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Supplimentary Information

Synthesis and Determination of Absolute Configuration of a non-peptidic $\alpha_v\beta_6$ Integrin Antagonist for the Treatment of Idiopathic Pulmonary Fibrosis.

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Methyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetate (23)

A solution of **22** (460 mg, 2 mmol) was dissolved in MeOH (70 mL) and treated with hydrogen chloride solution in cyclopentyl methyl ether (3M, 10 mL) and the mixture was heated to reflux for 2 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and sodium bicarbonate. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on a silica cartridge (20 g) eluting with a gradient of 0-25 % ethyl acetate-cyclohexane over 20 min. Appropriate fractions containing the major component were combined and evaporated to give **23** (251 mg, 51%) as a colourless oil: LCMS (System C) RT=0.96 min, 98%, ES+ve *m/z* 245 $(M+H)^+$; ^1H NMR δ ($CDCl_3$, 400 MHz) 7.44–7.38 (m, 2H), 7.35 (m, 1H), 7.30–7.27 (m, 1H), 6.00 (s, 1H), 3.72 (s, 3H), 3.69 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR δ (DMSO-d_6, 101 MHz) 171.3, 147.8, 139.6, 139.0, 135.4, 128.8, 127.8, 125.0, 122.2, 107.1, 51.6, 39.7, 13.2, 12.0. HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $(M+H)^+$ 245.1285, found 245.1279.

4-*tert*-Butyl 1-methyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)succinate (24)

A solution of lithium hexamethyldisilazide in THF (1M, 1.85 mL) was cooled to –78ºC and treated with a solution of **23** (453 mg, 1.85 mmol) in THF (2 mL). After 5 min the reaction mixture was treated with *tert*-butyl 2-bromoacetate (0.82 mL, 5.6 mmol) in THF (2 mL) and after 30 min at –78ºC the mixture was allowed to warm to room temperature. The mixture was stirred for 2.5 h and then was quenched with aqueous HCl solution (0.2 M, 10 mL) and extracted with EtOAc. The organic solution was washed with aqueous $NaHCO_3$ solution, 0.2M HCl, brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on a silica cartridge (50 g) eluting with 0–25% EtOAc-cyclohexane. The fractions containing the main peak were combined and evaporated under

reduced pressure to give a colourless oil (780 mg), which was further purified by chromatography on a silica cartridge (70 g) eluting with 0–50% TBME–cyclohexane to give **24** (479 mg, 72%) as a colourless oil: LCMS (System C) RT=1.19 min, ES+ve *m/z* 359 $(M+H)^+$; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.43–7.33 (m, 3H), 7.29–7.25 (m, 1H), 6.00 (s, 1H), 4.09 (dd, *J*=10.0, 5.5 Hz, 1H), 3.69 (s, 3H), 3.13 (dd, *J*=16.7, 10.0 Hz, 1H), 2.64 (dd, *J*=16.7, 5.5 Hz, 1H), 2.30 (s, 6H), 1.42 (s, 9H); ^{13}C NMR δ ($CDCl_3$; 101 MHz) 173.1, 170.4, 149.1, 140.3, 139.3, 138.8, 129.3, 126.6, 124.2, 123.7, 107.1, 81.1, 52.3, 47.1, 38.9, 28.0 (3C), 13.4, 12.4. The racemic mixture (690 mg) was separated by preparative HPLC on a Chiralcel OD-H column (30 mm × 250 mm) eluting with 5% IPA–hexane, flow rate = 20 mL/min to give (+)-**24** (267 mg) as a colourless oil: $[\alpha]_D^{22}$ + 81 (c=1.028 in $CHCl_3$); Analytical HPLC on Chiralcel OJ-H column (4.6 mm id × 250 mm) RT=7.75 min, 99.3% (contains the other enantiomer, RT=9.35 min, 0.7%), and (–)-**24** (230 mg) as a colourless oil: $[\alpha]_D^{22}$ –82 (c=1.016 in $CHCl_3$); Analytical HPLC on Chiralcel OJ-H column (4.6 mm id × 250 mm) RT=9.35 min, 98.6% (contains the other enantiomer, RT=7.75 min, 1.4%).

(+)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid [(+)-**25]**

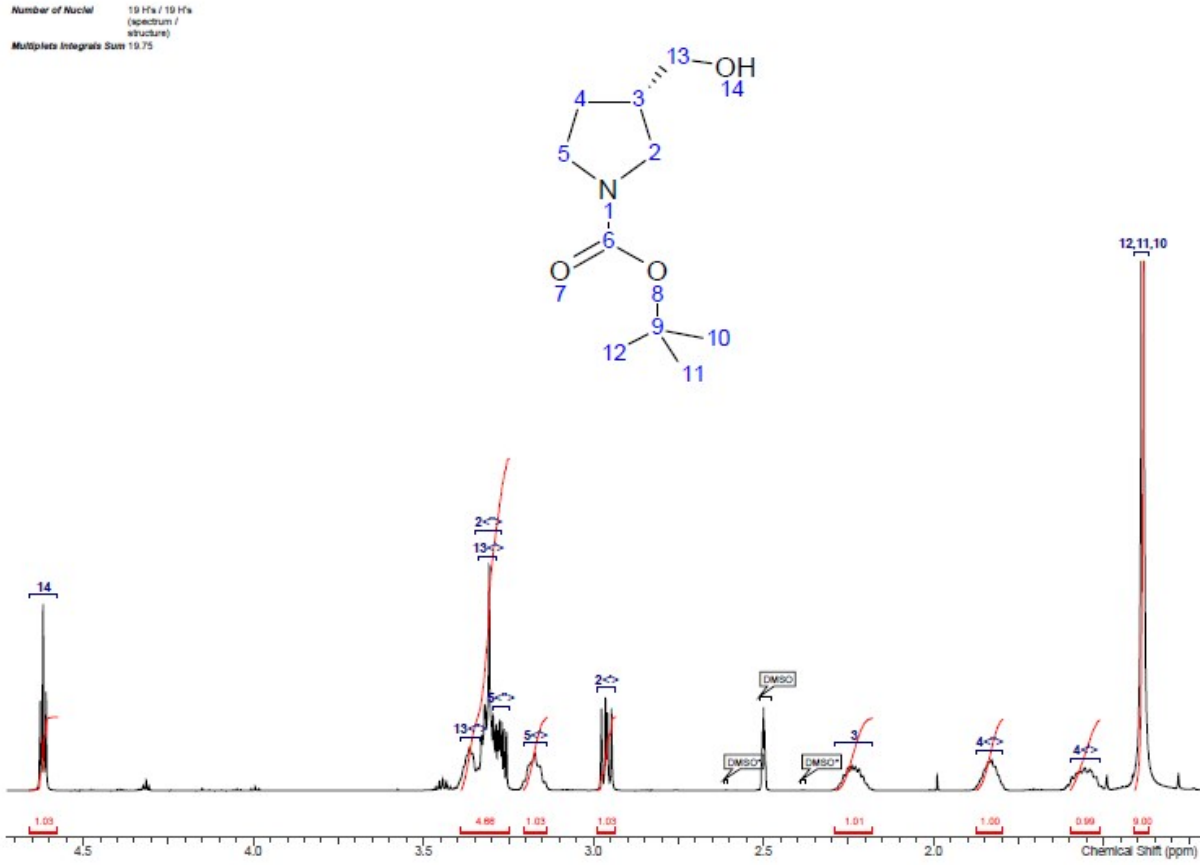
A solution of (+)-**24** (257 mg, 0.72 mmol) was dissolved in THF (2 mL) and cooled to 0 ºC (ice-cooling) before 30% H_2O_2 (0.366 mL, 3.6 mmol) and LiOH solution in water (1M, 2.15 mL) were added. After standing in the fridge at 4°C for 16 h the reaction mixture was treated with aqueous sodium metabisulfite solution (1M, 3 mL) and then acidified to pH 1 with 2M HCl solution. The reaction mixture was extracted three times with EtOAc and the organic solution was dried over $MgSO_4$. The solution was evaporated under reduced pressure and the residual white foam was purified by MDAP (Method B). The appropriate fractions were evaporated under reduced pressure to give (+)-**25** (140 mg, 57%) as a colourless oil: LCMS

(System C) RT=1.03 min, 84%, ES+ve *m/z* 345 $(M+H)^+$; $[\alpha]_D^{20}$ + 42 (c=1.037 in $CHCl_3$); ^1H NMR δ ($CDCl_3$; 500 MHz) 7.35–7.33 (m, 1H), 7.37–7.31 (m, 1H), 7.27–7.24 (m, 1H), 7.29–7.24 (m, 1H), 5.98 (s, 1H), 4.04 (dd, *J*=9.3, 6.2 Hz), 3.09 (dd, *J*=16.6, 9.3 Hz, 1H), 2.62 (dd, *J*=16.5, 6.1 Hz, 1H), 2.31 (s, 3H), 2.24 (s, 3H), 1.38 (s, 9H); ^{13}C NMR δ ($CDCl_3$, 126 MHz;) 175.2, 170.6, 149.1, 139.7, 139.3, 139.1, 129.1, 127.1, 124.8, 123.9, 107.0, 81.0, 47.1, 38.7, 27.9, 13.1, 12.2.

(–)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid [(–)-25]

A solution of (–)-**24** (220 mg, 0.61 mmol) was dissolved in THF (5 mL) and cooled to 0 ºC (ice-cooling) before 30% H_2O_2 (0.313 mL, 3.1 mmol) and LiOH solution in water (0.2M, 9.21 mL) was added. The reaction went to completion after 6 d. The reaction mixture was treated with sodium thiosulfate solution (1M, 3 mL) and sodium bicarbonate solution (0.5M, 8 mL) and the mixture (pH 8) was stirred for 10 min, and then acidified to pH 1 with 6M HCl solution. The reaction mixture was extracted three times with EtOAc and the organic solution was dried over $MgSO_4$. Evaporation under reduced pressure gave a white solid which was purified by MDAP (Method B). Evaporation of the appropriate fractions under reduced pressure gave (–)-**25** (105 mg, 50%) as a colourless oil: LCMS (System C) RT=1.03 min, 93%, ES+ve *m/z* 345 $(M+H)^+$; $[\alpha]_D^{20}$ –42 (c=1.482 in $CHCl_3$); ^1H NMR δ ($CDCl_3$; 400 MHz) 7.38–7.32 (m, 2H), 7.30–7.22 (m, 2H), 5.99 (s, 1H, s), 4.05 (dd, *J*=9.5, 6 Hz, 1H), 3.09 (dd, *J*=16.5, 9.5 Hz, 1H), 2.63 (dd, *J*=16.5, 6 Hz, 1H), 2.31 (s, 3H), 2.24 (s, 3H), 1.38 (s, 9H); ^{13}C NMR δ ($CDCl_3$; 101 MHz) 175.3, 170.6, 149.0, 140.0, 139.2, 139.0, 129.2, 127.3, 124.9, 123.9, 107.1, 81.1, 47.2, 38.7, 28.0, 13.0, 12.2.

(*S*)-*tert*-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (*S*)-2.



^{1}H NMR (DMSO-d_6 ,600MHz): δ (ppm) 4.62 (t, *J*=5.3 Hz, 1H, (H-14)), 3.34 - 3.39 (m, 1H, (H-13<>)), 3.28 - 3.34 (m, 1H, (H-13<>)), 3.27 - 3.35 (m, 1H, (H-2<>)), 3.25 - 3.30 (m, 1H, (H-5<>)), 3.14 - 3.21 (m, 1H, (H-5<>)), 2.96 (dd, *J*=10.6, 7.0 Hz, 1H, (H-2<>)), 2.18 - 2.29 (m, 1H, (H-3)), 1.80 - 1.87 (m, 1H, (H-4<>)), 1.51 - 1.60 (m, 1H, (H-4<>)), 1.39 (s, 9H, (H-12, 11, 10))

(*S*)-*tert*-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (*S*)-2.

Number of Nuclei 10 C's / 10 C's (spectrum / structure)
Multiplets Integrals Sum 0.00

Atom	Exp. Shift (ppm)
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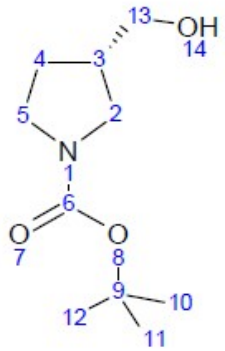
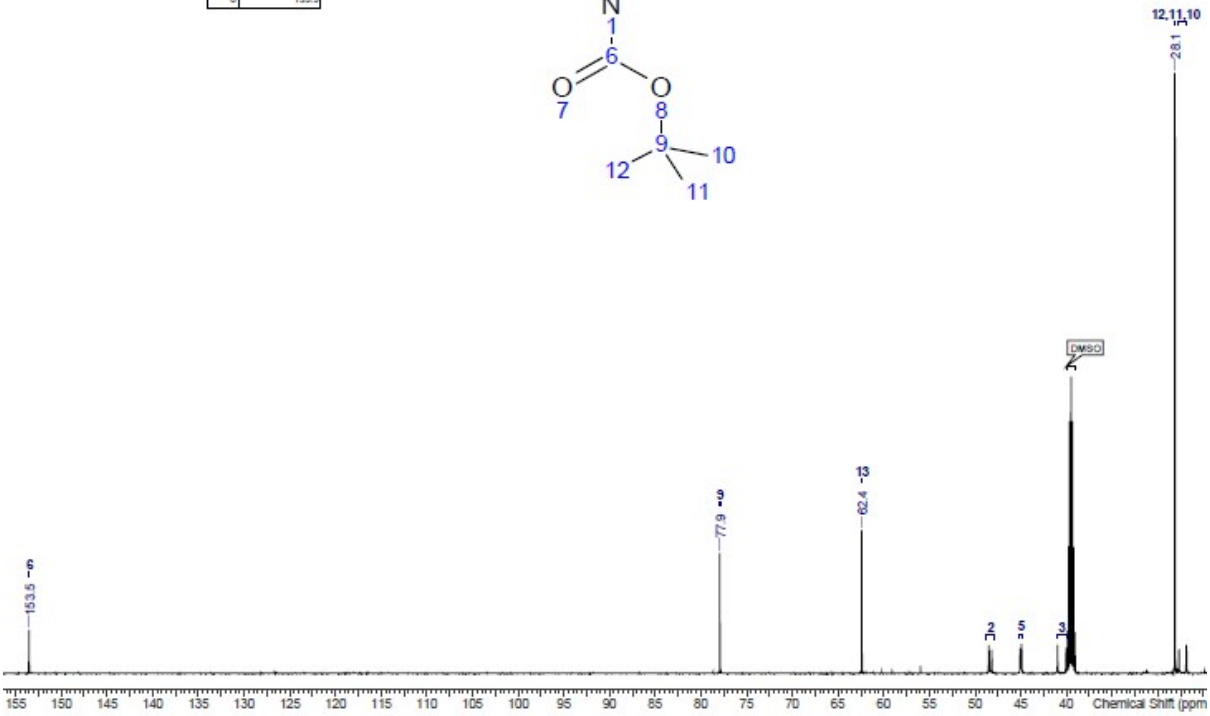
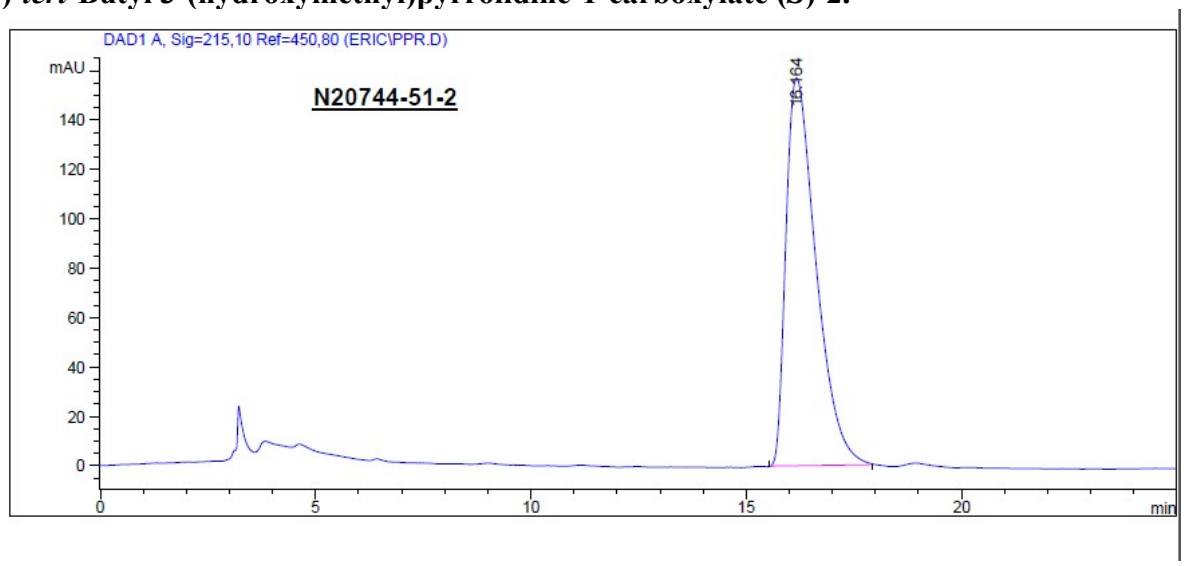
11	28.1
10	28.1
3	40.5
5	45.0
2	48.3
13	62.4
9	77.9
6	153.5



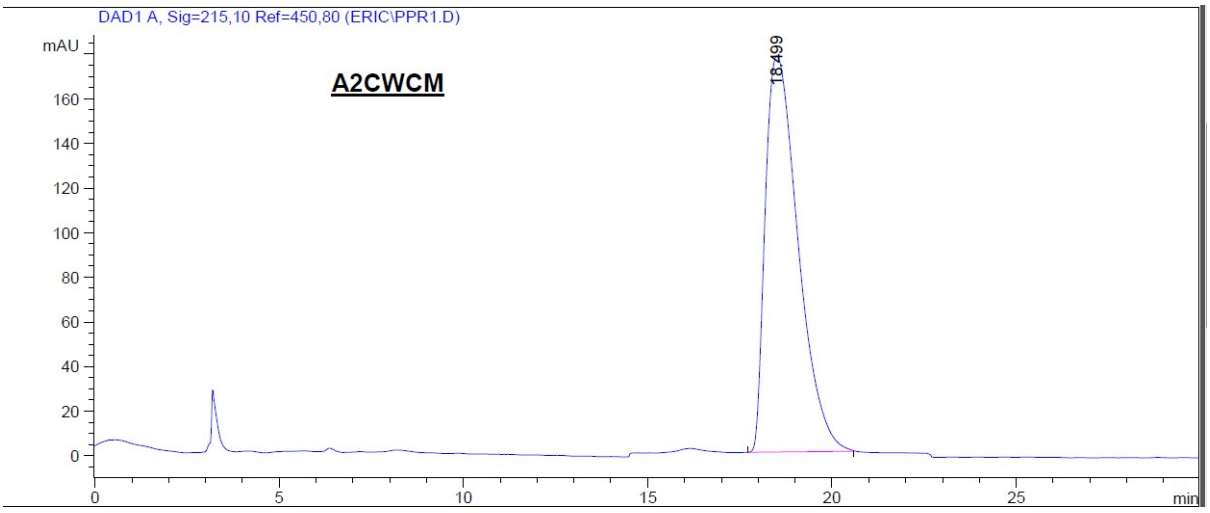


^{13}C NMR (DMSO-d_6 ,151MHz): δ (ppm) 153.5 (s, 1C, ((C-6)), 77.9 (s, 1C, (C-9)), 62.4 (s, 1C, ((C-13)), 47.9 - 48.7 (m, 1C, (C-2)), 44.8 - 45.2 (m, 1C, ((C-5)), 40.0 - 41.0 (m, 1C, ((C-3)), 28.1 (s, 3C, (C-12, 11, 10)), 26.8 - 27.7 (m, 1C, (C-4))

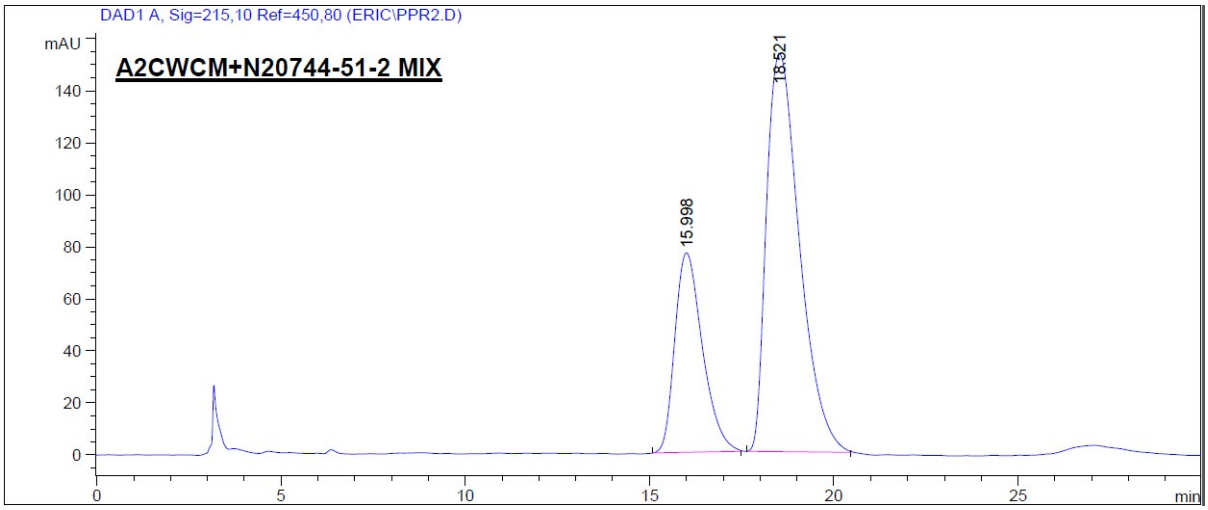
(*S*)-*tert*-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (*S*)-2.



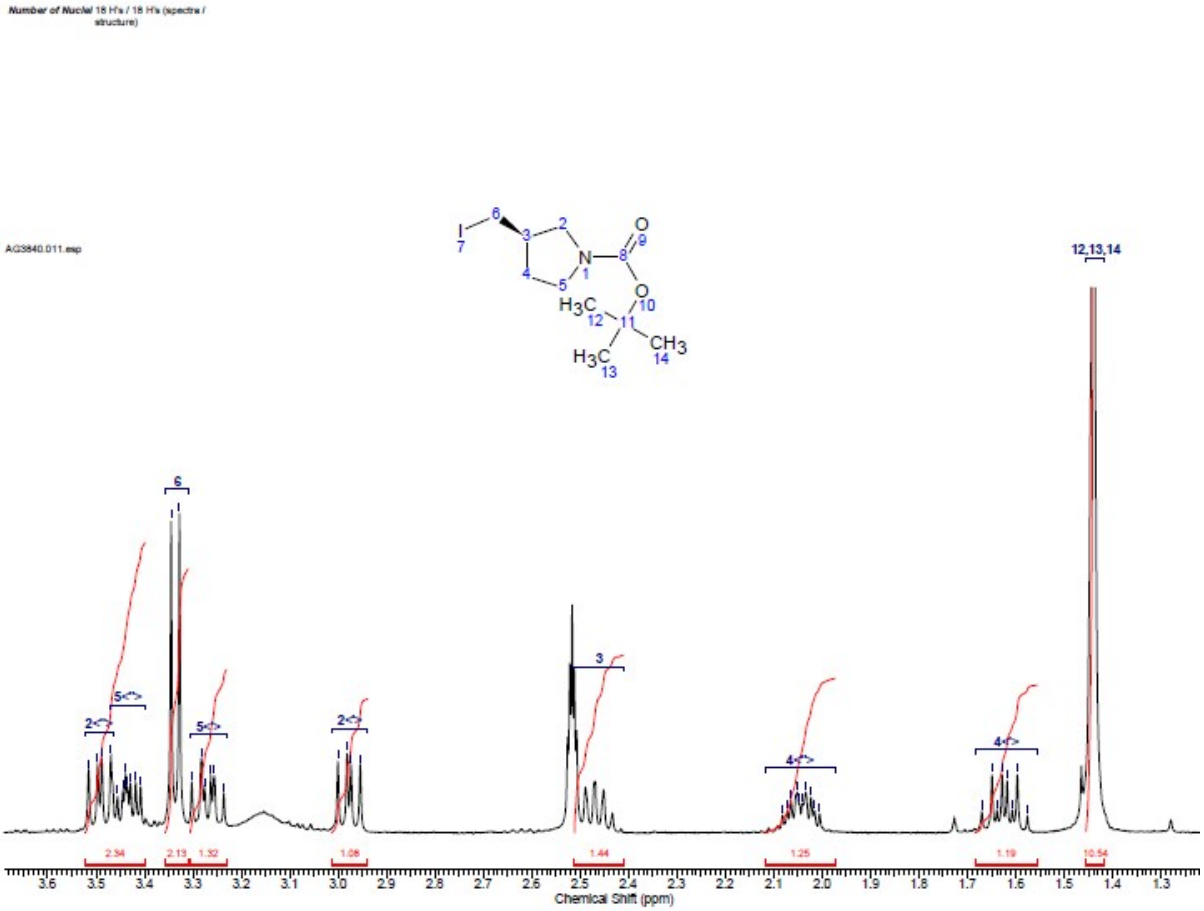
(*R*)-*tert*-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (*R*)-2.



Mixture of (*S*)-2 and (*R*)-2



(*R*)-*tert*-Butyl 3-(iodomethyl)pyrrolidine-1-carboxylate (8)



^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm) 3.49 (dd, *J*=10.9, 7.4 Hz, 1H, (H-2<>)), 3.44 (ddd, *J*=10.6, 8.5, 4.3 Hz, 1H, (H-5<>)), 3.34 (d, *J*=6.8 Hz, 2H, (H-6)), 3.27 (dt, *J*=10.6, 7.9 Hz, 1H, (H-5<>)), 2.98 (dd, *J*=10.8, 7.5 Hz, 1H, (H-2<>)), 2.47 (dqt, *J*=8.3, 7.5, 6.8 Hz, 1H, (H-3)), 1.97 - 2.12 (m, 1H, (H-4<>)), 1.62 (dq, *J*=12.4, 8.3 Hz, 1H, (H-4<>)), 1.44 (s, 9H, (H-12, 13, 14))

(*R*)-*tert*-Butyl 3-(iodomethyl)pyrrolidine-1-carboxylate (8)

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Multiplets Integrals Sum	0.00
Number of Nuclei	10 C's / 10 C's (spectrum / structure)

Atom	Exp. Shift (ppm)
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13	28.0
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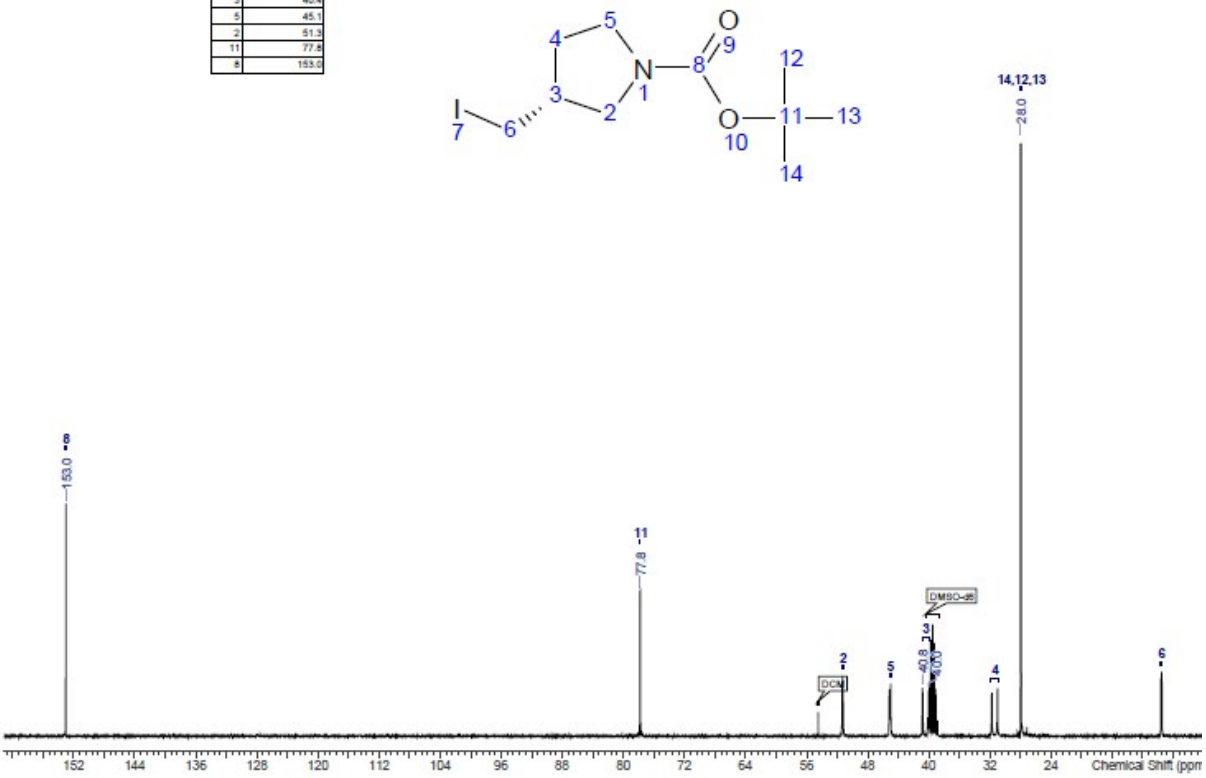
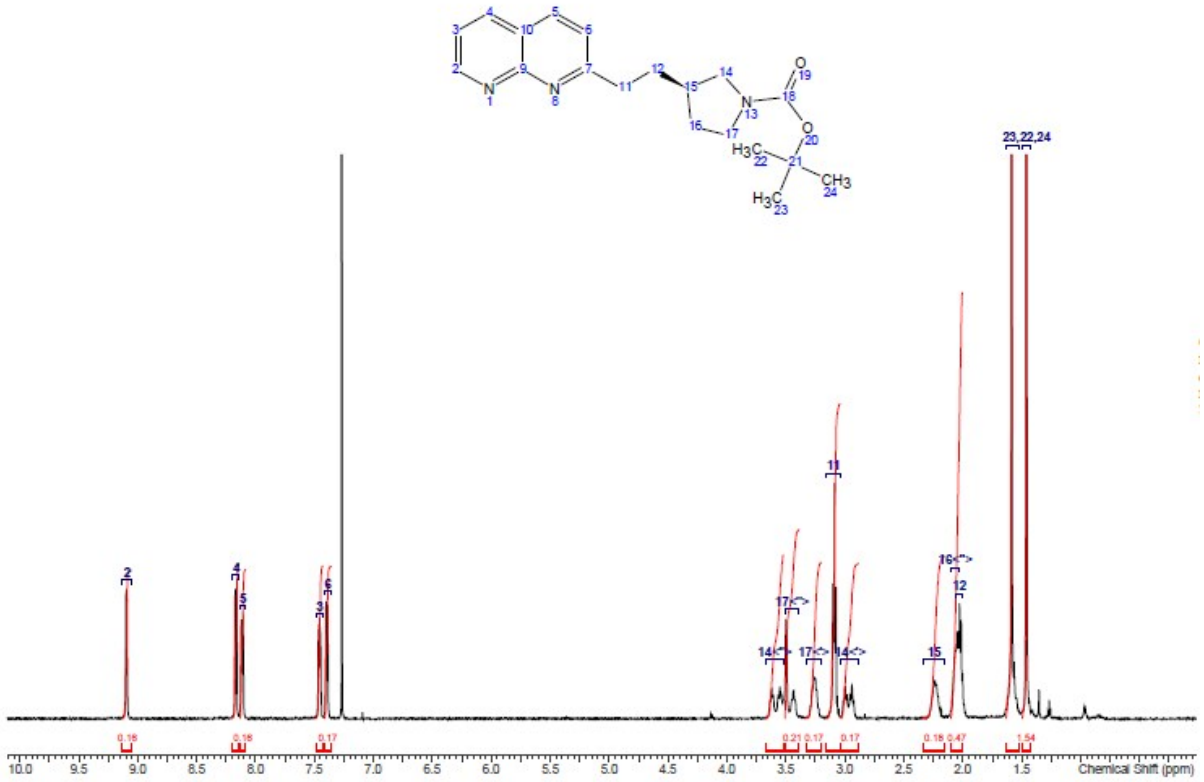
2	51.3
11	77.8
8	153.0



^{13}C NMR (DMSO-d_6 ,101MHz): δ (ppm) 153.0 (s, 1C, (C-8)), 77.8 (s, 1C, ((C-11)), 51.2 - 51.3 (m, 1C, (C-2)), 44.9 - 45.2 (m, 1C, (C-5)), 40.0 - 40.9 (m, 1C, (C-3)), 30.9 - 31.9 (m, 1C, (C-4)), 28.0 (s, 3C, (C-14, 12, 13)), 9.5 - 9.6 (m, 1C, (C-6))

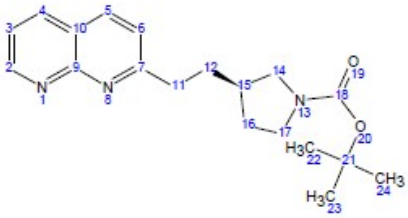
(*R*)-*tert*-Butyl 3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (9)

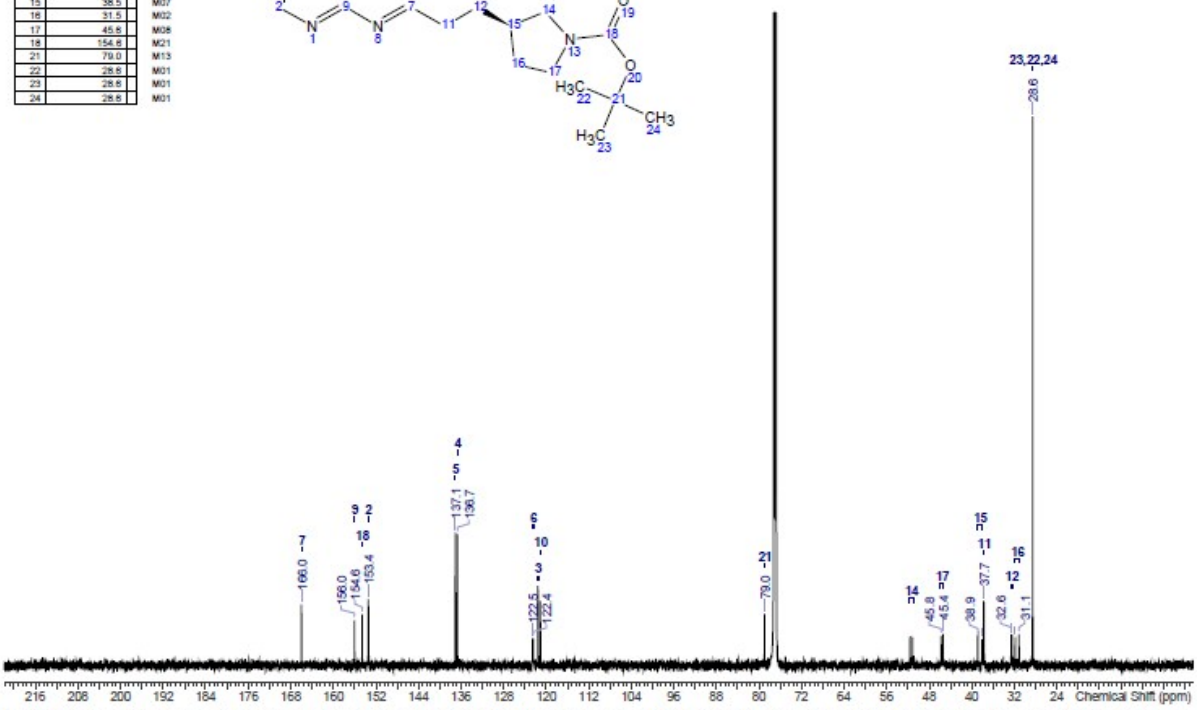


^{1}H NMR (CHLOROFORM-d ,600MHz): δ (ppm) 9.10 (d, J=2.2 Hz, 1H, (H-2)), 8.17 (dd, J=8.1, 1.7 Hz, 1H, (H-4)), 8.11 (d, J=8.1 Hz, 1H, (H-5)), 7.46 (dd, J=7.9, 4.2 Hz, 1H, (H-3)), 7.40 (d, J=8.3 Hz, 1H, (H-6)), 3.53 - 3.67 (m, 1H, (H-14<*>)), 3.44 (br. s., 1H, (H-17<*>)), 3.20 - 3.33 (m, 1H, (H-17<*>)), 3.04 - 3.16 (m, 2H, (H-11)), 2.88 - 3.03 (m, 1H, (H-14<*>)), 2.16 - 2.34 (m, 1H, (H-15)), 2.03 - 2.10 (m, 1H, (H-16<*>)), 2.00 - 2.06 (m, 2H, (H-12)), 1.52 - 1.64 (m, 1H, (H-16<*>)), 1.46 (s, 9H, (H-23, 22, 24))

(*R*)-*tert*-Butyl 3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (9)

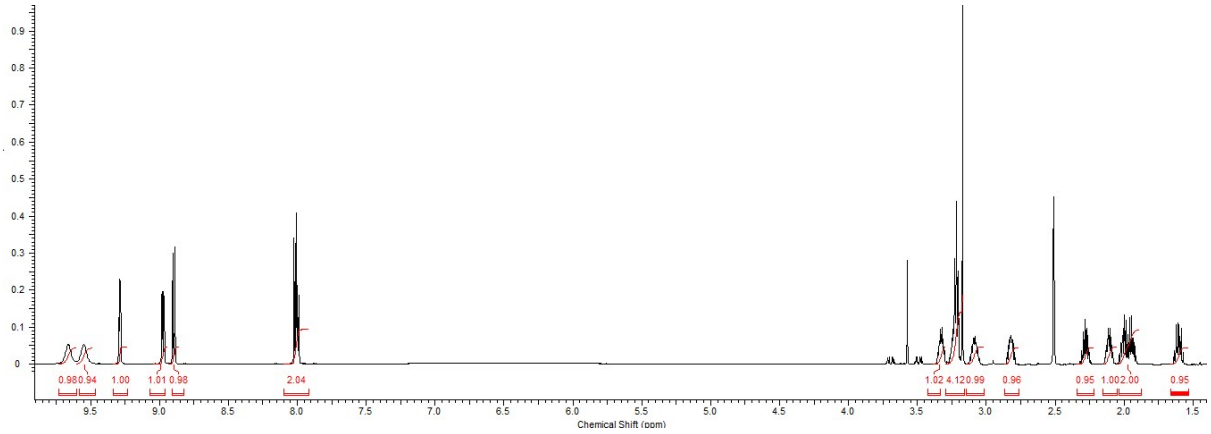
Atom	Exp. Shift (ppm)		Multiplet
2	153.4		M20
3	121.5		M15
4	136.7		M18
5	137.1		M19
6	122.5		M04
7	166.0		M23
9	156.0		M22
10	121.1		M14
11	37.7		M06
12	32.5		M03
14	51.4		M05
15	38.5		M07
16	31.5		M02
17	45.8		M08
18	154.6		M21
21	79.0		M13
22	28.6		M01
23	28.6		M01
24	28.6		M01



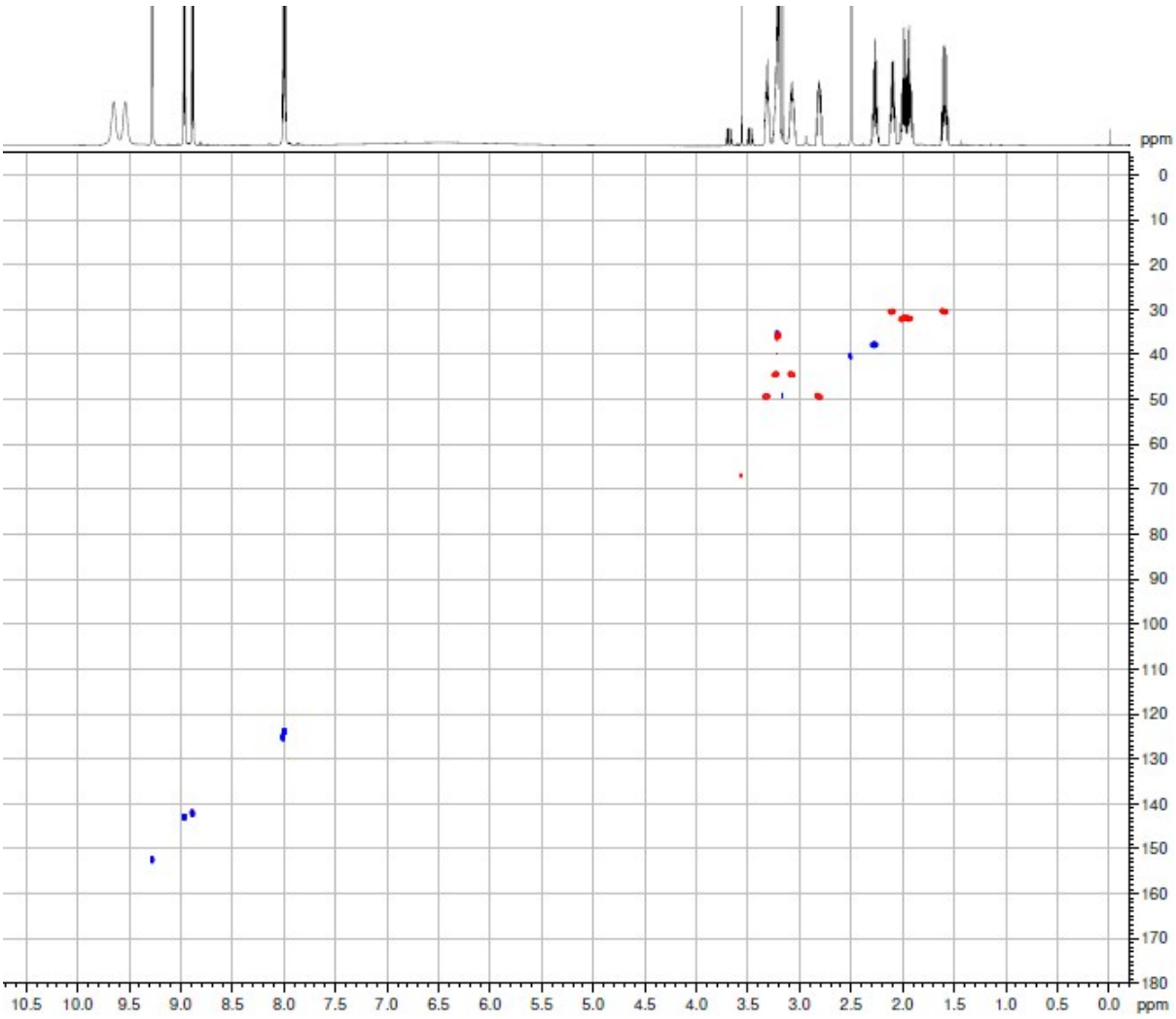


^{13}C NMR (CHLOROFORM-d ,151MHz): δ (ppm) 166.0 (s, 1C, (C-7)), 156.0 (s, 1C, (C-9)), 154.6 (s, 1C, (C-18)), 153.4 (s, 1C, (C-2)), 137.1 (s, 1C, (C-5)), 136.7 (s, 1C, (C-4)), 122.5 (s, 1C, (C-6)), 121.5 (s, 1C, (C-3)), 121.1 (s, 1C, (C-10)), 79.0 (s, 1C, (C-21)), 51.1 - 51.7 (m, 1C, (C-14)), 45.3 - 45.9 (m, 1C, (C-17)), 38.0 - 39.0 (m, 1C, (C-15)), 37.7 (s, 1C, (C-11)), 32.4 - 32.7 (m, 1C, (C-12)), 31.0 - 31.9 (m, 1C, (C-16)), 28.6 (s, 3C, (C-23, 22, 24))

(*R*)-2-(2-(Pyrrolidin-3-yl)ethyl)-1,8-naphthyridine, dihydrochloride salt (10)

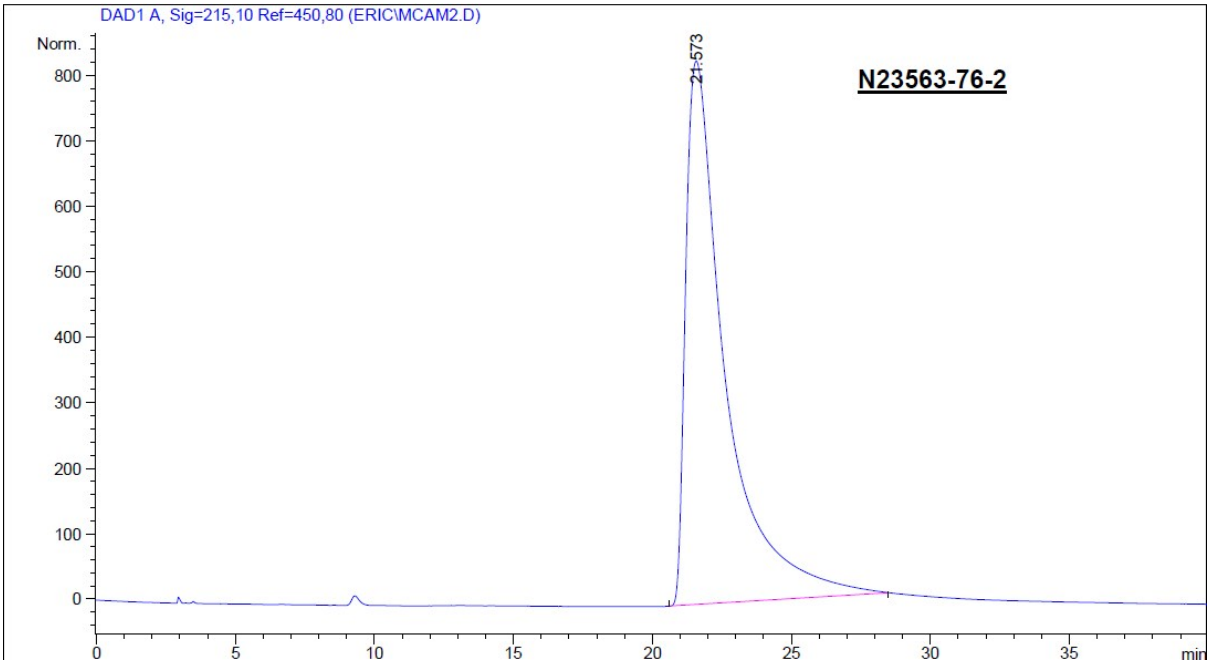


(*R*)-2-(2-(Pyrrolidin-3-yl)ethyl)-1,8-naphthyridine, dihydrochloride salt (10) Ed HSQC

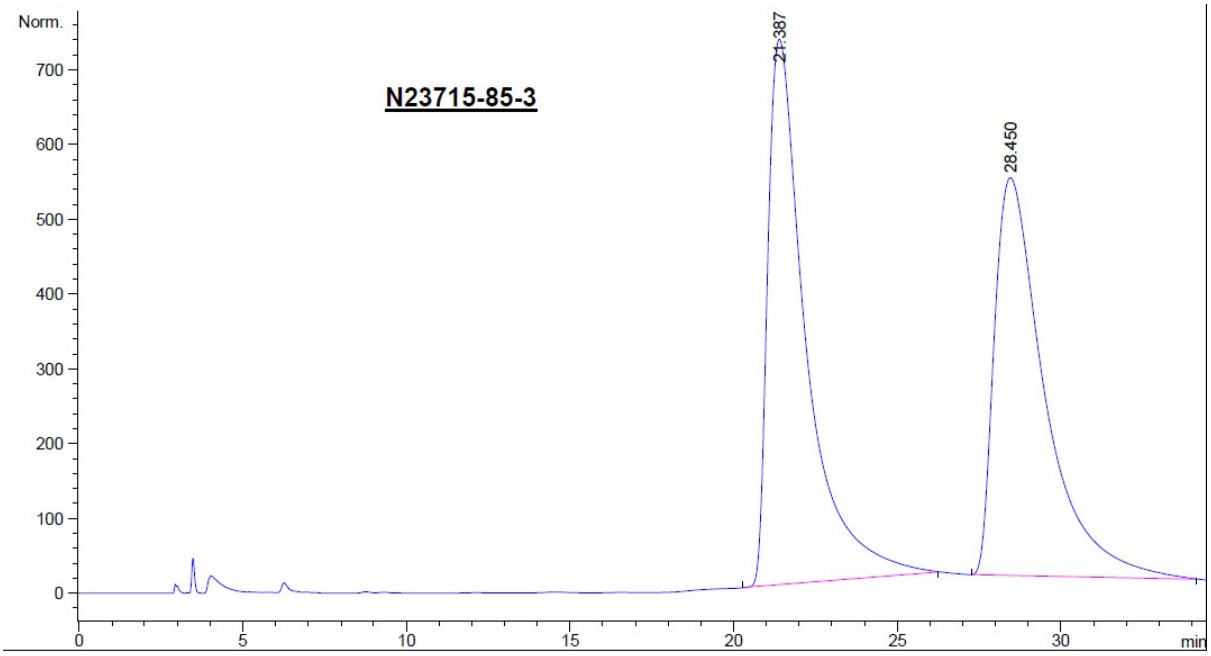


(*R*)-2-(2-(Pyrrolidin-3-yl)ethyl)-1,8-naphthyridine, dihydrochloride salt (10)

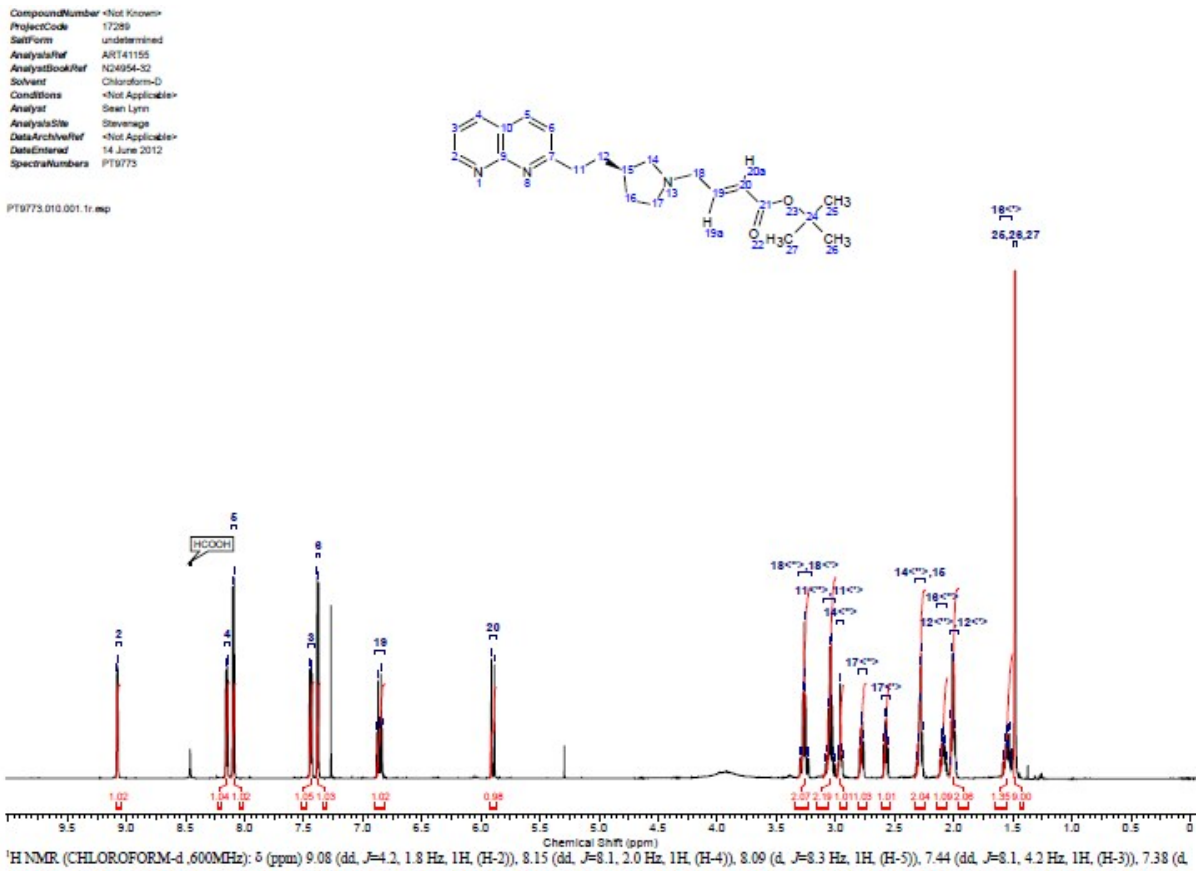
(*R*)-2-(2-(Pyrrolidin-3-yl)ethyl)-1,8-naphthyridine, dihydrochloride salt (10)



(±)-2-(2-(Pyrrolidin-3-yl)ethyl)-1,8-naphthyridine, dihydrochloride salt (10)



(*R*,*E*)-*tert*-Butyl 4-(3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)but-2-enoate (11)



^{1}H NMR (CHLOROFORM-d ,600MHz): δ (ppm) 9.08 (dd, *J*=4.2, 1.8 Hz, 1H, (H-2)), 8.15 (dd, *J*=8.1, 2.0 Hz, 1H, (H-4)), 8.09 (d, *J*=8.3 Hz, 1H, (H-5)), 7.44 (dd, *J*=8.1, 4.2 Hz, 1H, (H-3)), 7.38 (d, *J*=8.3 Hz, 1H, (H-6)), 6.86 (dt, *J*=15.7, 6.3 Hz, 1H, (H-19)), 5.90 (d, *J*=15.8 Hz, 1H, (H-20)), 3.20 - 3.32 (m, 2H, (H-18<*>, 18<>)), 3.00 - 3.11 (m, 2H, (H-11<*>, 11<>)), 2.93 - 2.99 (m, 1H, (H-14<*>)), 2.74 - 2.81 (m, 1H, (H-17<*>)), 2.57 (td, *J*=8.9, 6.1 Hz, 1H, (H-17<>)), 2.24 - 2.33 (m, 2H, (H-14<*>, 15)), 2.06 - 2.14 (m, 1H, (H-16<*>)), 1.96 - 2.04 (m, 2H, (H-12<*>, 12<>)), 1.50 - 1.60 (m, 1H, (H-16<>)), 1.48 (s, 9H, (H-25, 26, 27))

(*R*,*E*)-*tert*-Butyl 4-(3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)but-2-enoate (11)

Number of Nuclei	22 C's / 22 C's (spectra / structure)
ChemistBookRef	N23499-52-1
CompoundNumber	<Not Known>
ProjectCode	17289
SaltForm	undetermined
AnalysisRef	ART41155
AnalystBookRef	N24954-32
Solvent	Chloroform-D
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
DataArchiveRef	<Not Applicable>
DateEntered	14 June 2012
SpectraNumbers	PT9773

PT9773.011.001.1r.mp

Atom	Exp. Shift (ppm)
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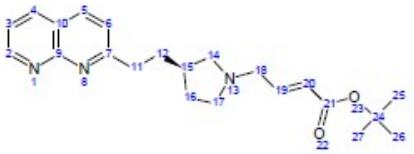
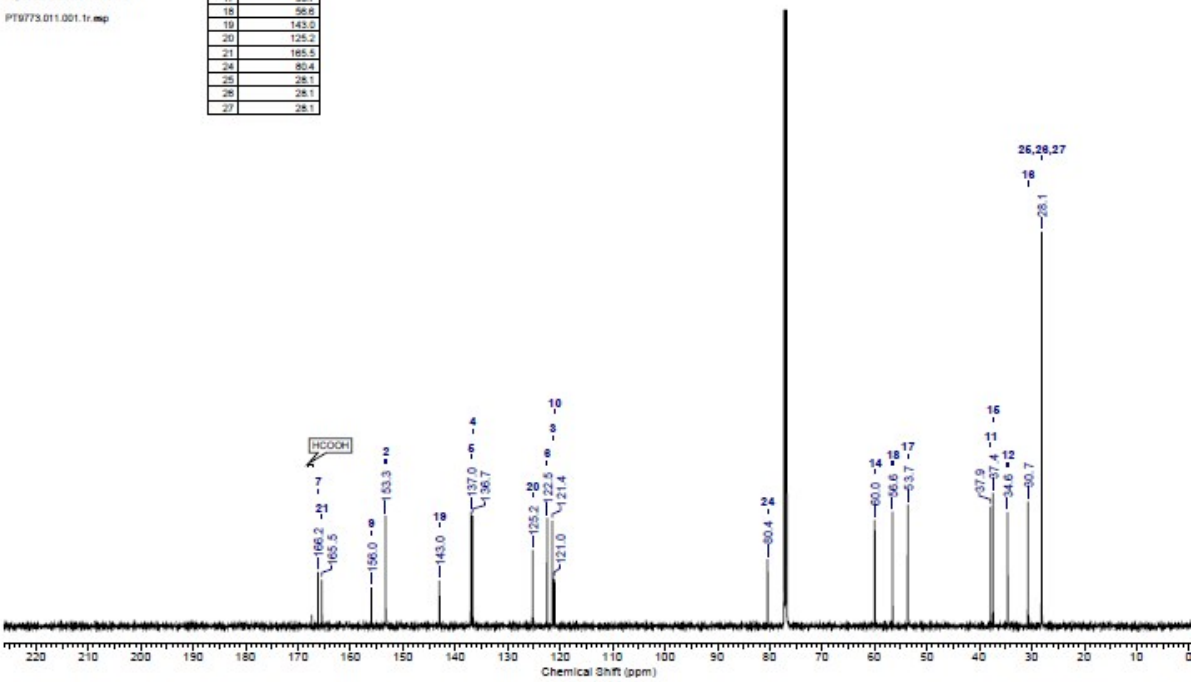
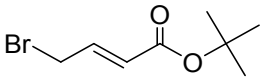
3	121.4
4	136.7
5	137.0
6	122.5
7	166.2
9	156.0
10	121.0
11	37.9
12	34.6
14	60.0
15	37.4
16	30.7
17	53.7
18	56.6
19	143.0
20	125.2
21	165.5
24	80.4
25	28.1
26	28.1
27	28.1

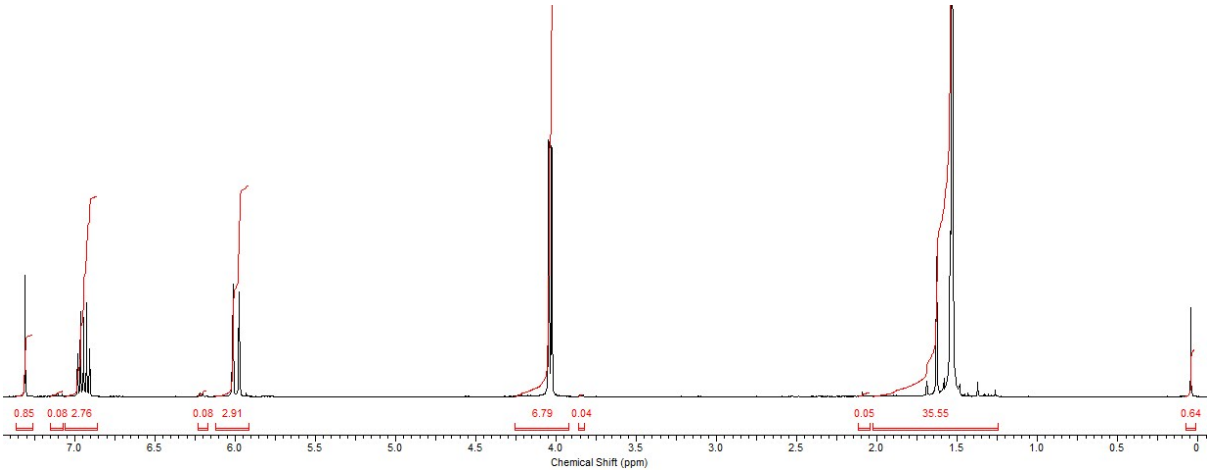




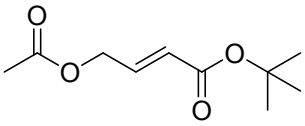
^{13}C NMR (CHLOROFORM-d ,151MHz): δ (ppm) 166.2 (s, 1C, (C-7)), 165.5 (s, 1C, (C-21)), 156.0 (s, 1C, (C-9)), 153.3 (s, 1C, (C-2)), 143.0 (s, 1C, ((C-19)), 137.0 (s, 1C, (C-5)), 136.7 (s, 1C, (C-4)), 125.2 (s, 1C, (C-20)), 122.5 (s, 1C, (C-6)), 121.4 (s, 1C, (C-3)), 121.0 (s, 1C, (C-10)), 80.4 (s, 1C, (C-24)), 60.0 (s, 1C, ((C-14)), 56.6 (s, 1C, ((C-18)), 53.7 (s, 1C, ((C-17)), 37.9 (s, 1C, ((C-11)), 37.4 (s, 1C, (C-15)), 34.6 (s, 1C, (C-12)), 30.7 (s, 1C, (C-16)), 28.1 (s, 3C, (C-25, 26, 27))

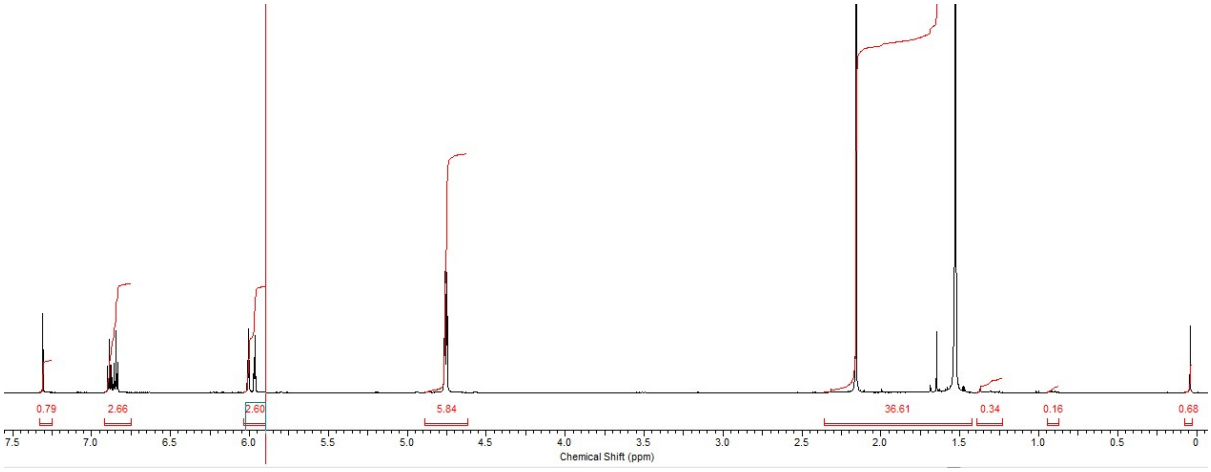
(*E*)-*tert*-Butyl 4-bromobut-2-enoate (12)



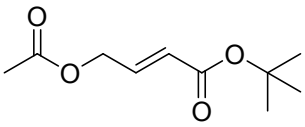


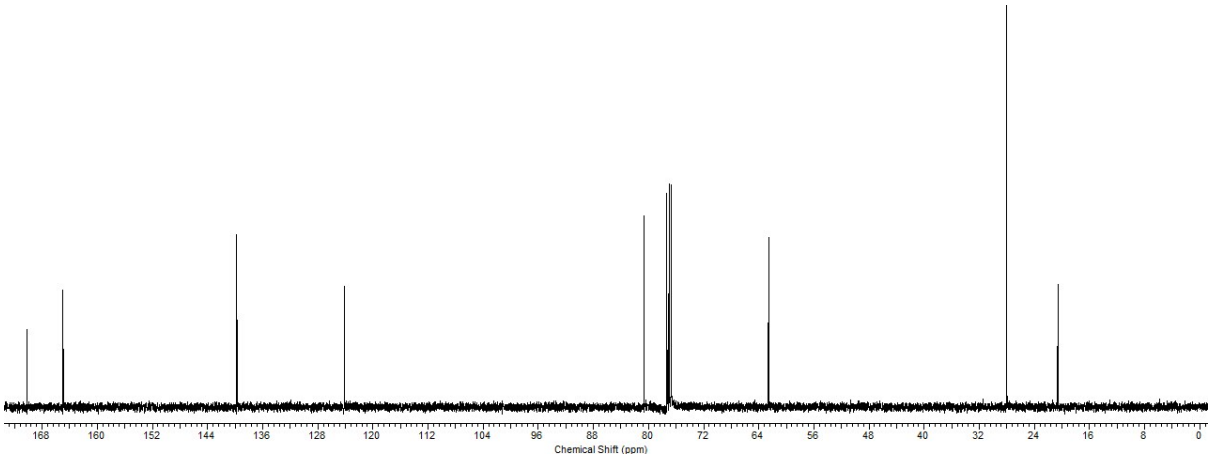
(*E*)-*tert*-Butyl 4-acetoxybut-2-enoate (14)



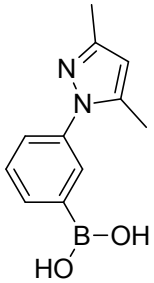


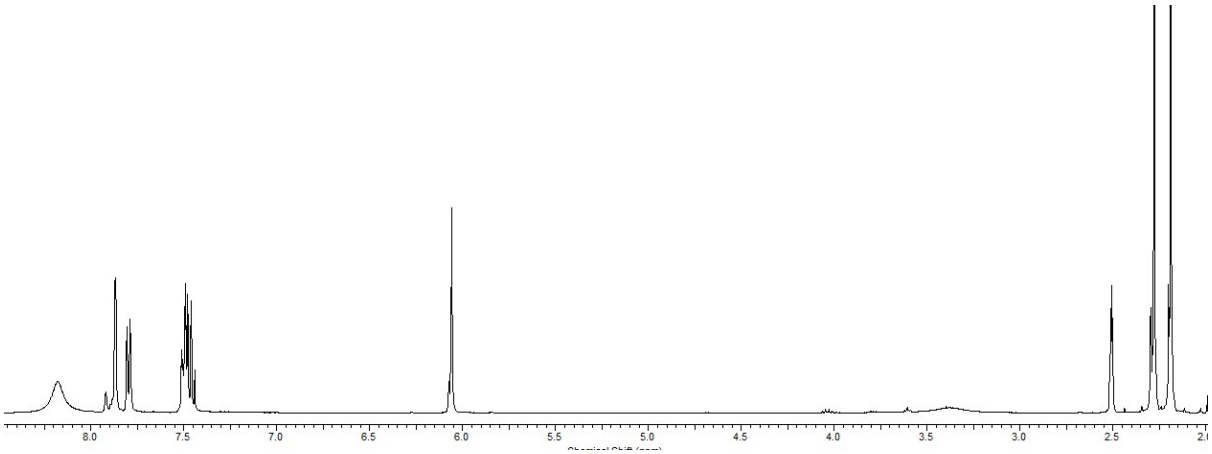
(*E*)-*tert*-Butyl 4-acetoxybut-2-enoate (14)

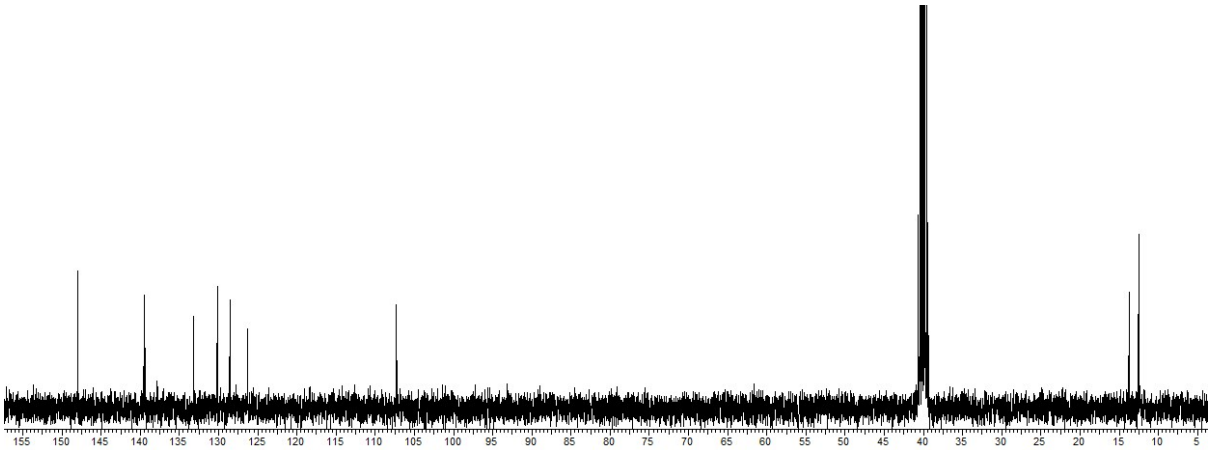




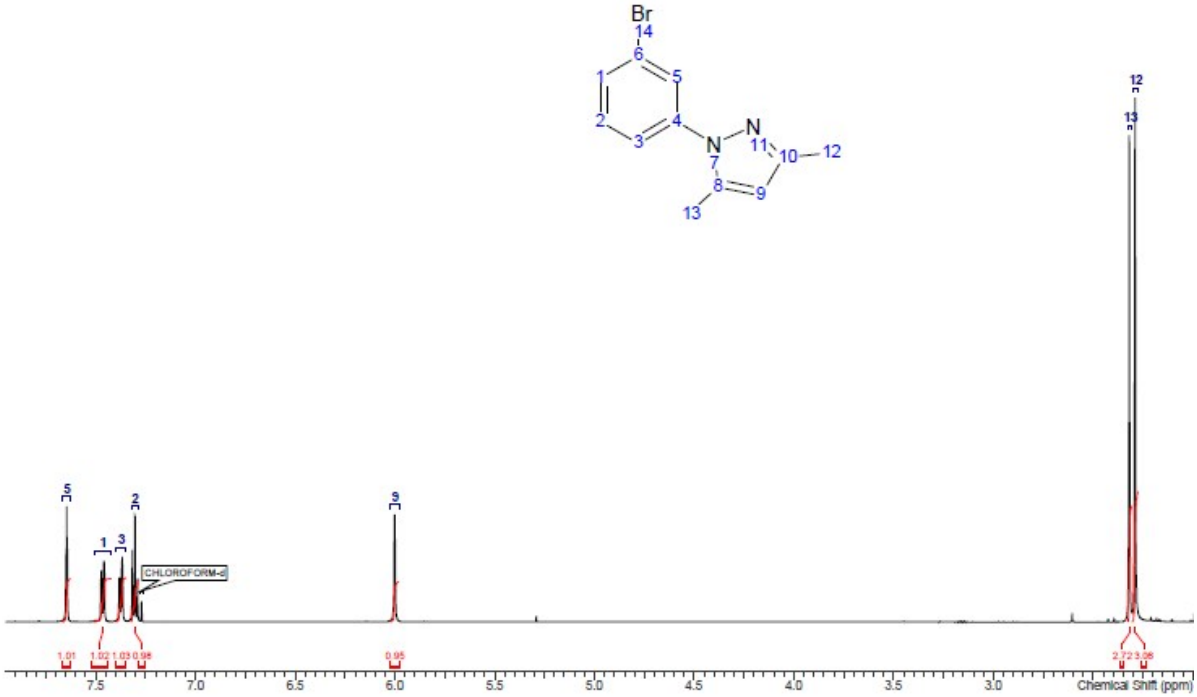
(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)boronic acid (15)



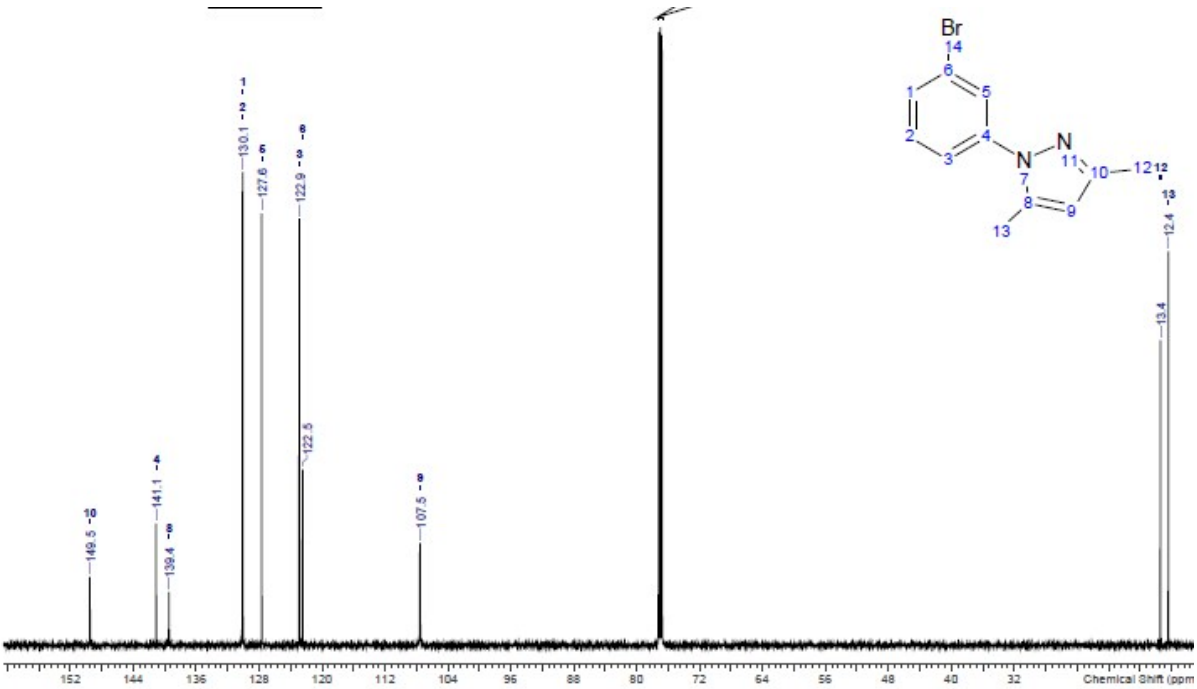




1-(3-Bromophenyl)-3,5-dimethyl-1*H*-pyrazole (17)

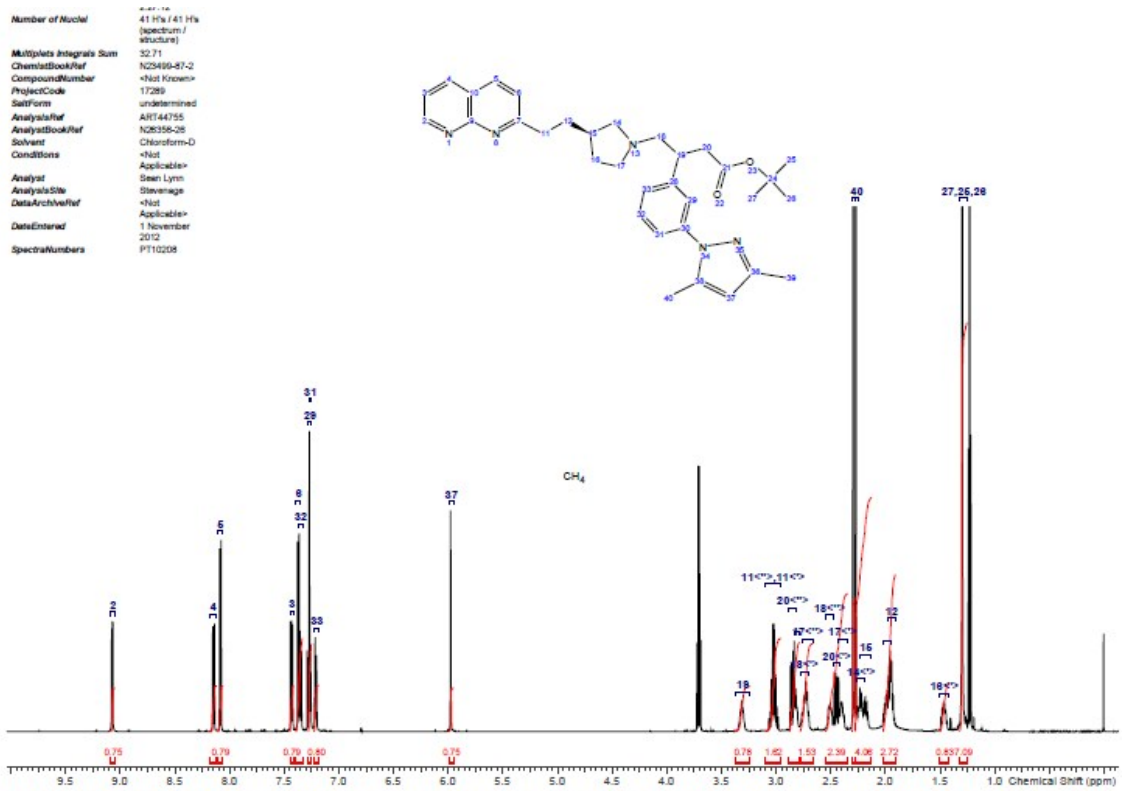


^{1}H NMR (CHLOROFORM-d ,600MHz): δ (ppm) 7.65 (t, *J*=1.5 Hz, 1H, (H-5)), 7.42 - 7.51 (m, 1H, (H-1)), 7.35 - 7.40 (m, 1H, (H-3)), 7.30 (t, *J*=8.0 Hz, 1H, (H-2)), 6.00 (s, 1H, (H-9)), 2.32 (s, 3H, (H-13)), 2.29 (s, 3H, (H-12))



^{13}C NMR (CHLOROFORM-d ,151MHz): δ (ppm) 149.5 (s, 1C, (C-10)), 141.1 (s, 1C, (C-4)), 139.4 (s, 1C, (C-8)), 130.1 (s, 1C, (C-2)), 130.1 (s, 1C, (C-1)), 127.6 (s, 1C, (C-5)), 122.9 (s, 1C, (C-3)), 122.5 (s, 1C, (C-6)), 107.5 (s, 1C, (C-9)), 13.4 (s, 1C, (C-12)), 12.4 (s, 1C, (C-13))

tert-Butyl 4-((_R_)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1_H_-pyrazol-1-yl)phenyl)butanoate (18a)

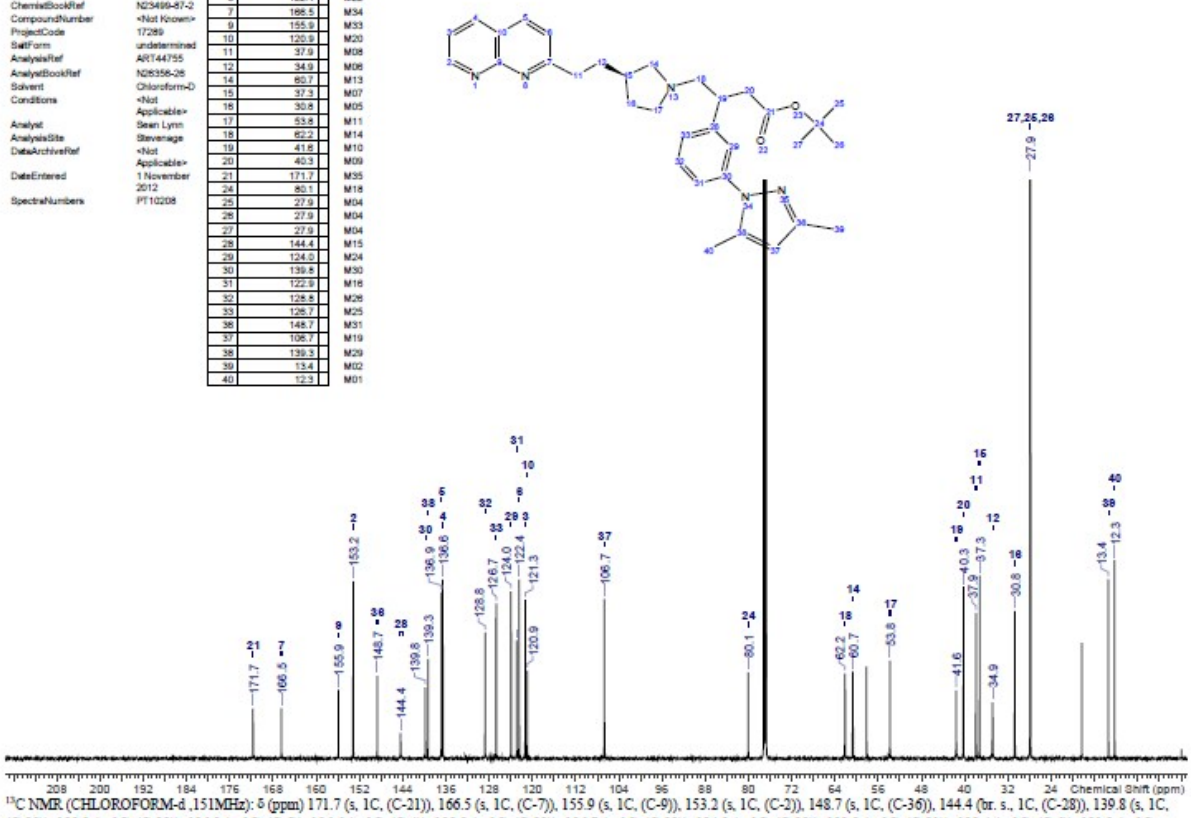


^{1}H NMR (CHLOROFORM-d ,600MHz): δ (ppm) 9.07 (dd, J=4.2, 2.0 Hz, 1H, (H-2)), 8.15 (dd, J=8.0, 1.9 Hz, 1H, (H-4)), 8.08 (d, J=8.4 Hz, 1H, (H-5)), 7.43 (dd, J=8.0, 4.3 Hz, 1H, (H-3)), 7.37 (d, J=8.3 Hz, 1H, (H-6)), 7.33 - 7.37 (m, 1H, (H-32)), 7.27 (d, J=1.1 Hz, 1H, (H-39)), 7.25 - 7.27 (m, 1H, (H-31)), 7.21 (d, J=7.7 Hz, 1H, (H-33)), 5.98 (s, 1H, (H-37)), 3.31 (d, J=5.3 Hz, 1H, (H-19)), 2.95 - 3.10 (m, 2H, (H-11<r>, 11<r>)), 2.85 (dd, J=15.4, 5.7 Hz, 1H, (H-20<r>)), 2.79 - 2.84 (m, 1H, (H-14<r>)), 2.71 - 2.78 (m, 1H, (H-18<r>)), 2.67 - 2.75 (m, 1H, (H-17<r>)), 2.47 - 2.55 (m, 1H, (H-18<r>)), 2.41 - 2.48 (m, 1H, (H-20<r>)), 2.35 - 2.43 (m, 1H, (H-17<r>)), 2.30 (s, 3H, (H-39)), 2.27 (s, 3H, (H-40)), 2.18 - 2.26 (m, 1H, (H-14<r>)), 2.13 - 2.23 (m, 1H, (H-15)), 1.95 - 2.02 (m, 1H, (H-16<r>)), 1.91 - 1.98 (m, 2H, (H-12)), 1.42 - 1.50 (m, 1H, (H-16<r>)), 1.30 (s, 9H, (H-27, 25, 26))

tert-Butyl 4-((_R_)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1_H_-pyrazol-1-yl)phenyl)butanoate (18a)

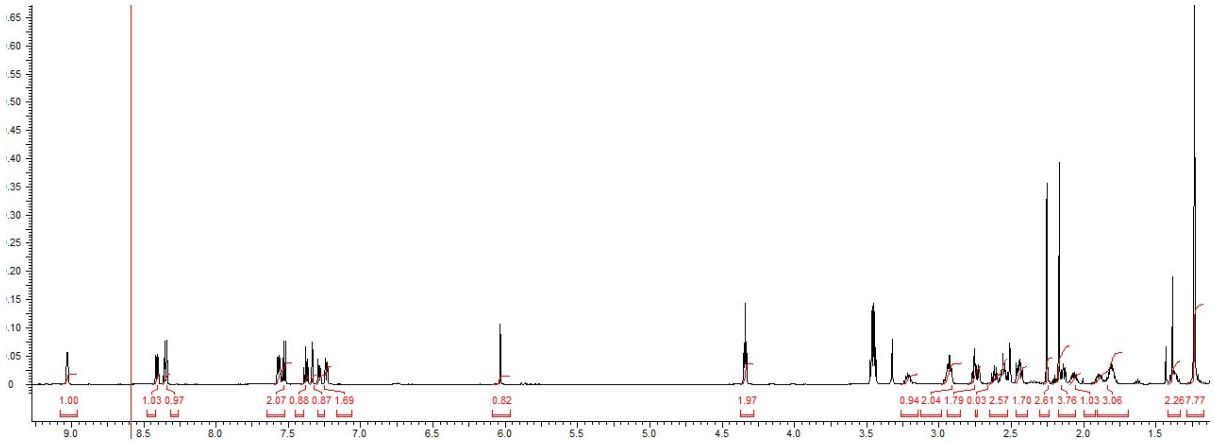
OriginalDateForRelativeTime	2012-10-31T07:36:32
Multiplets Integrals Sum	0.00
Number of Nuclei	33 C's / 33 C's (spectrum / structure)
ChemicalBookRef	N25499-87-2
CompoundNumber	<Not Known>
ProjectCode	17289
SaltForm	undetermined
AnalysisRef	ART44755
AnalystBookRef	N28358-26
Solvent	Chloroform-D
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
DataArchiveRef	<Not Applicable>
DateEntered	1 November 2012
SpectraNumbers	PT10208

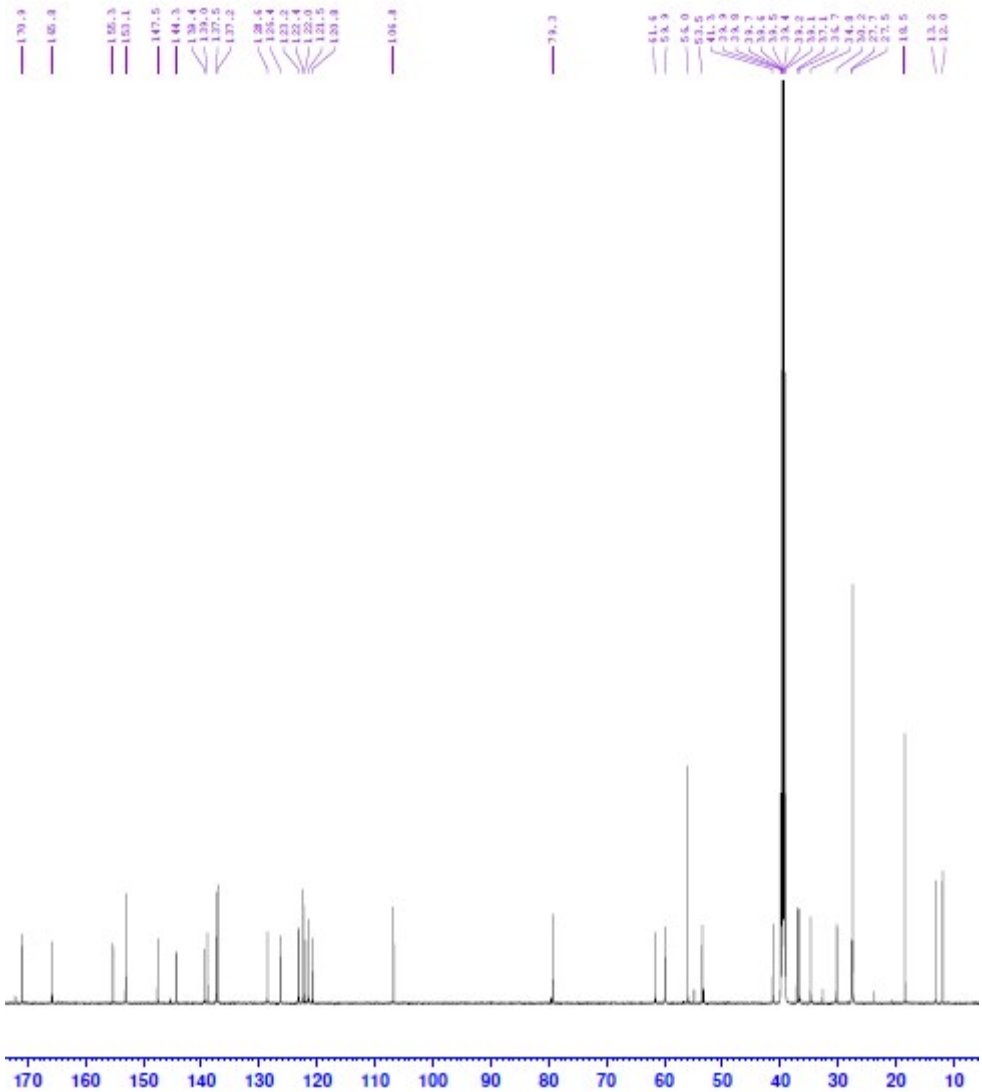
Atom	Exp. Shift (ppm)	Multiplet
2	153.2	M32
3	121.3	M21
4	136.6	M27
5	136.9	M26
6	122.4	M22
7	166.5	M34
9	155.9	M33
10	120.9	M20
11	37.9	M08
12	34.9	M06
14	60.7	M13
15	37.3	M07
16	30.8	M05
17	53.8	M11
18	62.2	M14
19	41.6	M10
20	40.3	M09
21	171.7	M35
24	80.1	M18
25	27.9	M04
26	27.9	M04
27	27.9	M04
28	144.4	M15
29	124.0	M24
30	139.8	M30
31	122.9	M16
32	126.8	M26
33	126.7	M25
36	148.7	M31
37	106.7	M19
38	139.3	M29
39	13.4	M02
40	12.3	M01



^{13}C NMR (CHLOROFORM-d ,151MHz): δ (ppm) 171.7 (s, 1C, (C-21)), 166.5 (s, 1C, (C-7)), 155.9 (s, 1C, (C-9)), 153.2 (s, 1C, (C-2)), 148.7 (s, 1C, (C-36)), 144.4 (br. s., 1C, (C-28)), 139.8 (s, 1C, (C-30)), 139.3 (s, 1C, (C-38)), 136.9 (s, 1C, (C-5)), 136.6 (s, 1C, (C-4)), 128.8 (s, 1C, (C-32)), 126.7 (s, 1C, (C-33)), 124.0 (s, 1C, (C-29)), 122.9 (s, 1C, (C-31)), 122.4 (s, 1C, (C-6)), 121.3 (s, 1C, (C-3)), 120.9 (s, 1C, (C-10)), 106.7 (s, 1C, (C-37)), 80.1 (s, 1C, (C-24)), 62.2 (s, 1C, (C-18)), 60.7 (s, 1C, (C-14)), 53.8 (s, 1C, (C-17)), 41.6 (s, 1C, (C-19)), 40.3 (s, 1C, (C-20)), 37.9 (s, 1C, (C-11)), 37.3 (s, 1C, (C-15)), 34.9 (s, 1C, (C-12)), 30.8 (s, 1C, (C-16)), 27.9 (s, 3C, (C-27, 25, 26)), 13.4 (s, 1C, (C-39)), 12.3 (s, 1C, (C-40))

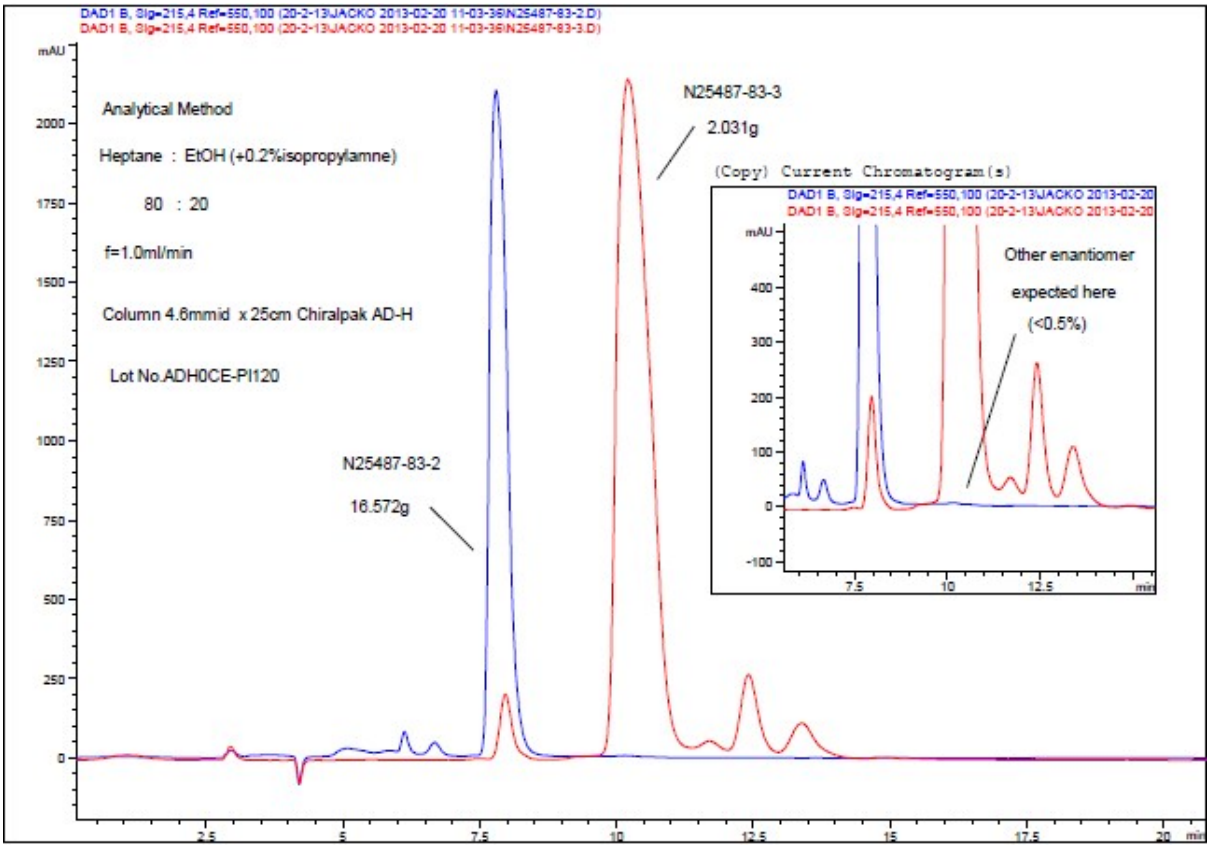
***tert*-Butyl 4-((*R*)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)butanoate (18b)**



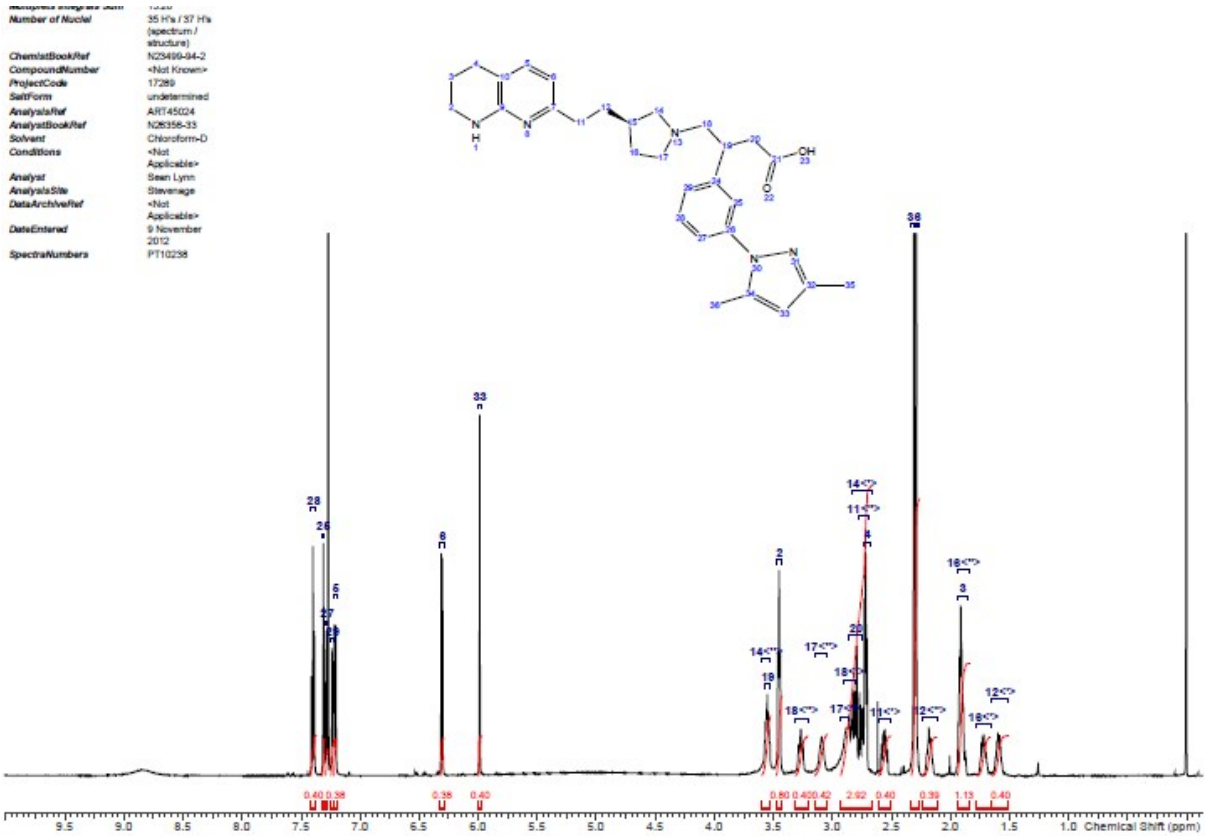


***tert*-Butyl 4-((*R*)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)butanoate (18a) and**

***tert*-Butyl 4-((*R*)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)butanoate (18b)**



3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (1a)



^{1}H NMR (CHLOROFORM-d ,600MHz): δ (ppm) 7.37 - 7.42 (m, 1H, (H-28)), 7.31 (d, *J*=1.5 Hz, 1H, (H-25)), 7.29 (d, *J*=0.9 Hz, 1H, (H-27)), 7.23 (d, *J*=7.7 Hz, 1H, (H-29)), 7.21 (d, *J*=7.3 Hz, 1H, (H-5)), 6.31 (d, *J*=7.3 Hz, 1H, (H-6)), 5.99 (s, 1H, (H-33)), 3.55 (br. s., 1H, (H-19)), 3.52 - 3.60 (m, 1H, (H-14<>)), 3.45 (t, *J*=5.4 Hz, 2H, (H-2)), 3.27 (t, *J*=10.6 Hz, 1H, (H-18<>)), 3.09 (br. s., 1H, (H-17<>)), 2.86 - 2.93 (m, 1H, (H-17<>)), 2.82 (d, *J*=10.1 Hz, 1H, (H-18<>)), 2.75 - 2.86 (m, 2H, (H-20)), 2.72 (t, *J*=6.2 Hz, 1H, (H-11<>)), 2.67 - 2.74 (m, 2H, (H-4)), 2.75 (d, *J*=9.0 Hz, 1H, (H-14<>)), 2.50 - 2.61 (m, 1H, (H-11<>)), 2.31 (s, 3H, (H-36)), 2.29 (s, 3H, (H-35)), 2.26 - 2.33 (m, 1H, (H-15)), 2.11 - 2.24 (m, 1H, (H-12<>)), 1.86 - 1.94 (m, 2H, (H-3)), 1.84 - 1.94 (m, 1H, (H-16<>)), 1.66 - 1.78 (m, 1H, (H-16<>)), 1.51 - 1.65 (m, 1H, (H-12<>))

3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (1a)

OriginalDateForRelativeTime	2012-11-08T19:31:12
Multiplets Integrals Sum	0.00
Number of Nuclei	29 C's / 29 C's (spectrum / structure)
ChemistBookRef	N25499-94-2
CompoundNumber	<Not Known>
ProjectCode	17289
SaltForm	undetermined
AnalysisRef	ART45024
AnalystBookRef	N26358-33
Solvent	Chloroform-D
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
DataArchiveRef	<Not Applicable>
DateEntered	9 November 2012
SpectraNumbers	PT10298

Atom	Exp. Shift (ppm)	Multiplet
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4	25.8	M05
5	139.3	M22
6	109.7	M16
7	150.6	M28
9	153.6	M26
10	117.4	M17
11	32.8	M07
12	30.3	M06
14	56.7	M01
15	36.9	M09
16	35.5	M08
17	54.5	M13
18	63.3	M14
19	40.0	M10
20	44.1	M12
21	177.7	M27
24	144.4	M29
25	123.7	M19
27	123.2	M18
28	129.4	M21
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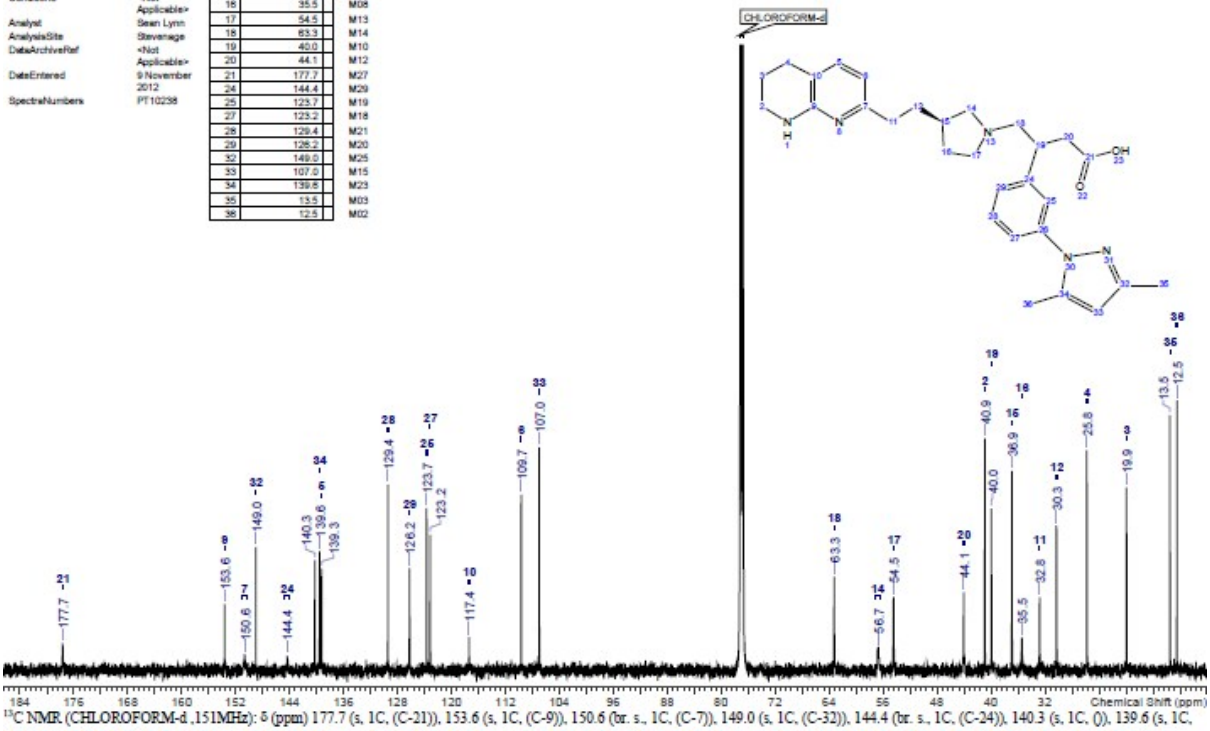
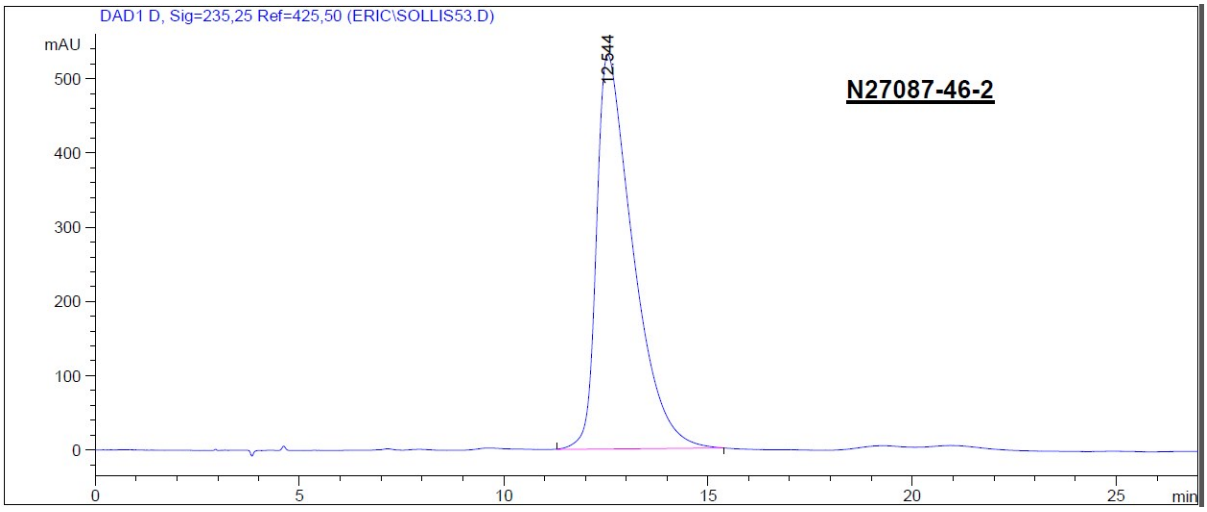
35	13.5	M03
36	12.5	M02

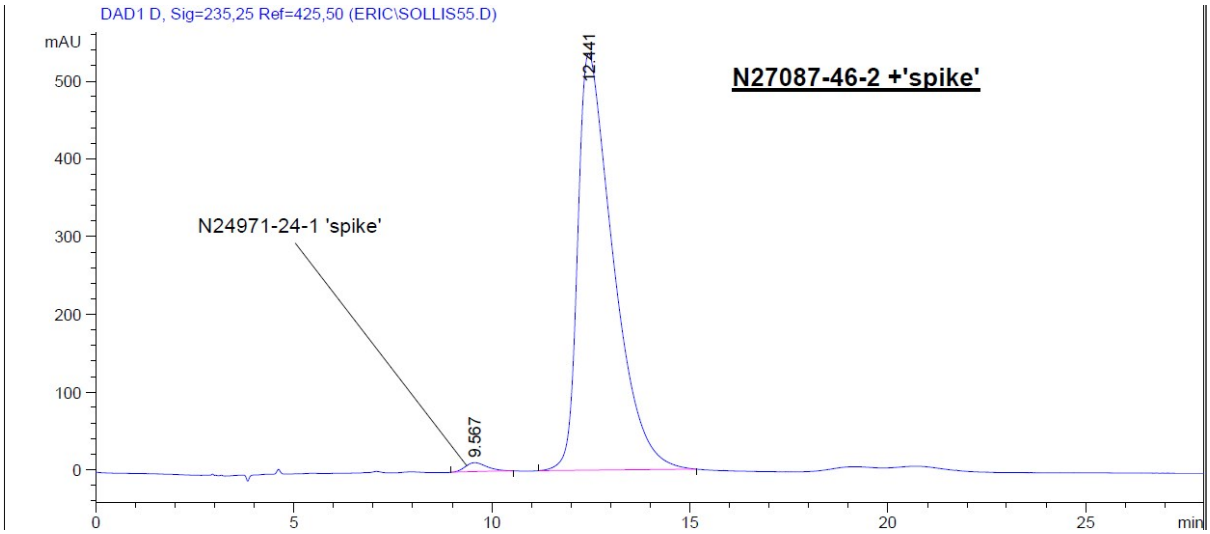


^{13}C NMR (CHLOROFORM-d ,151MHz): δ (ppm) 177.7 (s, 1C, (C-21)), 153.6 (s, 1C, (C-9)), 150.6 (br. s., 1C, (C-7)), 149.0 (s, 1C, (C-32)), 144.4 (br. s., 1C, (C-24)), 140.3 (s, 1C, ()), 139.6 (s, 1C, (C-34)), 139.3 (s, 1C, (C-5)), 129.4 (s, 1C, (C-28)), 126.2 (s, 1C, (C-29)), 123.7 (s, 1C, (C-25)), 123.2 (s, 1C, (C-27)), 117.4 (s, 1C, (C-10)), 109.7 (s, 1C, (C-6)), 107.0 (s, 1C, (C-33)), 63.3 (s, 1C, (C-18)), 56.7 (br. s., 1C, (C-14)), 54.5 (s, 1C, (C-17)), 44.1 (s, 1C, (C-20)), 40.9 (s, 1C, (C-2)), 40.0 (s, 1C, (C-19)), 36.9 (s, 1C, (C-15)), 35.5 (s, 1C, (C-16)), 32.8 (s, 1C, (C-11)), 30.3 (s, 1C, (C-12)), 25.8 (s, 1C, (C-4)), 19.9 (s, 1C, (C-3)), 13.5 (s, 1C, (C-35)), 12.5 (s, 1C, (C-36))

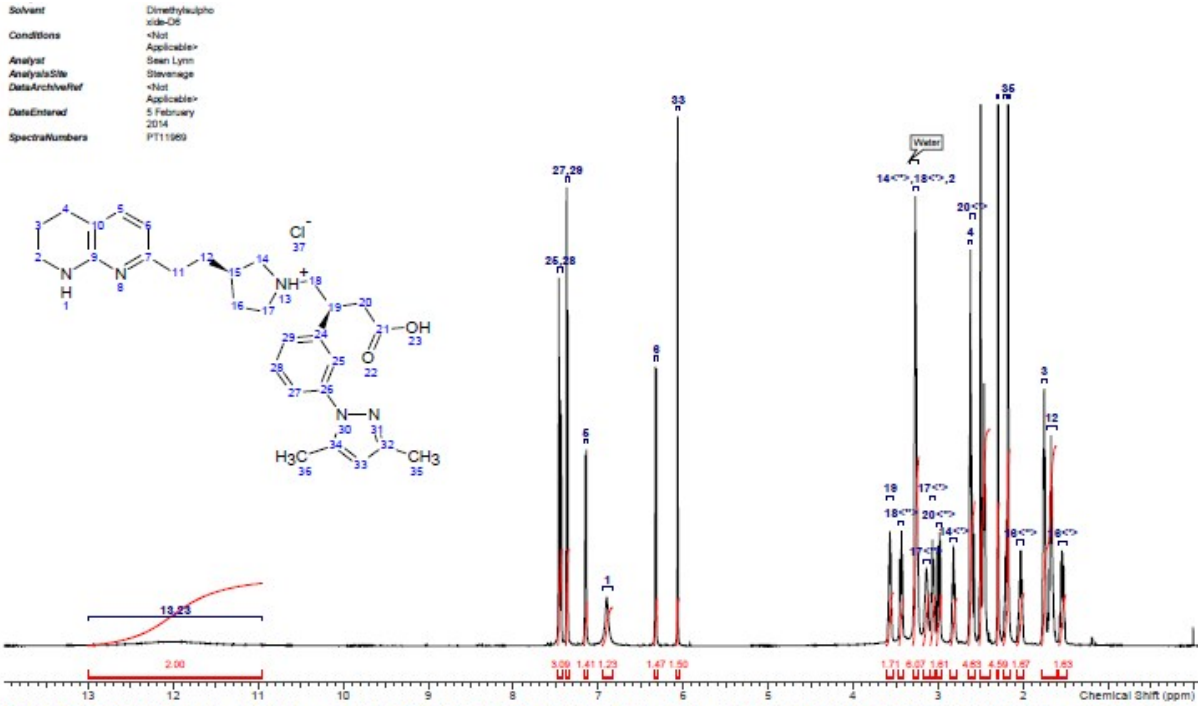
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (1a)



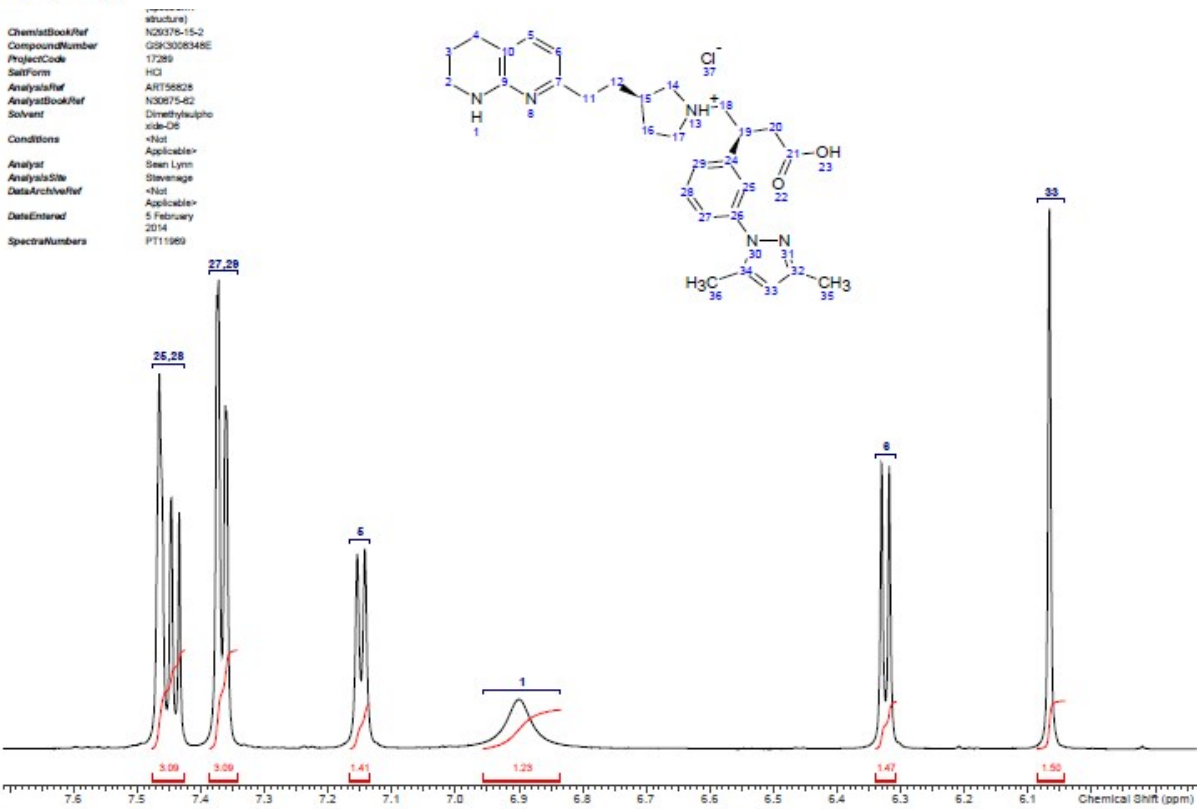
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (1a) + spike with (1b)



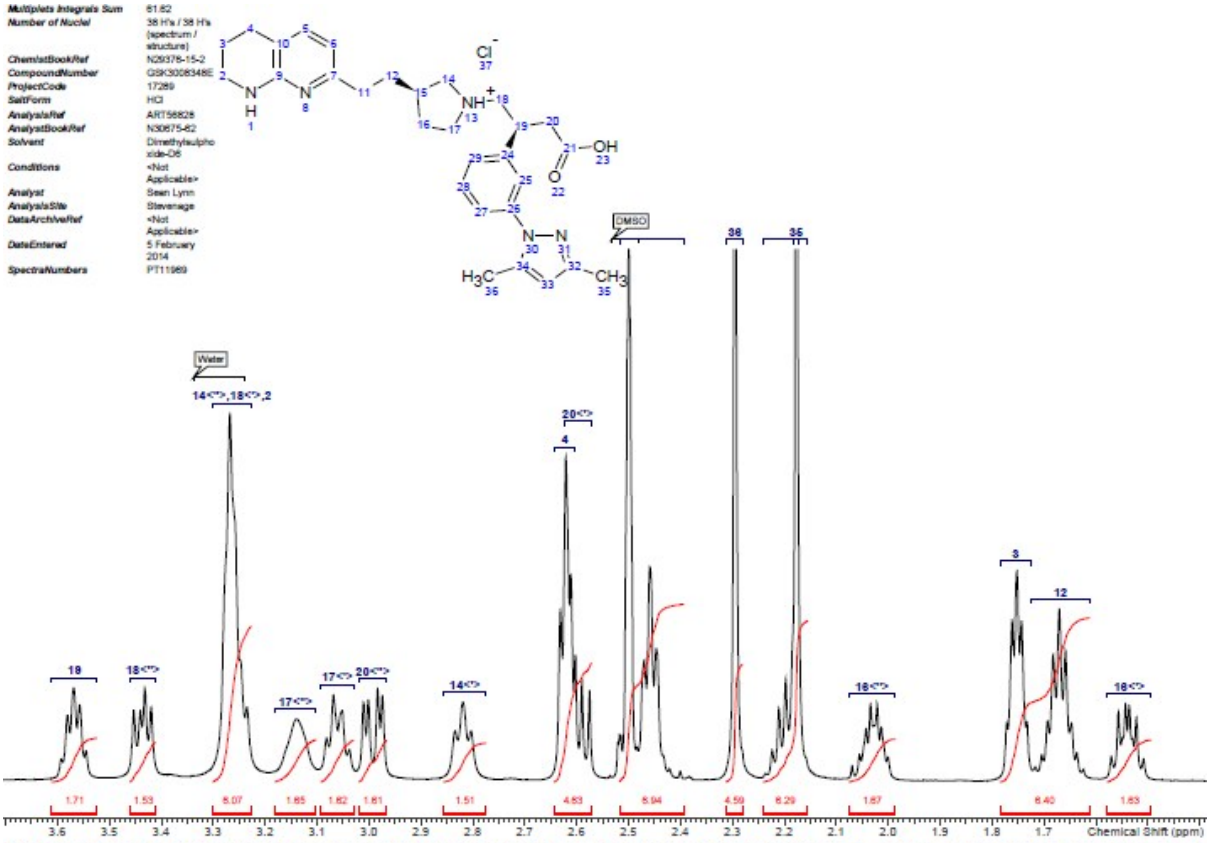
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl).



^{1}H NMR (DMSO-d_6 ,600MHz): ā (ppm) 12.01 (br. s., 2H, (H-13, 23)), 7.43 - 7.48 (m, 2H, (H-25, 28)), 7.34 - 7.39 (m, 2H, (H-27, 29)), 7.15 (d, J=7.5 Hz, 1H, (H-5)), 6.90 (br. s., 1H, (H-1)), 6.32 (d, J=7.5 Hz, 1H, (H-6)), 6.07 (s, 1H, (H-33)), 3.57 (quin, J=7.0 Hz, 1H, (H-19)), 3.44 (dd, J=13.0, 7.4 Hz, 1H, (H-18<>)), 3.23 - 3.30 (m, 4H, (H-14<>, 18<>, 2)), 3.10 - 3.18 (m, 1H, (H-17<>)), 3.03 - 3.09 (m, 1H, (H-17<>)), 2.99 (dd, J=16.0, 5.5 Hz, 1H, (H-20<>)), 2.82 (t, J=9.5 Hz, 1H, (H-14<>)), 2.62 (t, J=6.1 Hz, 2H, (H-4)), 2.57 - 2.62 (m, 1H, (H-20<>)), 2.39 - 2.52 (m, 2H, (H-11)), 2.30 (s, 3H, (H-36)), 2.18 (s, 3H, (H-35)), 2.16 - 2.24 (m, 1H, (H-15)), 1.99 - 2.08 (m, 1H, (H-16<>)), 1.75 (quin, J=6.0 Hz, 2H, (H-3)), 1.61 - 1.72 (m, 2H, (H-12)), 1.54 (dq, J=13.0, 8.0 Hz, 1H, (H-16<>))

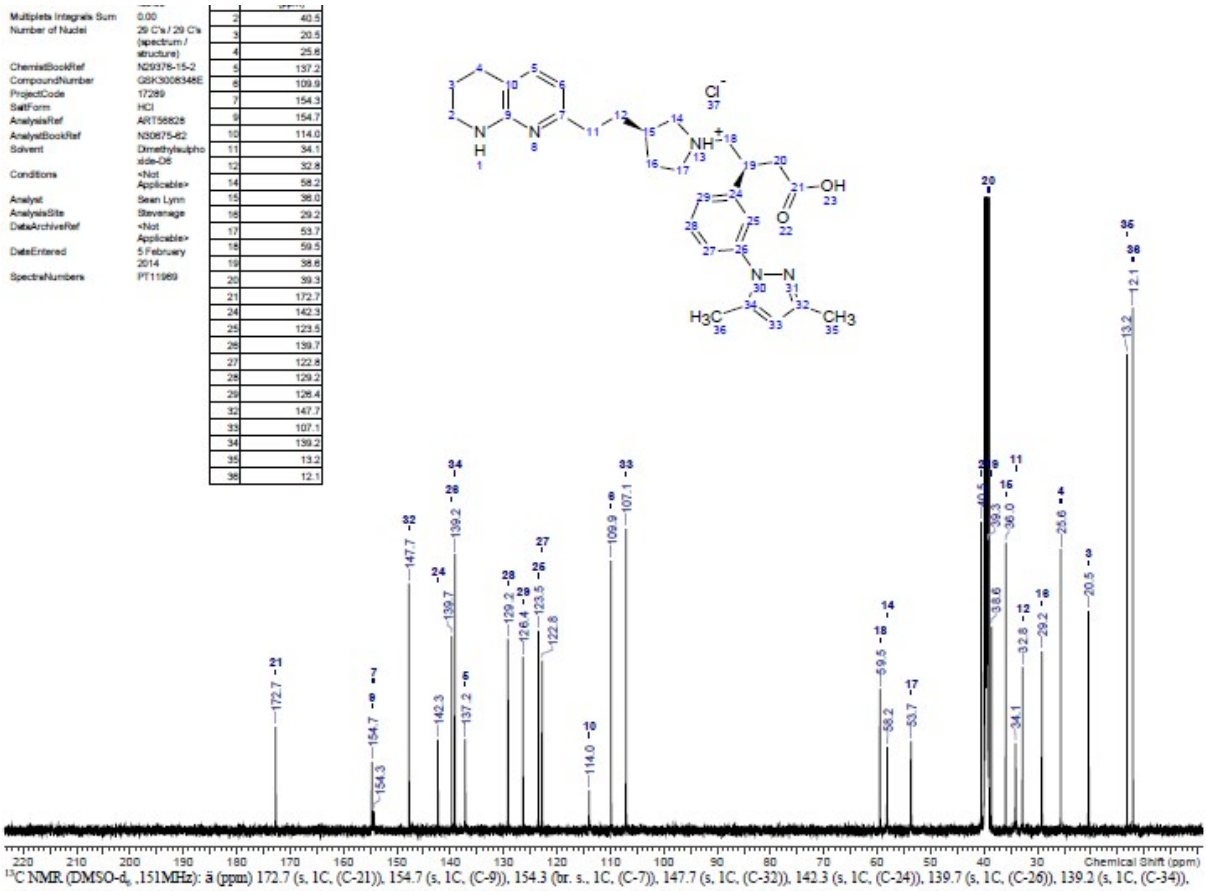


^{1}H NMR (DMSO-d_6 ,600MHz): ā (ppm) 12.01 (br. s., 2H, (H-13, 23)), 7.43 - 7.48 (m, 2H, (H-25, 28)), 7.34 - 7.39 (m, 2H, (H-27, 29)), 7.15 (d, J=7.5 Hz, 1H, (H-5)), 6.90 (br. s., 1H, (H-1)), 6.32 (d, J=7.5 Hz, 1H, (H-6)), 6.07 (s, 1H, (H-33)), 3.57 (quin, J=7.0 Hz, 1H, (H-19)), 3.44 (dd, J=13.0, 7.4 Hz, 1H, (H-18<>)), 3.23 - 3.30 (m, 4H, (H-14<>, 18<>, 2)), 3.10 - 3.18 (m, 1H, (H-17<>)), 3.03 - 3.09 (m, 1H, (H-17<>)), 2.99 (dd, J=16.0, 5.5 Hz, 1H, (H-20<>)), 2.82 (t, J=9.5 Hz, 1H, (H-14<>)), 2.62 (t, J=6.1 Hz, 2H, (H-4)), 2.57 - 2.62 (m, 1H, (H-20<>)), 2.39 - 2.52 (m, 2H, (H-11)), 2.30 (s, 3H, (H-36)), 2.18 (s, 3H, (H-35)), 2.16 - 2.24 (m, 1H, (H-15)), 1.99 - 2.08 (m, 1H, (H-16<>)), 1.75 (quin, J=6.0 Hz, 2H, (H-3)), 1.61 - 1.72 (m, 2H, (H-12)), 1.54 (dq, J=13.0, 8.0 Hz, 1H, (H-16<>))



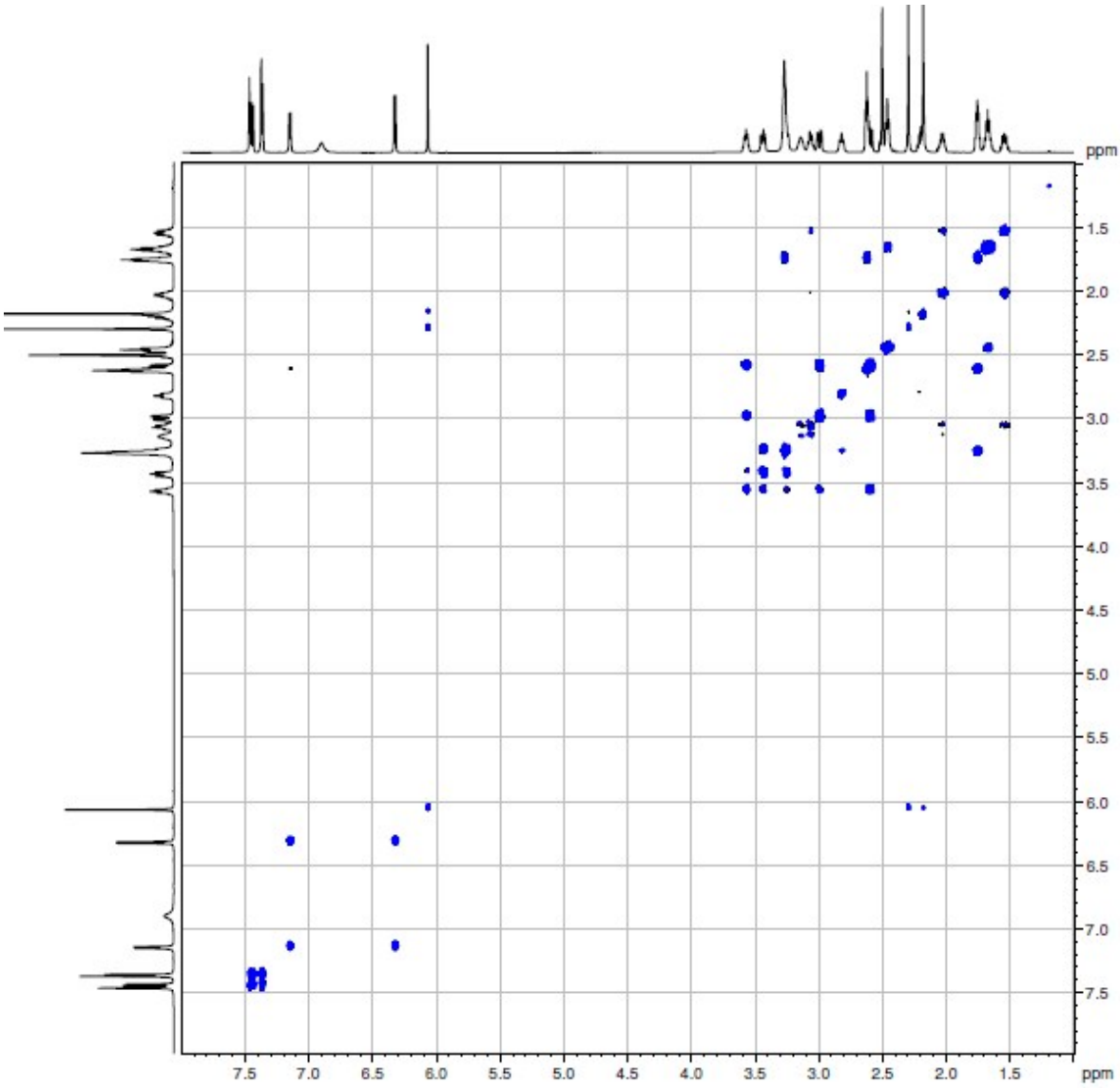
^{1}H NMR (DMSO-d_6 ,600MHz): ā (ppm) 12.01 (br. s., 2H, (H-13, 23)), 7.43 - 7.48 (m, 2H, (H-25, 28)), 7.34 - 7.39 (m, 2H, (H-27, 29)), 7.15 (d, J=7.5 Hz, 1H, (H-5)), 6.90 (br. s., 1H, (H-1)), 6.32 (d, J=7.5 Hz, 1H, (H-6)), 6.07 (s, 1H, (H-33)), 3.57 (quin, J=7.0 Hz, 1H, (H-19)), 3.44 (dd, J=13.0, 7.4 Hz, 1H, (H-18<*>)), 3.23 - 3.30 (m, 4H, (H-14<*>, 18<*>, 2)), 3.10 - 3.18 (m, 1H, (H-17<*>)), 3.03 - 3.09 (m, 1H, (H-17<*>)), 2.99 (dd, J=16.0, 5.5 Hz, 1H, (H-20<*>)), 2.82 (t, J=9.5 Hz, 1H, (H-14<*>)), 2.62 (t, J=6.1 Hz, 2H, (H-4)), 2.57 - 2.62 (m, 1H, (H-20<*>)), 2.39 - 2.52 (m, 2H, (H-11)), 2.30 (s, 3H, (H-36)), 2.18 (s, 3H, (H-35)), 2.16 - 2.24 (m, 1H, (H-15)), 1.99 - 2.08 (m, 1H, (H-16<*>)), 1.75 (quin, J=6.0 Hz, 2H, (H-3)), 1.61 - 1.72 (m, 2H, (H-12)), 1.54 (dq, J=13.0, 8.0 Hz, 1H, (H-16<*>))

3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl).

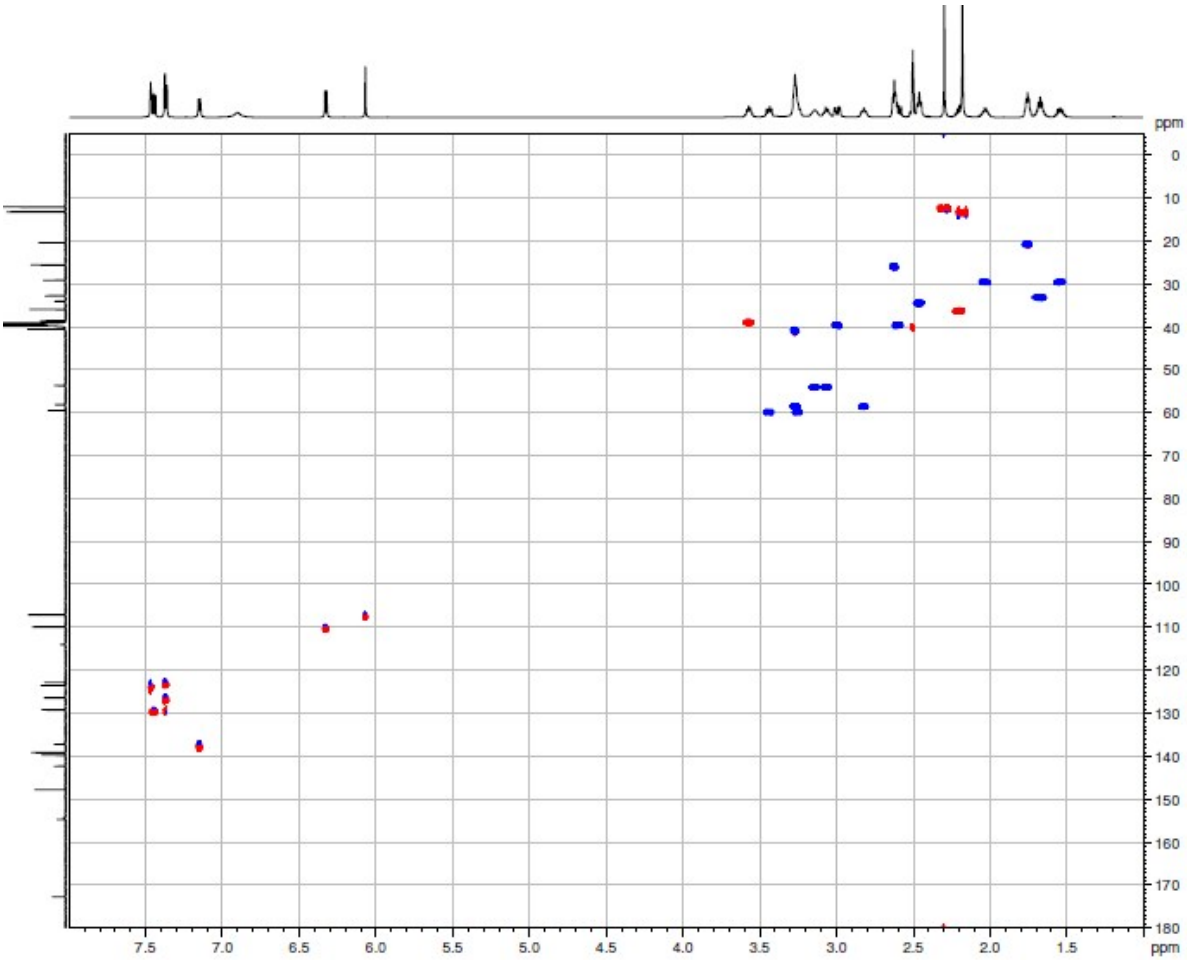


^{13}C NMR (DMSO-d_6 ,151MHz): ä (ppm) 172.7 (s, 1C, (C-21)), 154.7 (s, 1C, (C-9)), 154.3 (br. s., 1C, (C-7)), 147.7 (s, 1C, (C-32)), 142.3 (s, 1C, (C-24)), 139.7 (s, 1C, (C-26)), 139.2 (s, 1C, (C-34)), 137.2 (s, 1C, (C-5)), 129.2 (s, 1C, (C-28)), 126.4 (s, 1C, (C-29)), 123.5 (s, 1C, (C-25)), 122.8 (s, 1C, (C-27)), 114.0 (s, 1C, (C-10)), 109.9 (s, 1C, (C-6)), 107.1 (s, 1C, (C-33)), 59.5 (s, 1C, (C-18)), 58.2 (s, 1C, (C-14)), 53.7 (s, 1C, (C-17)), 40.5 (s, 1C, (C-2)), 39.3 (br. s., 1C, (C-20)), 38.6 (s, 1C, (C-19)), 36.0 (s, 1C, (C-15)), 34.1 (s, 1C, (C-11)), 32.8 (s, 1C, (C-12)), 29.2 (s, 1C, (C-16)), 25.6 (s, 1C, (C-4)), 20.5 (s, 1C, ((C-3)), 13.2 (s, 1C, (C-35)), 12.1 (s, 1C, (C-36))

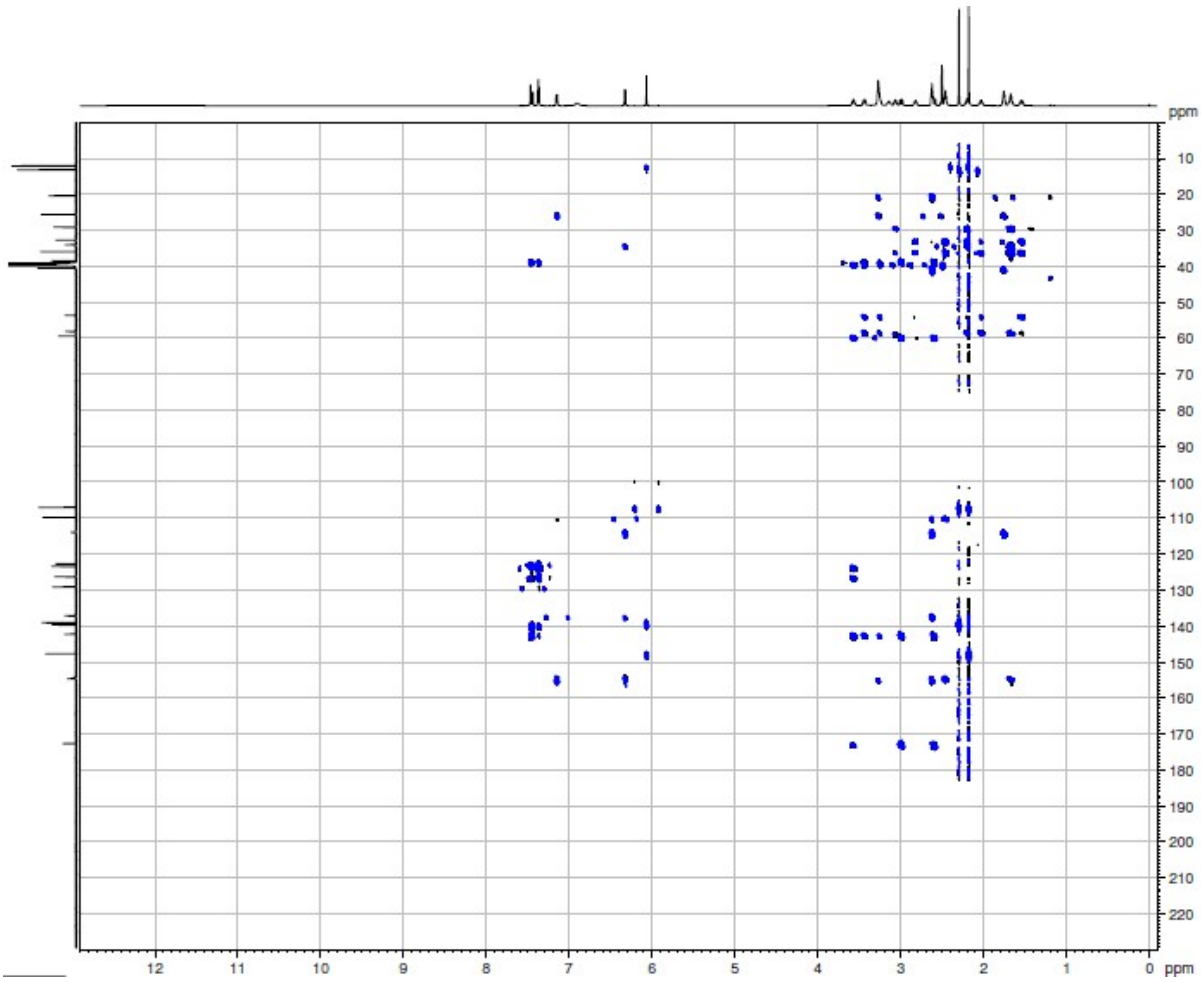
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl).
COSY



3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl).
Ed HSQC

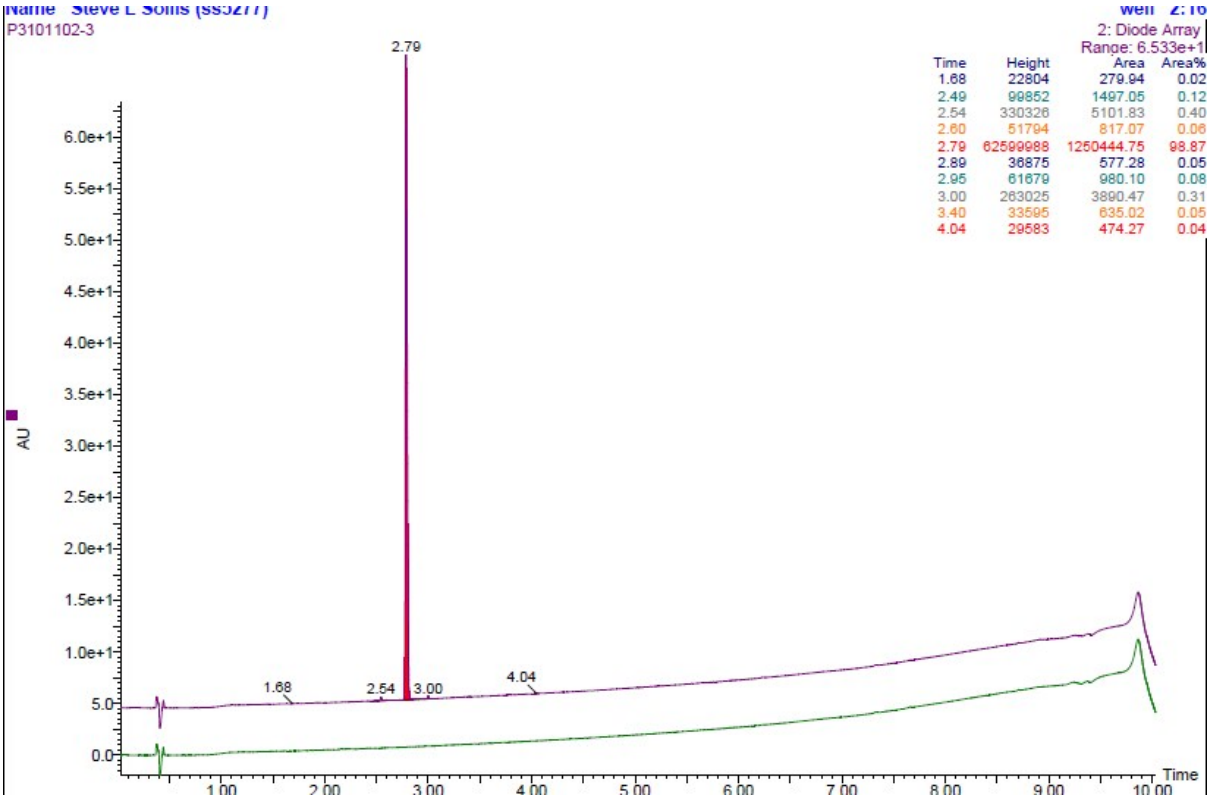


3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl). HMBC

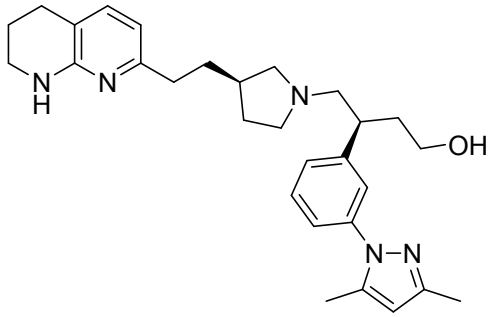


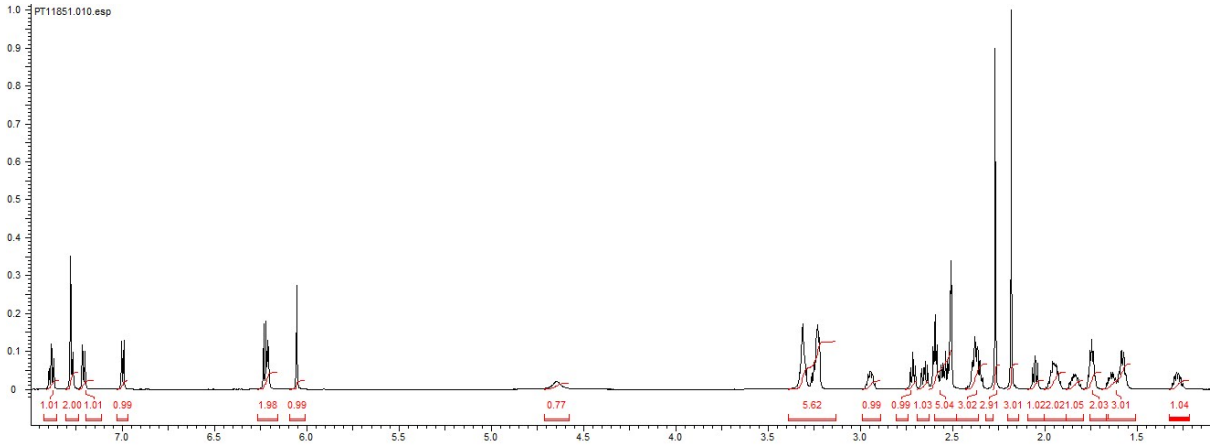
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, hydrochloride salt (1a.HCl).

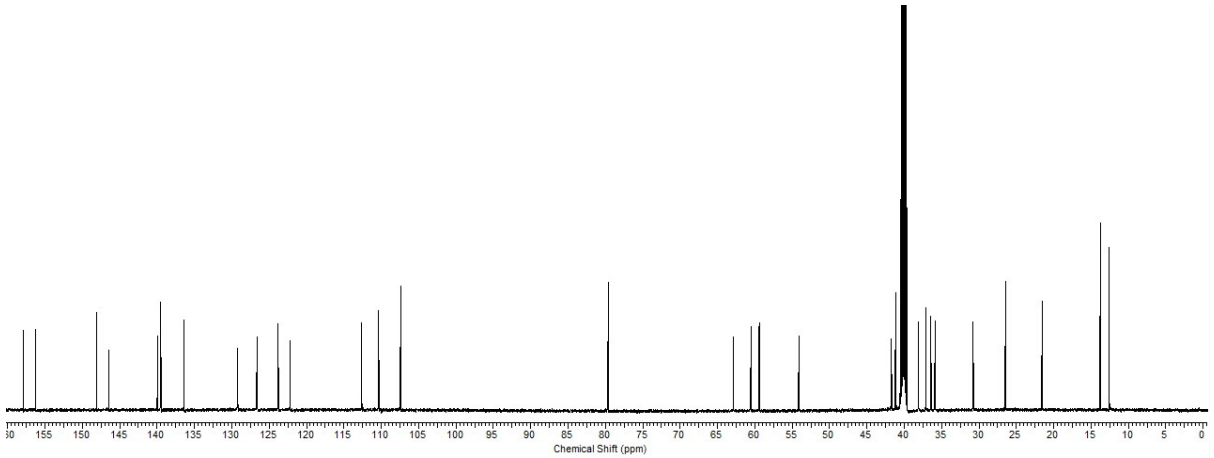
HPLC



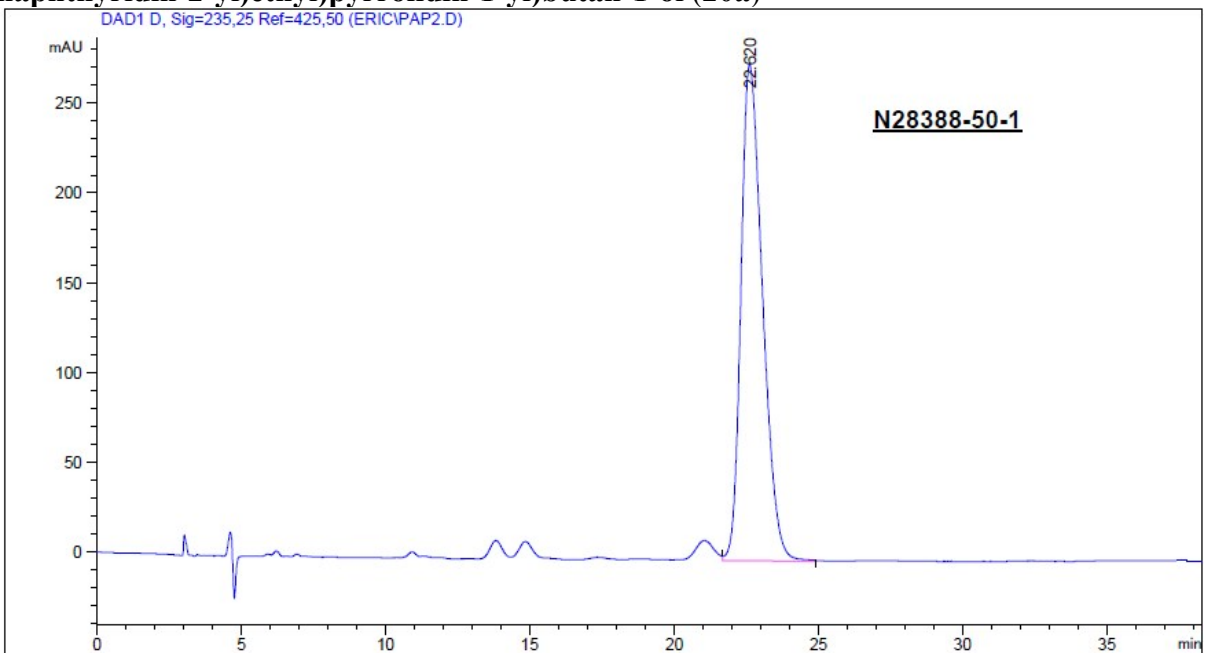
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (20a)



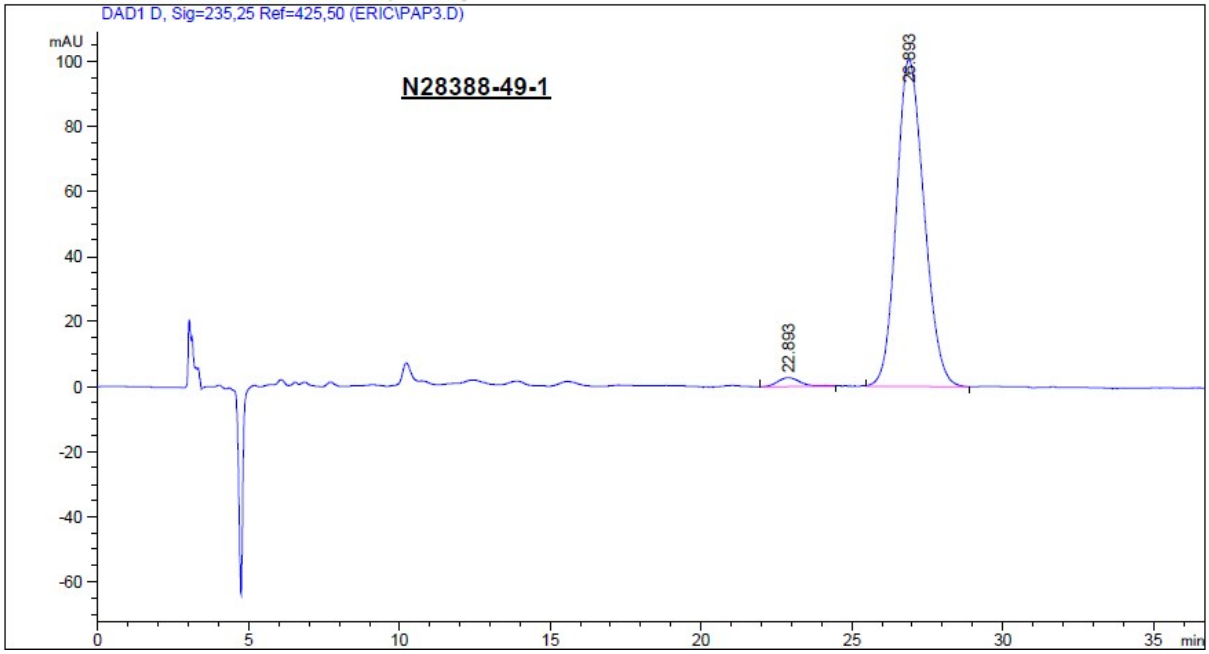




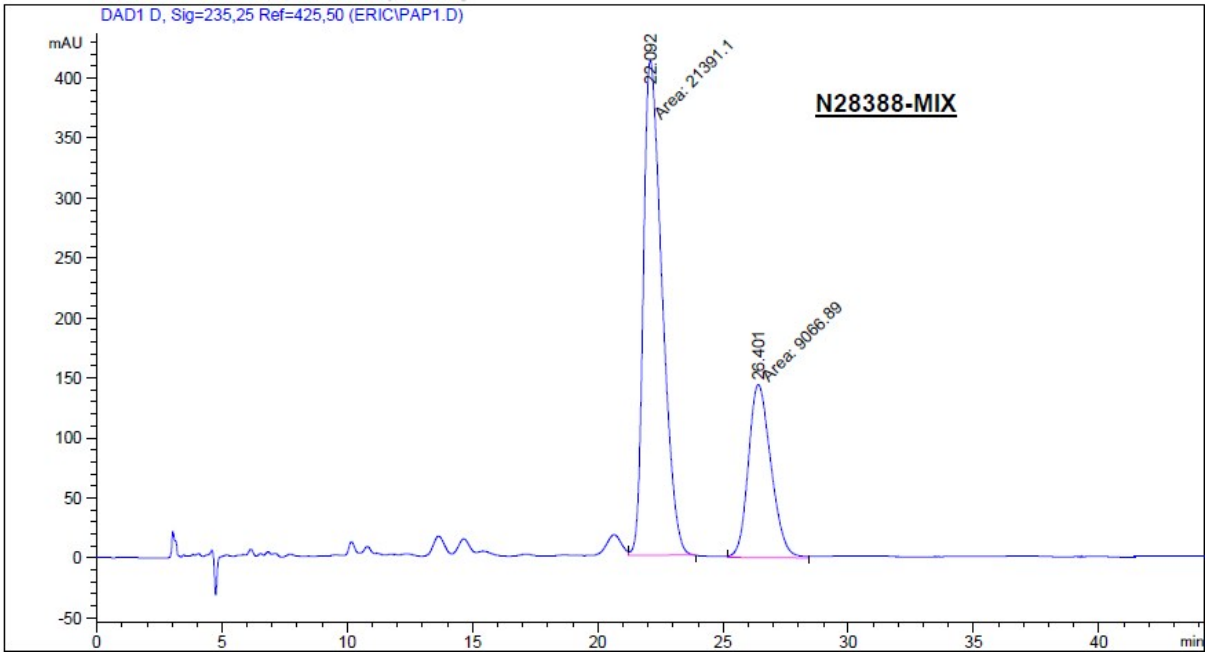
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (20a)



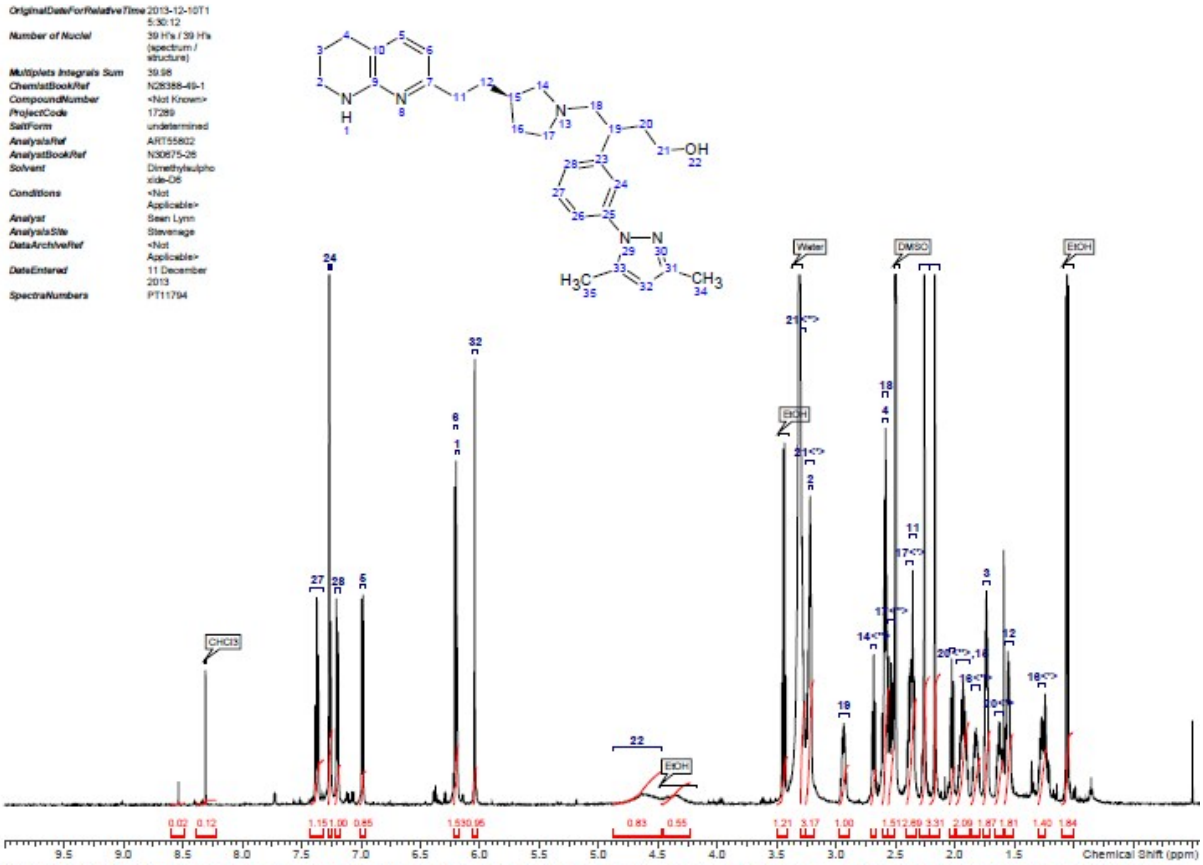
3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (20b)



Mixture of 20a with 20b



3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (20b)

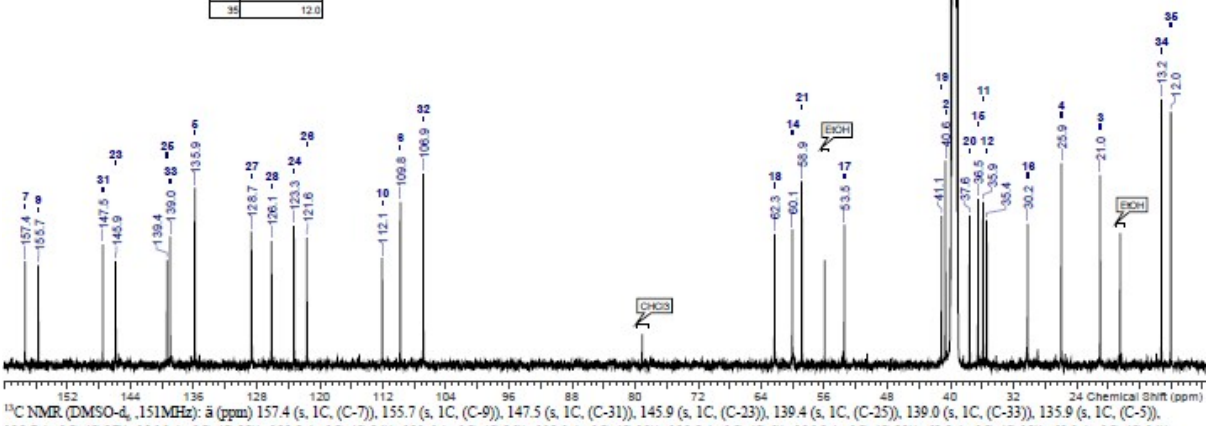


^{1}H NMR (DMSO-d_6 ,600MHz): ā (ppm) 7.37 (t, *J*=7.8 Hz, 1H, (H-27)), 7.26 - 7.28 (m, 1H, (H-24)), 7.24 - 7.27 (m, 1H, (H-26)), 7.20 (d, *J*=7.7 Hz, 1H, (H-28)), 6.99 (d, *J*=7.3 Hz, 1H, (H-5)), 6.21 (d, *J*=7.2 Hz, 1H, (H-6)), 6.19 (br. s., 1H, (H-1)), 6.04 (s, 1H, (H-32)), 4.61 (br. s., 1H, (H-22)), 3.27 - 3.30 (m, 1H, (H-21<>)), 3.21 - 3.23 (m, 2H, (H-2)), 3.19 - 3.25 (m, 1H, (H-21<>)), 2.90 - 2.98 (m, 1H, (H-19)), 2.68 (t, *J*=8.1 Hz, 1H, (H-14<>)), 2.57 - 2.61 (m, 2H, (H-4)), 2.56 - 2.61 (m, 2H, (H-18)), 2.51 - 2.56 (m, 1H, (H-17<>)), 2.35 - 2.41 (m, 1H, (H-17<>)), 2.32 - 2.39 (m, 2H, (H-11)), 2.26 (s, 3H, (H-35)), 2.17 (s, 3H, (H-34)), 2.03 (dd, *J*=8.5, 7.1 Hz, 1H, (H-14<>)), 1.88 - 1.99 (m, 2H, (H-20<>, 15)), 1.78 - 1.87 (m, 1H, (H-16<>)), 1.73 (quin, *J*=5.9 Hz, 2H, (H-3)), 1.60 - 1.66 (m, 1H, (H-20<>)), 1.51 - 1.58 (m, 2H, (H-12)), 1.24 - 1.30 (m, 1H, (H-16<>))

3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (20b)

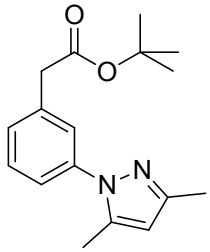
Multiplets Integrals Sum	0.00
Number of Nuclei	29 C's / 29 C's (spectrum / structure)
ChemistBookRef	N28388-49-1
CompoundNumber	<Not Known>
ProjectCode	17289
SaltForm	undetermined
AnalysisRef	ART55802
AnalystBookRef	N30875-26
Solvent	Dimethylsulphoxide-D6
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
DataArchiveRef	<Not Applicable>
DateEntered	11 December 2013
SpectraNumbers	PT11794

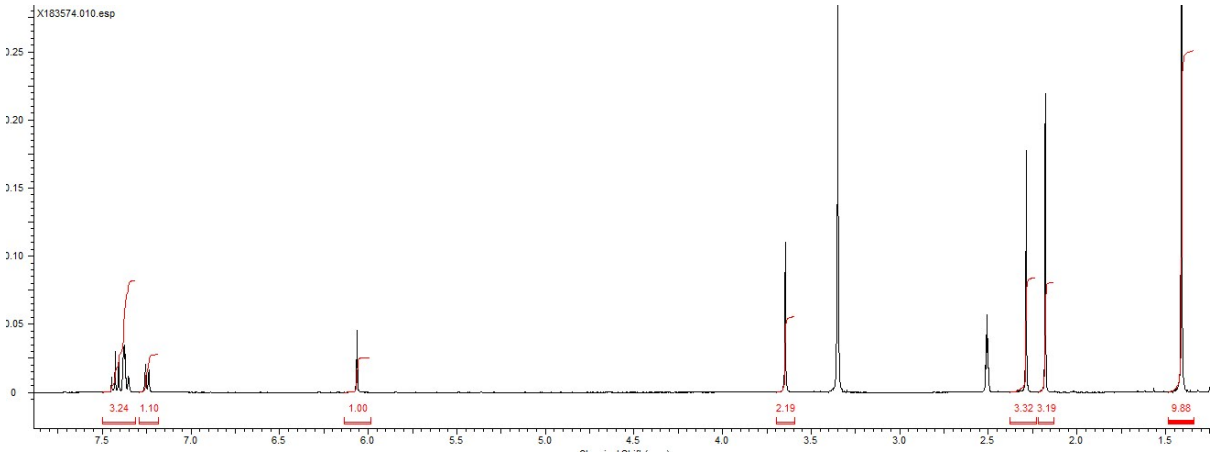
2	40.6
3	21.0
4	25.9
5	135.9
6	109.8
7	157.4
9	155.7
10	112.1
11	35.9
12	35.4
14	60.1
15	36.5
16	30.2
17	53.5
18	62.3
19	41.1
20	37.6
21	58.9
23	145.9
24	123.3
25	139.4
26	121.6
27	128.7
28	126.1
31	147.5
32	106.9
33	139.0
34	13.2
35	12.0



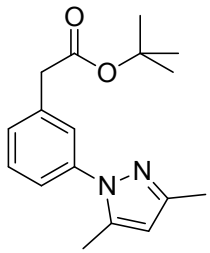
^{13}C NMR (DMSO-d_6, 151MHz): ä (ppm) 157.4 (s, 1C, (C-7)), 155.7 (s, 1C, (C-9)), 147.5 (s, 1C, (C-31)), 145.9 (s, 1C, (C-23)), 139.4 (s, 1C, (C-25)), 139.0 (s, 1C, (C-33)), 135.9 (s, 1C, (C-5)), 128.7 (s, 1C, (C-27)), 126.1 (s, 1C, (C-28)), 123.3 (s, 1C, (C-24)), 121.6 (s, 1C, (C-26)), 112.1 (s, 1C, (C-10)), 109.8 (s, 1C, (C-6)), 106.9 (s, 1C, (C-32)), 62.3 (s, 1C, (C-18)), 60.1 (s, 1C, (C-14)), 58.9 (s, 1C, (C-21)), 53.5 (s, 1C, (C-17)), 41.1 (s, 1C, (C-19)), 40.6 (s, 1C, (C-2)), 37.6 (s, 1C, (C-20)), 36.5 (s, 1C, (C-15)), 35.9 (s, 1C, (C-11)), 35.4 (s, 1C, (C-12)), 30.2 (s, 1C, (C-16)), 25.9 (s, 1C, (C-4)), 21.0 (s, 1C, (C-3)), 13.2 (s, 1C, ((C-34)), 12.0 (s, 1C, ((C-35))

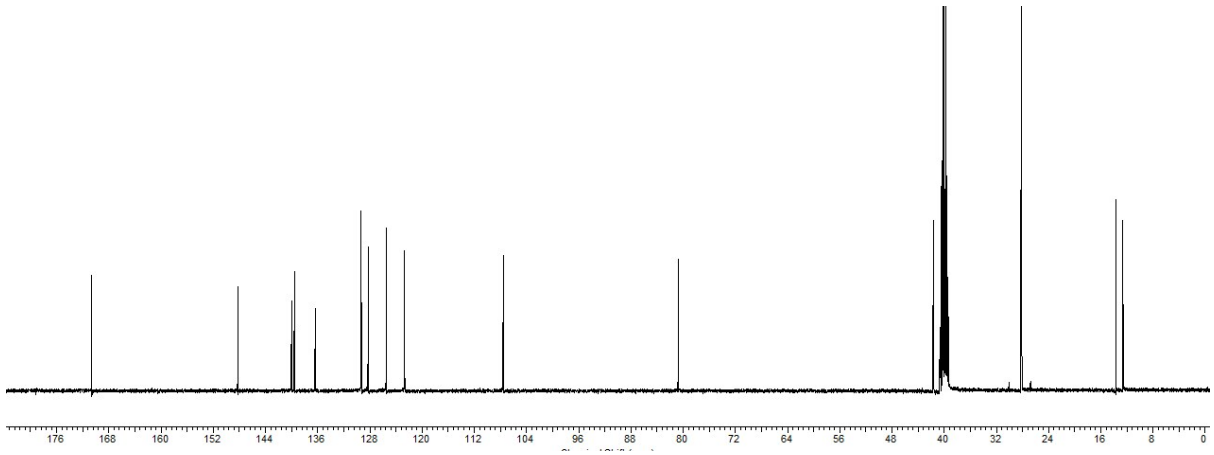
***tert*-Butyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetate (21)**



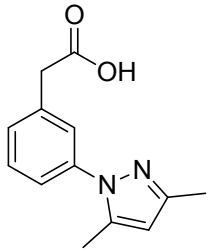


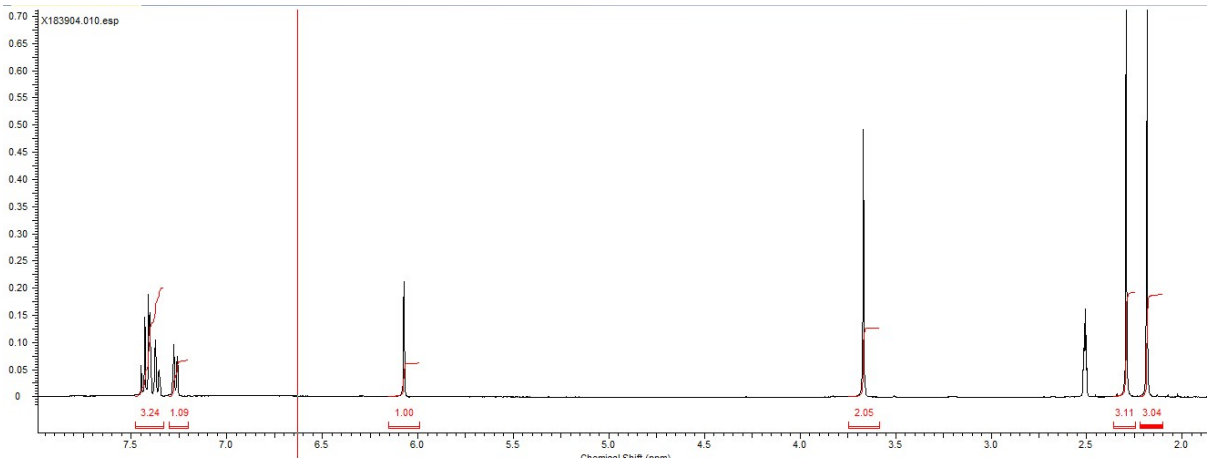
***tert*-Butyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetate (21)**



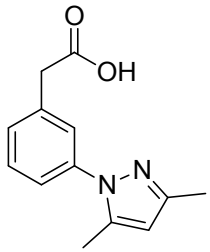


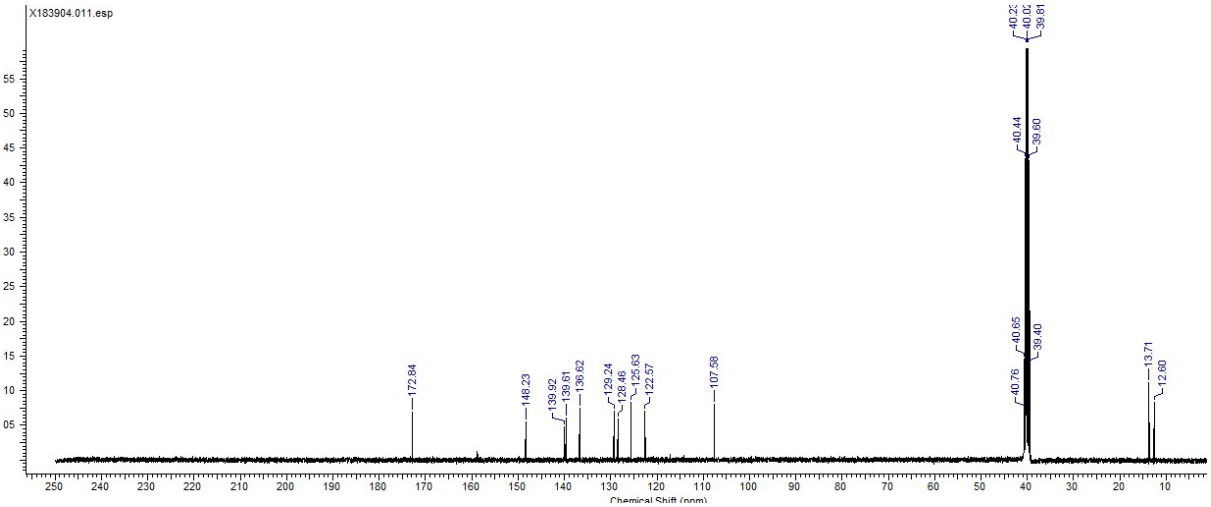
2-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)acetic acid (22)



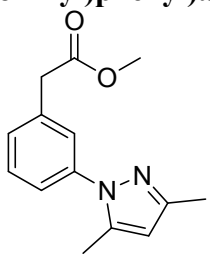


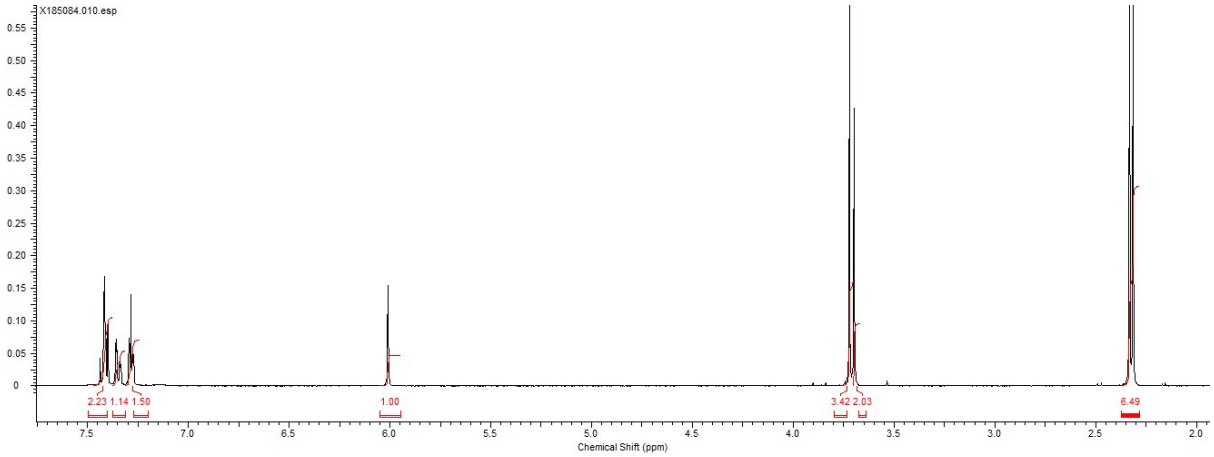
2-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)acetic acid (22)

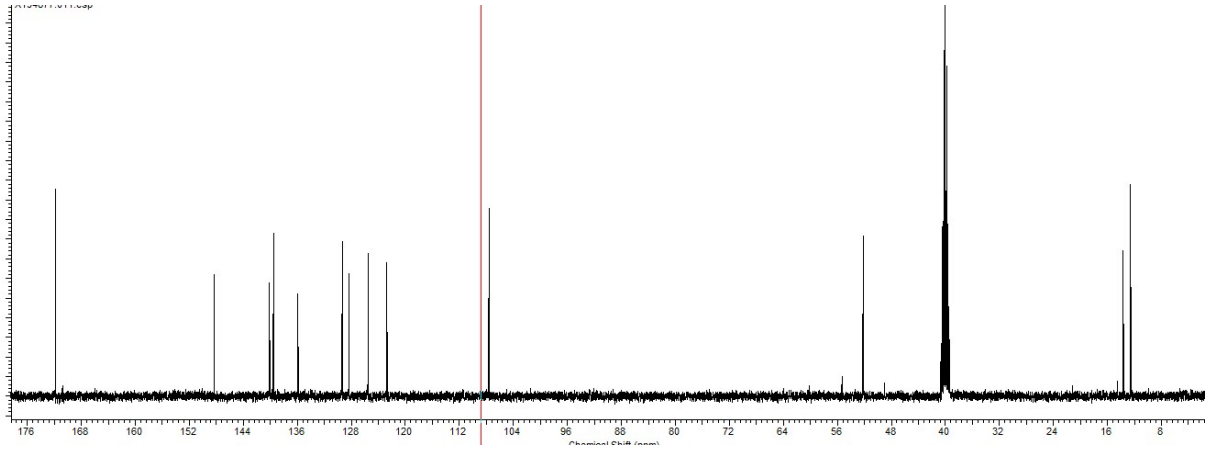




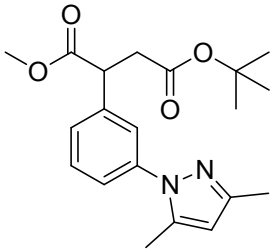
Methyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetate (23)

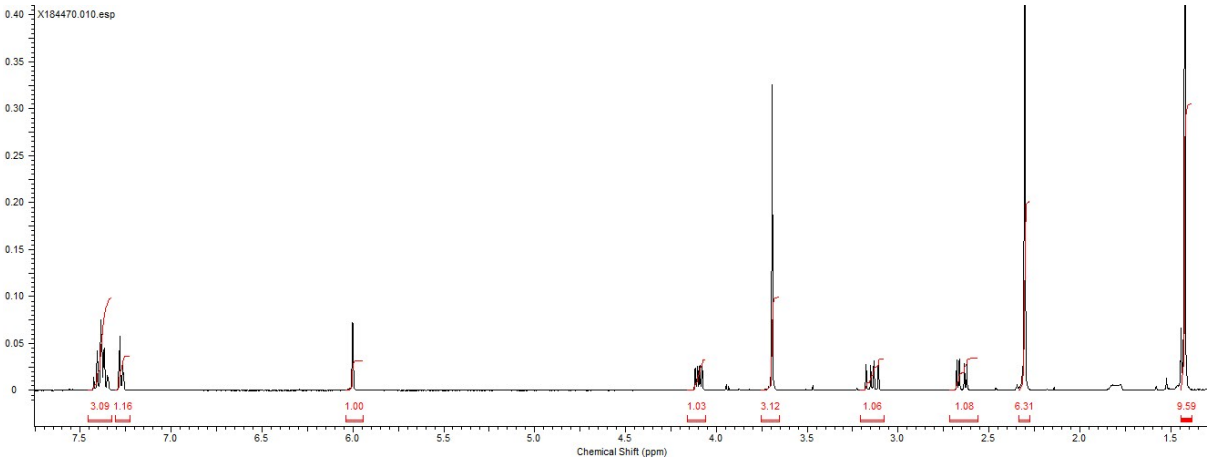


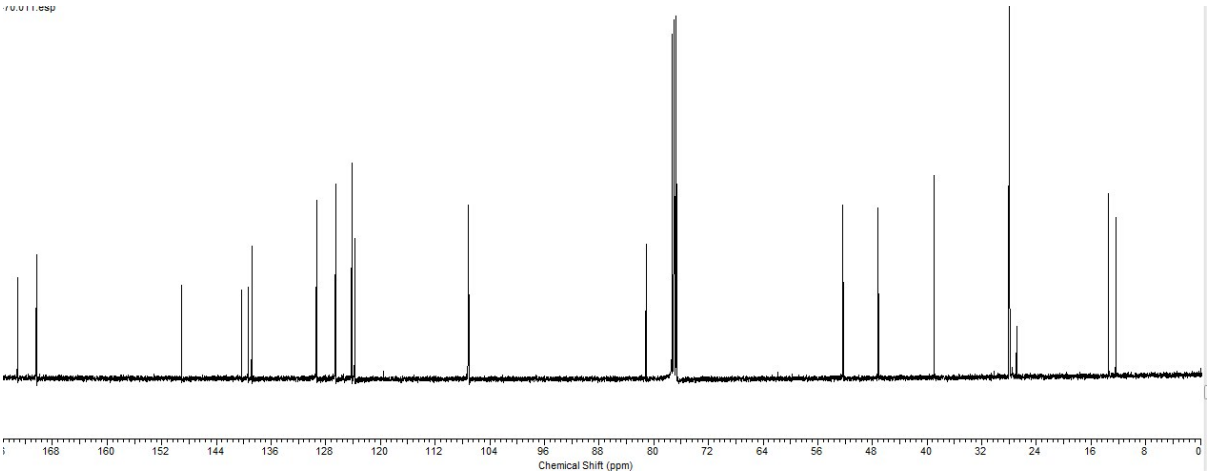




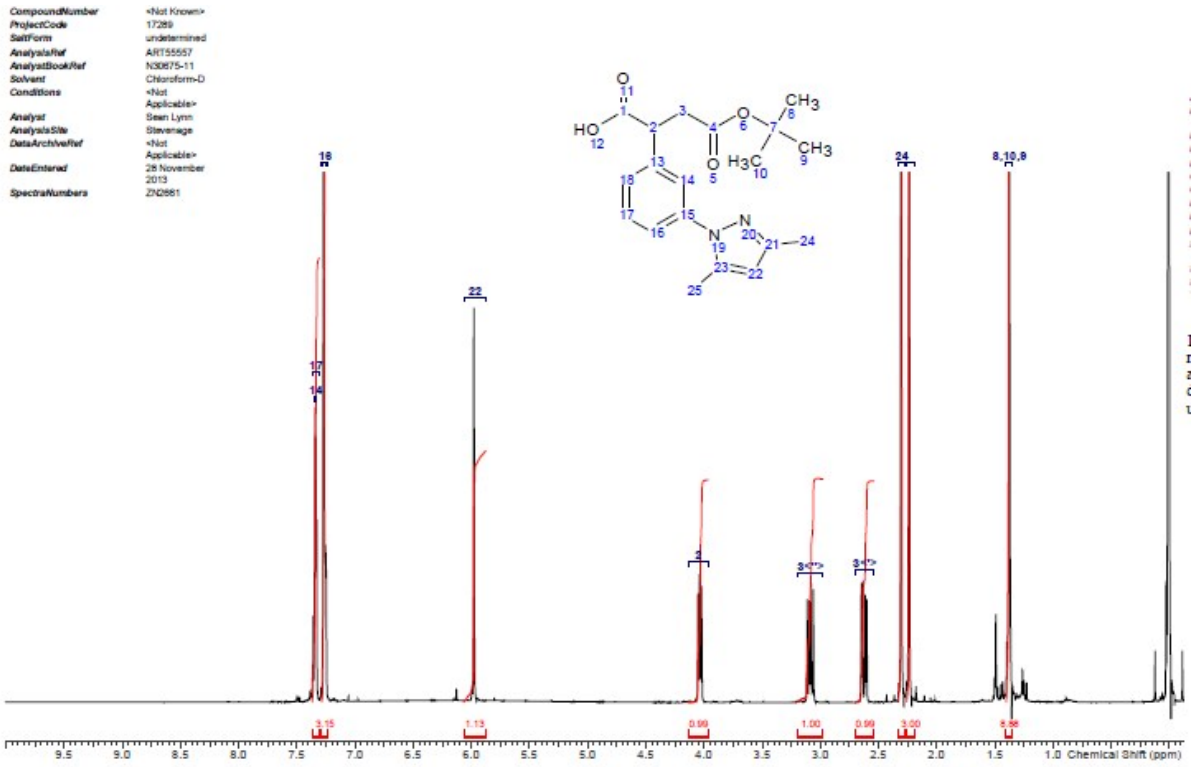
(±)-4-*tert*-Butyl 1-methyl 2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)succinate (24)



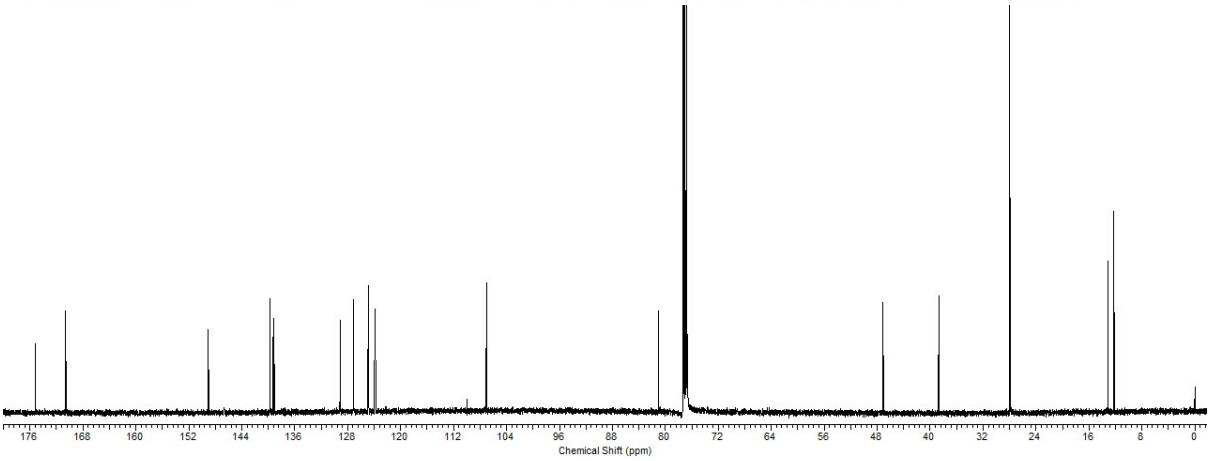




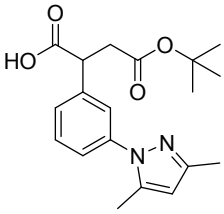
(+)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid [(+)-25]

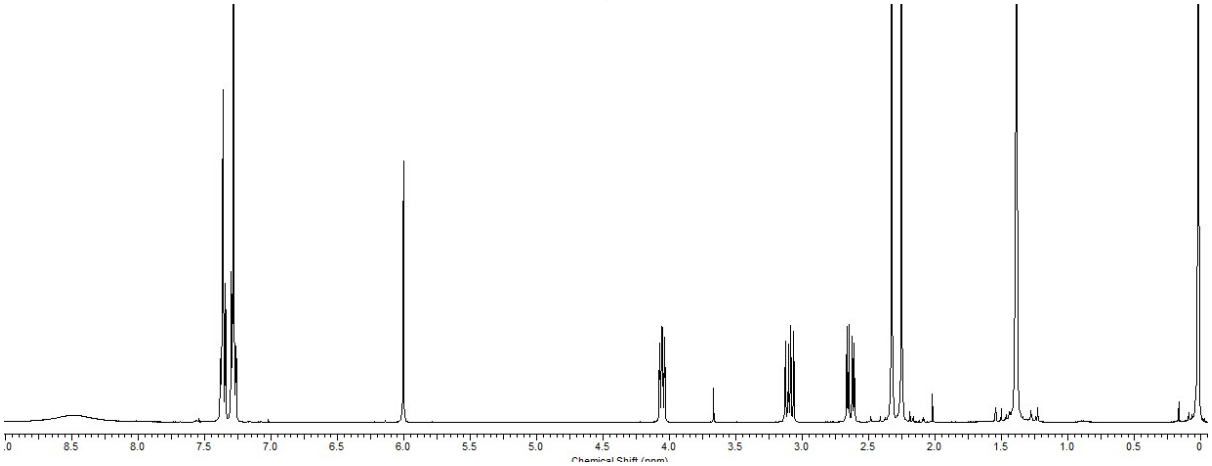


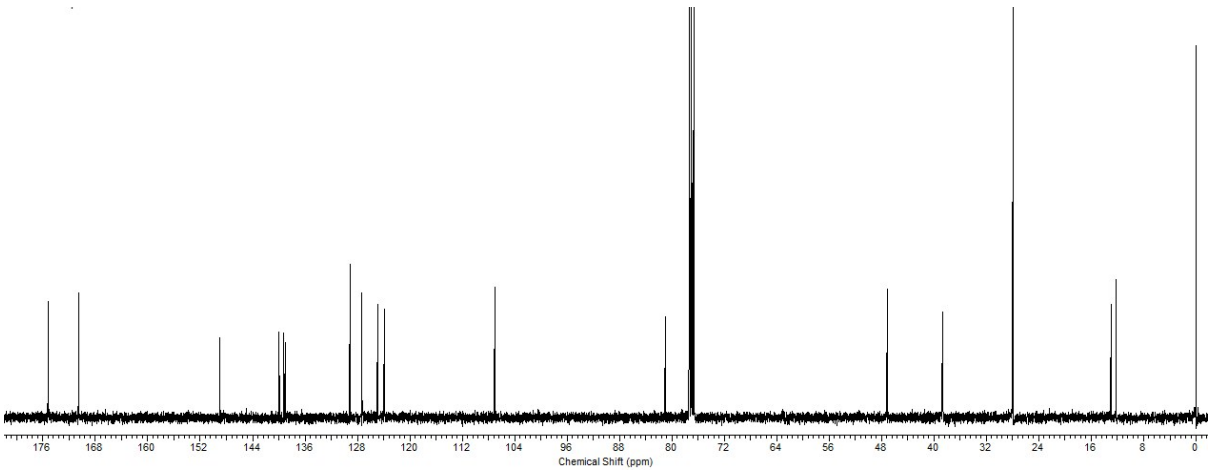
^{1}H NMR (CHLOROFORM-d ,500MHz): ä (ppm) 7.33 - 7.35 (m, 1H, (H-14)), 7.31 - 7.37 (m, 1H, (H-17)), 7.24 - 7.27 (m, 1H, (H-16)), 7.24 - 7.29 (m, 1H, (H-18)), 5.98 (s, 1H, (H-22)), 4.04 (dd, *J*=9.3, 6.2 Hz, 1H, (H-2)), 3.09 (dd, *J*=16.6, 9.3 Hz, 1H, (H-3<*>)), 2.62 (dd, *J*=16.5, 6.1 Hz, 1H, (H-3<*>)), 2.31 (s, 3H, (H-24)), 2.24 (s, 3H, (H-25)), 1.38 (s, 9H, (H-8, 10, 9))



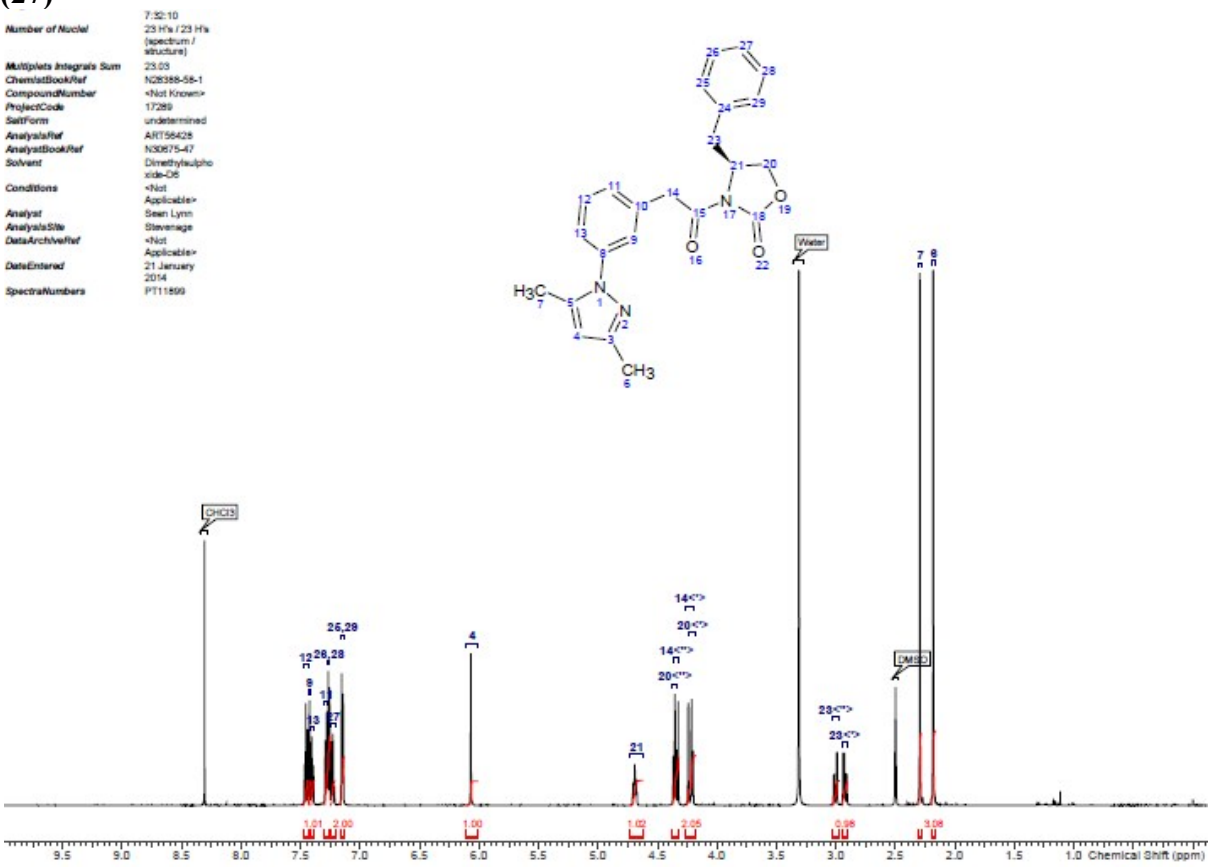
(–)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid [(–)-25]





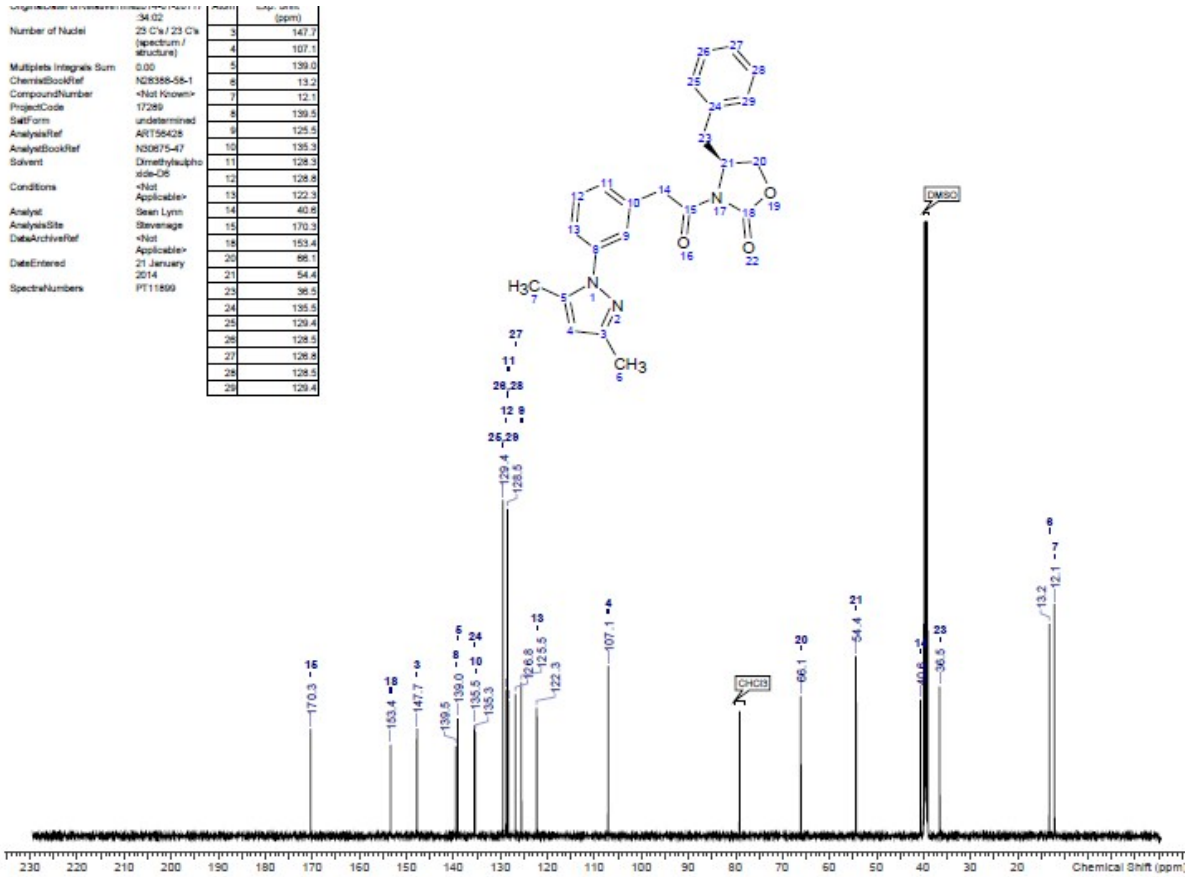


(*S*)-(+)-4-Benzyl-3-(2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetyl)oxazolidin-2-one (27)



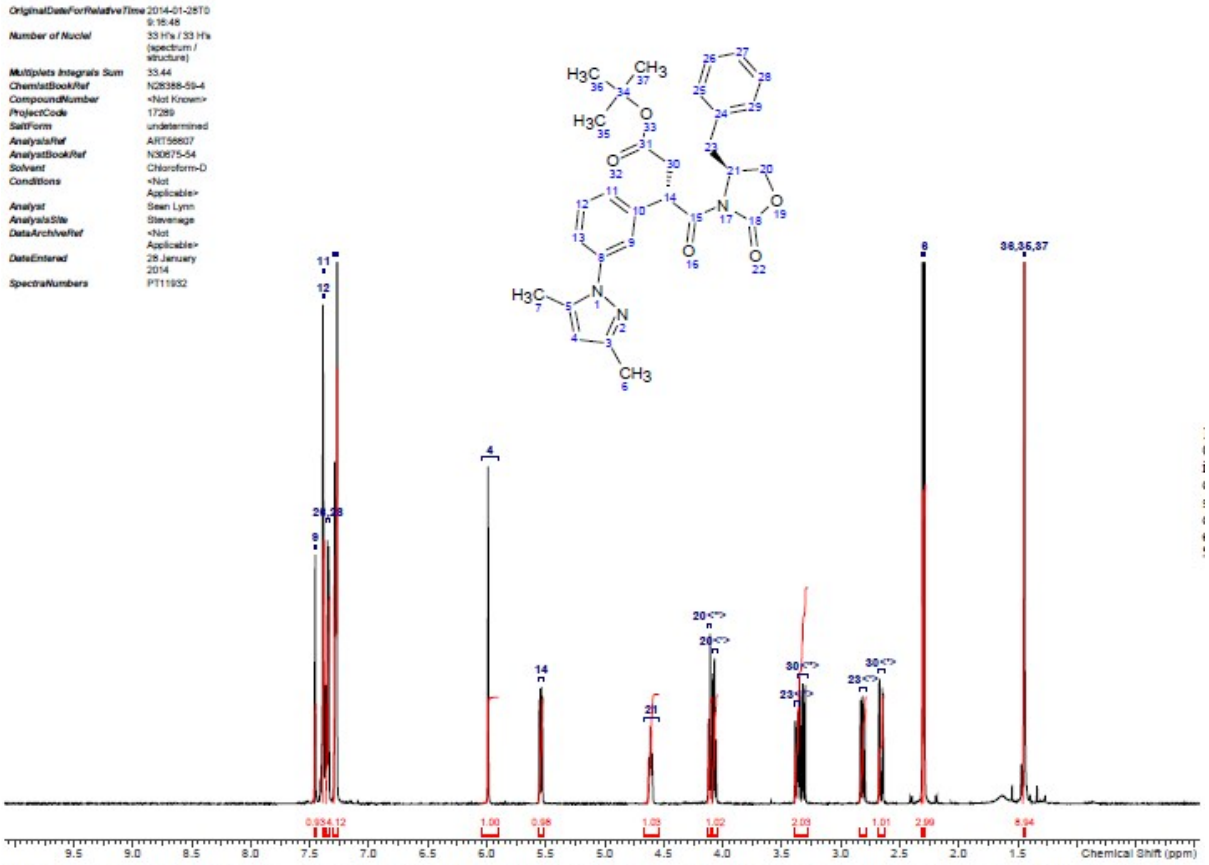
H NMR (DMSO-d_6 ,600MHz): ā (ppm) 7.44 - 7.48 (m, 1H, (H-12)), 7.43 (s, 1H, (H-9)), 7.38 - 7.41 (m, 1H, (H-13)), 7.29 (d, J=8.3 Hz, 1H, (H-11)), 7.25 - 7.28 (m, 2H, (H-26, 28)), 7.21 - 7.25 (m, 1H, (H-27)), 7.13 - 7.17 (m, 2H, (H-25, 29)), 6.07 (s, 1H, (H-4)), 4.69 (tt, J=7.8, 3.0 Hz, 1H, (H-21)), 4.36 (t, J=8.5 Hz, 1H, (H-20<*>)), 4.32 - 4.36 (m, 1H, (H-14<*>)), 4.20 - 4.26 (m, 1H, (H-14<*>)), 4.18 - 4.23 (m, 1H, (H-20<*>)), 2.97 - 3.03 (m, 1H, (H-23<*>)), 2.90 - 2.95 (m, 1H, (H-23<*>)), 2.29 (s, 3H, (H-7)), 2.18 (s, 3H, (H-6))

(*S*)-(+)-4-Benzyl-3-(2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)acetyl)oxazolidin-2-one (27)



^{13}C NMR (DMSO-d_6 ,151MHz): ä (ppm) 170.3 (s, 1C, (C-15)), 153.4 (s, 1C, (C-18)), 147.7 (s, 1C, (C-3)), 139.5 (s, 1C, (C-8)), 139.0 (s, 1C, (C-5)), 135.5 (s, 1C, (C-24)), 135.3 (s, 1C, (C-10)), 129.4 (s, 2C, (C-25, 29)), 128.8 (s, 1C, (C-12)), 128.5 (s, 2C, ((C-26, 28)), 128.3 (s, 1C, (C-11)), 126.8 (s, 1C, ((C-27)), 125.5 (s, 1C, (C-9)), 122.3 (s, 1C, (C-13)), 107.1 (s, 1C, (C-4)), 66.1 (s, 1C, (C-20)), 54.4 (s, 1C, (C-21)), 40.6 (s, 1C, (C-14)), 36.5 (s, 1C, (C-23)), 13.2 (s, 1C, (C-6)), 12.1 (s, 1C, (C-7))

(*S*)-*tert*-Butyl 4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoate (28)



^{1}H NMR (CHLOROFORM-d ,600MHz): ä (ppm) 7.46 (s, 1H, (H-9)), 7.38 - 7.39 (m, 1H, (H-12)), 7.38 - 7.39 (m, 1H, (H-11)), 7.38 - 7.39 (m, 1H, (H-13)), 7.34 (d, J=7.3 Hz, 2H, (H-26, 28)), 7.27 - 7.29 (m, 2H, (H-25, 29)), 7.27 (s, 1H, (H-27)), 5.99 (s, 1H, (H-4)), 5.54 (dd, J=11.3, 4.3 Hz, 1H, (H-14)), 4.61 (ddt, J=10.0, 7.3, 2.8 Hz, 1H, (H-21)), 4.11 (dd, J=9.0, 2.0 Hz, 1H, (H-20<*>)), 4.07 (dd, J=9.0, 7.5 Hz, 1H, (H-20<*>)), 3.37 (dd, J=13.6, 3.1 Hz, 1H, (H-23<*>)), 3.33 (dd, J=17.1, 11.4 Hz, 1H, (H-30<*>)), 2.81 (dd, J=13.4, 9.9 Hz, 1H, (H-23<*>)), 2.66 (dd, J=17.1, 4.2 Hz, 1H, (H-30<*>)), 2.31 (s, 3H, (H-7)), 2.29 (s, 3H, (H-6)), 1.44 (s, 9H, (H-36, 35, 37))

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Solvent	Chloroform-D
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
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DateEntered	28 January 2014
SpectraNumbers	PT11932

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12	129.4
13	124.1
14	44.7
15	170.7
18	152.7
20	65.8
21	55.7
23	37.5
24	135.6
25	129.5
26	128.9
27	127.3
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29	129.5
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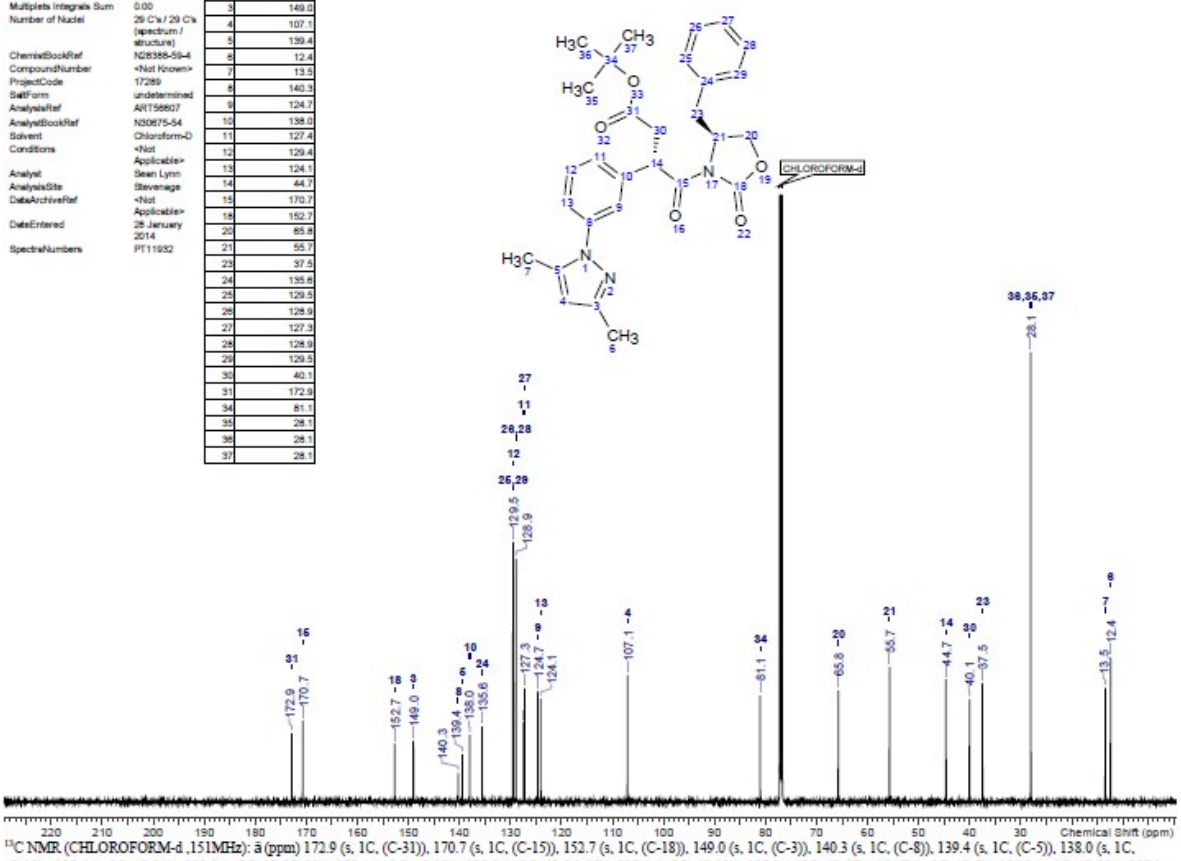
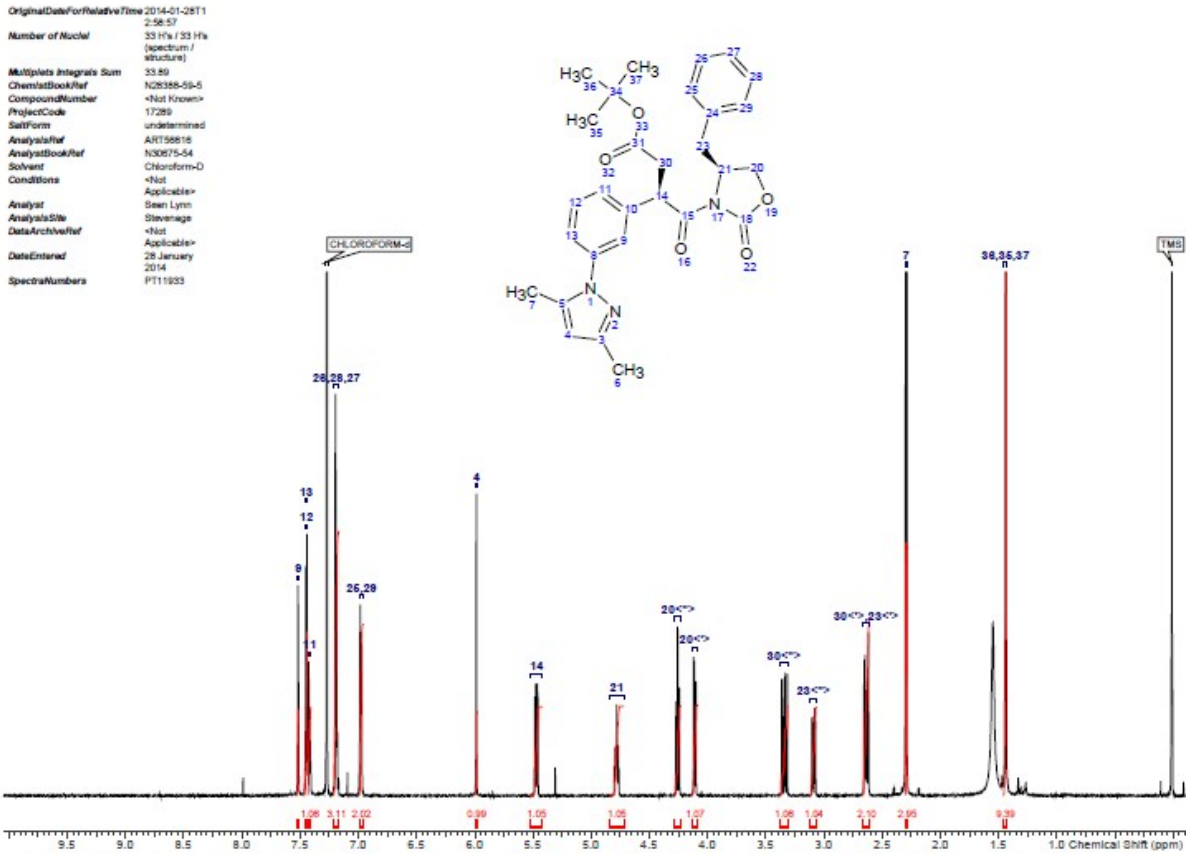
31	172.9
34	81.1
35	28.1
36	28.1
37	28.1



^{13}C NMR (CHLOROFORM-d ,151MHz): ã (ppm) 172.9 (s, 1C, (C-31)), 170.7 (s, 1C, (C-15)), 152.7 (s, 1C, (C-18)), 149.0 (s, 1C, (C-3)), 140.3 (s, 1C, (C-8)), 139.4 (s, 1C, (C-5)), 138.0 (s, 1C, (C-10)), 135.6 (s, 1C, (C-24)), 129.5 (s, 2C, (C-25, 29)), 129.4 (s, 1C, (C-12)), 128.9 (s, 2C, (C-26, 28)), 127.4 (s, 1C, (C-11)), 127.3 (s, 1C, (C-27)), 124.7 (s, 1C, (C-9)), 124.1 (s, 1C, (C-13)), 107.1 (s, 1C, (C-4)), 81.1 (s, 1C, (C-34)), 65.8 (s, 1C, (C-20)), 55.7 (s, 1C, (C-21)), 44.7 (s, 1C, (C-14)), 40.1 (s, 1C, (C-30)), 37.5 (s, 1C, (C-23)), 28.1 (s, 3C, ((C-36, 35, 37)), 13.5 (s, 1C, (C-7)), 12.4 (s, 1C, (C-6))

(*R*)-*tert*-butyl 4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoate (29)



^{1}H NMR (CHLOROFORM-d ,600MHz): ä (ppm) 7.51 - 7.52 (m, 1H, (H-9)), 7.44 - 7.46 (m, 1H, (H-12)), 7.44 - 7.46 (m, 1H, (H-13)), 7.41 - 7.43 (m, 1H, (H-11)), 7.17 - 7.21 (m, 3H, (H-26, 28, 27)), 6.96 - 6.99 (m, 2H, (H-25, 29)), 5.99 (s, 1H, (H-4)), 5.47 (dd, *J*=11.4, 4.0 Hz, 1H, (H-14)), 4.78 (tt, *J*=8.4, 3.3 Hz, 1H, (H-21)), 4.26 (dd, *J*=9.0, 8.0 Hz, 1H, (H-20<*>)), 4.11 (dd, *J*=9.1, 3.0 Hz, 1H, (H-20<>)), 3.34 (dd, *J*=17.1, 11.4 Hz, 1H, (H-30<*>)), 3.09 (dd, *J*=13.6, 3.5 Hz, 1H, (H-23<*>)), 2.61 - 2.67 (m, 2H, (H-30<>, 23<>)), 2.30 (s, 3H, (H-7)), 2.29 (s, 3H, (H-6)), 1.44 (s, 9H, (H-36, 35, 37))

(*R*)-*tert*-butyl 4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoate (29)

OriginalDateForRelativeTime	2014-01-28T14:02:00
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AnalystBookRef	N30875-54
Solvent	Chloroform-D
Conditions	<Not Applicable>
Analyst	Sean Lynn
AnalysisSite	Stevenage
DataArchiveRef	<Not Applicable>
DateEntered	28 January 2014
SpectraNumbers	PT11933

Atom	Exp. Shift (ppm)
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5	139.4
6	13.5
7	12.5
8	140.4
9	124.9
10	137.9
11	127.1
12	129.5
13	124.1
14	44.6
15	170.7
18	152.9
20	65.9
21	54.9
23	37.5
24	134.8
25	129.4
26	128.8
27	127.2
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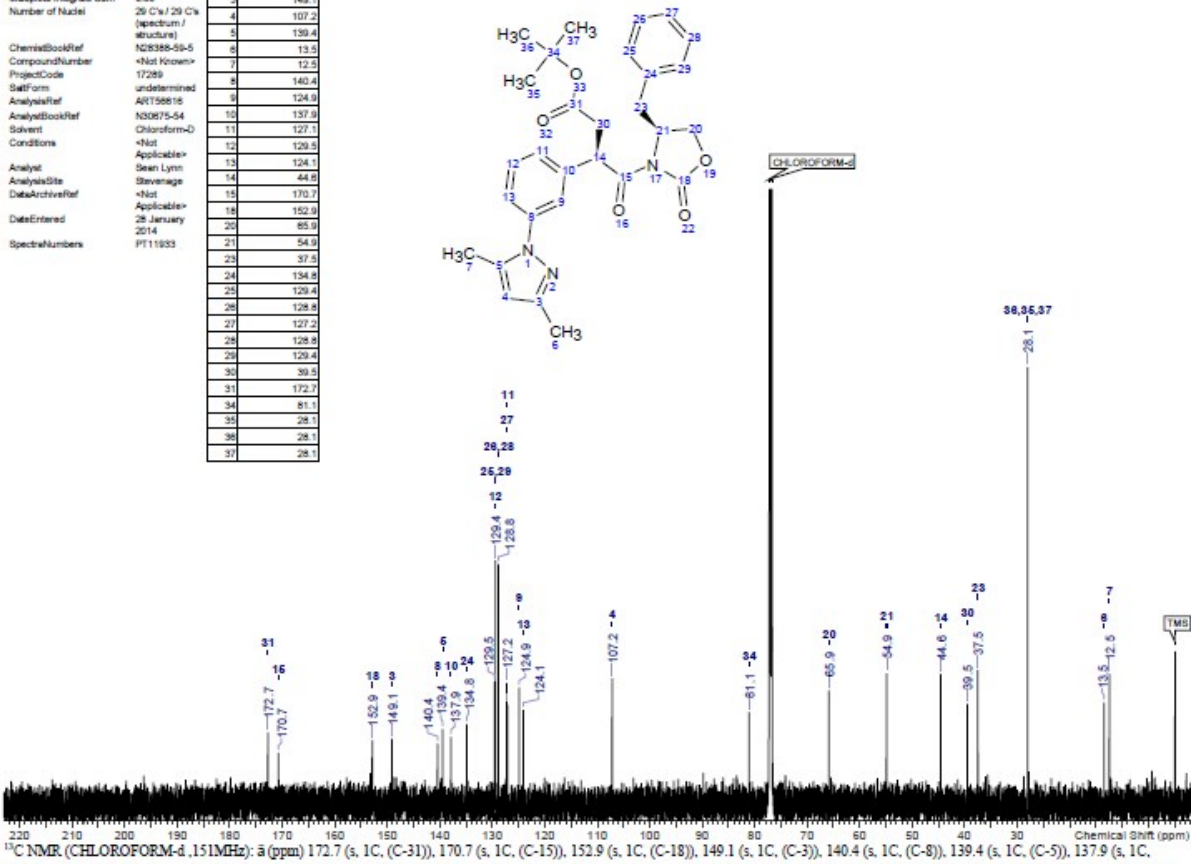
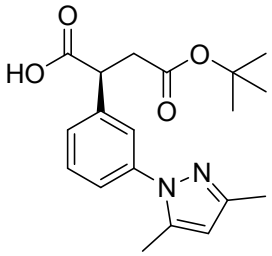
30	39.5
31	172.7
34	81.1
35	28.1
36	28.1
37	28.1

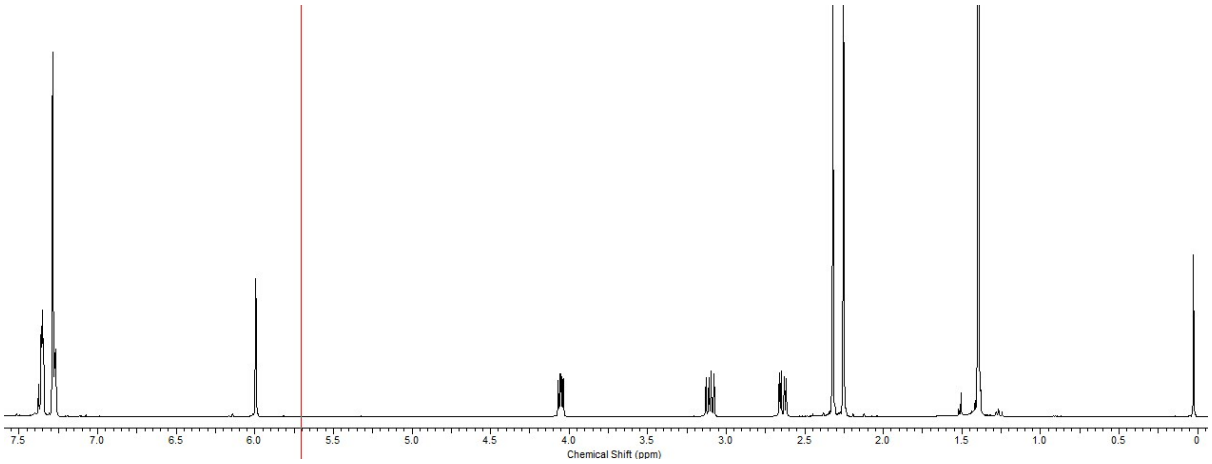


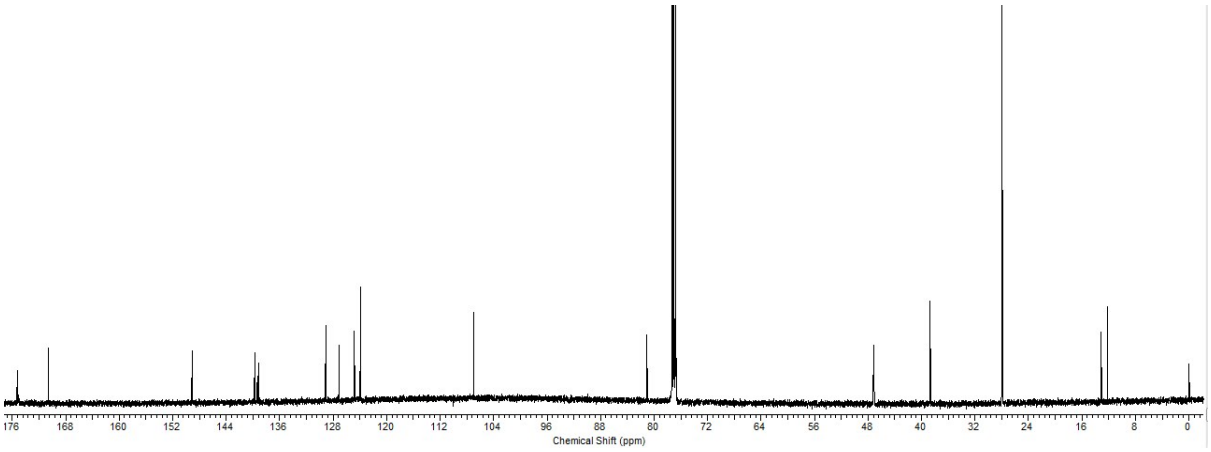
^{13}C NMR (CHLOROFORM-d ,151MHz): ā (ppm) 172.7 (s, 1C, (C-31)), 170.7 (s, 1C, (C-15)), 152.9 (s, 1C, (C-18)), 149.1 (s, 1C, ((C-3)), 140.4 (s, 1C, ((C-8)), 139.4 (s, 1C, ((C-5)), 137.9 (s, 1C, (C-10)), 134.8 (s, 1C, (C-24)), 129.5 (s, 1C, (C-12)), 129.4 (s, 2C, (C-25, 29)), 128.8 (s, 2C, (C-26, 28)), 127.2 (s, 1C, (C-27)), 127.1 (s, 1C, (C-11)), 124.9 (s, 1C, (C-9)), 124.1 (s, 1C, (C-13)), 107.2 (s, 1C, (C-4)), 81.1 (s, 1C, (C-34)), 65.9 (s, 1C, (C-20)), 54.9 (s, 1C, (C-21)), 44.6 (s, 1C, (C-14)), 39.5 (s, 1C, (C-30)), 37.5 (s, 1C, ((C-23)), 28.1 (s, 3C, ((C-36, 35, 37)), 13.5 (s, 1C, ((C-6)), 12.5 (s, 1C, ((C-7))

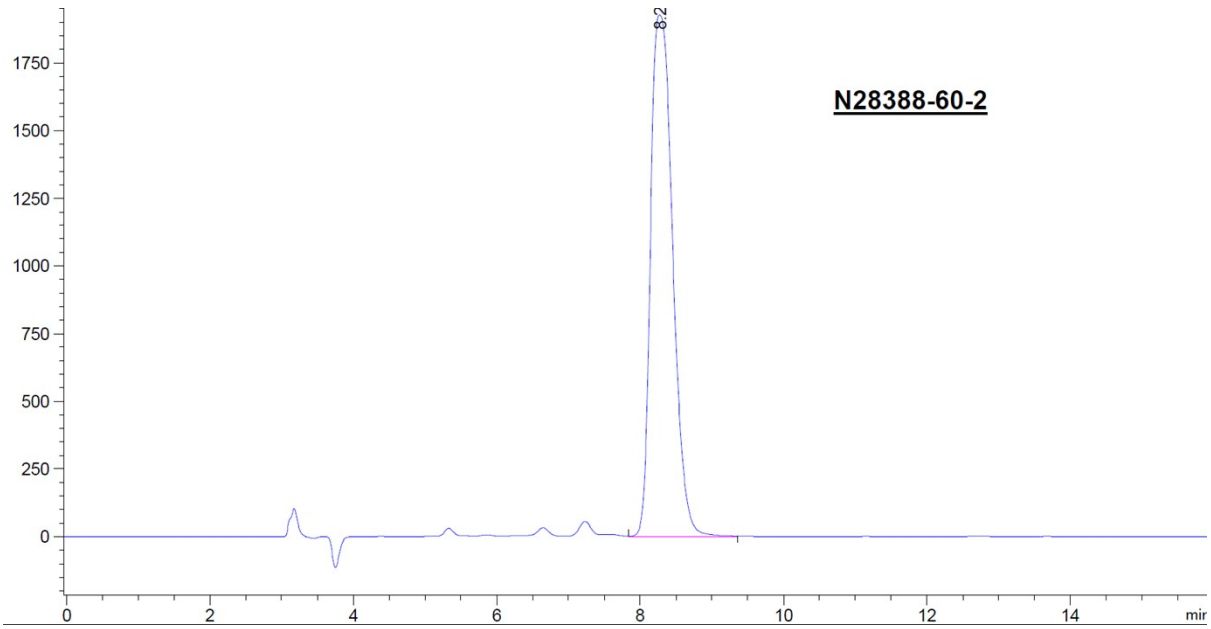
(*S*)-(+)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid

(*S*)-(+)-**25**





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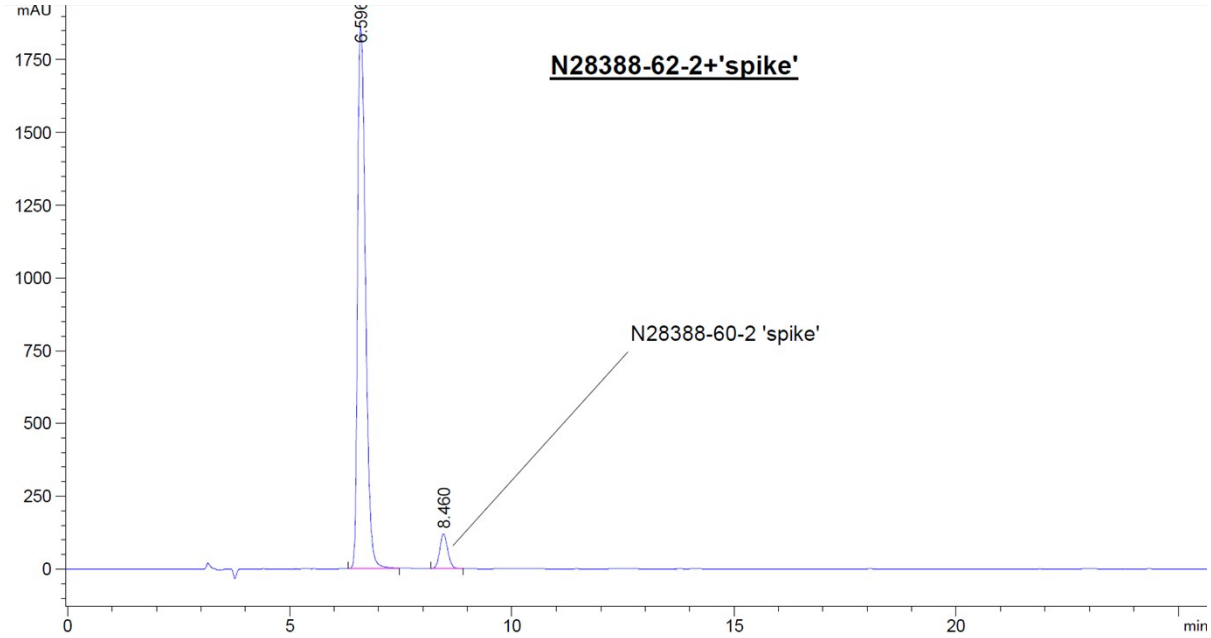
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10
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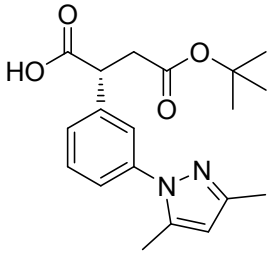
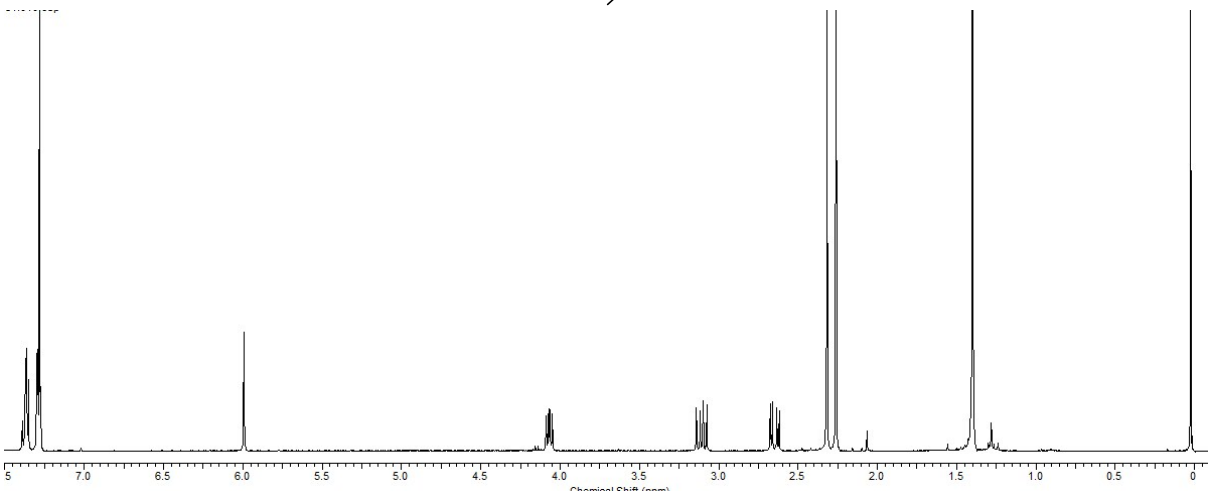
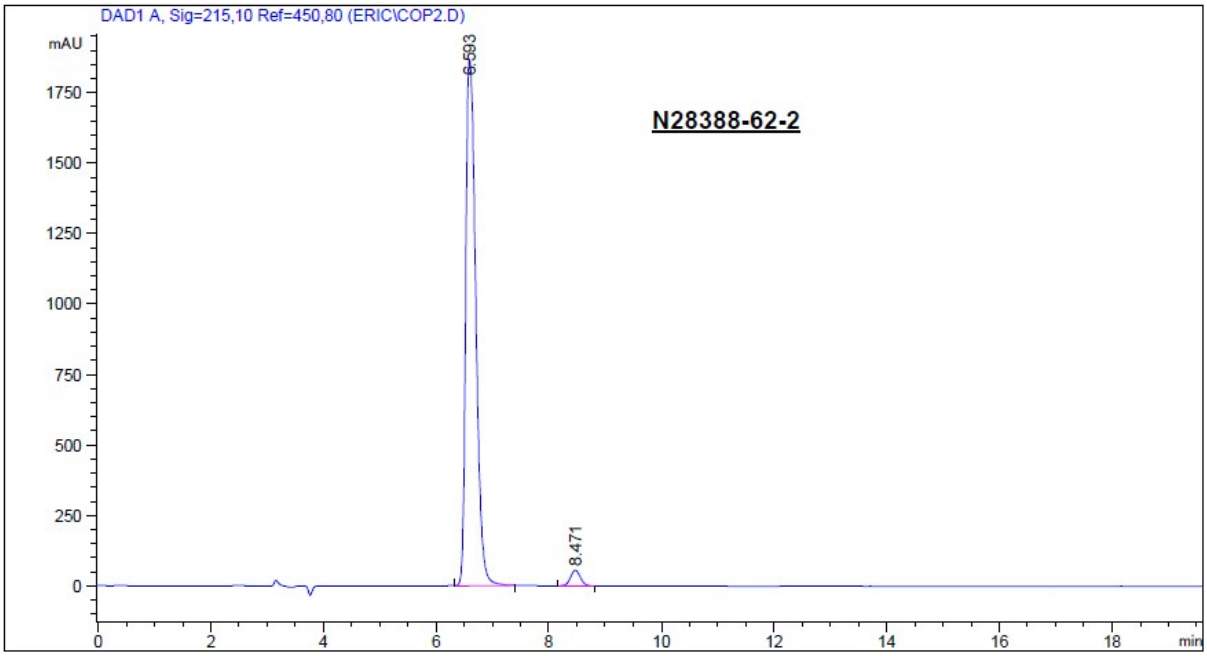
20
min

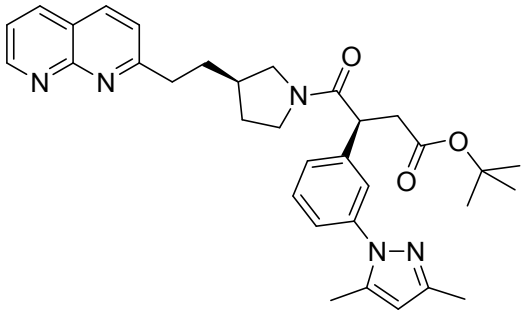
(*R*)-(-)-4-(*tert*-Butoxy)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoic acid (*R*)-(–)-25.

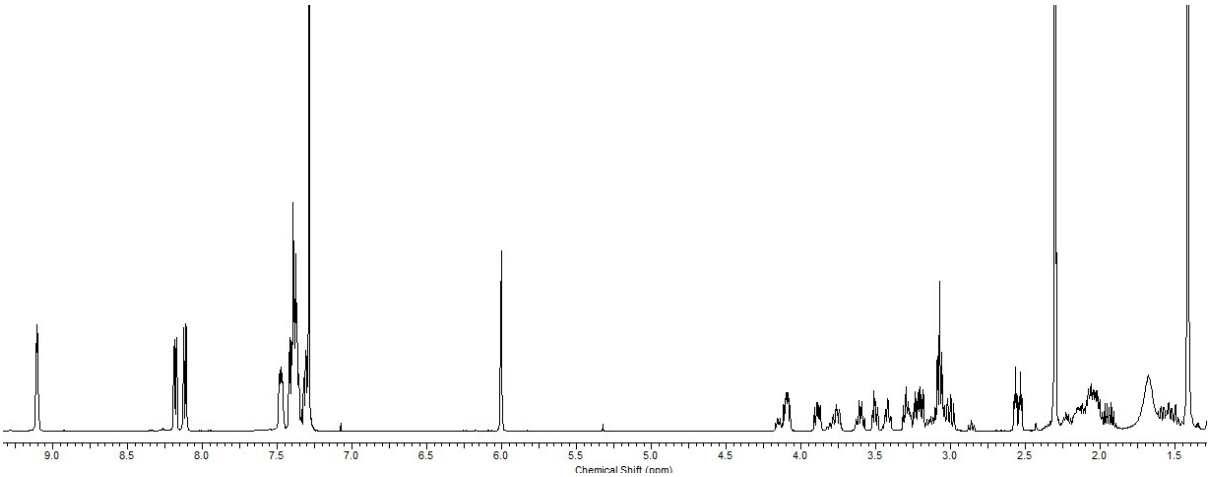


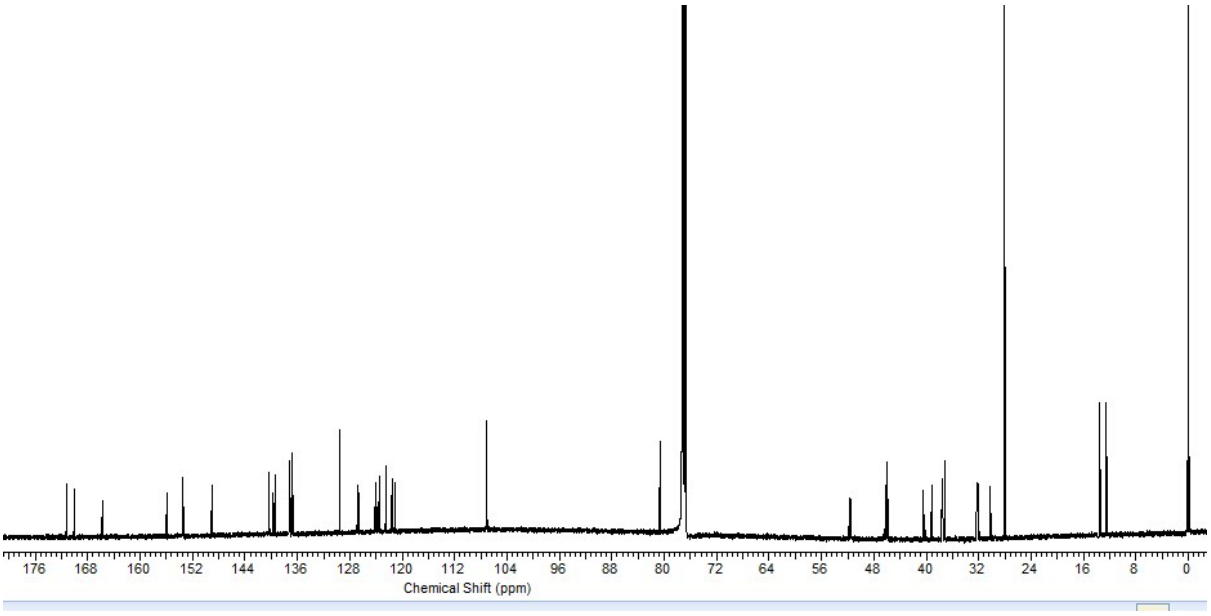




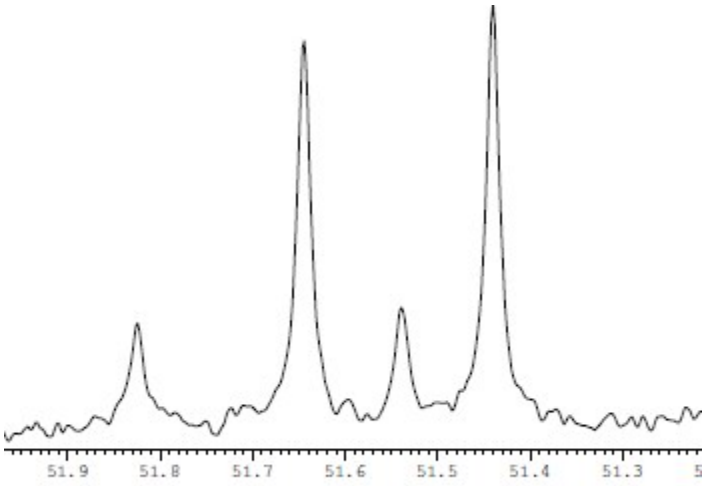
(*S*)-(+)-*tert*-Butyl 4-((*R*)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoate (30)



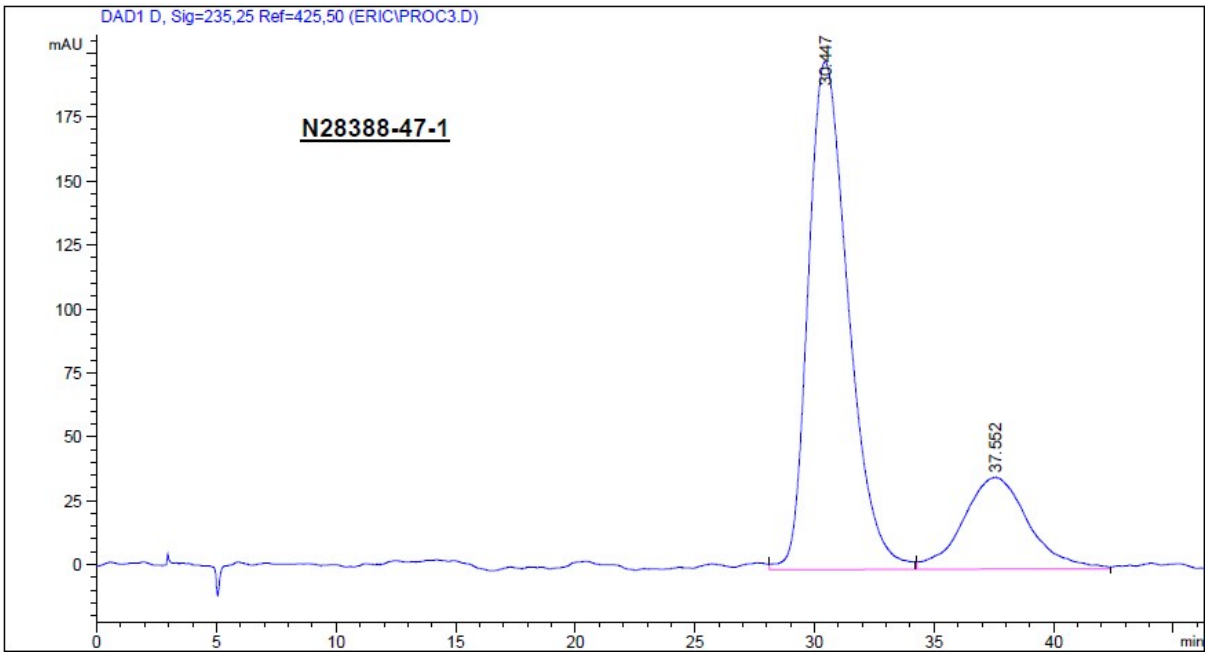




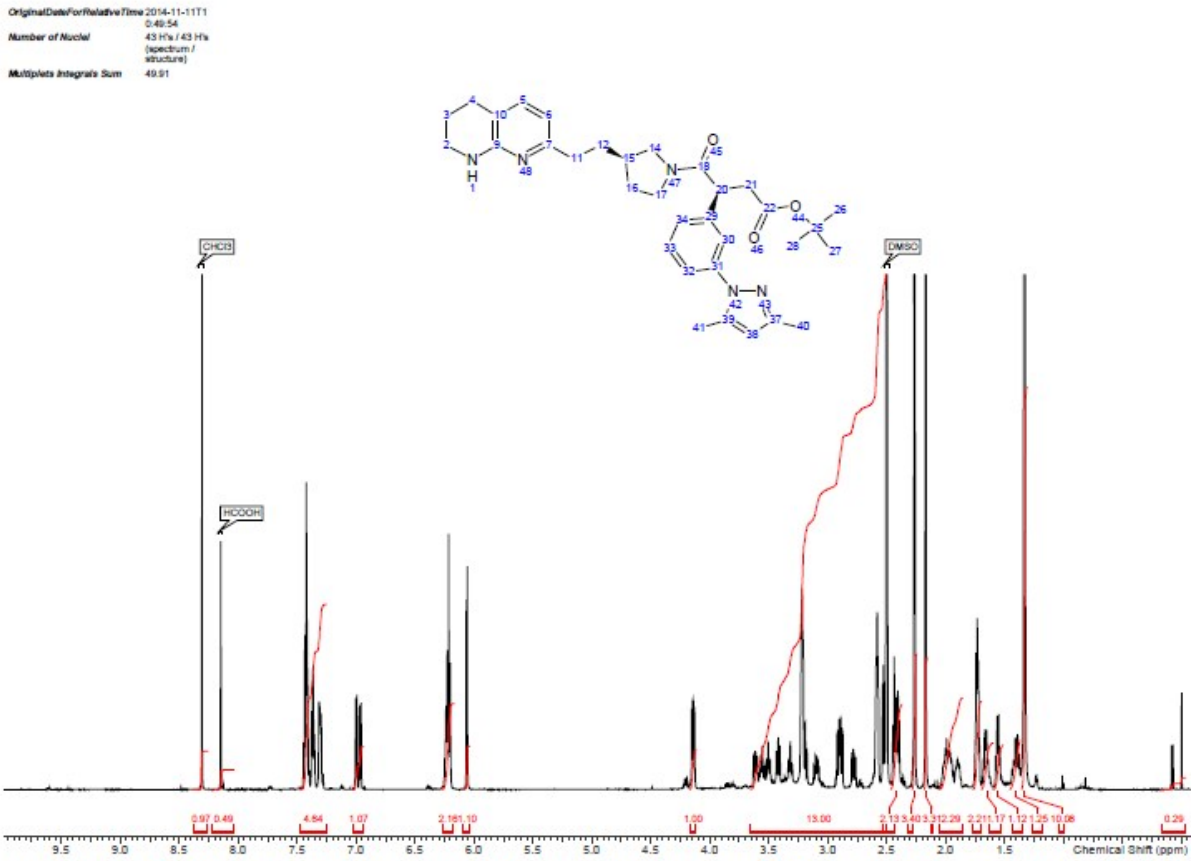
(*S*)-(+)-*tert*-Butyl 4-((*R*)-3-(2-(1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxobutanoate (30)



Expansion of ^{13}C NMR showing rotamers and diastereoisomer

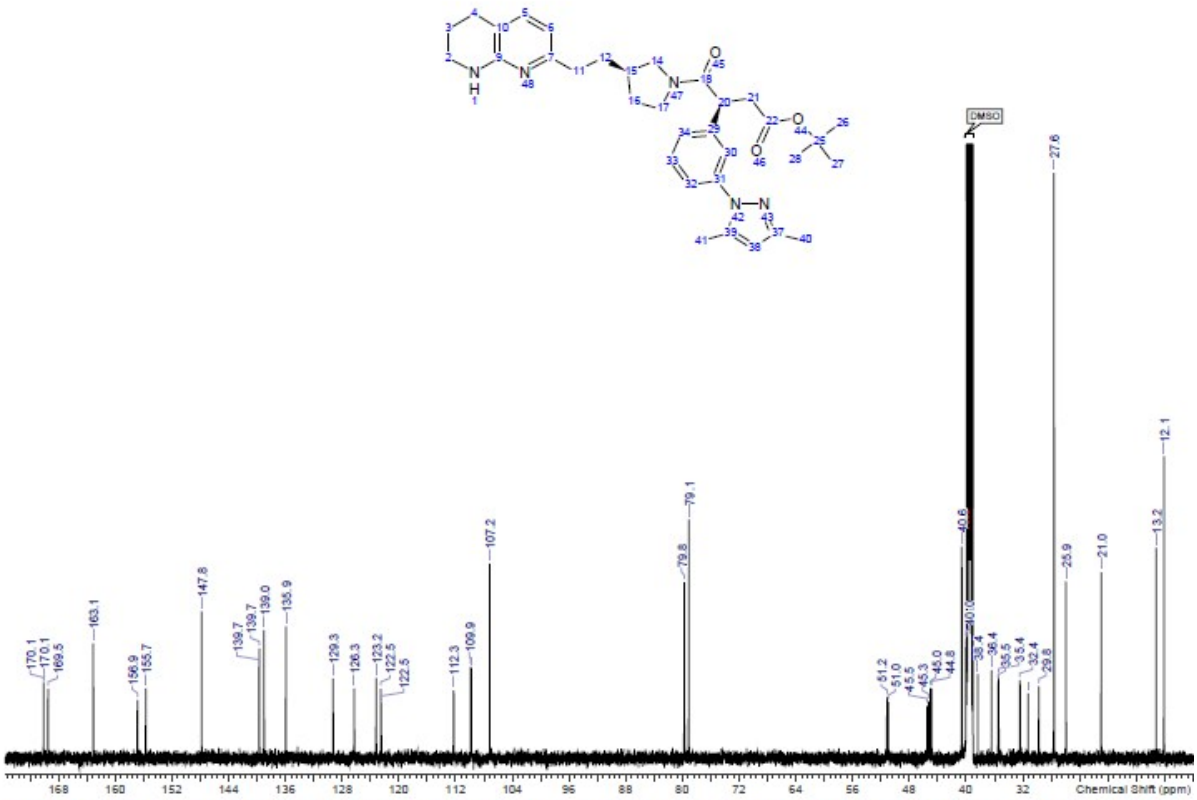


(*S*)-*tert*-Butyl 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoate (31).



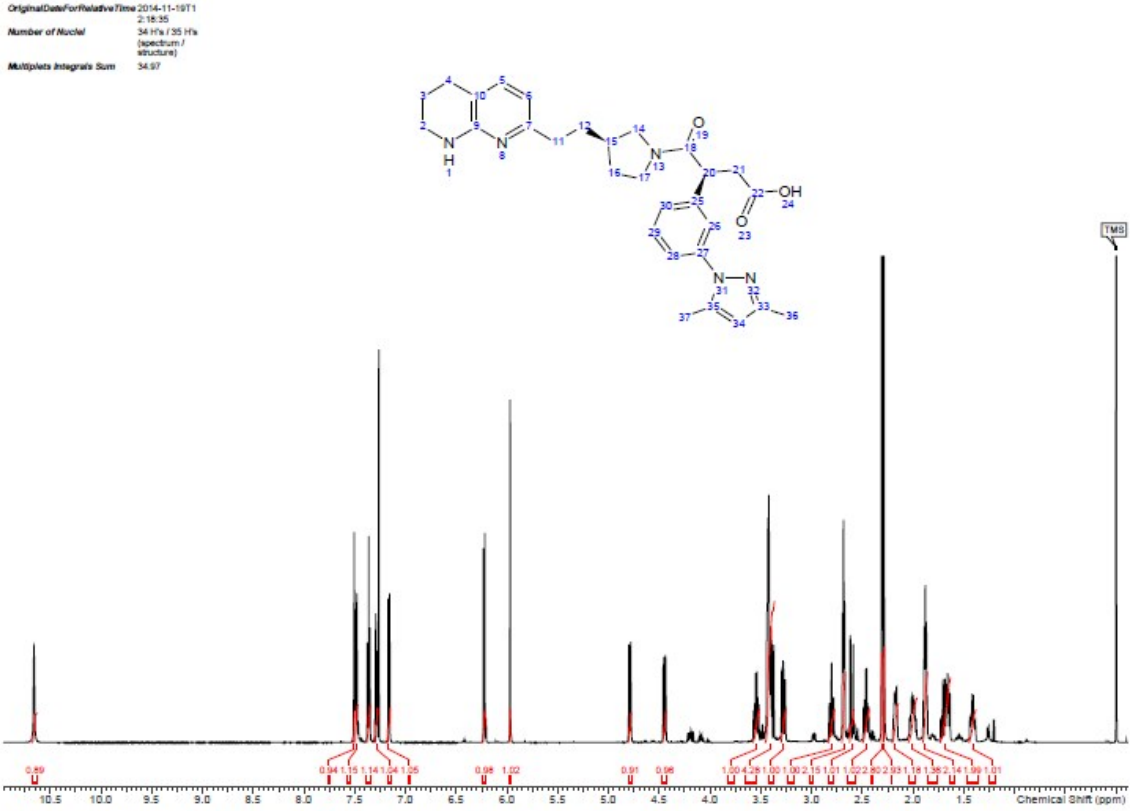
1H NMR (DMSO-d6, 600MHz): Shift (ppm) 7.26-7.48 (m, 4H), 6.94-7.03 (m, 1H), 6.17-6.27 (m, 2H), 6.04-6.09 (m, 1H), 4.12-4.17 (m, 1H), 2.51-3.65 (m, 10H+, includes water and edge of DMSO), 2.37-2.47 (m, 2H), 2.24-2.28 (m, 3H), 2.15-2.18 (m, 3H), 1.86-2.06 (m, 2H), 1.70-1.77 (m, 2H), 1.60-1.70 (m, 1H), 1.51-1.60 (m, 1H), 1.37-1.4 (m, 1H), 1.31-1.35 (m, 9H) [1:1 mixture of rotamers]

(*S*)-*tert*-Butyl 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoate (31).



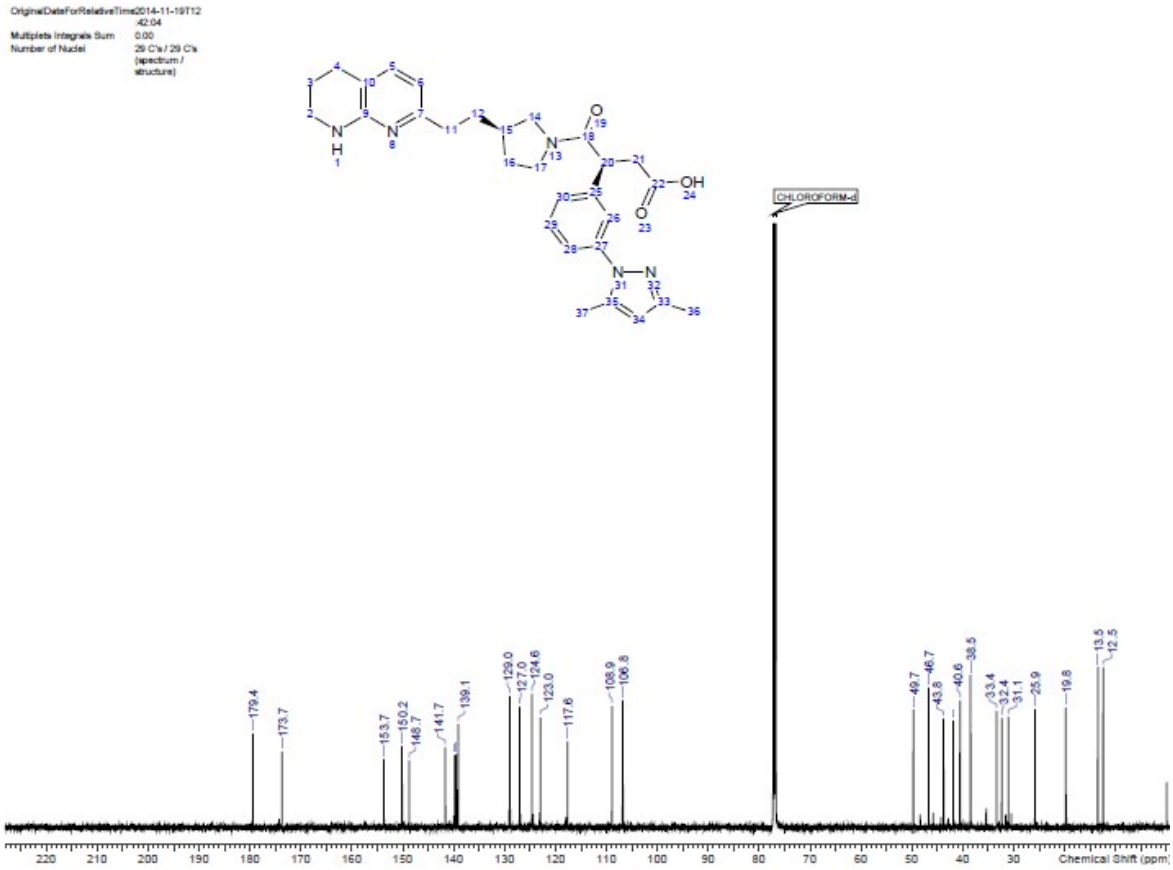
13C NMR (DMSO-d6, 151MHz): Shift (ppm) 170.1, 170.1, 169.5, 169.5, 163.1, 156.9, 156.9, 155.7, 155.7, 147.8, 139.7, 139.7, 139.0, 135.9, 129.3, 129.3, 126.3, 126.3, 123.2, 123.2, 122.5, 122.5, 112.3, 112.3, 109.9, 109.8, 107.2, 79.8, 79.1, 51.2, 51.0, 45.5, 45.3, 45.0, 44.8, 40.6, 40.0, 40.0, 38.4, 36.4, 35.5, 35.4, 32.4, 32.4, 31.3, 29.8, 27.6, 27.6, 25.9, 21.0, 13.2, 12.1 [1:1 mixture of rotamers, both sets listed where resolved, although many peaks are coincidental]

(*S*)-(+)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (32)



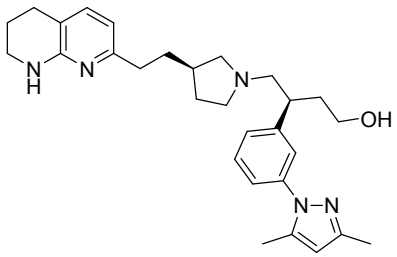
^{1}H NMR (CHLOROFORM-d, 600MHz): δ (ppm) 10.66 (br s, 1H), 7.51 (s, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.36 (t, *J*=8.0 Hz, 1H), 7.29 (br d, *J*=8.0 Hz, 1H), 7.16 (d, *J*=7.0 Hz, 1H), 6.23 (d, *J*=7.0 Hz, 1H), 5.97 (s, 1H), 4.79 (d, *J*=10.0 Hz, 1H), 4.45 (dd, *J*=12.0, 2.5 Hz, 1H), 3.55 (td, *J*=12.0, 7.5 Hz, 1H), 3.36-3.46 (m, 4H), 3.28 (dd, *J*=12.0, 9.5 Hz, 1H), 2.77-2.83 (m, 1H), 2.69 (t, *J*=6.0 Hz, 2H), 2.61 (dd, *J*=17.0, 2.5 Hz, 1H), 2.46 (td, *J*=13.0, 6.0 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.14-2.21 (m, 1H), 1.96-2.05 (m, 1H), 1.88 (quin, *J*=6.0 Hz, 2H), 1.64-1.74 (m, 2H), 1.38-1.45 (m, 1H)

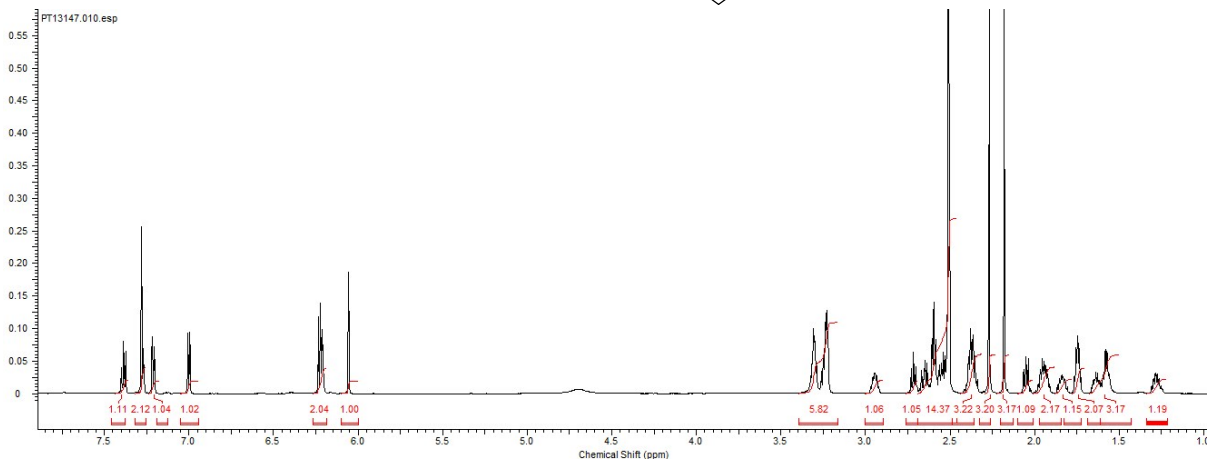
(*S*)-(+)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid (32)

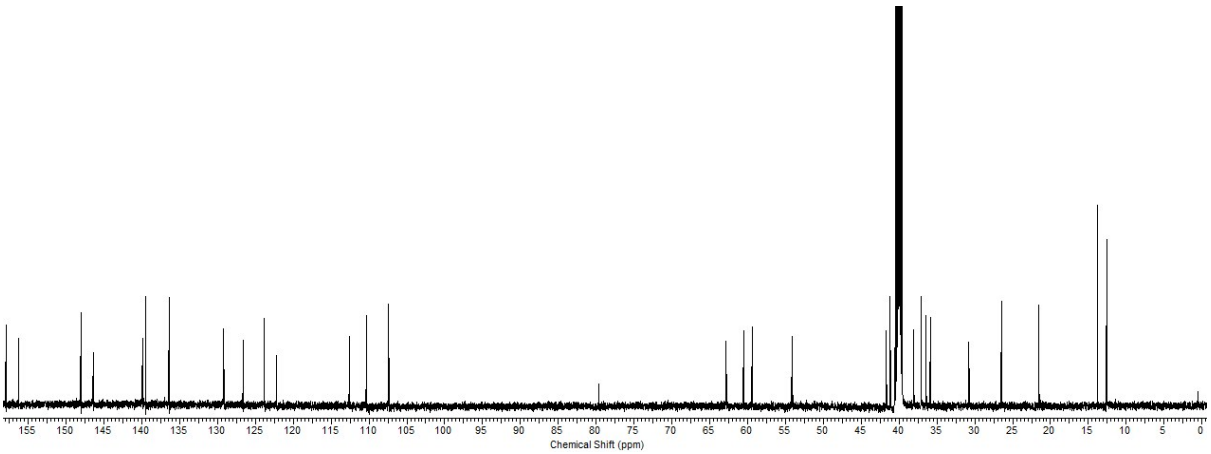


^{13}C NMR (CHLOROFORM-d, 151MHz): δ (ppm) 179.4, 173.7, 153.7, 150.2, 148.7, 141.7, 139.8, 139.5, 139.1, 129.0, 127.0, 124.6, 123.0, 117.6, 108.9, 106.8, 49.7, 46.7, 43.8, 41.9, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8, 13.5, 12.5

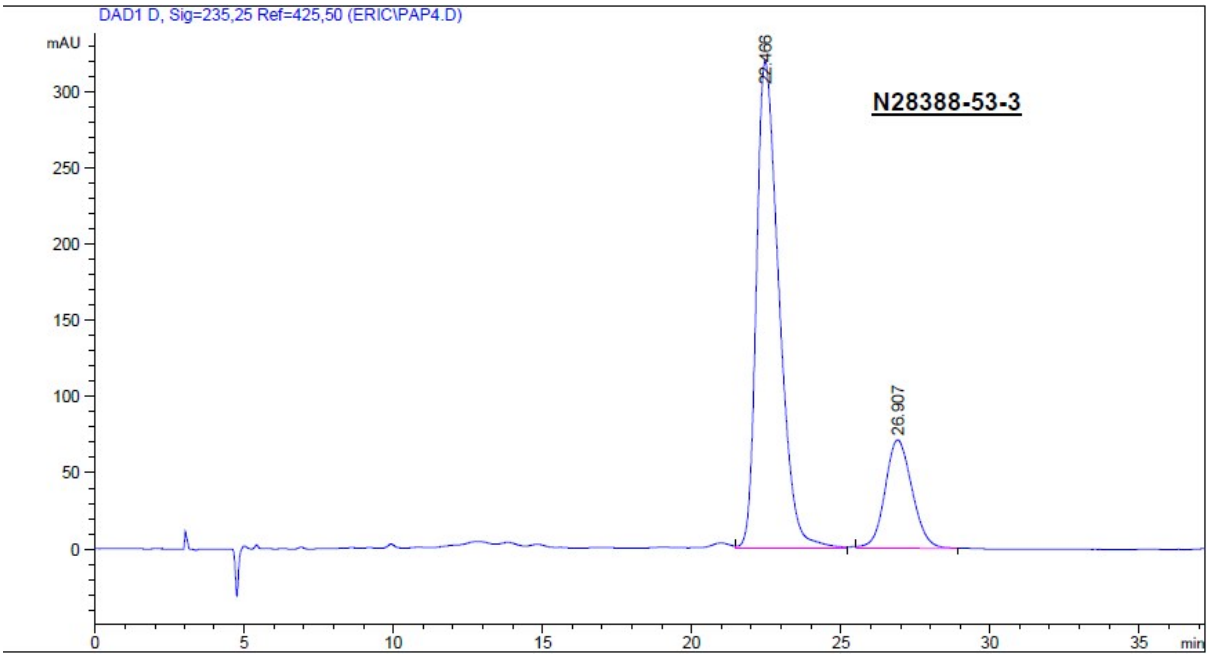
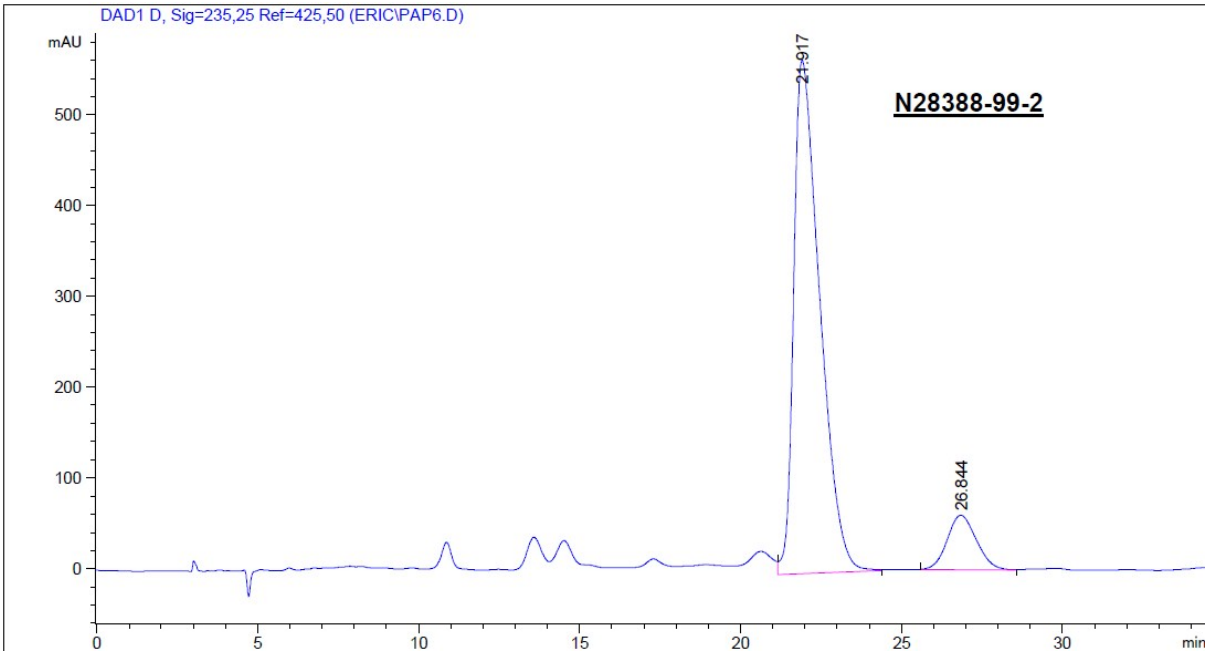
(*S*)-(+)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (33).







(*S*)-(+)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (33).



(*S*)-(+)-3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butan-1-ol (33).