Supporting Information

Discovery of 1,5-Diphenylpyrazole-3-Carboxamide Derivatives as Potent, Reversible, and Selective Monoacylglycerol Lipase (MAGL) Inhibitors

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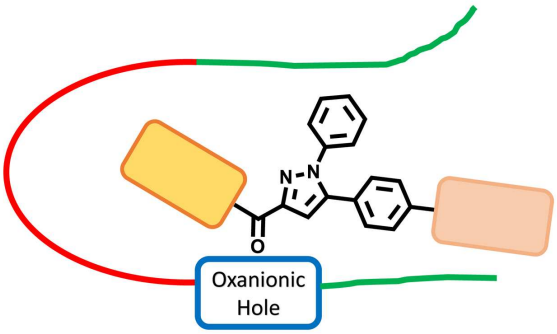

Figure S1. General binding hypothesis for the design of diphenylpyrazole MAGL inhibitors.

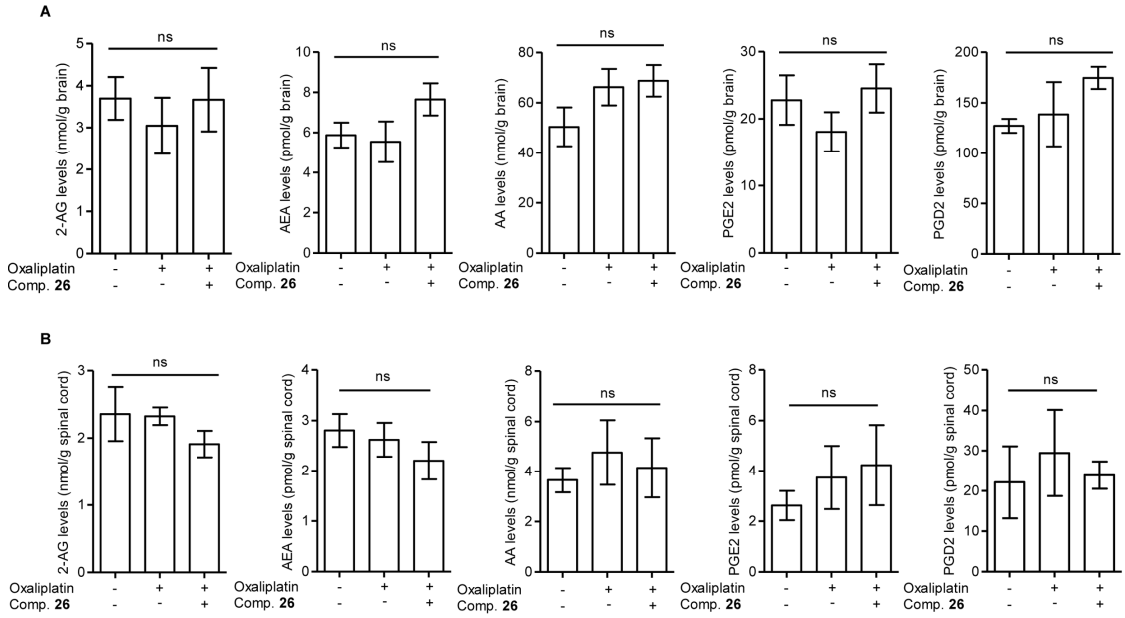

Figure S2. LC-MS/MS quantification of endocannabinoids and other metabolites. The amount of 2-AG, AEA, arachidonic acid (AA), prostaglandin-E2 (PGE2) and prostaglandin-D2 (PGD2) were measured in (A) brain and (B) spinal cord of mice treated for 14 days with oxaliplatin (2.4 mg/kg) and compound **26** (30 mg/kg, p.o.) or vehicle following the protocol described in the Methods. At day 15, animals were sacrificed by decapitation 1 h after the last dose and brain and spinal cord were collected. ns= not significant; n=5-7 mice per group.

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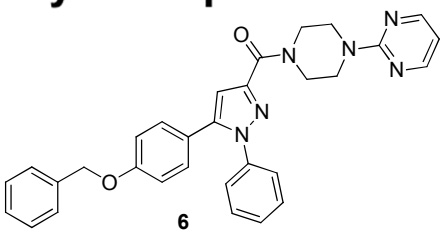
==== Shimadzu LabSolutions Analysis Report ====

Sample Name : MAGL8_125uM
Sample ID : MAGL8_125uM
Data Filename : MAGL8_125uM_p.lcd
Method Filename : MAGL254.lcm



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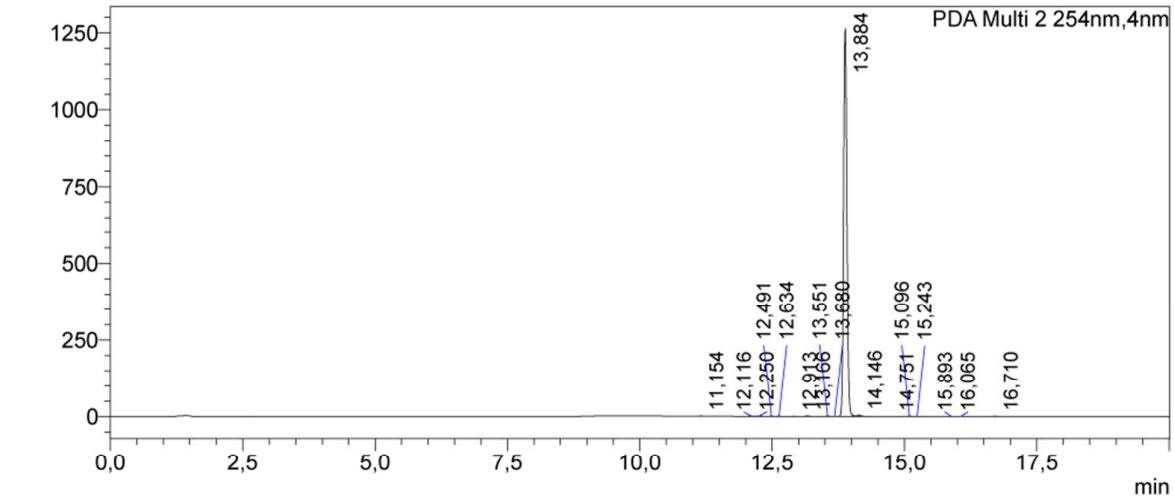

PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,154	11740	0,210	875
2	12,116	4734	0,085	871
3	12,250	2964	0,053	516
4	12,491	1334	0,024	237
5	12,634	1595	0,029	415
6	12,913	1752	0,031	396
7	13,166	8672	0,155	1958
8	13,551	4932	0,088	1253
9	13,680	1775	0,032	298
10	13,884	5503510	98,501	1263639
11	14,146	27956	0,500	4719
12	14,751	1886	0,034	353
13	15,096	4709	0,084	830
14	15,243	1318	0,024	184
15	15,893	2088	0,037	319
16	16,065	2186	0,039	342
17	16,710	4138	0,074	569
Total		5587289	100,000	1277774

Figure S1. HPLC chromatogram of compound 6.

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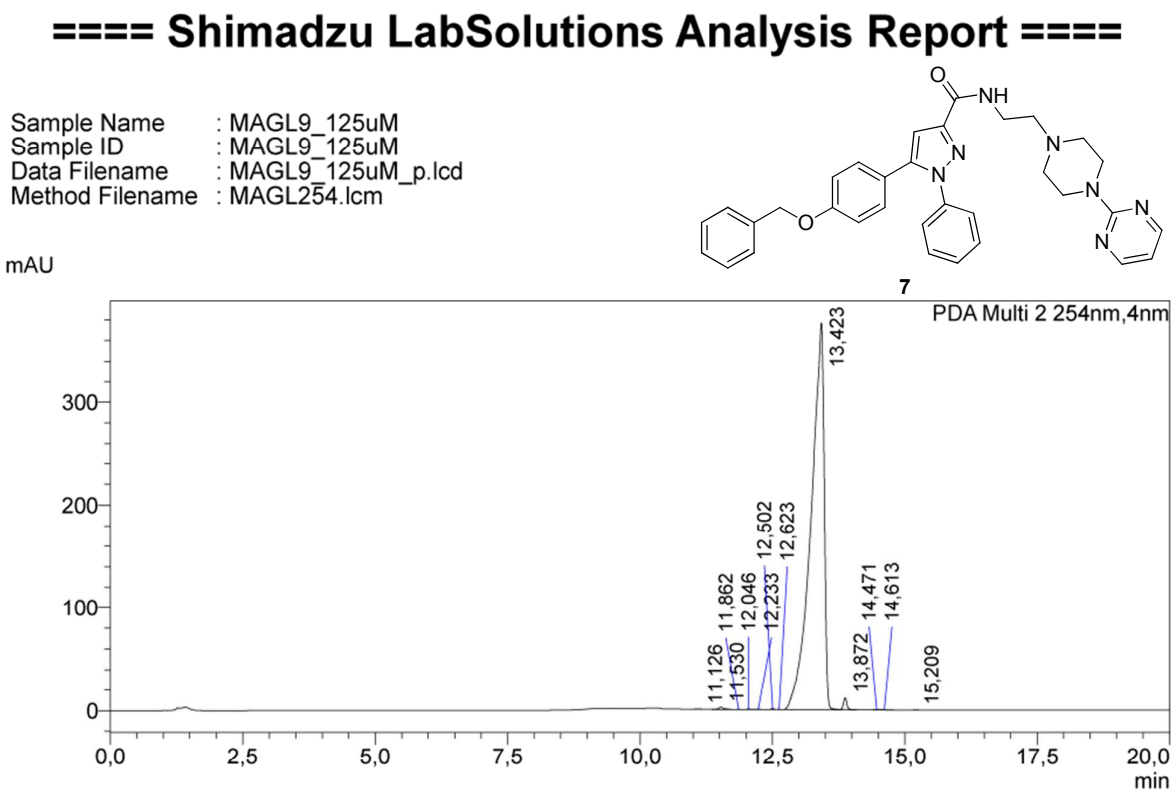
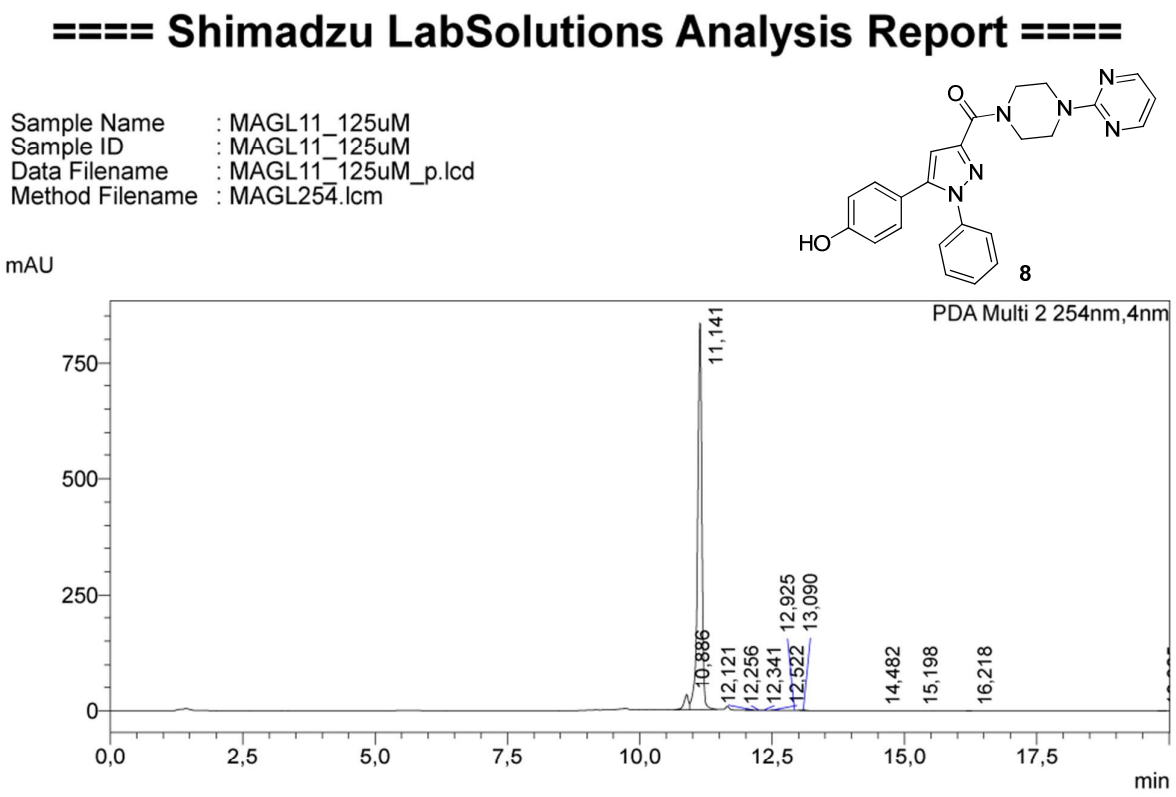


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,126	4472	0,068	278
2	11,530	18931	0,287	2204
3	11,862	1056	0,016	259
4	12,046	3773	0,057	778
5	12,233	4153	0,063	516
6	12,502	5306	0,080	1102
7	12,623	1489	0,023	363
8	13,423	6504383	98,440	376176
9	13,872	56781	0,859	11601
10	14,471	3789	0,057	386
11	14,613	2257	0,034	296
12	15,209	1090	0,017	166
Total		6607480	100,000	394125

Figure S2. HPLC chromatogram of compound 7.

8

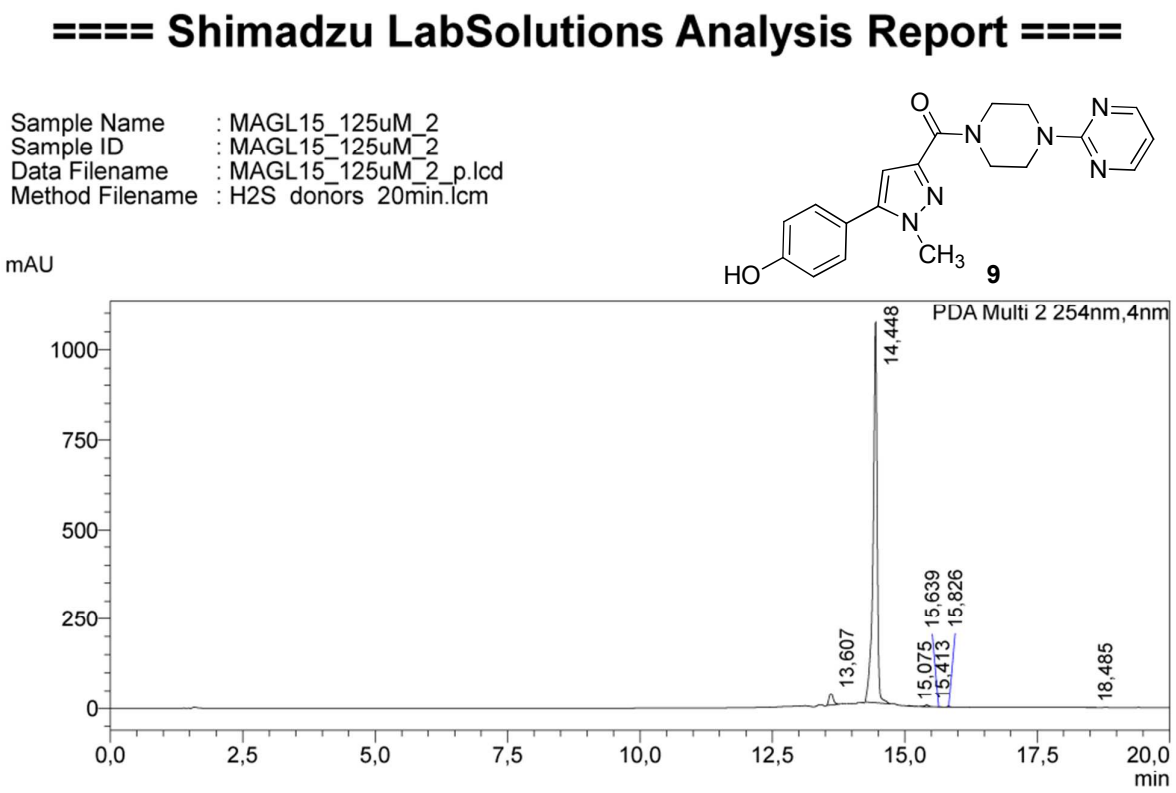


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	10,886	195409	4,053	32616
2	11,141	4585965	95,118	832702
3	12,121	11458	0,238	1325
4	12,256	1390	0,029	291
5	12,341	1362	0,028	263
6	12,522	8113	0,168	1088
7	12,925	1538	0,032	422
8	13,090	10532	0,218	1695
9	14,482	1019	0,021	140
10	15,198	1859	0,039	234
11	16,218	1117	0,023	186
12	19,865	1574	0,033	174
Total		4821336	100,000	871138

Figure S3. HPLC chromatogram of compound 8.

9



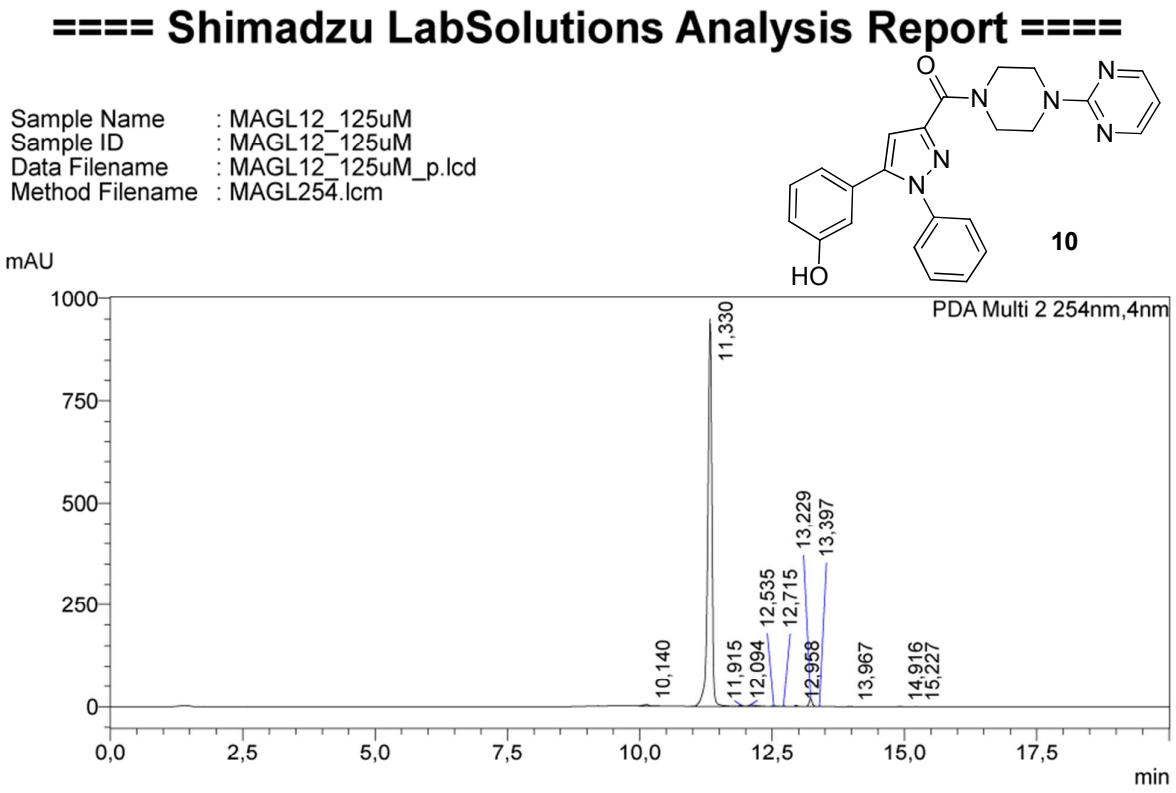
9

PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	13,607	191892	3,346	33590
2	14,448	5499559	95,908	1062172
3	15,075	5216	0,091	1328
4	15,413	26886	0,469	4932
5	15,639	1475	0,026	454
6	15,826	7801	0,136	2135
7	18,485	1382	0,024	251
Total		5734211	100,000	1104861

Figure S4. HPLC chromatogram of compound 9.

10

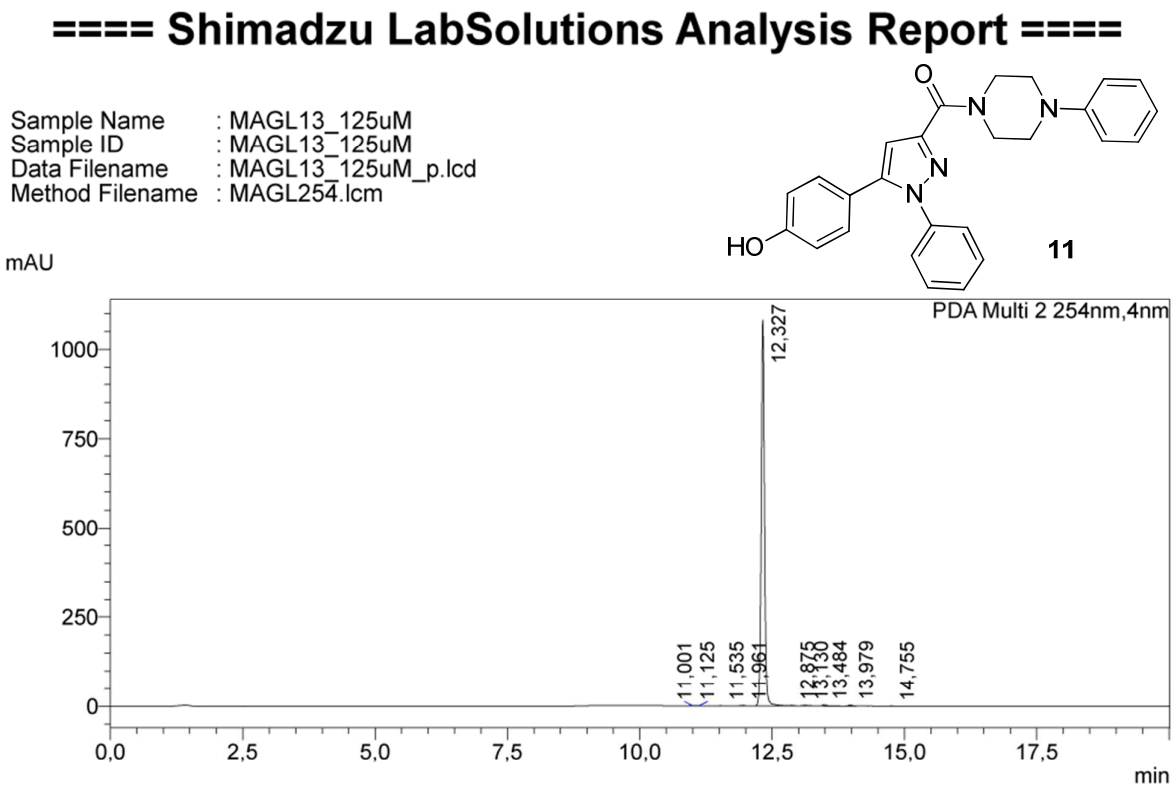


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	10,140	37872	0,729	3738
2	11,330	5001600	96,254	949195
3	11,915	10996	0,212	2745
4	12,094	30102	0,579	3518
5	12,535	7415	0,143	1316
6	12,715	4292	0,083	763
7	12,958	11792	0,227	2903
8	13,229	83647	1,610	19948
9	13,397	4125	0,079	964
10	13,967	1057	0,020	128
11	14,916	2366	0,046	391
12	15,227	1008	0,019	165
Total		5196272	100,000	985774

Figure S5. HPLC chromatogram of compound 10.

11

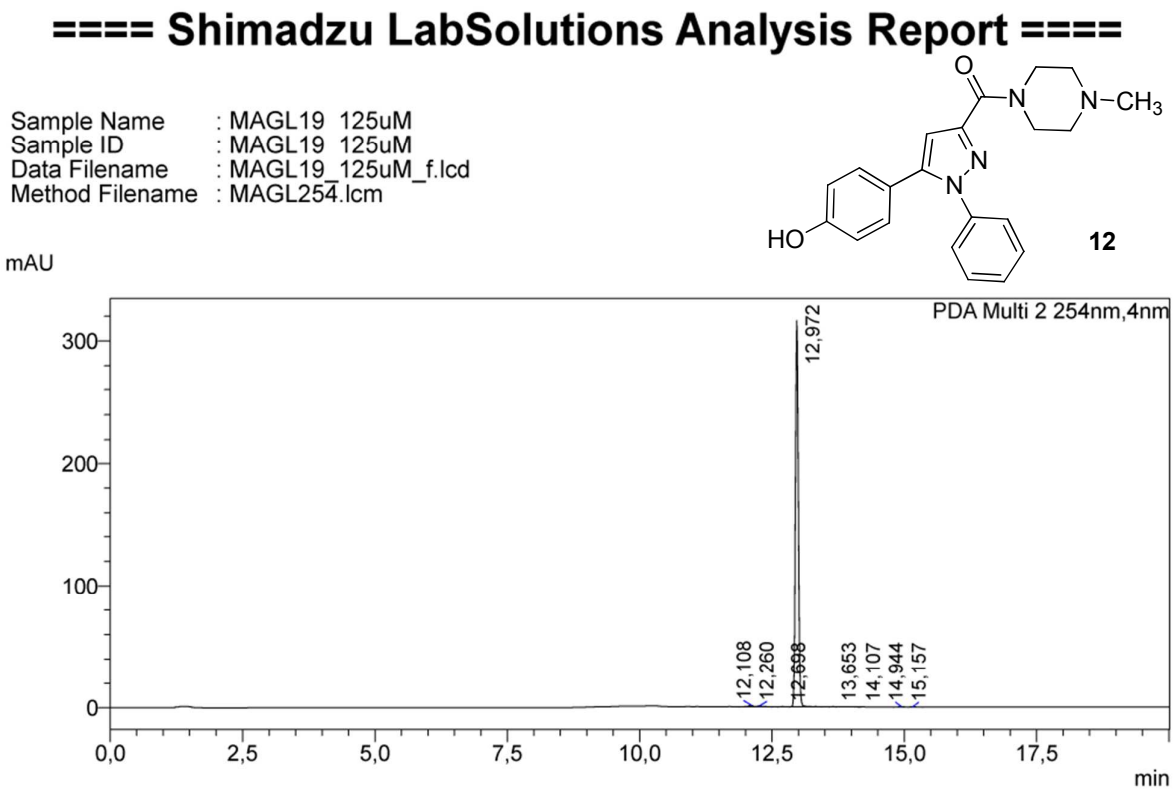


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,001	2262	0,047	285
2	11,125	1102	0,023	198
3	11,535	2124	0,044	479
4	11,961	10380	0,215	1534
5	12,327	4756501	98,600	1081489
6	12,875	2950	0,061	825
7	13,130	14415	0,299	1873
8	13,484	18488	0,383	3723
9	13,979	14259	0,296	2972
10	14,755	1563	0,032	276
Total		4824044	100,000	1093654

Figure S6. HPLC chromatogram of compound 11.

12

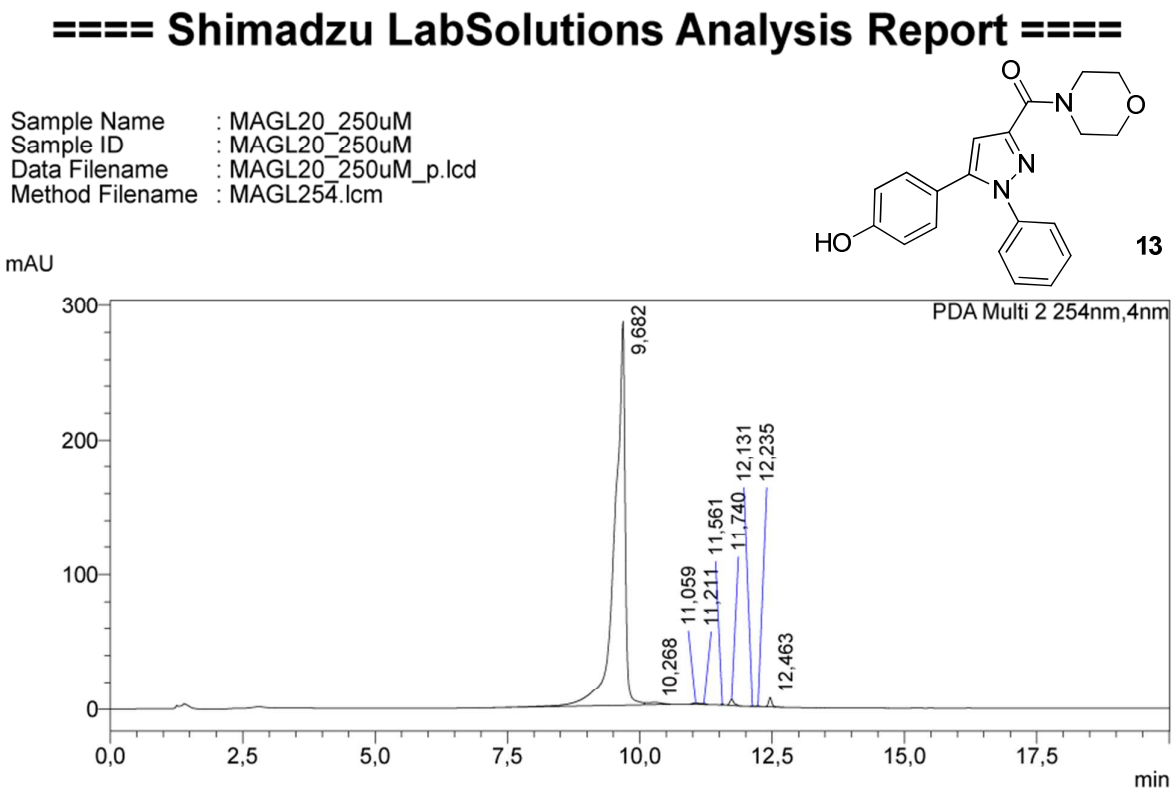


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,108	7233	0,594	1352
2	12,260	4504	0,370	638
3	12,698	1280	0,105	185
4	12,972	1200591	98,517	315906
5	13,653	1165	0,096	232
6	14,107	1191	0,098	235
7	14,944	1685	0,138	303
8	15,157	1015	0,083	156
Total		1218664	100,000	319007

Figure S7. HPLC chromatogram of compound 12.

13

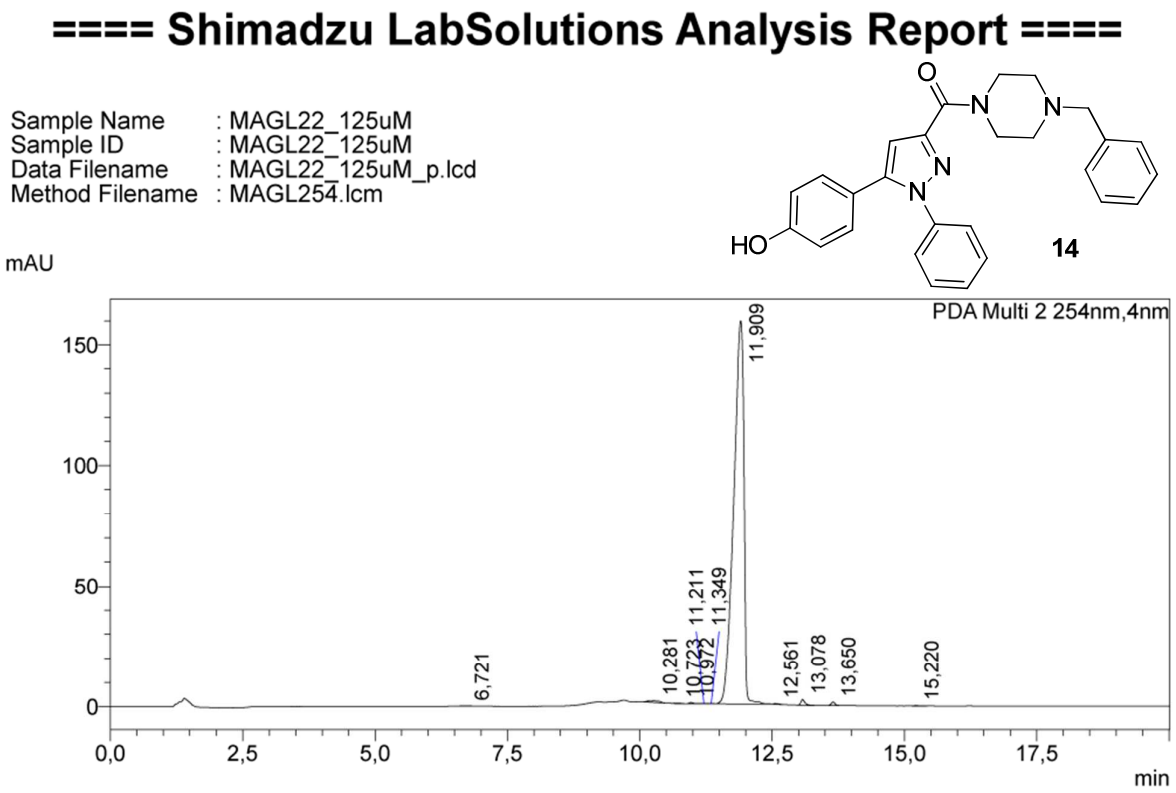


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	9,682	3897286	97,284	285267
2	10,268	31061	0,775	1544
3	11,059	10495	0,262	1180
4	11,211	4277	0,107	783
5	11,561	2706	0,068	838
6	11,740	25297	0,631	4638
7	12,131	1544	0,039	340
8	12,235	2188	0,055	413
9	12,463	31240	0,780	7040
Total		4006096	100,000	302042

Figure S8. HPLC chromatogram of compound 13.

14

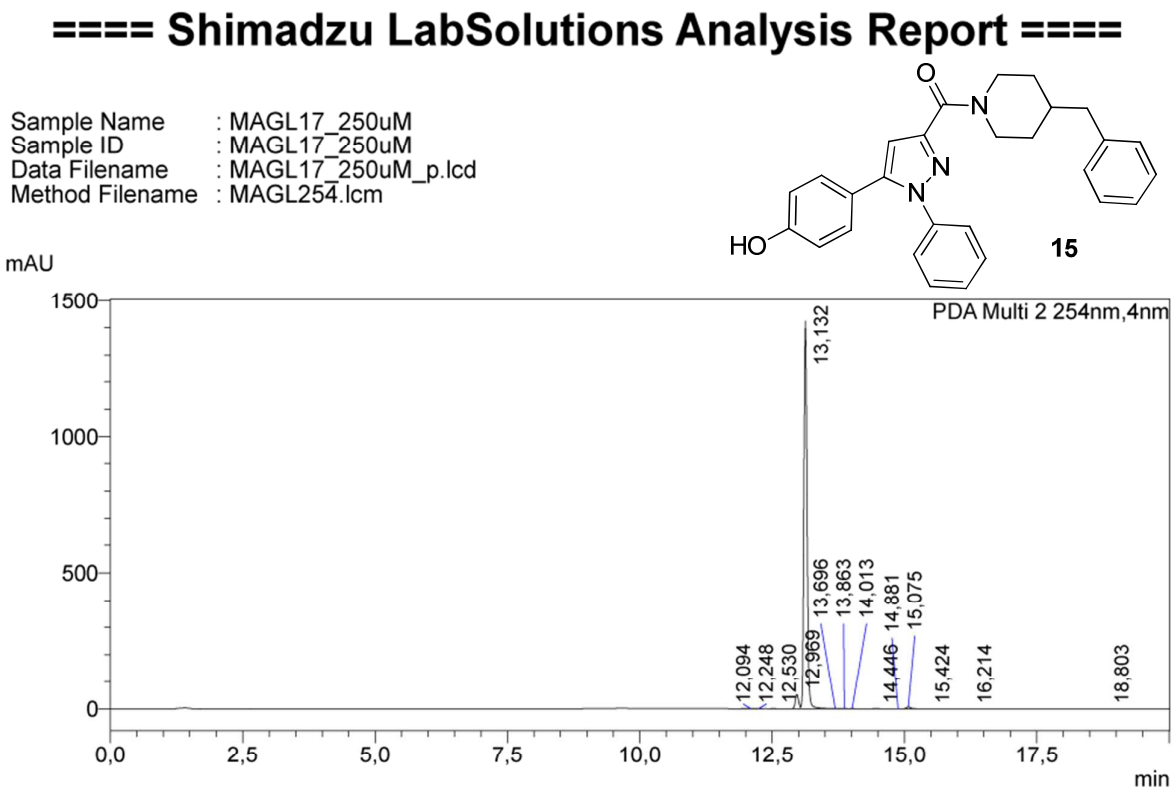


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	6,721	2822	0,131	210
2	10,281	9599	0,446	617
3	10,723	1193	0,055	166
4	10,972	3183	0,148	537
5	11,211	1285	0,060	149
6	11,349	1213	0,056	186
7	11,909	2107819	97,984	158820
8	12,561	1737	0,081	249
9	13,078	13194	0,613	2448
10	13,650	7877	0,366	1452
11	15,220	1268	0,059	176
Total		2151190	100,000	165009

Figure S9. HPLC chromatogram of compound 14.

15

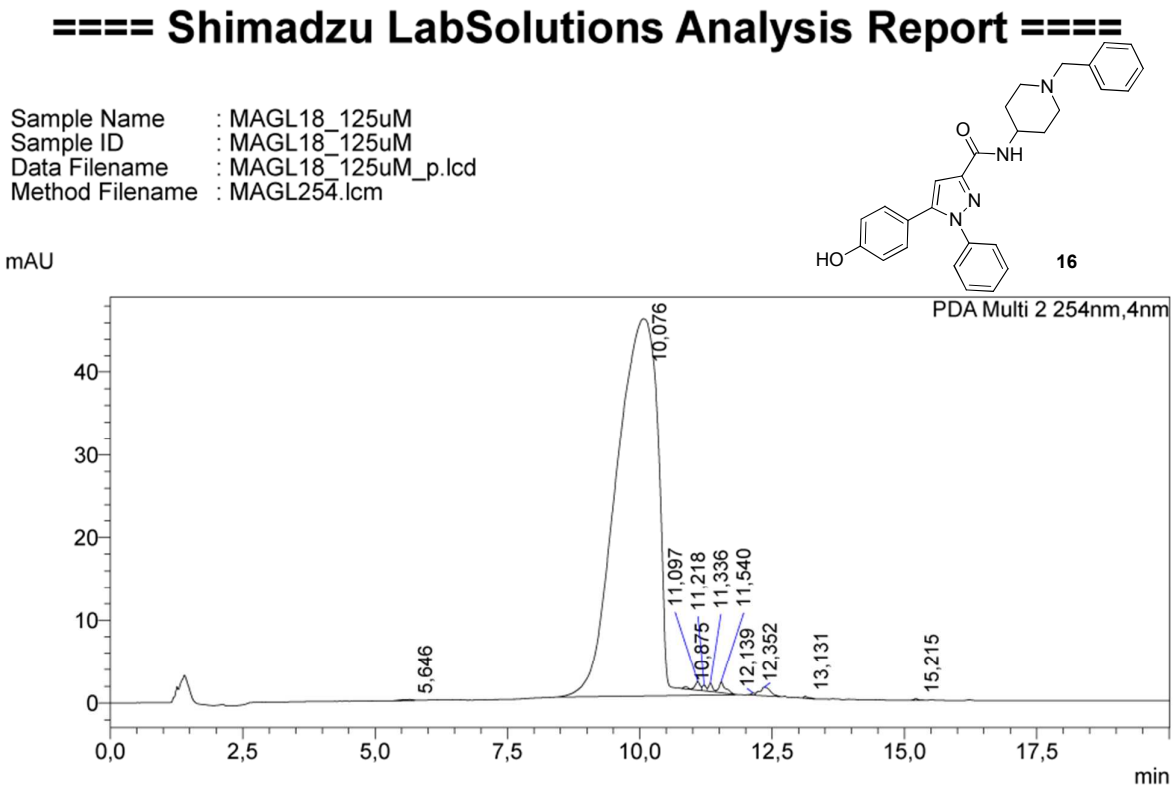


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,094	8637	0,141	700
2	12,248	3221	0,053	537
3	12,530	3370	0,055	685
4	12,969	224485	3,663	51953
5	13,132	5818806	94,951	1424030
6	13,696	1242	0,020	362
7	13,863	1626	0,027	454
8	14,013	1834	0,030	346
9	14,446	9295	0,152	1420
10	14,881	1171	0,019	201
11	15,075	49286	0,804	7422
12	15,424	2035	0,033	225
13	16,214	1765	0,029	278
14	18,803	1463	0,024	141
Total		6128236	100,000	1488754

Figure S10. HPLC chromatogram of compound 15.

16

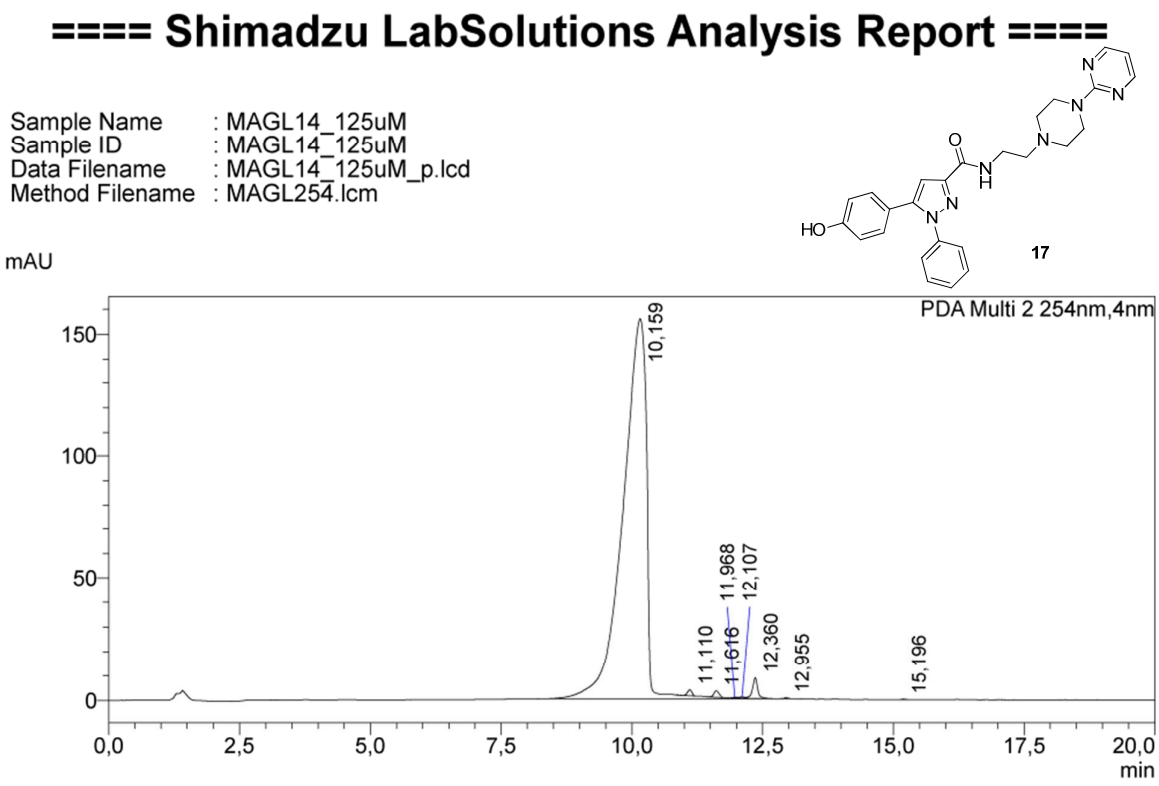


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	5,646	2096	0,082	119
2	10,076	2503836	98,129	45633
3	10,875	1463	0,057	249
4	11,097	6847	0,268	1074
5	11,218	3462	0,136	687
6	11,336	5236	0,205	1022
7	11,540	10814	0,424	1310
8	12,139	1180	0,046	248
9	12,352	14083	0,552	1004
10	13,131	1387	0,054	251
11	15,215	1164	0,046	169
Total		2551569	100,000	51765

Figure S11. HPLC chromatogram of compound 16.

17

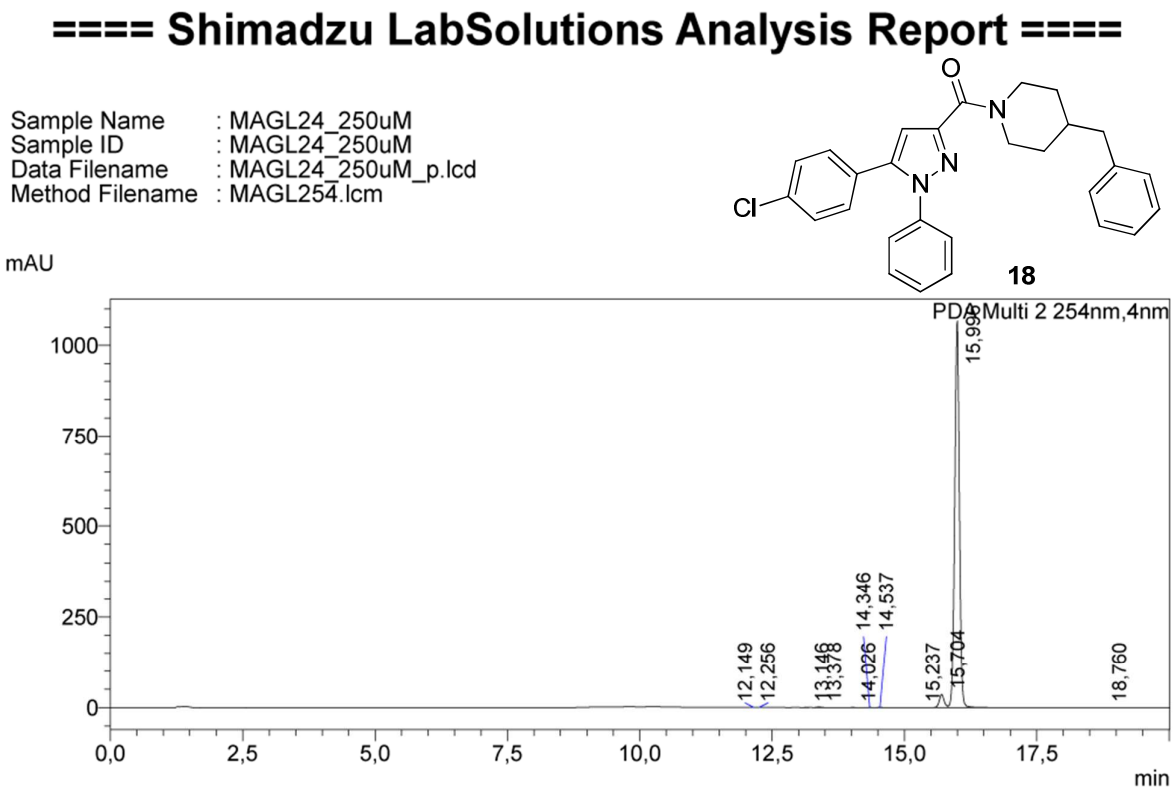


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	10,159	4873770	97,980	155693
2	11,110	15025	0,302	2444
3	11,616	18337	0,369	2615
4	11,968	1714	0,034	258
5	12,107	3206	0,064	473
6	12,360	57929	1,165	8415
7	12,955	2852	0,057	444
8	15,196	1403	0,028	201
Total		4974235	100,000	170545

Figure S12. HPLC chromatogram of compound 17.

18

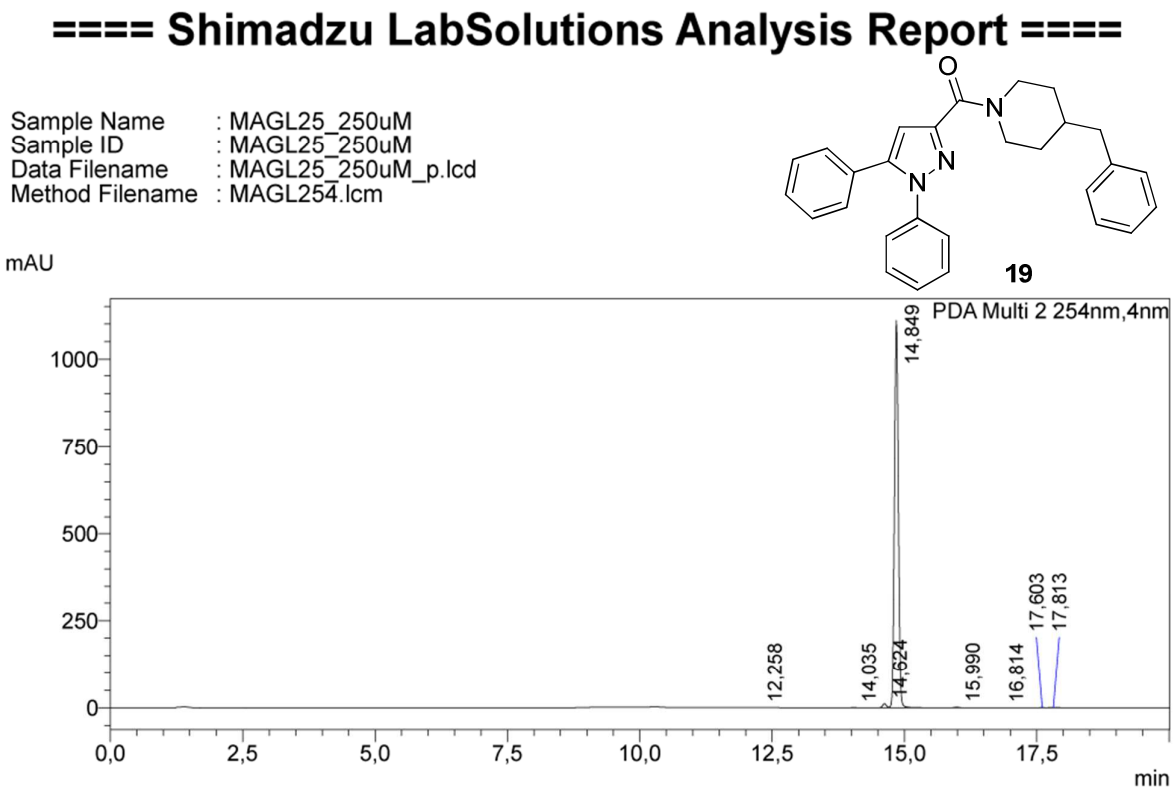


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,149	1749	0,025	332
2	12,256	3292	0,048	527
3	13,146	1121	0,016	284
4	13,378	8769	0,127	1654
5	14,026	1760	0,025	314
6	14,346	1438	0,021	319
7	14,537	3372	0,049	710
8	15,237	1497	0,022	208
9	15,704	234038	3,380	36140
10	15,996	6666766	96,270	1067347
11	18,760	1298	0,019	140
Total		6925098	100,000	1107974

Figure S13. HPLC chromatogram of compound 18.

19

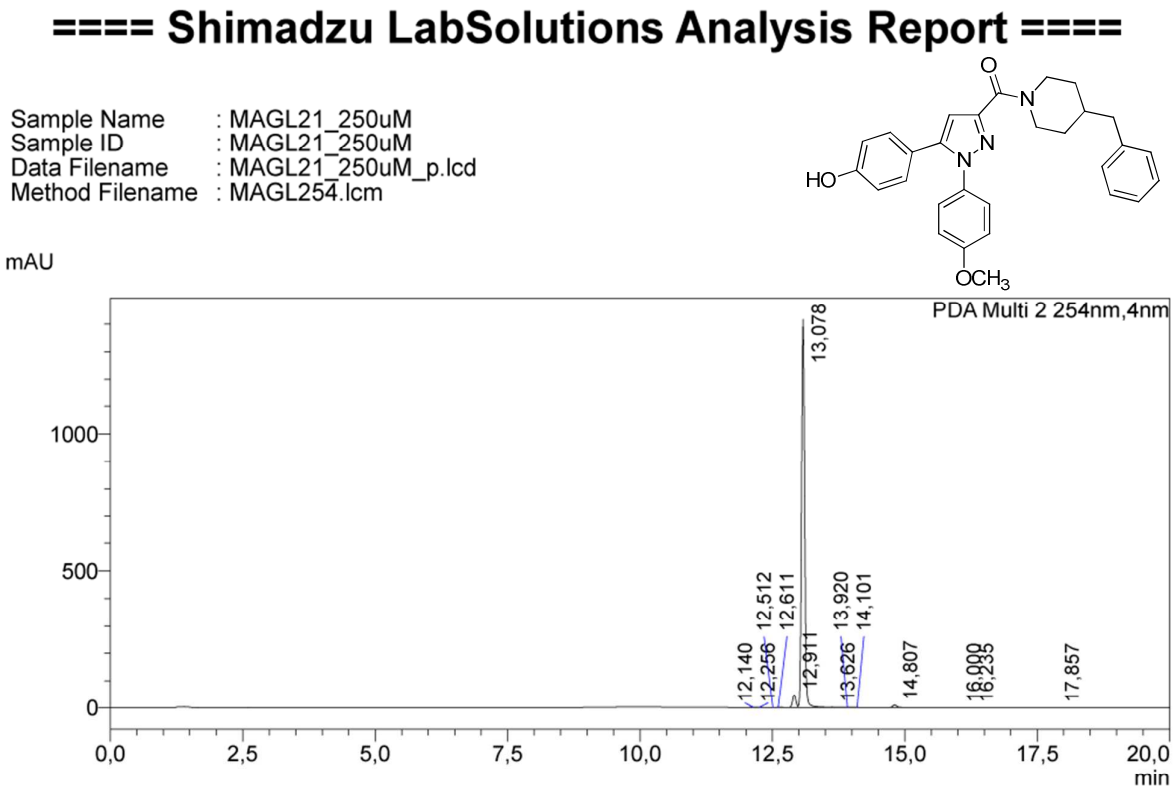


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,258	4170	0,073	503
2	14,035	4532	0,080	731
3	14,624	60659	1,067	11823
4	14,849	5588320	98,305	1109593
5	15,990	10003	0,176	1651
6	16,814	1337	0,024	186
7	17,603	3764	0,066	482
8	17,813	11863	0,209	1109
Total		5684648	100,000	1126079

Figure S14. HPLC chromatogram of compound 19.

20

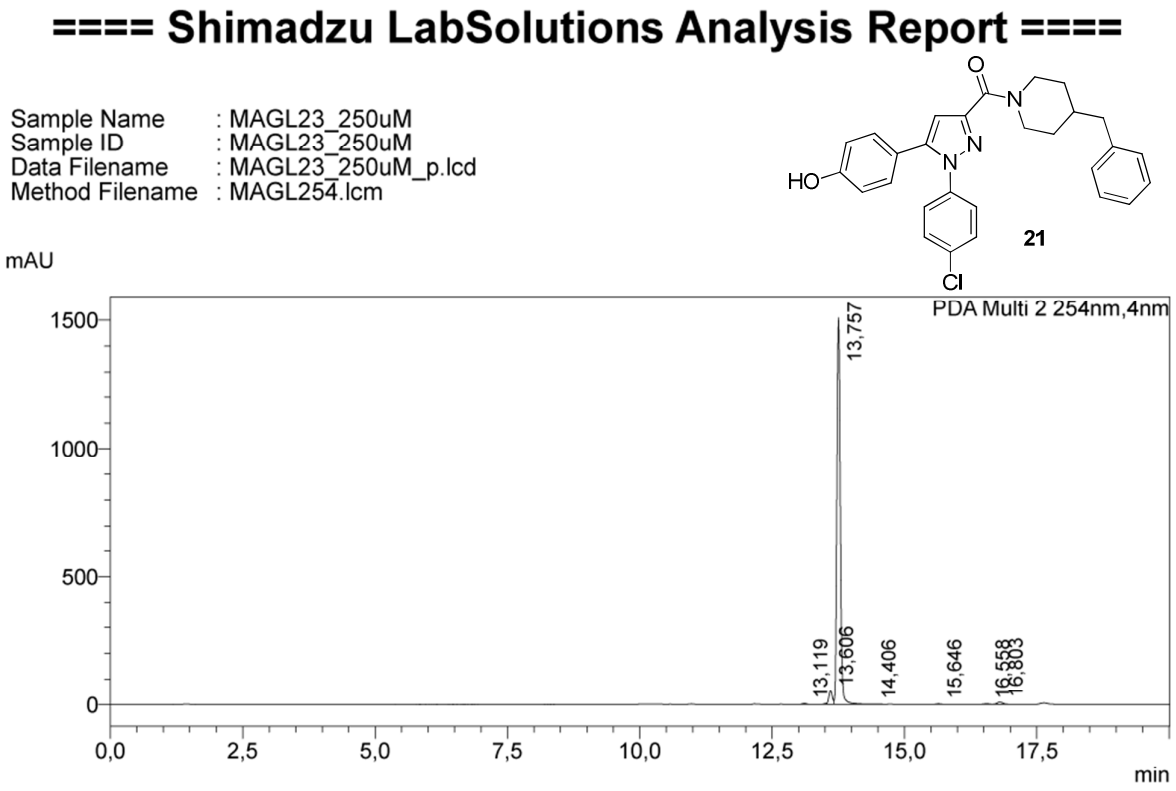


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,140	3193	0,053	427
2	12,256	3272	0,055	563
3	12,512	1594	0,027	206
4	12,611	3296	0,055	393
5	12,911	201825	3,376	47083
6	13,078	5692771	95,222	1416689
7	13,626	2399	0,040	619
8	13,920	4202	0,070	646
9	14,101	1149	0,019	272
10	14,807	55064	0,921	9268
11	16,000	4911	0,082	543
12	16,235	2547	0,043	233
13	17,857	2185	0,037	223
Total		5978407	100,000	1477163

Figure S15. HPLC chromatogram of compound 20.

21

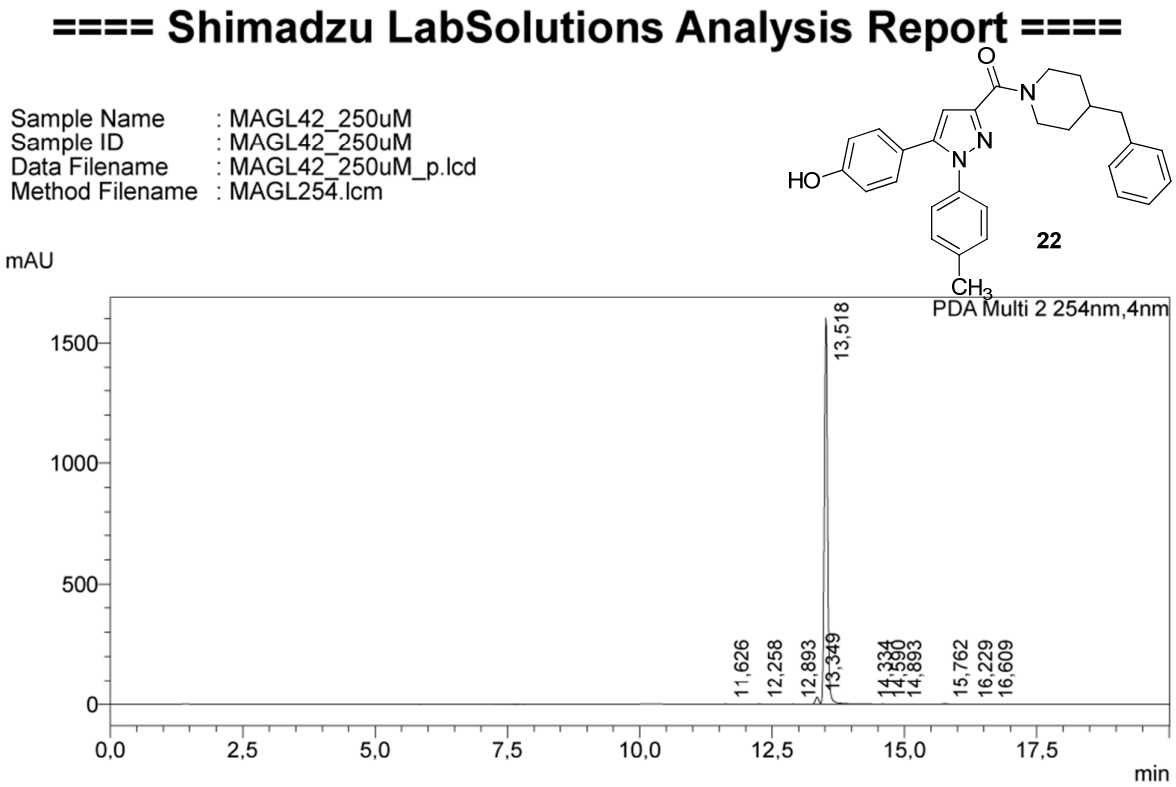


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	13,119	20181	0,289	3519
2	13,606	245858	3,517	52383
3	13,757	6611152	94,577	1507811
4	14,406	8417	0,120	1105
5	15,646	13378	0,191	1968
6	16,558	20858	0,298	2477
7	16,803	70364	1,007	8513
Total		6990209	100,000	1577776

Figure S16. HPLC chromatogram of compound 21.

22

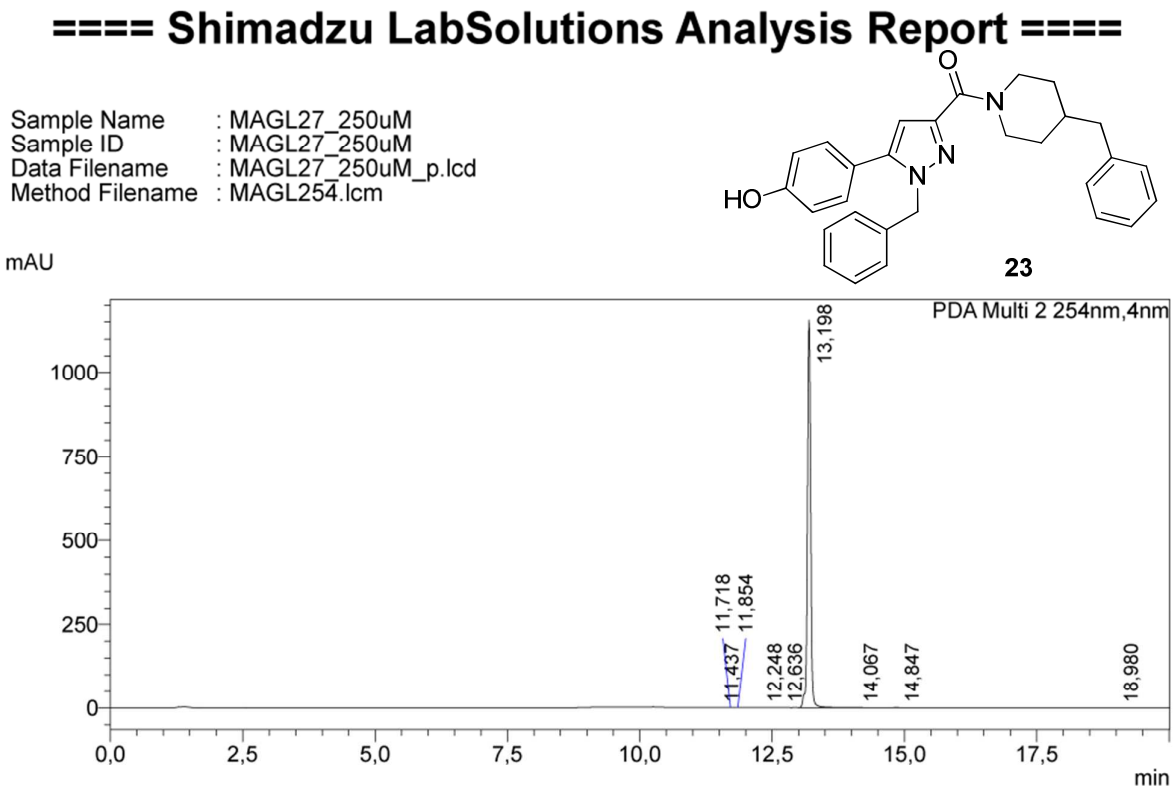


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,626	2991	0,042	821
2	12,258	5746	0,080	823
3	12,893	3539	0,049	728
4	13,349	132787	1,848	29617
5	13,518	7012920	97,588	1603229
6	14,334	1093	0,015	261
7	14,590	2271	0,032	341
8	14,893	2381	0,033	420
9	15,762	16363	0,228	2029
10	16,229	1754	0,024	290
11	16,609	4441	0,062	518
Total		7186285	100,000	1639077

Figure S17. HPLC chromatogram of compound 22.

23

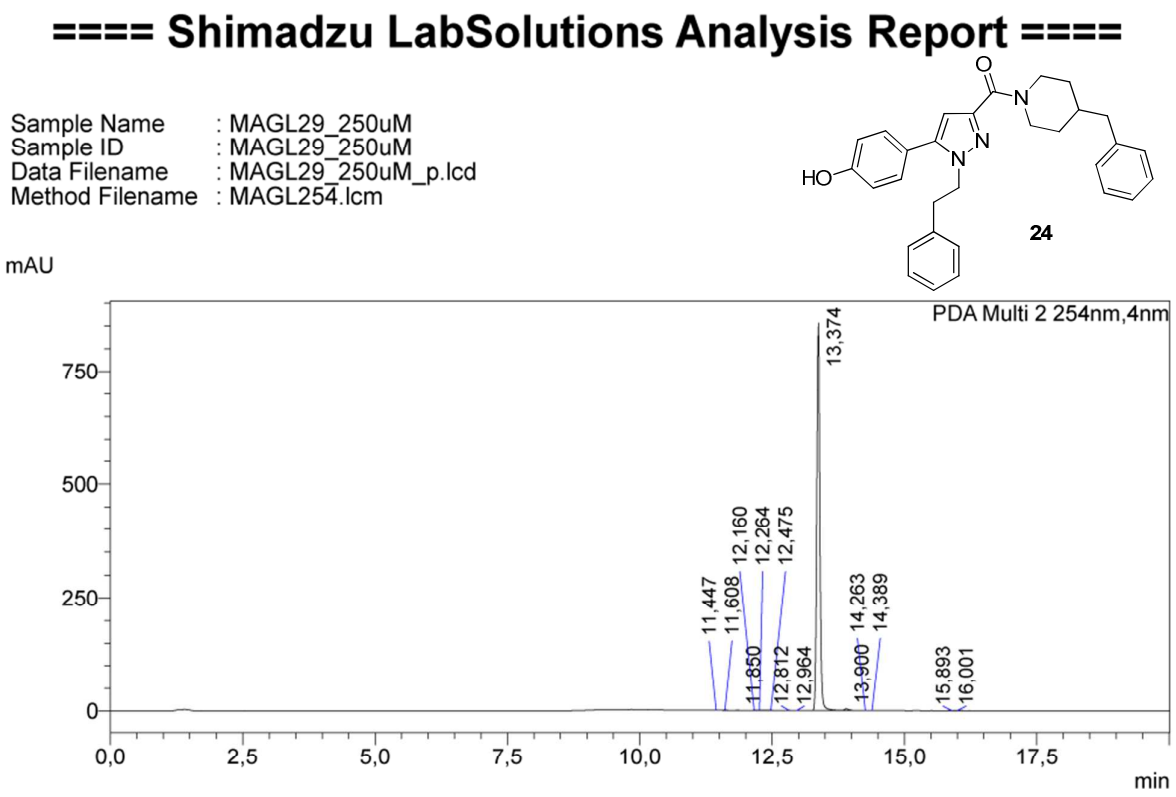


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,437	1501	0,031	215
2	11,718	1321	0,027	338
3	11,854	1248	0,025	283
4	12,248	5922	0,121	549
5	12,636	3920	0,080	780
6	13,198	4875978	99,546	1155395
7	14,067	2598	0,053	416
8	14,847	3114	0,064	601
9	18,980	2591	0,053	230
Total		4898193	100,000	1158808

Figure S18. HPLC chromatogram of compound 23.

24

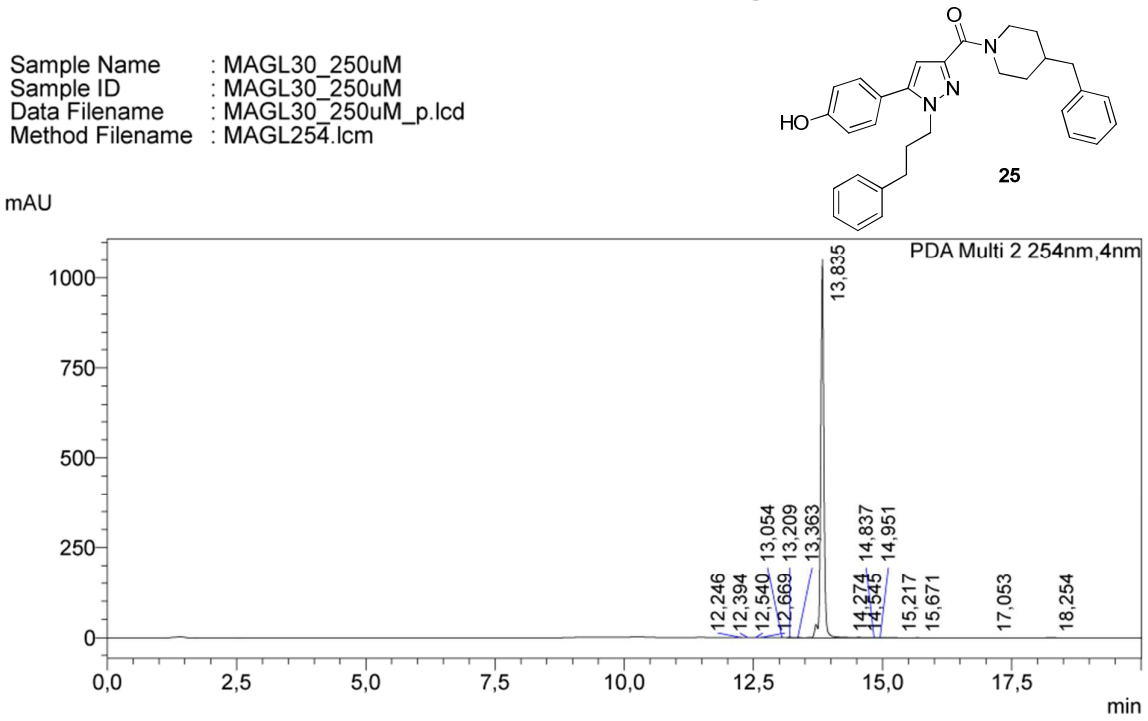


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,447	1621	0,045	260
2	11,608	3690	0,102	800
3	11,850	1680	0,046	433
4	12,160	1192	0,033	239
5	12,264	4158	0,115	449
6	12,475	2651	0,073	582
7	12,812	2825	0,078	736
8	12,964	1736	0,048	214
9	13,374	3571897	98,720	855681
10	13,900	17795	0,492	3326
11	14,263	1540	0,043	280
12	14,389	1375	0,038	227
13	15,893	2187	0,060	367
14	16,001	3847	0,106	546
Total		3618195	100,000	864142

Figure S19. HPLC chromatogram of compound 24.

25

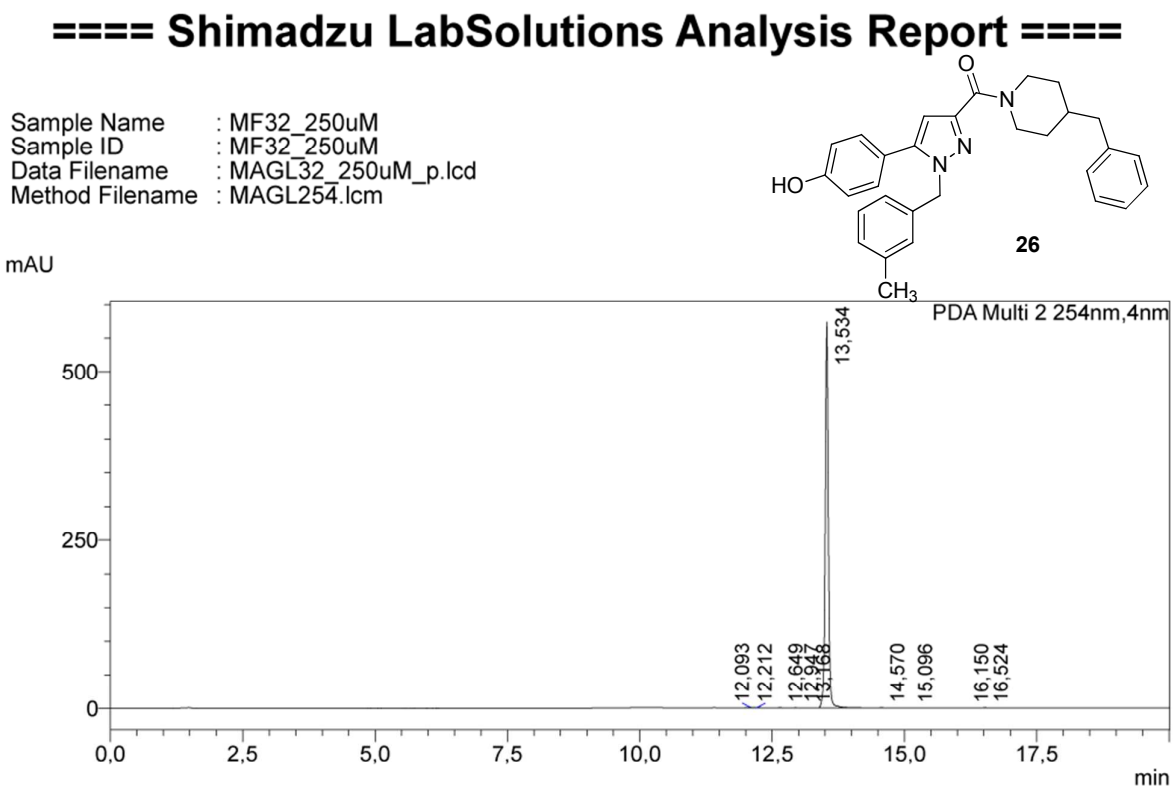


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,246	9080	0,193	1138
2	12,394	1838	0,039	318
3	12,540	1774	0,038	342
4	12,669	5576	0,118	1003
5	13,054	5237	0,111	1122
6	13,209	8257	0,175	1539
7	13,363	4717	0,100	930
8	13,835	4653273	98,732	1050100
9	14,274	1197	0,025	375
10	14,545	3759	0,080	809
11	14,837	1131	0,024	192
12	14,951	2325	0,049	293
13	15,217	1190	0,025	174
14	15,671	1540	0,033	202
15	17,053	2597	0,055	317
16	18,254	9545	0,203	888
Total		4713035	100,000	1059742

Figure S20. HPLC chromatogram of compound 25.

26

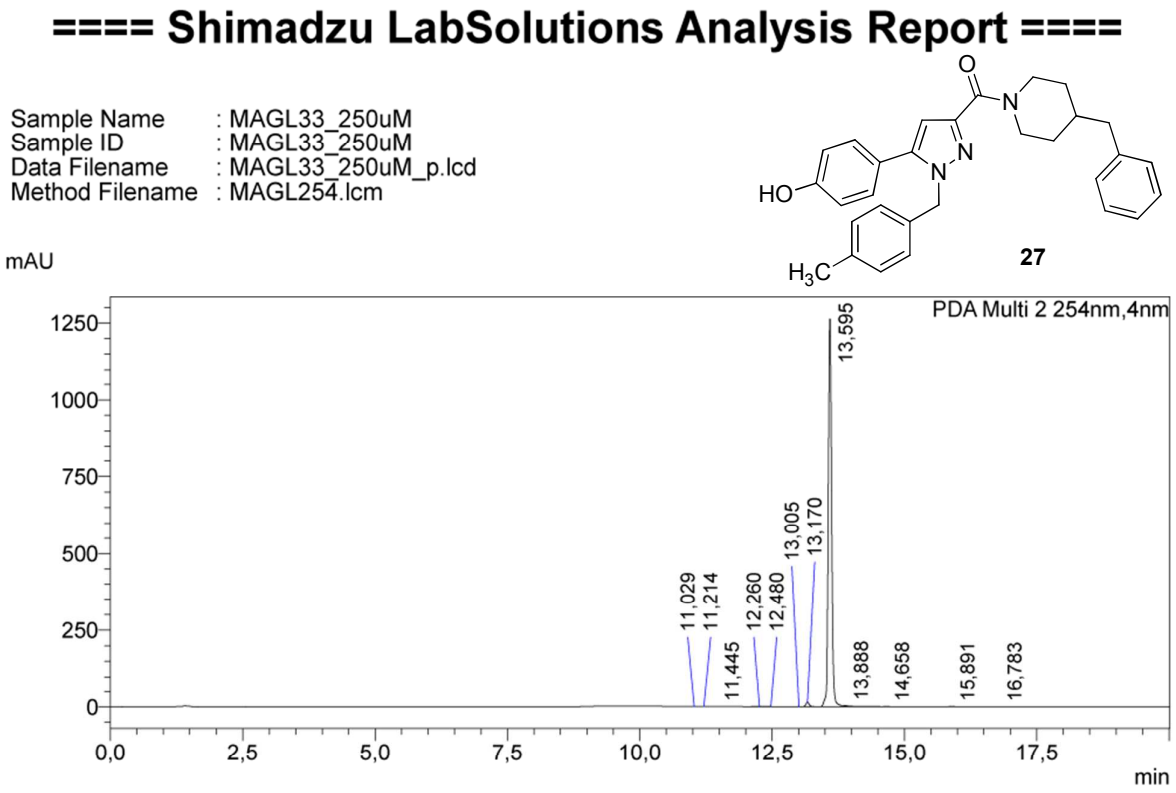


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,093	4508	0,186	710
2	12,212	2425	0,100	302
3	12,649	1698	0,070	405
4	12,947	1445	0,060	264
5	13,168	1180	0,049	242
6	13,534	2406979	99,223	573470
7	14,570	1905	0,079	302
8	15,096	1092	0,045	160
9	16,150	1735	0,072	229
10	16,524	2856	0,118	373
Total		2425822	100,000	576457

Figure S21. HPLC chromatogram of compound 26.

27

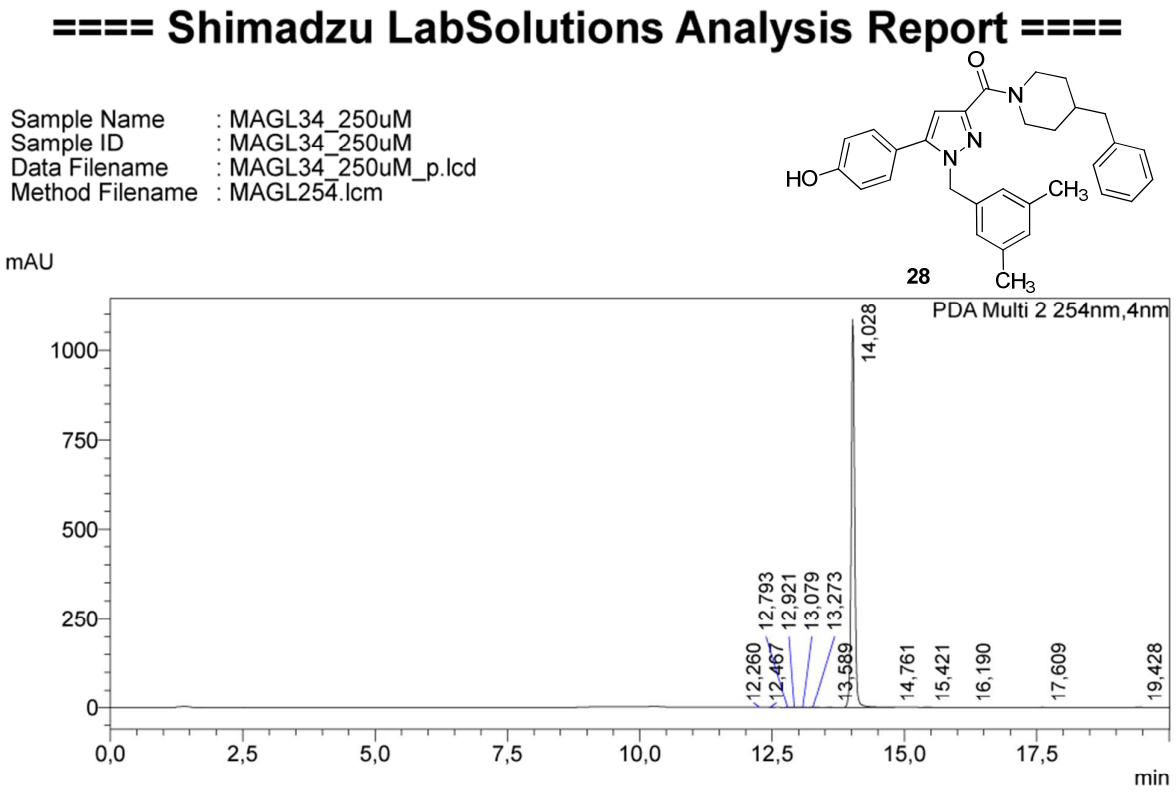


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	11,029	2706	0,048	231
2	11,214	3623	0,065	361
3	11,445	4207	0,075	313
4	12,260	4505	0,080	520
5	12,480	1374	0,025	160
6	13,005	1585	0,028	230
7	13,170	62143	1,110	14840
8	13,595	5503863	98,337	1262608
9	13,888	2171	0,039	773
10	14,658	1240	0,022	211
11	15,891	7333	0,131	1131
12	16,783	2197	0,039	282
Total		5596946	100,000	1281660

Figure S22. HPLC chromatogram of compound 27.

28

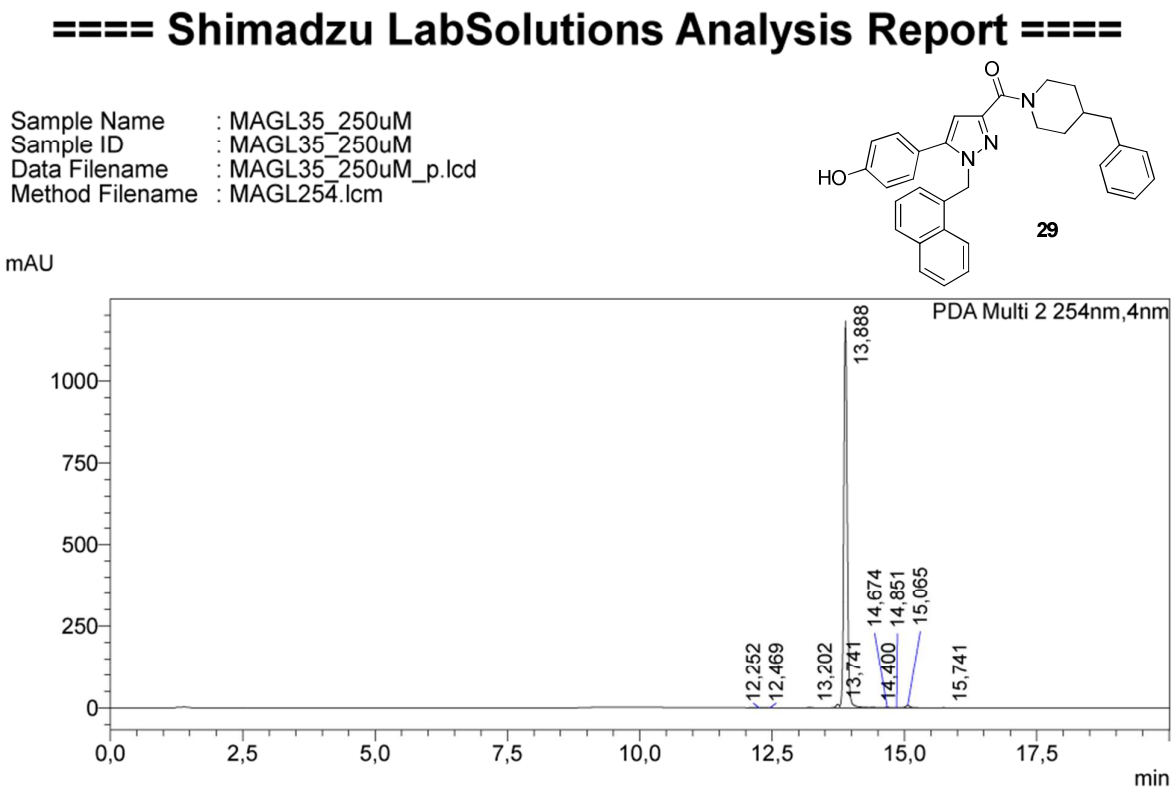


PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,260	6149	0,122	585
2	12,467	1499	0,030	260
3	12,793	1215	0,024	313
4	12,921	1370	0,027	306
5	13,079	4279	0,085	604
6	13,273	6154	0,122	971
7	13,589	2379	0,047	553
8	14,028	5005452	99,252	1085573
9	14,761	2315	0,046	473
10	15,421	2144	0,043	236
11	16,190	1157	0,023	137
12	17,609	2932	0,058	339
13	19,428	6128	0,122	481
Total		5043173	100,000	1090830

Figure S23. HPLC chromatogram of compound 28.

29



PDA Ch2 254nm

Peak#	Ret. Time	Area	Area%	Height
1	12,252	5141	0,096	555
2	12,469	1501	0,028	188
3	13,202	6705	0,125	1282
4	13,741	47365	0,885	10163
5	13,888	5237741	97,838	1182530
6	14,400	3128	0,058	733
7	14,674	6084	0,114	1125
8	14,851	1703	0,032	350
9	15,065	42150	0,787	6999
10	15,741	1951	0,036	286
Total		5353470	100,000	1204212

Figure S24. HPLC chromatogram of compound 29.