Supporting Information (SI)

Discovery and Synthesis of a Pyrimidine-Based Aurora Kinase Inhibitor to Reduce Levels of MYC Oncoproteins

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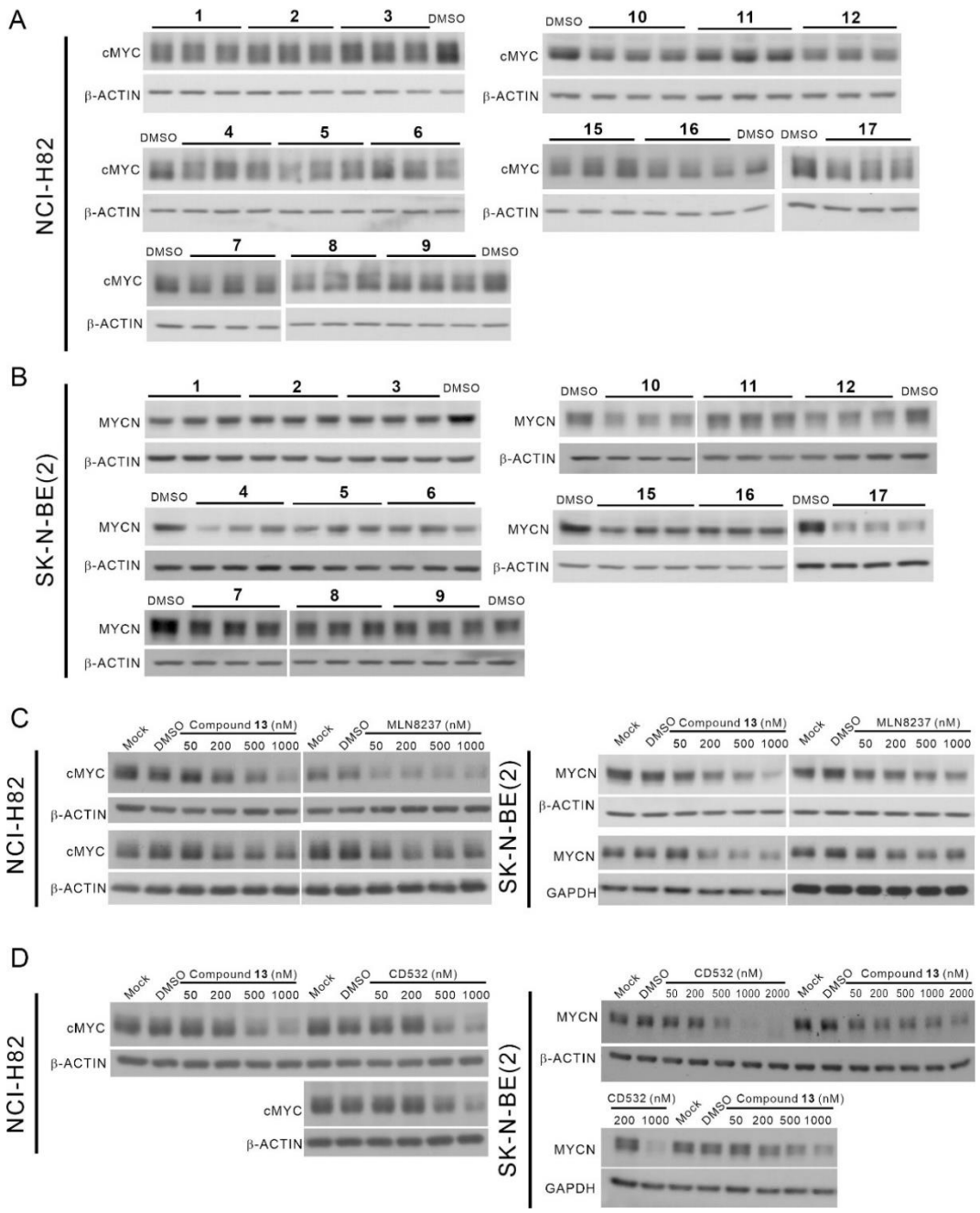


Figure S1. (A-C) Western blot analysis for the expression levels of cMYC and MYCN in NCI-H82 and SK-N-BE(2) cells respectively treated with 1.0 μM of the indicated compounds, or various concentrations of **13**/MLN8237 for 24 h. The cMYC/MYCN levels undertaken in triplicate were normalized to β-ACTIN or GAPDH, and are presented in Table 1. (D) Western blot analysis for the comparison of cMYC/MYCN protein expression profiles in NCI-H82 and SK-N-BE(2) cells respectively treated with various concentrations of **13** and CD532 for 24 h.

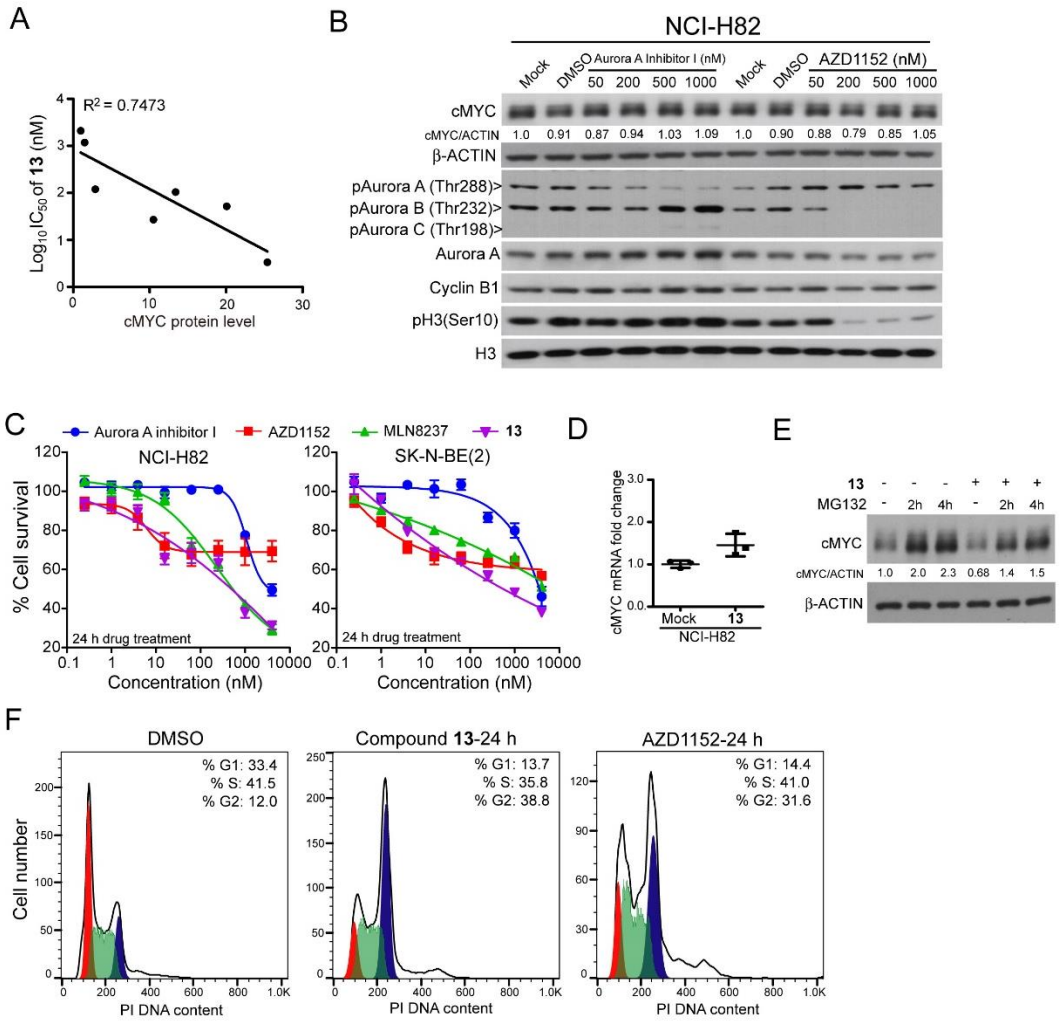
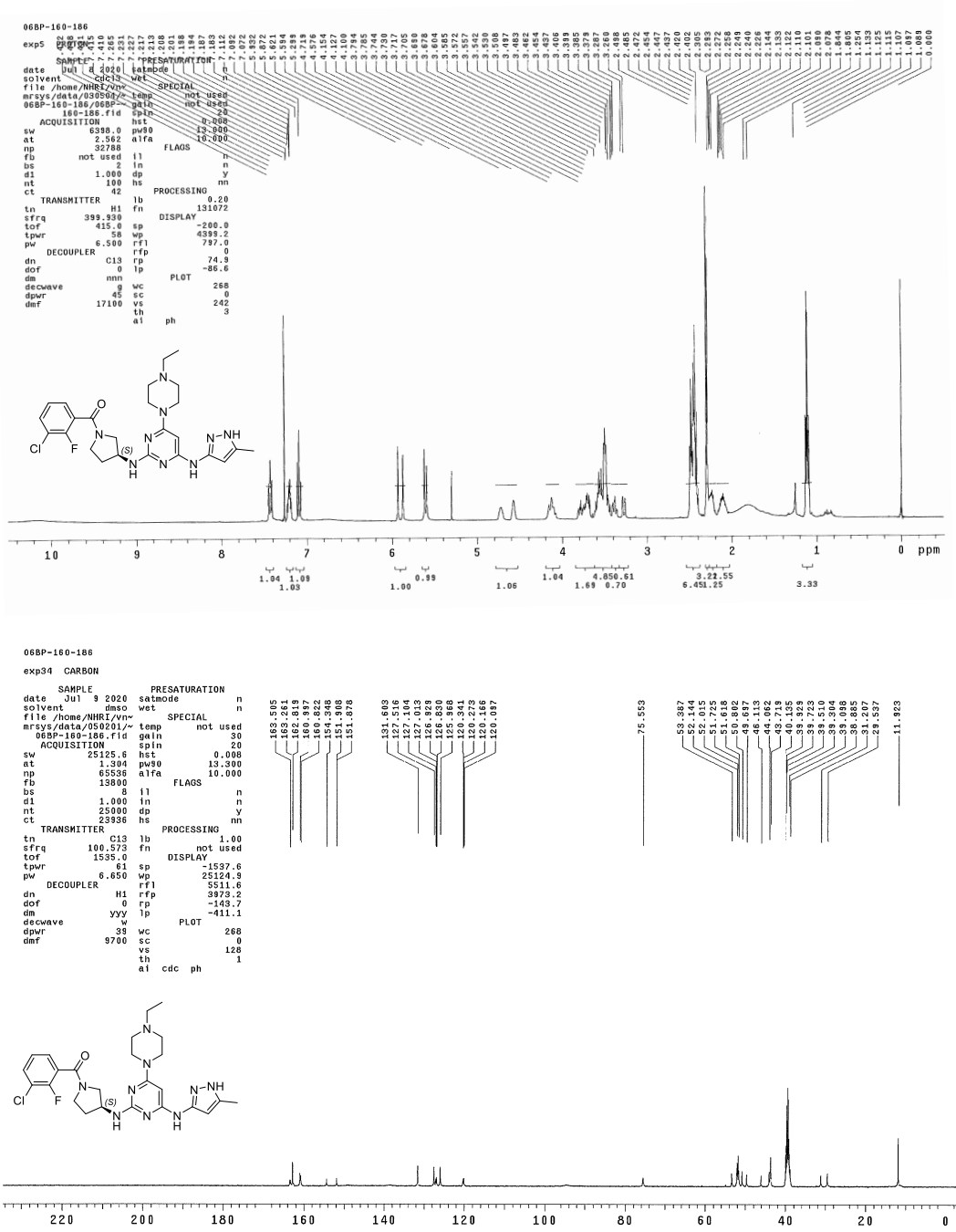


Figure S2. (A) Correlation between half growth inhibition concentrations (IC_{50}, $\log_{10}$ scale) of **13** and relative expression levels of cMYC in the seven SCLC cell lines (i.e. NCI-H82, NCI-H446, NCI-H211, NCI-H524, NCI-H2171, NCI-H146 and NCI-H841) in Figure 2E. The computed coefficient of determination R^2 is 0.7473. (B) Western blot analysis for the expression levels of cMYC, phosphorylated Aurora kinase A/B/C and cell cycle markers Cyclin B1 and pH3(Ser10), in NCI-H82 cells respectively treated with Aurora A inhibitor I and AZD1152 at the indicated concentrations for 24 h. Immunoblotting of β-ACTIN was used as a loading control. Relative expression of cMYC normalized to β-ACTIN was denoted. (C) Percent survival of NCI-H82 and SK-N-BE(2) cells treated with Aurora A inhibitor I, AZD1152, **13**, or MLN8237 for 24 h. (D) Relative mRNA level of *cMYC* in NCI-H82 mock- or **13**- treated for 24 h. (E) Western blotting analysis for the cMYC protein expression in NCI-H82 cells with/without **13** treatment for 5 h, and in the presence/absence of 1.0 μg/mL MG132 for 2 or 4 h. Immunoblotting of β-ACTIN was used as a loading control. A slight reduction in cMYC level was observed in NCI-H82 cells treated with **13** for 5 h. (F) Cell cycle analysis of NCI-H82 treated with 0.1% DMSO, 1.0 μM of **13** or 1.0 μM of AZD1152 for 24 h. Cells were fixed in 70% ethanol, stained with propidium iodide (PI)/0.1 % Triton X-100 staining solution, and were analyzed using a FACSCalibur™ (BD Biosciences). Data were processed by FlowJo™ software. Percent of cells in G1, S or G2/M (i.e. G2 in FlowJo™ software) phases are denoted on the figure.

Figure S3. NMR and HPLC spectra of compound 1.
(*S*)-(3-chloro-2-fluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (1)



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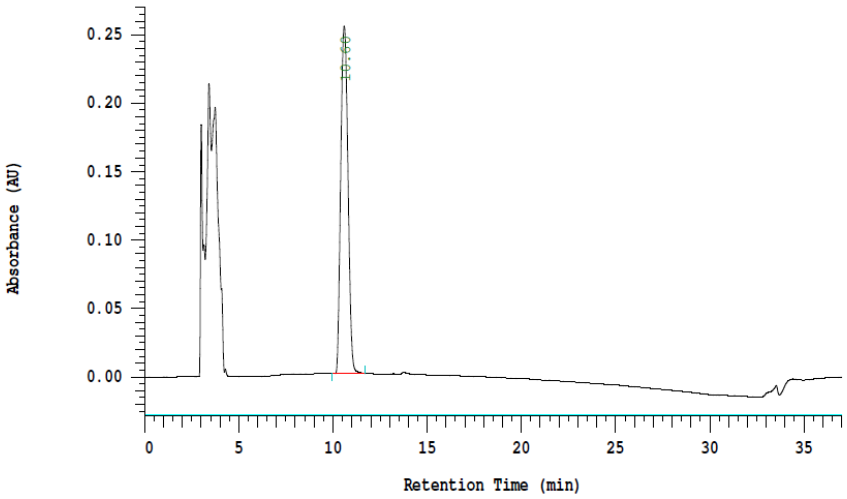

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Calculation Method: AREA%

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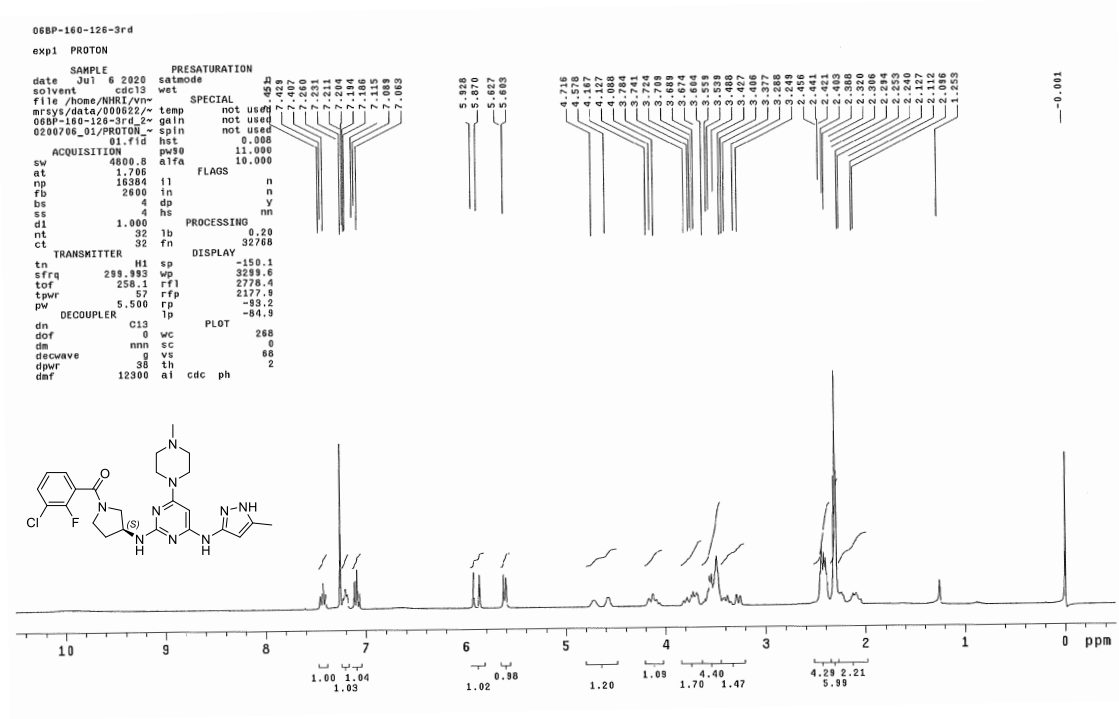
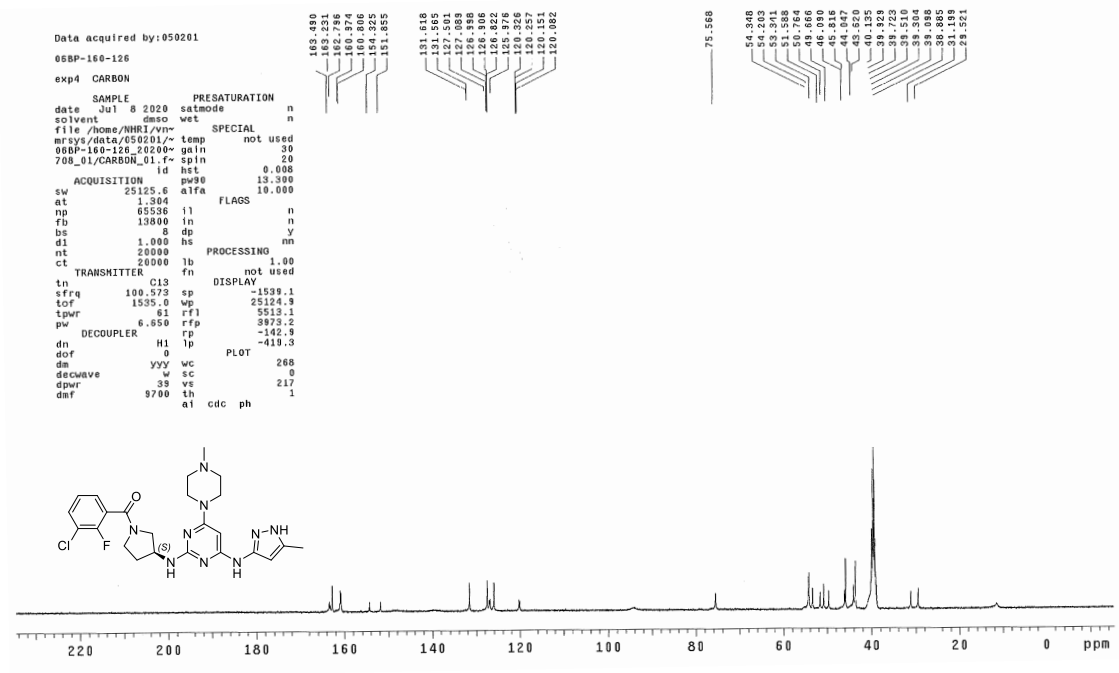
		3357313	126883	100.000

Peak rejection level: 0

Figure S4. NMR and HPLC spectra of compound 2.
(*S*)-(3-chloro-2-fluorophenyl)(3-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (2)





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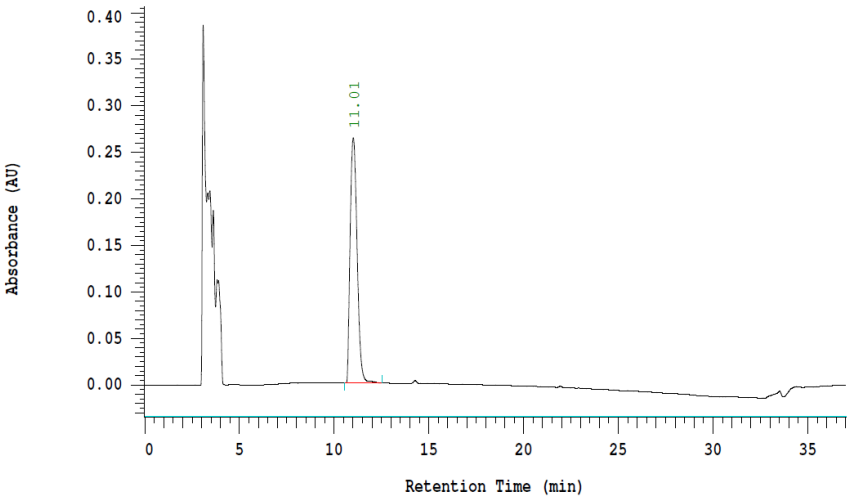

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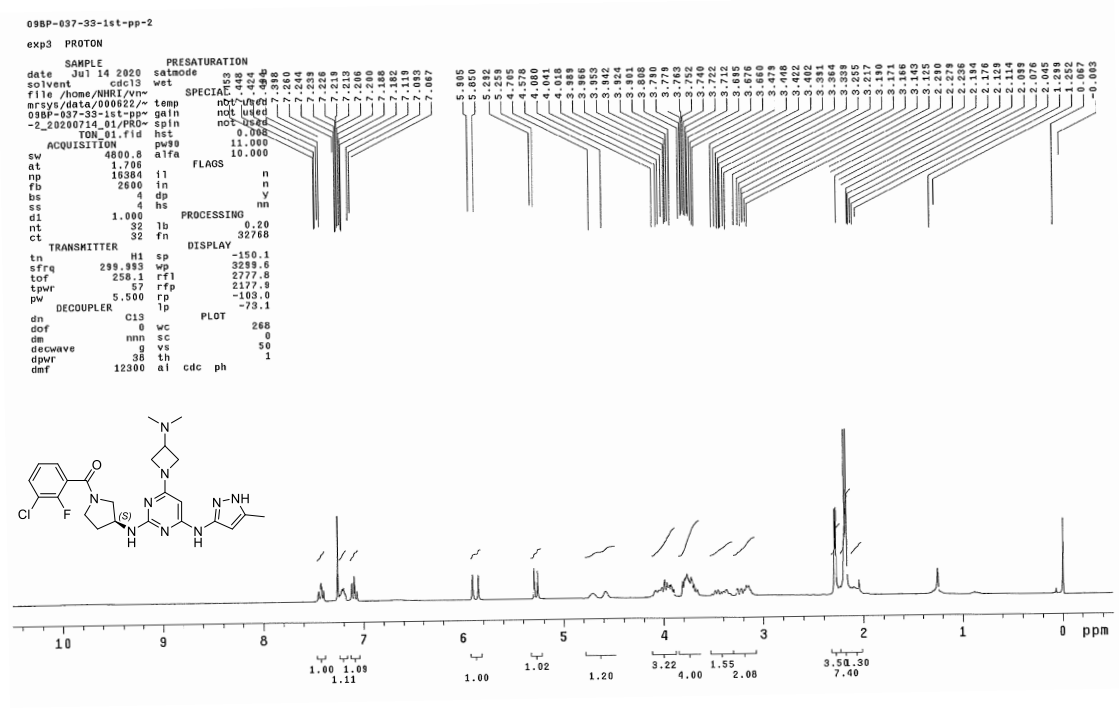
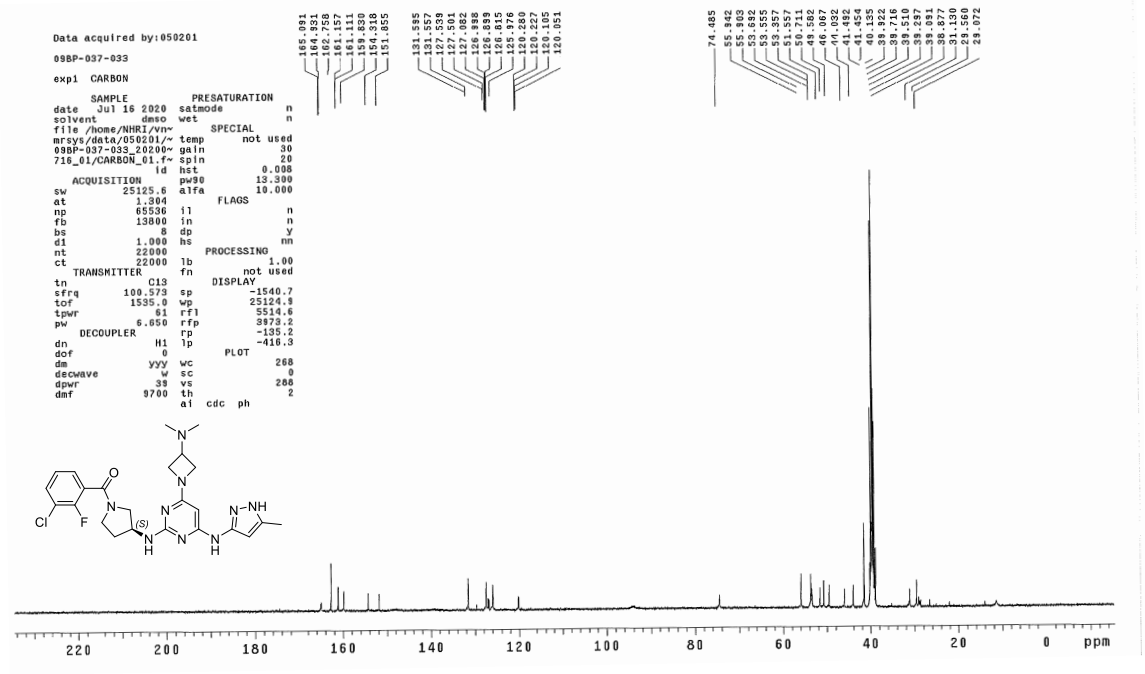
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	11.01	3333011	131560	100.000
		3333011	131560	100.000

Peak rejection level: 0

Figure S5. NMR and HPLC spectra of compound 3.
(*S*)-(3-chloro-2-fluorophenyl)(3-((4-(3-(dimethylamino)azetidin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (3)





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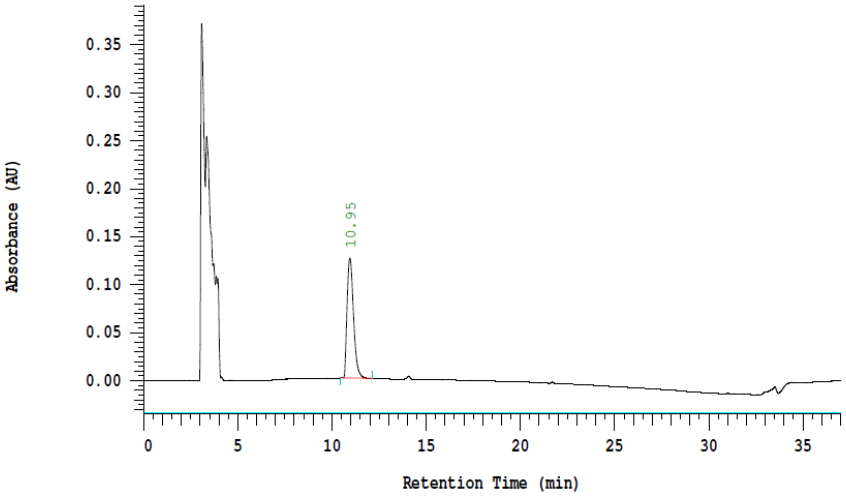

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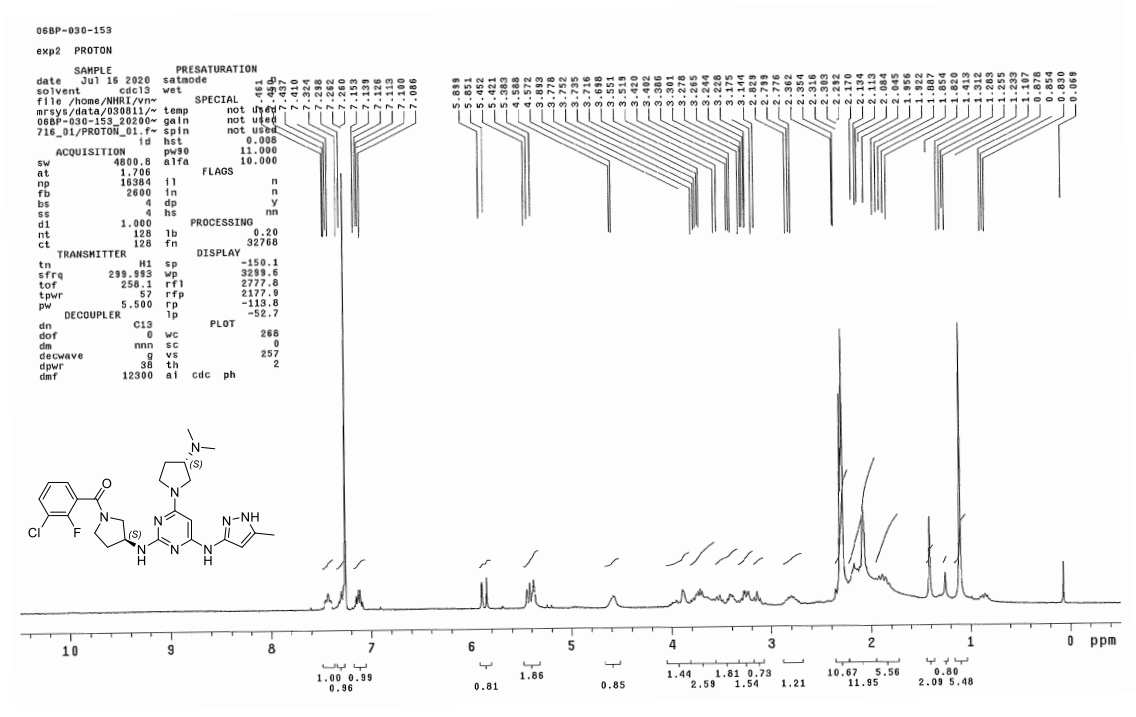
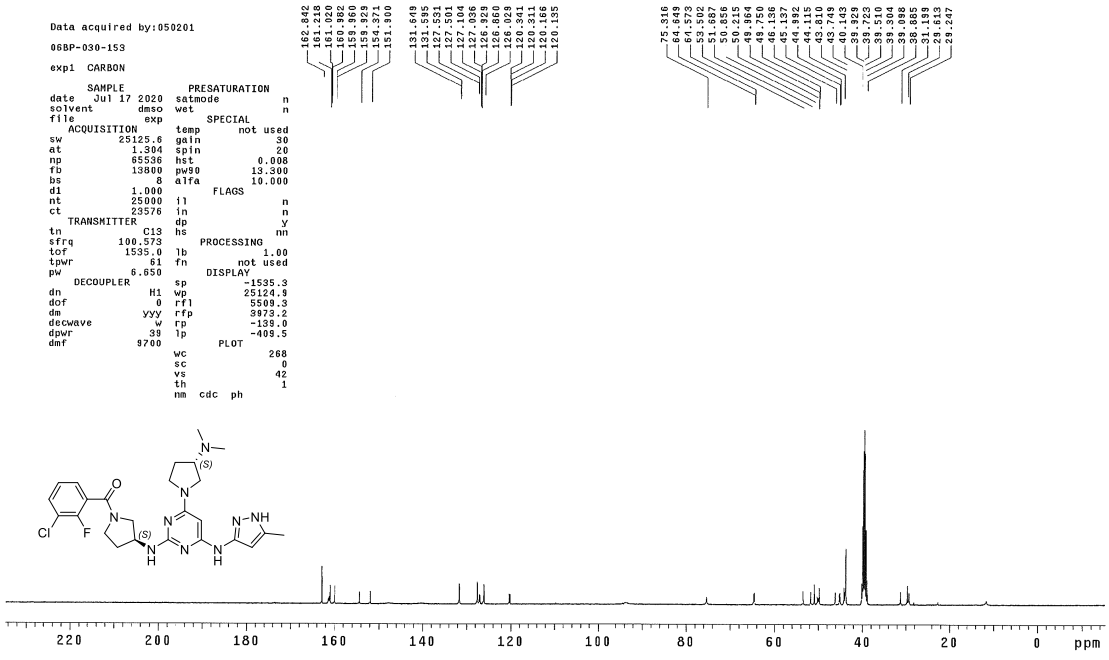
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.95	1468768	62258	100.000
		1468768	62258	100.000

Peak rejection level: 0

Figure S6. NMR and HPLC spectra of compound 4. (3-chloro-2-fluorophenyl)((S)-3-((4-((S)-3-(dimethylamino)pyrrolidin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (4)





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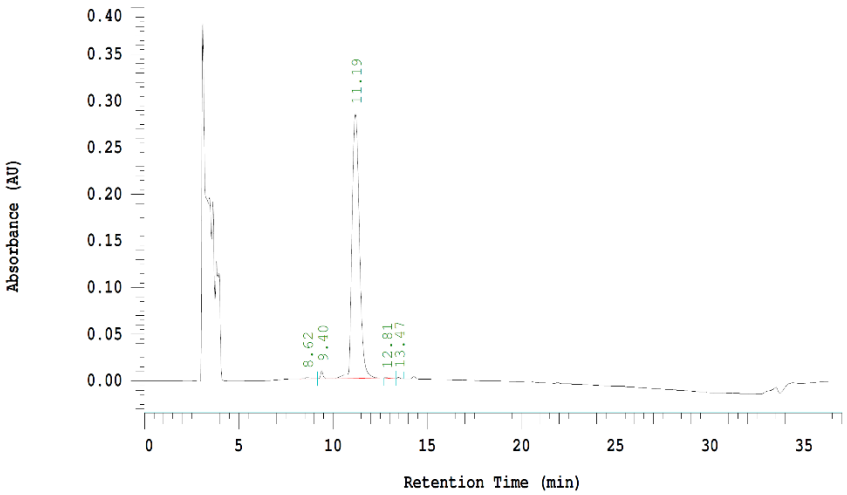


Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

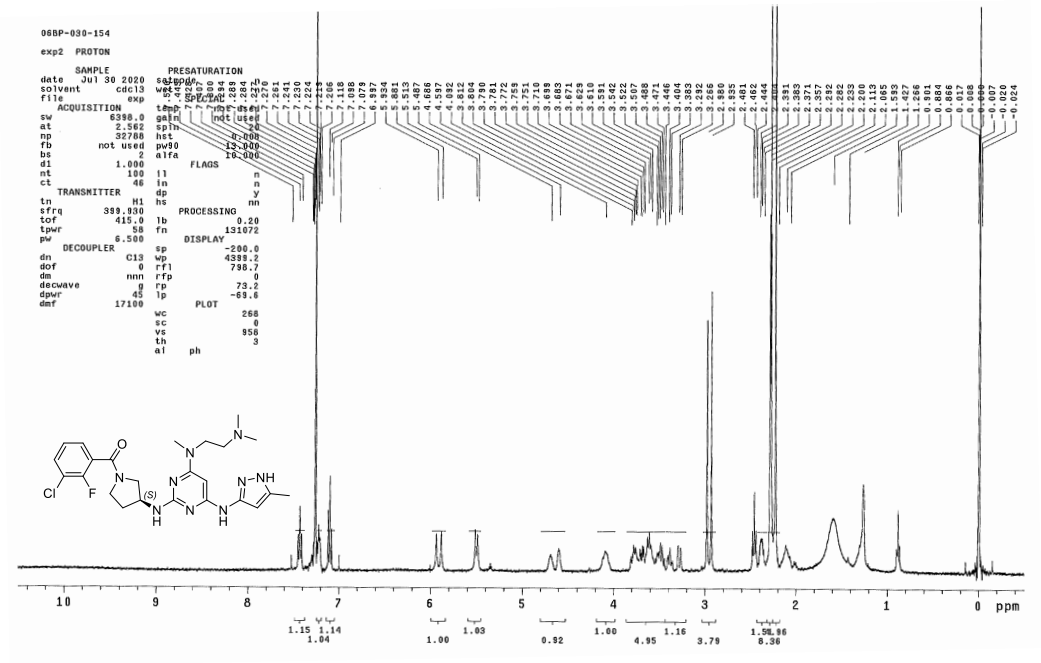
Peak Quantitation: AREA
Calculation Method: AREA%

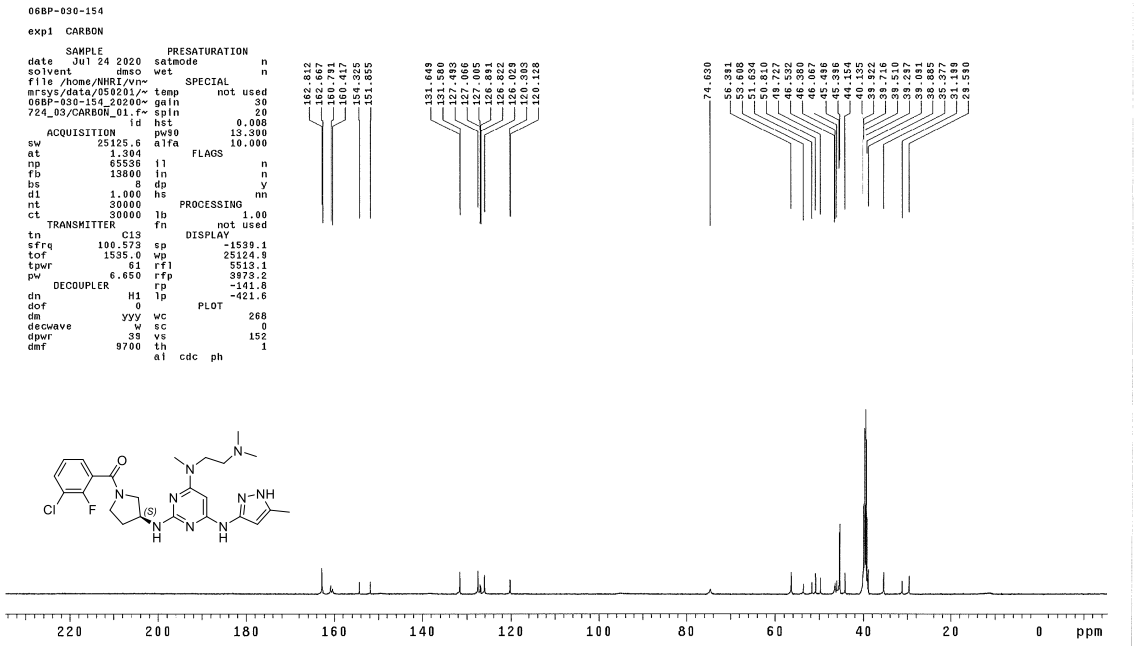
No.	RT	Area	Height	Conc 1
1	8.62	14326	556	0.367
2	9.40	37144	4226	0.952
3	11.19	3842063	141755	98.474
4	12.81	1836	215	0.047
5	13.47	6239	743	0.160
		3901608	147495	100.000

Peak rejection level: 0

Figure S7. NMR and HPLC spectra of compound 5.

(*S*)-(3-chloro-2-fluorophenyl)(3-((4-((2-(dimethylamino)ethyl)(methyl)amino)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (5)





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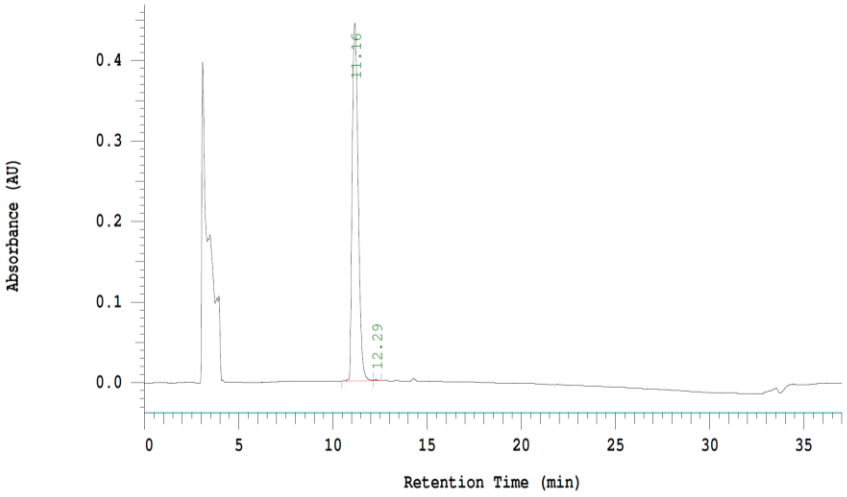

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Method Description:

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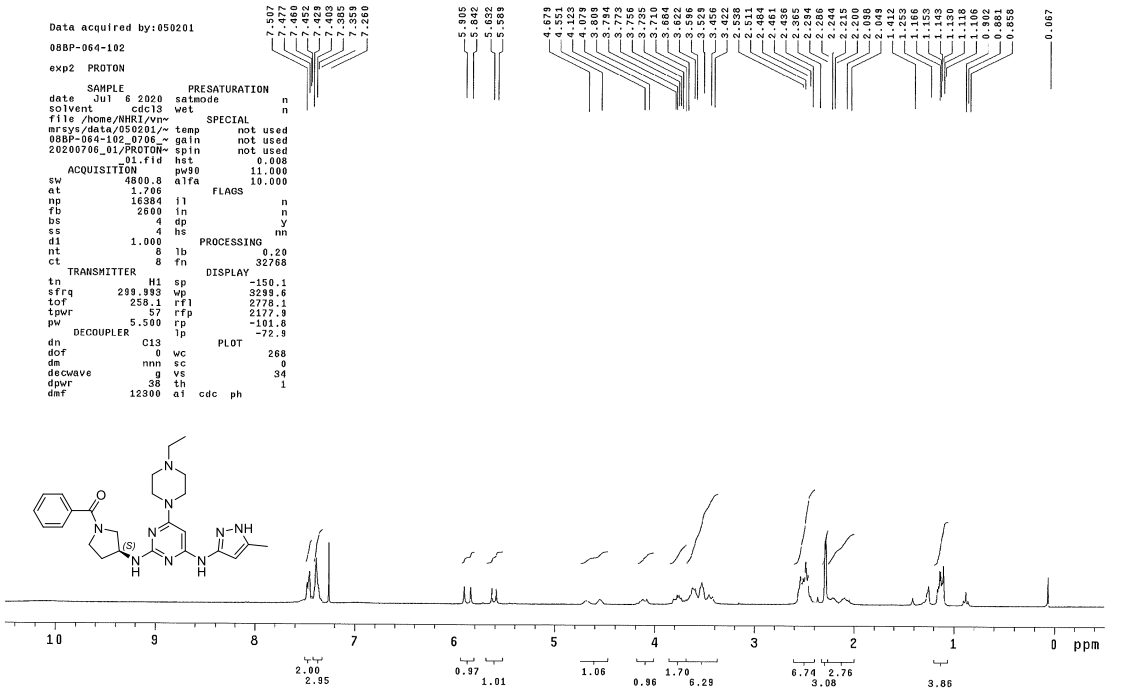
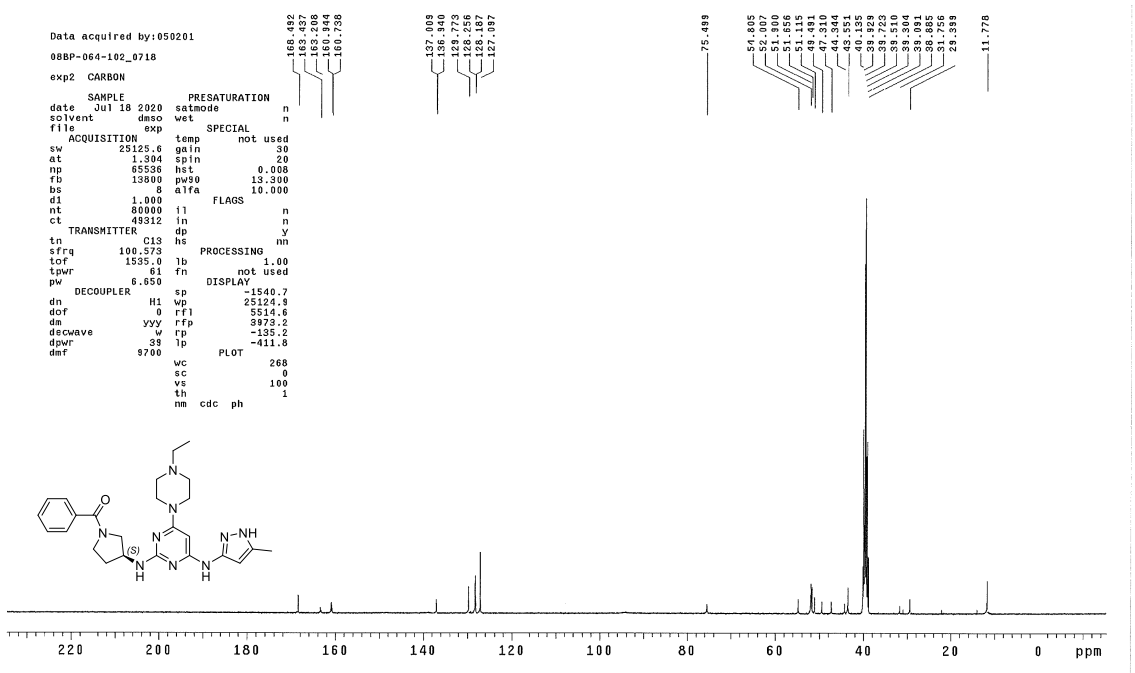
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	11.16	4852782	221908	99.906
2	12.29	4585	464	0.094
		4857367	222372	100.000

Peak rejection level: 0

Figure S8. NMR and HPLC spectra of compound 6.
(*S*)-(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)(phenyl)methanone (6)





Sample Name: 08BP-064-102-50 Vial Number: 4
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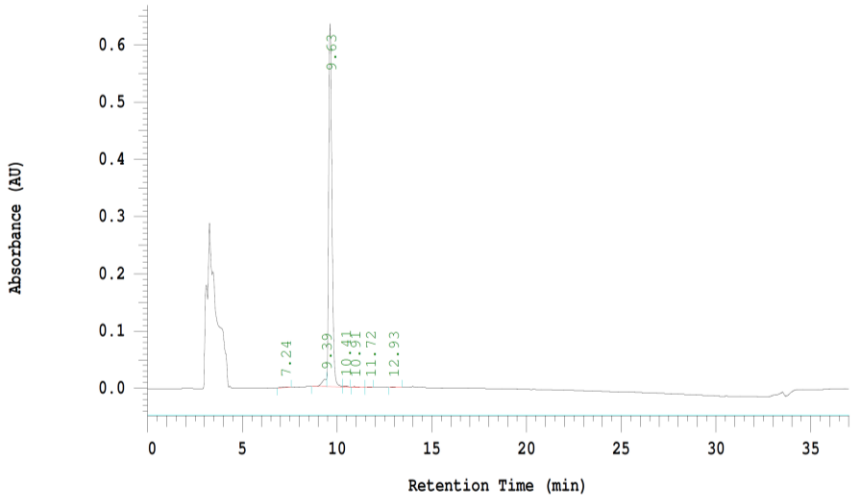
Chrom Type: Fixed WL Chromatogram, 254 nm



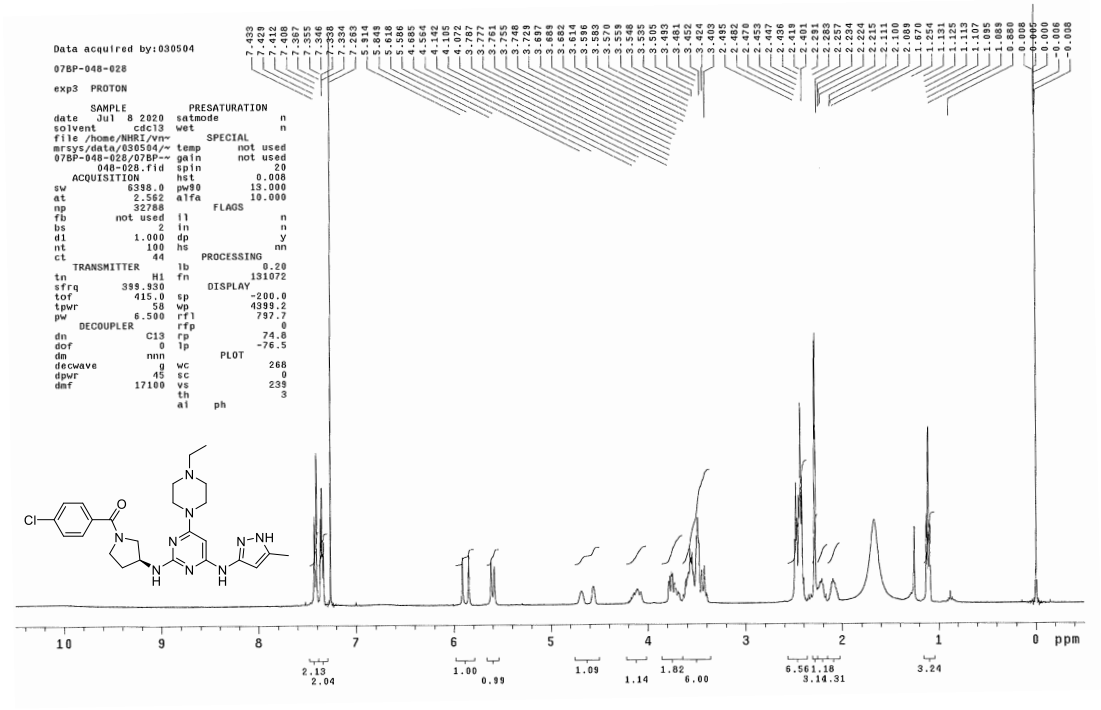
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

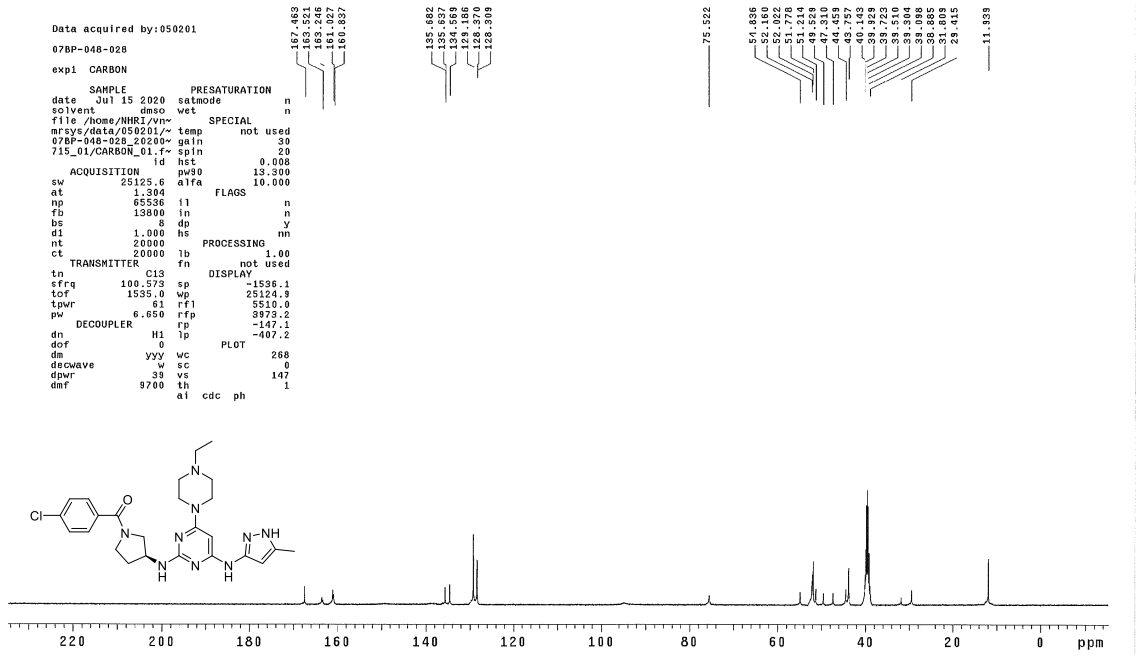
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	7.24	10782	527	0.279
2	9.39	106876	6567	2.765
3	9.63	3726693	316638	96.407
4	10.41	7022	568	0.182
5	10.91	5611	421	0.145
6	11.72	3650	306	0.094
7	12.93	4944	348	0.128
		3865578	325375	100.000

Peak rejection level: 0

Figure S9. NMR and HPLC spectra of compound 7.
(*S*)-(4-chlorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (7)





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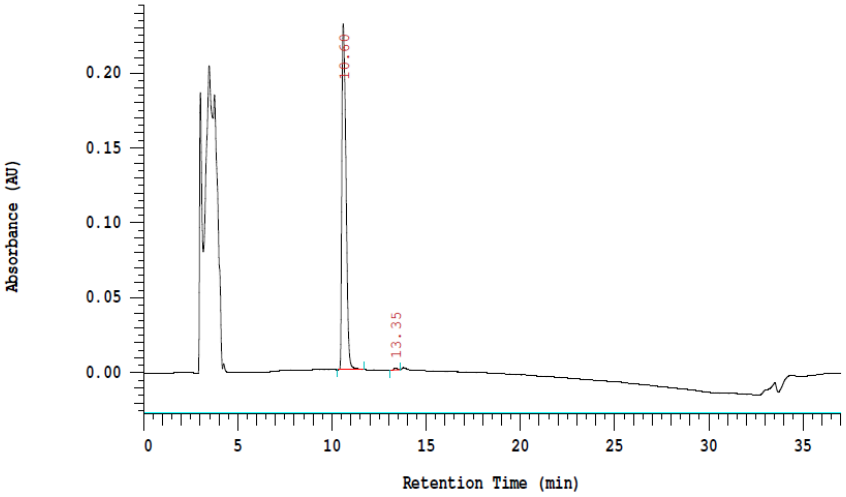

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Peak Quantitation: AREA
Calculation Method: AREA%

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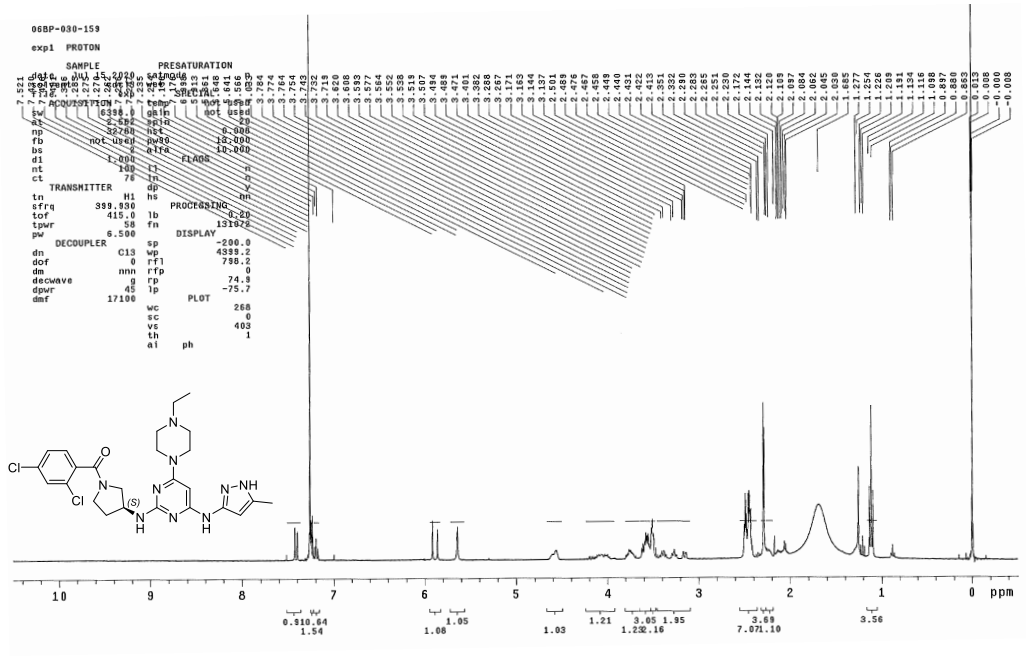
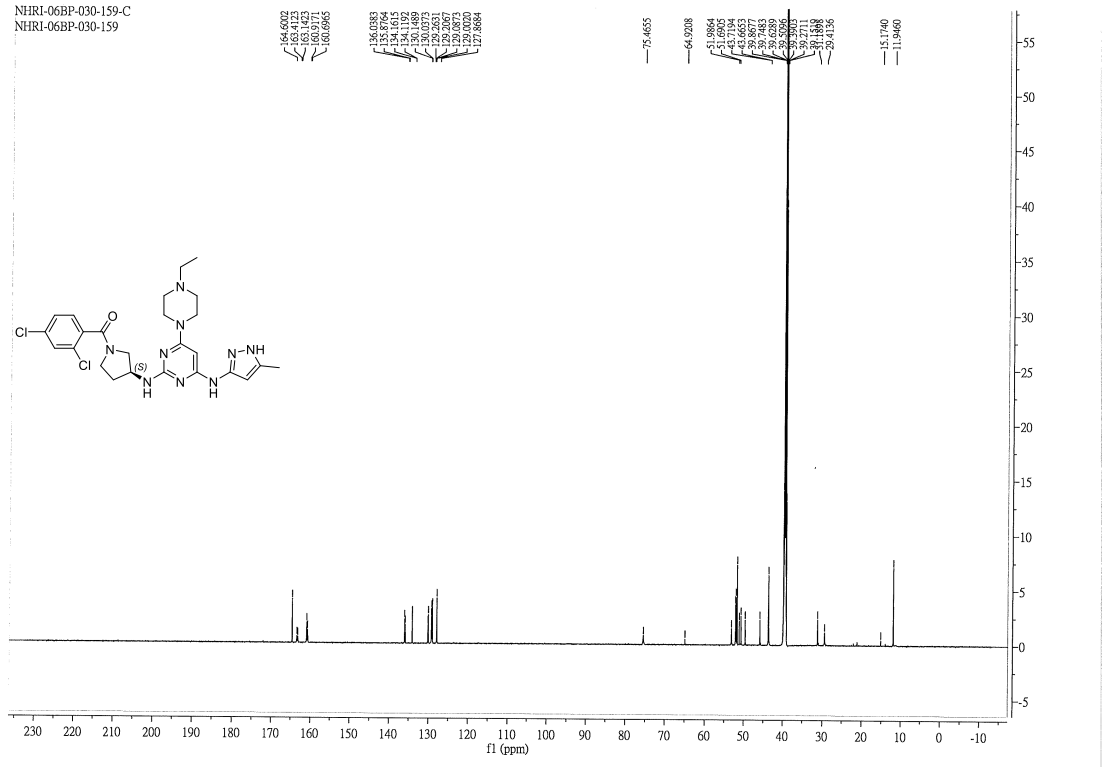
1	10.60	1721077	115221	99.629
2	13.35	6406	514	0.371
		1727483	115735	100.000

Peak rejection level: 0

Figure S10. NMR and HPLC spectra of compound 8.
(*S*)-(2,4-dichlorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (8)





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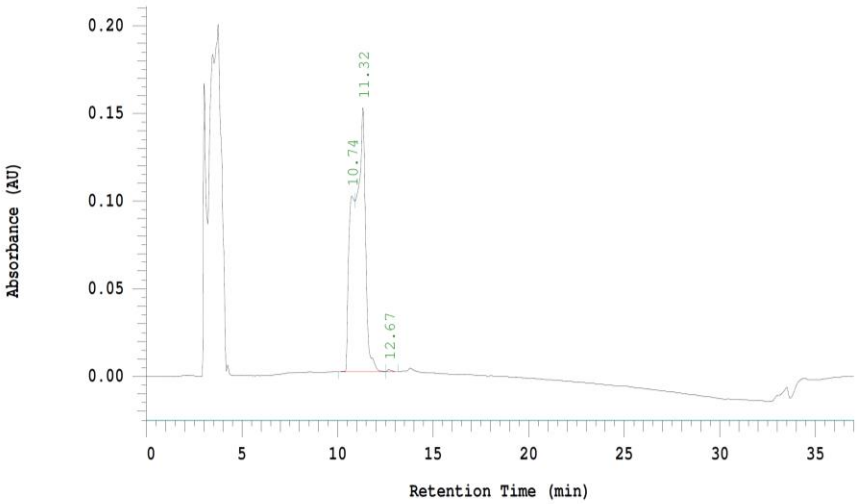

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Method Description:

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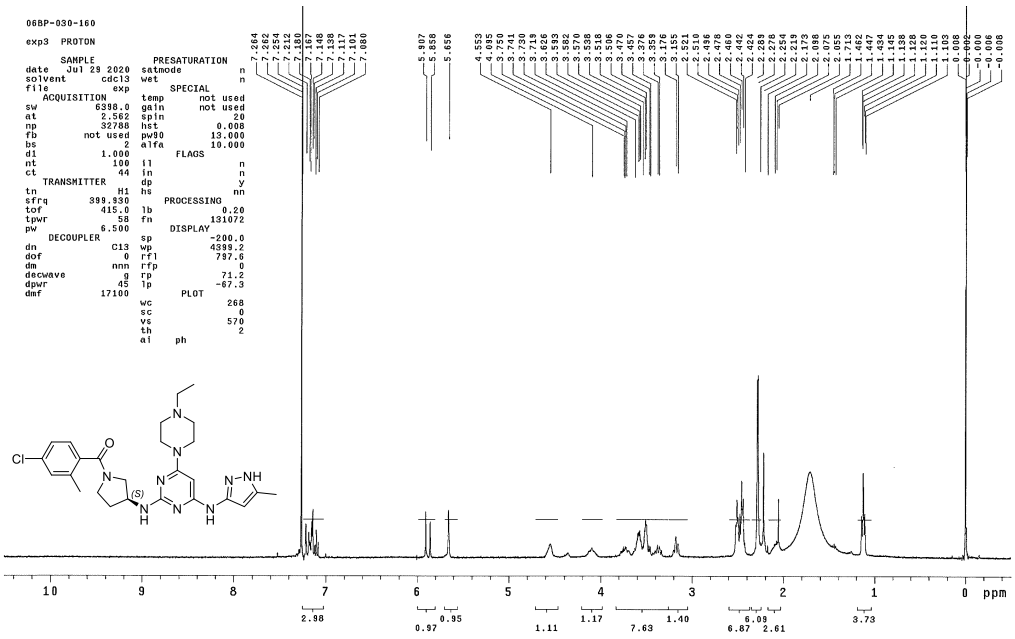
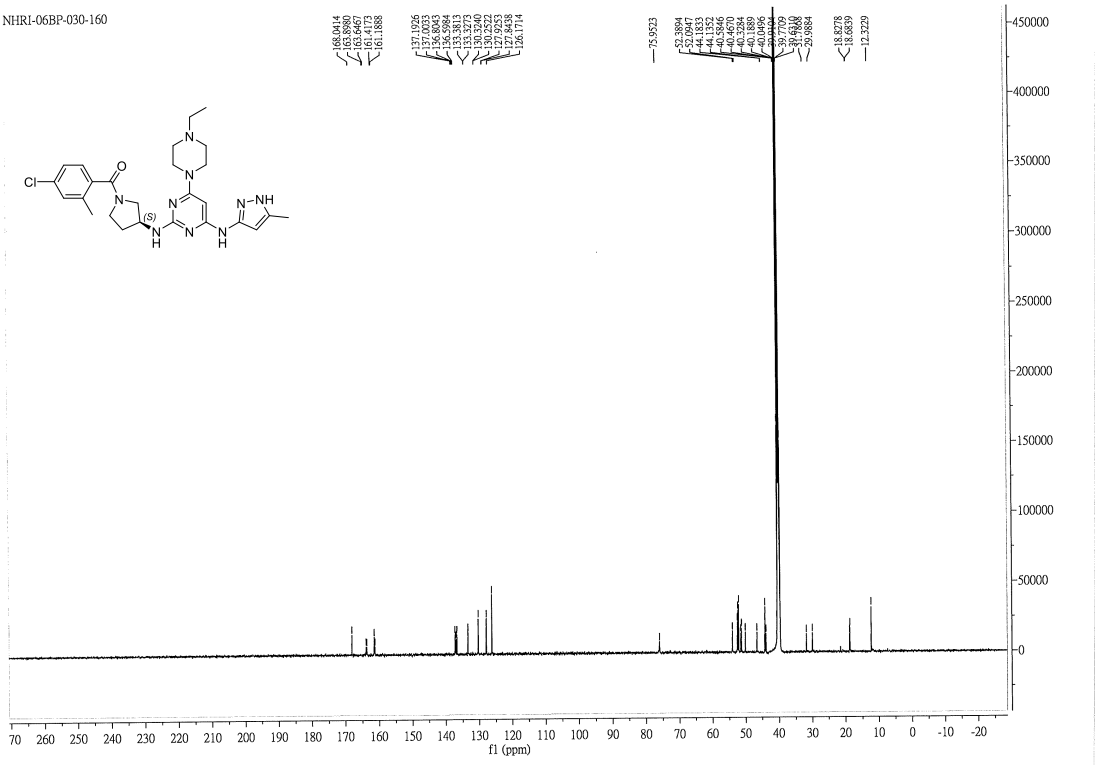
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.74	1043036	50100	32.101
2	11.32	2197890	75149	67.644
3	12.67	8257	590	0.254
		3249183	125839	100.000

Peak rejection level: 0

Figure S11. NMR and HPLC spectra of compound 9.
(*S*)-(4-chloro-2-methylphenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (9)





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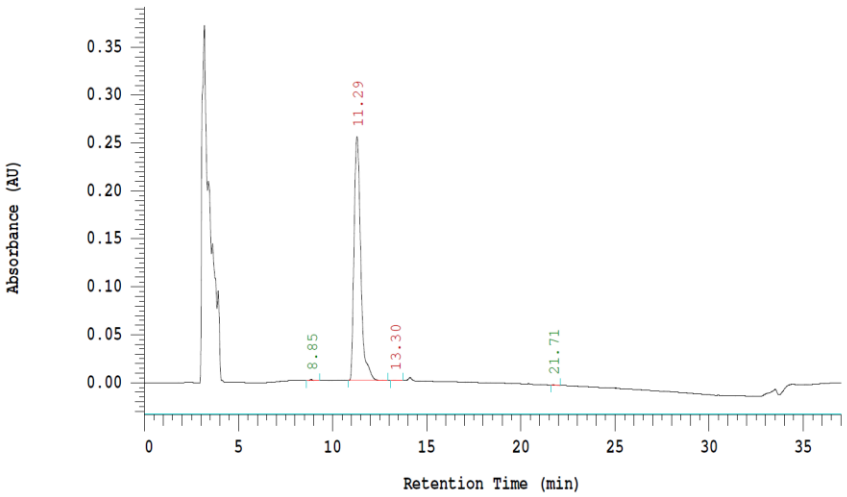


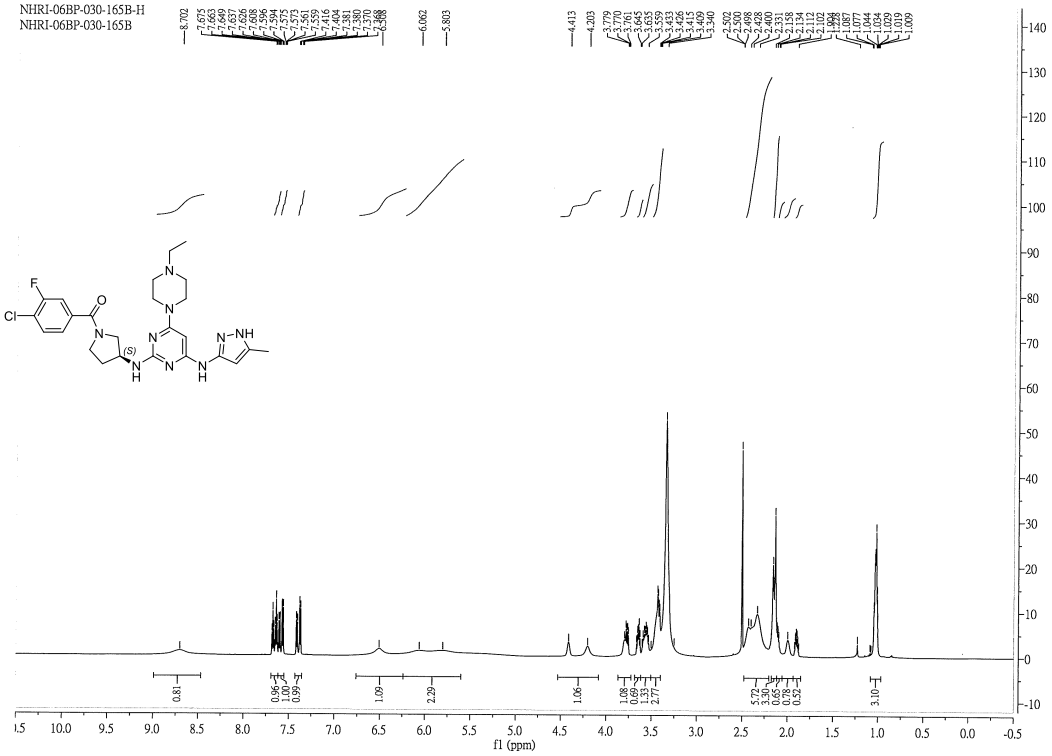
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

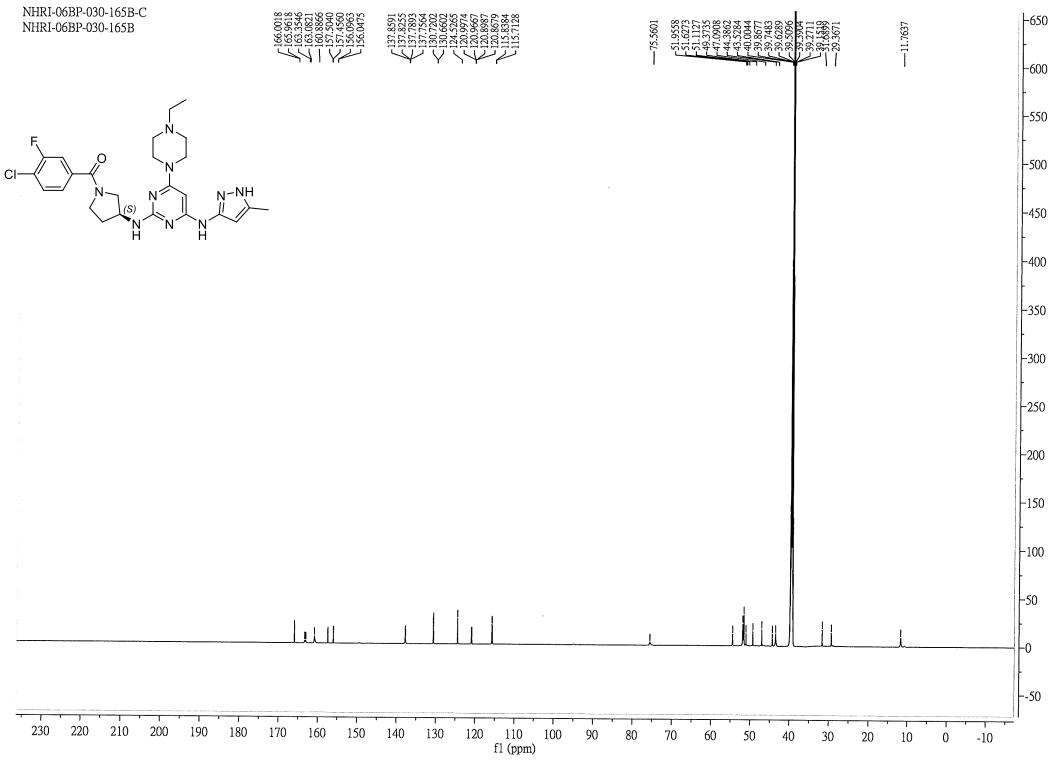
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	8.85	6463	640	0.208
2	11.29	3096628	127017	99.646
3	13.30	2501	147	0.080
4	21.71	2048	202	0.066
		3107640	128006	100.000

Peak rejection level: 0

Figure S12. NMR and HPLC spectra of compound 10.
(*S*)-(4-chloro-3-fluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (10)





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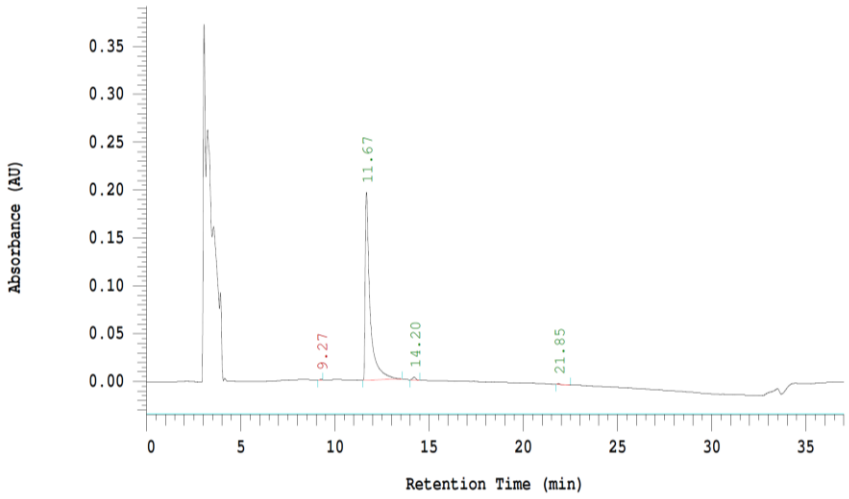

Processing Method: Purity_37min
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Peak Quantitation: AREA
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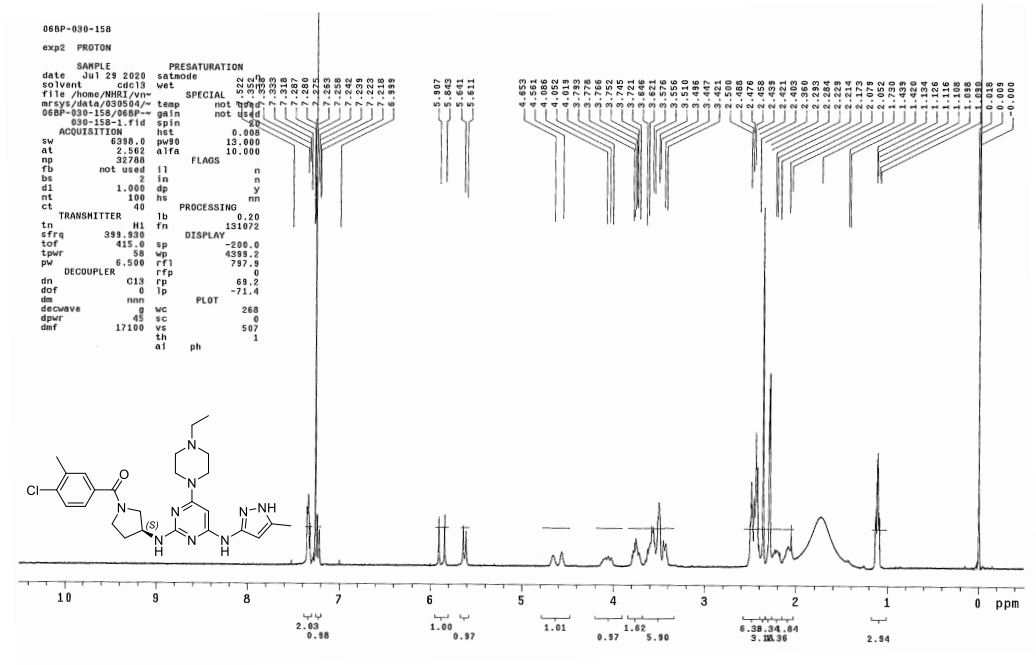
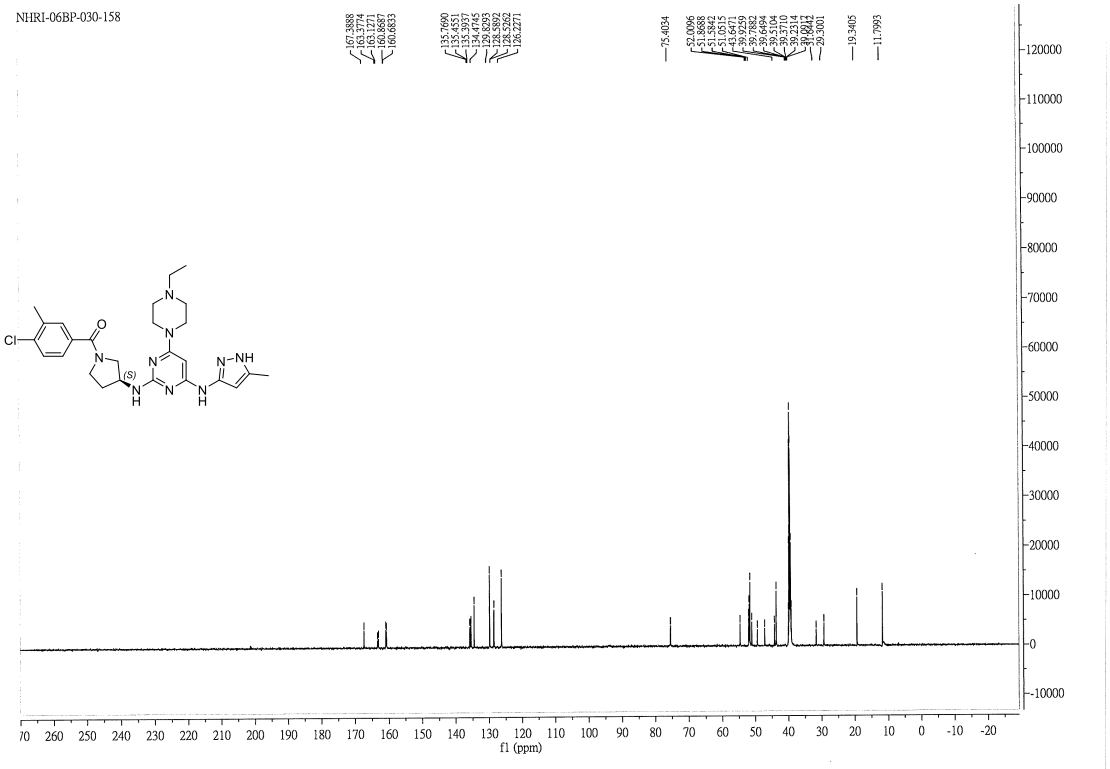
No.	RT	Area	Height	Conc 1
1	9.27	935	129	0.053
2	11.67	1747304	97958	98.786
3	14.20	16524	1525	0.934
4	21.85	4014	362	0.227
		1768777	99974	100.000

Peak rejection level: 0

Figure S13. NMR and HPLC spectra of compound 11.
(*S*)-(4-chloro-3-methylphenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (11)





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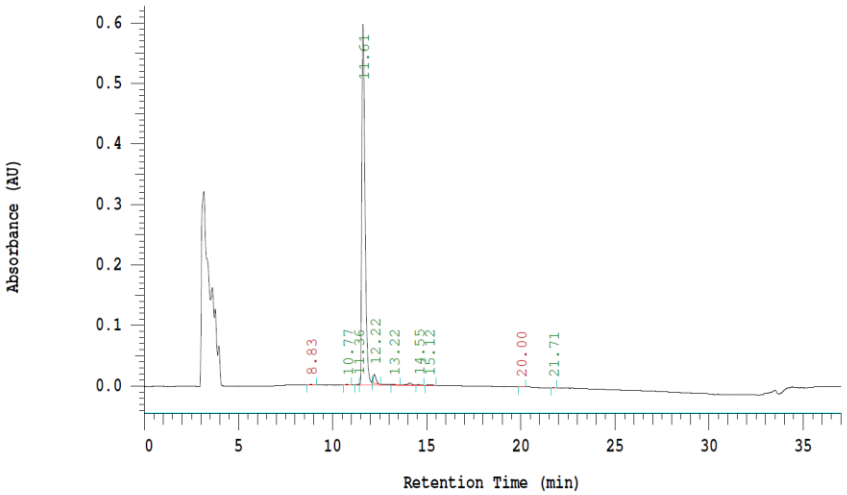

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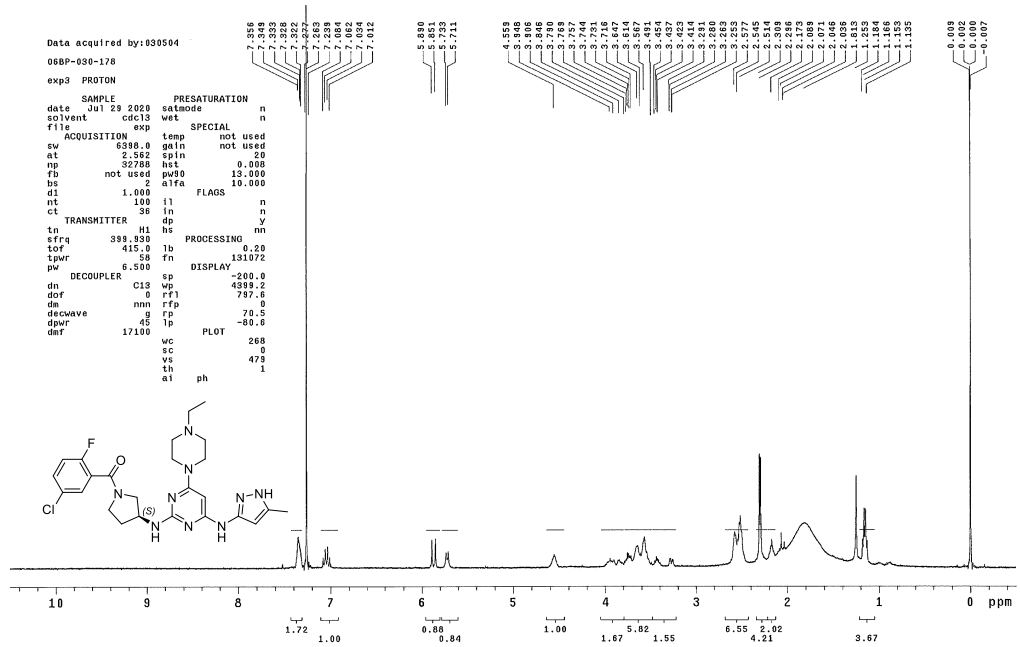
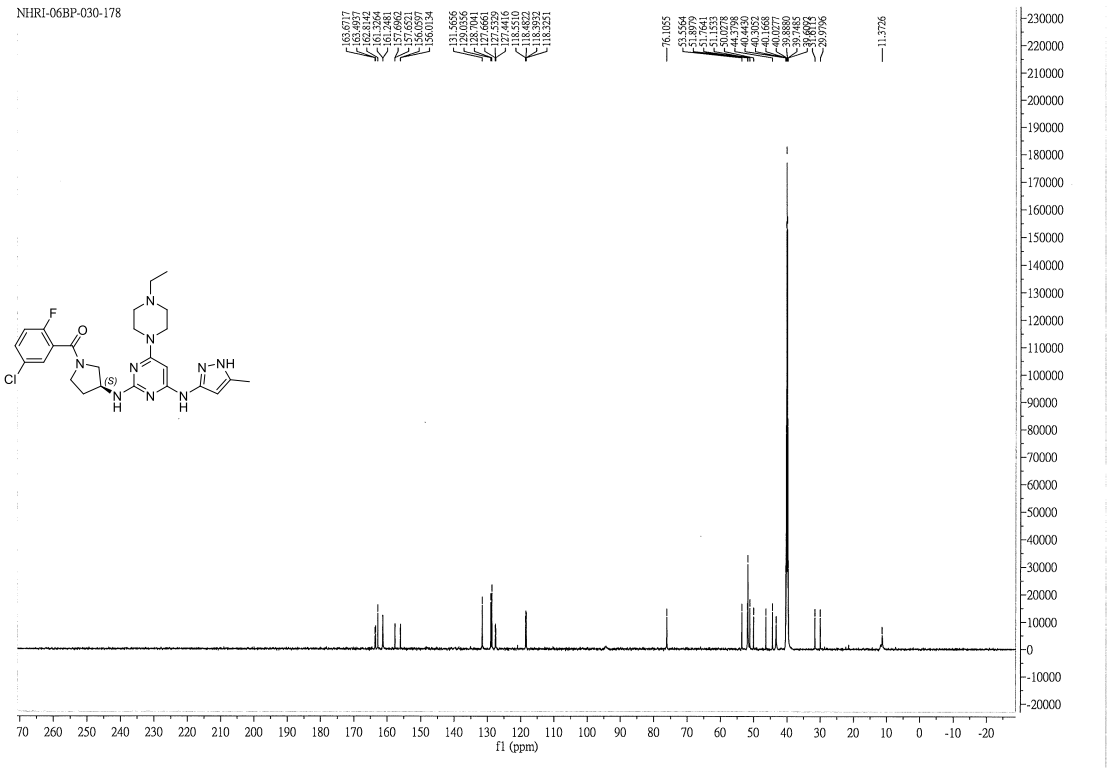
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	8.83	3461	378	0.096
2	10.77	3020	230	0.083
3	11.36	2568	352	0.071
4	11.61	3523496	297667	97.327
5	12.22	69811	7172	1.928
6	13.22	4761	511	0.132
7	14.55	5766	486	0.159
8	15.12	3168	170	0.088
9	20.00	1436	192	0.040
10	21.71	2760	328	0.076
		3620247	307486	100.000

Peak rejection level: 0

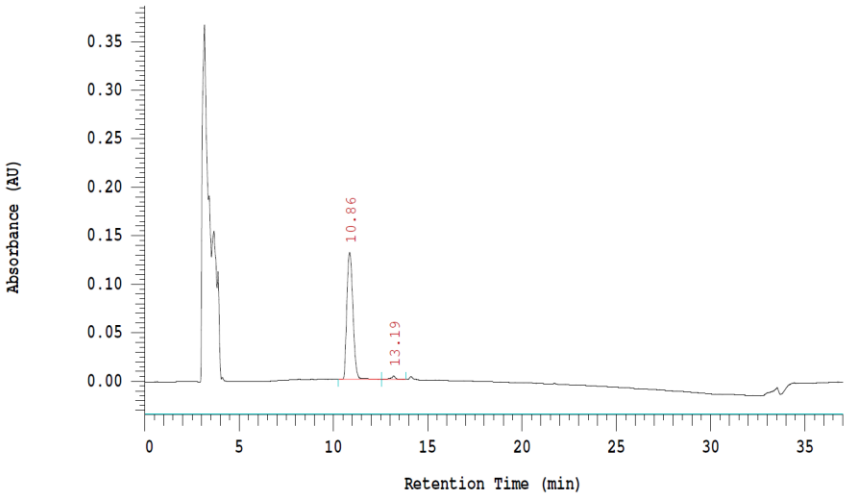
Figure S14. NMR and HPLC spectra of compound 12.
(*S*)-(5-chloro-2-fluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (12)





Sample Name: 06BP-030-178-50 Vial Number: 66
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

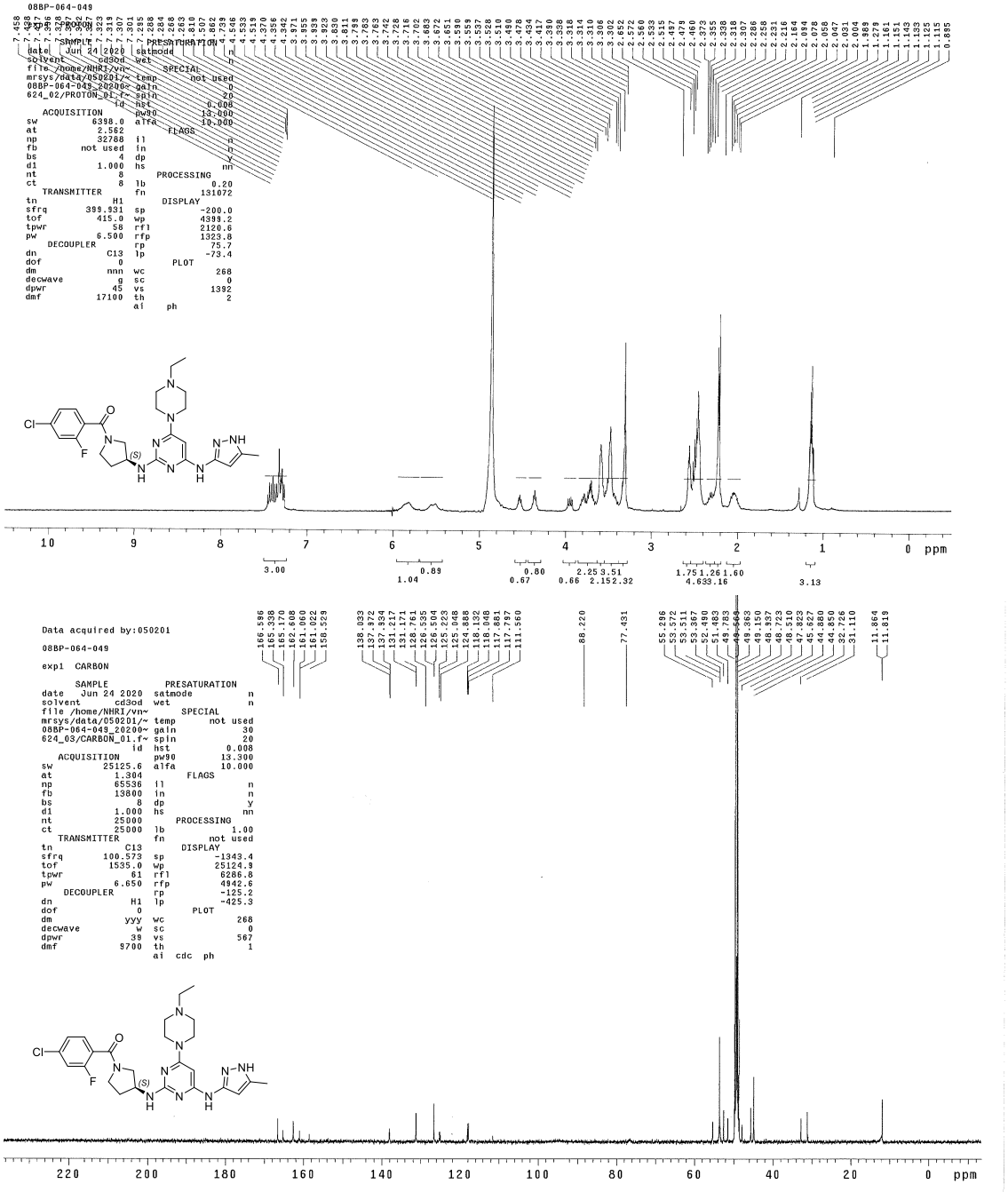
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.86	1451846	65396	97.888
2	13.19	31331	1831	2.112
		1483177	67227	100.000

Peak rejection level: 0

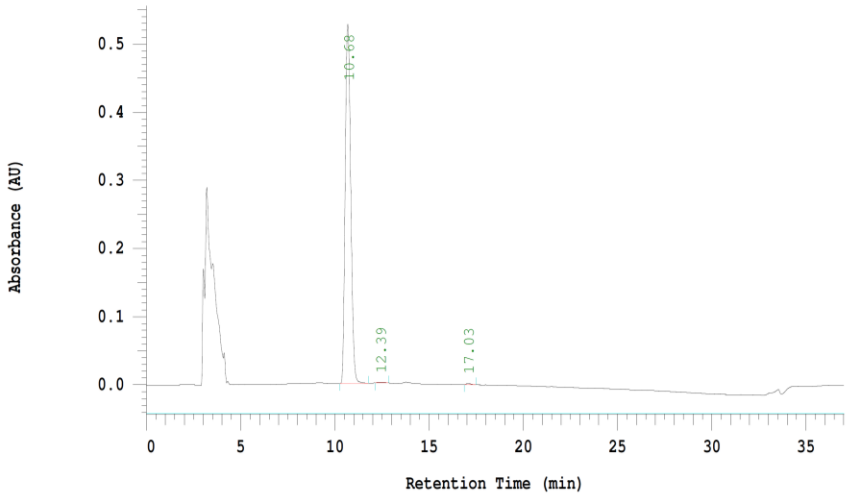
Figure S15. NMR and HPLC spectra of compound 13.

(*S*)-(4-chloro-2-fluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (13)



Sample Name: 08BP-064-049-50 Vial Number: 160
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



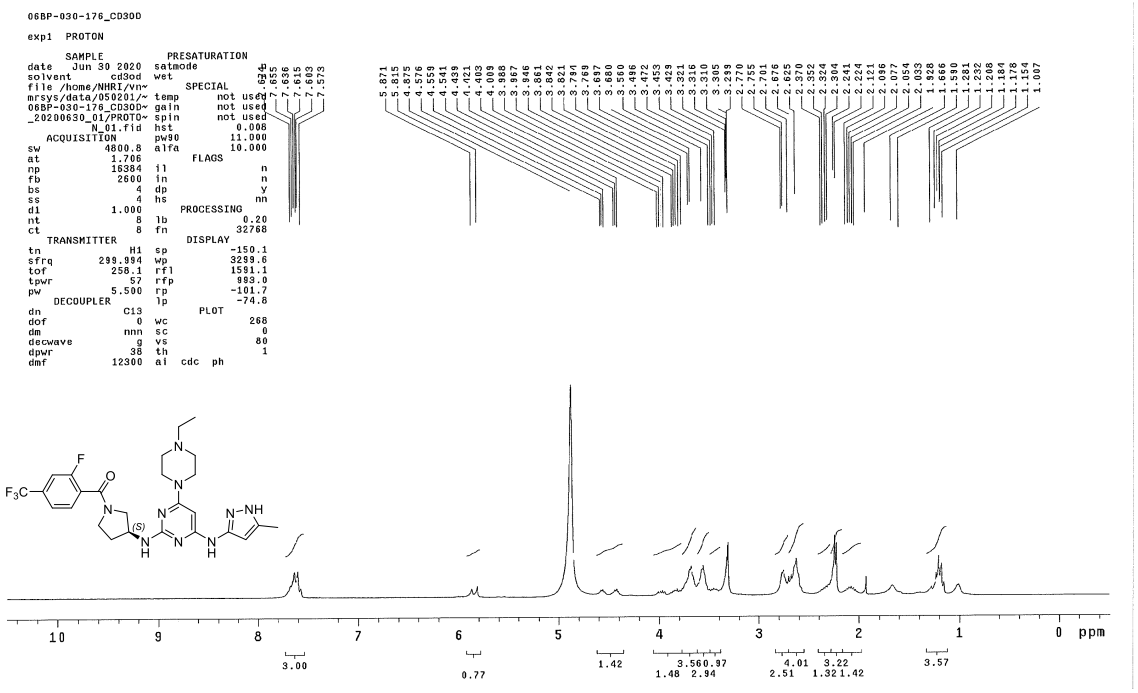
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

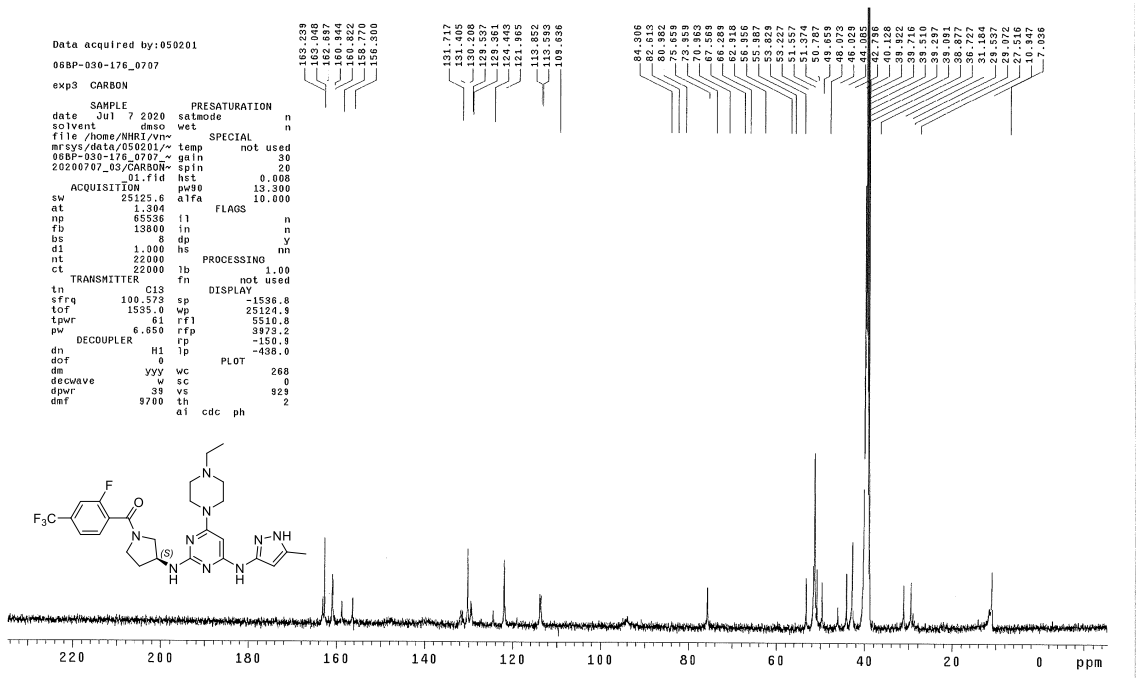
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.68	5307798	263279	99.573
2	12.39	6130	232	0.115
3	17.03	16648	984	0.312
		5330576	264495	100.000

Peak rejection level: 0

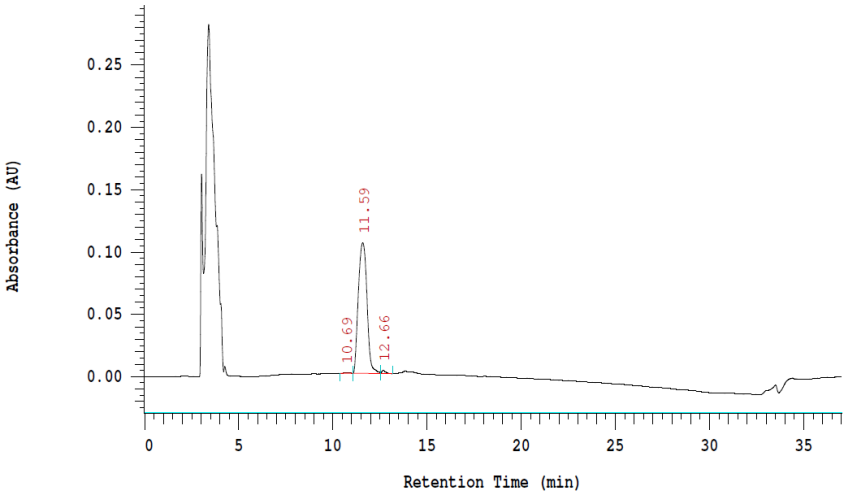
Figure S16. NMR and HPLC spectra of compound 14.
(*S*)-(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)(2-fluoro-4-(trifluoromethyl)phenyl)methanone (14)





Sample Name: 06BP-030-176-50 Vial Number: 116
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

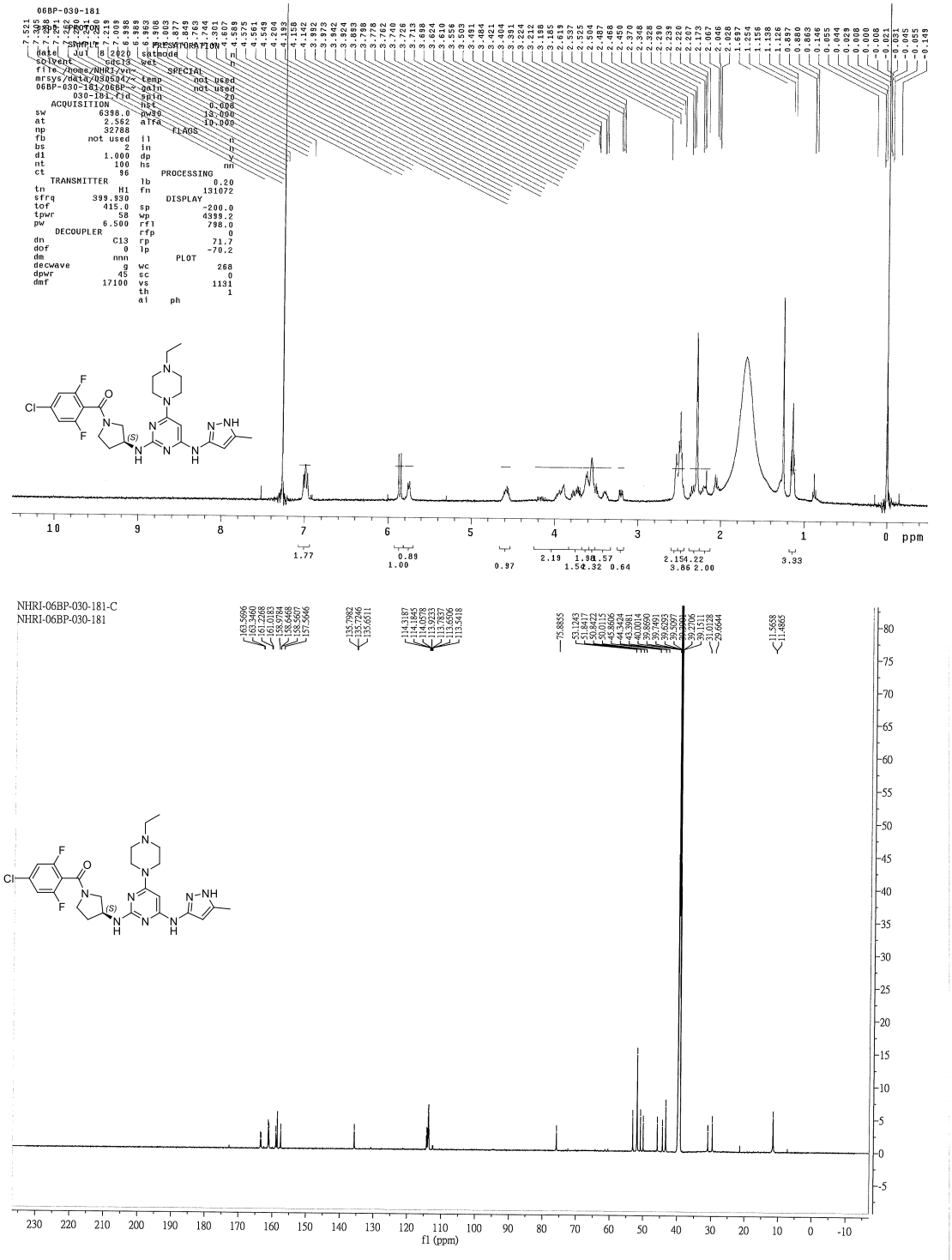
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.69	4455	175	0.264
2	11.59	1665806	52411	98.605
3	12.66	19113	1360	1.131
		1689374	53946	100.000

Peak rejection level: 0

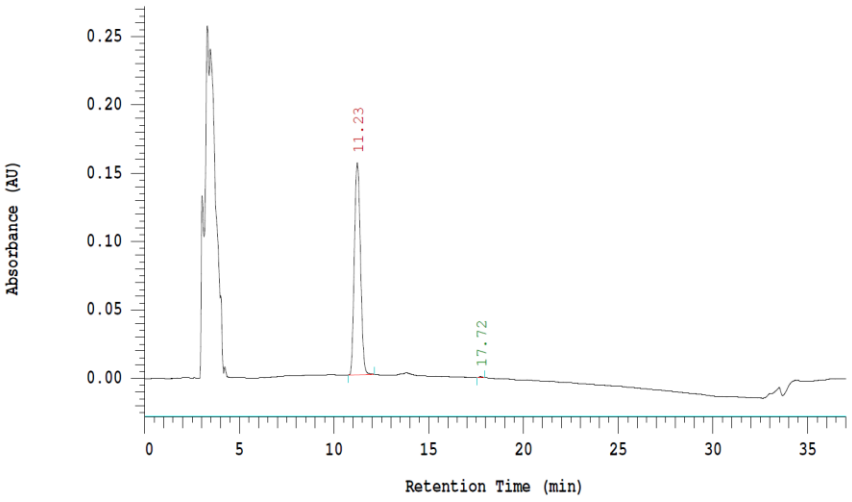
Figure S17. NMR and HPLC spectra of compound 15.

(*S*)-(4-chloro-2,6-difluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (15)



Sample Name: 06BP-030-181-50 Vial Number: 120
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

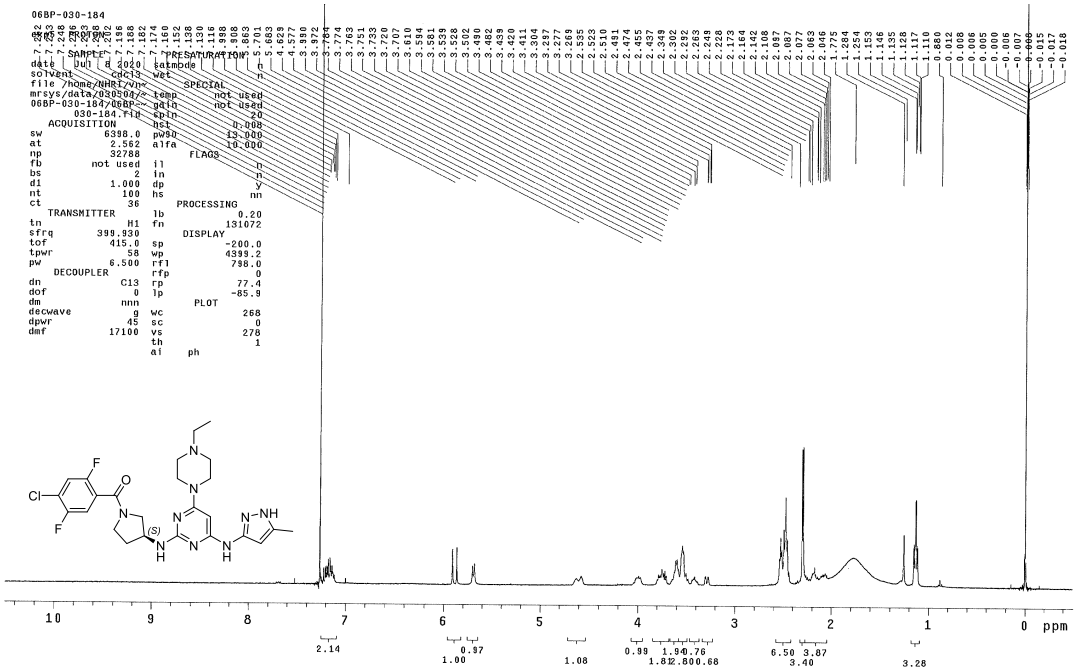
Peak Quantitation: AREA
Calculation Method: AREA%

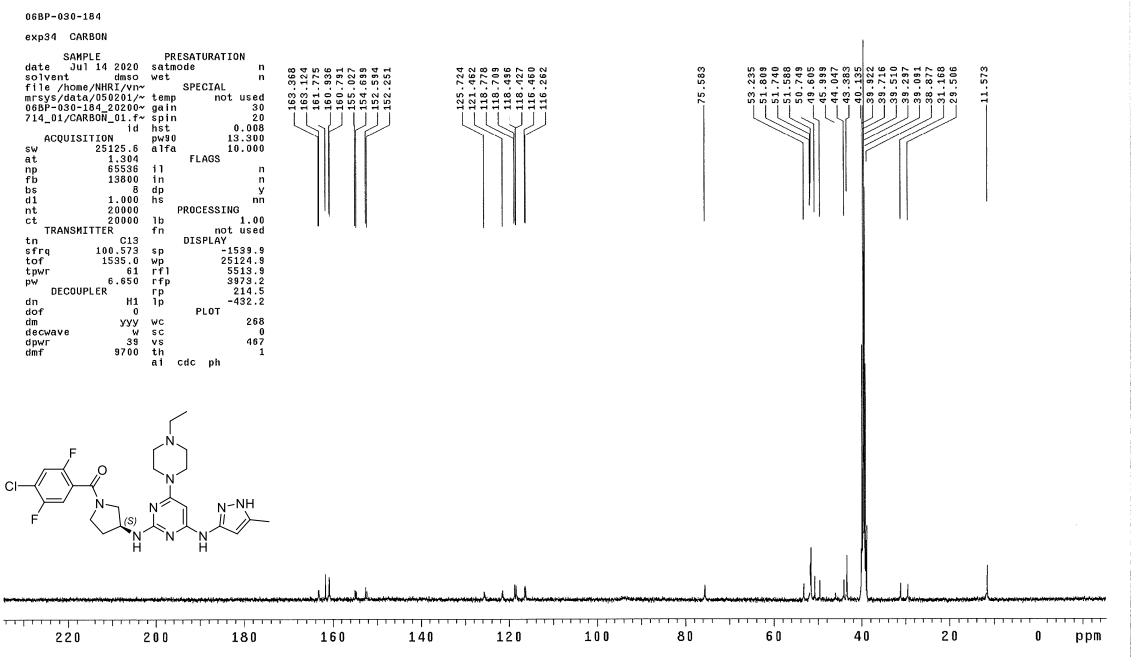
No.	RT	Area	Height	Conc 1
1	11.23	1710714	77480	99.745
2	17.72	4377	428	0.255
		1715091	77908	100.000

Peak rejection level: 0

Figure S18. NMR and HPLC spectra of compound 16.

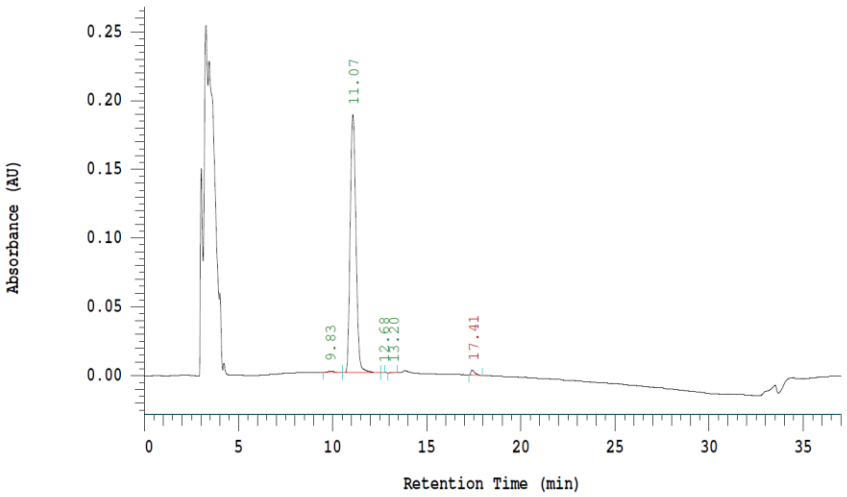
(*S*)-(4-chloro-2,5-difluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (16)





Sample Name: 06BP-030-184-50 Vial Number: 124
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



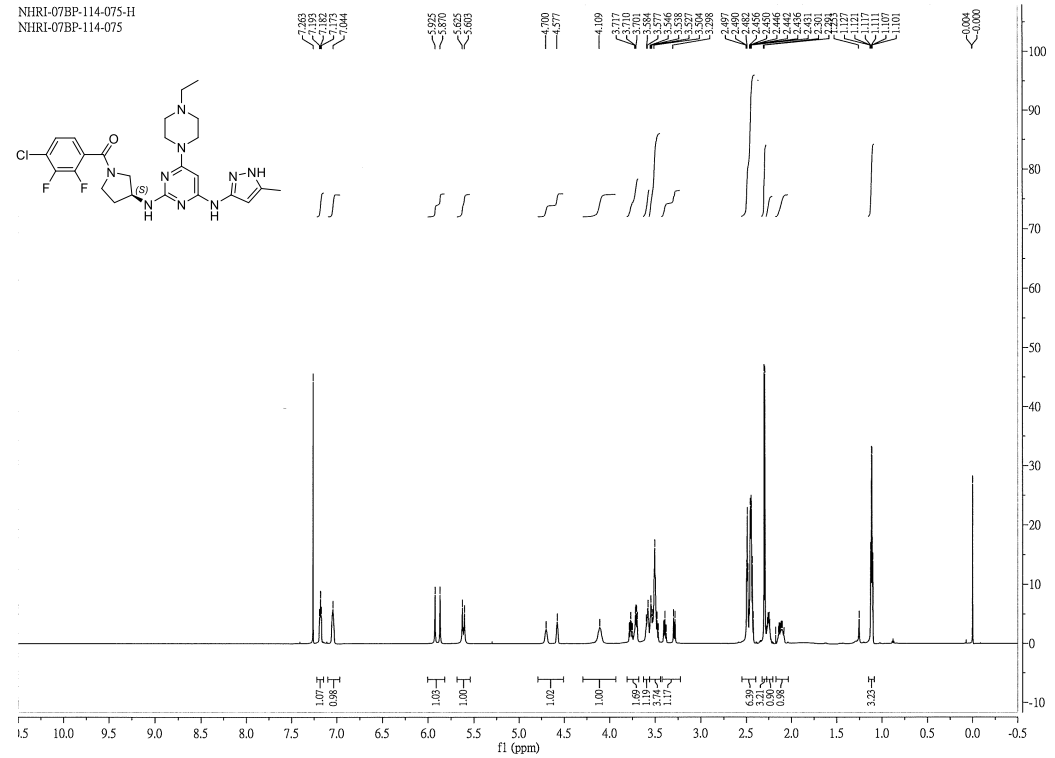
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

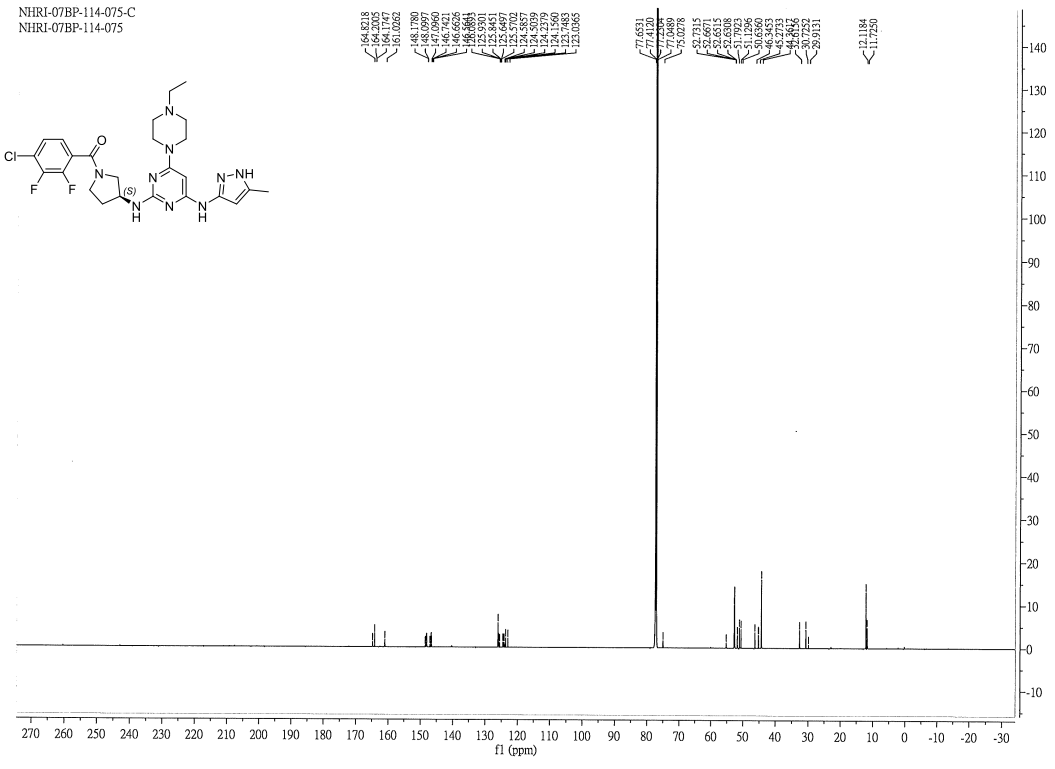
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	9.83	11809	546	0.587
2	11.07	1971673	93614	97.981
3	12.68	634	106	0.032
4	13.20	2412	164	0.120
5	17.41	25770	1845	1.281
		2012298	96275	100.000

Peak rejection level: 0

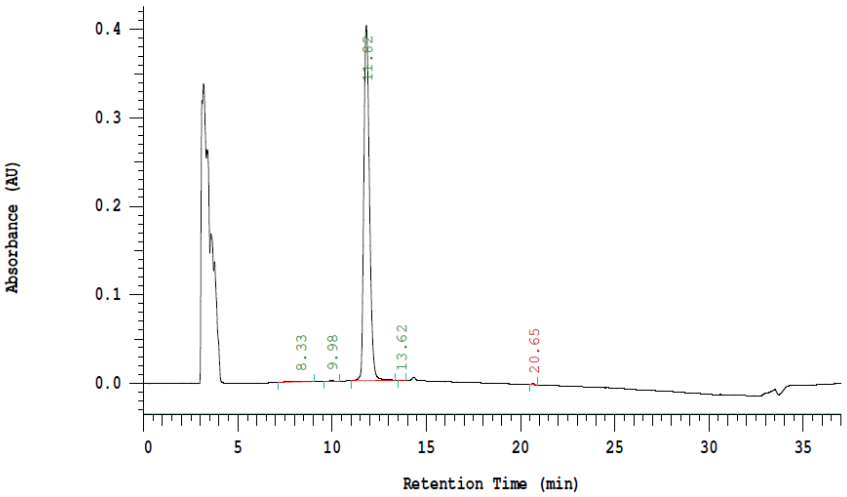
Figure S19. NMR and HPLC spectra of compound 17.
(*S*)-(4-chloro-2,3-difluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (17)





Sample Name: 07BP-114-075-50 Vial Number: 30
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



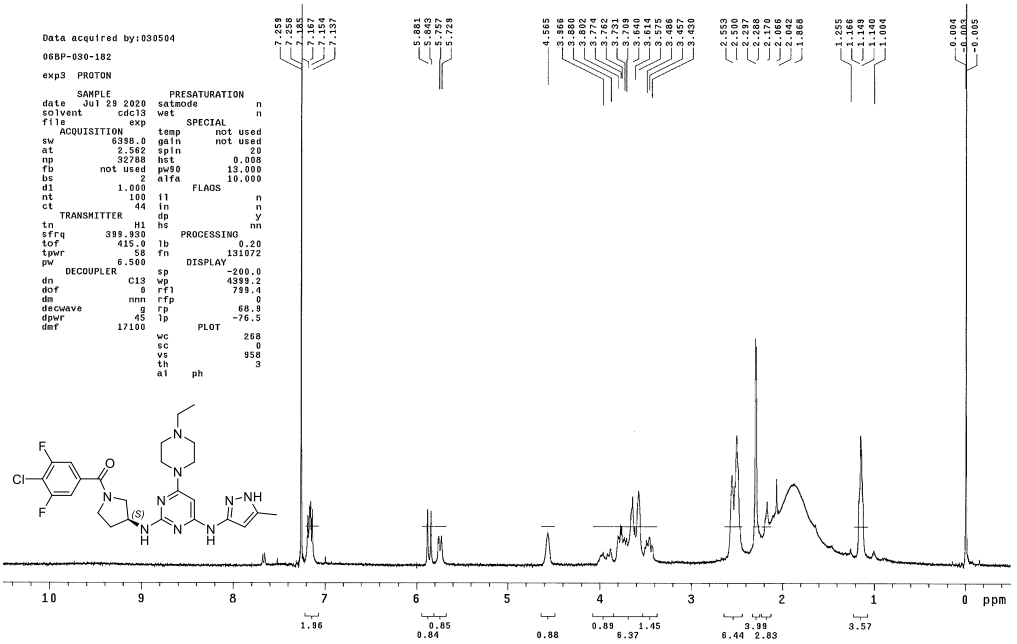
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

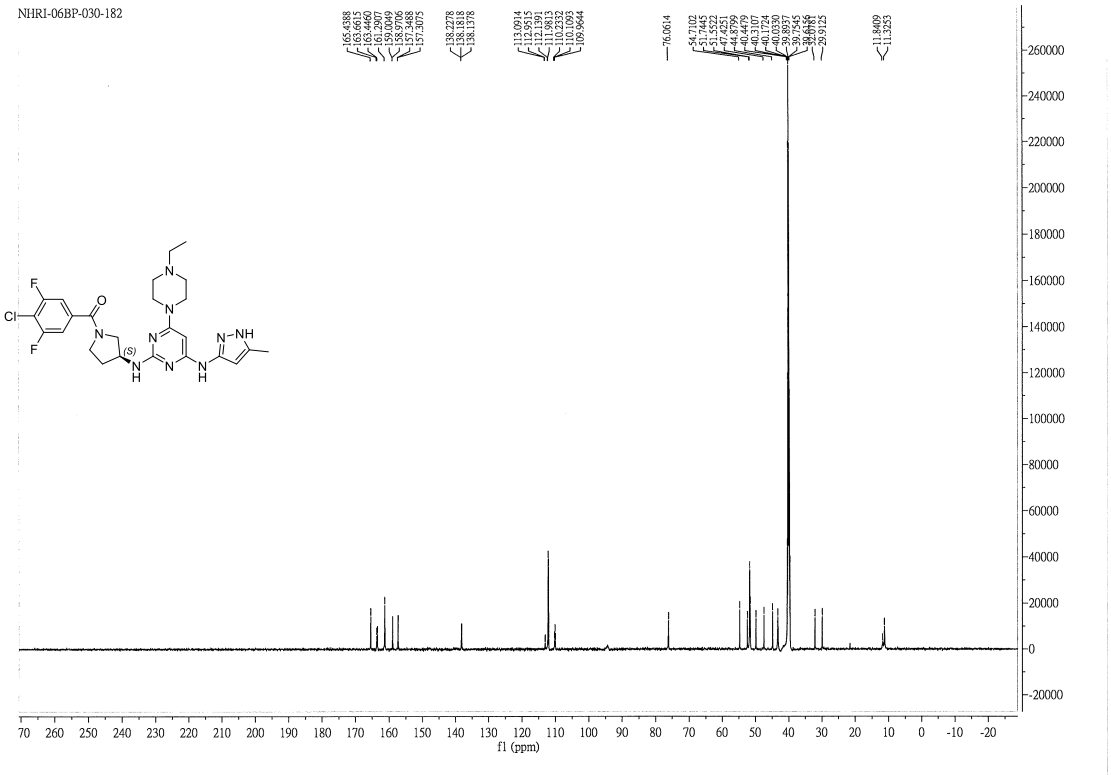
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	8.33	22832	315	0.548
2	9.98	3663	233	0.088
3	11.82	4128163	200684	99.163
4	13.62	1867	135	0.045
5	20.65	6479	794	0.156
		4163004	202161	100.000

Peak rejection level: 0

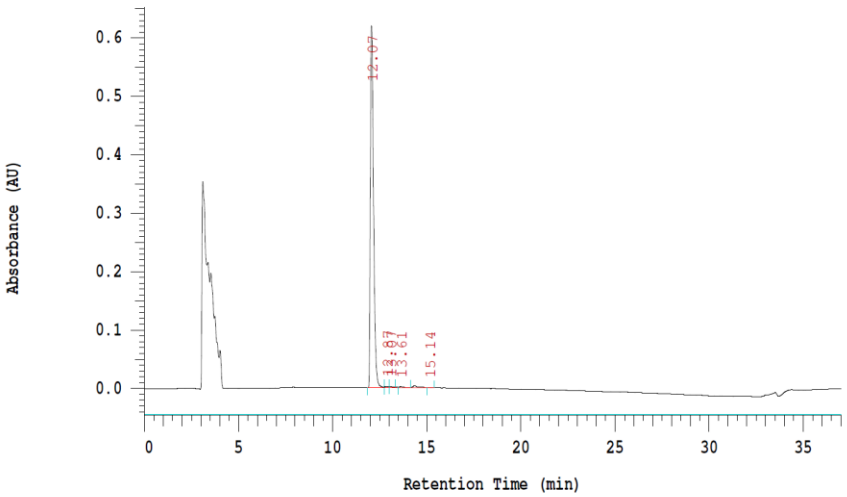
Figure S20. NMR and HPLC spectra of compound 18.
(*S*)-(4-chloro-3,5-difluorophenyl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (18)





Sample Name: 06BP-030-182-50 Vial Number: 152
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



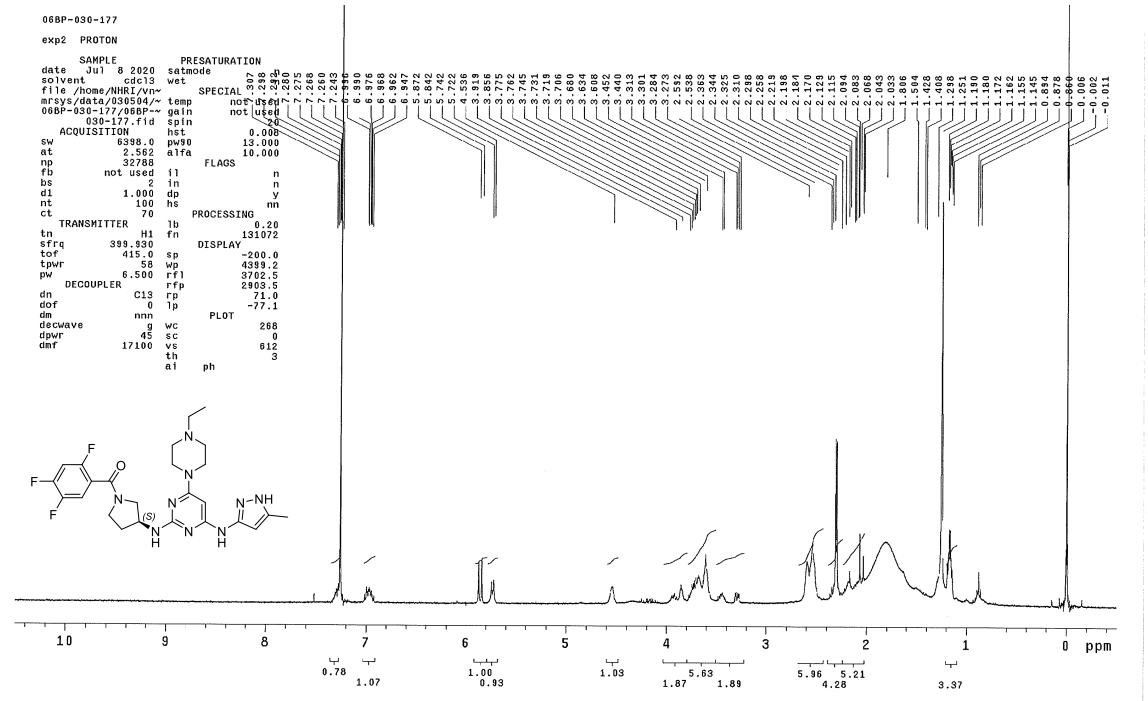
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

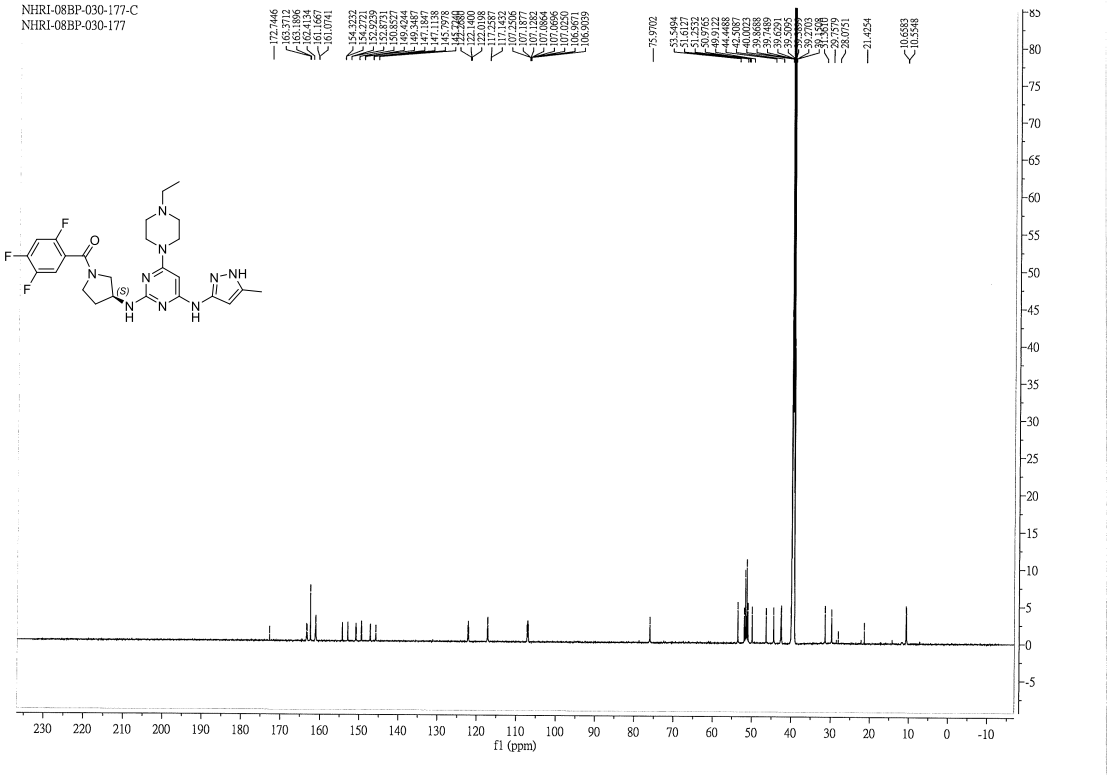
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	12.07	3542144	309584	98.778
2	12.87	13516	1111	0.377
3	13.07	12178	957	0.340
4	13.61	14727	929	0.411
5	15.14	3384	285	0.094
		3585949	312866	100.000

Peak rejection level: 0

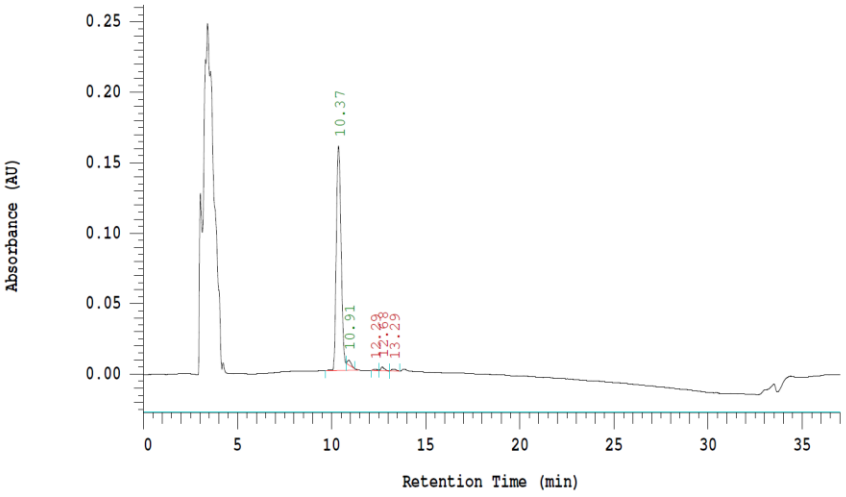
Figure S21. NMR and HPLC spectra of compound 19.
(*S*)-(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)(2,4,5-trifluorophenyl)methanone (19)





Sample Name: 06BP-030-177-50 Vial Number: 118
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



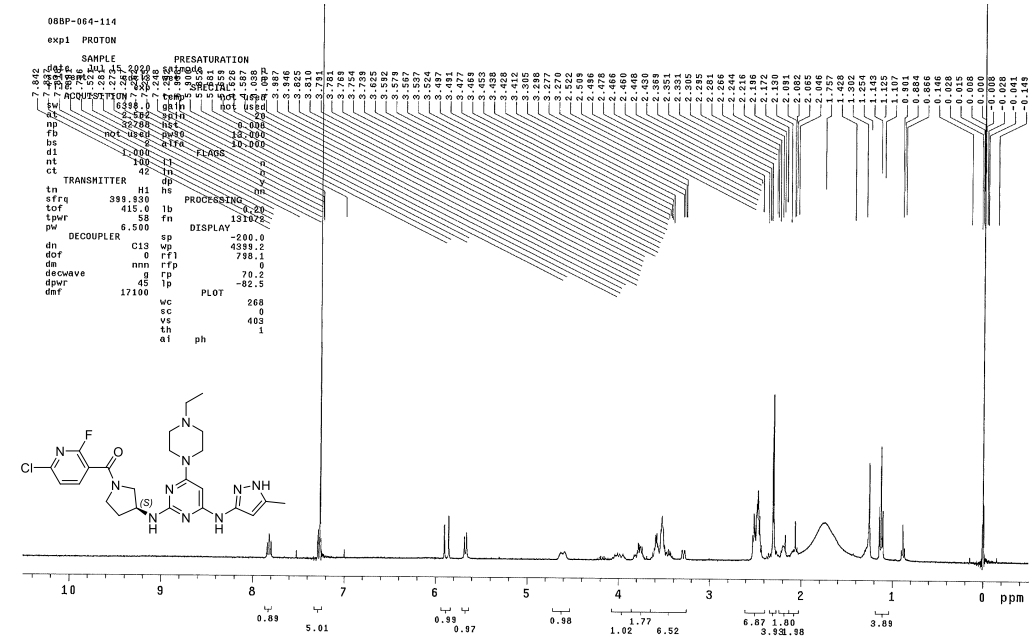
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

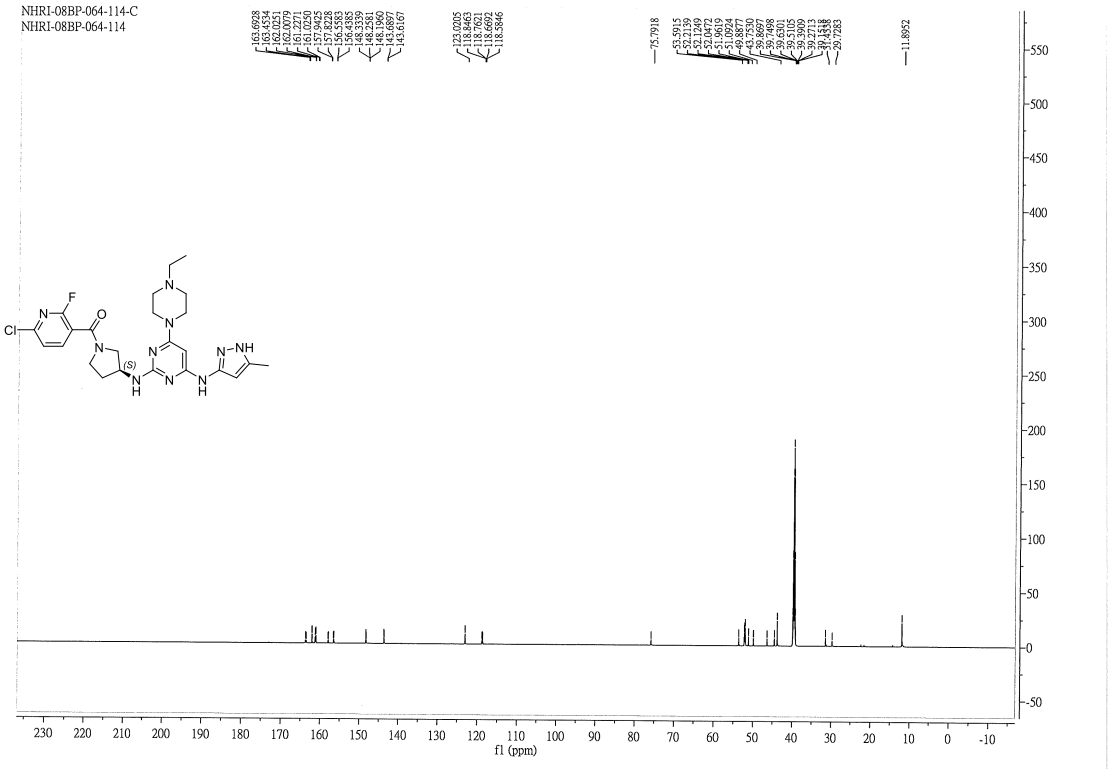
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.37	1438636	79559	96.235
2	10.91	22159	1636	1.482
3	12.29	6921	441	0.463
4	12.68	16414	1251	1.098
5	13.29	10781	691	0.721
		1494911	83578	100.000

Peak rejection level: 0

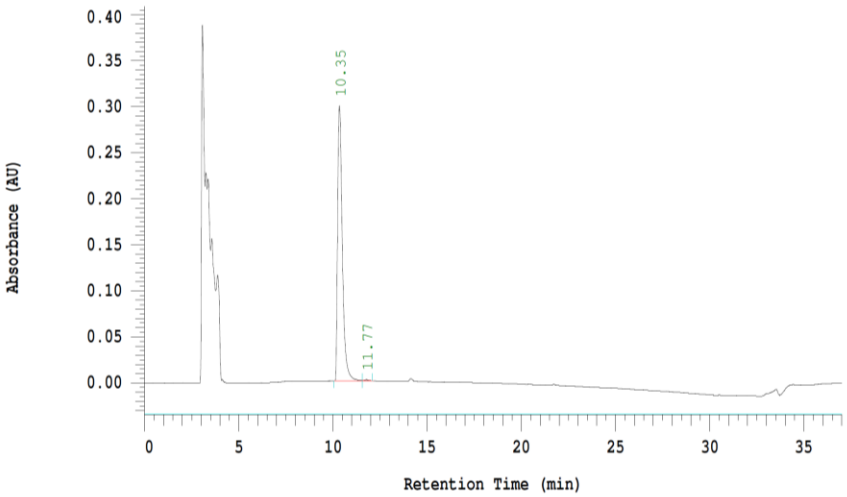
Figure S22. NMR and HPLC spectra of compound 20.
(*S*)-(6-chloro-2-fluoropyridin-3-yl)(3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (20)





Sample Name: 08BP-064-114-50 Vial Number: 114
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



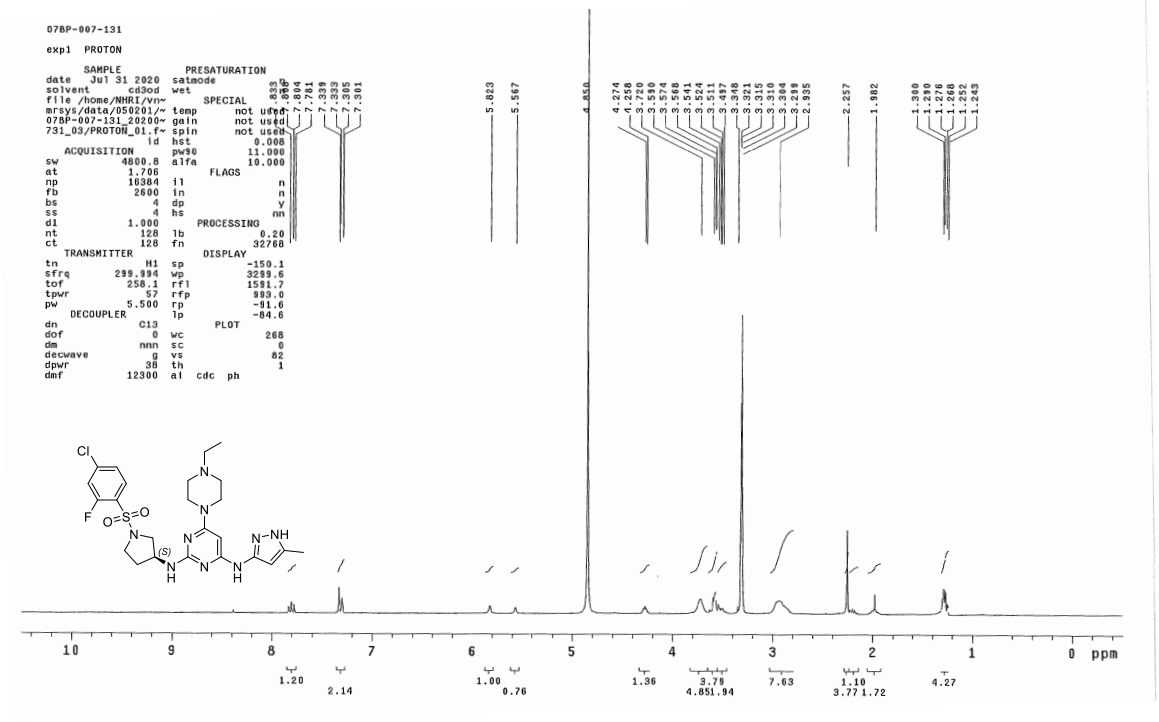
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

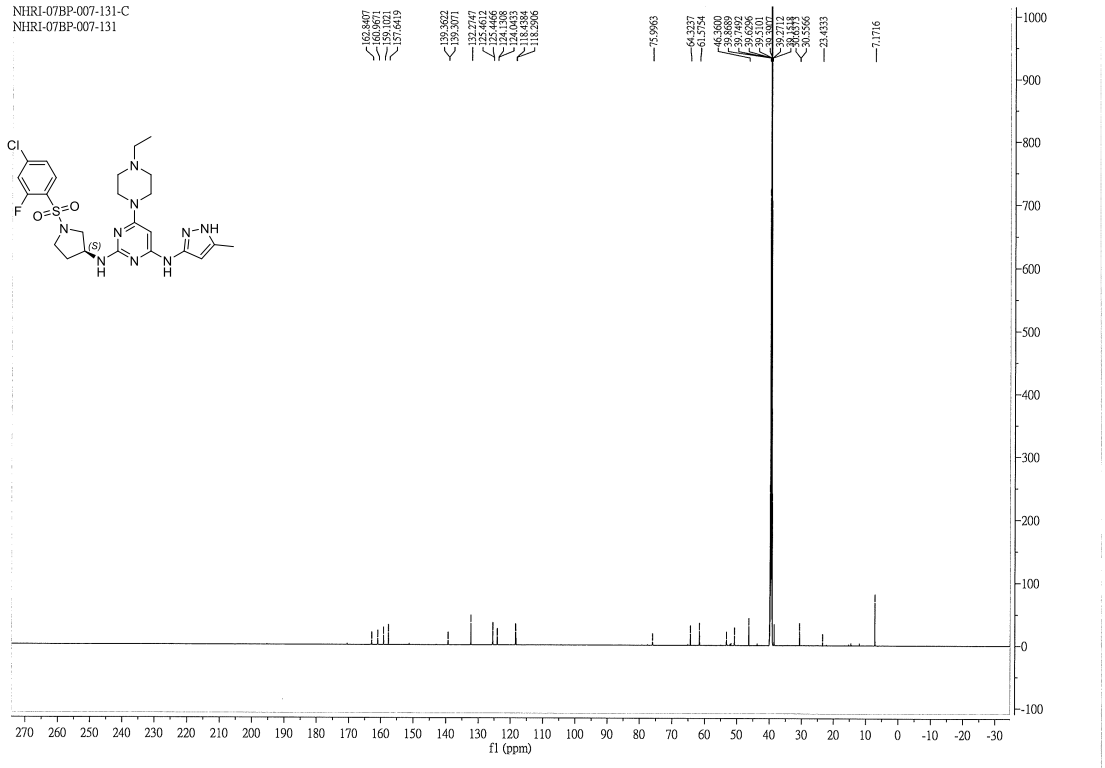
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.35	2563056	149367	99.709
2	11.77	7488	450	0.291
		2570544	149817	100.000

Peak rejection level: 0

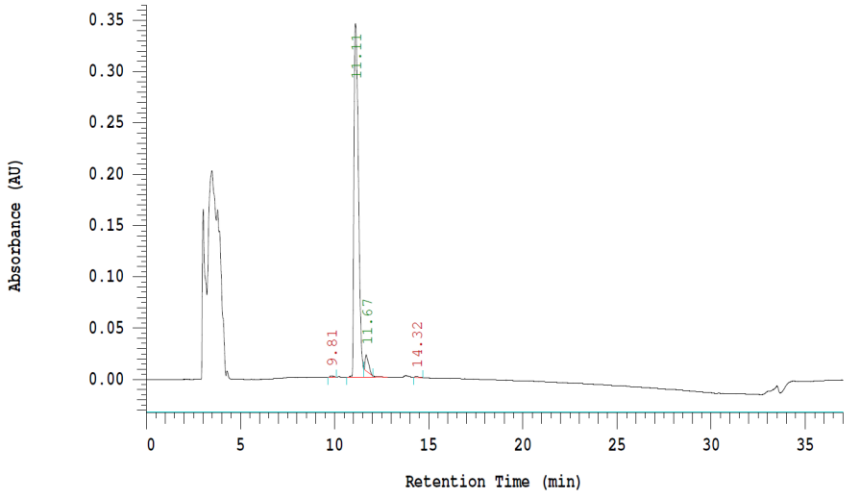
Figure S23. NMR and HPLC spectra of compound 21.
(*S*)-N2-(1-((4-chloro-2-fluorophenyl)sulfonyl)pyrrolidin-3-yl)-6-(4-ethylpiperazin-1-yl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (21)





Sample Name: 07BP-007-131-50 Vial Number: 106
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



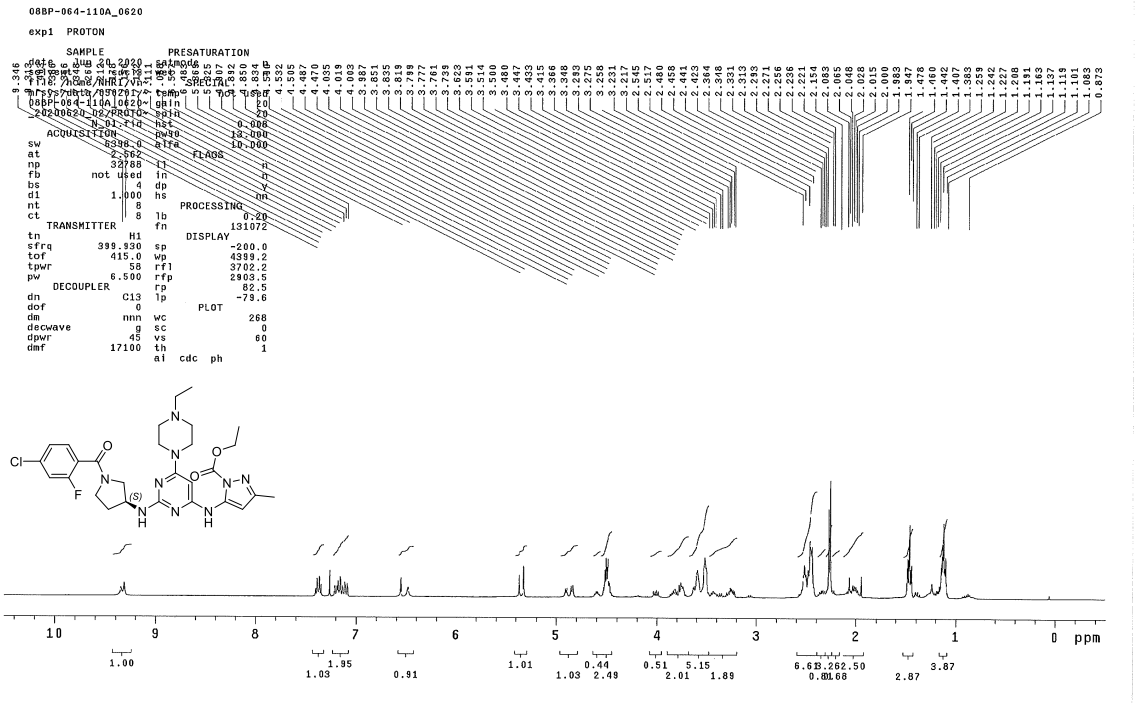
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

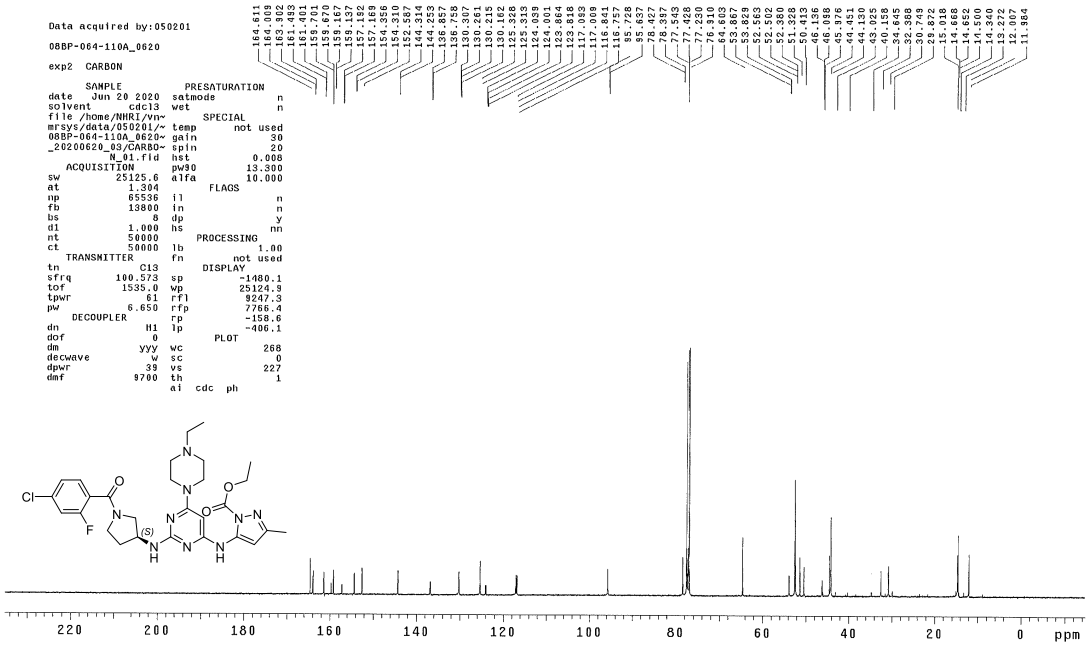
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	9.81	8130	651	0.272
2	11.11	2878906	172210	96.337
3	11.67	95794	7855	3.206
4	14.32	5532	334	0.185
		2988362	181050	100.000

Peak rejection level: 0

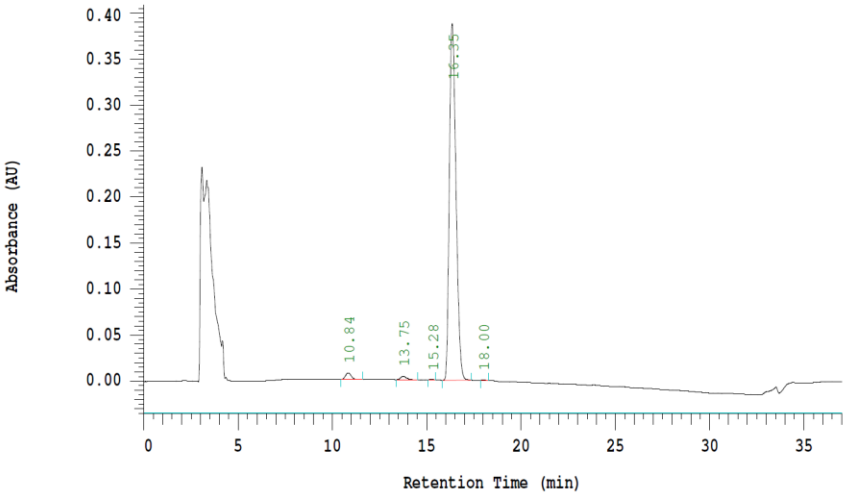
Figure S24. NMR and HPLC spectra of compound 22.
Ethyl (*S*)-5-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-3-methyl-1H-pyrazole-1-carboxylate (22)





Sample Name: 08BP-064-110A-50 Vial Number: 164
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



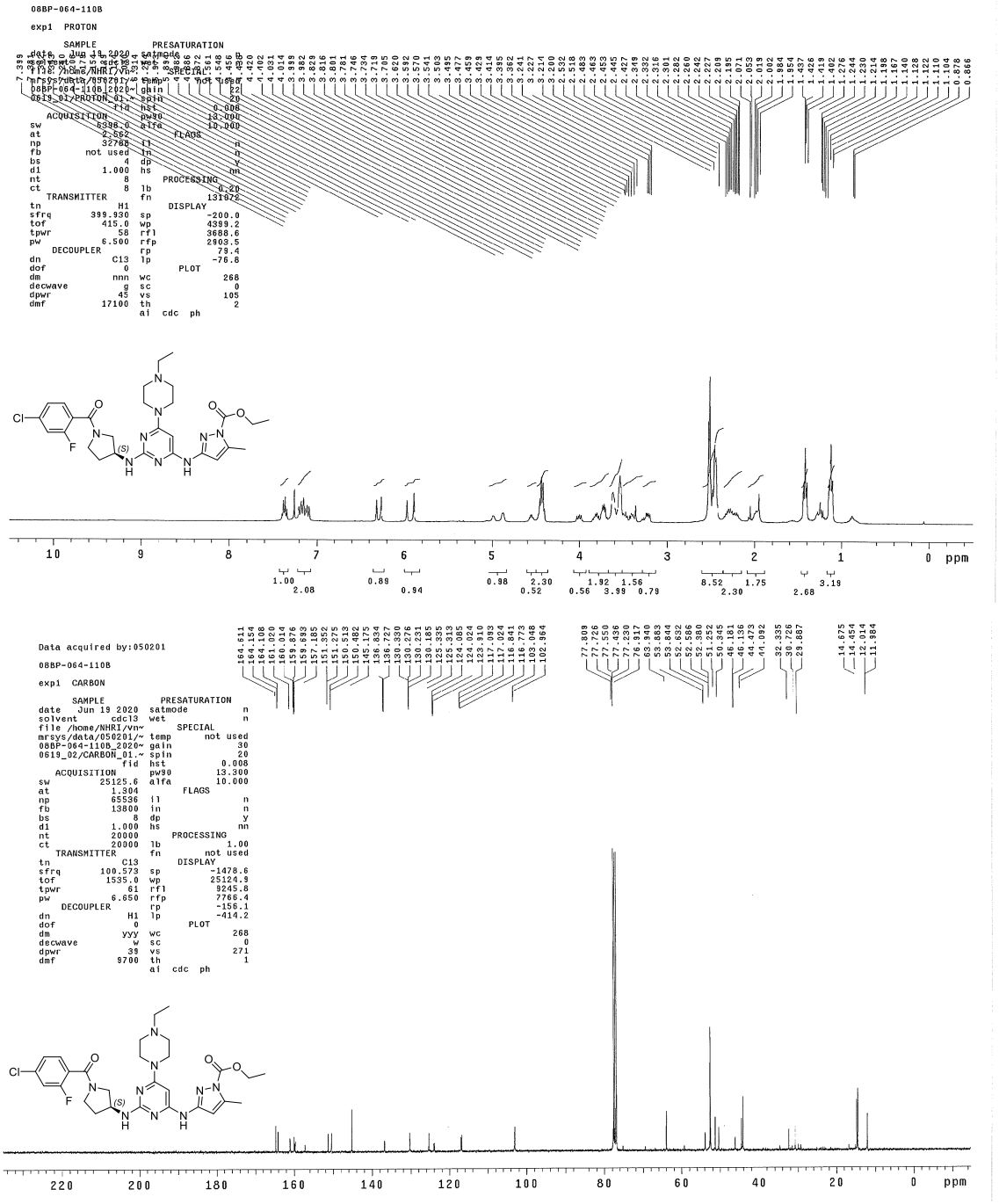
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.84	71168	3494	1.485
2	13.75	42392	1954	0.884
3	15.28	1760	140	0.037
4	16.35	4675766	193693	97.548
5	18.00	2210	184	0.046
		4793296	199465	100.000

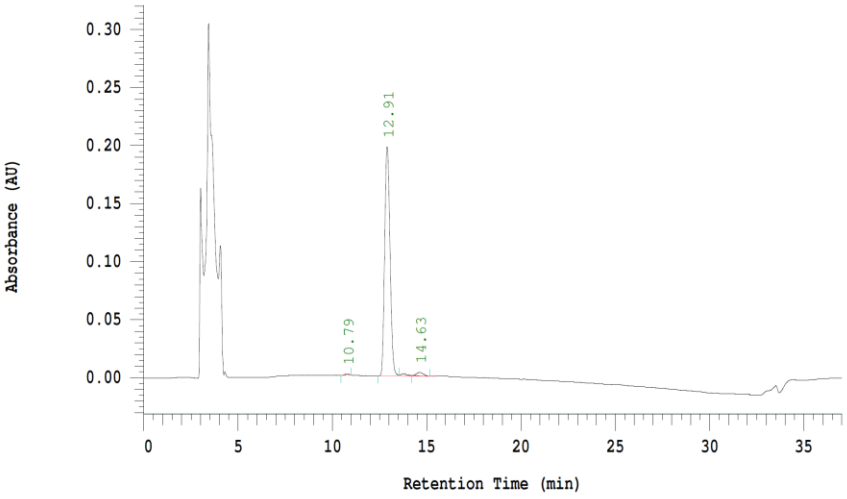
Peak rejection level: 0

Figure S25. NMR and HPLC spectra of compound 23.
Ethyl (*S*)-3-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-5-methyl-1H-pyrazole-1-carboxylate (23)



Sample Name: 08BP-064-110B-50 Vial Number: 76
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

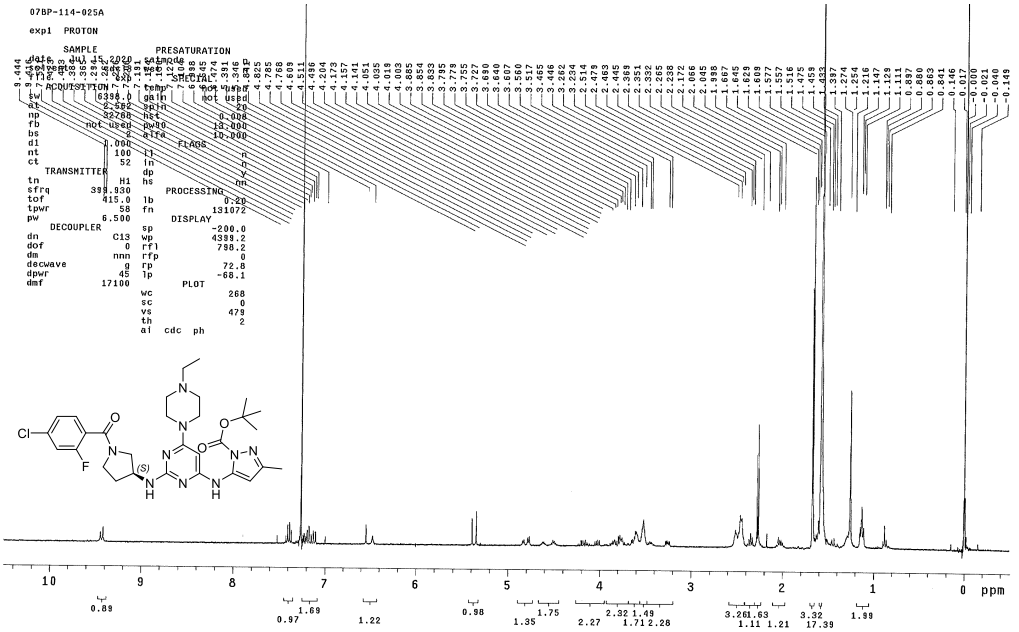
Peak Quantitation: AREA
Calculation Method: AREA%

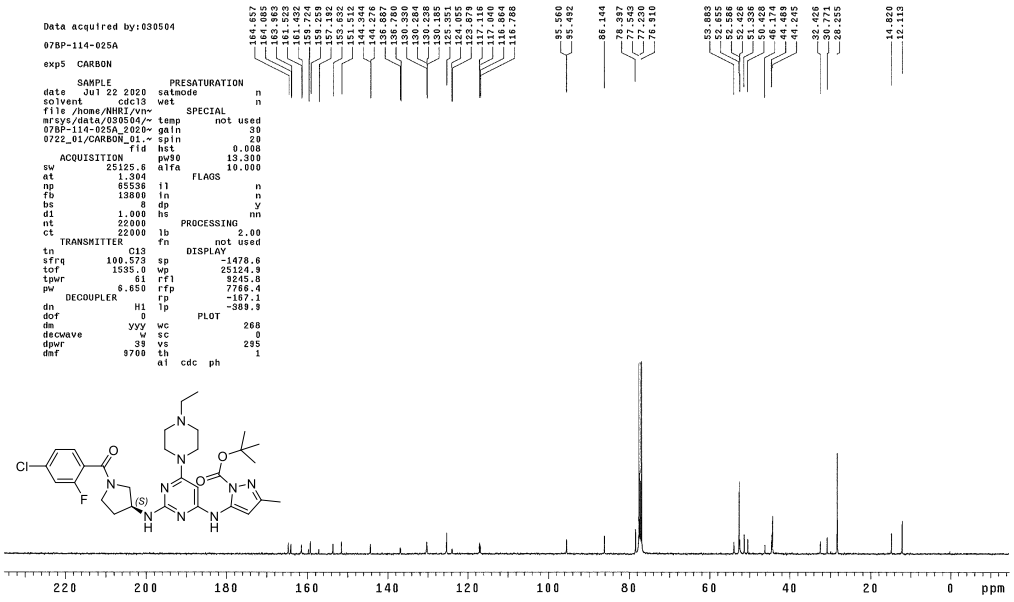
No.	RT	Area	Height	Conc 1
1	10.79	7474	435	0.380
2	12.91	1920236	98637	97.667
3	14.63	38385	1542	1.952
		1966095	100614	100.000

Peak rejection level: 0

Figure S26. NMR and HPLC spectra of compound 24.

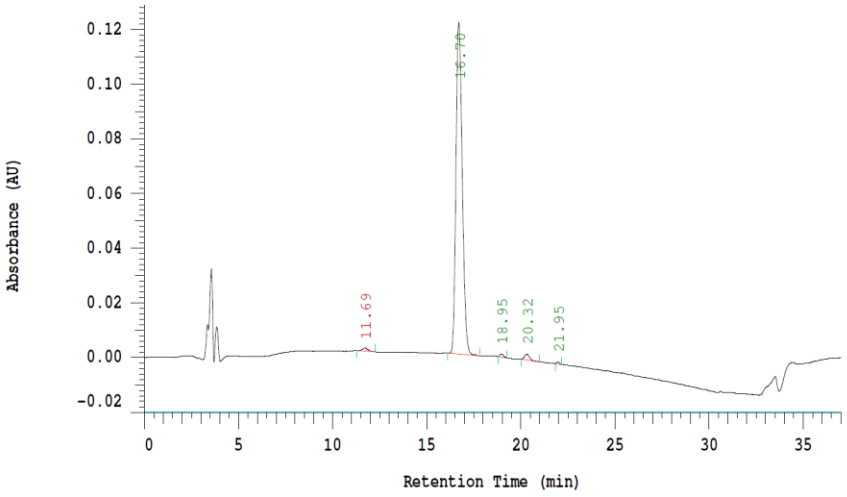
***tert*-butyl (*S*)-5-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-3-methyl-1H-pyrazole-1-carboxylate (24)**





Sample Name: 07BP-114-025A-1-50 Vial Number: 56
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



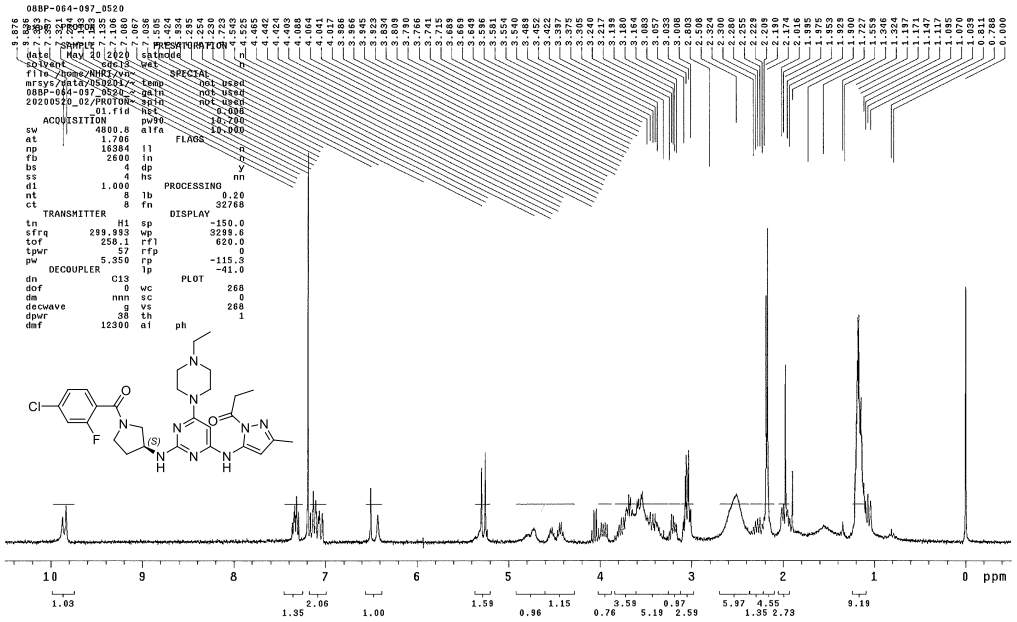
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

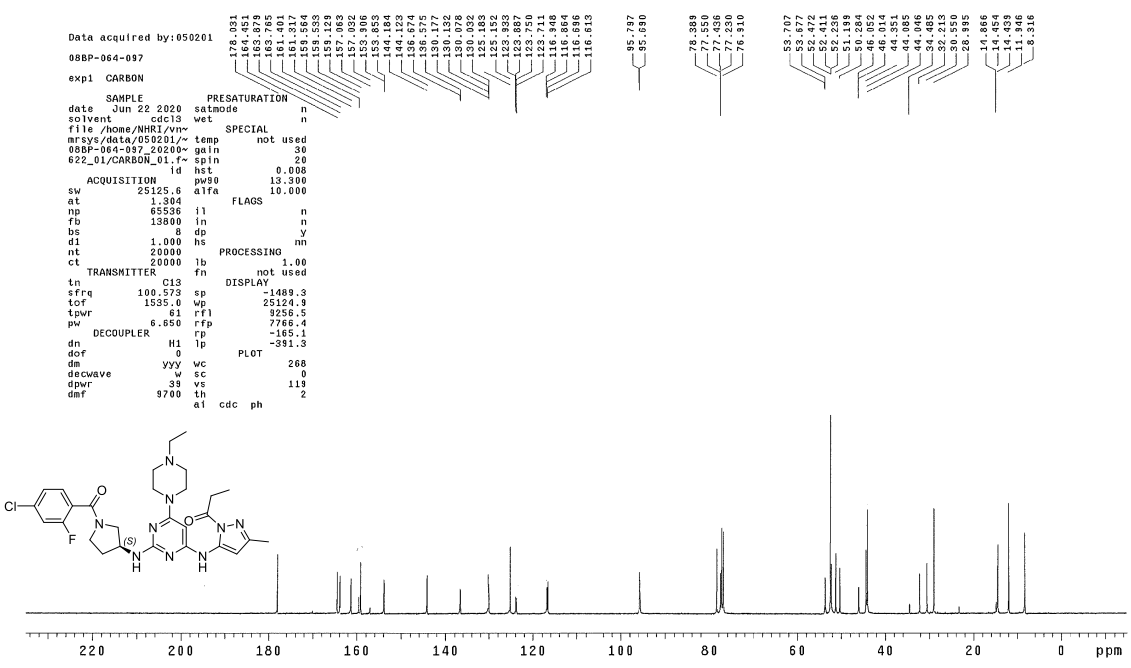
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	11.69	10749	505	0.754
2	16.70	1384707	60567	97.101
3	18.95	7700	598	0.540
4	20.32	19485	1043	1.366
5	21.95	3406	397	0.239
		1426047	63110	100.000

Peak rejection level: 0

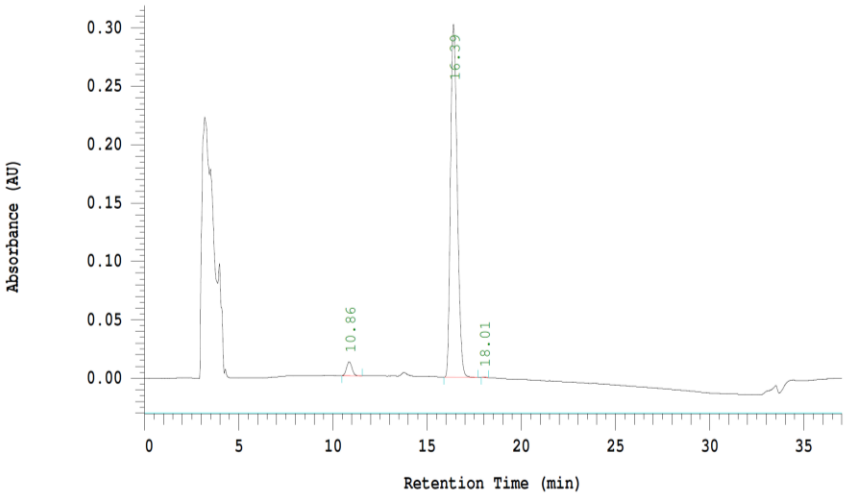
Figure S27. NMR and HPLC spectra of compound 25.
(*S*)-1-(5-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-3-methyl-1H-pyrazol-1-yl)propan-1-one (25)





Sample Name: 08BP-064-097A_0630-50 Vial Number: 84
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



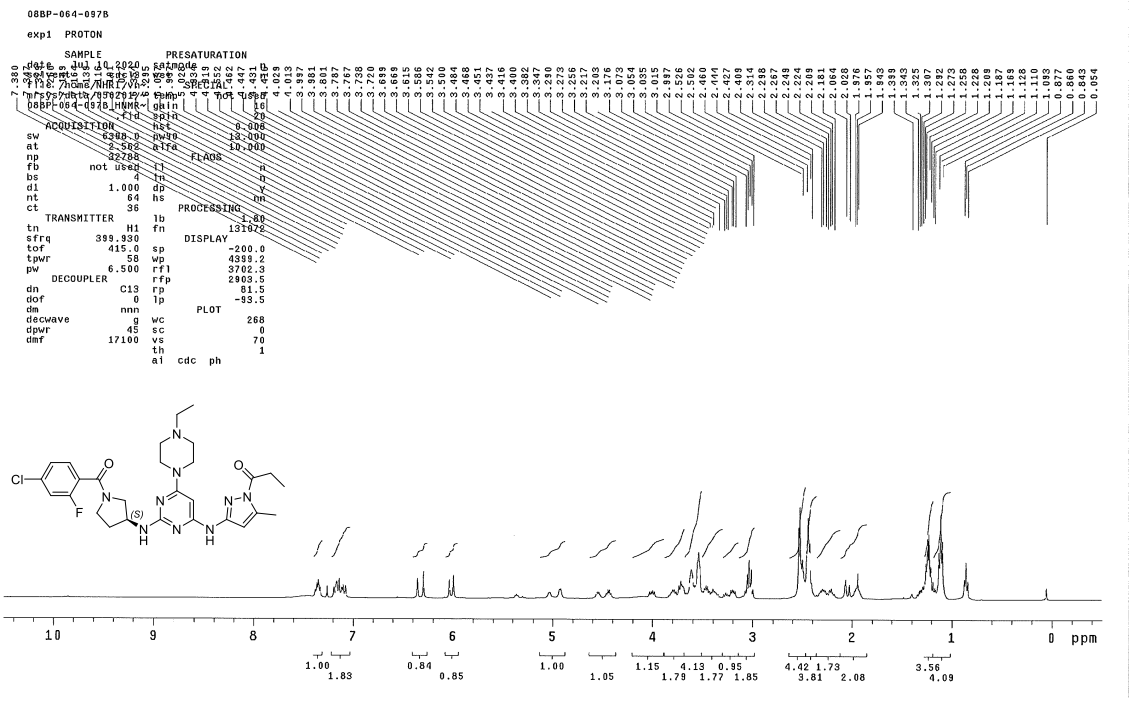
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

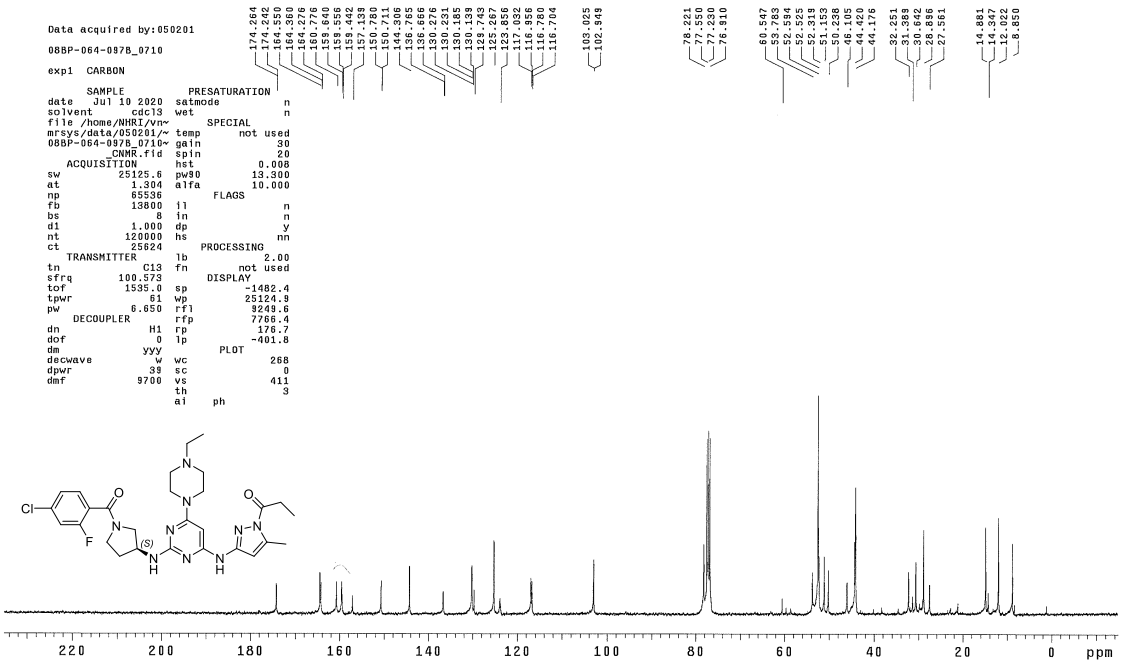
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.86	118935	5933	3.122
2	16.39	3688002	150897	96.812
3	18.01	2522	200	0.066
		3809459	157030	100.000

Peak rejection level: 0

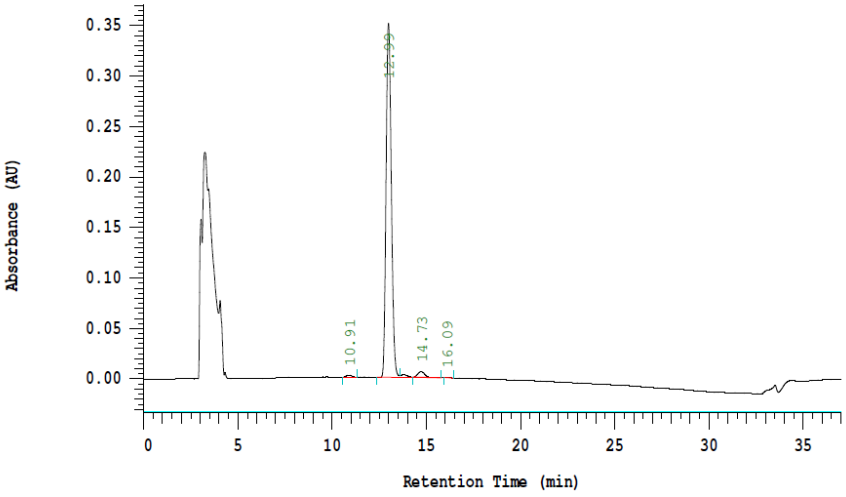
Figure S28. NMR and HPLC spectra of compound 26.
(*S*)-1-(3-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-5-methyl-1H-pyrazol-1-yl)propan-1-one (26)





Sample Name: 08BP-064-097B-50 Vial Number: 82
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



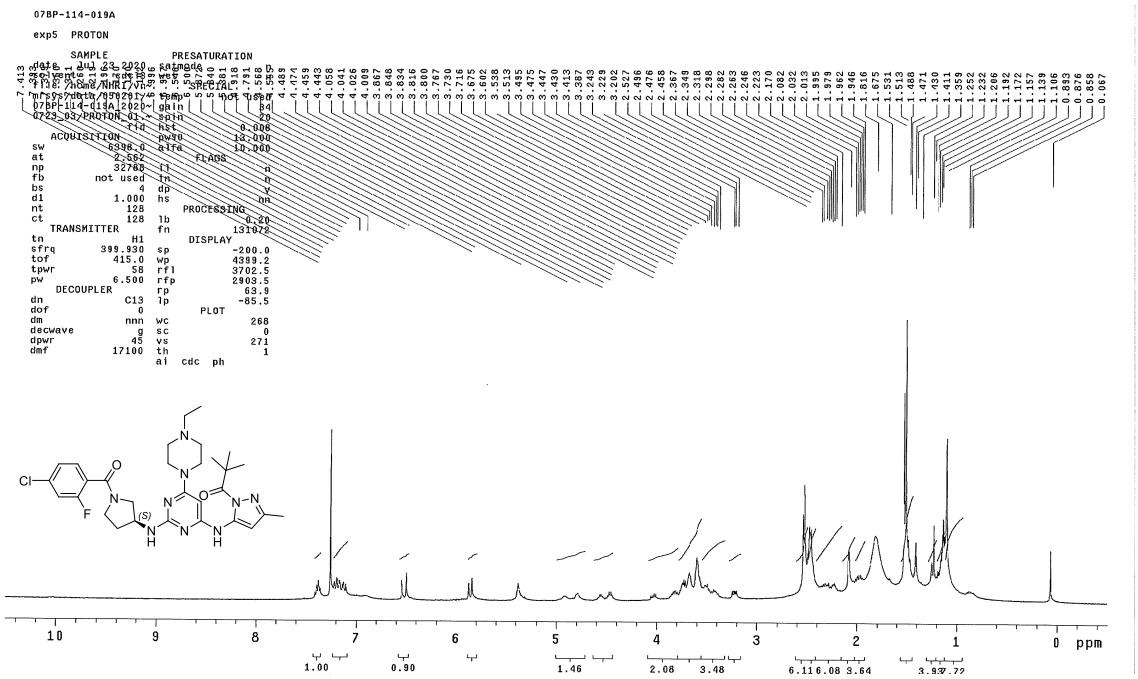
Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

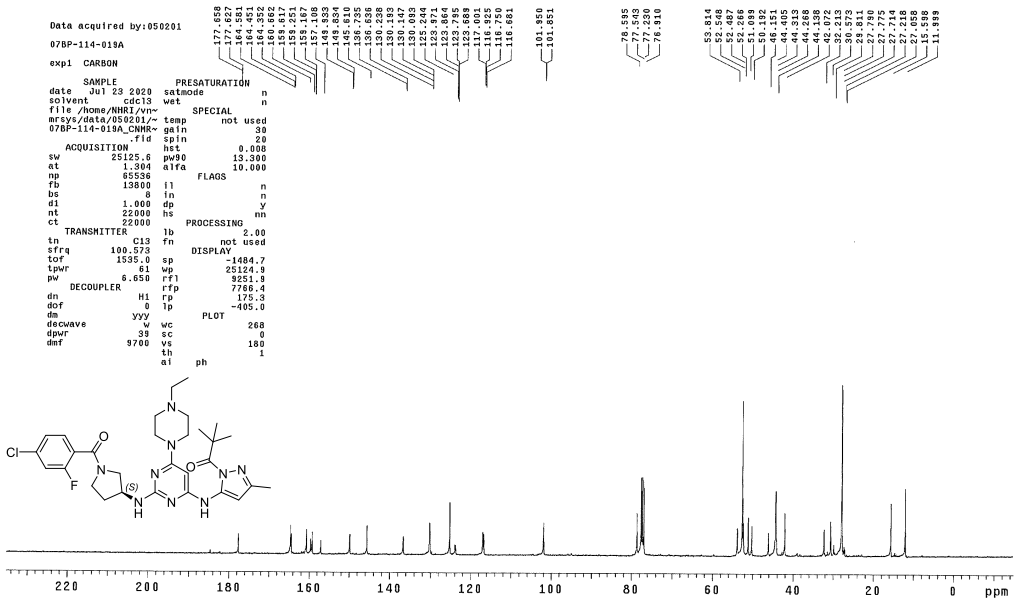
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	10.91	18112	916	0.527
2	12.99	3342574	175226	97.322
3	14.73	70140	2817	2.042
4	16.09	3723	215	0.108
		3434549	179174	100.000

Peak rejection level: 0

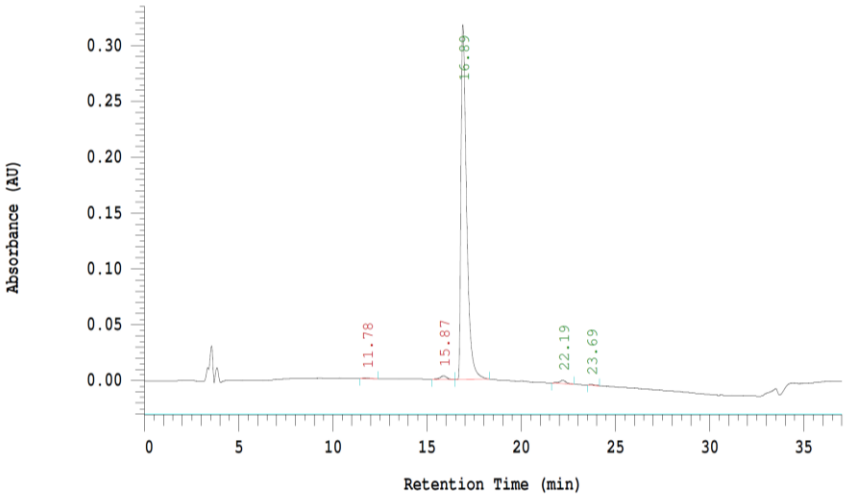
Figure S29. NMR and HPLC spectra of compound 27. (*S*)-1-(5-((2-((1-(4-chloro-2-fluorobenzoyl)pyrrolidin-3-yl)amino)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)amino)-3-methyl-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one (27)





Sample Name: 07BP-114-019A-50 Vial Number: 52
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity_37min
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	11.78	5807	275	0.173
2	15.87	37714	1492	1.123
3	16.89	3273011	158605	97.451
4	22.19	35921	1444	1.070
5	23.69	6180	353	0.184
		3358633	162169	100.000

Peak rejection level: 0

Figure S30. ^{1}H NMR spectrum of compound 29.
2,6-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (29)

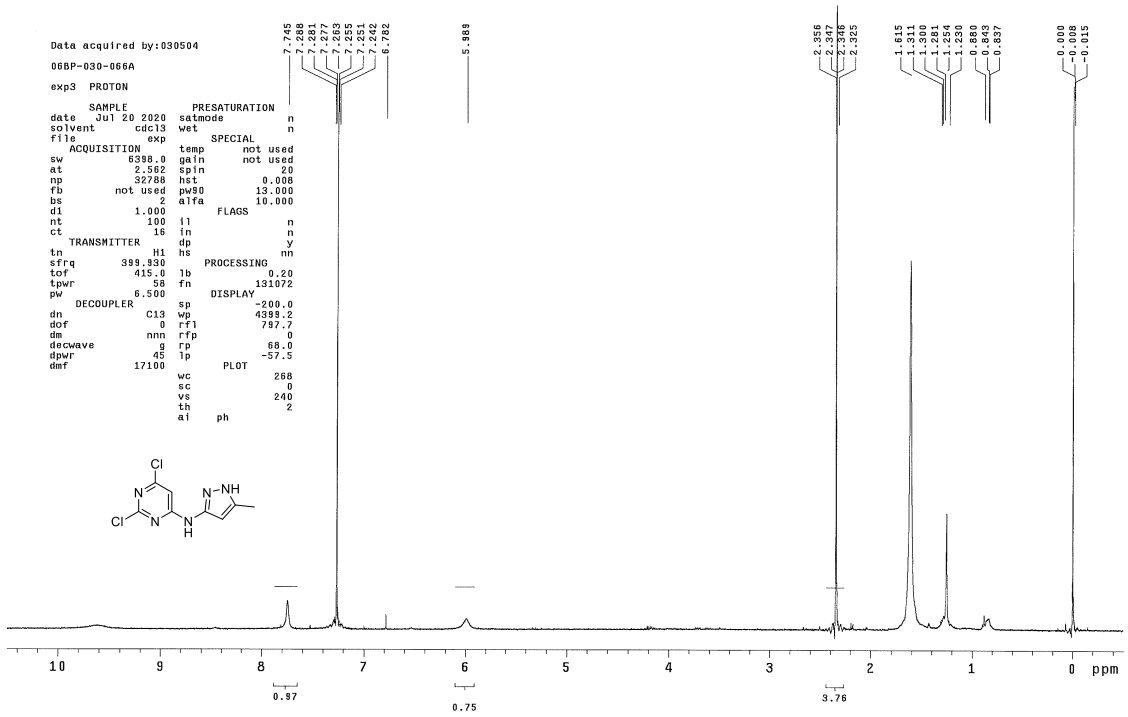


Figure S31. ^{1}H NMR spectrum of compound 30.
(*S*)-(3-chloro-2-fluorophenyl)(3-((4-chloro-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (30)

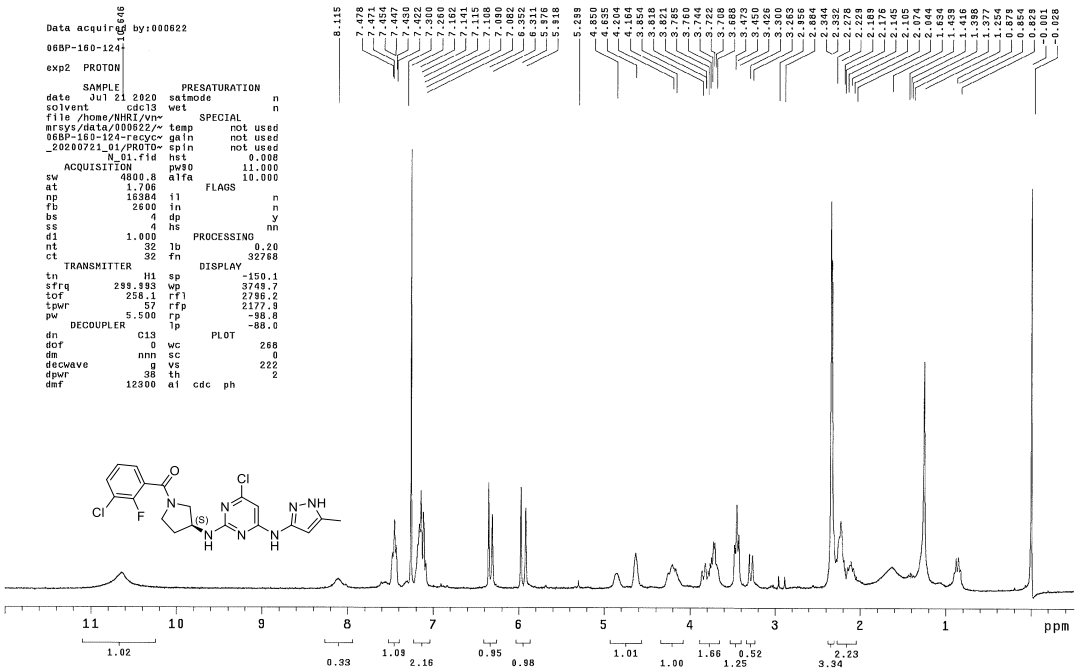


Figure S32. ^{1}H NMR spectrum of compound 32.
***tert*-butyl (*S*)-3-((4,6-dichloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (32)**

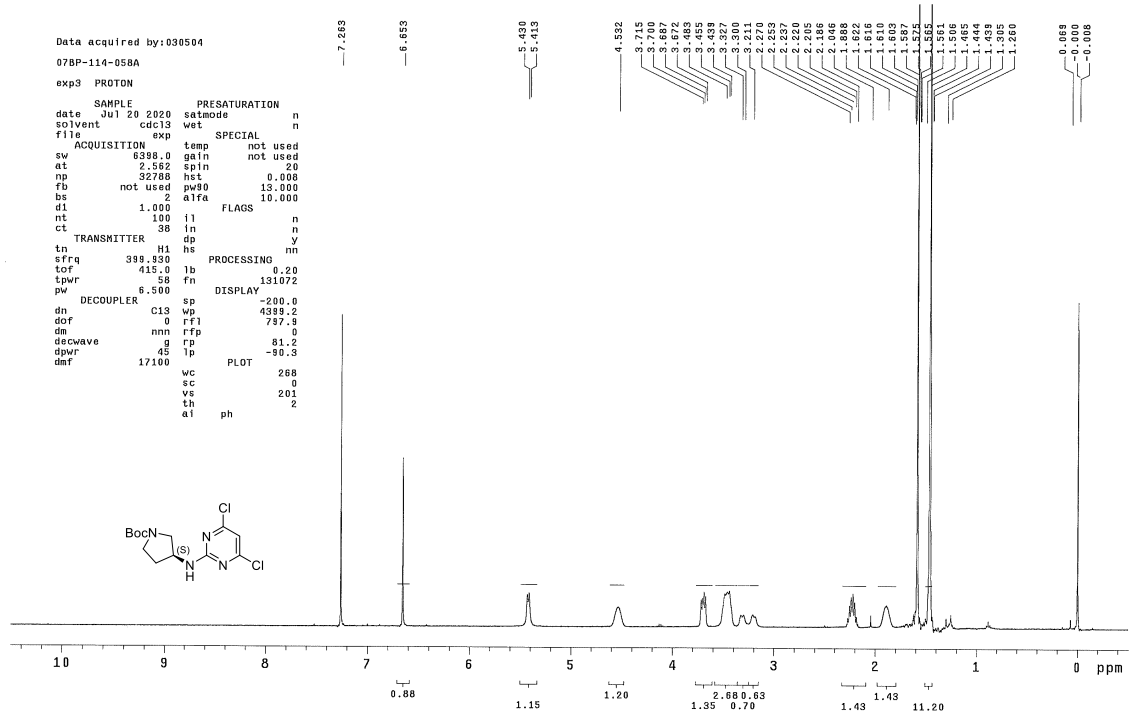


Figure S33. ^{1}H NMR spectrum of compound 33.

***tert*-butyl (*S*)-3-((4-chloro-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (33)**

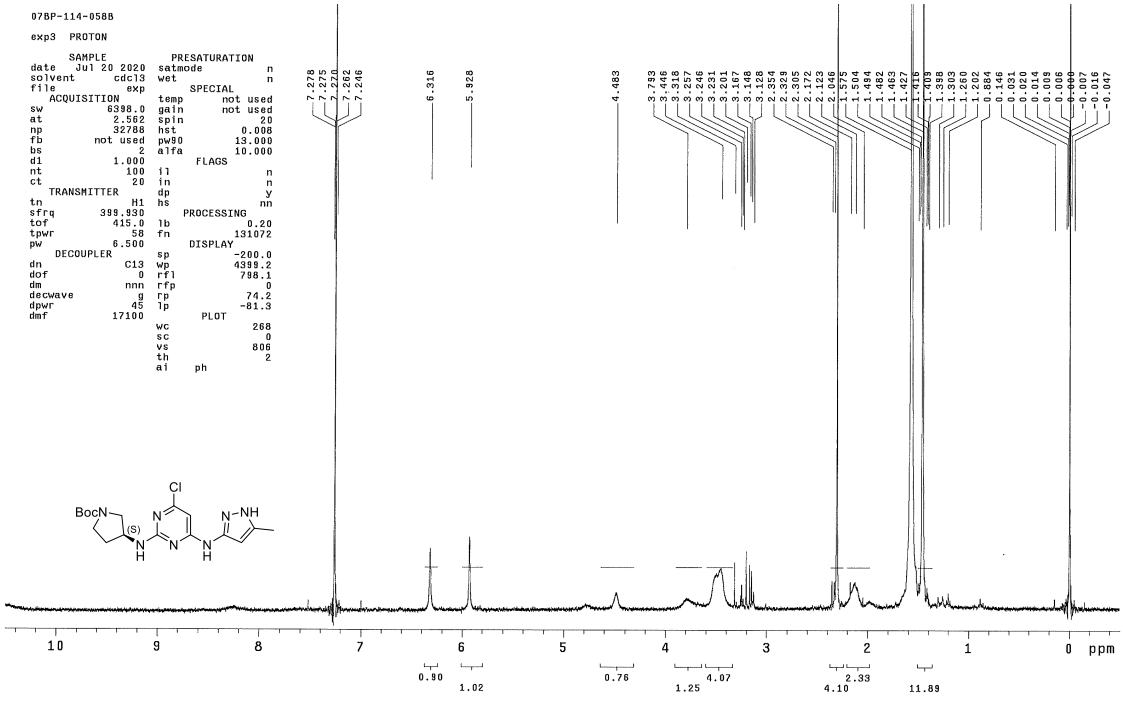


Figure S34. ^{1}H NMR spectrum of compound 34.

***tert*-butyl (*S*)-3-((4-(4-ethylpiperazin-1-yl)-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (34)**