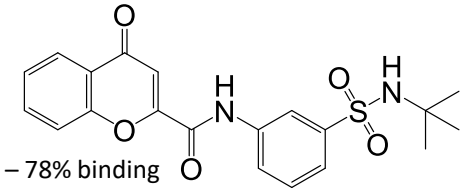
CACHE 1 – LRRK2_WDR

Participant 1179

PARENT MOLECULE



CACHE_1179_36
KD LRRK2 129µM – 78% binding
KD NSD2 – NA – 24% binding
100% solub /no agg. at 200 µM

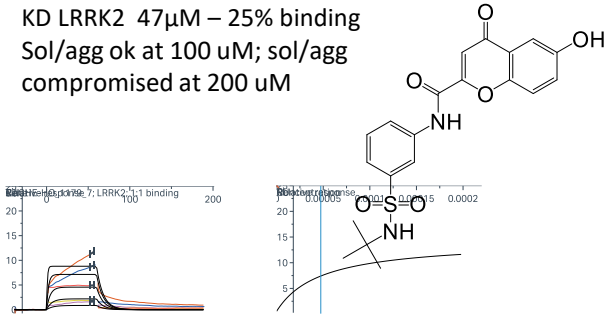
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1179_1	845	1166	1258	100	100	100
CACHE-HO_1179_10	1052	428	546	100	100	100
CACHE-HO_1179_2	1415	1125	842	100	100	100
CACHE-HO_1179_44	804	938	1251	93	100	100
CACHE-HO_1179_6	3832	774	897	60	100	100
CACHE-HO_1179_7	1647	1327	532	73	100	100

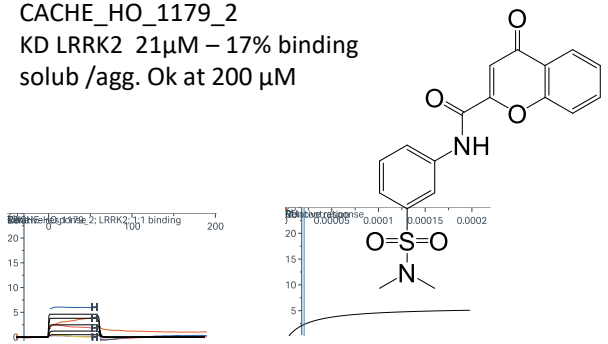
33 analogs of chemotype 1 submitted in round 2. 6 of these show dose-response binding by SPR; one is a resupply of the original hit CACHE_1179_36.

Lacks orthogonal confirmation by a second experimental method. CACHE_HO_1179_1 destabilizes the target instead of stabilizing it (DSF experiment)

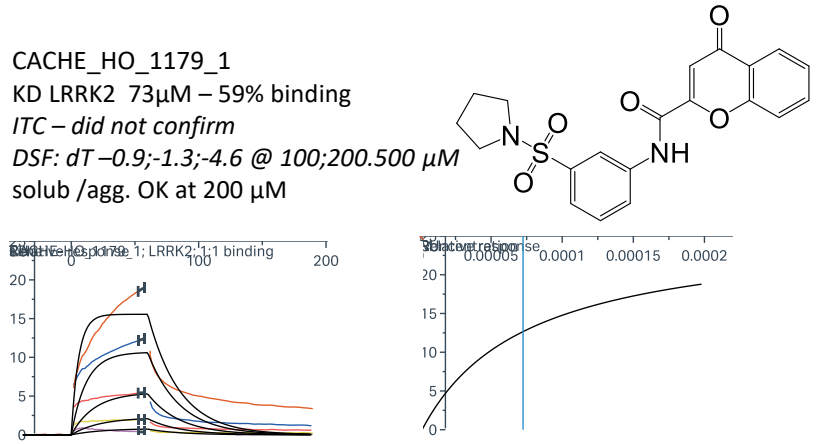
CACHE_HO_1179_7
KD LRRK2 47µM – 25% binding
Sol/agg ok at 100 uM; sol/agg compromised at 200 uM



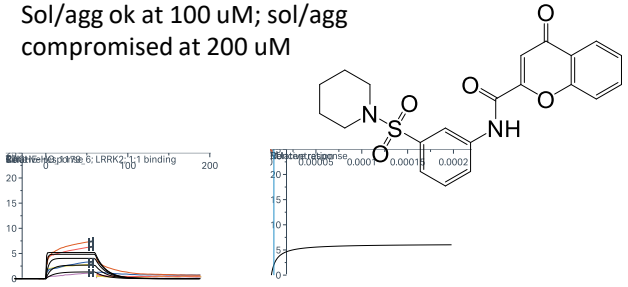
CACHE_HO_1179_2
KD LRRK2 21µM – 17% binding
solub /agg. Ok at 200 µM



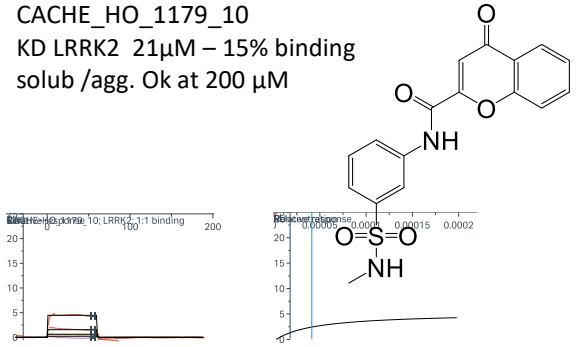
CACHE_HO_1179_1
KD LRRK2 73µM – 59% binding
ITC – did not confirm
DSF: dT –0.9;-1.3;-4.6 @ 100;200.500 µM
solub /agg. OK at 200 µM



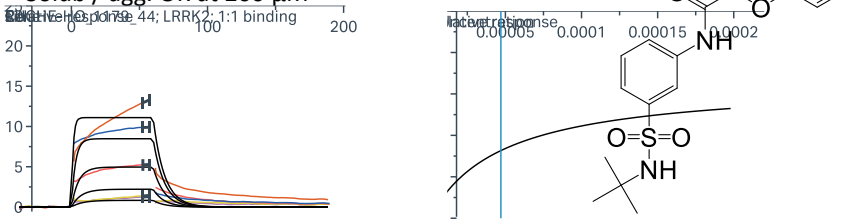
CACHE_HO_1179_6
KD LRRK2 4µM – 18% binding
Sol/agg ok at 100 uM; sol/agg compromised at 200 uM



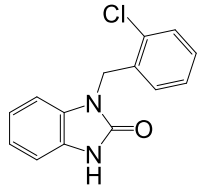
CACHE_HO_1179_10
KD LRRK2 21µM – 15% binding
solub /agg. Ok at 200 µM



CACHE_HO_1179_44
KD LRRK2 47µM – 39% binding
ITC – did not confirm
Solub / agg. OK at 200 µM



PARENT MOLECULE



CACHE_1179_94
KD LRRK2 22uM; 45% binding
NSD2 – 28% binding KD not determined
Aggregates, not soluble at 100 µM

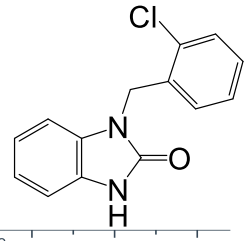
6 analogs of chemotype 2 were submitted in round 2. One is a resupply of the hit CACHE_1179_94. The resupply is more soluble and aggregates less.

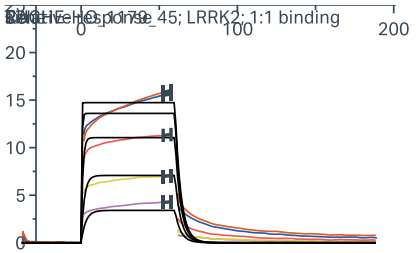
Compounds are not confirmed by DSF (compounds do not stabilize LRRK2).

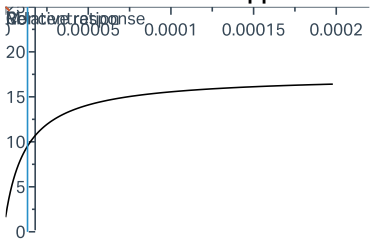
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1179_41	1334	1127	1697	100	100	100
CACHE-HO_1179_45	1506	1870	2892	100	100	100

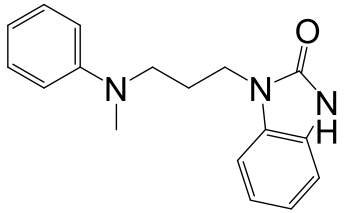
CACHE-HO_1179_45
KD LRRK2 13uM – 67%
DSF – did not confirm
Sol ok at 200uM; agg may be compromised from as low as 50 uM; strange trend of agg with concentration

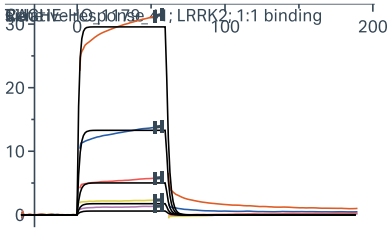


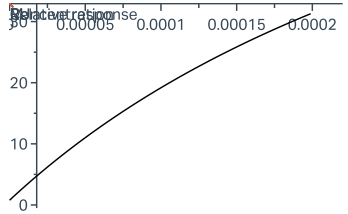




CACHE_HO_1179_41
KD LRRK2 >200µM (396 uM)– 115% binding
DSF – did not confirm
Sol ok at 200uM; strange trend of agg with concentration



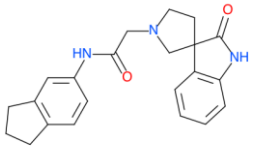




CACHE 1 – LRRK2_WDR

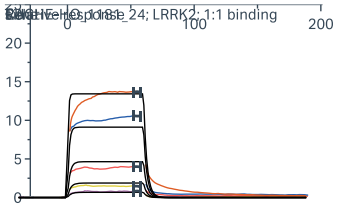
Participant 1181

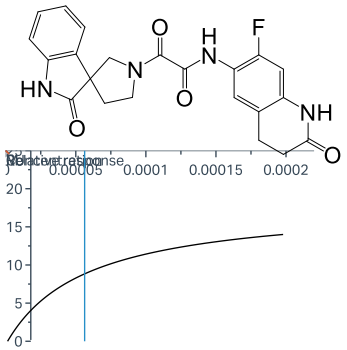
PARENT MOLECULE



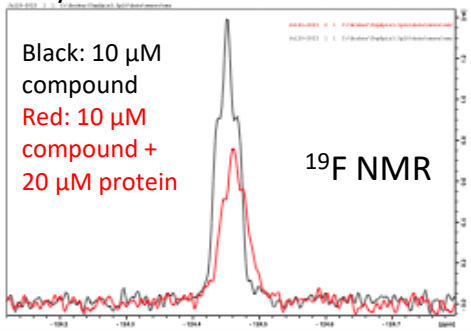
CACHE_1181_33
KD LRRK2 123µM – 100% binding
KD NSD2 – NA – 41% binding
25% solub / agg. at 200 µM

CACHE_HO_1181_24
KD LRRK2 56µM – 30% binding
19F-NMR – confirms binding
Sol / agg. OK at 200 µM





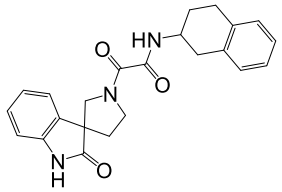
CACHE_HO_1181_24
Crystal trials



CACHE_1181_33 had 31 analogs submitted in round 2. Of these one confirms by 19F-NMR.

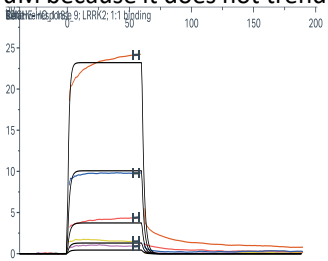
Aggregation/solubility measured by DLS

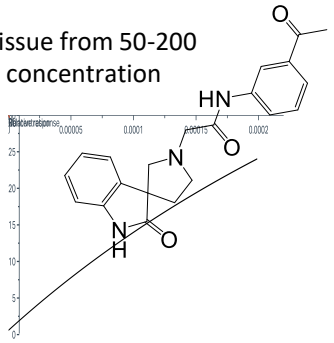
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1181_12	840	7770	1300	100	100	100
CACHE-HO_1181_2	3344	6792	7377	100	100	100
CACHE-HO_1181_24	740	1465	1654	100	100	100
CACHE-HO_1181_29	1720	2216	3239	100	100	95
CACHE-HO_1181_30	3788	2230	1398	68	100	100
CACHE-HO_1181_33	985	1115	2104	100	100	100
CACHE-HO_1181_9	2206	676	2151	100	100	100



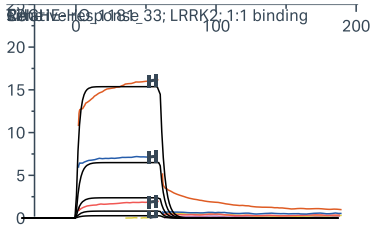
CACHE-HO_1181_30
>200uM (544uM)– 50% binding
Sol/agg compromised at 200 uM

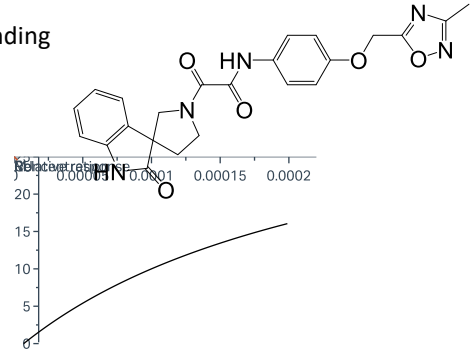
CACHE-HO_1181_9
>200 uM (622 uM) – 74% binding
Sol ok to 200 uM; agg could be an issue from 50-200 uM because it does not trend with concentration

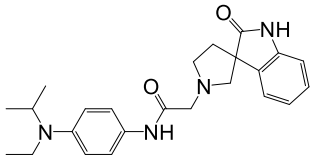




CACHE-HO_1181_33
KD LRRK2 >200 uM (246 uM)– 38% binding
DSF – did not confirm
solub / agg ok at 200 uM

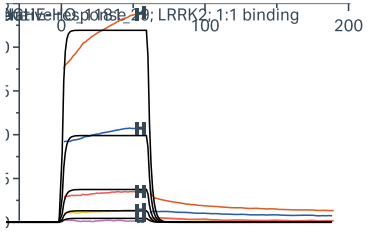


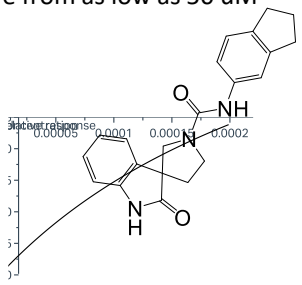




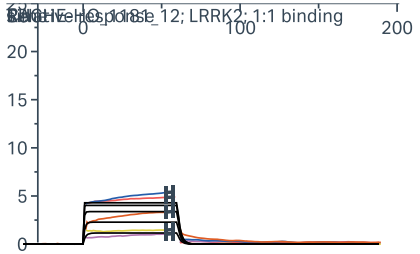
CACHE_HO_1181_2
KD LRRK2 155µM – 29% binding
Sol ok at 200 µM; agg likely from as low as 50 uM

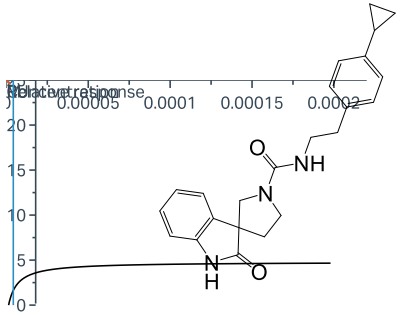
CACHE-HO_1181_29
(same as 1181_33)
KD >200uM (310uM)– 76% binding
Sol ok at 200 uM; agg could be an issue from as low as 50 uM
DSF – does not confirm





CACHE_HO_1181_12
KD LRRK2 4µM – 15% binding
Sol OK at 200 µM; agg has a strange trend



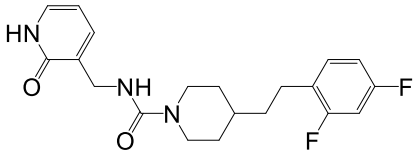


NA – did not yield usable/binding data

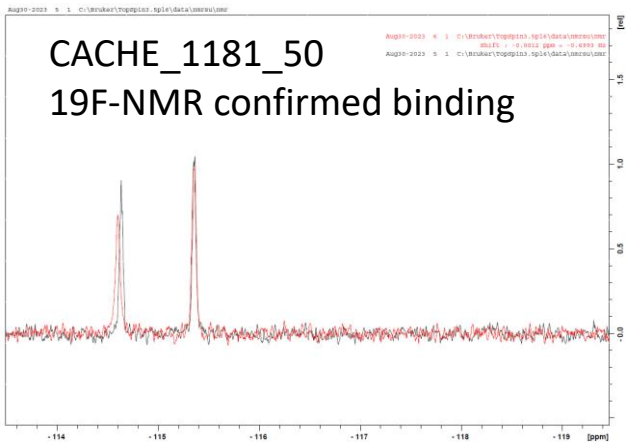
CACHE_1181_50 = CACHE-HO_1181_34
Both confirmed by 19F-NMR.

No analogs were submitted in round 2.

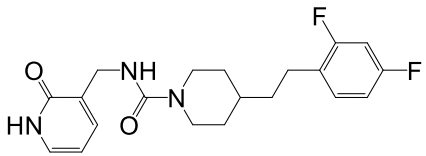
PARENT MOLECULE

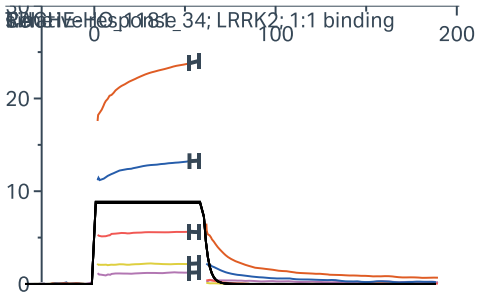


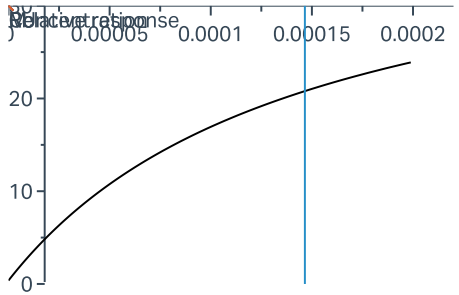
CACHE_1181_50
SPR LRRK2 137uM – 100% binding
SPR NSD2 linear – 104% binding
BLI – binds in DR



CACHE-HO_1181_34
147uM – 71% binding
Sol/agg ok at 200 uM
19F-NMR – binding confirmed
DSF – did not confirm

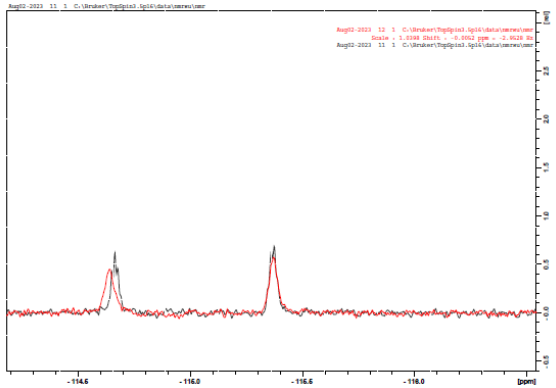


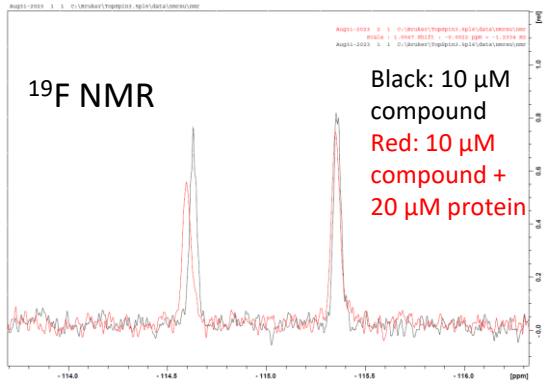




Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1181_34	893	644	603	100	100	100



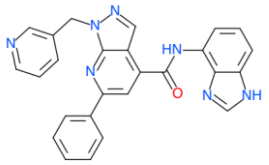


NA – did not yield usable/binding data

CACHE 1 – LRRK2_WDR

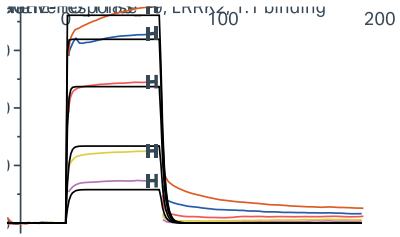
Participant 1183

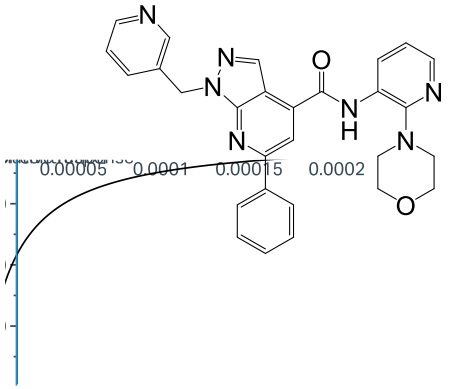
PARENT MOLECULE



CACHE_1183_25
KD LRRK2 16µM – 79% binding
KD NSD2 – NA – 49% binding
~30% solub / agg. at 200 µM

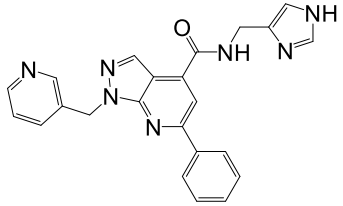
CACHE_HO_1183_19
KD LRRK2 18µM – 80% binding
DSF: 1.1 at 200 uM; 0.7 at 100 uM
Sol /agg ok to 200 uM

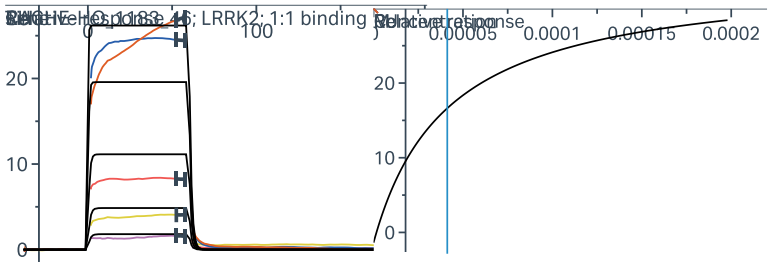




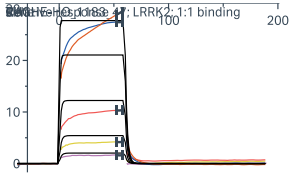
43 analogs submitted in round 2.
Six analogs show dose-response binding by SPR; one additionally confirms by DSF.

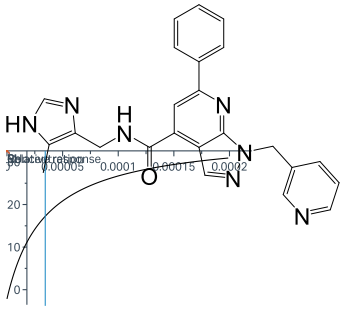
CACHE_HO_1183_46
KD LRRK2 41µM – 71% binding
Sol/agg compromised at 200 µM
DSF: 0.6 at 100uM; -0.3 at 200uM
but sol. Issues at 200 uM



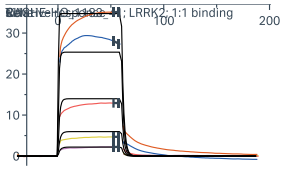


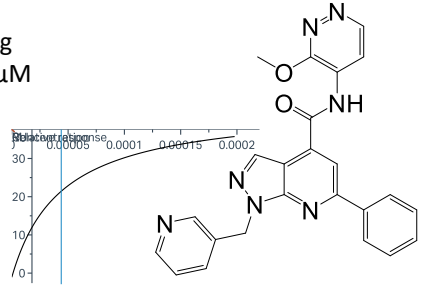
CACHE_HO_1183_47
KD LRRK2 34µM – 80% binding
DSF – did not confirm
solub /agg. OK at 200 µM



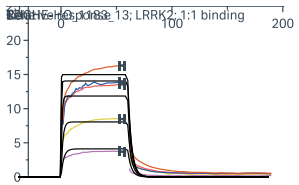


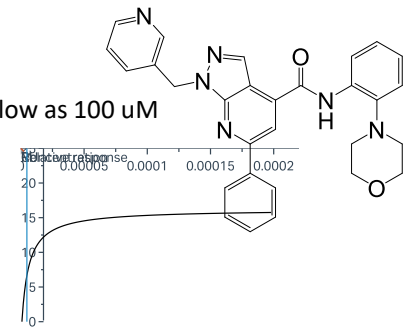
CACHE_HO_1183_41
KD LRRK2 44µM – 85% binding
Sol/agg compromised at 200 µM
DSF – did not confirm



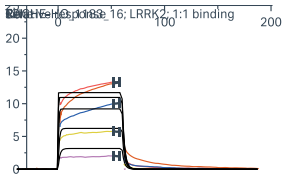


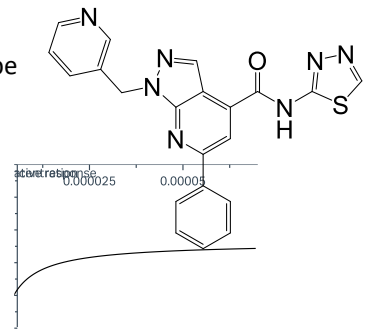
CACHE_HO_1183_13
KD LRRK2 5µM – 40% binding
DSF – did not confirm
Sol/agg compromised from as low as 100 uM





CACHE_HO_1183_16
KD LRRK2 3µM – 31% binding
Agg ok. to 200 µM; sol starts to be compromised at 100 uM
DSF – did not confirm



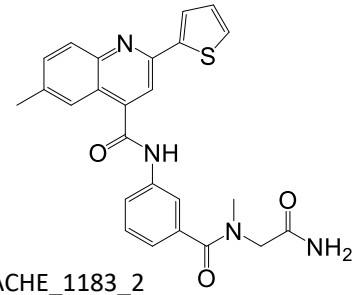


Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1183_13	1336	2895	2688	83	75	100
CACHE-HO_1183_16	789	718	1155	85	95	100
CACHE-HO_1183_19	1781	1381	1054	100	100	100
CACHE-HO_1183_41	4253	1564	1248	65	100	100
CACHE-HO_1183_46	2855	1108	1619	68	100	100
CACHE-HO_1183_47	1051	1040	769	100	100	100

NA – did not yield usable/binding data

PARENT MOLECULE



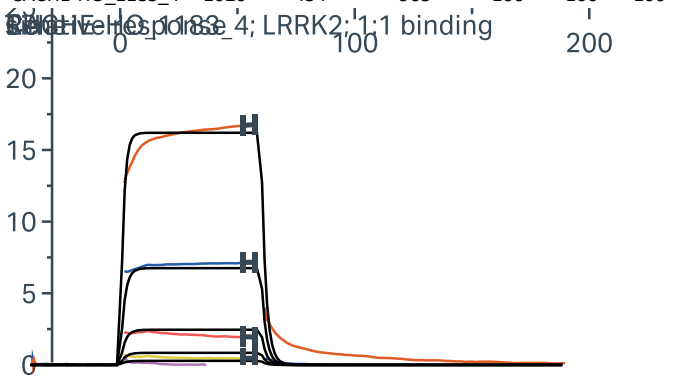
CACHE_1183_2
KD LRRK2 32µM – 68% binding
KD NSD2 42 uM – 43% binding

4 analogs submitted in round 2 with one showing dose-response binding by SPR.

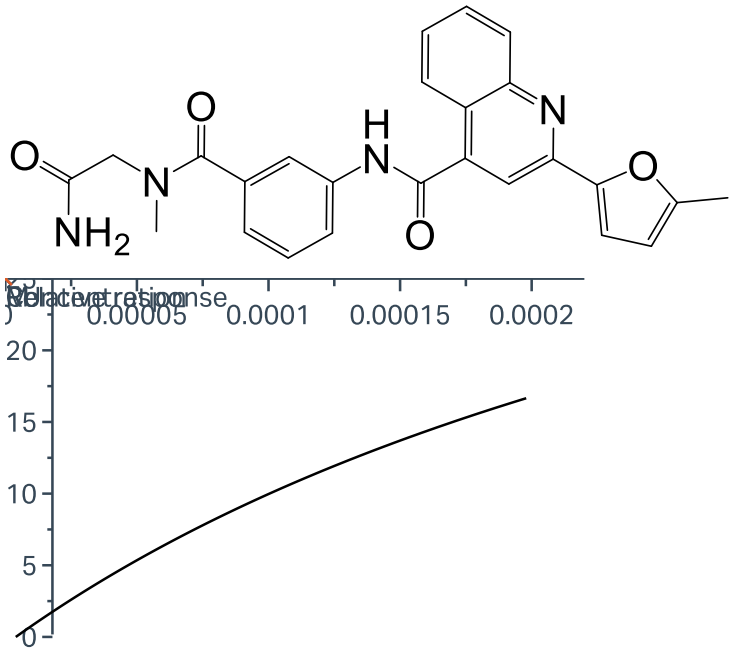
Parent molecule binds an unrelated target: NSD2-PWWP1 domain

CACHE_HO_1183_4
KD LRRK2 >200µM (370uM) – 41% binding
Sol/agg ok to 200 uM

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1183_4	1020	434	905	100	100	100



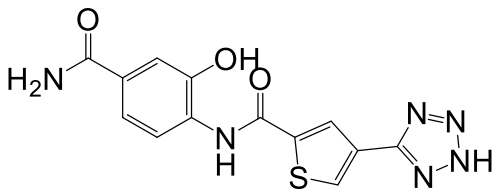
CACHE_HO_1183_4; LRRK2; 1:1 binding



CACHE 1 – LRRK2_WDR

Participant 1184

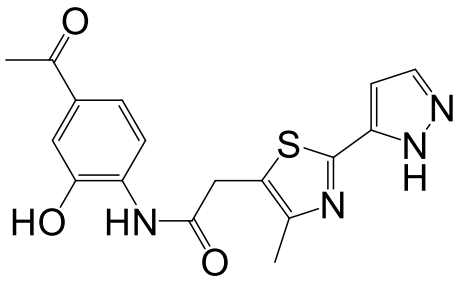
PARENT MOLECULE



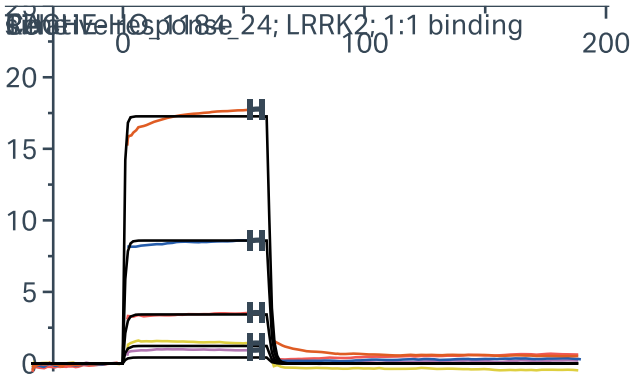
CACHE_1184_17
LRRK2 145 uM – 120% binding
NSD2 185% binding

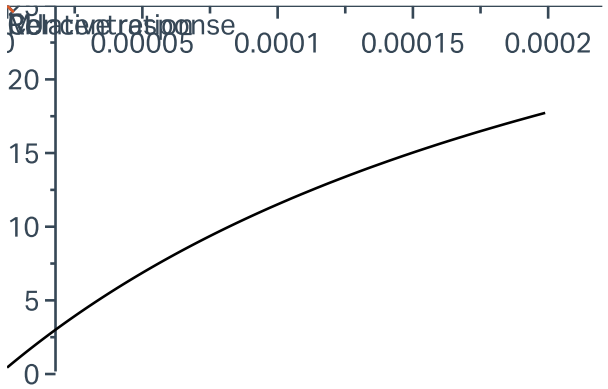
10 analogs submitted in round 2. One has dose-response binding by SPR.
Solubility and aggregation look good up to 200 µM.

No orthogonal confirmation of compounds.



CACHE_HO-1184_24
SPR >200µM (260uM) – 53% binding
Sol/agg fine up to 200 uM
DSF – did not confirm

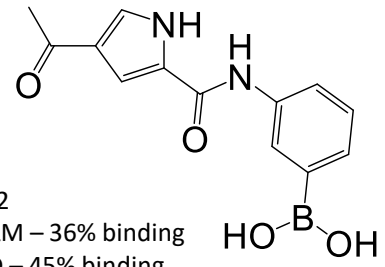




Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1184_24	873	741	1009	100	100	100

PARENT MOLECULE



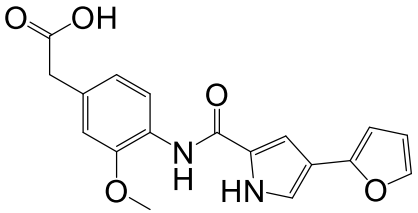
CACHE_1184_22
SPR LRRK2 33 µM – 36% binding
SPR NSD2 no KD – 45% binding
Sol/agg fine up to 200 uM

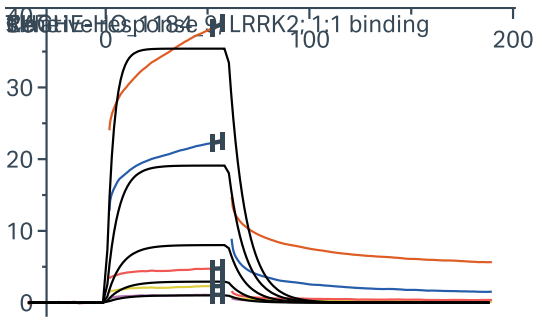
Aggregation/solubility measured by DLS

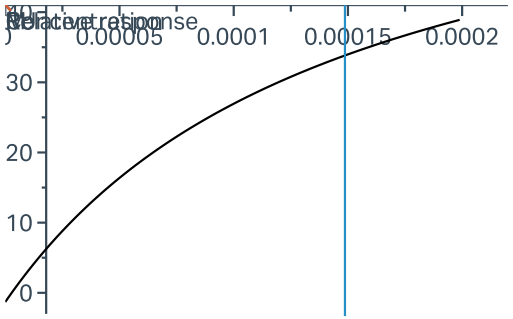
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1184_7	875	574	646	100	100	100
CACHE-HO_1184_9	915	988	1515	98	100	100

32 analogs submitted in round 2; two analogs with dose-response binding. Neither compound is confirmed in an orthogonal method.

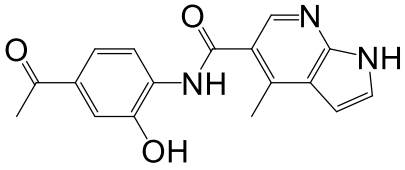
CACHE-HO_1184_9
SPR LRRK2 149 µM – 109% binding
Sol/agg fine up to 200 uM
DSF – did not confirm

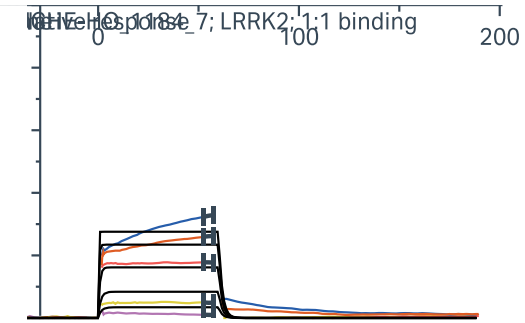


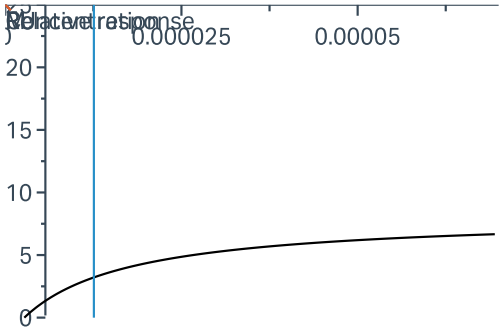




CACHE_HO-1184_7
SPR LRRK2 13 µM – 25% binding
Sol/agg fine up to 200 uM
DSF, ITC – did not confirm



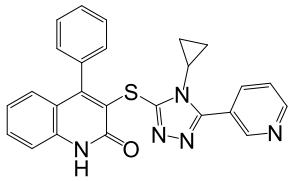




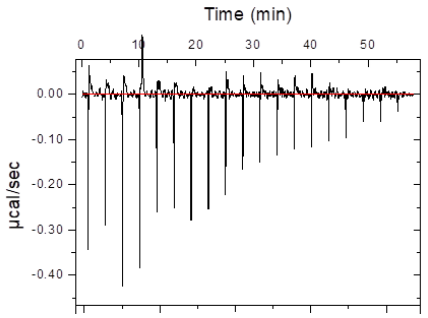
CACHE 1 – LRRK2_WDR

Participant 1186

PARENT MOLECULES



CACHE_1186_2
SPR LRRK2 26 µM – 90% binding
SPR NSD2 46 uM – 67% binding
ITC – 38 uM

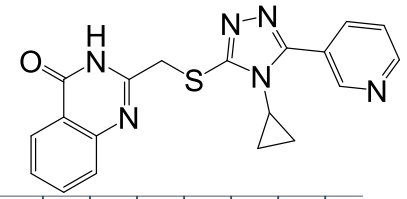


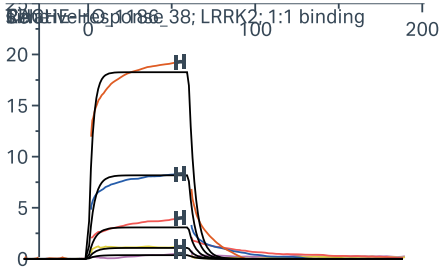
Parent molecule binds unrelated target (NSD2-PWWP1)
17 compounds submitted in round 2.
Two compounds show dose-response binding by SPR.

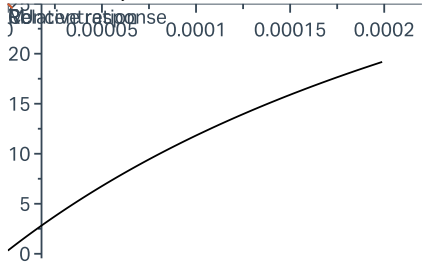
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1186_1	1018	1000	1141	98	100	100
CACHE-HO_1186_38	578	1572	701	100	100	100
CACHE-HO_1186_39	1237	1024	1533	83	100	100

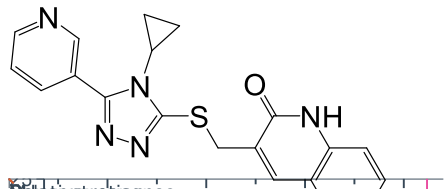
CACHE_HO_1186_38
SPR >200 µM (364uM) – 57% binding
DSF – not tested; ITC – no binding

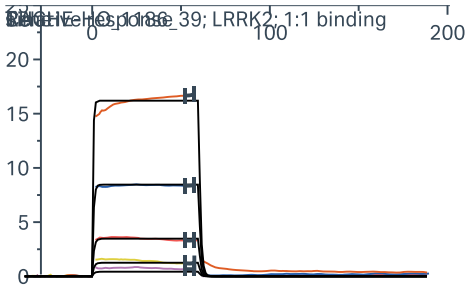


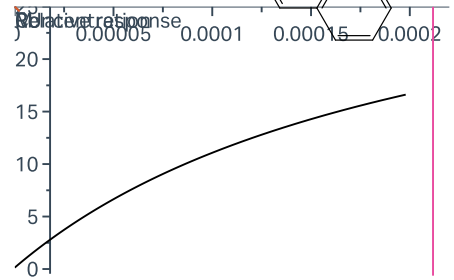




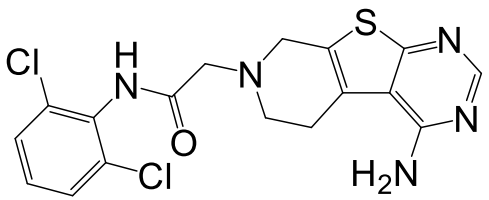
CACHE_HO_1186_39
SPR 212 µM – 49% binding
DSF – not tested; ITC – no binding







PARENT MOLECULE



CACHE_1186_85
KD LRRK2 53µM – 75% binding
KD NSD2 – 138 µM – 60% binding
solub / agg. OK at 200 µM

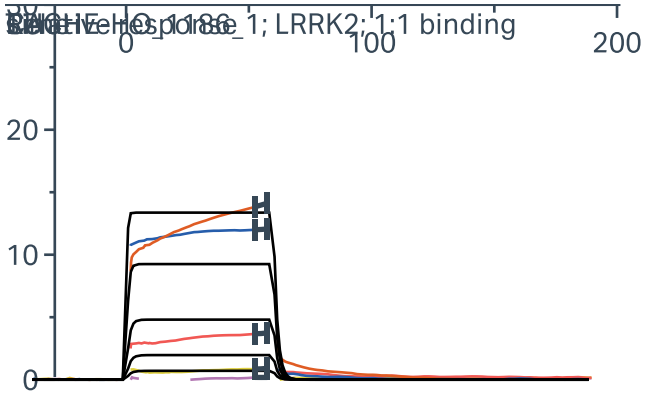
Parent molecule binds NSD2-PWWP1

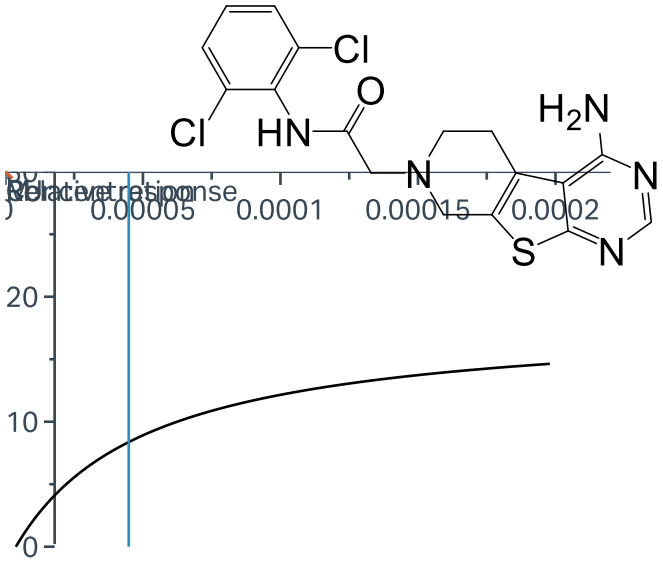
8 analogs were submitted in round 2.
Only the resupplied compound shows binding in dose-response by SPR. It does not confirm by DSF.

Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1186_1	1018	1000	1141	98	100	100

CACHE_HO_1186_1
SPR 45 µM – 39% binding
DSF – not tested



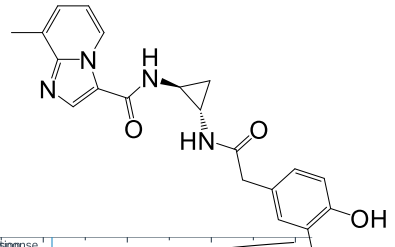


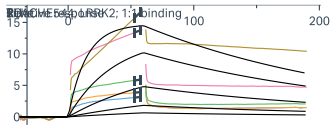
CACHE 1 – LRRK2_WDR

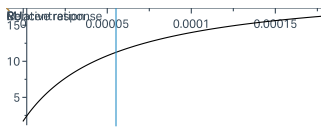
Participant 1187

PARENT MOLECULE

CACHE_1187_84
SPR 55 uM, 36% binding
SPR – NSD2 13% binding
NMR – did not confirm



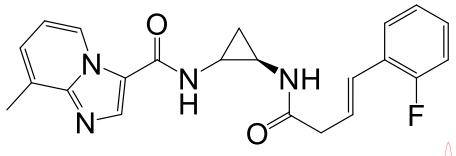




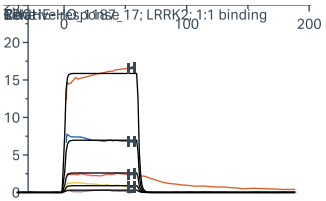
7 analogs submitted in round 2. two show dose-response binding by SPR.

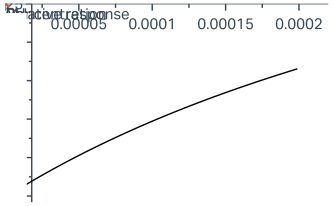
One confirms by 19F-NMR.

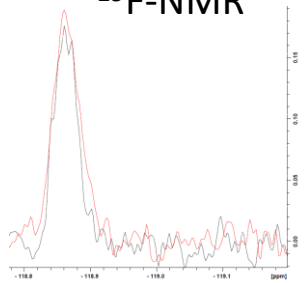
CACHE_HO-1187_17
SPR >200µM (459 uM) – 43% binding
Sol/agg ok to only to 100 uM
DSF – does not confirm
19F NMR: does not confirm



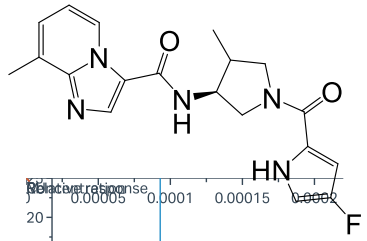
^{19}F-NMR

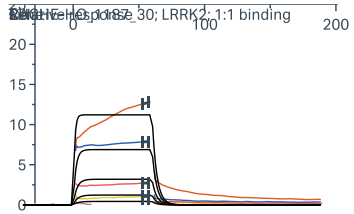


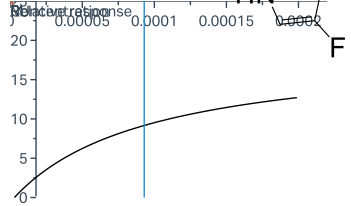




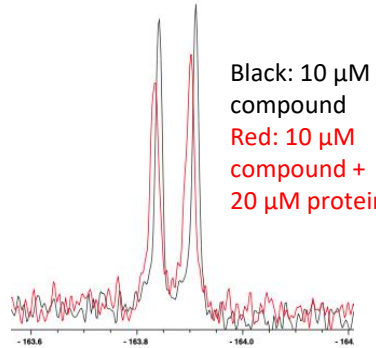
CACHE-HO_1187_30
SPR 93µM – 34% binding;
19F-NMR – shows binding
Sol/agg good to 200 uM







^{19}F-NMR

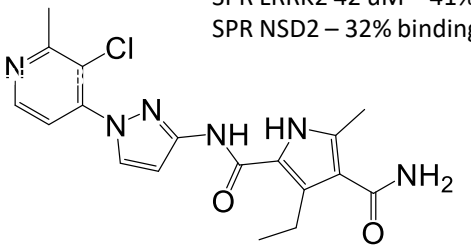


Black: 10 µM compound
Red: 10 µM compound + 20 µM protein

Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1187_17	8853	2519	1512	58	78	100
CACHE-HO_1187_18	608	1373	651	100	100	100
CACHE-HO_1187_19	657	431	604	100	100	100
CACHE-HO_1187_20	566	1066	858	100	100	100
CACHE-HO_1187_30	1466	1753	649	100	100	100

PARENT MOLECULE



CACHE_1187_74
SPR LRRK2 42 uM – 41% binding
SPR NSD2 – 32% binding

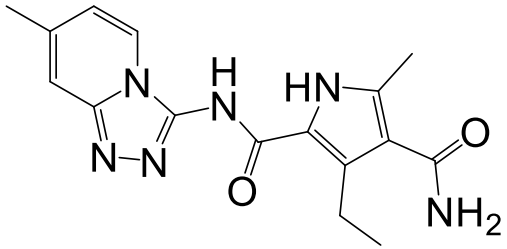
9 compounds submitted in round 2.

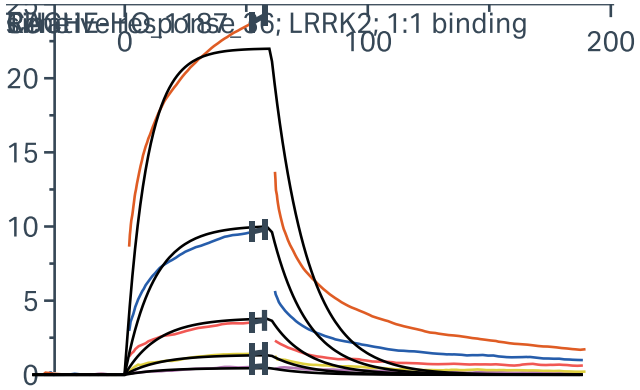
1 binds weakly in dose-response in SPR at concentration where solubility is poor

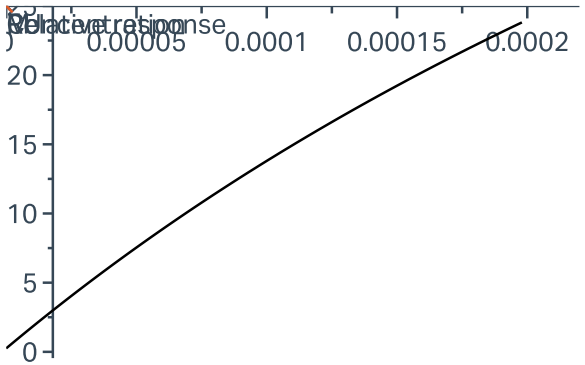
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1187_36	4091	1544	1001	58	100	100

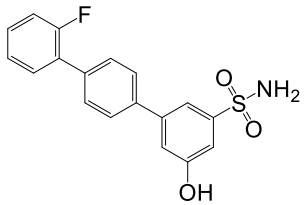
CACHE_HO_1187_36
SPR >200µM (600 uM) – 81% binding
Sol/agg is compromised at 200 uM
DSF – no binding



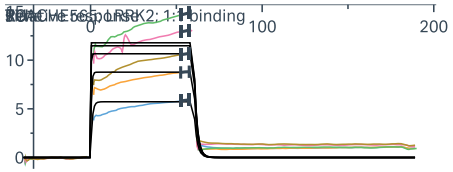


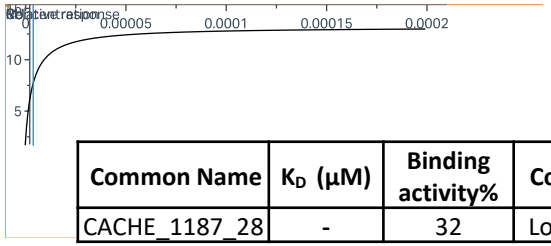


PARENT MOLECULES (no analog in Round 2)

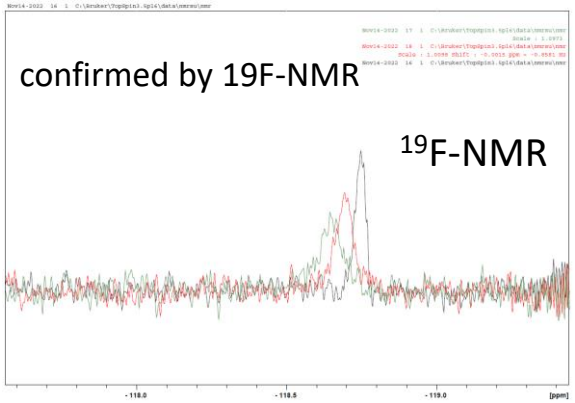


CACHE_1187_28
SPR LRRK2 no KD reported – 32% binding
SPR NSD2 – 14% binding
19F NMR – Yes in DR

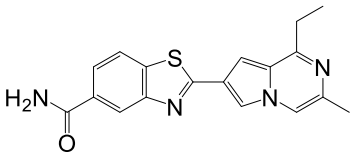


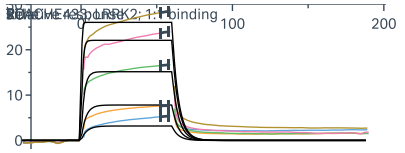


Common Name	K_D (µM)	Binding activity%	Comment
CACHE_1187_28	-	32	Low signal

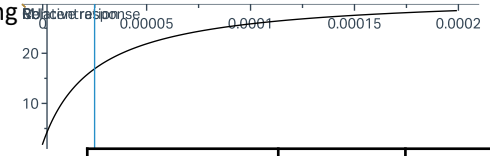


Black: 10 µM compound
Red: 10 µM compound + 10 µM protein
Green: 10 µM compound + 20 µM protein





CACHE_1187_59
SPR LRRK2 25uM – 64% binding
SPR NSD2 – 22% binding



Common Name	K_D (µM)	Binding activity%	Comment
CACHE_1187_59	**25**	64	

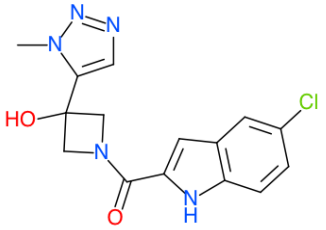
Aggregation/solubility measured by DLS

Compound Name	Solubility (% Laser Power)						Aggregation (Intensity - kCnt/s)					
	12.5µM	25µM	50µM	100µM	150µM	200µM	12.5µM	25µM	50µM	100µM	150µM	200µM
CACHE_1187_59	98	100	95	100	100	98	926	557	1366	1005	1827	914
CACHE_1187_28	100	100	100	55	75	20	546	402	444	1703	1319	27594

CACHE 1 – LRRK2_WDR

Participant 1188

PARENT MOLECULE



CACHE_1188_92
KD LRRK2 18µM – 46% binding
KD NSD2 – NA – 37% binding
DSF does not confirm binding
~55% solub / agg. at 200 µM

Aggregation/solubility measured by DLS

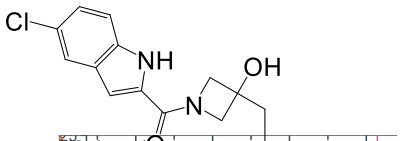
Compound Name	Normalized Intensity (kCnt/s)				Laser Power (%)			
	500 µM	200µM	100µM	50µM	500 µM	200µM	100µM	50µM
2% DMSO control		487	827	1595		100	100	100
CACHE-HO_1188_1		1269	1998	792		100	100	100
CACHE-HO_1188_30		1736	659	821		100	100	100
CACHE-HO_1188_33		1223	896	825		100	100	100
CACHE-HO_1188_36		1237	504	648		100	100	100
CACHE-HO_1188_37		1115	498	1140		100	100	100
CACHE-HO_1188_38		619	662	849		100	98	100
CACHE-HO_1188_41	1150	361	412	466	98	100	100	100
CACHE-HO_1188_48		619	867	986		100	100	100

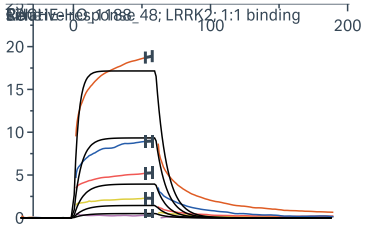
20 analogs submitted in round 2.

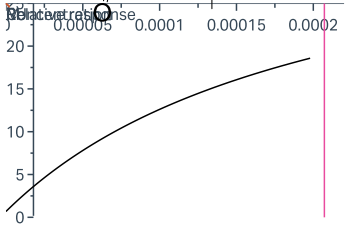
Four show dose-response binding by SPR.

CACHE_HO_1188_41 appears to confirm by DSF.

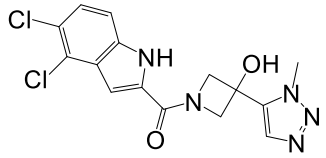
CACHE_HO_1188_30
KD LRRK2 169µM – 23% binding
Solub / agg. Ok to 200 µM
DSF – does not confirm

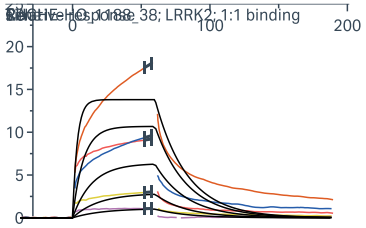


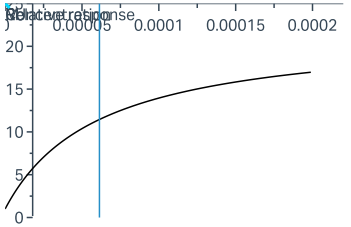




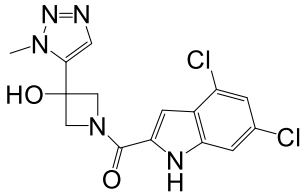
CACHE_HO_1188_38
KD LRRK2 61µM – 50% binding
Solub / agg. Ok to 200 µM
DSF – does not confirm

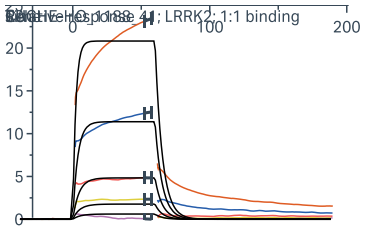


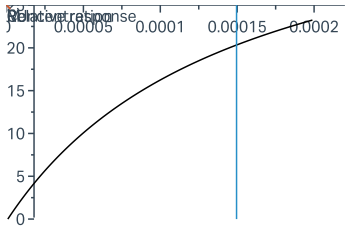




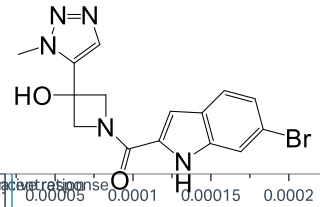
CACHE_HO_1188_41
KD LRRK2 150µM – 74% binding
DSF – dT 0.8;0.4;1C @ 100;200;500uM
Solub / agg. Ok to 500 µM

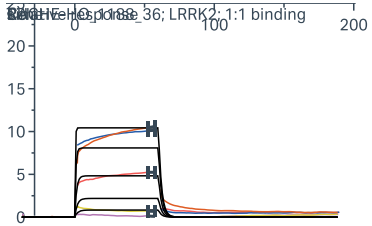


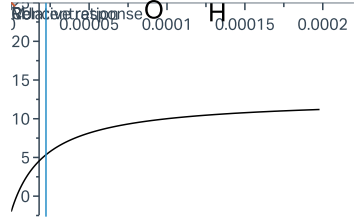




CACHE_HO_1188_36
KD LRRK2 22µM – 29% binding
ITC – did not confirm
DSF – does not confirm
Solub /agg. Ok to 200 µM

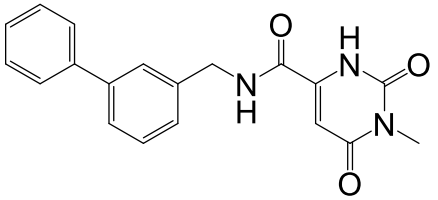


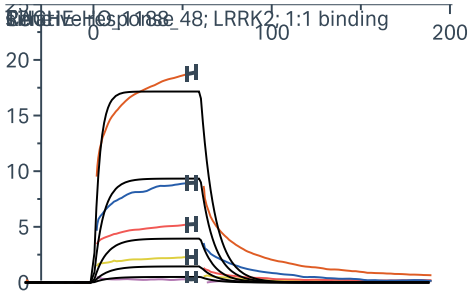


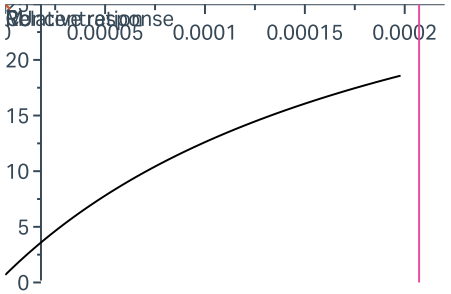


13 analogs submitted in round 2.
Only the resupplied parent compound shows weak dose-response binding by SPR.

CACHE-HO_1188_48
SPR 207uM – 65% binding
Sol/agg good to 200 uM







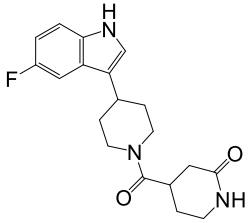
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1188_48	619	867	986	100	100	100

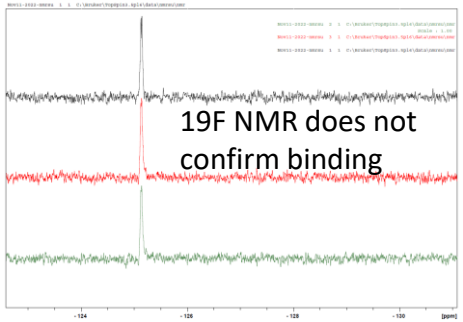
CACHE 1 – LRRK2_WDR

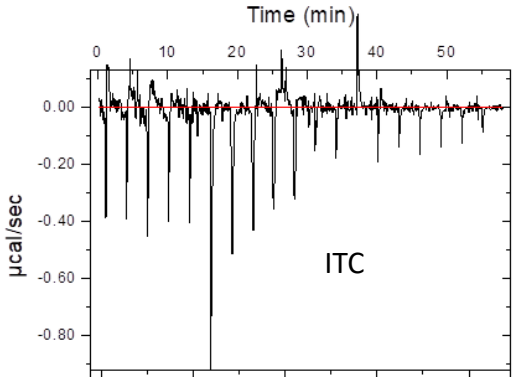
Participant 1193

PARENT MOLECULES

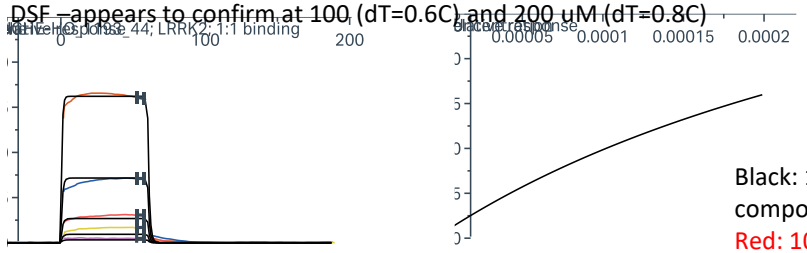


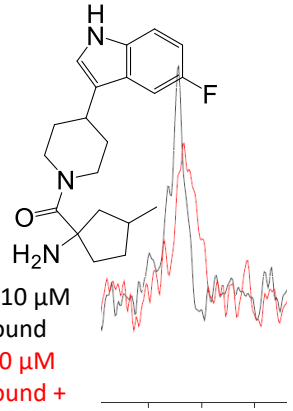
CACHE_1193_26
SPR LRRK2 48µM – 58% binding
SPR NSD2 – NA – 36% binding
100% solub /no agg. at 200 µM
Co-crystallized in-side pocket





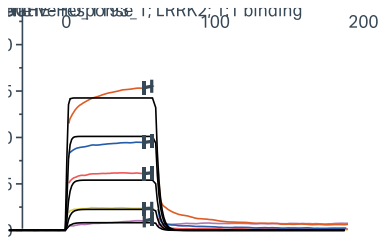
CACHE_HO_1193_40
KD LRRK2 140µM – 38% binding
19F-NMR – appears to confirm binding
Sol, agg. compromised at 50 µM
DSF –appears to confirm at 100 (dT=0.6C) and 200 uM (dT=0.8C)

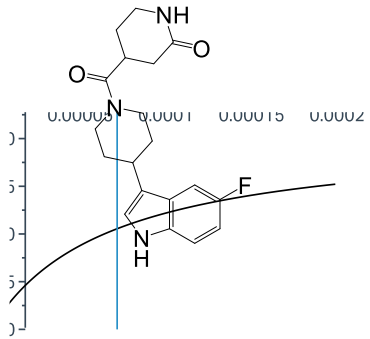


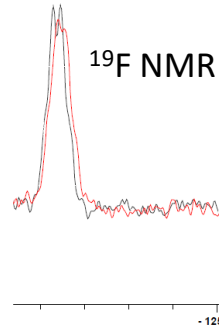


Black: 10 µM compound
Red: 10 µM compound + 20 µM protein

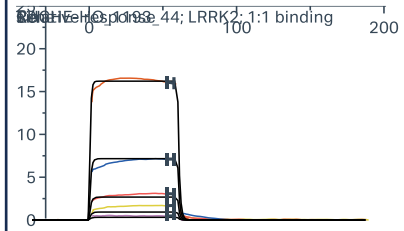
CACHE_HO_1193_1
KD LRRK2 72µM – 50% binding
Solub / agg. good to 200 µM
19F-NMR – not confirmed

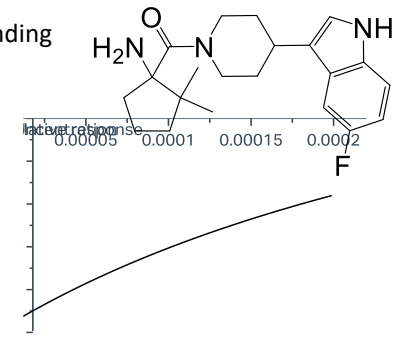


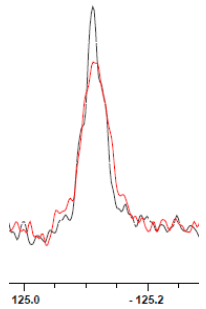




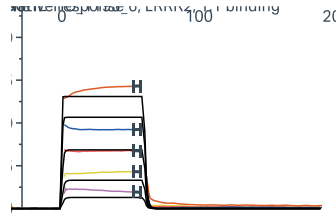
CACHE_HO_1193_44
KD LRRK2 >200 uM (390µM) – 52% binding
19F-NMR – not convincing
Sol/agg good to 100 uM

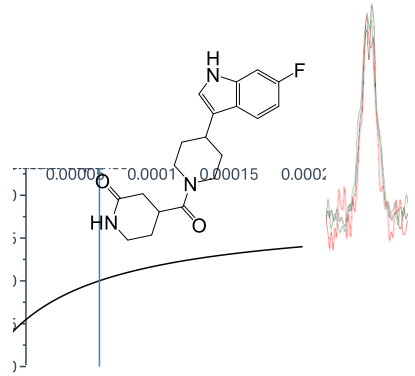






CACHE_HO_1193_6
KD LRRK2 66µM – 47% binding
19F-NMR – not confirmed
Solub / agg. Good to 200 µM





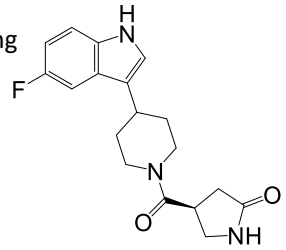
Parent cmpd crystallized in unexpected side-pocket. 25 compounds submitted in round 2. Four analogs show dose-response binding by SPR.

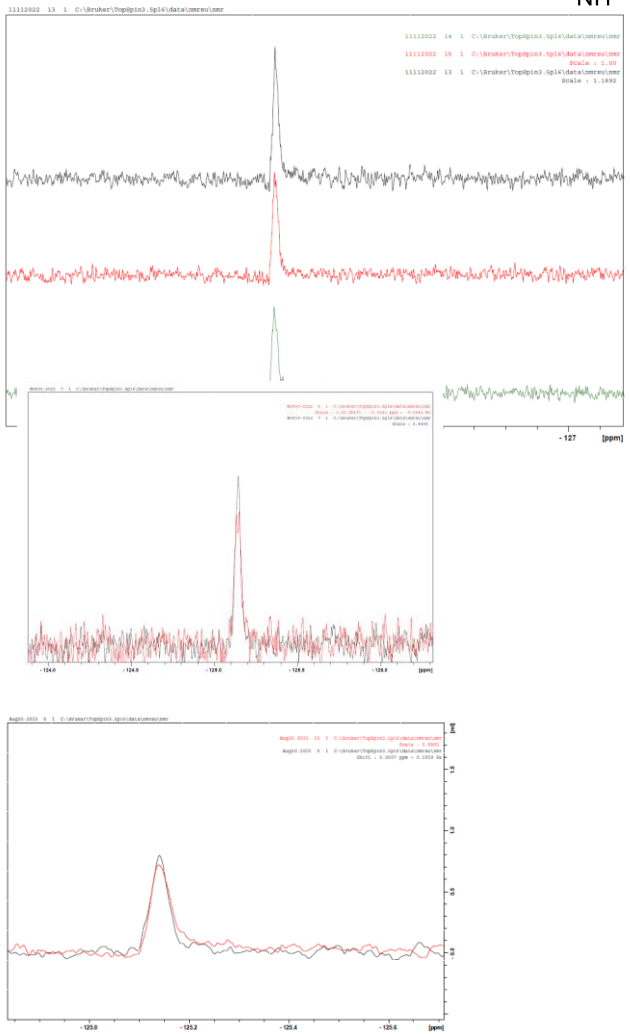
One analog seems to confirm by 19F-NMR ; agg and sol. Compromised at 200 uM.

Aggregation/solubility measured by DLS

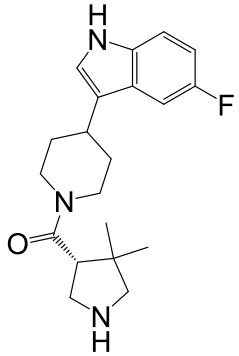
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1193_1	1061	899	570	100	100	100
CACHE-HO_1193_10	1307	582	1156	100	100	100
CACHE-HO_1193_13	1067	1651	702	100	100	100
CACHE-HO_1193_17	1349	745	1170	100	100	100
CACHE-HO_1193_18	4399	844	1048	70	100	100
CACHE-HO_1193_20	788	609	805	100	100	100
CACHE-HO_1193_21	5156	1614	1690	65	100	100
CACHE-HO_1193_25	1407	2855	1504	100	100	100
CACHE-HO_1193_3	804	1018	691	100	100	100
CACHE-HO_1193_4	705	1071	782	100	100	100
CACHE-HO_1193_40	10682	33197	19871	NA	15	55
CACHE-HO_1193_44	4569	1406	1063	75	100	100
CACHE-HO_1193_6	1398	1622	1678	100	100	100
CACHE-HO_1193_7	1407	901	843	100	100	100
CACHE-HO_1193_9	524	448	921	100	100	100

CACHE_1193_8
SPR LRRK2 97µM – 84% binding
SPR NSD2 – NA – 37% binding
19F – binding not confirmed

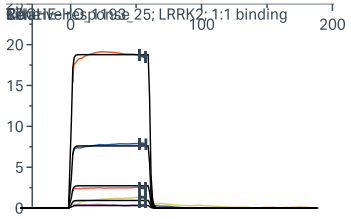


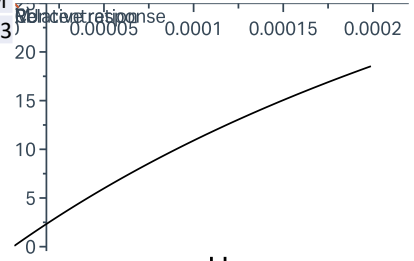


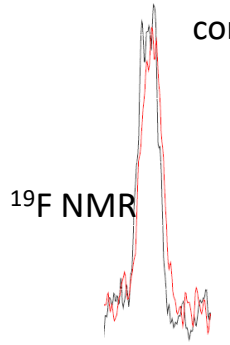
CACHE_HO_1193_25
KD LRRK2 >200 uM (500µM) – 63% binding
DSF – appears to confirm binding
19F-NMR – binding not confirmed
Solub / agg. Good to 200 µM



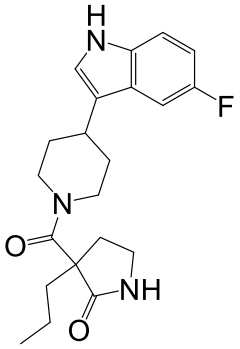
Compound Name	ΔTm		
		200µM	100µM
CACHE-HO_1193_25		1.7	1.3

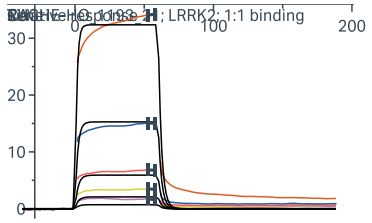


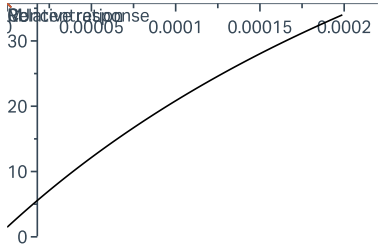


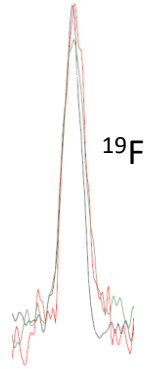


CACHE_HO_1193_21
KD LRRK2 >200uM (436µM) – 100% binding
19F-NMR – binding not confirmed
Sol good to 100 uM, Agg. Good to 200 µM









Same series as CACHE_1193_26

7 analogs submitted in round 2.

Two analogs shows dose-response binding but affinities are > 200 uM.

19F-NMR does not confirm binding.

DSF appears to show binding. There is no concentration dependence of binding.

Aggregation/solubility measured by DLS

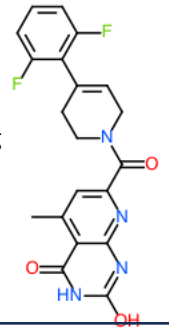
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1193_21	5156	1614	1690	65	100	100
CACHE-HO_1193_25	1407	2855	1504	100	100	100

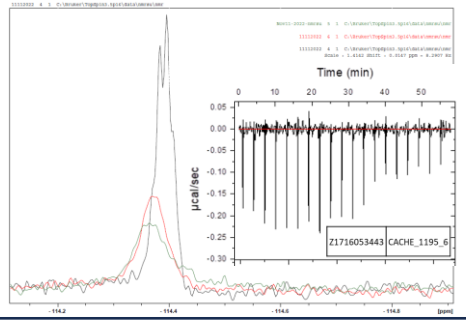
CACHE 1 – LRRK2_WDR

Participant 1195

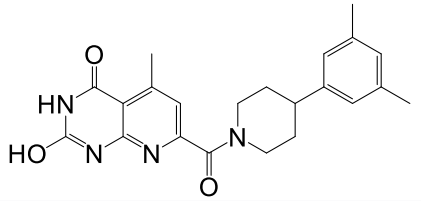
PARENT MOLECULES

CACHE_1195_6
KD LRRK2 117µM – 100% binding
KD NSD2 – NA – 25% binding
ITC: ??; **19F NMR: binds**
100% solub / no agg. at 200 µM



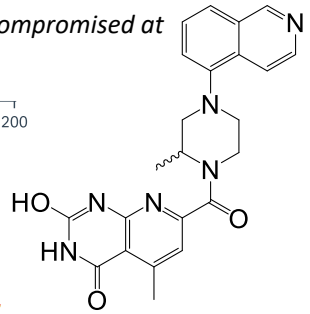


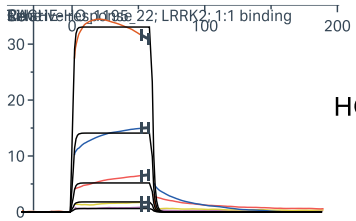
CACHE_1195_32
KD LRRK2 113 uM – 64% binding
NSD2: linear
100% solb / sign of aggreg at 100 µM

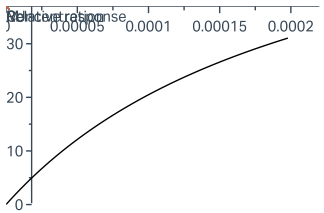


7 analogs submitted in round 2.
Parent molecule resupply confirmed by NMR
3 analogs confirm by dose-response SPR; 1 appears to confirm by DSF

CACHE-HO_1195_22
KD 220uM - 88 % binding
DSF – does not confirm
Sol/agg ok up to 100 uM; *compromised at 200 uM*

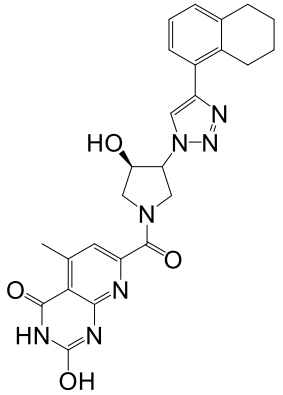


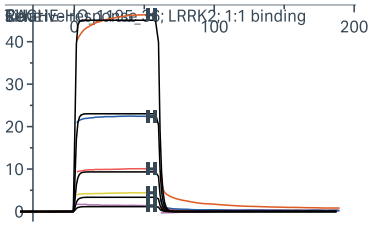


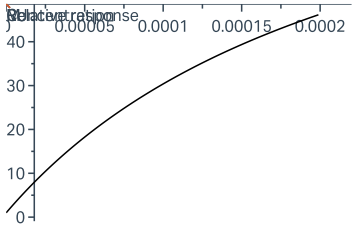


CACHE_HO_1195_36
KD LRRK2 240µM – 100% binding
DSF – 1.3 at 200 uM
Solub / agg. Good to 200 µM

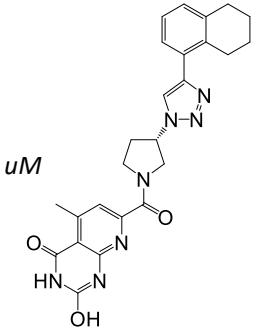
Compound Name	ΔTm		
		200µM	100µM
CACHE-HO_1195_36		1.3	0.3

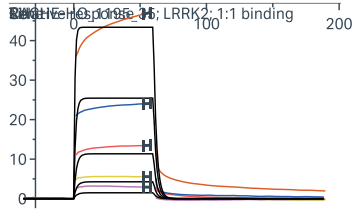


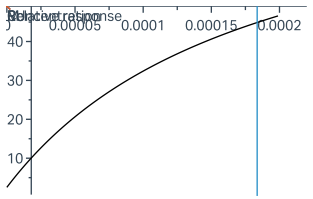




CACHE_HO_1195_35
KD LRRK2 180µM – 103% binding
DSF – does not confirm
Sol/agg good to 100 uM; *compromised at 200 uM*





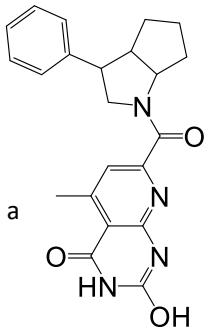


Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1195_22	2275	963	506	60	100	100
CACHE-HO_1195_35	4169	1440	727	68	100	100
CACHE-HO_1195_36	1083	920	1140	100	100	100

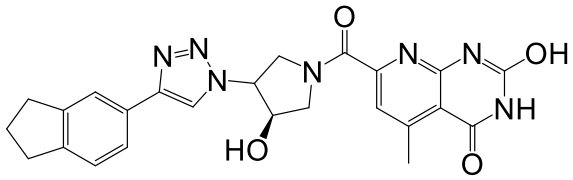
CACHE_1195_43

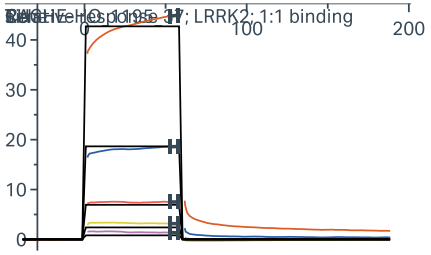
KD LRRK2 141 µM – 48% binding
KD NSD2 linear, 63% binding
Sol ok at 500 uM but aggregation is a problem (15K counts/s in duplicate samples)

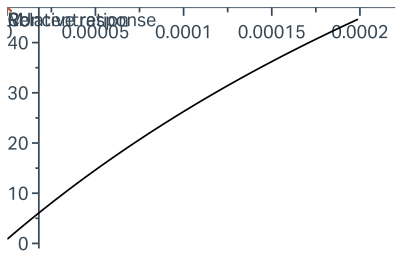


Same series as CACHE_1195_6
11 analogs submitted in round 2.
Two have dose-response binding by SPR.
One confirms by 19F NMR

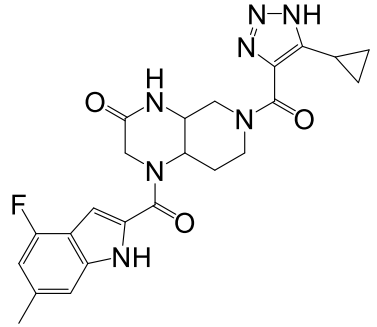
CACHE_HO_1195_37
KD LRRK2 54µM – 98% binding
Sol good to 200 uM; *agg may be compromised from as low as 50 uM*
DSF – did not confirm

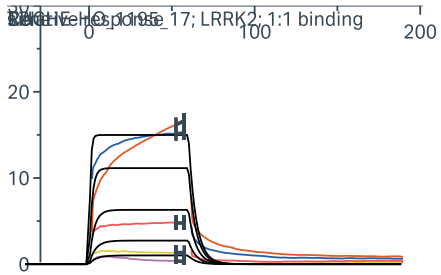


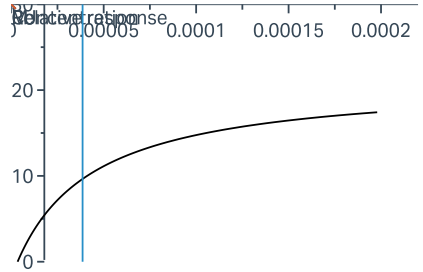




CACHE_HO_1195_17
KD LRRK2 39µM – 34% binding
19F-NMR – confirms binding
Solub / agg. Good to 200 µM

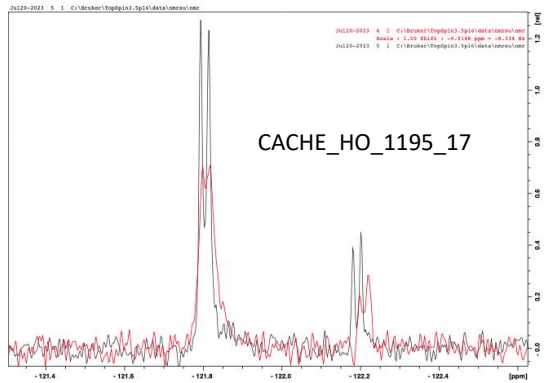




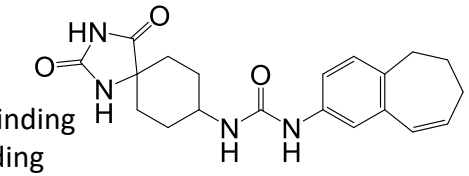


Aggregation/solubility measured by DLS

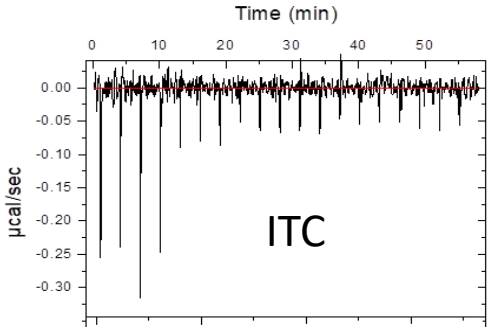
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1195_17	986	965	936	100	100	100
CACHE-HO_1195_37	1882	1439	1425	100	100	100



PARENT MOLECULE

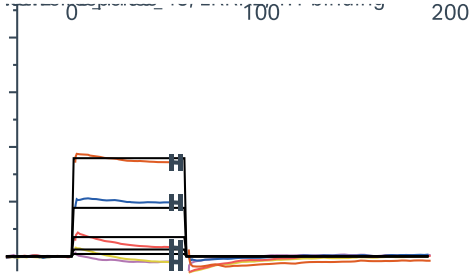


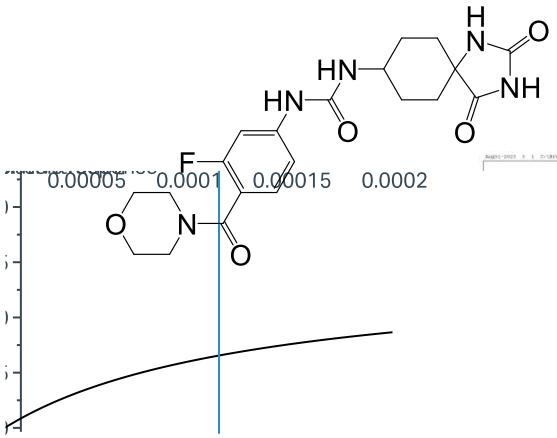
CACHE_1195_60
KD LRRK2 44µM – 48% binding
KD NSD2 – NA – 46% binding
ITC: seems to bind
Poor solubility and aggregation at 500 uM (which was used for ITC)

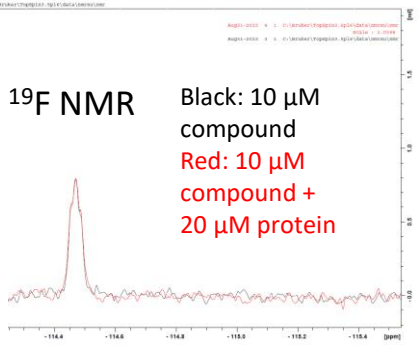


3 analogs submitted in round 2.
2 analogs confirm by dose-response SPR.
One tested and does not confirm by 19F-NMR.

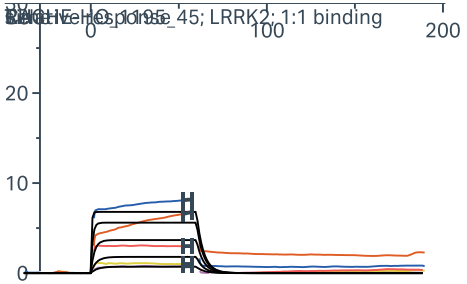
CACHE-HO_1195_43
SPR 110 uM – 28% binding
19F-NMR – does not confirm
Sol/agg ok to 200 uM

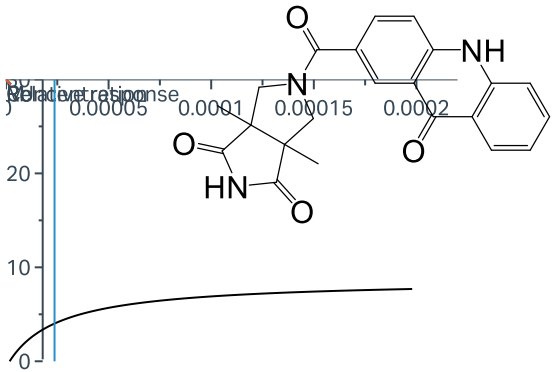






CACHE-HO_1195_45
SPR 24 uM – 25% binding
Sol/agg good at 100 uM*; trend is strange*





Aggregation/solubility measured by DLS

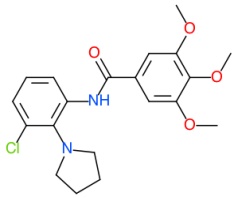
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1195_43	1140	1105	566	100	100	100
CACHE-HO_1195_45	1658	910	12881	63	100	100

CACHE 1 – LRRK2_WDR

Participant 1200

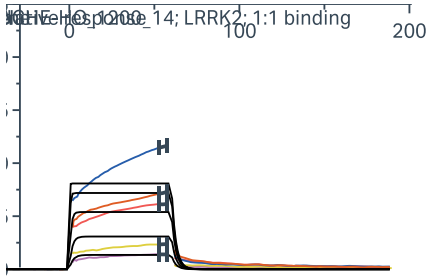
PARENT MOLECULE

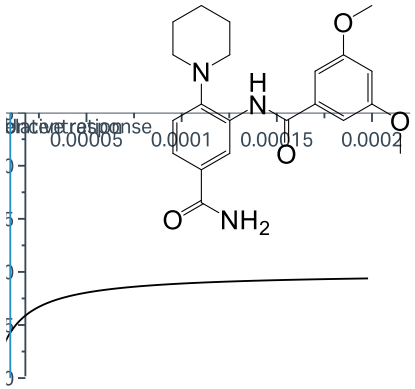
CACHE_1200_39
KD LRRK2 101µM – 83% binding
KD NSD2 – NA – 19% binding
DSF does not confirm binding
100% solub /no agg. at 200 µM



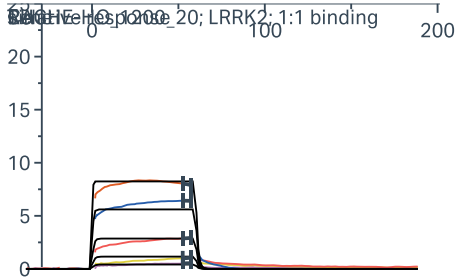
36 analogs submitted in round 2.
Three analogs show dose-response binding in SPR.
Non confirms in orthogonal method.

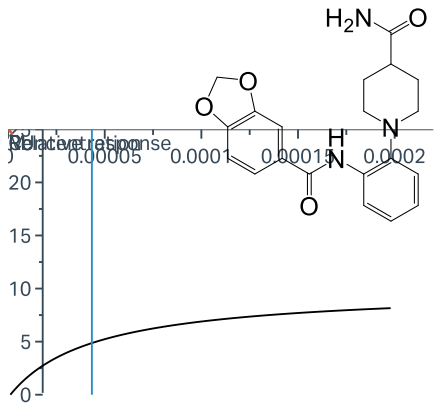
CACHE_HO_1200_14
KD LRRK2 10µM – 27% binding
solub / agg. Good to 200 µM
DSF does not confirm binding



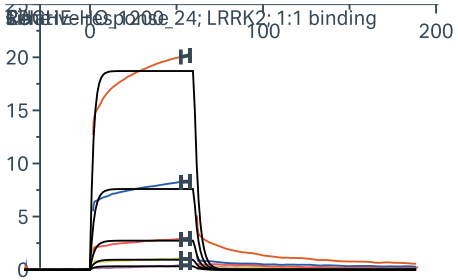


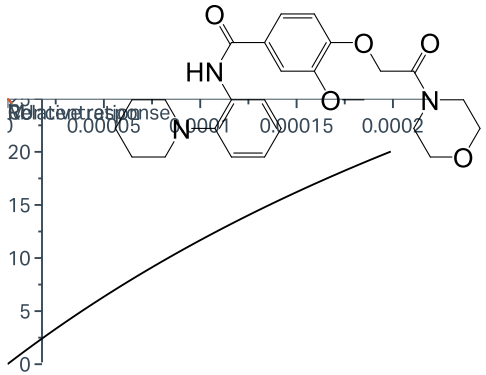
CACHE_HO_1200_20
KD LRRK2 43µM – 20% binding
ITC – did not confirm
DSF does not confirm binding
Solub / agg. Good to 200 µM



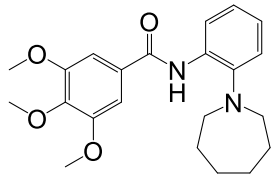


CACHE_HO_1200_24
KD LRRK2 >200uM (520µM) – 52% binding
solub / agg. Good to 200 µM





CACHE_HO_1200_9
KD LRRK2 120µM – 14% binding
solub / agg. Good to 200 µM



Aggregation/solubility measured by DLS

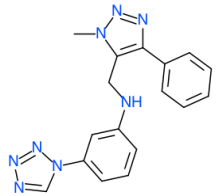
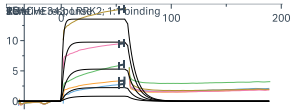
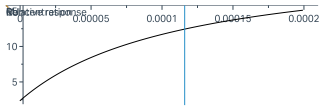
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1200_14	1982	1277	973	100	100	100
CACHE-HO_1200_20	1587	953	595	100	100	100
CACHE-HO_1200_24	1260	469	1683	100	100	100
CACHE-HO_1200_9	657	1490	1507	100	100	100

CACHE 1 – LRRK2_WDR

Participant 1201

PARENT MOLECULE

CACHE_1201_96
KD LRRK2 116µM – 44% binding
KD NSD2 – NA – 44% binding
100% solub / no agg. at 200 µM

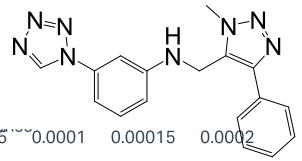
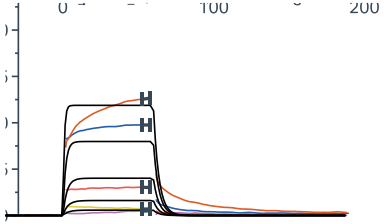
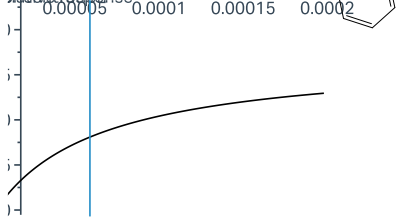




37 analogs sent in round 2; 5 compounds have measurable KDs.
DSF: weak stabilization by one analog

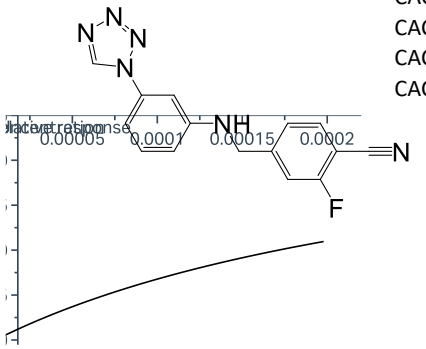
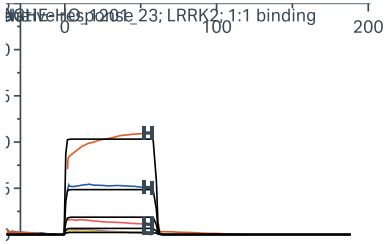
Aggregation/solubility measured by DLS

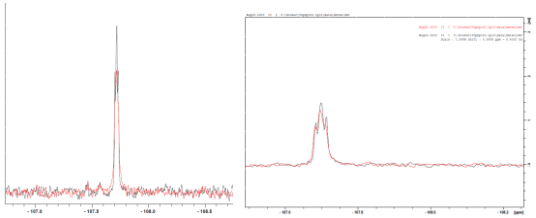
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1201_1	424	810	767	100	100	100
CACHE-HO_1201_18	2340	3364	987	78	100	100
CACHE-HO_1201_23	639	1373	773	100	100	100
CACHE-HO_1201_35	1120	663	1545	100	100	100
CACHE-HO_1201_36	1209	1432	1266	90	95	100

CACHE_HO_1201_1
KD LRRK2 59µM – 48% binding
ITC – does not confirm
DSF does not confirm
solub / agg. Good to 200 µM

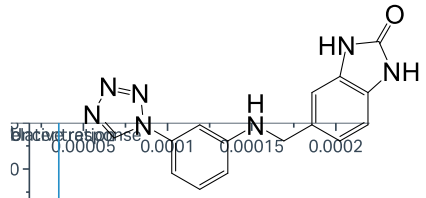
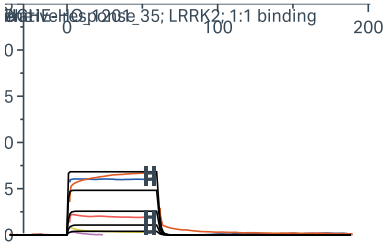
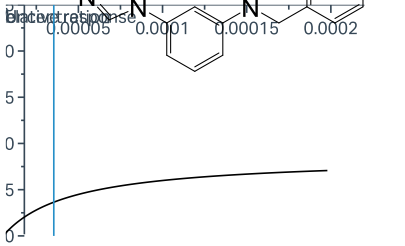




CACHE_HO_1201_23
KD LRRK2 290µM – 46% binding
solub / agg. Ok to 200 µM
19F-NMR – does not confirm (ran twice)

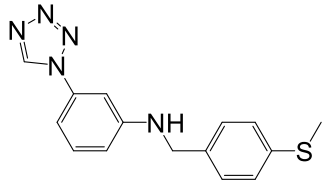
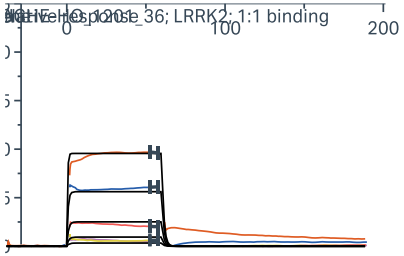
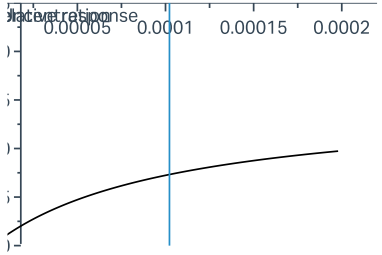





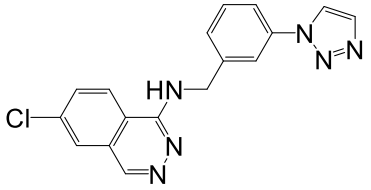
CACHE_HO_1201_35
KD LRRK2 35µM – 25% binding
Solub / agg. Good to 200 µM

CACHE_HO_1201_36
KD LRRK2 100µM – 36% binding
Solub up to 200 uM ok / agg. Good to 200 µM
DSF: 0.7C;0.6C at 100;200uM

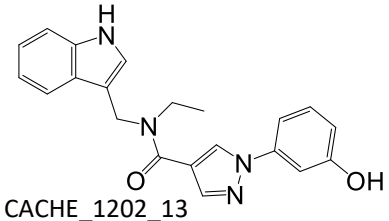
CACHE_HO_1201_18
KD LRRK2 >200uM (335µM) – 125% binding
Sol good to 100 uM; aggregation compromised at 100 and 200 uM
DSF – does not confirm

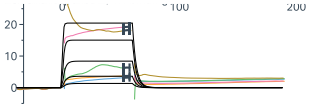


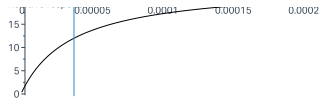
CACHE 1 – LRRK2_WDR

Participant 1202

PARENT MOLECULES

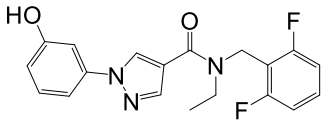


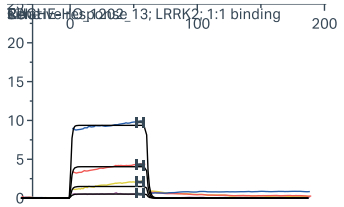


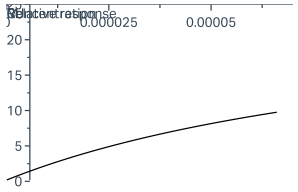


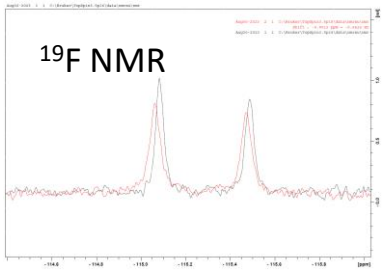
CACHE_1202_13
SPR LRRK2 37uM – 46% binding
SPR NSD2 – 149% binding

CACHE_HO_1202_13/DR002553a
SPR LRRK2 111uM – 30% binding
19F-NMR – confirms binding
Sol compromised at 200 uM; agg has a strange trend









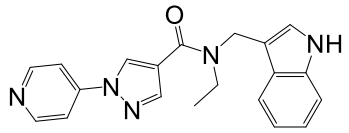
Black: 10 µM compound
Red: 10 µM compound + 20 µM protein

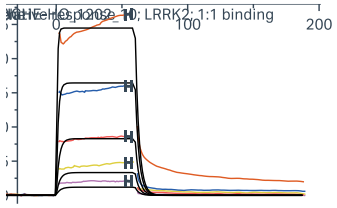
28 analogs sent in round 2;

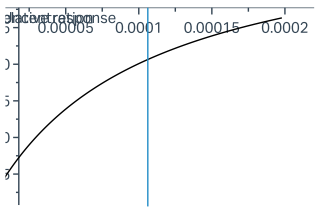
5 hits in round 2 with measurable KDs, of which three have good fit, $K_D \leq 100$ uM.

One analog shows binding by 19F-NMR and maybe one by DSF.

CACHE_HO_1202_10
SPR 106µM – 84% binding
DSF – did not confirm
Sol ok to 200 uM; agg compromised from 50 uM



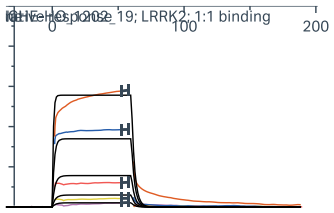


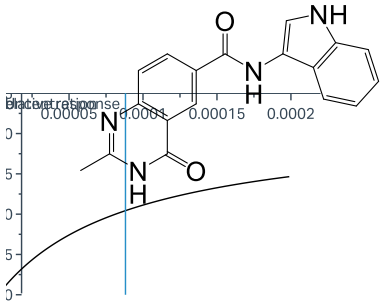


Aggregation/solubility measured by DLS

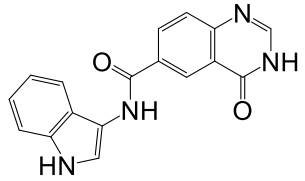
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1202_10	2886	1318	3887	100	100	100
CACHE-HO_1202_13	6338	1643	1948	65	100	100
CACHE-HO_1202_14	1154	780	914	100	100	100
CACHE-HO_1202_19	1401	857	826	68	100	100
CACHE-HO_1202_22	513	710	1156	100	100	100

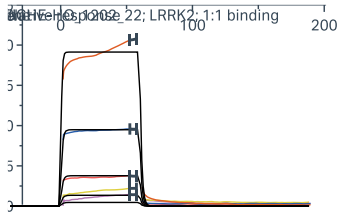
CACHE_HO_1202_19
SPR 88 µM – 50% binding
ITC, DSF – did not confirm

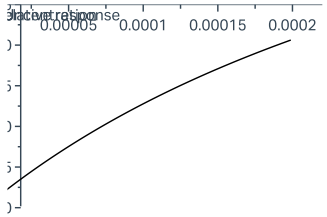




CACHE_HO_1202_22
SPR >200 uM (410 µM) – 72% binding
Sol/agg ok to 100 uM; but compromised at 200 uM

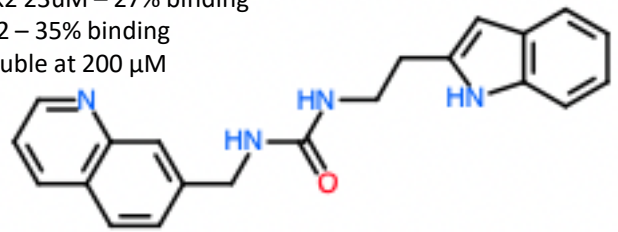


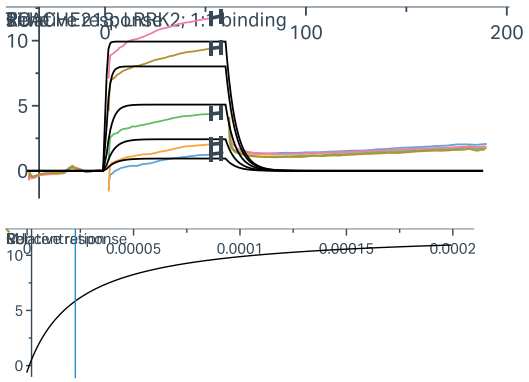




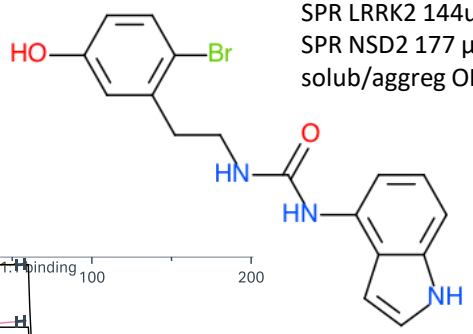
PARENT MOLECULES

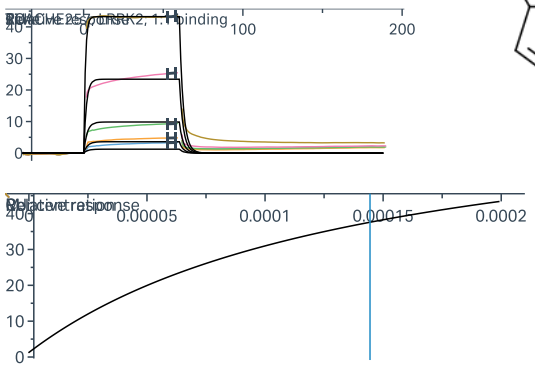
CACHE_1202_37
SPR LRRK2 23uM – 27% binding
SPR NSD2 – 35% binding
~50% soluble at 200 µM



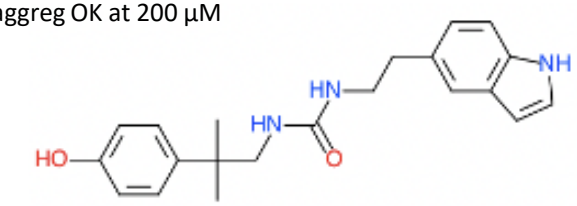


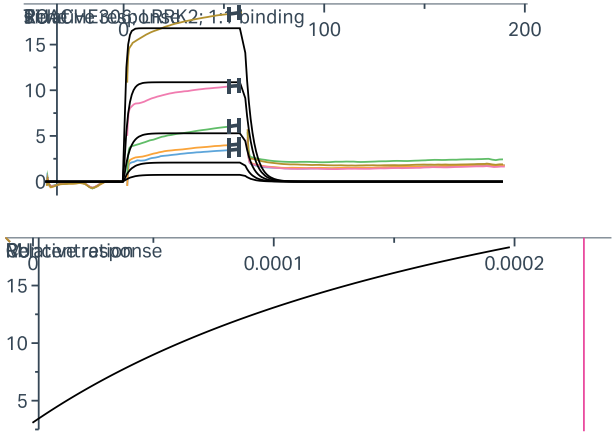
CACHE_1202_25
SPR LRRK2 144uM – 87% binding
SPR NSD2 177 µM– 163% binding
solub/aggreg OK at 200 µM





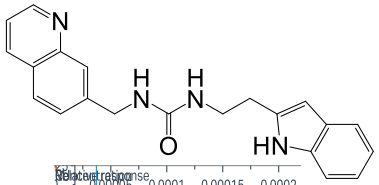
CACHE_1202_69
SPR LRRK2 >200uM – 67% binding
solub/aggreg OK at 200 µM

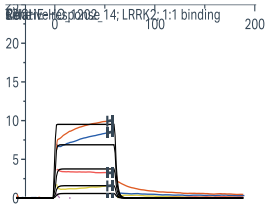


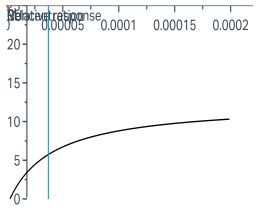


Same compound

CACHE-HO_1202_14
SPR 37 µM – 31% binding
Sol/agg ok to 200 uM
DSF: 0.7C at 100 and 200 µM



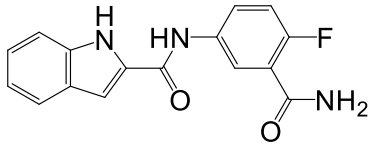




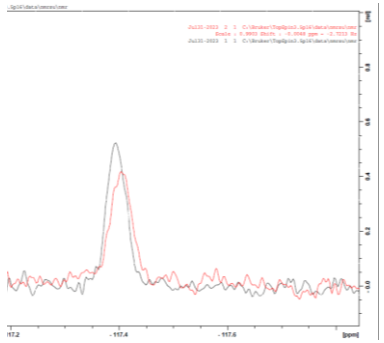
CACHE 1 – LRRK2_WDR

Participant 1205

PARENT MOLECULES



CACHE_1205_40
KD LRRK2 35µM – 53% binding
KD NSD2 – NA – 16% binding



26 analogs of CACHE_1205_93 and 18 analogs of CACHE_1205_40 were submitted in round 2.

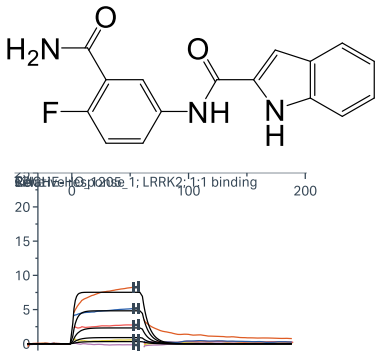
Three show dose-response binding by SPR. One appears to thermally stabilize upon binding.

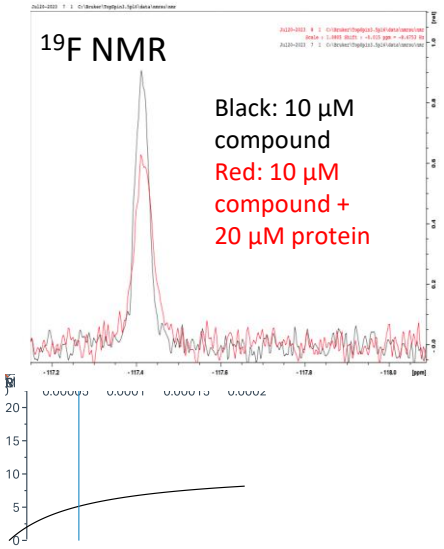
The resupplied hit (CACHE_HO_1205_1) confirms by SPR and 19F-NMR.

Aggregation/solubility measured by DLS

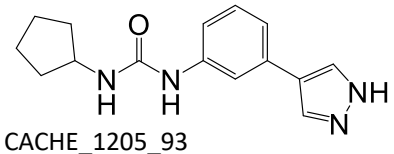
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1205_1	1227	619	1195	100	100	100
CACHE-HO_1205_14	1361	995	1564	100	100	100
CACHE-HO_1205_22	898	1583	1489	100	100	100
CACHE-HO_1205_3	632	1257	1093	100	100	100

CACHE-HO_1205_1
61 uM – 29% binding
19F-NMR – binding confirmed
Sol/agg good to 200 uM





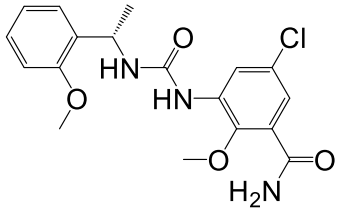
PARENT MOLECULES

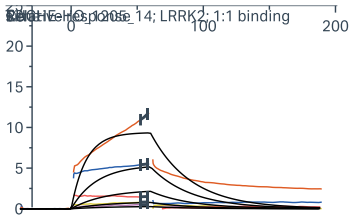


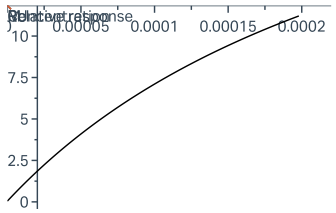
CACHE_1205_93
KD LRRK2 126µM – 72% binding
KD NSD2 – NA – 36% binding
100% solub /no agg. at 200 µM

CACHE_HO_1205_14
KD LRRK2 290µM – 33% binding
DSF: seems to weakly stabilize at 200 uM
Solub /agg. Good to 200 µM

Compound Name	ΔTm	
	200µM	100µM
CACHE-HO_1205_14	0.9	0.5







26 analogs of CACHE_1205_93 and 18 analogs of CACHE_1205_40 were submitted in round 2.

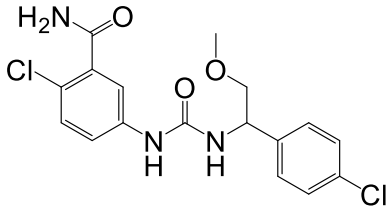
Three show dose-response binding by SPR. One appears to thermally stabilize upon binding.

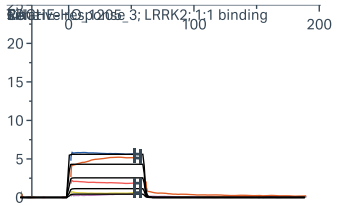
The resupplied hit (CACHE_HO_1205_1) confirms by SPR and 19F-NMR.

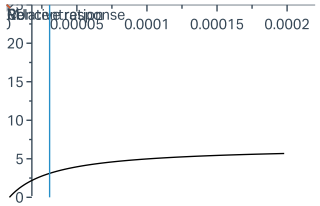
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1205_1	1227	619	1195	100	100	100
CACHE-HO_1205_14	1361	995	1564	100	100	100
CACHE-HO_1205_22	898	1583	1489	100	100	100
CACHE-HO_1205_3	632	1257	1093	100	100	100

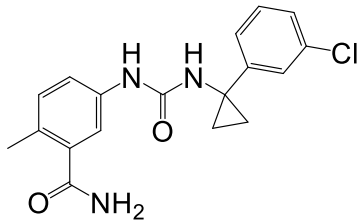
CACHE_HO_1205_3
KD LRRK2 31µM – 17% binding
ITC: did not confirm
DSF does not confirm
Solub / agg. Good to 200 µM

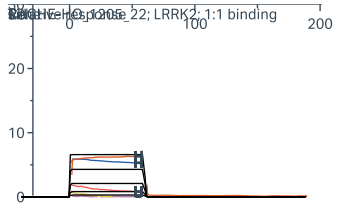


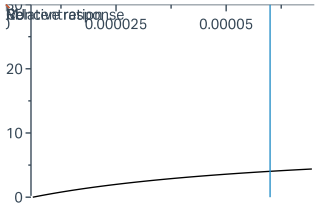




CACHE_HO_1205_22
KD LRRK2 60µM – 19% binding
Solub /agg. Good to 200 µM



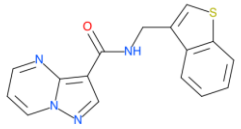




CACHE 1 – LRRK2_WDR

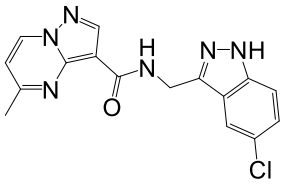
Participant 1207

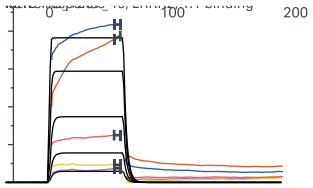
PARENT MOLECULE

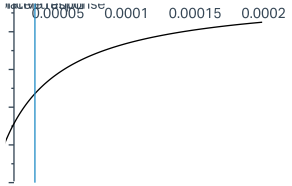


CACHE_1207_98
KD LRRK2 22µM – 51% binding
KD NSD2 – NA – 40% binding
~70% solub / agg. at 200 µM

CACHE_HO_1207_46
KD LRRK2 33µM – 63% binding
ITC – does not confirm; DSF- does not confirm
Solub good to 200 µM; agg good to 100 uM





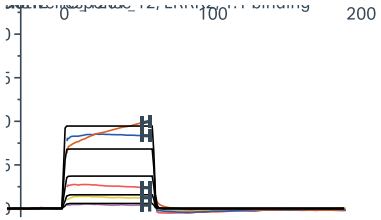


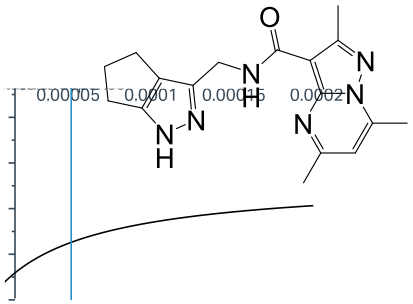
49 analogs were submitted in round 2.

4 analogs show dose-response binding by SPR.

None confirm by DSF

CACHE_HO_1207_12
KD LRRK2 52µM – 33% binding
Solub / agg. Good to 100 µM

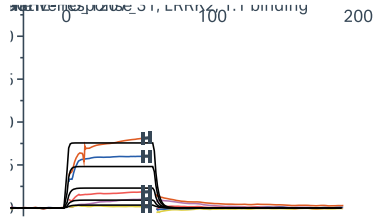


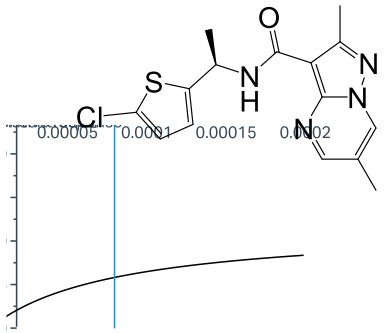


Aggregation/solubility measured by DLS

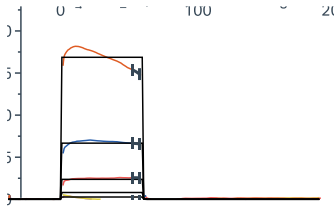
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1207_12	2111	471	604	78	100	100
CACHE-HO_1207_21	442	719	636	100	100	100
CACHE-HO_1207_31	682	1006	523	100	100	100
CACHE-HO_1207_46	3850	1202	969	100	100	100

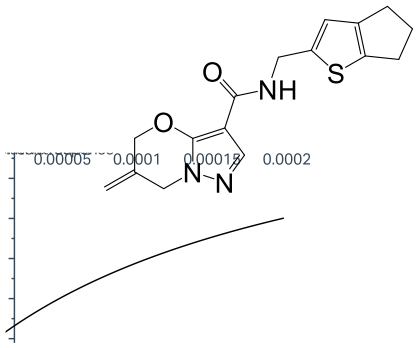
CACHE_HO_1207_31
KD LRRK2 80µM – 24% binding
DSF- did not confirm
Solub / agg. Good to 200 µM





CACHE_HO_1207_21
KD LRRK2 240µM – 57% binding
DSF – did not confirm
Solub / agg. Good to 200 µM

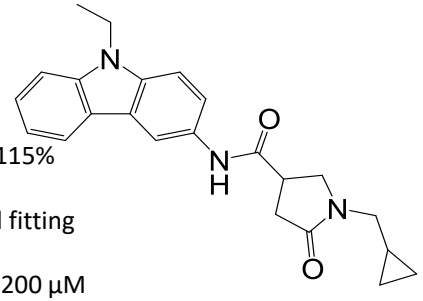




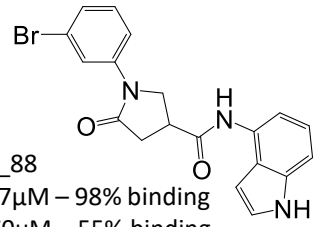
CACHE 1 – LRRK2_WDR

Participant 1208

PARENT MOLECULES



CACHE_1208_98
KD LRRK2 41µM – 115% binding
KD NSD2 – 78 – bad fitting
BLI – binds in DR
15% solub / agg. at 200 µM



CACHE_1208_88
KD LRRK2 137µM – 98% binding
KD NSD2 – 170uM – 55% binding

46 analogs submitted in round 2.

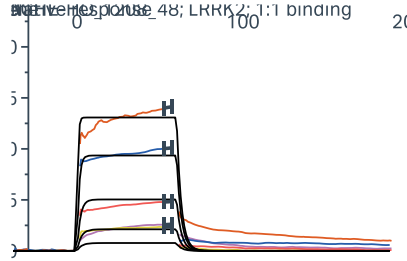
re-supply of the 2 parent molecules confirmed.

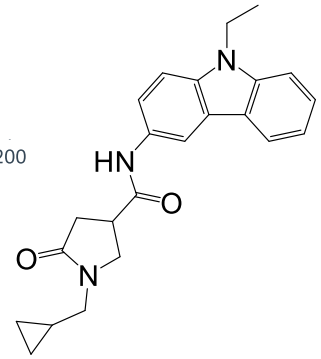
One validated by DSF. But parent binds unrelated target NSD2-PWWP1

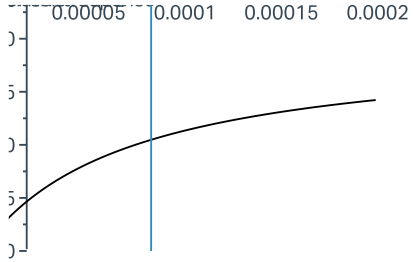
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1208_49	965	1541	726	100	100	100
CACHE-HO_1208_48	419	711	1021	100	100	100

CACHE_HO_1208_48
KD LRRK2 82µM – 43% binding
DSF does not confirm
Solub / agg. Good to 200 µM

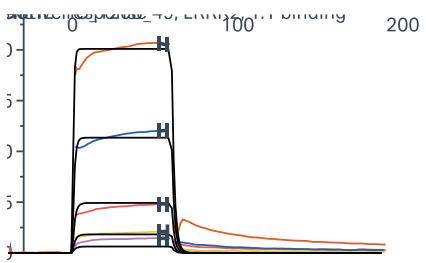


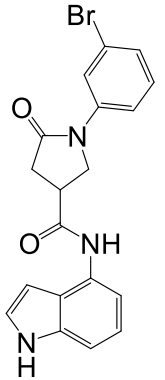


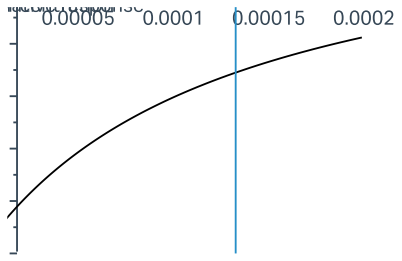


CACHE_HO_1208_49
KD LRRK2 133µM – 59% binding
DSF stabilization
Solub / agg. Good to 200 µM

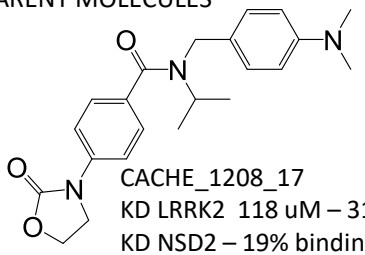
Compound Name	ΔTm	
	200µM	100µM
CACHE-HO_1208_49	2	1.7







PARENT MOLECULES



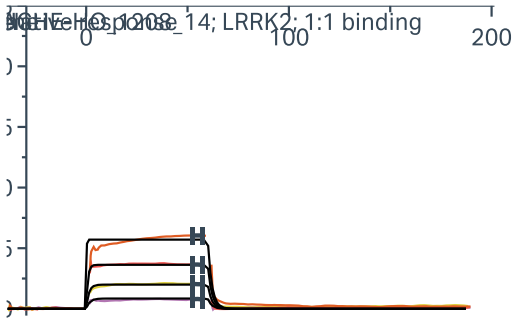
CACHE_1208_17
KD LRRK2 118 uM – 31% binding
KD NSD2 – 19% binding

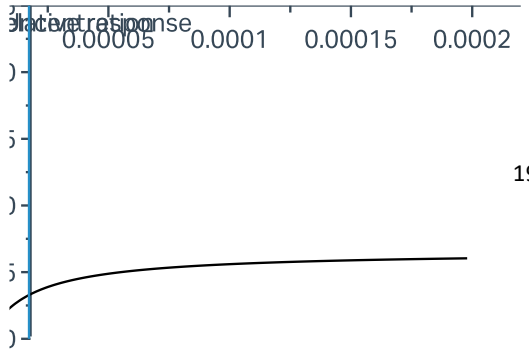
9 analogs of 1208_17 were submitted in round 2.

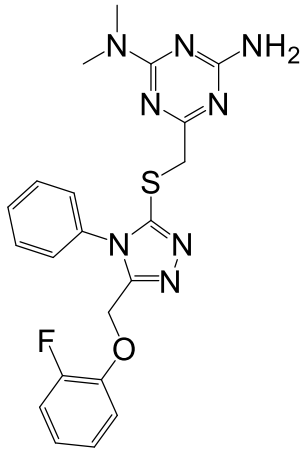
One seemingly unrelated followup shows dose-response binding by SPR (with low % binding).

It does not confirm by 19F-NMR

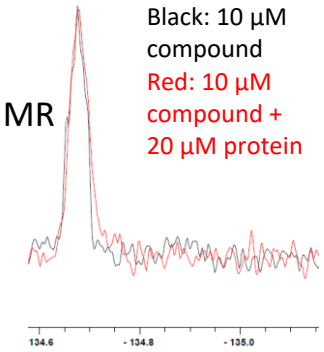
CACHE-HO_1208_14
KD LRRK2 - 17uM - 23 %
19F-NMR – does not confirm binding
Solubiility/ agg good to 200 uM







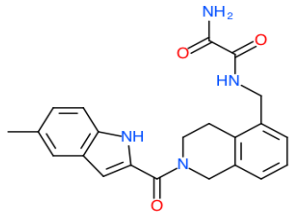
^{19}F NMR



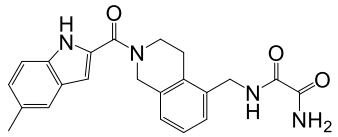
Black: 10 µM compound
Red: 10 µM compound + 20 µM protein

CACHE 1 – LRRK2_WDR

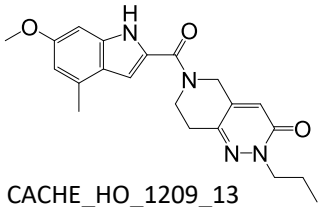
Participant 1209



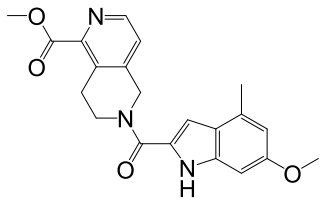
CACHE_1209_15
KD LRRK2 11µM – 37% binding
KD NSD2 – NA – 31% binding
100% solub / agg. at 200 µM



CACHE_HO_1209_41
KD LRRK2 >200uM (480µM) – 109% binding
solub / agg. OK to 200 µM
Resupply of parent molecule

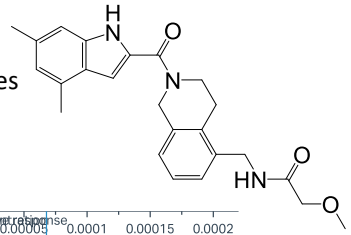


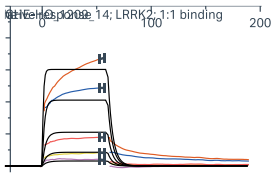
CACHE_HO_1209_13
KD LRRK2 14µM – 18% binding
Solub / agg. Ok to 200 µM

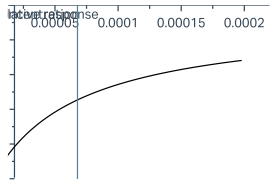


CACHE_HO_1209_22
KD LRRK2 19µM – 28% binding
Solub / agg. Ok to 200 µM

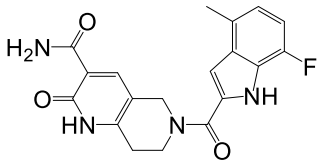
CACHE_HO_1209_14
KD LRRK2 68µM – 45% binding
DSF – does not confirm; ITC – does not confirm
Solub/agg. good to 200 µM

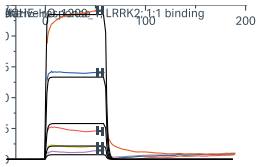


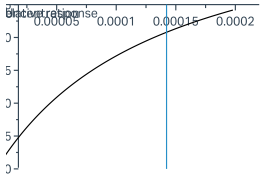




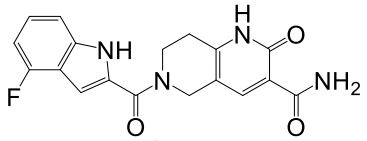
CACHE_HO_1209_1
KD LRRK2 142µM – 74% binding
DSF – 1C;1.3C at 100;200uM
Solub / agg. good to 200 µM

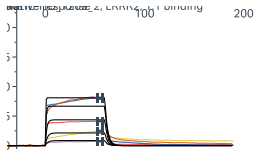


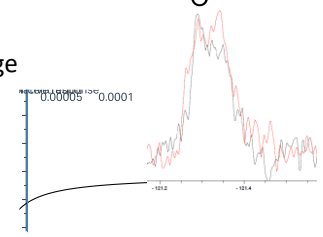


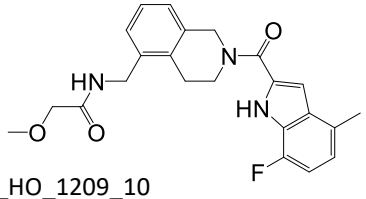


CACHE_HO_1209_2
KD LRRK2 19µM – 24% binding
19F-NMR – no binding
Solub good to 200 µM;
aggregation trend is strange



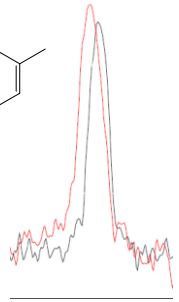




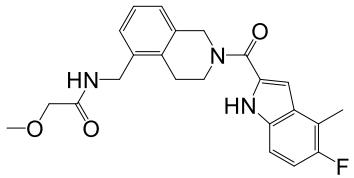


CACHE_HO_1209_10
KD LRRK2 250 – 71% binding
19F-NMR – confirms binding
Agg may be an issue. Sol is OK

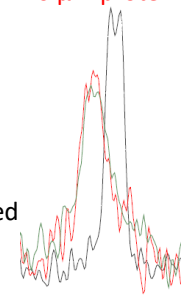
^{19}F NMR



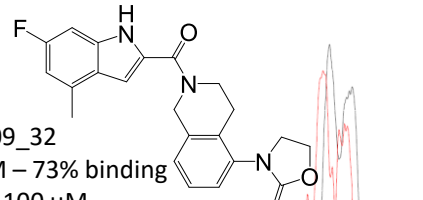
Black: 10 µM compound
Red: 10 µM compound + 20 µM protein



CACHE_HO_1209_12
KD LRRK2 110µM – 68% binding
19F-NMR – confirms binding
Sol good to 100 µM; agg compromised from 50-200 uM



^{19}F NMR



CACHE_HO_1209_32
KD LRRK2 65µM – 73% binding
Sol/agg good to 100 µM
DSF – does not confirm

Compound Name	ΔTm	
	200µM	100µM
CACHE-HO_1209_32	0.4	0.3

Black: 10 µM compound
Red: 10 µM compound + 20 µM protein

32 analogs submitted in round 2.

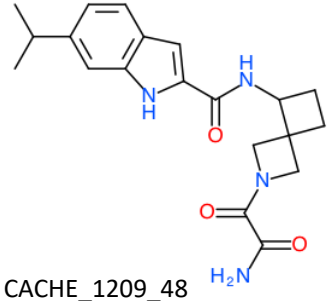
Two show orthogonal confirmation by 19F-NMR; One confirms by DSF.

There are some issues with aggregation and solubility for the hits.

Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1209_1	1144	1486	811	100	100	100
CACHE-HO_1209_10	1931	1577	1980	100	100	100
CACHE-HO_1209_12	4286	1769	1846	75	100	100
CACHE-HO_1209_13	598	917	735	100	100	100
CACHE-HO_1209_14	435	941	1241	100	100	100
CACHE-HO_1209_2	917	1781	894	100	100	100
CACHE-HO_1209_22	587	513	668	100	100	100
CACHE-HO_1209_32	1939	552	829	68	100	100
CACHE-HO_1209_41	871	725	1016	100	100	100

PARENT MOLECULEs



CACHE_1209_48
KD LRRK2 44µM – 68% binding
KD NSD2 – Linear – 53% binding
70% solub / no agg. at 200 µM

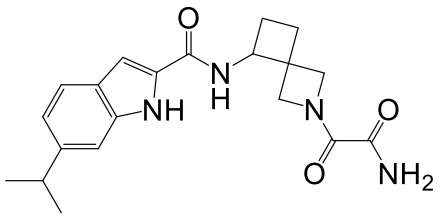
3 analogs submitted in round 2.

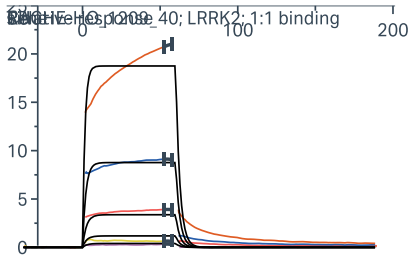
One is resupplied hit that weakly binds in dose-response in SPR.

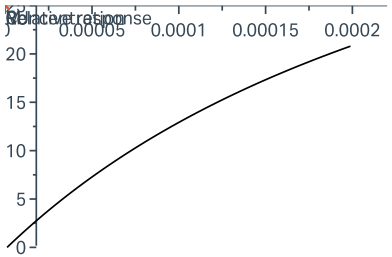
Aggregation/solubility measured by DLS

Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1209_40	1421	1188	1139	100	100	100

CACHE-HO_1209_40
SPR >200uM (310 µM) – 64% binding
Sol/agg good to 200 uM



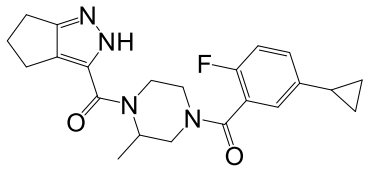




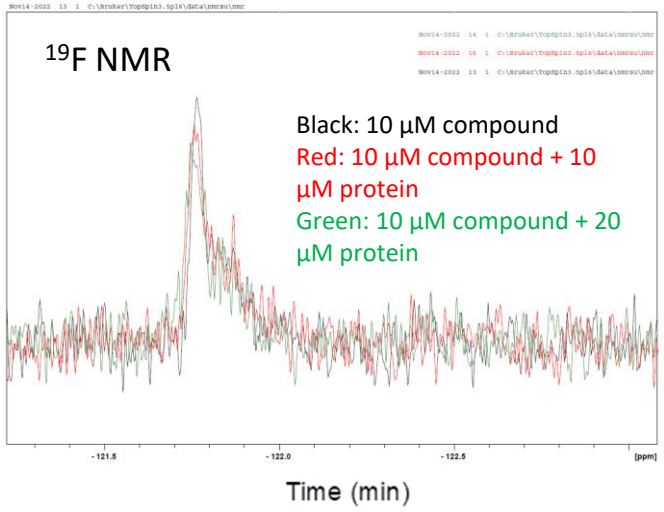
CACHE 1 – LRRK2_WDR

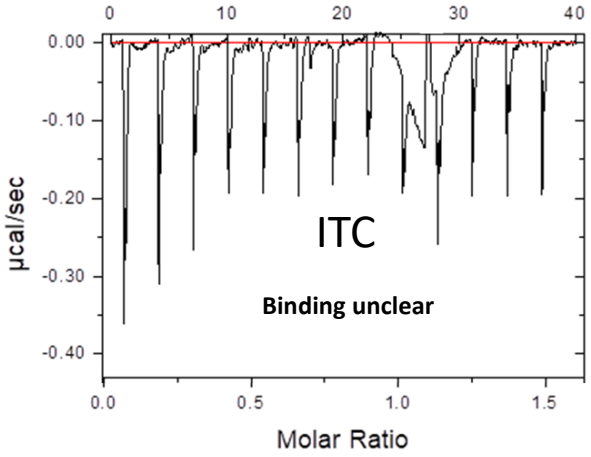
Participant 1210

PARENT MOLECULE



CACHE_1210_69
KD LRRK2 117µM – 67% binding
KD NSD2 – NA – 37% binding
19F-NMR: binds in DR
100% solub / agg. at 200 µM



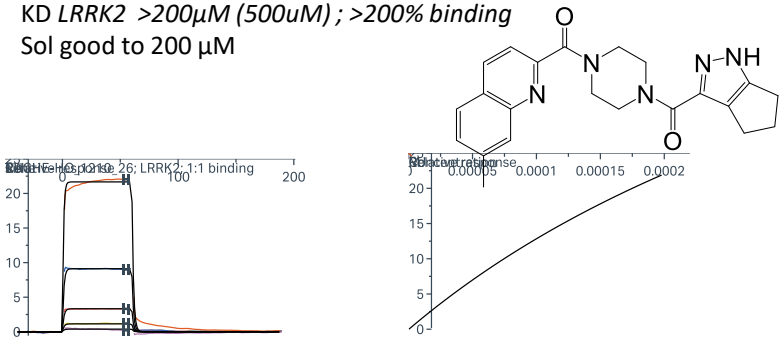


Aggregation/solubility measured by DLS

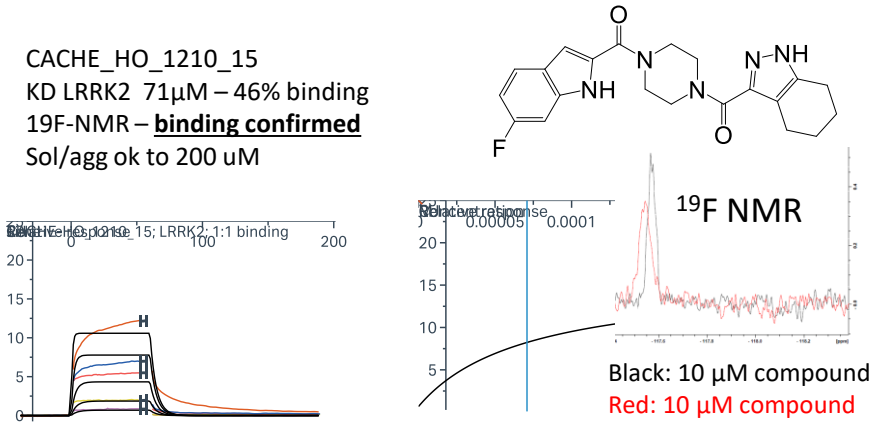
Compound Name	Normalized Intensity (kCnt/s)			Laser Power (%)		
	200µM	100µM	50µM	200µM	100µM	50µM
2% DMSO control	487	827	1595	100	100	100
CACHE-HO_1210_13	1290	1758	1142	100	100	100
CACHE-HO_1210_15	1521	1786	5537	100	100	100
CACHE-HO_1210_2	947	617	841	75	100	100
CACHE-HO_1210_26	1500	1399	1206	100	100	100

14 round-2 compounds were submitted.
Four showed dose-response binding by SPR.
Binding confirmed by 19F-NMR for one.

CACHE_HO_1210_26
KD *LRRK2 >200µM (500uM) ; >200% binding*
Sol good to 200 µM

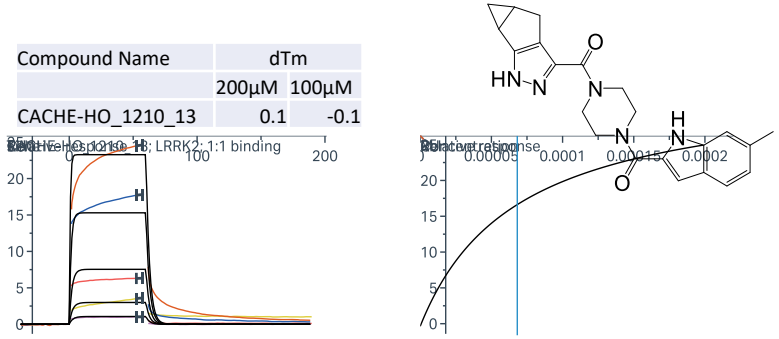


CACHE_HO_1210_15
KD LRRK2 71µM – 46% binding
19F-NMR – **binding confirmed**
Sol/agg ok to 200 uM



CACHE_HO_1210_13
KD LRRK2 68µM – 91% binding
DSF – does not confirm
Sol OK to 200 uM; agg compromised at 100 and 200 uM

Compound Name	dTm	
	200µM	100µM
CACHE-HO_1210_13	0.1	-0.1



CACHE_HO_1210_2
KD LRRK2 120µM – 78% binding
DSF – does not confirm (solubility good to 100 uM); Agg. Good to 200 µM

Compound Name	dTm	
	200µM	100µM
CACHE-HO_1210_2	0.5	0.1