Electronic supplementary information (ESI) for

An optimized and versatile synthesis to pyridinylimidazole-type p38α mitogen activated protein kinase inhibitors

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Contents:

General information and Instrumentation:

All reagents and solvents were of commercial quality and utilized without further purification.

The purity of all final compounds are > 95% as determined via reverse phase high performance liquid chromatography (HPLC) on a Hewlett Packard HP 1090 Series II LC equipped with a UV diode array detector (DAD, detection at 230 nm and 254 nm). The chromatographic separation was performed on a Phenomenex Luna 5u C8 column (150 mm x 4.6 mm, 5 μm) at 35 °C oven temperature. The injection volume was 5 μL and the flow 1.5 mL / min using the following gradient: 0.01 M KH_2PO_4, pH 2.30 (Solvent A), Methanol (Solvent B), 40% B to 85% B in 8 min; 85% B for 5 min; 85% to 40% B in 1 min; 40% B for 2 min; stop time 16 min.

TLC reaction controls were performed for all reactions using fluorescent silica gel 60 F_{254} plates (Merck) and visualized under natural light and UV illumination at 254 and 365 nm.

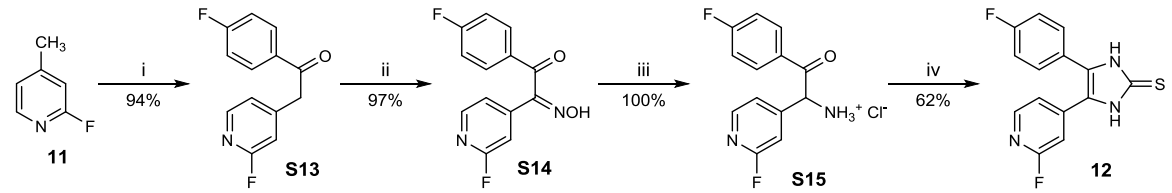
Column chromatography was performed on Davisil LC60A 20-45 micron silica from Grace Davison and Geduran Si60 63-200 micron silica from Merck for the pre-column using an Interchim PuriFlash 430 automated flash chromatography system.

NMR spectra were measured on a Bruker Avance NMR spectrometer at 250 MHz in the Organic Chemistry Institute, Eberhard Karls Universität Tübingen, Germany, on a Bruker Avance 200 NMR spectrometer or Bruker Avance 400 NMR spectrometer in Institute of Pharmaceutical Sciences, Eberhard Karls Universität Tübingen, Germany. Chemical shifts are reported in parts per million relative to TMS. All spectra were calibrated against the (residual proton) peak of the deuterated solvent that has been used. Mass spectra were obtained from the mass spectrometry department, Eberhard Karls Universität Tübingen, Germany.

The optical rotation data were obtained on a Perkin-Elmer polarimeter model 241 (589 nm).

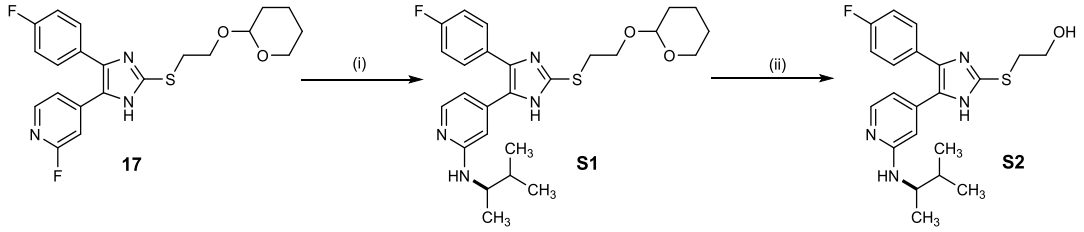
Schemes S1-S7:

Scheme S1: Synthesis of 4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**12**).



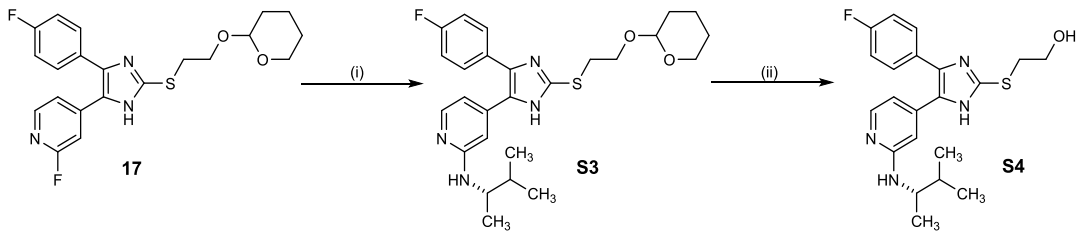
Reagents and conditions: (i) NaHMDS, ethyl 4-fluorobenzoate, THF, 0 °C – r.t.; (ii) $NaNO_2$, acetic acid, 10 °C – r.t.; (iii) Pd/C 10%, IsOH/HCl, H_2, atmospheric pressure, r.t.; (iv) KSCN, MeOH, reflux temperature, 1.5 h.

Scheme S2: Synthesis of (*R*)-2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (**S2**).



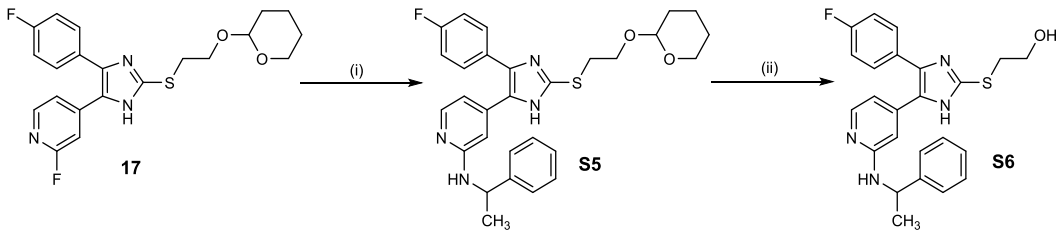
Reagents and conditions: (i) (*R*)-(-)-3-methyl-2-butylamine 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.

Scheme S3: Synthesis of (*S*)-2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (**S4**).



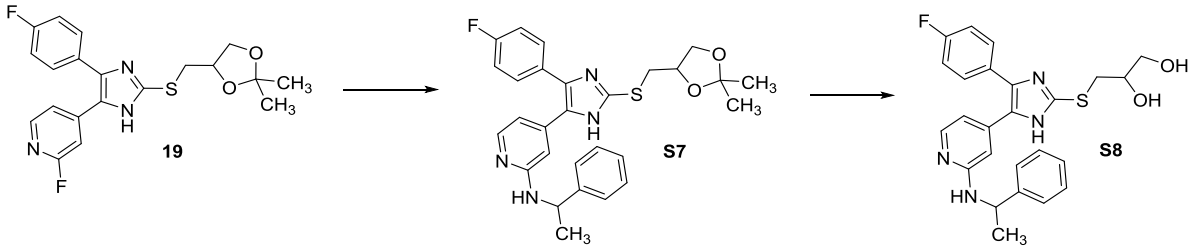
Reagents and conditions: (i) (*S*)-(+)-3-methyl-2-butylamine, 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.

Scheme S4: Synthesis of 2-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (**S6**).



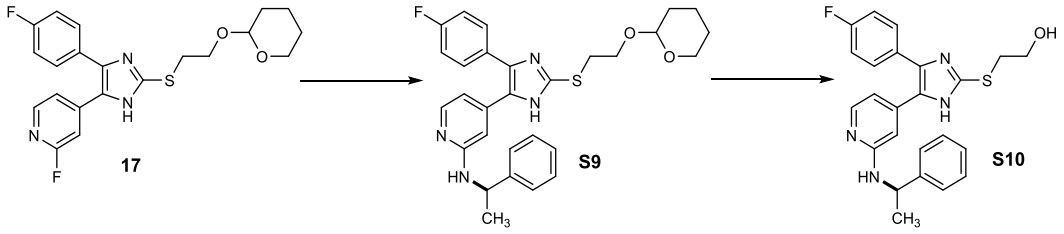
Reagents and conditions: (i) 1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.

Scheme S5: Synthesis of 3-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)propane-1,2-diol (**S8**).



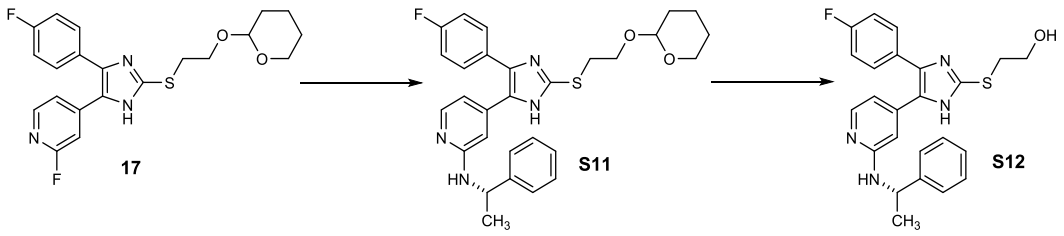
Reagents and conditions: (i) 1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.

Scheme S6: Synthesis of (*R*)-3-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)propane-1,2-diol (**S10**).



Reagents and conditions: (i) (*R*)-(+)-1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.

Scheme S7: Synthesis of (*S*)-3-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)propane-1,2-diol (**S12**).



Reagents and conditions: (i) (*S*)-(-)-1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.

General procedure for the introduction of an amino moiety at the pyridine C^2-position via nucleophilic aromatic substitution (General Procedure A)

The 2-fluoropyridinyl-containing compound and the corresponding amine were stirred in a 10 cm^3 pressure glass tube for 16 h at 160 °C. After cooling to r.t., the solvent was removed and the residue was purified by flash chromatography (SiO_2, dichloromethane-ethanol 95-5) to afford a light brown solid of the pure product.

General procedure for the cleavage of the THP-protecting group or the acetal protecting group (General Procedure B)

In a round flask the THP or acetal-protected alcohol (0.07 – 0.34 mmol) was dissolved in 4 mL of 1.25 M HCl/ethanol or 2 M aq. HCl. The reaction mixture was stirred for 3 h at r.t. The solvent was removed and the residue was purified by flash chromatography (SiO_2, dichloromethane-ethanol 99-1 to 9-1).

1-(4-Fluorophenyl)-2-(fluoropyridin-4-yl)ethanone (S13)

2-Fluoro-4-methylpyridine (4.40 g, 40 mmol) and ethyl 4-fluorobenzoate (6.73 g, 40 mmol) were treated with THF (10 ml) and cooled to 0 °C. NaHMDS (40.0 mL, 80 mmol, 2 M in THF) was added dropwise and the reaction mixture was stirred for 2 h at 0 °C and 1 h at r.t. Ethyl acetate followed by 10% aq. HCl were added. The organic layer was washed twice with 10% aq. HCl. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford 8.81 g (94%) of **S13** as a colorless solid.

Spectroscopic data were in agreement with those in the literature.[1,2]

1-(4-Fluorophenyl)-2-(fluoropyridin-4-yl)ethan-1,2-dion-2-oxime (S14)

A solution of ethanone **S13** (1.35 g, 5.8 mmol) in glacial acetic acid was cooled to 10 °C and a solution of $NaNO_2$ (1.21 g, 17.5 mmol) in water (7 mL) was added dropwise. The reaction was stirred for 30 min at 10 °C and warmed to r.t. while the product precipitates as a colorless solid. Water (80 mL) was added, the precipitate was filtered and dried in vacuo.

Yield: 1,47 g (97%), colorless solid

Spectroscopic data were in agreement with those in the literature.[1,2]

2-Amino-1-(4-fluorophenyl)-2-(4-fluoropyridin-4-yl)ethanone hydrochloride (S15)

In a three-necked flask oxime **S14** (2.01 g, 77 mmol) was dissolved in isopropanol (20 mL) and saturated isopropanolic hydrogen chloride (25 mL). Pd/C 10% (0.35 g) was added. The reaction flask was evacuated and flooded with hydrogen (4-times). The suspension was agitated at r.t. under hydrogen atmosphere at atmospheric pressure for 6 h. The catalyst was filtered off and washed thoroughly with methanol. The filtrate was concentrated in vacuo to yield 2.20 g (100%) of **S15** as a yellow solid.

Spectroscopic data were in agreement with those in the literature.[1,2]

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12)

α-Aminoketone **S15** (0.43 g, 1.5 mmol) was dissolved in methanol (15 mL) and potassium thiocyanate (0.30 g, 3.1 mmol) was added. The reaction mixture was heated to reflux temperature for 1.5 h. The suspension was cooled to room temperature. The formed yellow precipitate was filtered off and washed with ethanol and acetone.

Yield: 0.27 g (62%), yellow solid

Spectroscopic data were in agreement with those in the literature.[2]

2-((4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethyl acetate (16)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**12**) (1.07 g, 3.68 mmol) in DMF (30 mL) was placed in a round flask. Cs_2CO_3 (1.00 g, 3.07 mmol) was added followed by 2-bromoethylester (510 μL, 4.60 mmol) at 25 °C. The reaction mixture was further heated for 30 min at 55 °C. Water (10 ml) was added and the contents were extracted with ethyl acetate (3 x 15 mL). The combined organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2, hexane-ethyl acetate 6-4) to afford 1.0 g (71%) of a white solid product.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.97 (s, 3H, CH_3), 3.41 (t, J = 4.8 Hz, 2H, CH_2), 4.32 (t, J = 4.5 Hz, 2H, CH_2), 7.10 (s, 1H, C^3-H Pyr), 7.15 – 7.40 (m, 3H, C^5-H Pyr, C^3/C^5-H, 4-F-Phe), 7.45 – 7.60 (m, 2H, C^2/C^6-H, 4-F-Phe), 8.10 (s, 1H, C^6-H Pyr), 12.97 (br. s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 20.4 (CH_3), 31.1 (CH_2), 62.8 (CH_2), 104.7 (d, J = 40.5 Hz, C^3 Pyr), 115.8 (d, J = 25.1 Hz, C^3/C^5 4-F-Phe), 118.4 (C^5 Pyr), 126.2 (C^5 Imid.), 130.1 (C^1 4-F-Phe), 130.9 (d, J = 7.7 Hz, C^2/C^6 4-F-Phe), 131.3 (C^4 Imid.), 133.2 (C^2 Imid.), 140.8 (C^4 Pyr), 160.1 (d, J = 248.7 Hz, C^4 4-F-Phe), 162.43 (d, J = 235.0 Hz, C^2 Pyr), 170.0 (C=O).

EIMS, m/z ($C_{18}H_{15}F_2N_3O_2S$) calcd, 375.09 $[M]^+$; found, 375.1.

4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridine-4-yl)-1,3-dihydro-2*H*-imidazol-2-one (15)

Compound **16** (100 mg, 0.27 mmol) and 3-methylbutyl-2-amine (614 μL, 5.33 mmol) were stirred in a pressure glass tube for 10 h at 160 °C. After cooling to r.t. the solvent was removed and the residue was purified by flash chromatography (SiO_2, dichloromethane-ethanol 95-5) to afford 55 mg (61%) of a yellow solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ 0.81 (d, J = 5.1 Hz, 3H, CH_3), 0.84 (d, J = 5.4 Hz, 3H, CH_3), 0.98 (d, J = 6.6 Hz, 3H, CH_3), 1.64 – 1.79 (m, 1H, CH), 3.53 – 3.73 (m, 1H, CH), 6.22 (d, J = 8.5 Hz, 1H. NH), 6.29 (d, J = 5.4 Hz, 1H, C^5-H Pyr), 6.34 (s, 1H, C^3-H Pyr), 7.12 – 7.28 (m, 2H, C^3/C^5-H 4-F-Phe), 7.34 – 7.47 (m, 2H, C^2/C^6-H 4-F-Phe), 7.81 (d, J = 5.13 Hz, 1H, C^6-H Pyr), 10.56 (br. s, 1H, NH), 10.65 (br. s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 16.4 (CH_3), 17.8 (CH_3), 19.3 (CH_3), 31.9 (CH), 50.8 (CH), 104.2 (C^3 Pyr), 108.8 (C^5 Pyr), 115.5 (d, J = 20.0 Hz, C^3/C^5 4-F-Phe), 116.4 (C^3 Imid.), 119.1 (C^4 Imid.), 126.4 (d, J = 3.4 Hz, C^1 4-F-Phe), 129.8 (d, J = 10.0 Hz, C^2/C^6 4-F-Phe), 137.8 (C^4 Pyr), 147.8 (C^6 Pyr), 154.0 (C^2-Pyr), 158.9 (C=O), 160.4 (d, J = 243.1 C^4 4-F-Phe).

EIMS, m/z ($C_{19}H_{21}FN_4O$) calcd, 340.17 $[M]^+$; found, 340.3.

2-Fluoro-4-(4-(4-fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)pyridine (17)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**12**) (500 mg, 1.73 mmol) and sodium *tert*-butoxide (182 mg, 1.90 mmol) were suspended in MeOH abs. (10 mL). 2-(2-Bromethoxy)–tetrahydro-2*H*-pyran (314 μL, 2.07 mmol) was added. The reaction mixture was heated for 30 min at 50 °C. After cooling to r.t., the solvent was removed. Water (10 mL) was added and the contents were extracted with ethyl acetate (3 x 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated. The crude product was purified by flash chromatography (SiO_2, hexane-ethyl acetate 65-35) to afford 480 mg (67%) of a white solid product.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28 – 1.52 (m, 4H, 2 x CH_2), 1.53 – 1.77 (m, 2H, CH_2), 3.15 – 3.40 (m, 3H, CH_2 + C***H***H), 3.63 – 3.83 (m, 2H, CH_2), 3.86 – 3.99 (m, 1H, CH***H***), 4.62 (s,1H, CH), 7.09 (s, 1H, C^3-H Pyr), 7.14 – 7.40 (m, 3H, C^5-H Pyr, C^3/C^5 4-F-Phe), 7.41 – 7.62 (m, 2H, C^2/C^6-H 4-F-Phe), 8.07 (s, 1H, C^6-H Pyr), 12.91 (s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 18.9 (CH_2), 25.0 (CH_2), 30.1 (CH_2), 32.3 (CH_2), 61.3 (CH_2), 65.9 (CH_2), 97.8 (CH), 104.8 (d, J = 40.5 Hz, C^3 Pyr), 115.9 (d, J = 20.6 Hz, C^3/C^5 4-F-Phe), 118.5 (C^5 Imid.), 131.0 (C^4 Imid.), 141.6 (C^2 Imid.), 147.7 (C^4 Pyr), 161.0 (d, J = 243.0 Hz, C^4 4-Fe-Phe), 162.5 (d, J = 232.6, C^2 Pyr).

HPLC: t = 7.82 min, purity: 99% (λ = 254 nm), t = 7.82 min, purity: 95% (λ = 230 nm).

EIMS, m/z ($C_{21}H_{21}F_2N_3O_2S$) calcd, 417.13 $[M]^+$; found, 417.0.

4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(3-methylbutan-2-yl)pyridin-2-amine (18)

Compound **18** was prepared according to general procedure A starting from compound **17** (200 mg, 0.48 mmol) and 3-methylbutyl-2-amine (1.1 mL, 9.58 mmol).

Yield: 179 mg (77%) of a light brown solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ 0.83 (t, *J* = 6.1 Hz, 6H, 2 x CH_3), 0.99 (d, *J* = 6.6 Hz, 3H, CH_3), 1.28 – 1.49 (m, 4H, 2 x CH_2), 1.49 – 1.84 (m, 3H, CH_2 + CH), 3.24 – 3.38 (m, 3H, CH_2 + C*H*H), 3.59 – 3.76 (m, 3H, CH*H* +CH_2), 3.77 – 3.94 (m, 1H, CH), 4.60 (br. s, 1H, CH), 6.12 – 6.33 (m, 1H, NH), 6.37 (m, 1H, C^5-H Pyr), 6.65 (br. s, 1H, C^3-H Pyr), 7.04 – 7.36 (m, 2 H, C^3/C^5-H 4-F-Phe), 7.36 – 7.58 (m, 2H, C^2/C^6-H 4-F-Phe), 7.71 – 7.95 (m, 1H, C^6-H Pyr), 12.65 (br. s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 16.5 (CH_3), 17.8 (CH_3), 18.9 (CH_2), 19.2 (CH_3), 24.9 (CH_2), 30.1 (CH_2), 31.9 (CH), 32.4 (CH_2), 50.6 (CH), 61.2 (CH_2), 65.9 (CH_2), 97.8 (CH), 105.2 (C^3 Pyr), 109.2, 109.6 (C^5 Pyr), 114.9 (d, *J* = 26.9 Hz), 115.5 (d, *J* = 30.5 Hz, C^3/C^5 4-F-Phe), 126.7, 126.9 (C^5 Imid.), 129.2 (d, *J* = 8.15 Hz), 130.5 (d, *J* = 8.15 Hz, C^2/C^6 4-F-Phe), 131.1 (C^1 4-F-Phe), 135.4, 137.5 (C^4 Imid.), 140.2, 140.8, 142.3 (C^2 Imid.), 147.0, 147.9 (C^6 Pyr),158.8 (C^2 Pyr), 160.5 (d, *J* = 254.4 Hz, C^4 4-F-Phe).

^{13}C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 5.91 min, purity: 100% (λ = 254 nm), t = 5.91 min, purity: 98% (λ = 230 nm).

FABMS, m/z ($C_{26}H_{33}FN_4O_2S$) calcd, 485.23 $[M + H]^+$; found, 485.3.

2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (3)

Compound **3** was prepared according to general procedure B starting from compound **18** (74 mg, 0.15 mmol) using 1.25 M HCl/ethanol.

Yield: 61 mg (100%) of a light yellow solid.

Spectroscopic data were in agreement with those in the literature.[3]

HPLC: t = 5.13 min, purity: 100% (λ = 254 nm), t = 5.13 min, purity: 100% (λ = 230 nm).

4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-2-fluoropyridine (19)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**12**) (500 mg, 1.73 mmol) and sodium *tert*-butoxide (182 mg, 1.90 mmol) were suspended in MeOH abs. (10 mL). 3-Bromo-1,2-propanediol (181.5 μL, 2.07 mmol) was added. The reaction mixture was heated for 1 h at 70 °C, the solvent was removed. Water (10 mL) was added and the contents were extracted with ethyl acetate (3 x 10 ml). The combined organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated to form compound **13b** as a crude product which was used for the next step without any further purification. Compound **13b** was dissolved in acetone 50 mL and *p*-toluenesulfonic acid monohydrate (15.71 mg, 0.08 mmol) was added. The reaction mixture was refluxed 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2, dichloromethane-ethanol 95-5) to afford 400 mg (57%) of a white solid product.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.20 - 3.52 (m, 2H, CH_2), 3.65 - 3.85 (m, 1H, C***H***H), 4.00 - 4.12 (m, 1H, CH***H***), 4.32 - 4.43 (m, 1H, CH), 7.09 (s, 1H, C^3-H Pyr), 7.17 - 7.41 (m, 3H, C^5-H Pyr + C^3/C^5-H 4-F-Phe), 7.45 - 7.62 (m, 2H, C^2/C^6-H 4-F-Phe), 8.10 (s, 1H, C^6-H Pyr), 12.94 (s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 25.4 (CH_3), 26.7 (CH_3), 35.5 (CH_2), 54.8 ($C(CH_3)_2$), 67.7 (CH_2), 74.4 (CH), 104.9 (d, *J* = 40.4 Hz, C^3-Pyr), 108.8 (C^5 Imid.), 115.8 (d, *J* = 21.1 Hz, C^3/C^5 4-F-Phe), 118.5 (C^6 Pyr), 128.0 (C^1 4-F-Phe), 130.8 (d, *J* = 5.8 Hz, C^2/C^6 4-F-Phe), 133.0 (C^4 Imid.), 146.2 (C^4 Pyr), 147.6 (d, *J* = 13.9 Hz, C^5 Pyr), 160.9 (d, *J* = 249.4 Hz, C^4 4-F-Phe), 162.5 (d, *J* = 232.8 Hz, C^2 Pyr).

HPLC: t = 7.47 min, purity: 98% (λ = 254 nm), t = 7.47 min, purity: 98% (λ = 230 nm).

EIMS, m/z ($C_{20}H_{19}F2N_3O_2S$) calcd, 403.12 $[M]^+$; found, 403.1.

4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-(3-methylbutan-2-yl)pyridin-2-amine (20)

Compound **20** was prepared according to general procedure A starting from compound **19** (100 mg, 0.25 mmol) and 3-methylbutyl-2-amine (571 μL, 4.96 mmol).

Yield: 99 mg (85%) of a light brown oily product.

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.8 Hz, 6H, 2 x CH_3), 1.04 (d, *J* = 6.6 Hz, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.61 - 1.79 (m, 1H, CH), 3.24 (d, *J* = 5.6 Hz, 2H, CH_2), 3.38 (br. s, 1H, CH), 3.80 (dd, *J* = 8.5, 6.8 Hz, 1H, CH), 4.14 (dd, *J* = 8.5, 6.1 Hz, 1H, CH), 4.48 (q, *J* = 5.9 Hz, 1H, CH), 6.20 - 6.71 (m, 2H, C^3/C^5-H Pyr), 6.79 - 7.15 (m, 2H, C^3/C^5-H 4-F-Phe), 7.44 (br. s, 2H, C^2/C^6-H 4-F-Phe), 7.89 (br. s, 1H, C^6-H Pyr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8 (CH_3), 17.6 (CH_3), 18.7 (CH_3), 25.4 (CH_3), 26.7 (CH_3), 32.5 (CH), 36.7 (CH_2), 52.3 (CH), 57.9 ($C(CH_3)_2$), 68.3 (CH_2), 75.6 (CH), 103.8 (C^3 Pyr), 109.8 (C^5 Imid.), 110.5 (C^6 Pyr.), 115.4 (d, *J* = 21.7 Hz, C^3/C^5 4-F-Phe), 130.12 (d, *J* = 7.9 Hz, C^2/C^6 4-F-Phe), 140.9 (C^2 Imid.), 147.4 (C^4 Pyr), 158.4 (C^2 Pyr), 161.1 (d, *J* = 21.7 Hz, C^4 4-F-Phe).

HPLC: t = 6.87 min, purity: 99% (λ = 254 nm), t = 6.87 min, purity: 98% (λ = 230 nm).

FABMS, m/z ($C_{25}H_{31}FN_4O_2S$) calcd, 471.22 $[M + H]^+$; found, 471.3.

3-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)propane-1,2-diol (4)

Compound **4** was prepared according to general procedure B starting from compound **20** (90 mg, 0.19 mmol) using 2 M aq. HCl.

Yield: 60 mg (73%) of a colorless oily product.

Spectroscopic data were in agreement with those in the literature.[3]

HPLC: t = 5.06 min, purity: 97% (λ = 254 nm), t = 7.47 min, purity: 97% (λ = 230 nm).

(*R*)-4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(3-methylbutan-2-yl)pyridin-2-amine (S1)

Compound **S1** was prepared according to general procedure A starting from compound **17** (100 mg, 0.24 mmol) was followed using (*R*)-(-)-3-methylbutyl-2-amine (557 *µ*L, 4.79 mmol).

Yield: 65 mg (56%), as light brown solid product, which was directly used for the next step.

ESI-MS, m/z ($C_{26}H_{33}FN_4O_2S$) calcd, 485.23 $[M + H]^+$; found, 485.4.

(*R*)-2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (S2)

Compound **S2** was prepared according to general procedure B starting from compound **S1** (65 mg, 0.13 mmol).

Yield: 53 mg (99%), as light yellow solid product.

^{1}H NMR (200 MHz, CD_3OD): δ 0.89 (d, *J* = 6.6 Hz, 3H, CH_3), 0.91 (d, *J* = 6.6 Hz, 3H, CH_3), 1.06 (d, *J* = 6.6 Hz, 3H, CH_3), 1.64 - 1.80 (m, 1H, CH), 3.19 (t, *J* = 6.2 Hz, 2H, CH_2), 3.48 - 3.58 (m, 1H, CH), 3.81 (t, *J* = 6.3 Hz, 2H, CH_2), 6.50 - 6.53 (m, 2H, C^3/C^5-H Pyr), 7.09 - 7.18 (m, 2H, C^3/C^5-H 4-F-Phe), 7.43 - 7.50 (m, 2H, C^2/C^6-H 4-F-Phe), 7.80 (d, *J* = 5.4 Hz, 1H, C^6-H Pyr).

^{13}C NMR (50 MHz, CD_3OD): δ 17.4 (CH_3), 18.5 (CH_3), 19.7 (CH_3), 34.1 (CH), 37.9 (CH_2), 53.2 (CH), 62.8 (CH_2), 107.1 (C^3 Pyr), 111.4 (C^5 Pyr), 116.6 (d, *J* = 21.9 Hz, C^3/C^5 4-F-Phe), 131.9 (d, *J* = 8.1 Hz, C^2/C^6 4-F-Phe), 142.8 (C^4 Pyr), 148.3 (C^6 Pyr), 160.4 (C^2 Pyr), 161.8 (d, *J* = 245.2 Hz, C^4 4-F-Phe).

$[\alpha]_D^{20}$ = -23.4° (*c* 1.19 in MeOH).

HPLC: t = 5.2 min, purity: 100% (λ = 254 nm), t = 5.2 min, purity: 100% (λ = 230 nm).

ESIMS, m/z ($C_{21}H_{25}FN_4OS$) calcd, 401.17 $[M + H]^+$; found, 401.4.

(*S*)-4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(3-methylbutan-2-yl)pyridin-2-amine (S3)

Compound **S3** was prepared according to general procedure A starting from compound **17** (100 mg, 0.24 mmol) and (*S*)-(+)-3-methylbutyl-2-amine (670 *µ*L, 5.99 mmol).

Yield: 77 mg (66%), as light yellow solid product.

^{1}H NMR (250 MHz, DMSO-*d*$_6$): δ 0.84 (t, *J* = 5.86 Hz, 6H, 2 x CH_3), 0.93 - 1.06 (m, 3H, CH_3), 1.31 - 1.51 (m, 4H, 2 x CH_2), 1.52 - 1.83 (m, 3H, CH_2 + CH), 3.25 - 3.51 (m, 3H, CH_2 + CH), 3.58 - 3.99 (m, 4H, 2 x CH_2), 4.62 (br. s, 1H, CH_{THP}), 6.07 - 6.78 (m, 3H, NH + C^3/C^5-H Pyr), 7.04 - 7.35 (m, 2H, C^3/C^5-H 4-F-Phe), 7.38 - 7.60 (m, 2H, C^2/C^6-H 4-F-Phe), 7.69 - 7.98 (m, 1H, C^6-H Pyr), 12.62 (br. s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 16.5 (CH_3), 17.8 (CH_3), 18.9 (CH_2), 19.2 (CH_3), 24.9 (CH_2), 30.0 (CH_2), 31.9 (CH), 32.4 (CH_2), 50.5 (CH), 61.2 (CH_2), 65.9 (CH_2), 97.8 (CH), 105.1, 105.4 (C^3 Pyr), 109.2, 109.6 (C^5 Pyr), 114.9 (d, *J* = 21.14 Hz), 115.4 (d, *J* = 24.67 Hz, C^3/C^5 4-F-Phe), 126.7, 126.9 (C^5 Imid.), 129.2 (d, *J* = 10.57 Hz), 130.4 (d, *J* = 12.53 Hz, C^2/C^6 4-F-Phe), 135.4, 138.2 (C^4 Imid.), 140.1, 142.2 (C^2 Imid.), 147.2, 148.0 (C^6 Pyr), 158.9 (C^2 Pyr), 160.5 (d, *J* = 243.8 Hz, C^4 4-F-Phe).

^{13}C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 5.93 min, purity: 96% (λ = 254 nm), t = 5.93 min, purity: 95% (λ = 230 nm).

ESIMS, m/z ($C_{26}H_{33}FN_4O_2S$) calcd, 485.23 $[M + H]^+$; found, 485.4.

(*S*)-2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (S4)

Compound **S4** was prepared according to general procedure B starting from compound **S3** (36 mg, 0.07 mmol).

Yield: 29 mg (97%), as light yellow solid product.

^{1}H NMR (200 MHz, CD_3OD): δ 0.90 (d, *J* = 6.6 Hz, 3H, CH_3), 0.91 (d, *J* = 6.7 Hz, 3H, CH_3), 1.07 (d, *J* = 6.6 Hz, 3H, CH_3), 1.64 - 1.82 (m, 1H, CH), 3.19 (t, *J* = 6.3 Hz, 2H, CH_2), 3.48 - 3.57 (m, 1H, CH), 3.81 (t, *J* = 6.2 Hz, 2H, CH_2), 6.52 - 6.56 (m, 2H, C^3/C^5-H Pyr), 7.10 - 7.19 (m, 2H, C^3/C^5-H 4-F-Phe), 7.43 - 7.50 (m, 2H, C^2/ C^6-H 4-F-Phe), 7.79 (d, *J* = 5.6 Hz, 1H, C^6-H Pyr).

^{13}C NMR (50 MHz, CD_3OD): δ 17.4 (CH_3), 18.5 (CH_3), 19.7 (CH_3), 34.1 (CH), 37.8 (CH_2), 53.3 (CH), 62.8 (CH_2), 107.2 (C^3 Pyr), 111.4 (C^5 Pyr), 116.6 (d, *J* = 21.8 Hz, C^3/C^5 4-F-Phe), 131.9 (d, *J* = 8.2 Hz, C^2/C^6 4-F-Phe), 142.9 (C^4 Pyr), 147.6 (C^6 Pyr), 160.0 (C^2 Pyr), 161.8 (d, *J* = 245.1 Hz, C^4 4-F-Phe).

$[\alpha]_D^{20}$ = +23.9° (*c* 1.22 in MeOH).

HPLC: t = 5.20 min, purity: 100% (λ = 254 nm), t = 5.20 min, purity: 100% (λ = 230 nm).

ESIMS, m/z ($C_{21}H_{25}FN_4OS$) calcd, 401.17 $[M + H]^+$; found, 401.4.

4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(1-phenylethyl)pyridin-2-amine (S5)

Compound **S5** was prepared according to general procedure A starting from compound **17** (200 mg, 0.48 mmol) and 1-phenyl-ethylamine (1.22 mL, 9.58 mmol).

Yield: 100 mg (40%) of a light yellow solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ 1.29 - 1.51 (m, 7H, CH_3 + 2 x CH_2), 1.51 - 1.77 (m, 2H, CH_2), 3.22 - 3.35 (m, 2H, CH_2), 3.59 - 3.97 (m, 4H, 2 x CH_2), 4.61 (br. s, 1H, CH), 4.80 - 5.02 (m, 1H, CH), 6.41 - 6.44 (m, 1H, NH), 6.45 - 6.73 (m, 1H, C^3-H Pyr), 6.86 - 7.08 (m, 1H, C^5-H Pyr), 7.08 - 7.20 (m, 2H, C^3/C^5-H, 4-F-Phe), 7.20 - 7.34 (m, 5H, C^2/C^6-H Phe), 7.34 - 7.57 (m, 2H, C^2/C^6-H 4-F-Phe), 7.68 - 7.95 (m, 1H, C^6-H Pyr), 12.62 (br. s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 18.9 (CH_2), 23.6, 23.7 (CH_3), 24.9 (CH_2), 30.1 (CH_2), 32.4, 32.4 (CH_2), 49.8 (CH), 61.2 (CH_2), 65.9 (CH_2), 97.8 (CH), 105.1, 105.5 (C^3 Pyr), 109.8, 110.2 (C^8 Pyr), 115.0 (d, *J* = 23.7 Hz), 115.5 (d, *J* = 28.9 Hz, C^3/C^5 4-F-Phe), 125.9 (C^4 Phe), 126.2, 126.3 (C^2/C^6 Phe), 126.6, 126.9 (C^5 Imid.), 128.0, 128.1 (C^3/C^5 Phe), 129.1 (d, *J* = 8.5 Hz), 130.5 (d, *J* = 8.2 Hz) (C^2/C^6 4-F-Phe), 131.0 (d, *J* = 4.1 Hz, C^3/C^5 4-F-Phe), 135.2, 137.6 (C^4 Imid.), 138.3, 140.3 (C^4 Pyr), 141.0, 142.3 (C^2 Imid.), 145.9, 146.2 (C^1 Phe), 147.2, 148.1, 158.4 (C^2 Pyr), 160.0 (d, *J* = 248.6 Hz), 160.6 (d, *J* = 246.3 Hz, C^4 4-F-Phe).

^{13}C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 7.83 min, purity: 99% (λ = 254 nm), t = 7.83 min, purity: 99% (λ = 230 nm).

FABMS, m/z ($C_{29}H_{31}FN_4O_2S$) calcd, 519.22 $[M + H]^+$; found, 519.3.

2-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (S6)

Compound **S6** was prepared according to general procedure B starting from compound **S5** (50 mg, 0.1 mmol).

Yield: 41 mg (98%) of a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, 3H, *J* = 4.5 Hz, CH_3), 1.90 - 2.00 (m, 1H, OH), 3.04 (br. s, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.34 (s, 1H, CH), 6.44 (s, 1H, NH), 6.58 (d, *J* = 4.5 Hz, 1H, C^3-H Pyr), 6.67 - 6.95 (m, 3H, C^5-H Pyr + C^3/C^5-H 4-F-Phe), 6.97 - 714 (m, 5H, C^2/C^6-H Phe), 7.15 - 7.35 (m, 2H, C^2/C^6-H 4-F-Phe), 7.54 (d, *J* = 3.6 Hz, 1H, C^6-H Pyr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1 (CH_3), 36.5 (CH_2), 52.4 (CH), 63.0 (CH_2), 104.5 (C^3 Pyr), 110.6 (C^5 Pyr), 115.8 (d, *J* = 22.2 Hz, C^3/C^5 4-F-Phe), 125.6 (C^2/C^6 Phe), 127.1 (C^5 Imid.), 127.3 (C^4 Phe), 128.7 (C^3/C^5 Phe), 130.3 (d, *J* = 11.1 Hz, C^2/C^6 4-F-Phe), 135.1 (C^4 Imid.), 142.1 (C^6 Pyr), 143.1 (d, *J* = 9.4 Hz, C^1 4-F-Phe), 144.5 (C^4 Pyr), 145.3 (C^1 Phe), 155.7 (C^2 Imid.), 161.5 (d, *J* = 249.0 Hz, C^4 4-F-Phe), 171.2 (C^3 Pyr).

ESIMS, m/z ($C_{24}H_{23}FN_4OS$) calcd, 435.16 $[M + H]^+$; found, 435.4.

HPLC: t = 5.45 min, purity: 98% (λ = 254 nm), t = 5.45 min, purity: 95% (λ = 230 nm).

4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-(1-phenylethyl)pyridin-2-amine (S7)

Compound **S7** was prepared according to general procedure A starting from compound **19** (100 mg, 0.25 mmol) and 1-phenyl-ethylamine (631.5 μL, 4.96 mmol).

Yield: 88 mg (70%) of a light yellow solid

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (s, 3H, CH_3), 1.30 - 1.47 (m, 6H, 2 x CH_3), 3.17 - 3.40 (m, 2H, CH_2), 3.65 - 3.82 (m, 1H, CH), 3.97 - 4.14 (m, 1H, C***H***H), 4.26 - 4.44 (m, 1H, CH***H***), 4.92 (br. s, 1H, CH), 6.43 (br. s, 1H, NH), 6.48 - 6.71 (m, 1H, C^3-H Pyr), 6.90 - 7.09 (m, 1H, C^5-H Pyr), 7.12 - 7.20 (m, 2H, C^3/C^5-H 4-F-Phe), 7.21 - 7.36 (m, 5H, C^2-C^6-H, Phe), 7.38 - 7.57 (m, 2H, C^2/C^6-H 4-F-Phe), 7.67-7.95 (m, 1H, C^6-H Pyr), 12.68 (s, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 23.5, 23.6 (CH_3), 25.4 (CH_3), 26.7 (CH_3), 35.7 (CH_2), 49.8 (CH), 56.0 ($C(CH_3)_2$), 67.7 (CH_2), 74.5 (CH), 105.1, 105.5 (C^3 Pyr), 108.7 (C^5 Imid.), 109.8, 110.2 (C^5 Pyr), 115.0 (d, *J* = 21.7 Hz), 115.5 (d, *J* = 22.3 Hz, C^3/C^5 4-F-Phe), 125.9 (C^2/C^6 Phe), 126.1, 126.2 (C^4 Phe), 126.4 (d, *J* = 12.1 Hz), 126.69 (d, *J* = 13.4 Hz, C^1 4-F-Phe), 128.0 (C^3/C^5 Phe), 129.3 (d, *J* = 9.6 Hz), 130.6 (d, *J* = 7.6 Hz, C^2/C^6 4-F-Phe), 135.3, 137.7 (C^4 Imid.), 138.3, 139.9 (C^4 Pyr), 140.6, 142.2 (C^2 Imid.), 145.0 (d, *J* = 19.4 Hz), 147.3, 148.0 (C^6 Pyr), 158.4 (C^2 Pyr), 160.0 (d, *J* = 246.5 Hz), 160.6 (d, *J* = 245.3 Hz, C^4 4-F-Phe).

^{13}C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 7.44 min, purity: 99% (λ = 254 nm), t = 7.44 min, purity: 99% (λ = 230 nm).

FABMS, m/z ($C_{28}H_{29}FN_4O_2S$) calcd, 505.2 $[M + H]^+$; found, 505.3.

3-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)propane-1,2-diol (S8)

Compound **S8** was prepared according to general procedure B starting from compound **S7** (61 mg, 0.12 mmol) using 2 M aq HCl.

Yield: 40 mg (71%) of a light yellow solid.

Spectroscopic data were in agreement with those in the literature.[3]

HPLC: t = 4.51 min, purity: 97% (λ = 254 nm), t = 4.51 min, purity: 97% (λ = 230 nm).

(*R*)-4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(1-phenylethyl)pyridin-2-amine (S9)

Compound **S9** was prepared according to general procedure A starting from compound **17** (157 mg, 0.12 mmol) and (*R*)-(+)-1-phenyl-ethylamine (967 *μ*L, 7.52 mmol).

Yield: 133 mg (68%), white semisolid of **S9** which will use for the next step.

ESIMS, m/z ($C_{29}H_{31}FN_4O_2S$) calcd, 519.22 $[M + H]^+$; found, 519.5.

(*R*)-2-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (S10)

Compound **S10** was prepared according to general procedure B starting from compound **S9** (133 mg, 0.26 mmol) 2 M aq. HCl.

Yield: 90 mg (81%) as a white solid product.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (d, J = 6.57 Hz, 3H, CH_3), 3.19 (t, J = 6.32 Hz, 2H, CH_2), 3.67 (t, J = 6.06 Hz, 2H, CH_2), 4.90 (br. s, 1H, CH), 5.09 (br. s, 1H, OH), 6.41 (d, J = 4.80 Hz, 1H, NH), 6.67 (br. s, 1H, C^3-H Pyr), 6.87 - 7.06 (m, 1H, C^5-H Pyr), 7.07 - 7.18 (m, 2H, C^3/C^5-H 4-F-Phe), 7.19 - 7.34 (m, 5H, Phe), 7.36 - 7.54 (m, 2H, C^2/C^6-H Pyr), 7.64 - 7.96 (m, 1H, C^6-H Pyr), 12.62 (br. s, 1H, NH).

HPLC: t = 4.51 min, purity: 95% (λ = 254 nm), t = 4.50 min, purity: 95% (λ = 230 nm).

ESIMS, m/z ($C_{24}H_{23}FN_4OS$) calcd, 435.16 $[M + H]^+$; found, 435.4.

$[\alpha]_D^{20}$ = +41.6° (*c* 0.72 in MeOH).

(*S*)-4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(1-phenylethyl)pyridin-2-amine (S11)

Compound **S11** was prepared according to general procedure A starting from compound **17** (200 mg, 0.48 mmol) and (*S*)-(-)1-phenyl-ethylamine (1.2 mL, 9.58 mmol).

Yield: 175 mg (70%) white semisolid product which will used for the next step.

ESIMS, m/z ($C_{29}H_{31}FN_4O_2S$) calcd, 519.22 $[M + H]^+$; found, 519.4.

(*S*)-2-((4-(4-Fluorophenyl)-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (S12)

Compound **S12** was prepared according to general procedure B starting from compound **S11** (175 mg, 0.34 mmol) using 2 M aq. HCl.

Yield: 94 mg (64%) as a white solid product.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (d, J = 6.32 Hz, 3 H, CH_3), 3.20 (t, J = 6.06 Hz, 2H, CH_2), 3.69 (t, J = 5.94 Hz, 2H, CH_2), 4.91 (br. s, 1H, CH), 5.10 (br. s, 1H, OH), 6.42 (d, J = 4.80 Hz, 1H, NH), 6.62 (br. s, 1H, C^3-H Pyr), 6.99 (br. s, 1H, C^5-H Pyr), 7.08 - 7.18 (m, 2H, C^3/C^5-H 4-F-Phe), 7.20 - 7.36 (m, 5 H, C^2-C^6-H, Phe), 7.37 - 7.61 (m, 2H, C^2/C^6-H 4-F-Phe), 7.81 (br. s, 1H, C^6-H Pyr), 12.61 (br. s, 1H, NH).

HPLC: t = 4.49 min, purity: 100% (λ = 254 nm), t = 4.49 min, purity: 99% (λ = 230 nm).

ESIMS, m/z ($C_{24}H_{23}FN_4OS$) calcd, 435.16 $[M + H]^+$; found, 435.4.

$[\alpha]_D^{20}$ = -53.8° (*c* 0.75 in MeOH).

Scale-up: synthesis of 2.3 g of inhibitor 3

2-Fluoro-4-(4-(4-fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)pyridine (17)

In a 50 mL pressure tube, 4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (**12**) (3.2 g, 11.13 mmol) and sodium *tert*-butoxide (1.2 g, 12.24 mmol) were suspended in MeOH abs. (40 mL). 2-(2-Bromethoxy)–tetrahydro-2*H*-pyran (2.02 mL, 13.36 mmol) was added. The reaction mixture was heated for 1 h at 70 °C. After cooling to r.t., the solvent was removed. Water (20 mL) was added and the contents were extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated. The crude product was purified by flash chromatography (SiO_2, hexane-ethyl acetate 65-35) to afford 3.2 g (69%) of a white solid product.

HPLC: t = 7.87 min, purity: 98% (λ = 254 nm), t = 7.87 min, purity: 100% (λ = 230 nm).

ESI-MS, m/z ($C_{21}H_{21}F_2N_3O_2S$) calcd, 440.46 $[M+Na]^+$; found, 440.4.

4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)thio)-1*H*-imidazol-5-yl)-*N*-(3-methylbutan-2-yl)-pyridin-2-amine (18)

Compound **18** was prepared according to general procedure A starting from compound **17** (3.2 g, 7.67 mmol) and 3-methylbutyl-2-amine (17.7 mL, 153.3 mmol). The reaction was heated in a 40 mL pressure tube for 5 d at 180 °C.

Yield: 3.0 g (80%) of a light brown solid.

HPLC: t = 5.88 min, purity: 94% (λ = 254 nm), t = 5.8 min, purity: 84% (λ = 230 nm).

ESI-MS, m/z ($C_{26}H_{33}FN_4O_2S$) calcd, 485.64 $[M + H]^+$; found, 485.7.

2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)ethan-1-ol (3)

In 100 mL round flask, Compound **3** was prepared according to general procedure B starting from compound **18** (3.0 g, 6.13 mmol) using 1.25 M HCl/ethanol (40 mL).

Yield: 2.3 g (94%) of a light yellow solid.

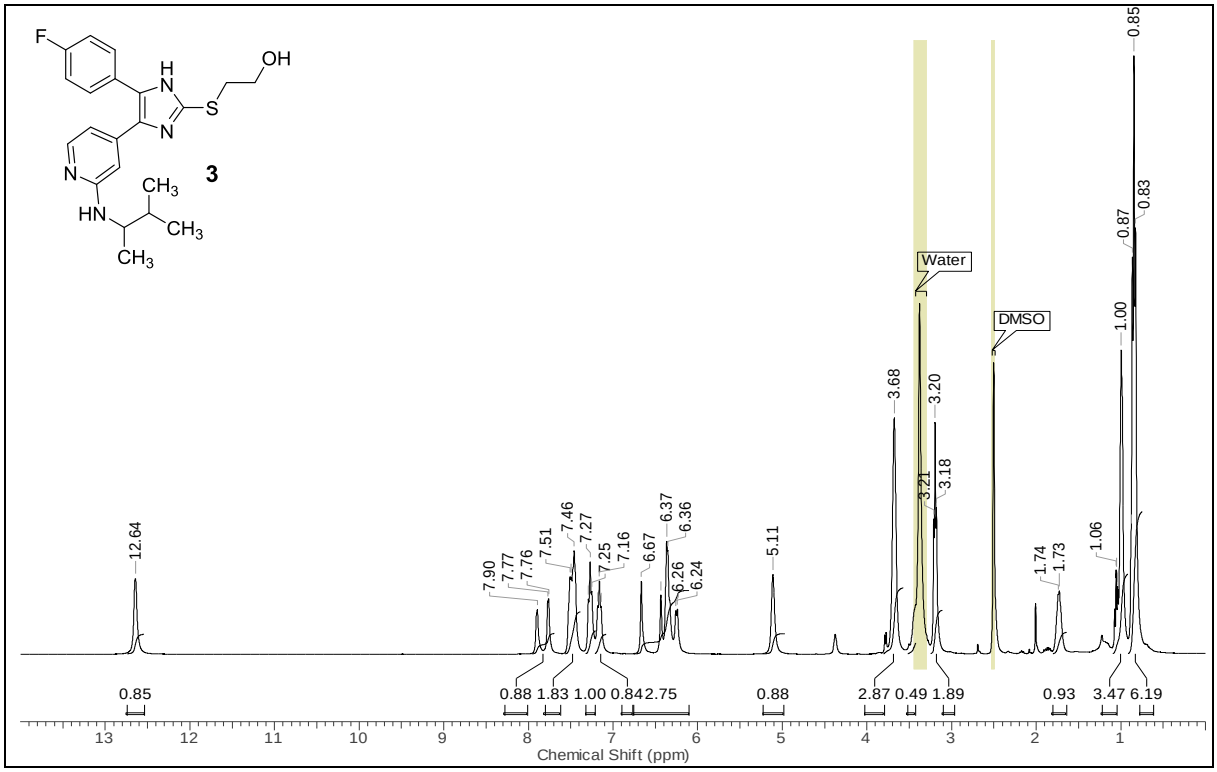
HPLC: t = 4.27 min, purity: 100% (λ = 254 nm), t = 4.27 min, purity: 99% (λ = 230 nm).

ESI-MS, m/z ($C_{21}H_{25}FN_4OS$) calcd, 401.5 $[M + H]^+$; found, 401.6.

References

1. S. A. Laufer and A. J. Liedtke, *Tetrahedron Lett.*, 2006, **47**, 7199-7203.
2. S. A. Laufer, G. K. Wagner, D. A. Kotschenreuther and W. Albrecht, *J. Med. Chem.*, 2003, **46**, 3230-3244.
3. P. Koch, C. Bäuerlein, H. Jank and S. Laufer, *J. Med. Chem.* 2008, **51**, 5630-5640.

NMR spectra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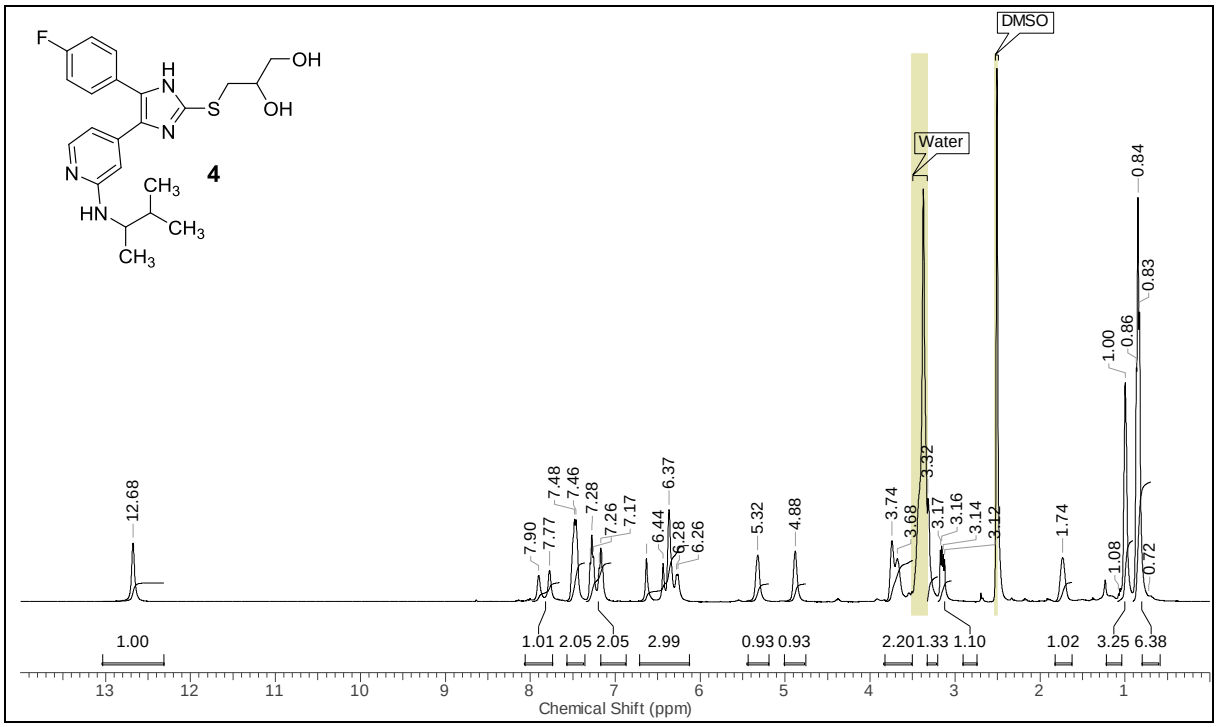
H
N
OH
S
N
N
3
CH3
HN
CH3
CH3
Water
DMSO
0.85
0.83
0.87
1.00
3.68
3.20
3.21
3.18
12.64
7.90
7.77
7.76
7.51
7.46
7.27
7.25
7.16
6.67
6.37
6.36
6.26
6.24
5.11
1.74
1.73
1.06
0.85
0.88 1.83 1.00 0.84 2.75
0.88
2.87 0.49 1.89
0.93
3.47 6.19
13 12 11 10 9 8 7 6 5 4 3 2 1
Chemical Shift (ppm)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N
OH
S
OH
N
N
4
CH3
HN
CH3
CH3
DMSO
Water
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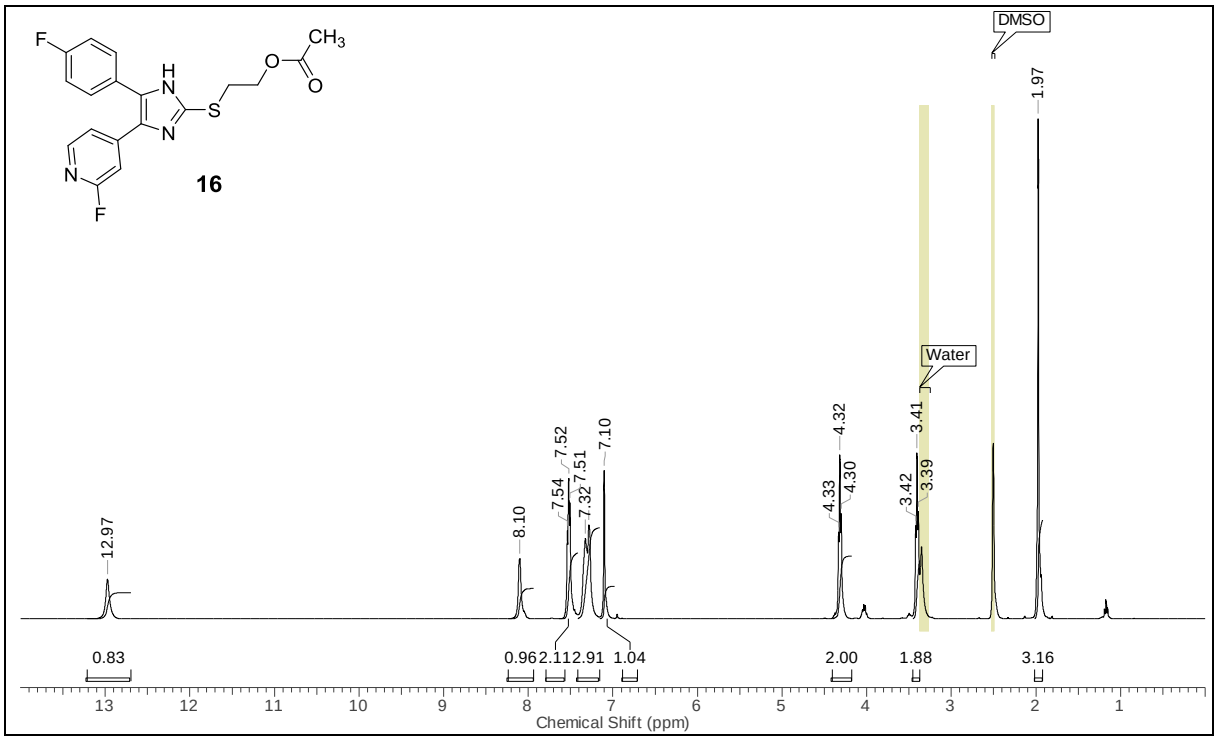
0.86
1.00
12.68
7.90
7.77
7.48
7.46
7.28
7.26
7.17
6.44
6.37
6.28
6.26
5.32
4.88
3.74
3.68
3.32
3.17
3.16
3.14
3.12
1.74
1.08
0.72
1.00
1.01 2.05 2.05 2.99
0.93 0.93
2.20 1.33 1.10
1.02
3.25 6.38
13 12 11 10 9 8 7 6 5 4 3 2 1
Chemical Shift (ppm)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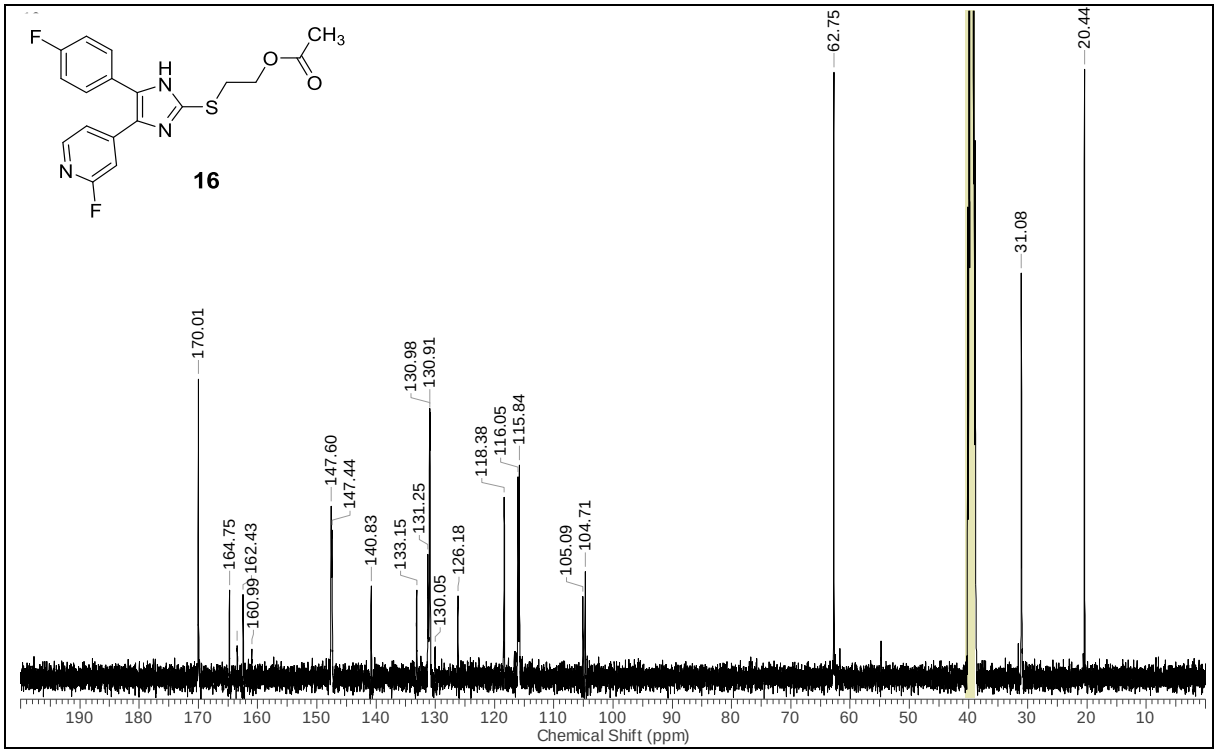
DMSO
Water
12.97
8.10
7.54
7.52
7.51
7.32
7.10
4.33
4.32
4.30
3.42
3.41
3.39
1.97
0.83
0.96
2.11
2.91
1.04
2.00
1.88
3.16
Chemical Shift (ppm)


16
170.01
164.75
162.43
160.99
147.60
147.44
140.83
133.15
131.25
130.98
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130.05
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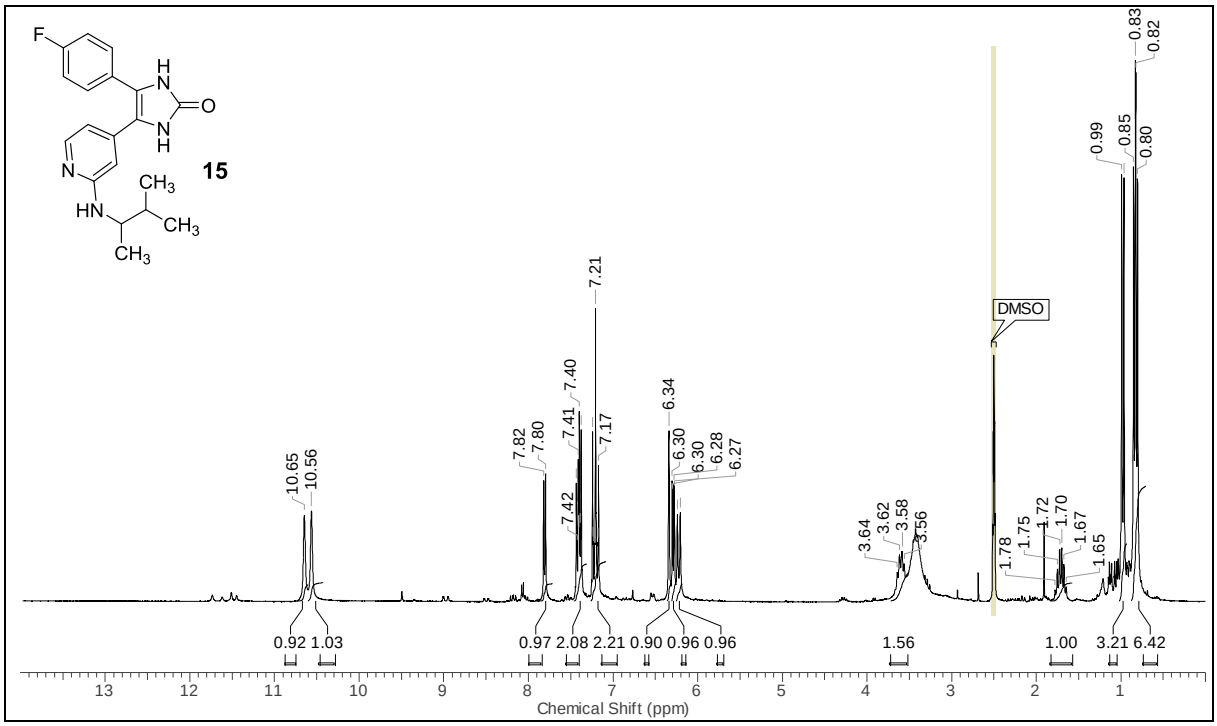
115.84
105.09
104.71
62.75
31.08
20.44
Chemical Shift (ppm)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DMSO
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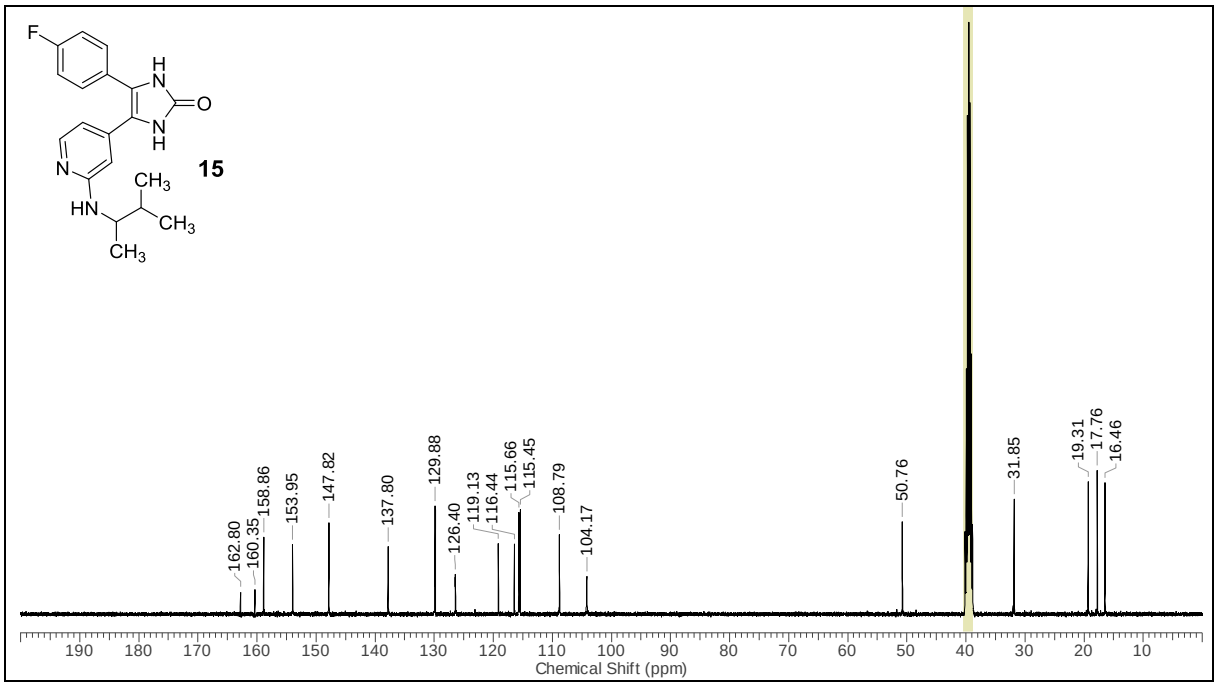
0.97 2.08 2.21 0.90 0.96 0.96
1.56
1.00
3.21 6.42
Chemical Shift (ppm)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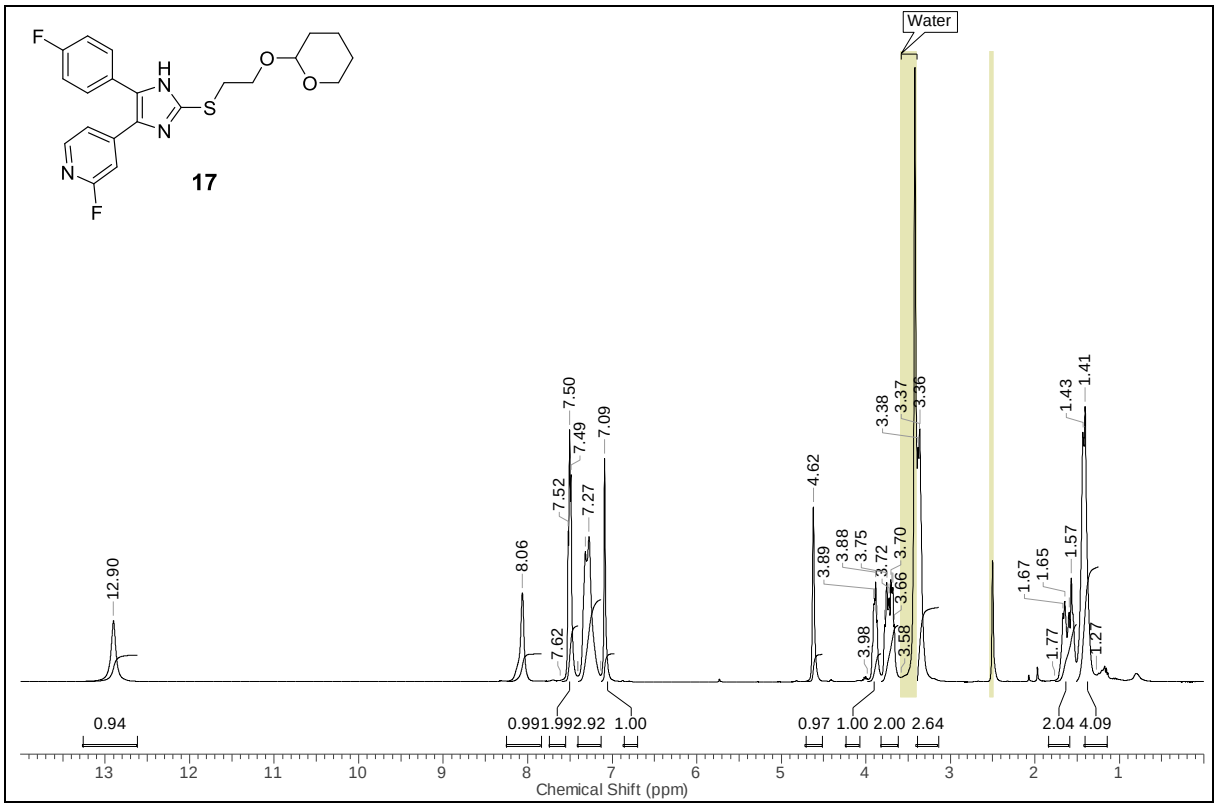
Chemical Shift (ppm)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Water
12.90
8.06
7.62
7.52
7.50
7.49
7.27
7.09
4.62
3.98
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3.88
3.75
3.72
3.70
3.66
3.58
3.38
3.37
3.36
1.77
1.67
1.65
1.57
1.43
1.41
1.27
0.94
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2.92
1.00
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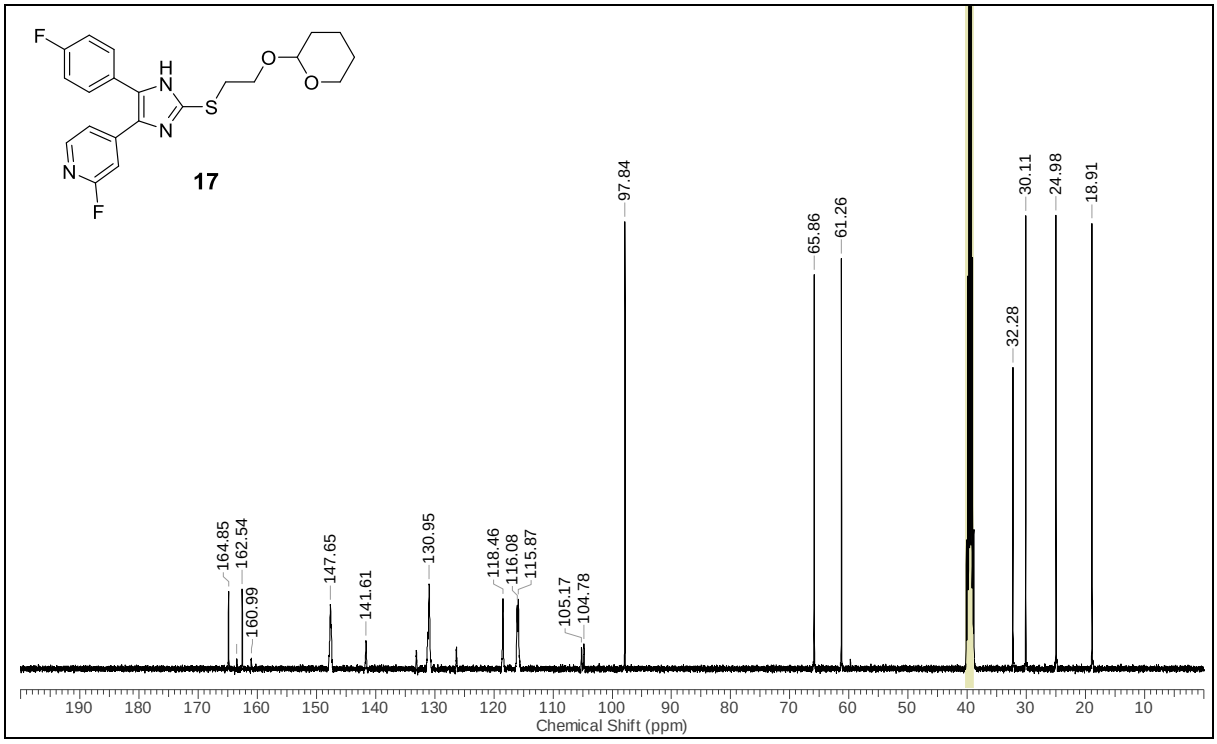
1.00
2.00
2.64
2.04
4.09
Chemical Shift (ppm)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118.46
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97.84
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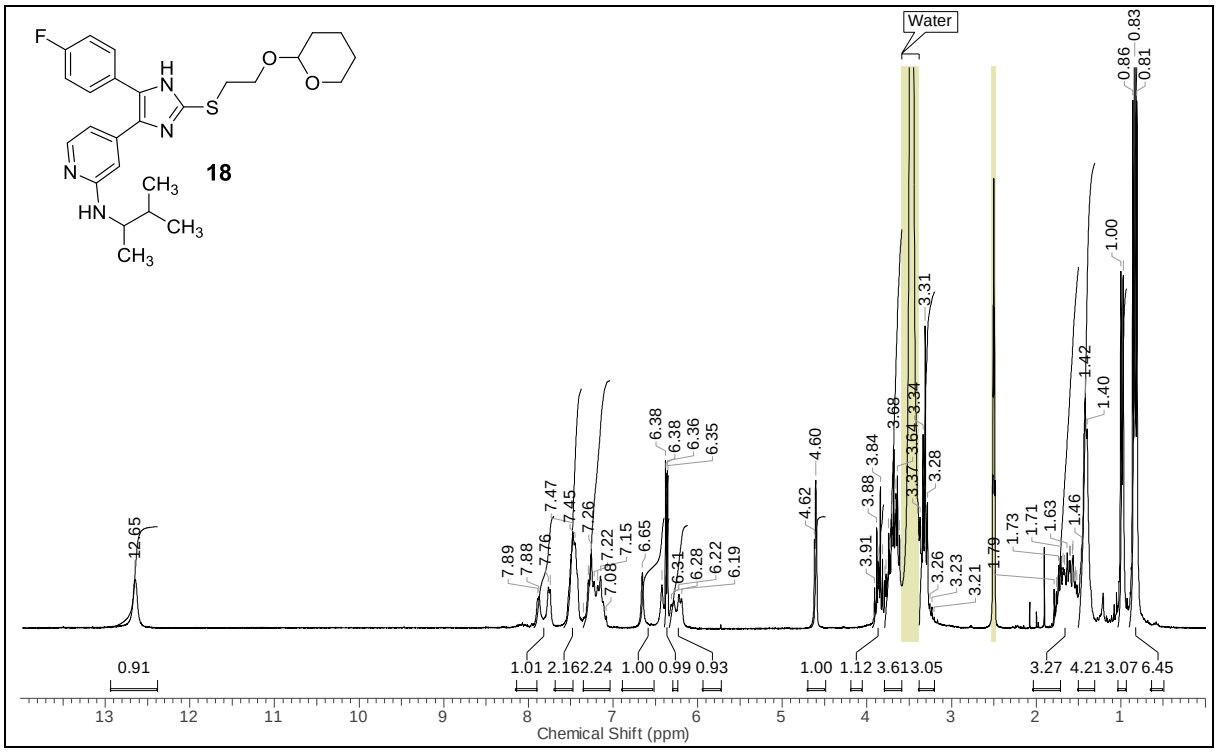
30.11
24.98
18.91
Chemical Shift (ppm)


18
Water
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7.89
7.88
7.76
7.47
7.45
7.26
7.22
7.15
7.08
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6.38
6.38
6.36
6.35
6.31
6.28
6.22
6.19
4.62
4.60
3.91
3.88
3.84
3.68
3.37
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3.31
3.28
3.26
3.23
3.21
1.79
1.73
1.71
1.63
1.46
1.42
1.40
1.00
0.86
0.83
0.81
0.91
1.01
2.16
2.24
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1.00
1.12
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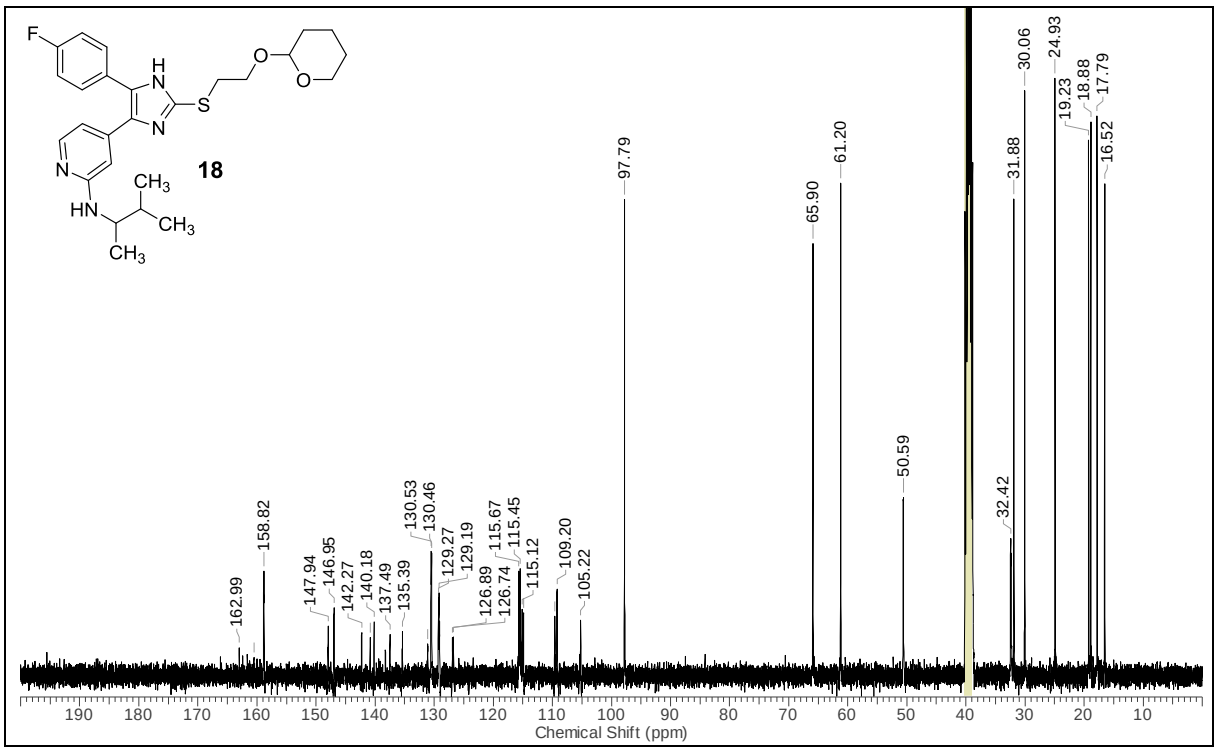
3.05
3.27
4.21
3.07
6.45
Chemical Shift (ppm)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130.53
130.46
129.27
129.19
126.89
126.74
115.67
115.45
115.12
109.20
105.22
97.79
65.90
61.20
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32.42
31.88
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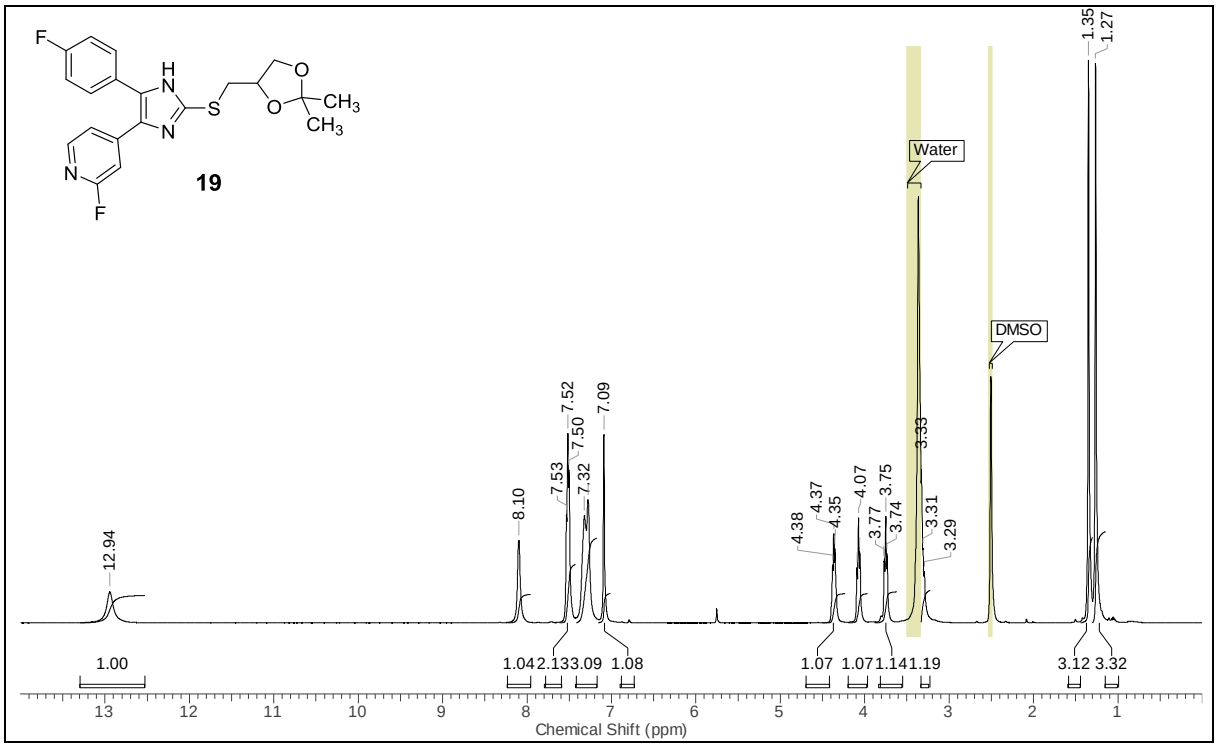
24.93
19.23
18.88
17.79
16.52
Chemical Shift (ppm)


19
Water
DMSO
1.35
1.27
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8.10
7.53
7.52
7.50
7.32
7.09
4.38
4.37
4.35
4.07
3.77
3.75
3.74
3.33
3.31
3.29
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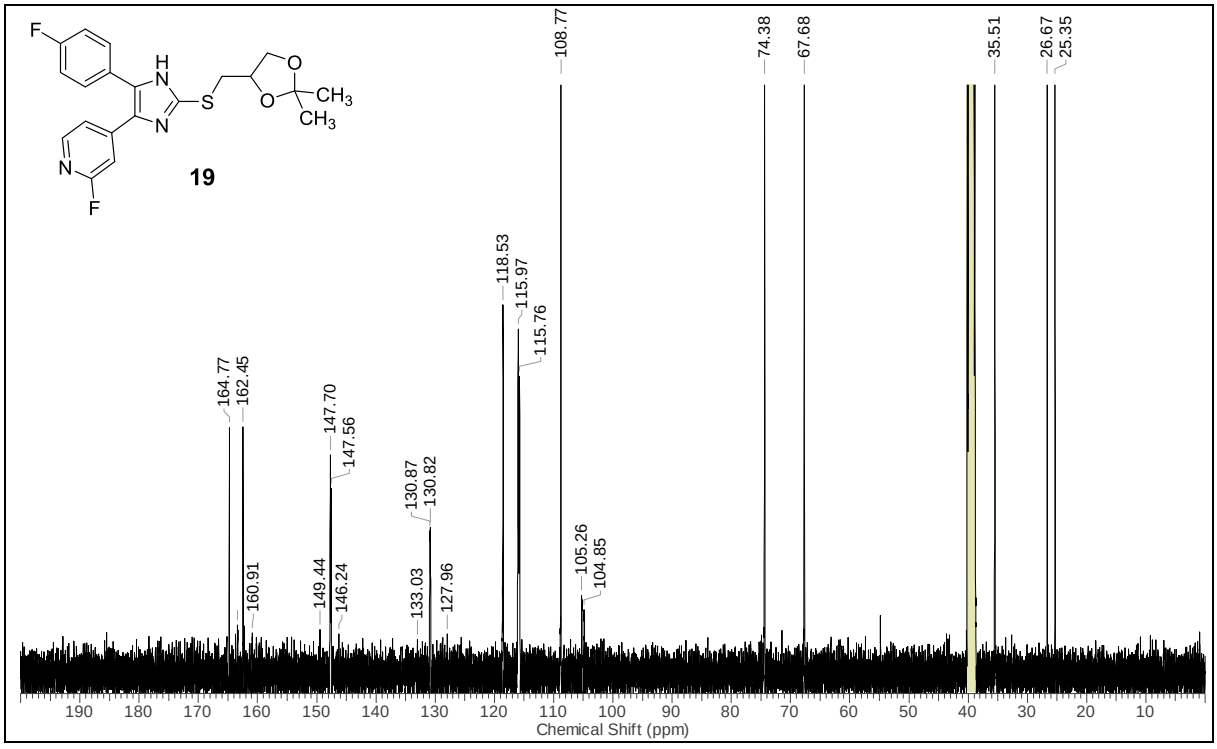
3.09
1.08
1.07
1.07
1.14
1.19
3.12
3.32
Chemical Shift (ppm)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147.56
146.24
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130.87
130.82
127.96
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35.51
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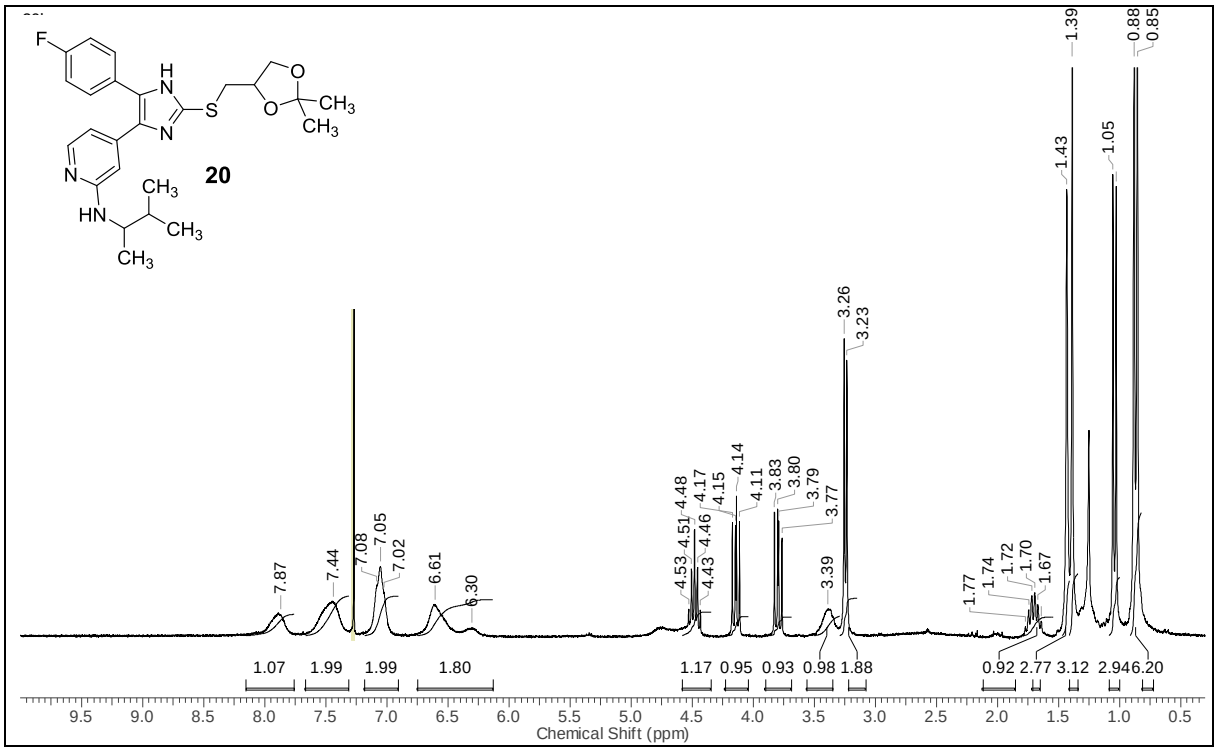
25.35
Chemical Shift (ppm)


20
7.87
7.44
7.08
7.05
7.02
6.61
6.30
4.53
4.51
4.48
4.46
4.43
4.17
4.15
4.14
4.11
3.83
3.80
3.79
3.77
3.39
3.26
3.23
1.77
1.74
1.72
1.70
1.67
1.43
1.39
1.05
0.88
0.85
1.07
1.99
1.99
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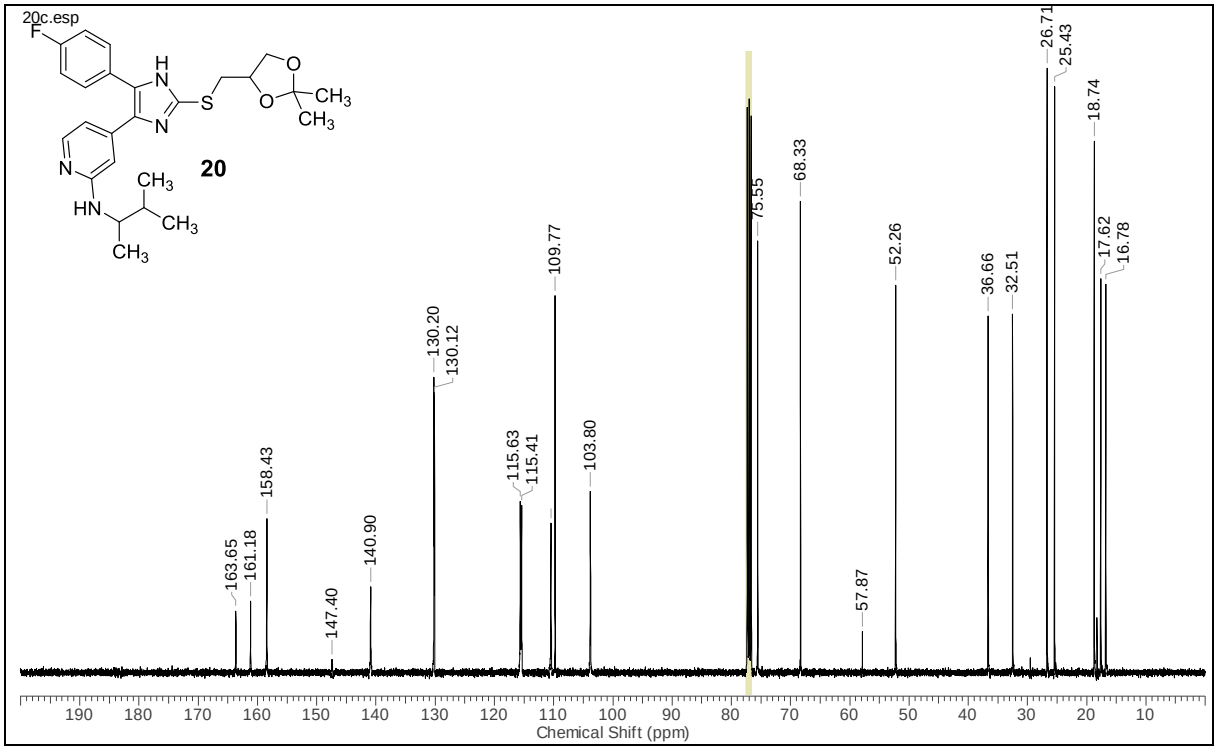
3.12
2.94
6.20
Chemical Shift (ppm)


20c.esp
20
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161.18
158.43
147.40
140.90
130.20
130.12
115.63
115.41
109.77
103.80
75.55
68.33
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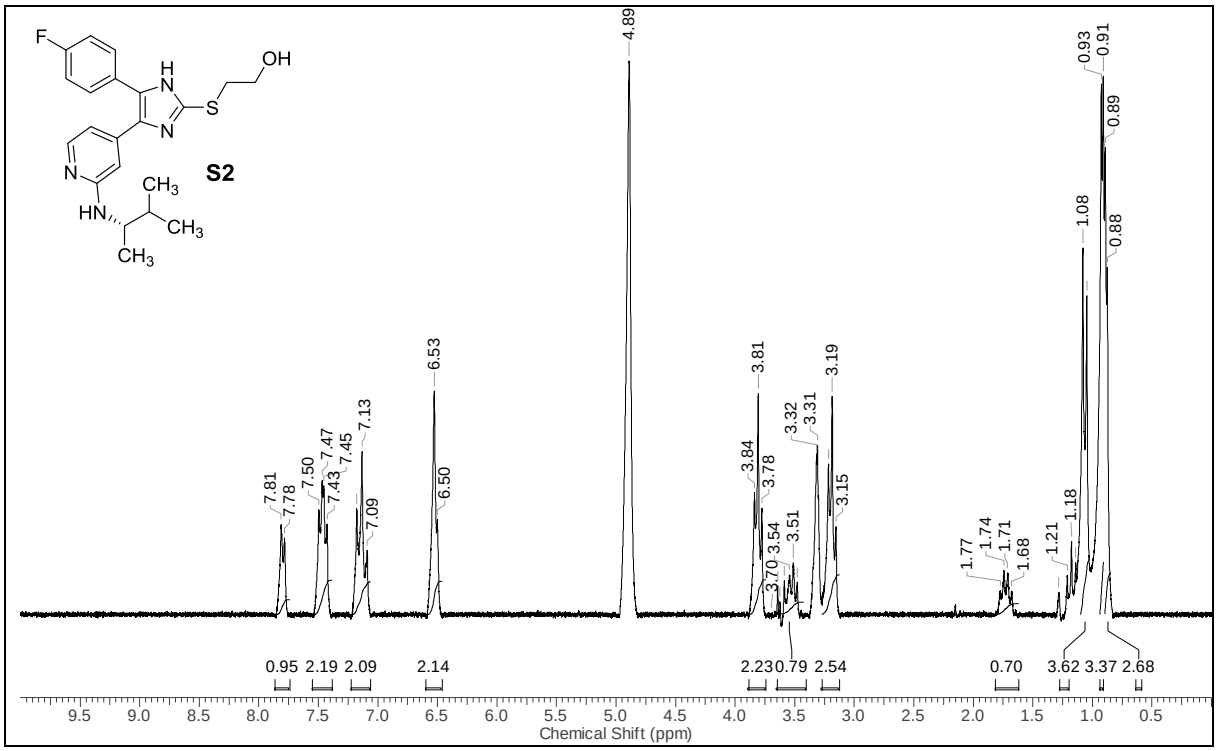
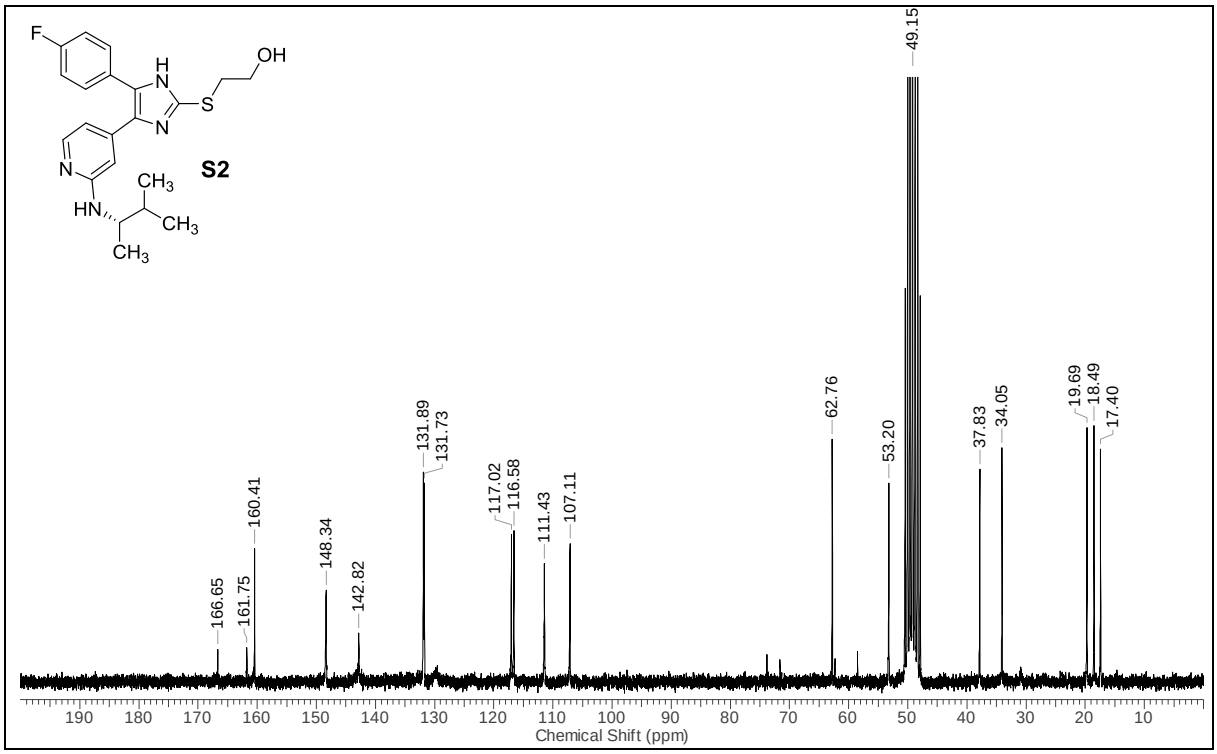
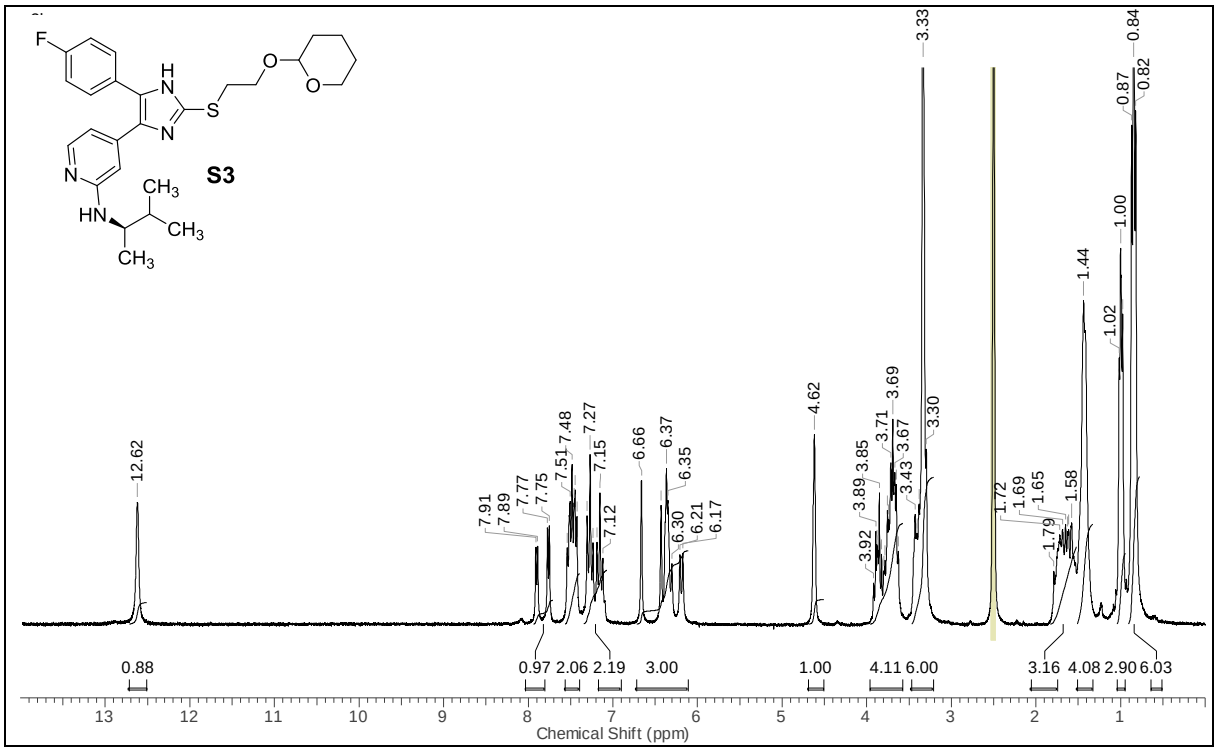
52.26
36.66
32.51
26.71
25.43
18.74
17.62
16.78
Chemical Shift (ppm)


S2
4.89
0.93
0.91
0.89
1.08
0.88
6.53
3.81
3.19
7.13
7.47
7.45
7.81
7.78
7.50
7.43
7.09
6.50
3.84
3.78
3.32
3.31
3.15
3.54
3.51
3.70
1.77
1.74
1.71
1.68
1.21
1.18
0.95 2.19 2.09 2.14 2.23 0.79 2.54 0.70 3.62 3.37 2.68
Chemical Shift (ppm)


S2
49.15
62.76
53.20
37.83
34.05
19.69
18.49
17.40
131.89
131.73
117.02
116.58
111.43
107.11
160.41
148.34
166.65
161.75
142.82
Chemical Shift (ppm)


S3
12.62
7.91
7.89
7.77
7.75
7.51
7.48
7.27
7.15
7.12
6.66
6.37
6.35
6.30
6.21
6.17
4.62
3.92
3.89
3.85
3.71
3.69
3.67
3.43
3.30
3.33
1.79
1.72
1.69
1.65
1.58
1.44
1.02
1.00
0.87
0.84
0.82
0.88
0.97
2.06
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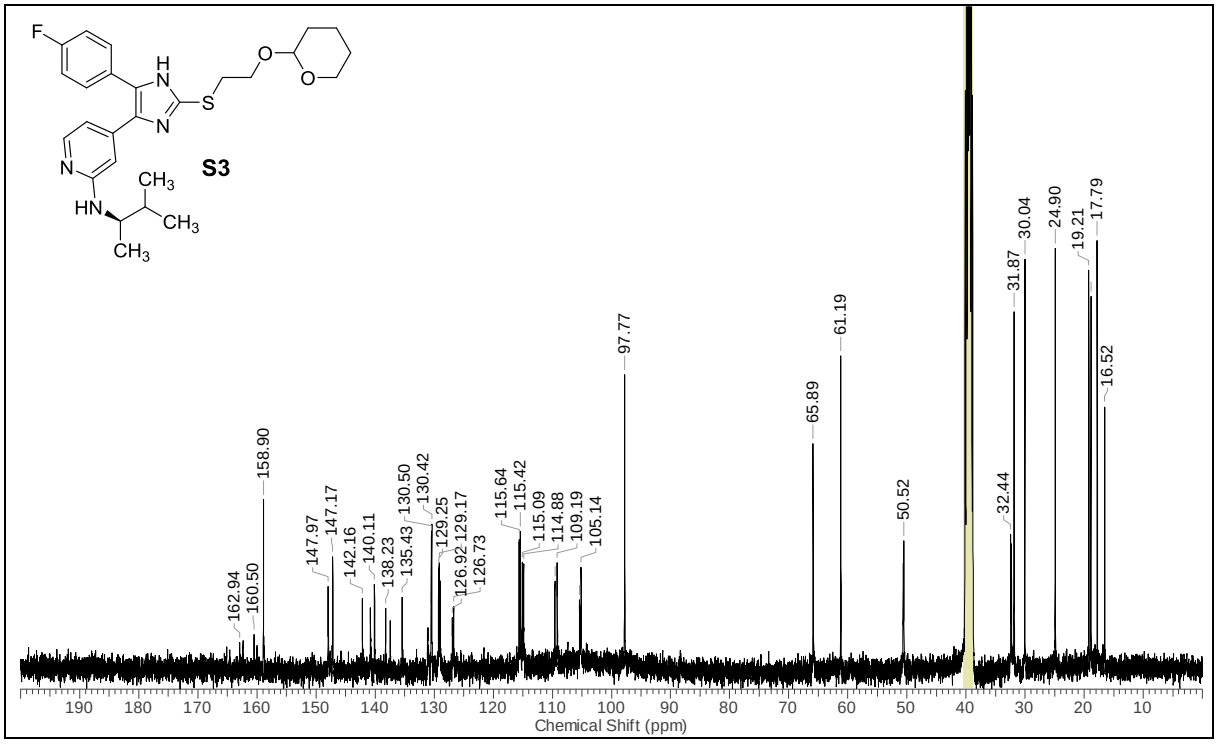
3.00
1.00
4.11
6.00
3.16
4.08
2.90
6.03
Chemical Shift (ppm)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158.90
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140.11
138.23
135.43
130.50
130.42
129.25
129.17
126.92
126.73
115.64
115.42
115.09
114.88
109.19
105.14
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32.44
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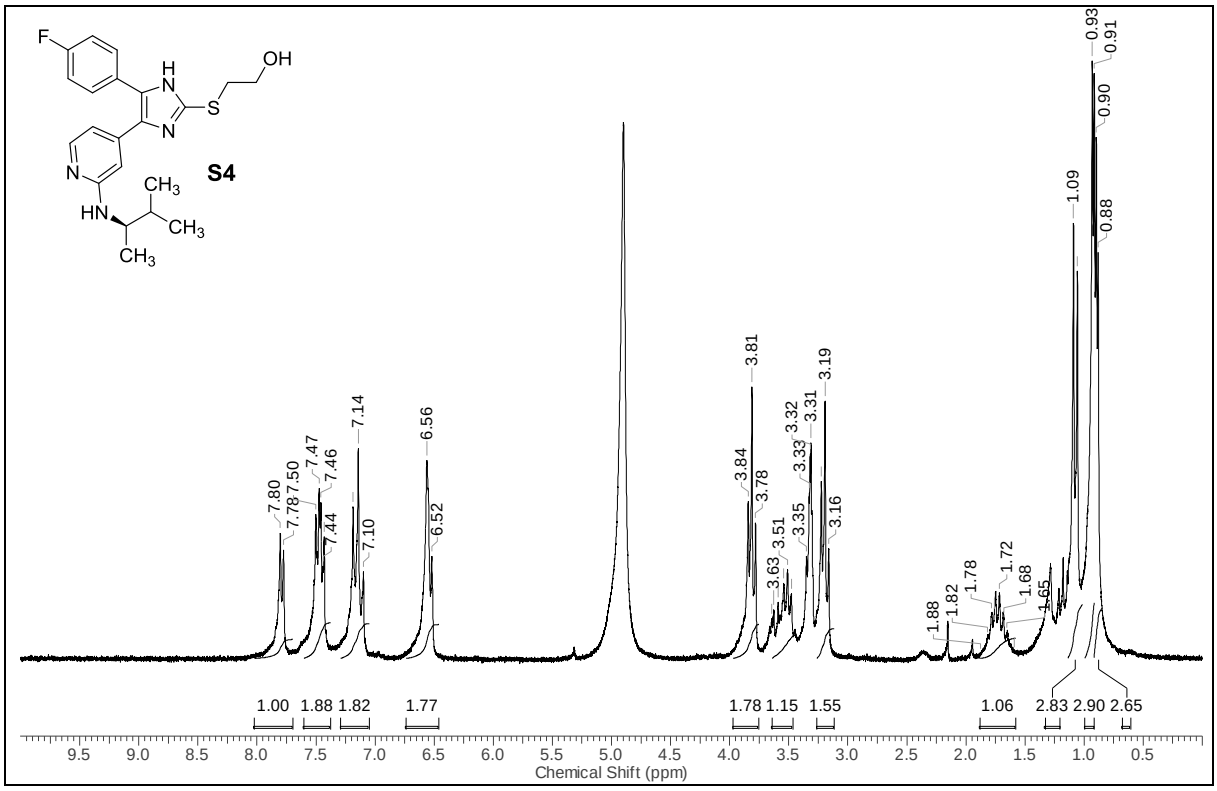
19.21
17.79
16.52
Chemical Shift (ppm)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6.56
6.52
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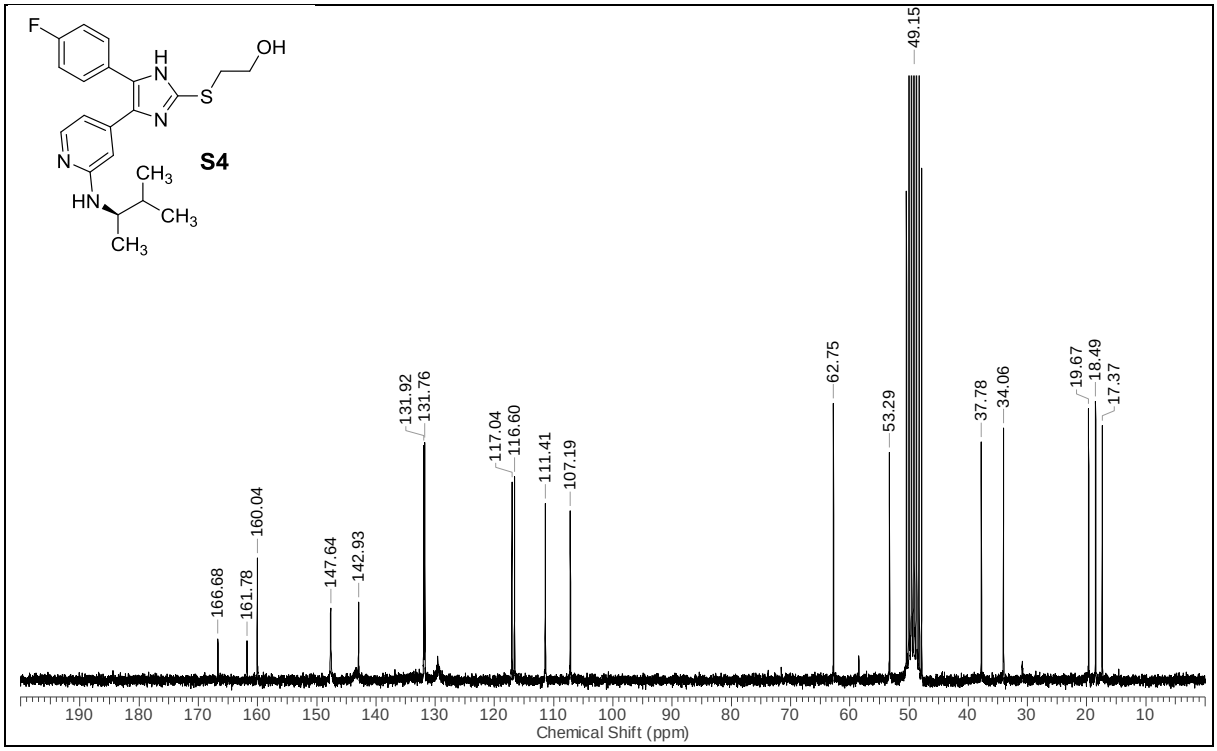
3.81
3.78
3.63
3.51
3.35
3.33
3.32
3.31
3.19
3.16
1.88
1.82
1.78
1.72
1.68
1.65
1.09
0.93
0.91
0.90
0.88
1.00 1.88 1.82 1.77 1.78 1.15 1.55 1.06 2.83 2.90 2.65
Chemical Shift (ppm)


S4
166.68
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160.04
147.64
142.93
131.92
131.76
117.04
116.60
111.41
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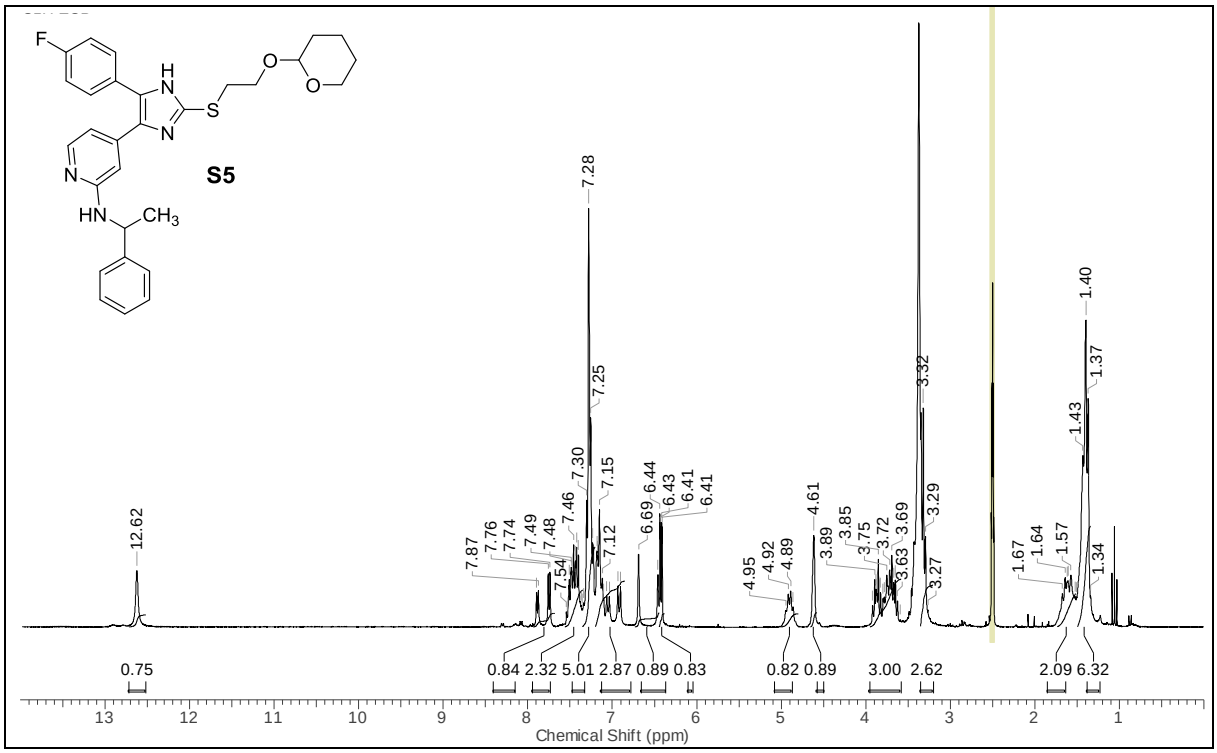
62.75
53.29
49.15
37.78
34.06
19.67
18.49
17.37
Chemical Shift (ppm)


S5
12.62
7.87
7.76
7.74
7.49
7.48
7.54
7.46
7.30
7.28
7.25
7.15
7.12
6.69
6.44
6.43
6.41
6.41
4.95
4.92
4.89
4.61
3.89
3.85
3.75
3.72
3.69
3.63
3.32
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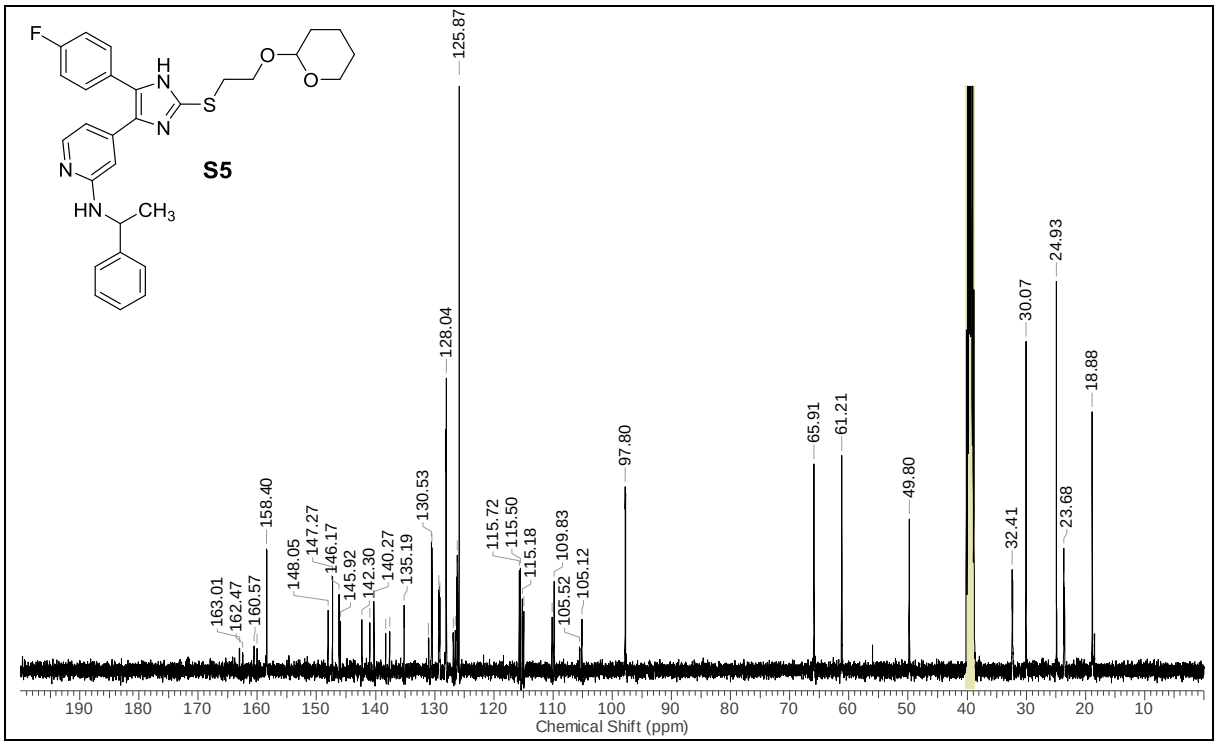
3.27
1.67
1.64
1.57
1.43
1.40
1.37
1.34
0.75
0.84
2.32
5.01
2.87
0.89
0.83
0.82
0.89
3.00
2.62
2.09
6.32
Chemical Shift (ppm)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65.91
61.21
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24.93
18.88
32.41
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158.40
148.05
147.27
146.17
145.92
142.30
140.27
135.19
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115.18
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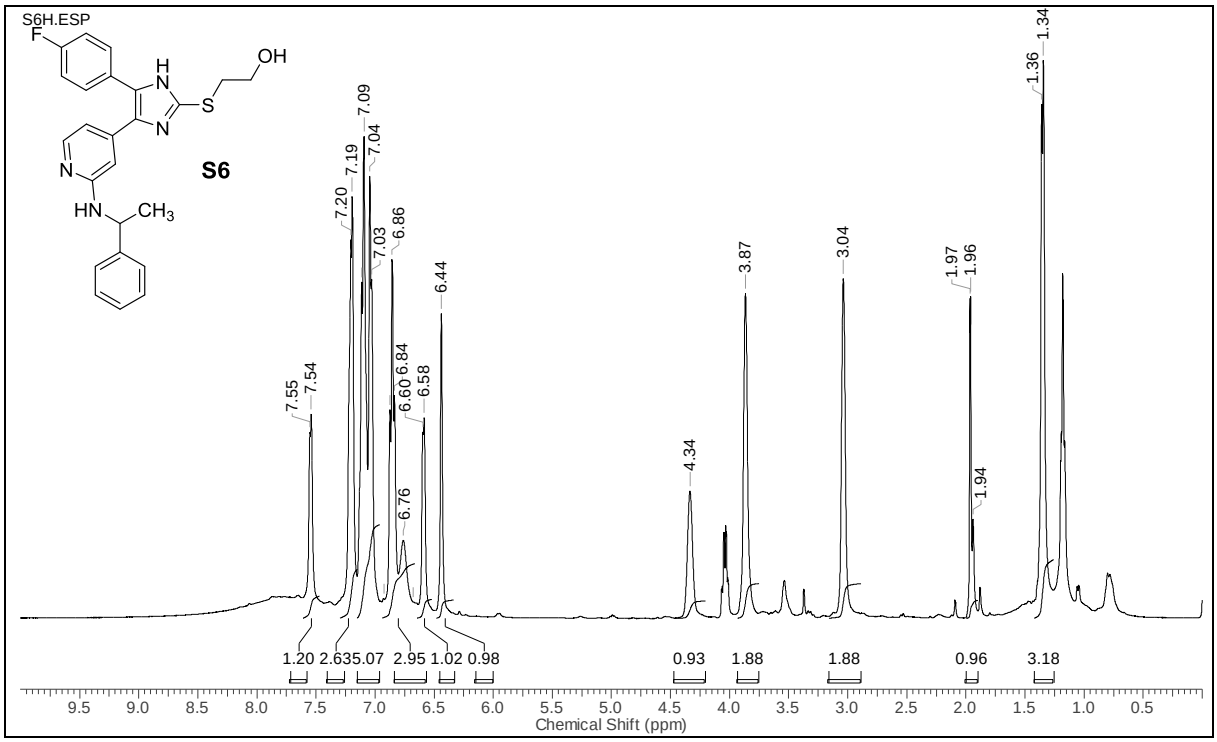
160.57
Chemical Shift (ppm)


S6H.ESP
S6
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7.54
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7.19
7.09
7.04
7.03
6.86
6.84
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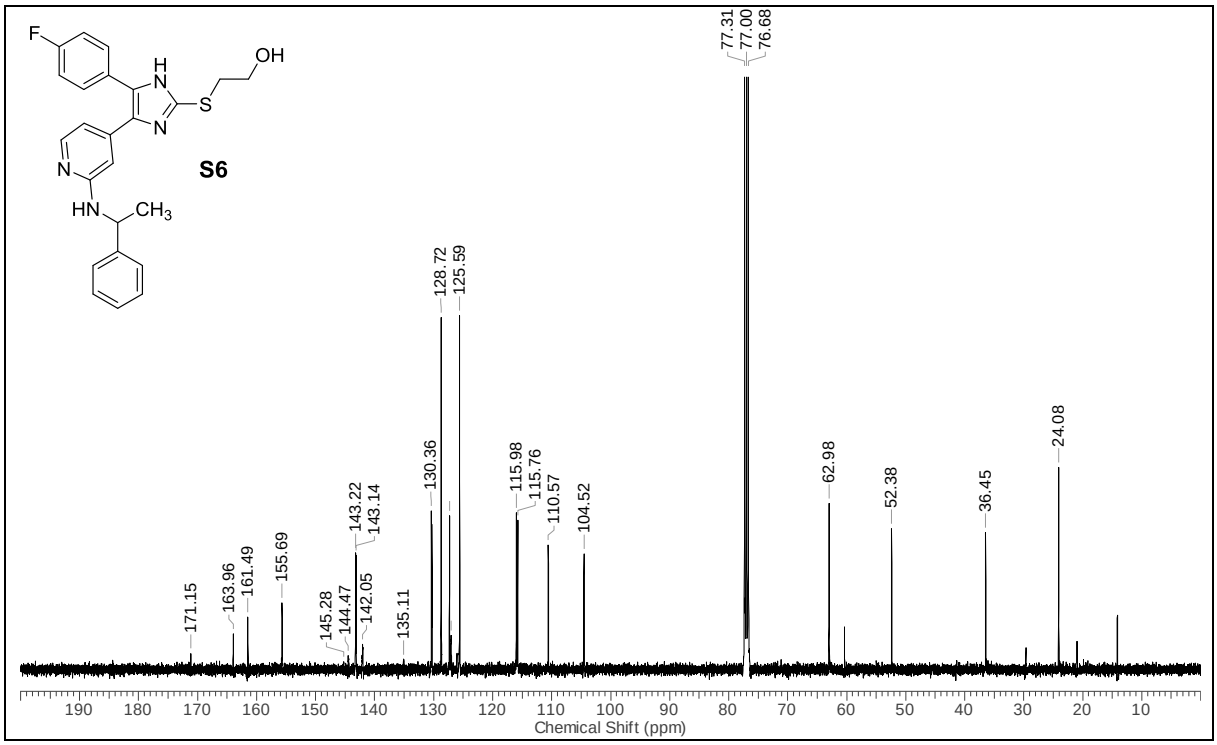
6.60
6.58
6.44
4.34
3.87
3.04
1.97
1.96
1.94
1.36
1.34
1.20 2.63 5.07 2.95 1.02 0.98
0.93 1.88 1.88 0.96 3.18
Chemical Shift (ppm)


S6
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76.68
171.15
163.96
161.49
155.69
145.28
144.47
143.22
143.14
142.05
135.11
130.36
128.72
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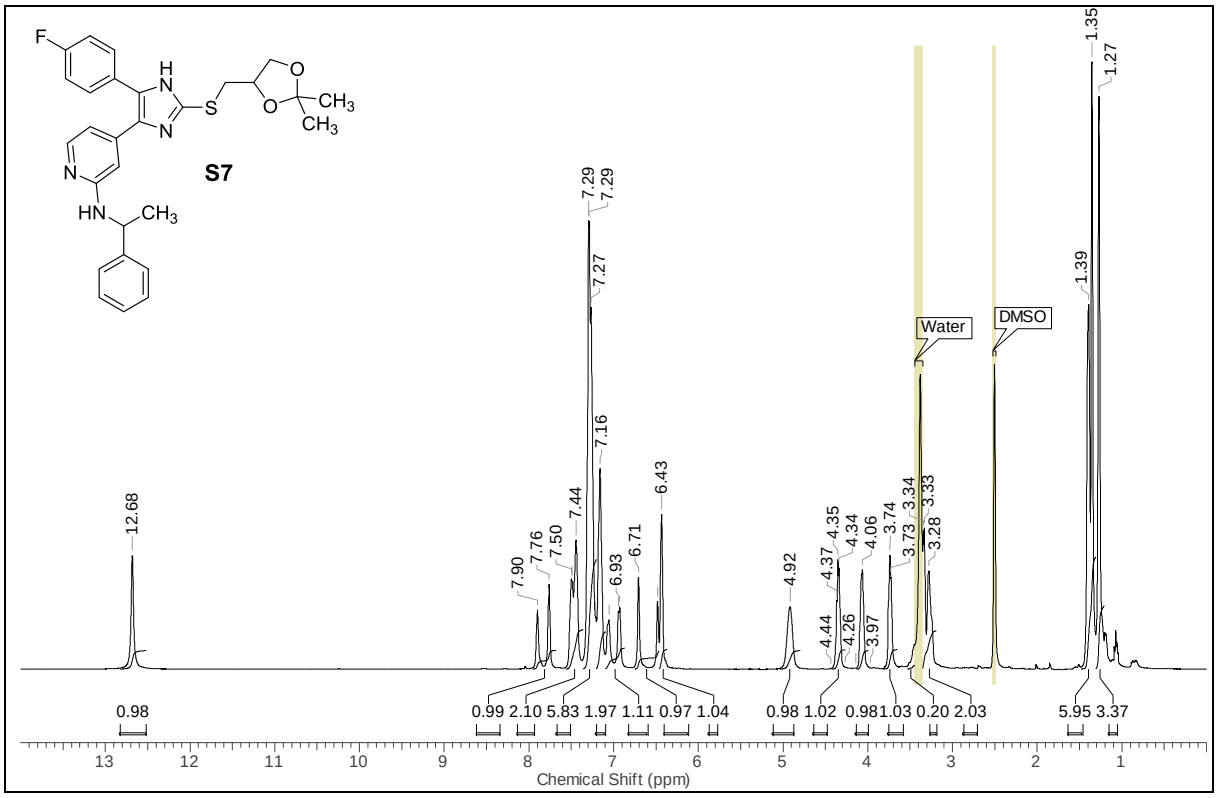
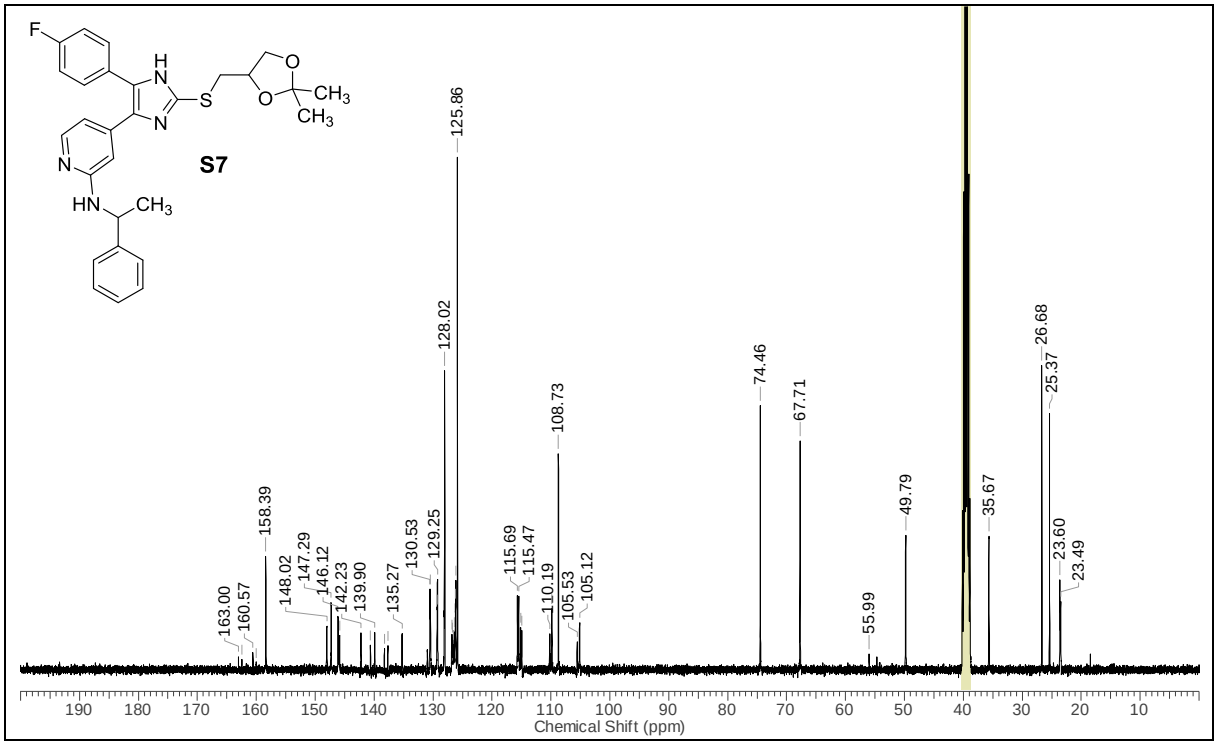
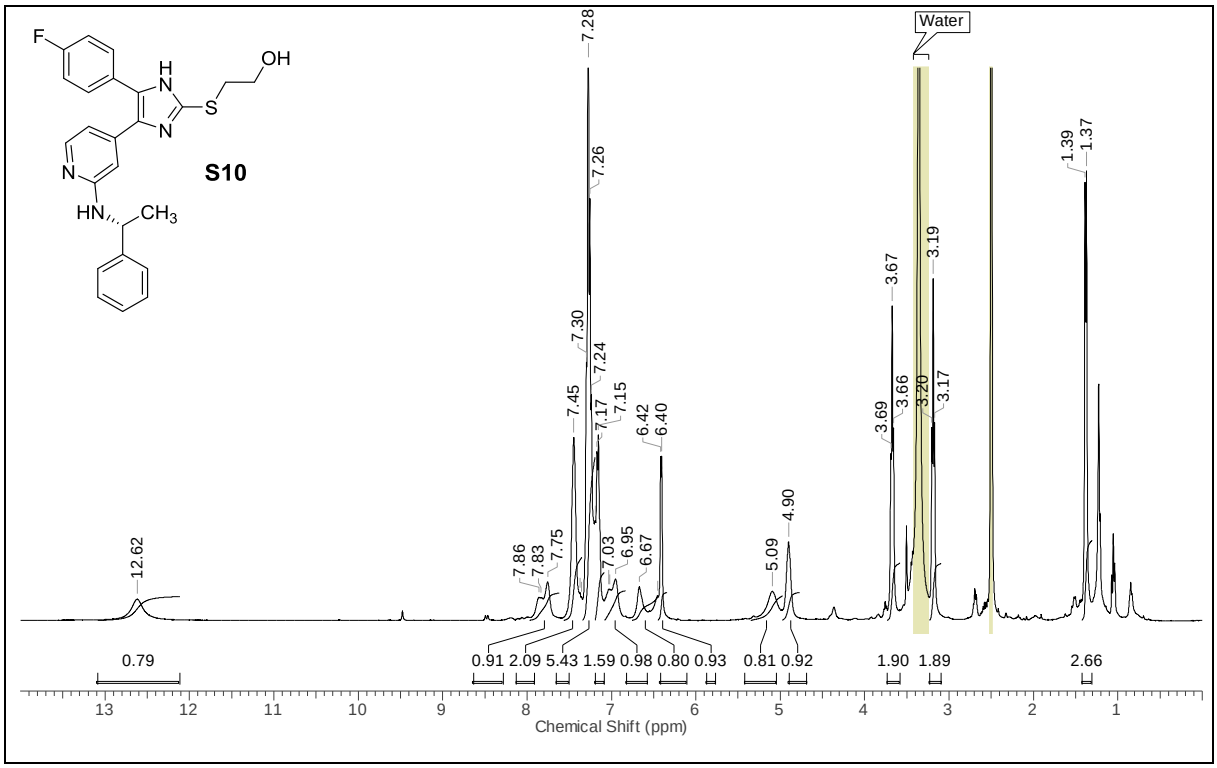
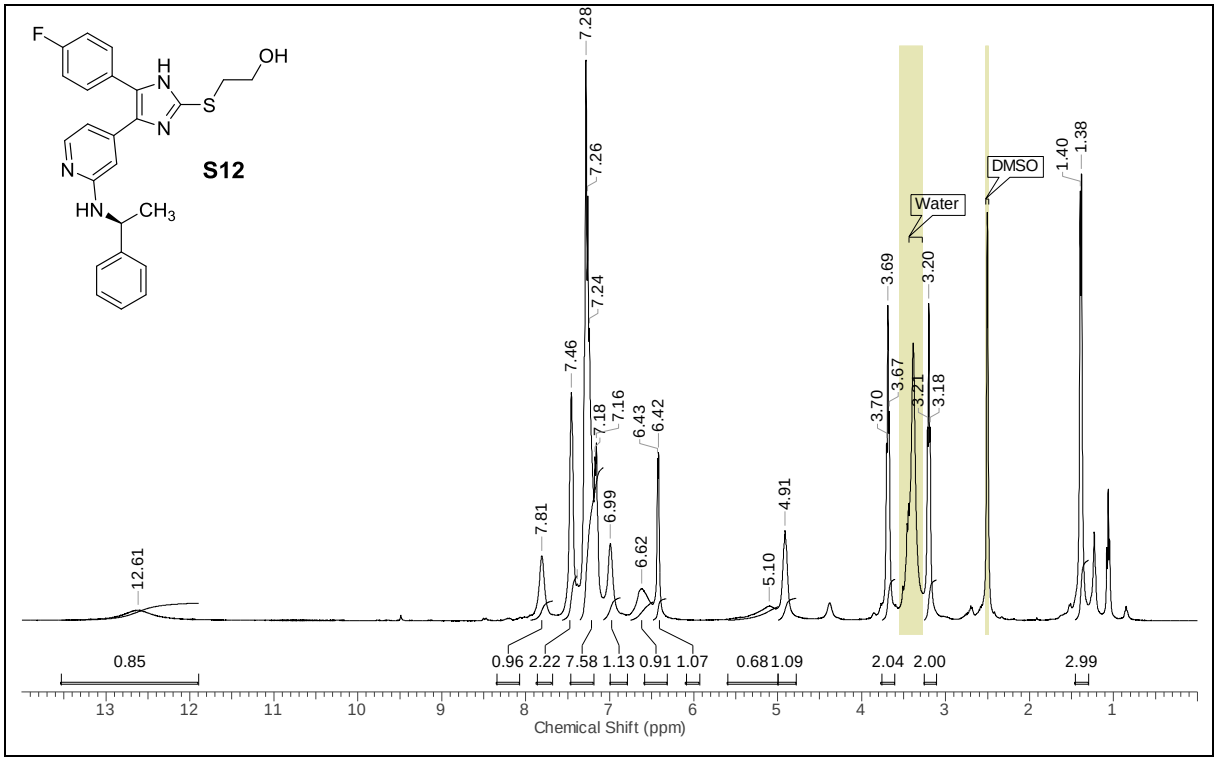
115.98
115.76
110.57
104.52
62.98
52.38
36.45
24.08
Chemical Shift (ppm)


S7
Water
DMSO
Chemical Shift (ppm)


S7
Chemical Shift (ppm)


S10
Water
7.28
7.26
7.30
7.24
7.45
7.17
7.15
6.42
6.40
12.62
7.86
7.83
7.75
7.03
6.95
6.67
5.09
4.90
3.67
3.19
3.69
3.66
3.20
3.17
1.39
1.37
0.79
0.91 2.09 5.43 1.59 0.98 0.80 0.93 0.81 0.92 1.90 1.89 2.66
Chemical Shift (ppm)


S12
DMSO
Water
7.28
7.26
7.24
7.46
7.18
7.16
6.43
6.42
7.81
6.99
6.62
12.61
5.10
4.91
3.69
3.20
3.70
3.67
3.21
3.18
1.40
1.38
0.85
0.96 2.22 7.58 1.13 0.91 1.07 0.68 1.09 2.04 2.00 2.99
Chemical Shift (ppm)