60 (d, *J* = 4.5 Hz, 3H), 2.19 – 2.03 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for: $C_{26}H_{25}FN_4O_4S$ $[M+H]^+$ 491.1675; found 491.1673.

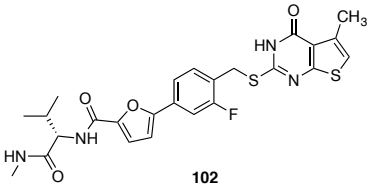


101

(*S*)-5-(3-Fluoro-4-(((4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**101**). Compound **101** was synthesized following the same procedure as described above for **100** using **95**[4] and **89** as starting materials and was isolated in 18% (62 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.83 (s, 1H), 8.41 (d, *J* = 8.9 Hz, 1H), 8.12 – 8.00 (m, 1H), 7.89 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.73 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 5.8 Hz, 1H), 7.31 (d, *J* = 5.8 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.51 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.22 – 2.02 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for: $C_{24}H_{23}FN_4O_4S_2$ $[M+H]^+$ 515.1223; found 515.1227.

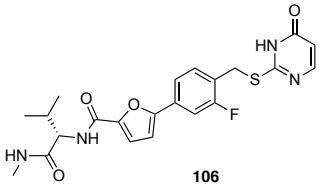


102

(*S*)-5-(3-Fluoro-4-(((5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**102**). Compound **102** was synthesized following the same procedure as described above for **100** using **95**[4] and **90** as starting materials and was isolated in 18% (62 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.70 (s, 1H), 8.41 (d, *J* = 8.9 Hz, 1H), 8.11 – 8.01 (m, 1H), 7.89 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.73 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.03 (d, *J* = 1.4 Hz, 1H), 4.49 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.42 (d, *J* = 1.2 Hz, 3H), 2.21 – 2.03 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for: $C_{25}H_{25}FN_4O_4S_2$ $[M+H]^+$ 529.1380; found 529.1383.



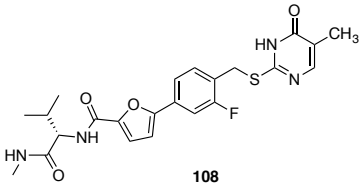
106

(*S*)-5-(3-Fluoro-4-(((6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**106**). Compound **106** was synthesized following the same procedure as described above for **100** using **95**[4] and **75** as starting materials and was isolated in 28% (35 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.74 (s, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.06 (q, *J* = 4.6 Hz, 1H), 7.93 (s, 1H), 7.87 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.72 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* =

3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.16 (s, 1H), 4.45 (s, 2H), 4.21 (t, *J* = 8.7 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H), 2.21 – 2.02 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{22}H_{23}FN_4O_4S$ $[M+H]^+$ 459.1502; found 459.1497.

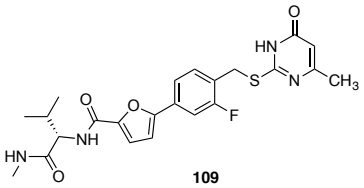


108

(*S*)-5-(3-Fluoro-4-(((5-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**108**). Compound **108** was synthesized following the same procedure as described above for **100** using **95**[4] and **77** as starting materials and was isolated in 49% (61 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.77 (bs, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.87 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.78 (bs, 1H), 7.71 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 4.44 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.20 – 2.05 (m, 1H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.88 (d, *J* = 6.1 Hz, 3H).

HRMS (ESI) calcd. for $C_{23}H_{25}FN_4O_4S$ $[M+H]^+$ 473.1659; found 473.1656.

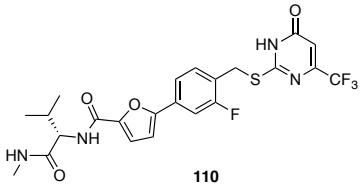


109

(*S*)-5-(3-fluoro-4-(((4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**109**). Compound **109** was synthesized following the same procedure as described above for **100** using **95**[4] and **76** as starting materials and was isolated in 39% (58 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.62 (s, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.87 (dd, *J* = 1.6, 11.2 Hz, 1H), 7.72 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.00 (s, 1H), 4.43 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H), 2.19 – 2.04 (m, 1H), 0.91 (d, *J* = 7.6 Hz, 3H) 0.89 (d, *J* = 7.6 Hz, 3H).

HRMS (ESI) calcd. for $C_{23}H_{25}FN_4O_4S$ $[M+H]^+$ 473.1659; found 473.1656.



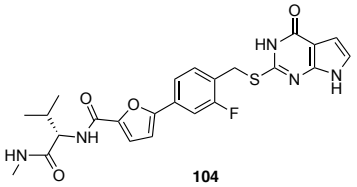
110

(*S*)-5-(3-Fluoro-4-(((6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**110**). Compound **110** was synthesized following the same procedure as described above for **100** using **95**[4] and **78** as starting materials and was

isolated in 14% (38 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 13.43 (bs, 1H), 8.42 (d, *J* = 8.9 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.88 (dd, *J* = 1.7, 11.2 Hz, 1H), 7.71 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 6.61 (s, 1H), 4.45 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.20 – 2.07 (m, 1H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H).

HRMS (ESI) calcd. for $C_{23}H_{22}F_4N_4O_4S$ $[M+H]^+$ 527.1376; found 527.1381.

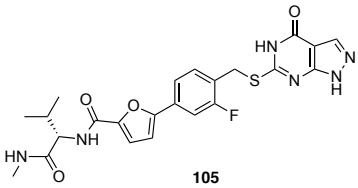


104

(*S*)-5-(3-Fluoro-4-(((4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**104**). Compound **104** was synthesized following the same procedure as described above for **100** using **95**[4] and **82** as starting materials and was isolated in 59% (61 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 12.11 (s, 1H), 11.83 (s, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.10 – 8.03 (m, 1H), 7.91 – 7.84 (m, 1H), 7.74 – 7.62 (m, 2H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.96 (dd, *J* = 2.3, 3.4 Hz, 1H), 6.38 (dd, *J* = 2.3, 3.4 Hz, 1H), 4.48 (s, 2H), 4.21 (t, *J* = 8.7 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.20 – 2.05 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{24}H_{24}FN_5O_4S$ $[M+H]^+$ 498.1611; found 498.1610.

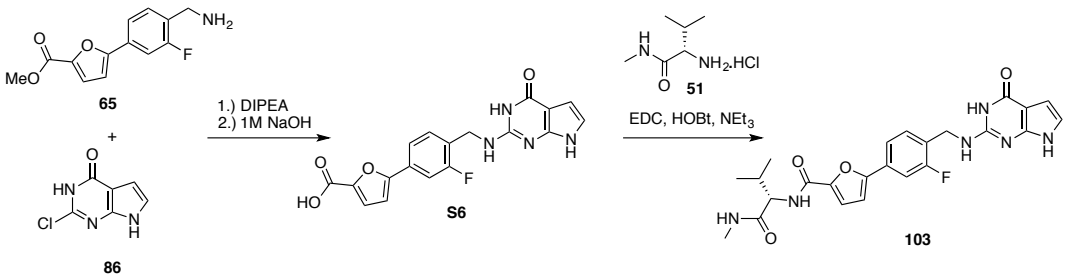


105

(*S*)-5-(3-fluoro-4-(((4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**105**). Compound **105** was synthesized following the same procedure as described above for **100** using **95**[4] and **79** as starting materials and was isolated in 39% (44 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 13.68 (s, 1H), 12.42 (s, 1H), 8.40 (d, *J* = 8.9 Hz, 1H), 8.11 – 8.04 (m, 1H), 7.93 – 7.85 (m, 1H), 7.78 – 7.61 (m, 2H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.51 (s, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.6 Hz, 3H), 2.23 – 1.98 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{23}H_{24}FN_7O_4$ $[M+H]^+$ 482.4884; found 482.4880.



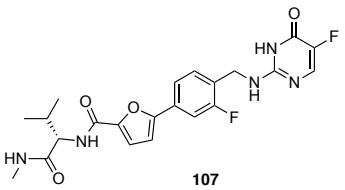
(*S*)-5-(3-Fluoro-4-(((4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**103**). 2-chloro-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (**86**, 59 mg, 0.35 mmol, 1.0 eq) and **65** (100 mg, 0.35 mmol, 1.0 eq) were dissolved in dioxane (4 mL). DIPEA (183 μL, 1.05 mmol, 3.0 eq) was added and the reaction mixture was stirred for 24 h at 120 °C. The reaction mixture was diluted with EtOAc /THF 1:1 (20 mL) and water (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc / THF 1:1 (3x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was transferred in a frit and washed with diethyl ether/methanol 20:1 (4x 5 mL) to provide the corresponding methyl ester (82 mg) in 61% yield.

A 1 M solution of NaOH (540 μL, 0.54 mmol, 3.0 eq) was added to the methyl ester (72 mg, 0.18 mmol, 1.0 eq) in THF/MeOH 2:1 (1.5 mL) and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature the mixture was diluted with 1 mL H_2O and acidified with 1 M HCl (pH~2, ca. 1 mL). The precipitated product was filtered and washed with water providing **S6** (61 mg, 92%) as a white solid.

To a solution of **S6** (50 mg, 0.136 mmol, 1.0 eq), EDCI•HCl (29 mg, 0.15 mmol, 1.1 eq), HOBt (20 mg, 0.15 mmol, 1.1 eq) and triethylamine (41 μL, 0.299 mmol, 2.2 eq) in 1 mL DMF was added (*S*)-2-amino-*N*,3-dimethylbutanamide hydrochloride[4] (**51**, 40 mg, 0.163 mmol, 1.2 eq). The reaction mixture was stirred for 12 h at room temperature before it was diluted with EtOAc (ca. 5 mL) and washed with 0.1 M HCl (2x 10 mL). The aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) and preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing compound **103** (28 mg, 43%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 11.17 (d, *J* = 2.3 Hz, 1H), 10.34 (s, 1H), 8.37 (d, *J* = 8.9 Hz, 1H), 8.07 (d, *J* = 4.7 Hz, 1H), 7.86 (dd, *J* = 1.7, 11.4 Hz, 1H), 7.72 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 6.66 – 6.56 (m, 2H), 6.21 (dd, *J* = 2.3, 3.4 Hz, 1H), 4.56 (d, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 8.7 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H), 2.22 – 1.97 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

HRMS (ESI) calcd. for $C_{24}H_{25}FN_6O_4$ $[M+H]^+$ 481.2000; found 481.2005.

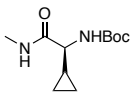


(*S*)-5-(3-Fluoro-4-(((5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)amino)methyl)phenyl)-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**107**). Compound **107** was synthesized following the same procedure as described above for **103** using **65**[4] and **84** as starting materials and was isolated in

12% (33 mg) yield over three steps.

^{1}H NMR (400 MHz, DMSO) δ 11.57 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.16 – 8.00 (m, 1H), 7.93 – 7.82 (m, 1H), 7.78 – 7.67 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 6.96 – 6.87 (m, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 4.21 (t, *J* = 8.8 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H), 2.20 – 2.04 (m, 1H), 0.91 (d, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 7.5 Hz, 3H).

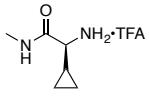
HRMS (ESI) calcd. for $C_{22}H_{23}F_2N_5O_4$ $[M+H]^+$ 460.1796; found 460.1800.



S7

Tert-butyl (*S*)-(1-cyclopropyl-2-(methylamino)-2-oxoethyl)carbamate (**S7**). To a solution of Boc-potected (*S*)-2-amino-2-cyclopropylacetic acid (934 mg, 4.34 mmol, 1.0 eq), EDCI•HCl (999 mg, 5.2 mmol, 1.2 eq), and DMAP (27 mg, 0.217 mmol, 0.05 eq) in 43 mL methylene chloride was added methylamine (2 M in THF, 2.6 mL, 5.21 mmol, 1.2 eq). The reaction mixture was stirred for 18 h at room temperature before it was transferred in a separatory funnel and washed with 1 M HCl (2x 50 mL), sat. $NaHCO_3$ (2x 100 mL) and brine (1x 100 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to provide **S7** (735 mg, 74%) as a yellow oil, which was used for the next step without any further purification.

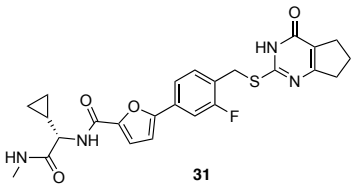
^{1}H NMR (400 MHz, MeOD) δ 3.35 – 3.33 (m, 1H), 2.76 (s, 3H), 1.45 (s, 9H), 1.13 – 0.98 (m, 1H), 0.65 – 0.53 (m, 2H), 0.51 – 0.42 (m, 1H), 0.41 – 0.26 (m, 1H).



S8

(*S)*-2-amino-2-cyclopropyl-N-methylacetamide TFA salt (**S8**). Compound **S7** (735 mg, 3.22 mmol, 1.0 eq) was dissolved in a 1:1 mixture of CH_2Cl_2 and trifluoroacetic acid (30 mL) and stirred for 90 min. The reaction mixture was concentrated under reduced pressure, the remaining yellow oil was re-dissolved in chloroform (ca. 10 mL) and the solvent was removed again in *vacuo*. This last step was repeated three times to eliminate all traces of trifluoroacetic acid and **S8** (TFA salt, 700 mg) was isolated in 90% yield. The NMR of the crude material showed clean product, which was used without further purification for the next step.

^{1}H NMR (400 MHz, MeOD) δ 3.14 (d, *J* = 9.9 Hz, 1H), 2.83 (s, 3H), 1.24 – 1.11 (m, 1H), 0.85 – 0.73 (m, 2H), 0.72 – 0.65 (m, 1H), 0.57 – 0.51 (m, 1H).



31

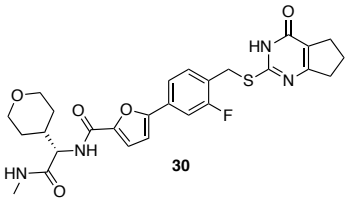
(*S*)-*N*-(1-Cyclopropyl-2-(methylamino)-2-oxoethyl)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**31**). To a solution of **24**[4] (50 mg, 0.129 mmol, 1.0 eq), EDCI•HCl (37 mg, 0.194 mmol, 1.5 eq), HOBt (26 mg, 0.194 mmol, 1.5 eq), and

DIPEA (3 μL, 0.194 mmol, 1.5 eq) in 1 mL DMF was added **S8** (62 mg, 0.258 mmol, 2.0 eq). The reaction mixture was stirred for 4 h at room temperature before it was diluted with EtOAc (ca. 5 mL) and washed with 0.1 M HCl (2x 10 mL). The aqueous phase was extracted with EtOAc (3x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1x 10 mL) and brine (1x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (0-10% methanol linear gradient in DCM) followed by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing **31** (61 mg, 79%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.02 – 7.82 (m, 2H), 7.73 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 4.44 (s, 2H), 3.73 (dd, *J* = 8.1, 9.5 Hz, 1H), 2.83 – 2.73 (m, 2H), 2.66 – 2.55 (m, 5H), 2.03 – 1.90 (m, 2H), 1.34 – 1.18 (m, 1H), 0.59 – 0.44 (m, 3H), 0.35 – 0.22 (m, 1H).

^{13}C NMR (176 MHz, DMSO) δ 171.32, 168.53, 160.86 (d, *J* = 245.42 Hz), 160.71, 159.22, 157.12, 153.09 (d, *J* = 2.8 Hz), 147.18, 132.06 (d, *J* = 4.3 Hz), 130.81 (d, *J* = 8.8 Hz), 124.35 (d, *J* = 14.9 Hz), 120.33 (d, *J* = 3.1 Hz), 119.56, 116.25, 111.20 (d, *J* = 24.1 Hz), 108.93, 57.10, 34.24, 27.22, 26.73, 25.62, 20.60, 13.85, 3.77, 3.56.

HRMS (ESI) calcd. for: $C_{25}H_{25}FN_4O_4S$ $[M+H]^+$ 497.1661; found 497.1659.

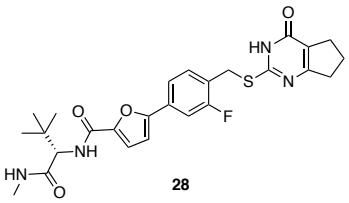


30

(*S*)-5-(3-Fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(2-(methylamino)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethyl)furan-2-carboxamide (**30**). Compound **30** was synthesized following the same procedure as described above for **31** using **24**[4] and (*S*)-2-amino-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)acetamide hydrochloride as starting materials and was isolated in 60% (33 mg) yield.

^{1}H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.18 – 8.11 (m, 1H), 7.88 (dd, *J* = 1.6, 11.2 Hz, 1H), 7.72 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 4.44 (s, 2H), 4.29 (t, *J* = 9.0 Hz, 1H), 3.92 – 3.79 (m, 2H), 3.25 (ddd, *J* = 5.2, 9.5, 11.5 Hz, 1H), 2.84 – 2.73 (m, 2H), 2.66 – 2.54 (m, 5H), 2.13 – 1.91 (m, 3H), 1.70 – 1.59 (m, 1H), 1.47 – 1.39 (m, 1H), 1.38 – 1.29 (m, 1H), 1.29 – 1.12 (m, 1H).

HRMS (ESI) calcd. for: $C_{27}H_{29}FN_4O_5S$ $[M+H]^+$ 541.1921; found 541.1921.



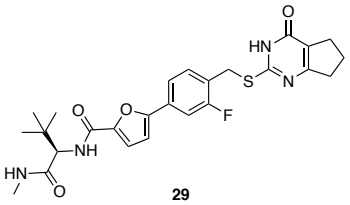
28

(*S*)-*N*-(3,3-Dimethyl-1-(methylamino)-1-oxobutan-2-yl)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**28**). Compound **28** was synthesized following the same procedure as described above for **31** using **24**[4] and (*S*)-2-amino-*N*,3,3-

trimethylbutanamide hydrochloride as starting materials and was isolated in 56% (37 mg) yield.

^{1}H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.17 – 8.08 (m, 1H), 7.88 – 7.76 (m, 2H), 7.71 – 7.57 (m, 2H), 7.35 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 4.51 – 4.33 (m, 3H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.56 (m, 5H), 2.05 – 1.85 (m, 2H), 0.98 (s, 9H).

HRMS (ESI) calcd. for: $C_{26}H_{29}FN_4O_4S$ $[M+H]^+$ 513.1972; found 513.1974.



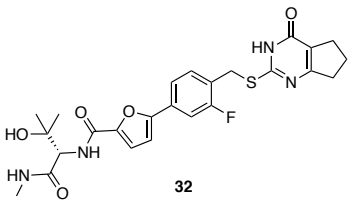
29

(*R*)-*N*-(3,3-Dimethyl-1-(methylamino)-1-oxobutan-2-yl)-5-(3-fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)furan-2-carboxamide (**29**). Compound **29** was synthesized following the same procedure as described above for **31** using **24**[4] and (*R*)-2-amino-*N*,3,3-trimethylbutanamide hydrochloride as starting materials and was isolated in 45% (30 mg) yield.

^{1}H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.17 – 8.08 (m, 1H), 7.88 – 7.76 (m, 2H), 7.71 – 7.57 (m, 2H), 7.35 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 4.51 – 4.33 (m, 3H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.56 (m, 5H), 2.05 – 1.85 (m, 2H), 0.98 (s, 9H).

^{13}C NMR (176 MHz, DMSO) δ 170.19, 168.52, 160.84 (d, *J* = 246.2 Hz), 160.83, 159.25, 157.29, 153.34 (d, *J* = 2.31 Hz), 146.99, 132.20 (d, *J* = 3.6 Hz), 130.74 (d, *J* = 8.8 Hz), 124.55 (d, *J* = 15.1 Hz), 120.34, 119.70, 116.61, 111.24 (d, *J* = 24.0 Hz), 109.14, 59.78, 34.53, 34.27, 27.24, 26.82, 26.77, 25.42, 20.65.

HRMS (ESI) calcd. for: $C_{26}H_{29}FN_4O_4S$ $[M+H]^+$ 513.1972; found 513.1974.

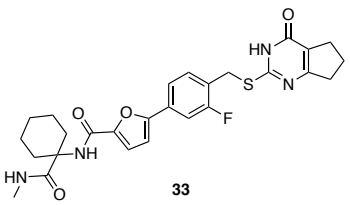


32

(*S*)-5-(3-Fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl) phenyl)-*N*-(3-hydroxy-3-methyl-1-(methylamino)-1-oxobutan-2-yl)furan-2-carboxamide (**32**). Compound **32** was synthesized following the same procedure as described above for **31** using **24**[4] and (*S*)-2-amino-3-hydroxy-*N*,3-dimethylbutanamide hydrochloride as starting materials and was isolated in 45% (51 mg) yield.

^{1}H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 8.04 – 7.95 (m, 2H), 7.79 (dd, *J* = 1.6, 11.1 Hz, 1H), 7.68 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 4.95 (s, 1H), 4.53 – 4.35 (m, 3H), 2.85 – 2.76 (m, 2H), 2.67 – 2.56 (m, 5H), 2.08 – 1.87 (m, 2H), 1.20 (s, 3H), 1.16 (s, 3H).

HRMS (ESI) calcd. for: $C_{25}H_{27}FN_4O_5S$ $[M+H]^+$ 515.1764; found 515.1769.



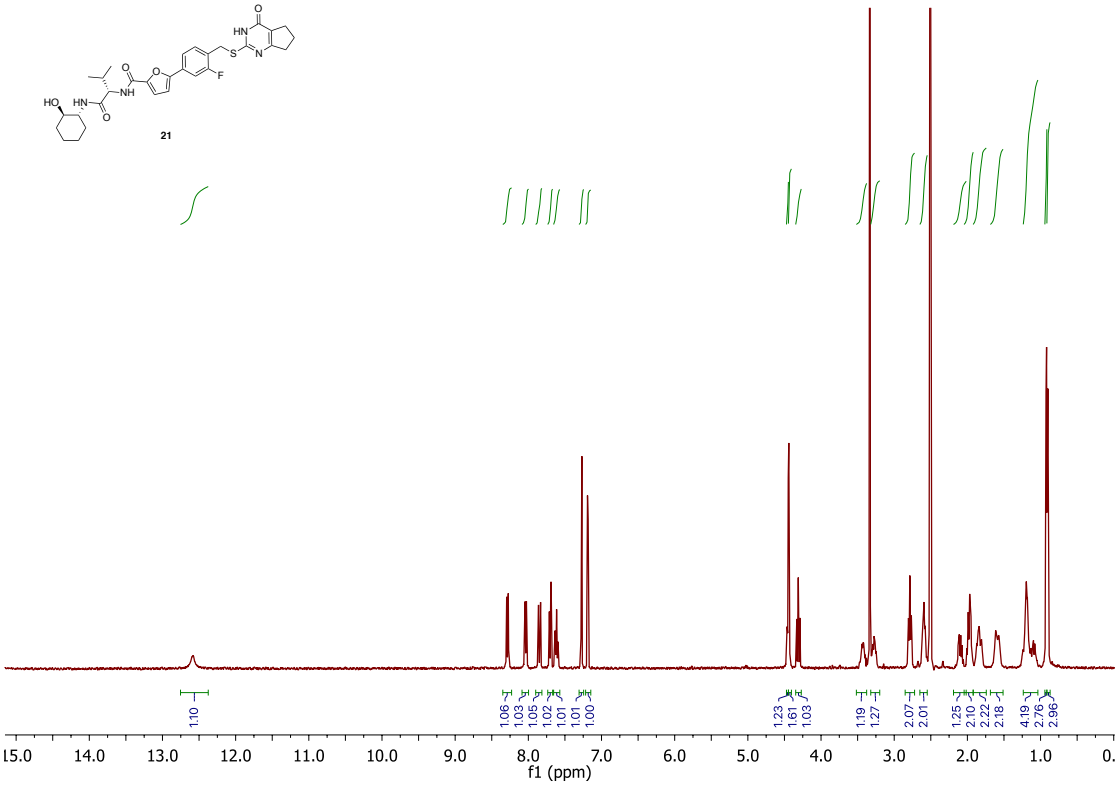
33

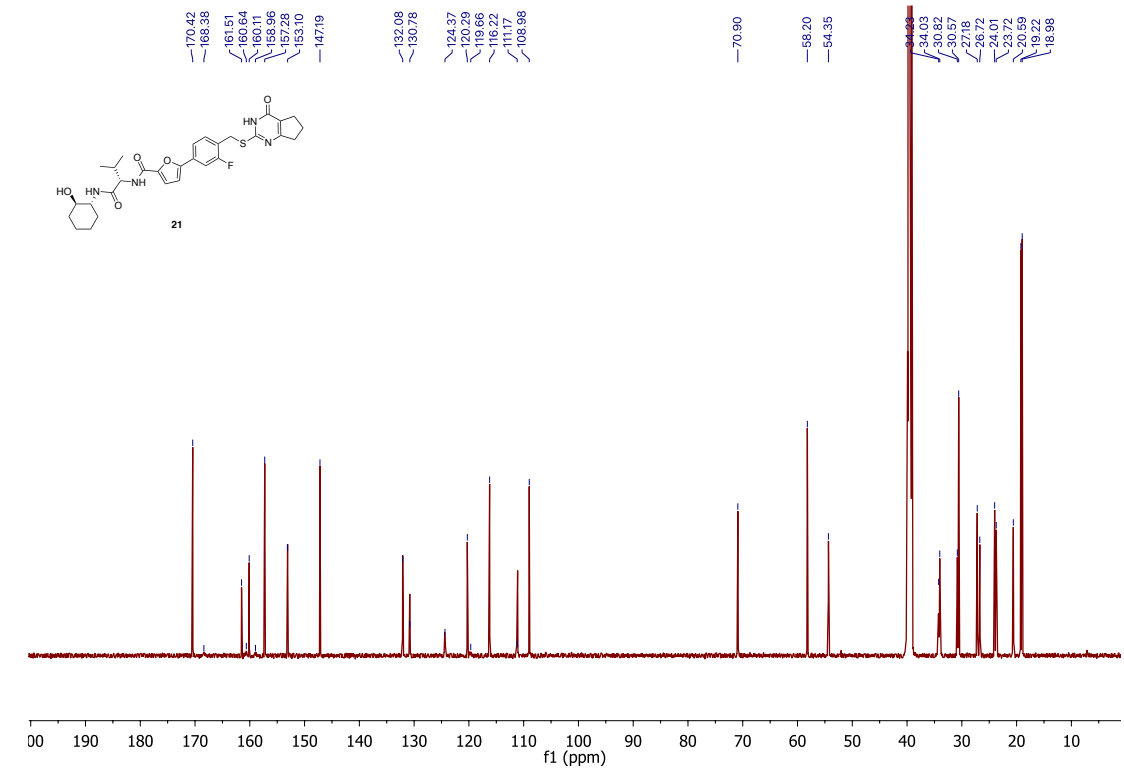
5-(3-Fluoro-4-(((4-oxo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*d*]pyrimidin-2-yl)thio)methyl)phenyl)-*N*-(1-(methylcarbamoyl)cyclohexyl)furan-2-carboxamide (**33**). Compound **33** was synthesized following the same procedure as described above for **31** using **24**[4] and 1-amino-*N*-methylcyclohexane-1-carboxamide hydrochloride as starting materials and was isolated in 70% (43 mg) yield.

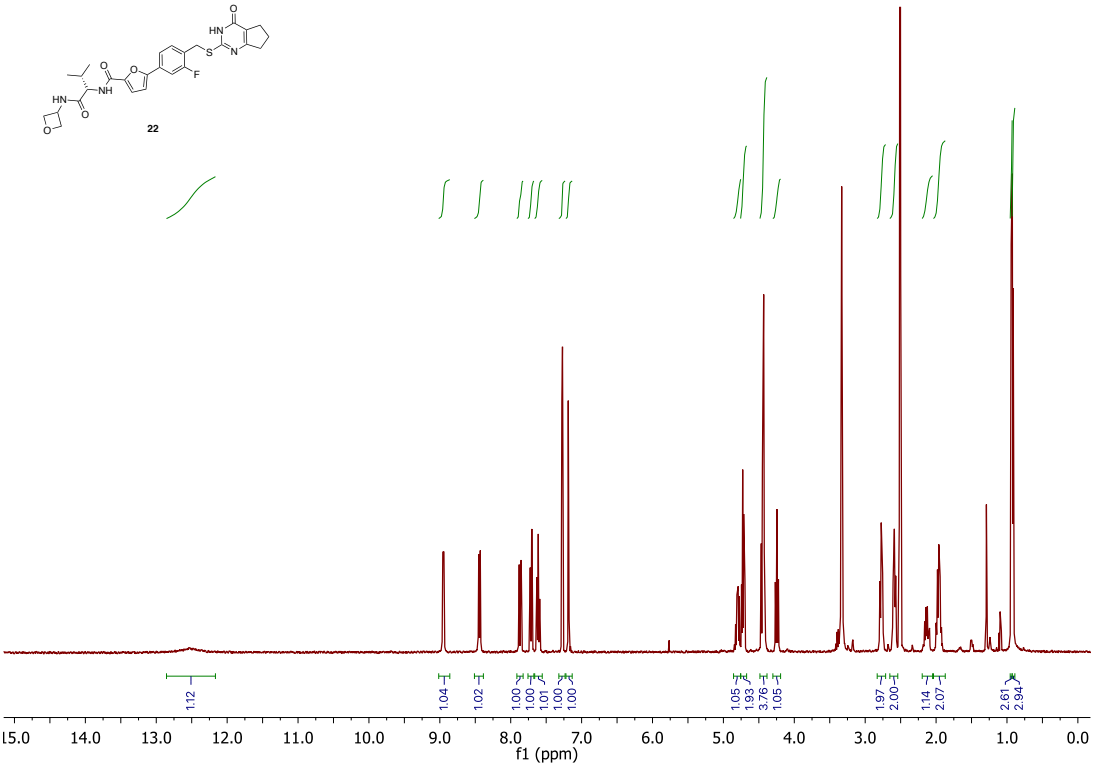
^{1}H NMR (400 MHz, MeOD) δ 7.80 – 7.73 (m, 1H), 7.72 – 7.67 (m, 1H), 7.66 – 7.58 (m, 2H), 7.25 (d, J = 3.6 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H), 4.52 (s, 2H), 2.92 – 2.84 (m, 2H), 2.78 – 2.67 (m, 5H), 2.33 – 2.21 (m, 2H), 2.15 – 2.02 (m, 2H), 1.96 – 1.84 (m, 2H), 1.75 – 1.65 (m, 3H), 1.65 – 1.51 (m, 2H), 1.45 – 1.33 (m, 1H).

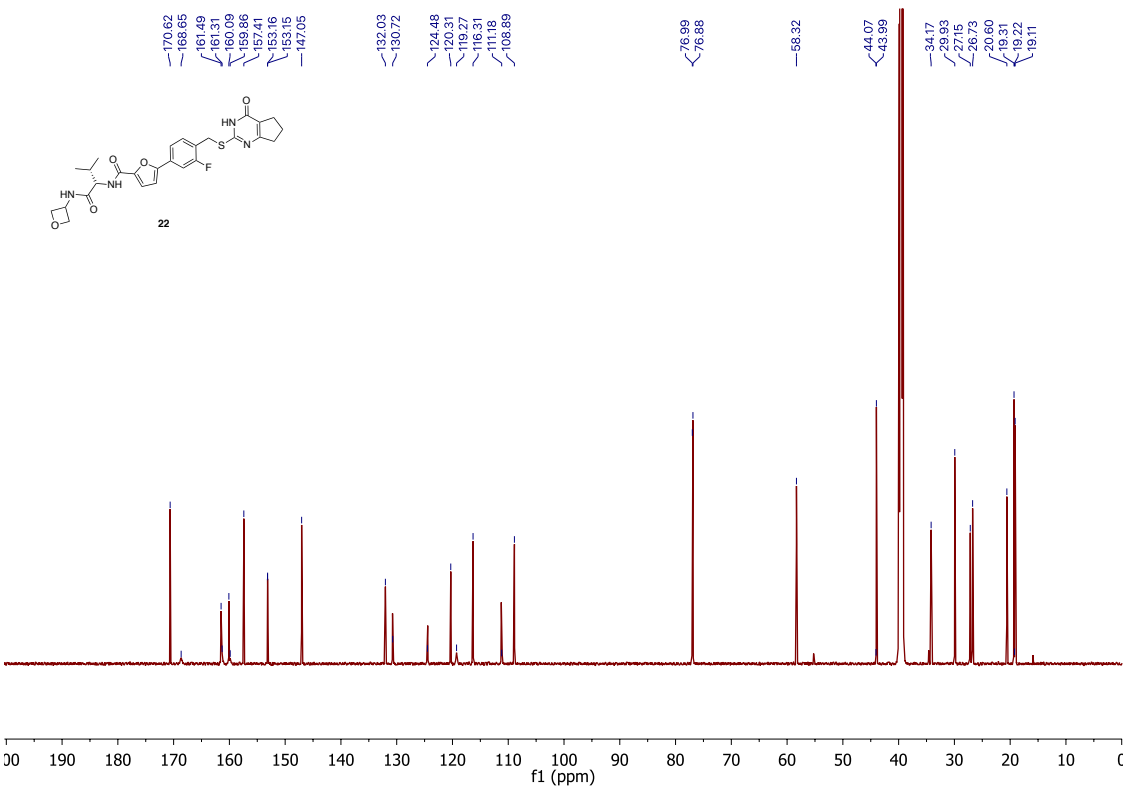
HRMS (ESI) calcd. for: $C_{27}H_{29}FN_4O_4S$ $[M+H]^+$ 525.1972; found 525.1978.

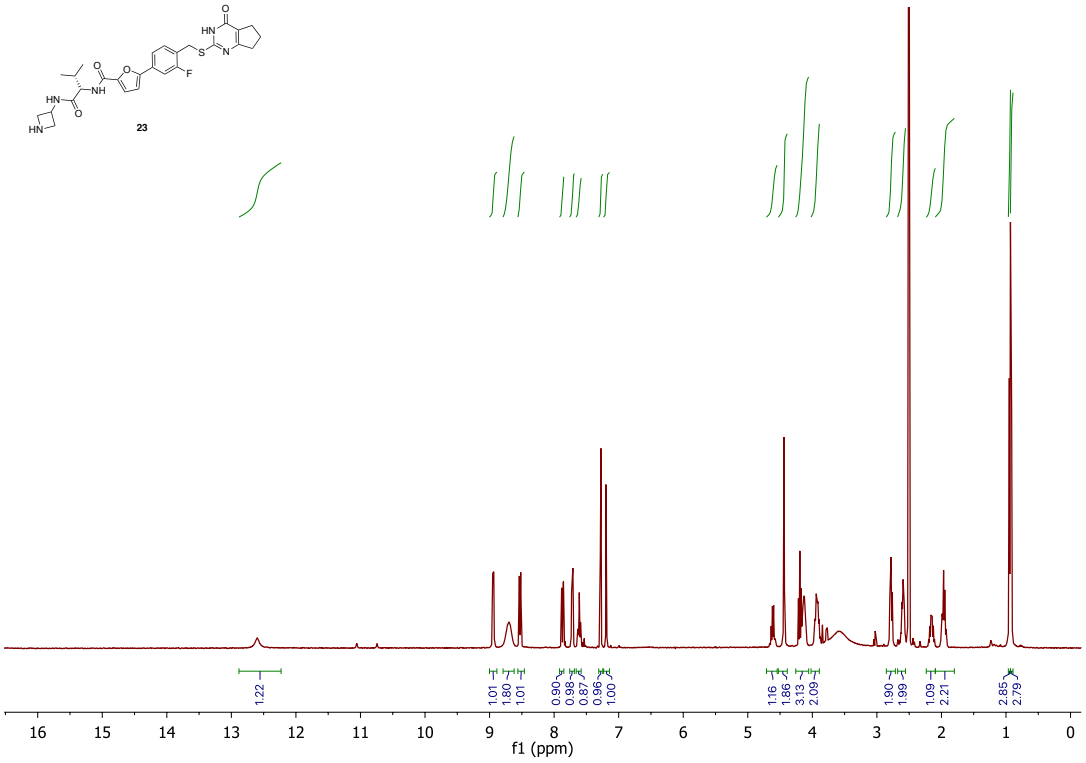
IV. NMR Spectra

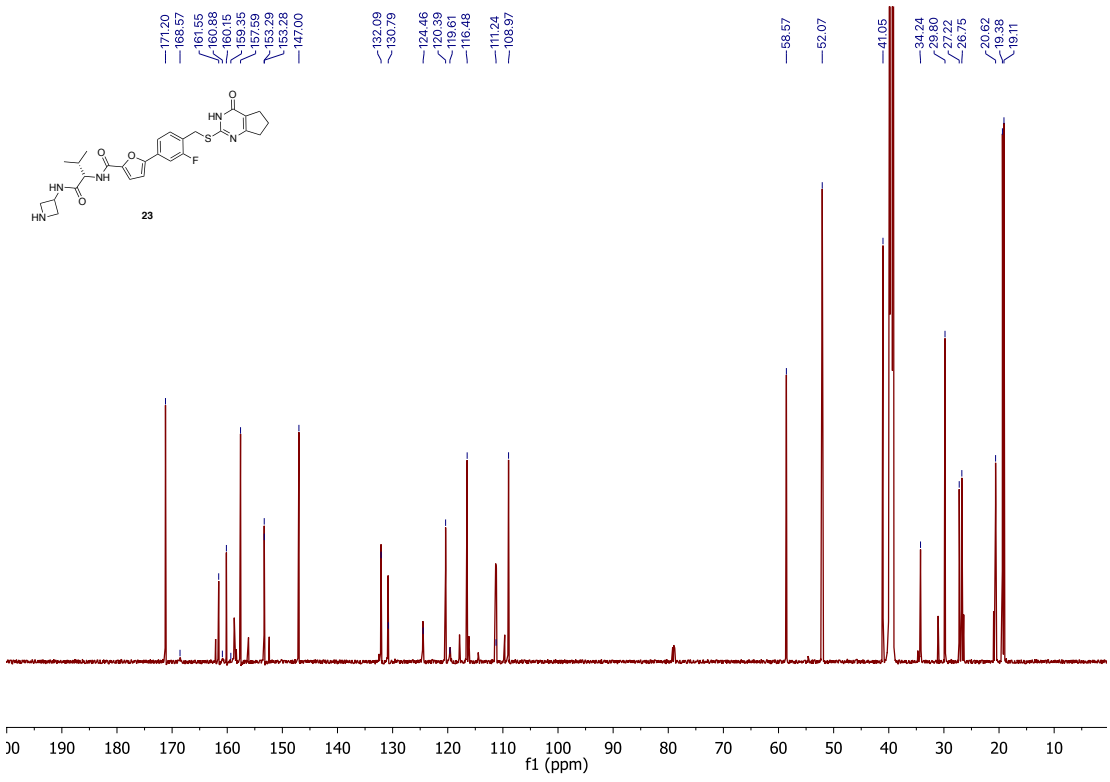





22
1.12
1.04
1.02
1.00
1.01
1.00
1.00
1.05
1.93
3.76
1.05
1.97
2.00
1.14
2.07
2.61
2.94
f1 (ppm)


170.62
168.65
161.49
161.31
160.09
159.86
157.41
153.16
153.15
147.05
132.03
130.72
124.48
120.31
119.27
116.31
111.18
108.89
76.99
76.88
58.32
44.07
43.99
34.17
29.93
27.15
26.73
20.60
19.31
19.22
19.11
22
f1 (ppm)


23
1.22
1.01
1.80
1.01
0.90
0.98
0.87
0.96
1.00
1.16
1.86
3.13
2.09
1.90
1.99
1.09
2.21
2.85
2.79
f1 (ppm)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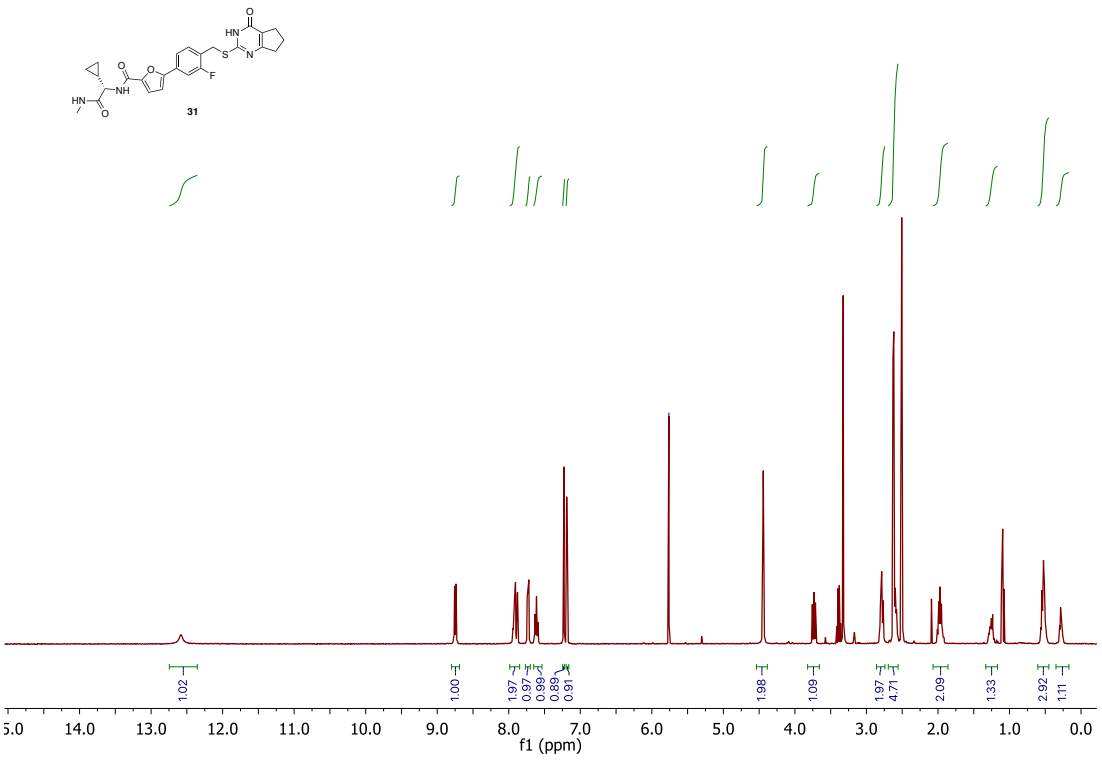
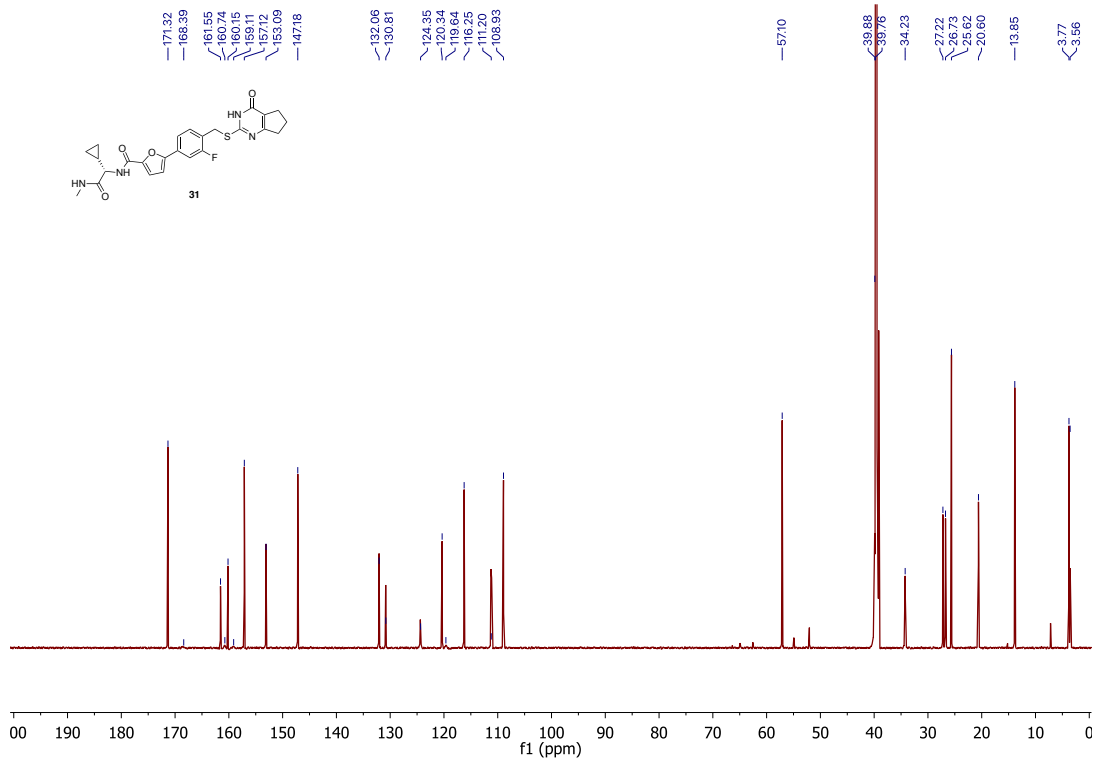
168.57
161.55
160.88
160.15
159.35
157.59
153.29
153.28
147.00
132.09
130.79
124.46
120.39
119.61
116.48
111.24
108.97
58.57
52.07
41.05
34.24
29.80
27.22
26.75
20.62
19.38
19.11
23
f1 (ppm)


31
1.02
1.00
1.97
0.97
0.99
0.89
0.91
1.98
1.09
1.97
4.71
2.09
1.33
2.92
1.11
f1 (ppm)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157.12
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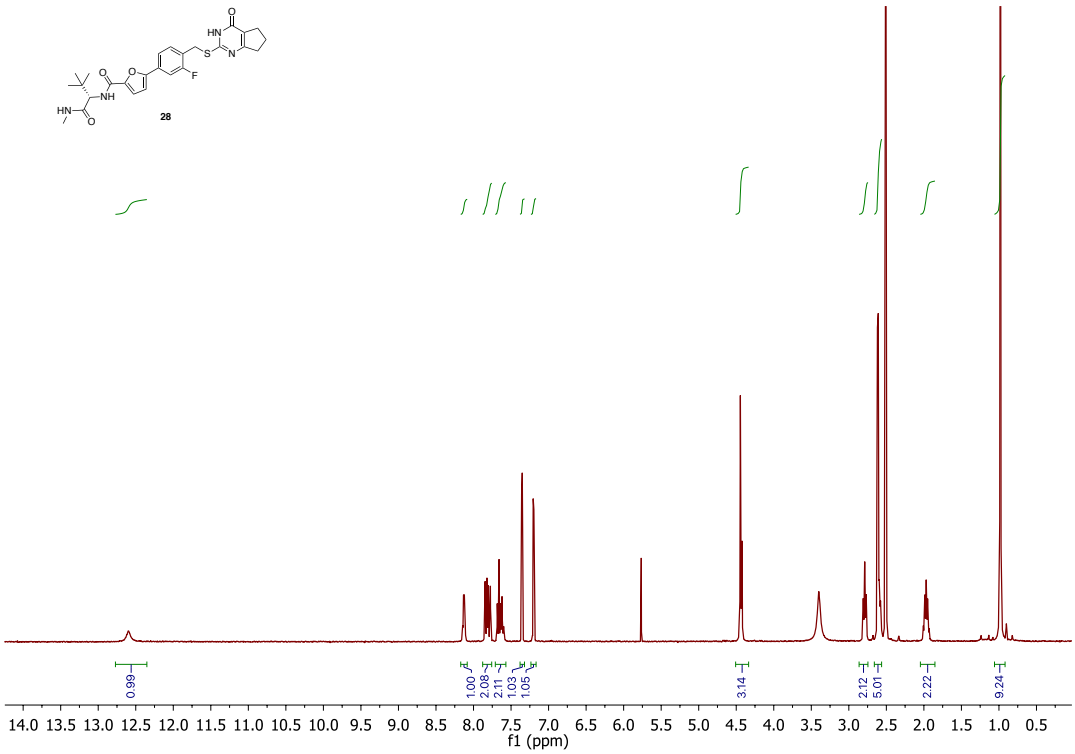
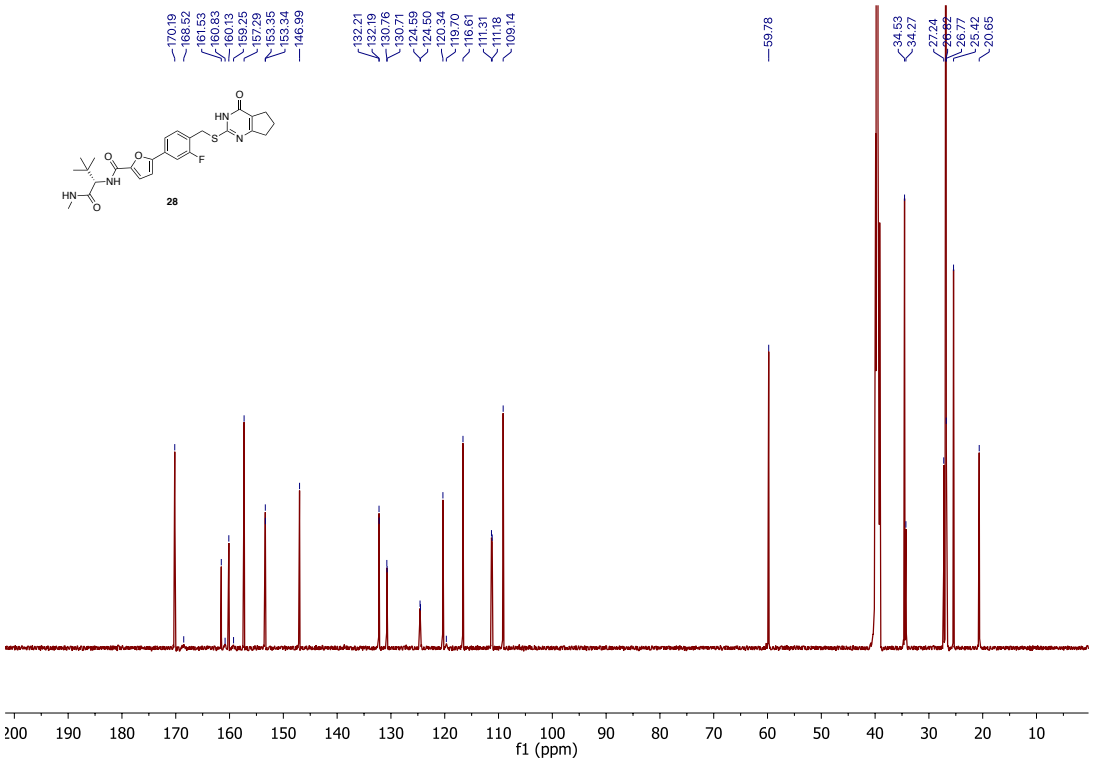
132.06
130.81
124.35
120.34
119.64
116.25
111.20
108.93
57.10
39.88
39.76
34.23
27.22
26.73
25.62
20.60
13.85
3.77
3.56
31
f1 (ppm)


28
0.99
1.00
2.08
2.11
1.03
1.05
3.14
2.12
5.01
2.22
9.24
f1 (ppm)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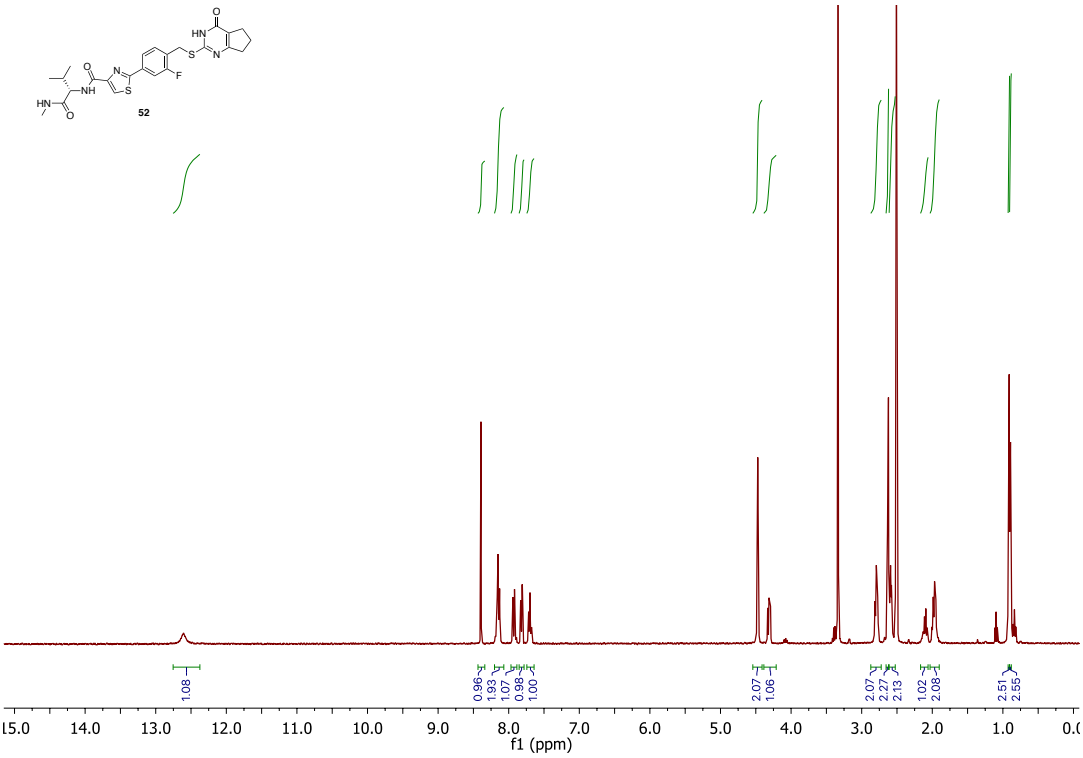
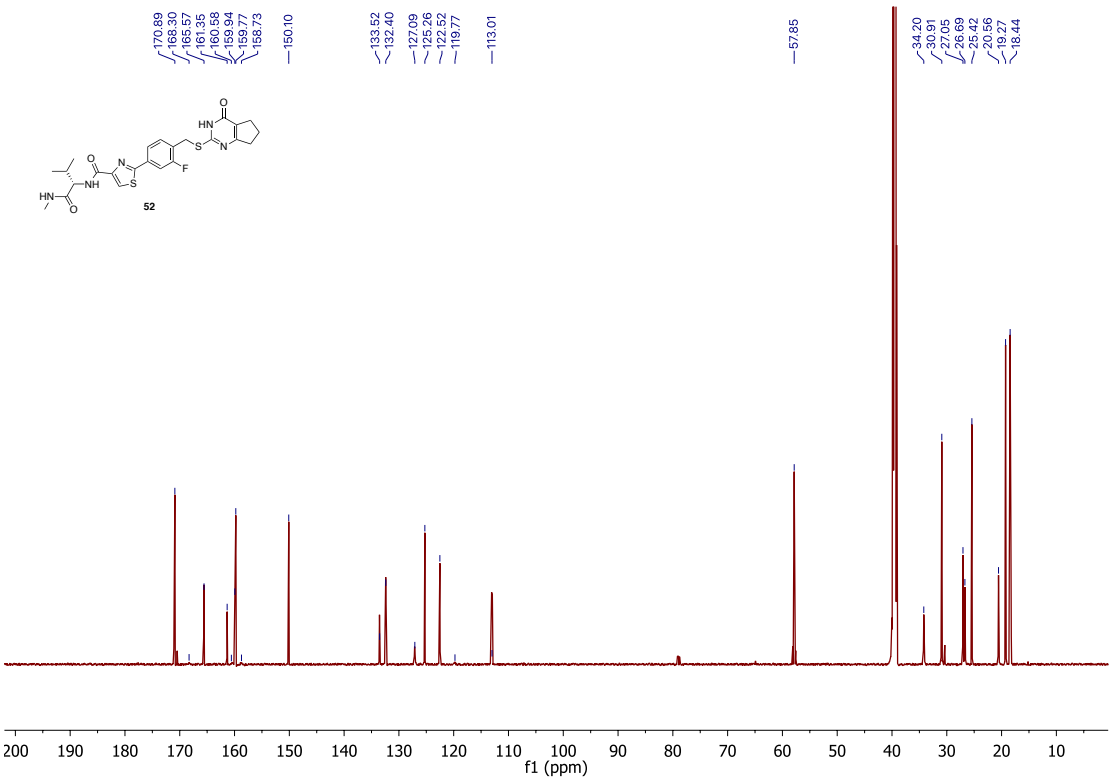
160.83
160.13
159.25
157.29
153.35
153.34
146.99
132.21
132.19
130.76
130.71
124.59
124.50
120.34
119.70
116.61
111.31
111.18
109.14
59.78
34.53
34.27
27.24
26.82
26.77
25.42
20.65
28
f1 (ppm)


52
1.08
0.96
1.93
1.07
0.98
1.00
2.07
1.06
2.07
2.27
2.13
1.02
2.08
2.51
2.55
f1 (ppm)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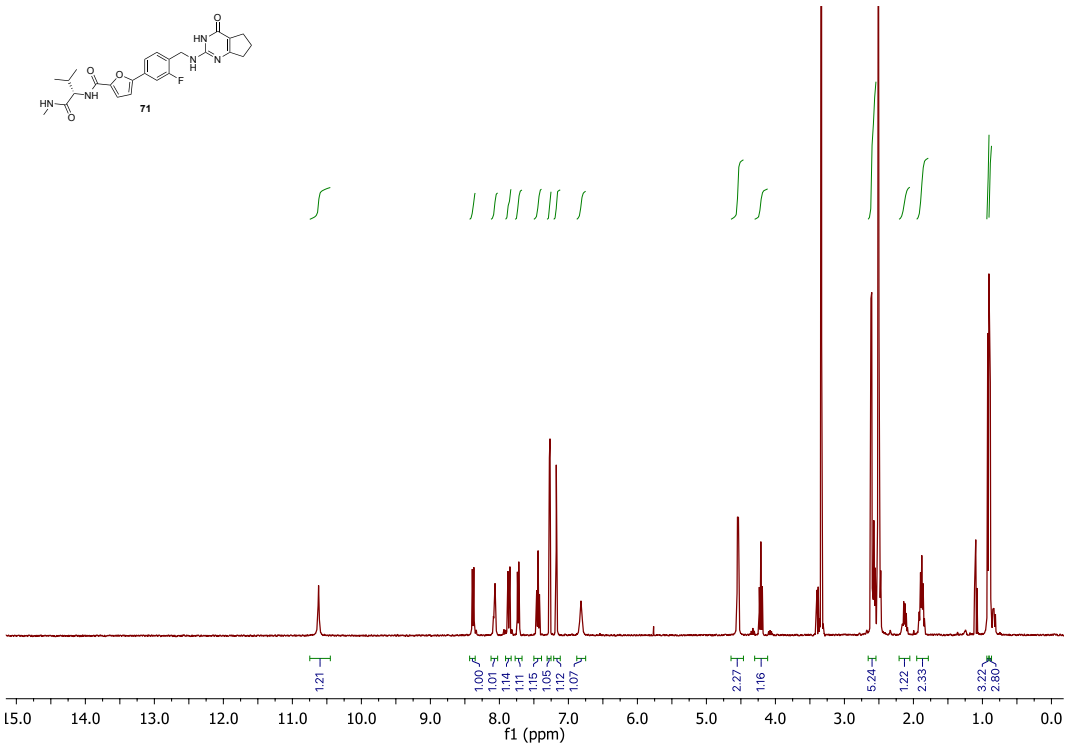
161.35
160.58
159.94
159.77
158.73
150.10
133.52
132.40
127.09
125.26
122.52
119.77
113.01
57.85
34.20
30.91
27.05
26.69
25.42
20.56
19.27
18.44
52
f1 (ppm)


71
1.21
1.00
1.01
1.14
1.11
1.15
1.05
1.12
1.07
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1.16
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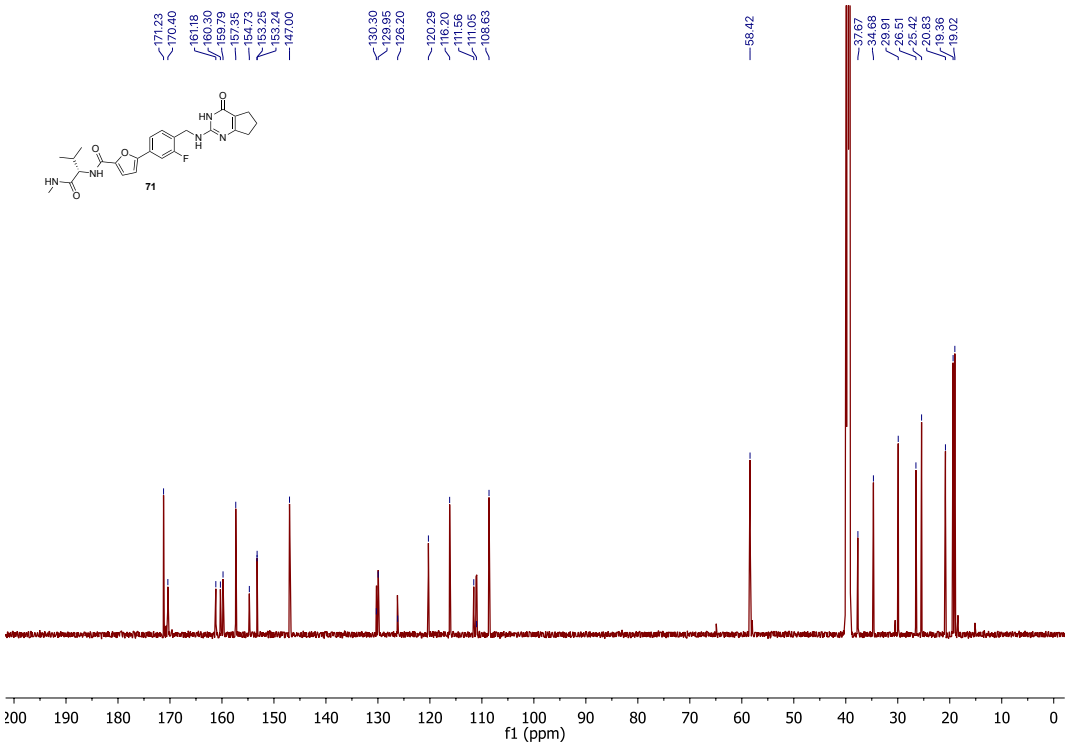
1.22
2.33
3.22
2.80
f1 (ppm)


171.23
170.40
161.18
160.30
159.79
157.35
154.73
154.25
153.24
147.00
130.30
129.95
128.20
120.29
116.20
111.56
111.05
108.63
58.42
37.67
34.68
29.91
26.51
25.42
20.83
19.36
19.02
71
f1 (ppm)

V. Docking studies

The X-ray crystallographic structure of MMP-13•(*S*)-**17a** (PDB ID: 5UWL) was refined with Protein Preparation Wizard implemented in Maestro 11.5. Briefly, the protein structure was imported into workspace and preprocessed to assign bond orders, add hydrogen atoms, create zero-order bonds to metals, create disulfide bonds, and to delete water molecules beyond 5 Å from hetero groups. In addition, missing atoms in residues were added using Prime to generate a complete protein structure, and only chain A was used for further refinement. The protein structure was refined via automated H-bond assignment and restrained minimization with OPLS 2005 force field by converging heavy atoms to 0.5 Å RMSD. The refined 3D structures of MMP-13 bound to each inhibitor were aligned and superimposed to analyze and compare binding poses of inhibitors.

Receptor grids for Glide dock were generated from the refined structures. The grid was set to a 20 $Å^3$ box centered on the bound ligand in MMP-13. Van der Waals radius was scaled by decreasing the default value of scaling factor to 0.8 to soften the potential for nonpolar parts of the receptor.
Ligand structures were obtained by converting SMILES to 3D molecular structures using KNIME, and prepared with LigPrep in Schrödinger program suite.
Ligand structures were docked into the active site (receptor grid) of MMP-13 by using Glide7.8 in extra precisions (XP) modes without any constraint. The binding poses of inhibitors in the MMP-13 active site were subsequently analyzed.

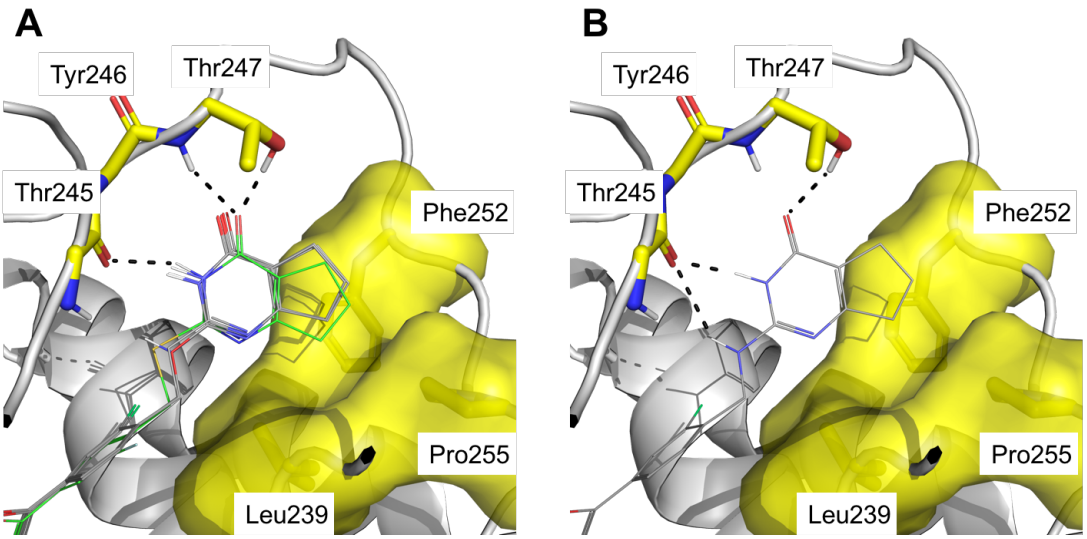


Fig S1. Predicted binding poses of **2**, **72**, **73**, and **74** in the active site of MMP-13. (A) Binding poses of inhibitors **2** (green), **72**, **73**, and **74** (gray) are presented in lines. (B) Binding poses of inhibitor **72** is presented in gray lines. Ligand-protein interactions are shown in black dashed lines. Hydrophobic area is presented as a yellow surface, and the amino acids near the inhibitors are in yellow sticks. Pymol was used to generate figures.

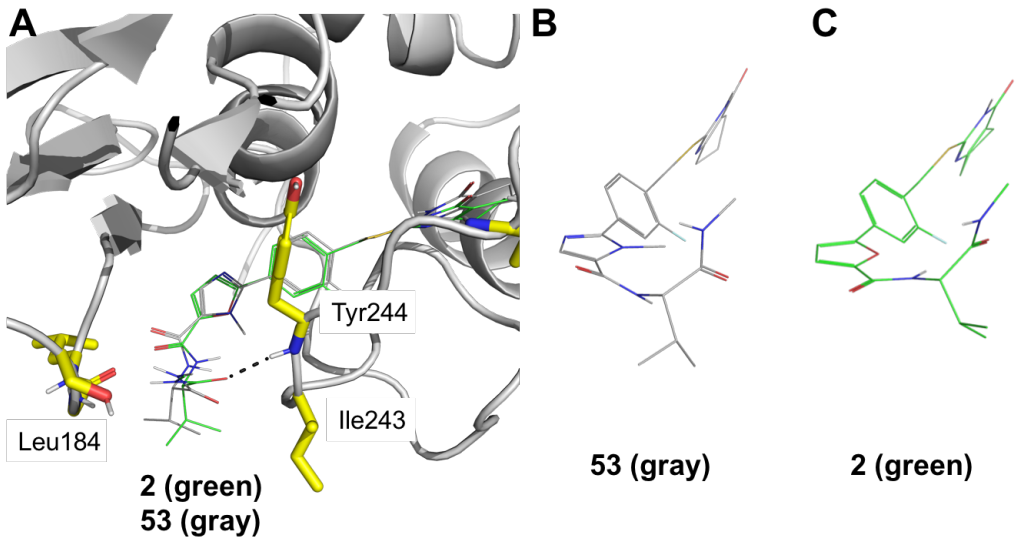


Fig S2. Predicted binding poses of **2** and **53** in the active site of MMP-13. (A) Binding poses of inhibitors **2** (green) and **53** (gray) are presented in lines. (B) The binding conformation of **53** in the active site of MMP-13 with the non-planar amide unit due to the N-methyl imidazole ring. (C) The binding conformation of **2** in the active site of MMP-13 with the planar amide unit bound to the furan ring. Ligand-protein interactions are shown in black dashed lines. Amino acids near inhibitors are in yellow sticks. Pymol was used to generate figures.

VI. References

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