

Supplementary Material

Novel potent and selective agonists of the GPR55 receptor based on the 3-benzylquinolin-2(1*H*)-one scaffold

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Figure S1. ^1H NMR and ^{13}C NMR of compound 1

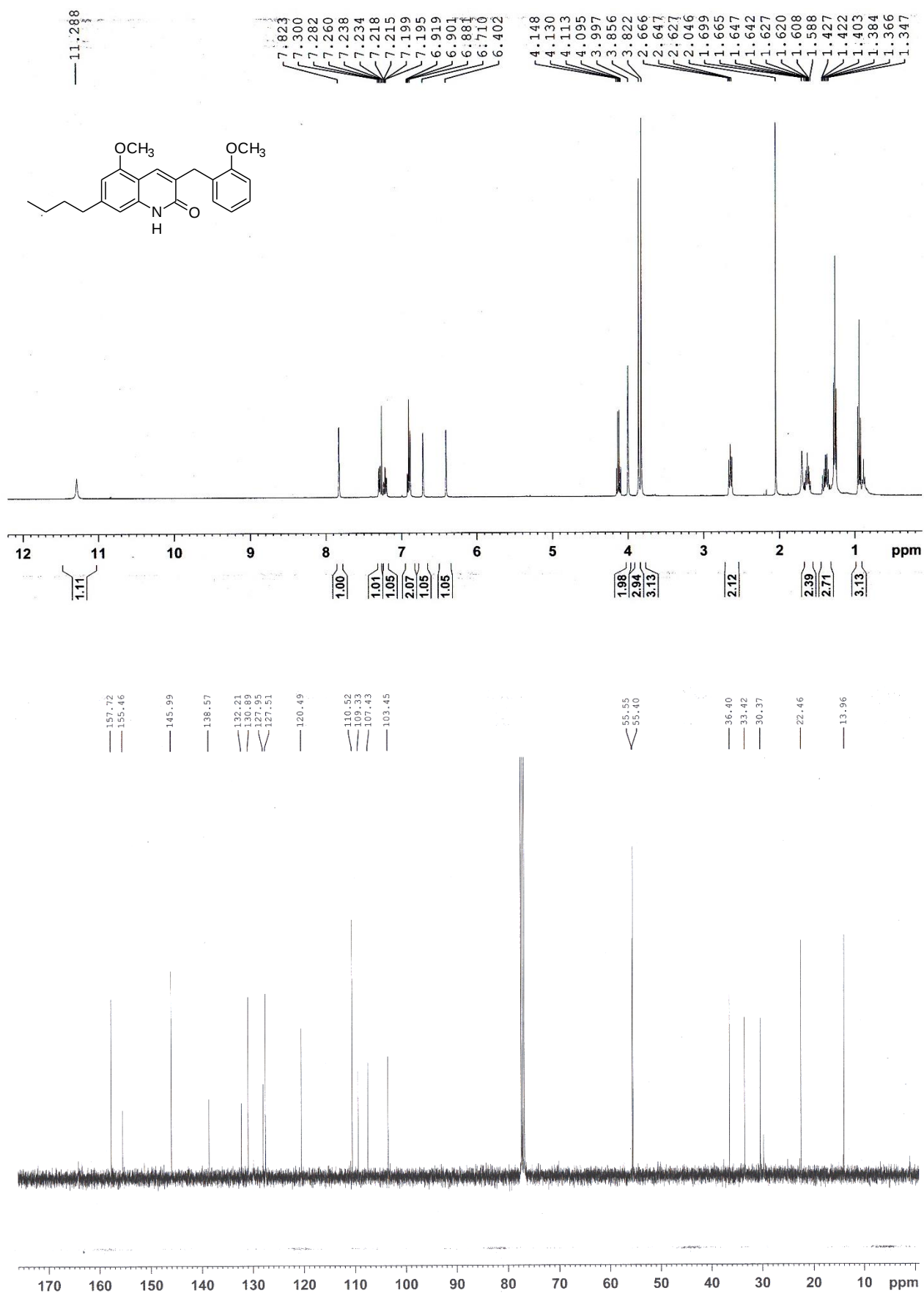


Figure S2. ^1H NMR and ^{13}C NMR of compound 2

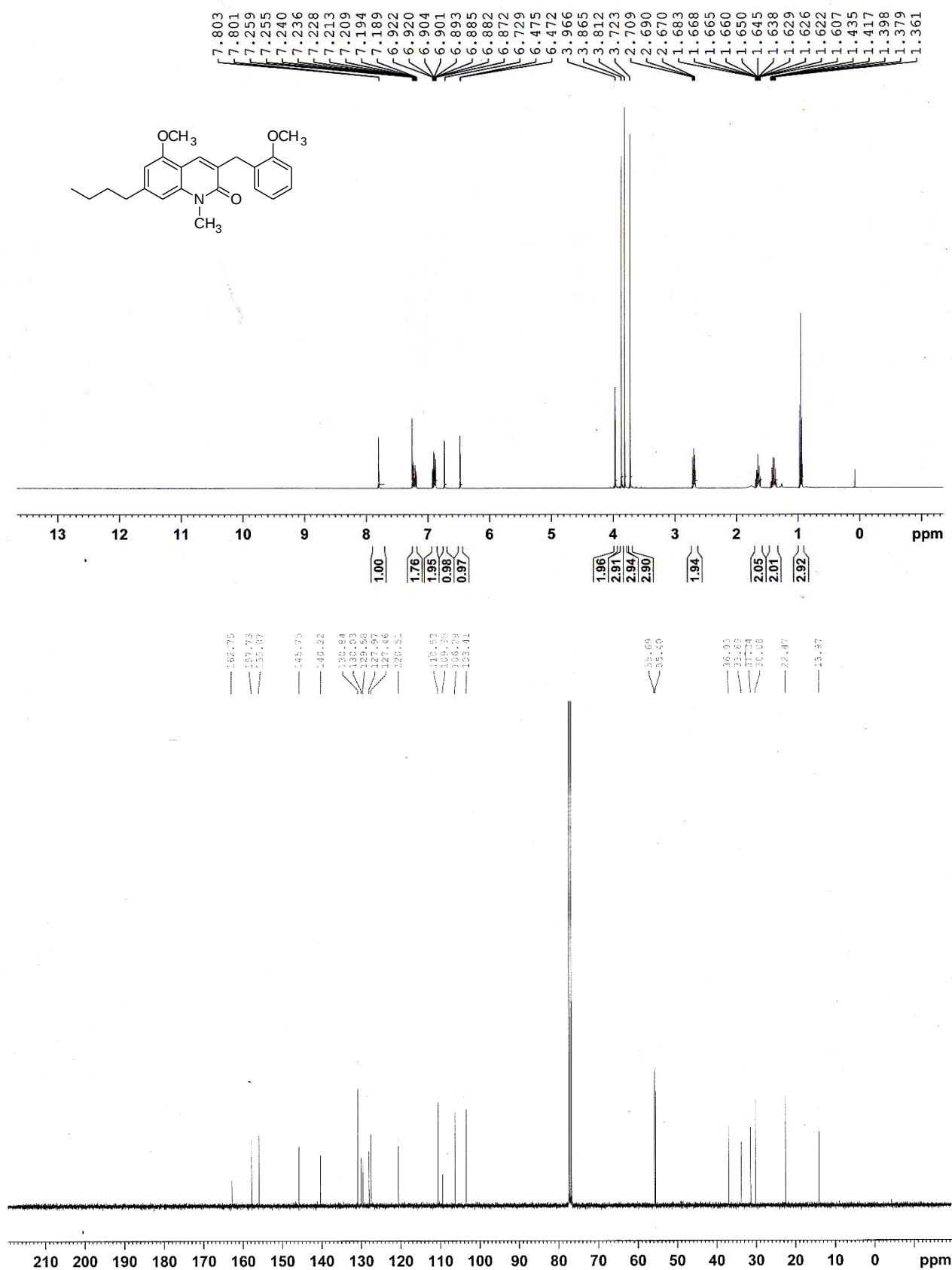


Figure S3. ^1H NMR and ^{13}C of compound 3

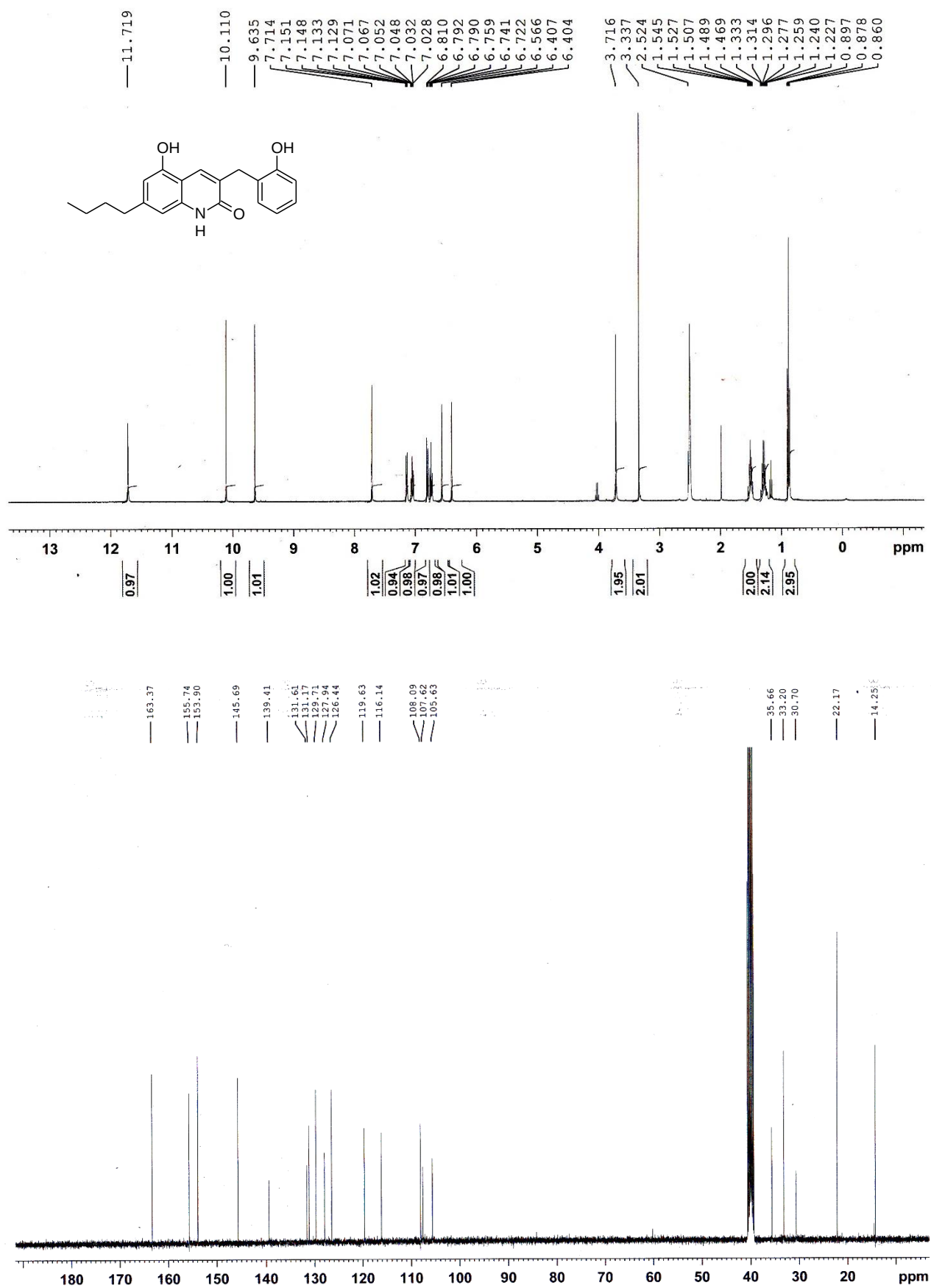


Figure S4. ^1H NMR and ^{13}C of compound 4

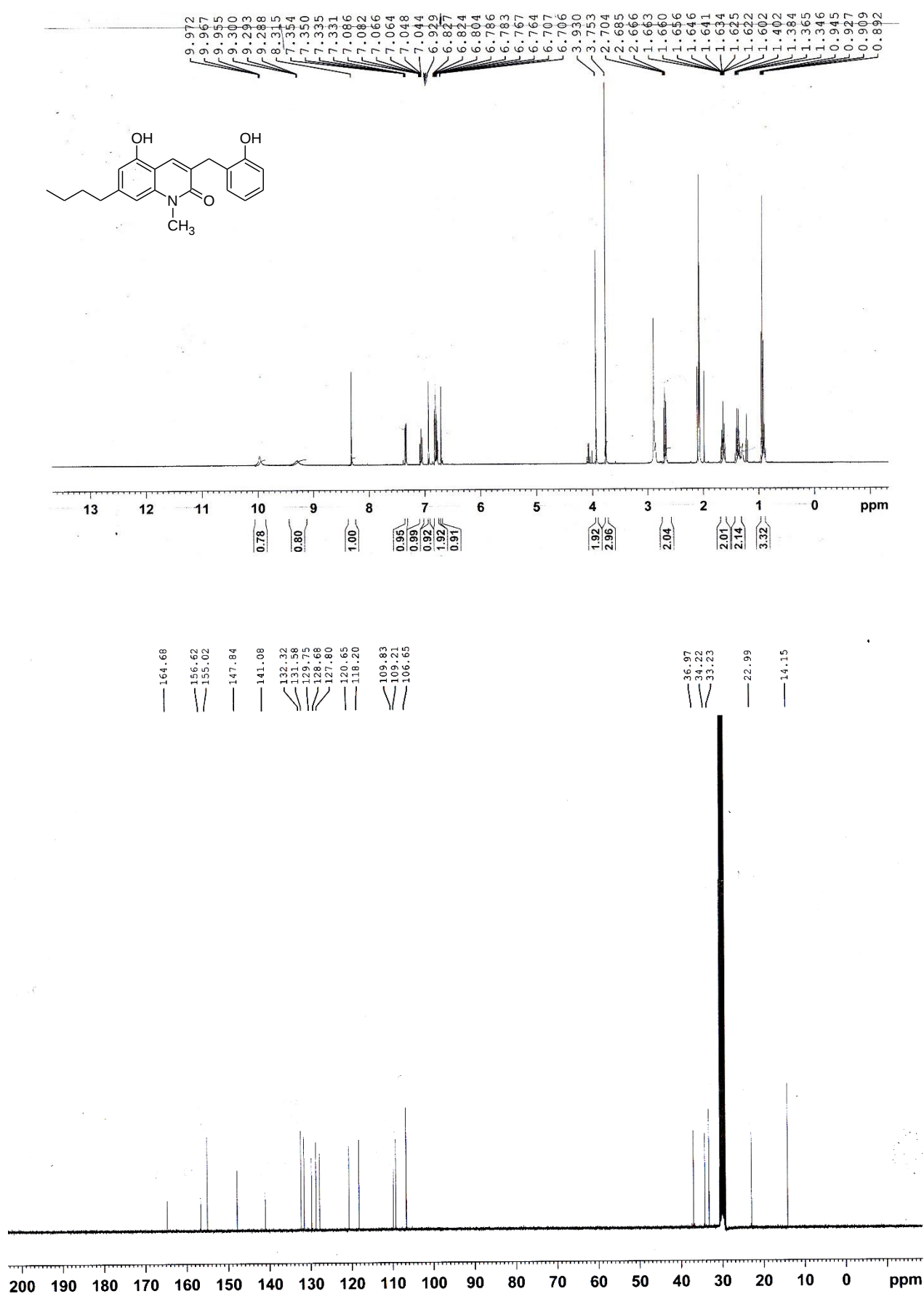


Figure S5. NOESY spectrum of compound **14**. Spatial interaction H₄/benzylic methylene (red circle) and H₄/methoxy (5-position) (green circle) is observed. Only a slight spatial interaction H₄/CH₃ (4'' position) (light blue circle) is present. The methylene group (1''-position) interacts with both aromatic hydrogens H₆ and H₈ (purple circles). The methoxy group (5-position) interacts with H₆ (cyan circle), but not with H₈.

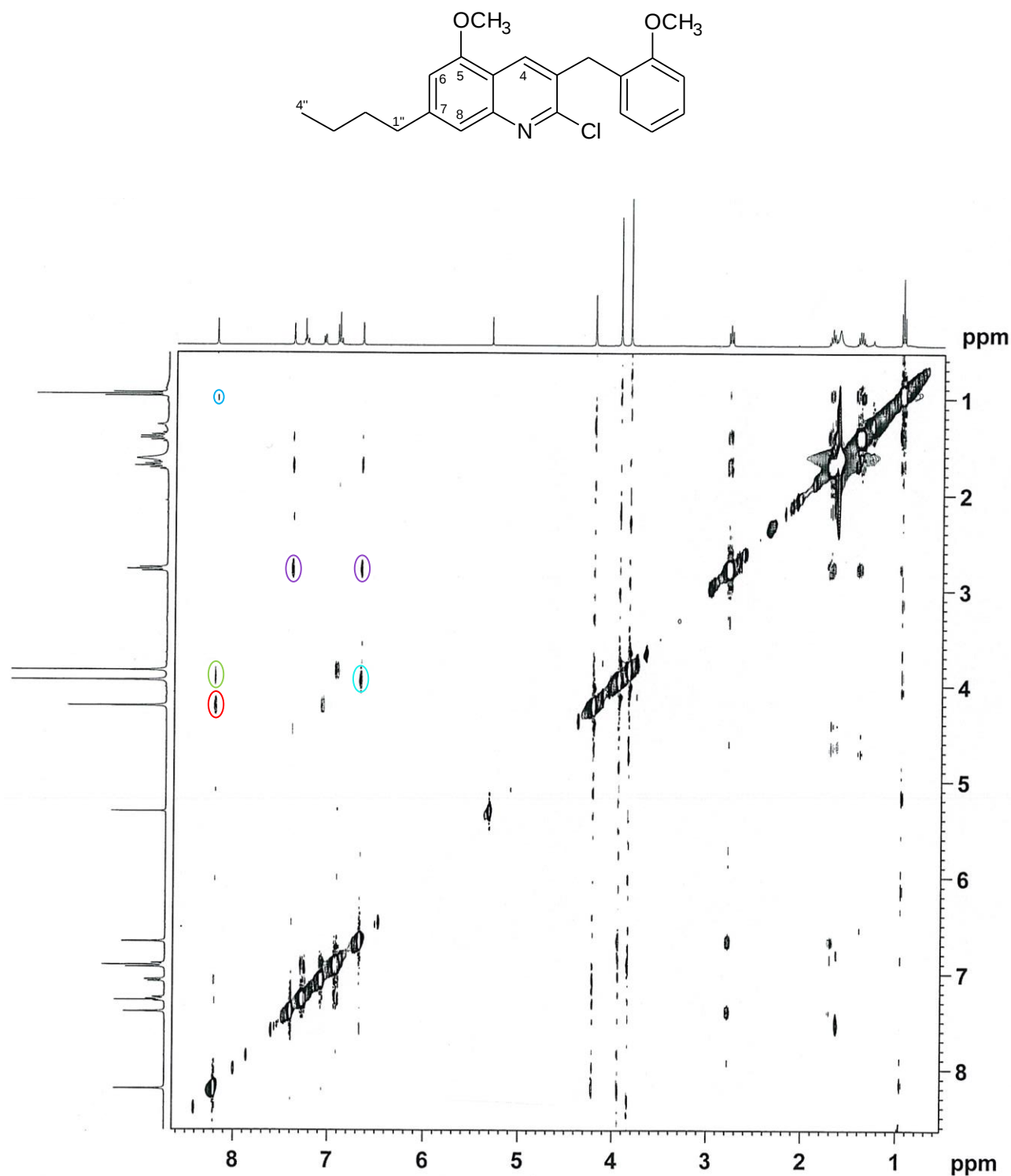


Figure S6. NOESY spectrum of compound **15**. Spatial interaction H₄/methylene (1''-position) (green circle) and H₄/benzylic methylene (red circle) is observed. The H₆ proton interacts with the methylene (1''- position) (light blue circle). The methoxy group (7-position) interacts with both H₆ and H₈ protons (purple circles).

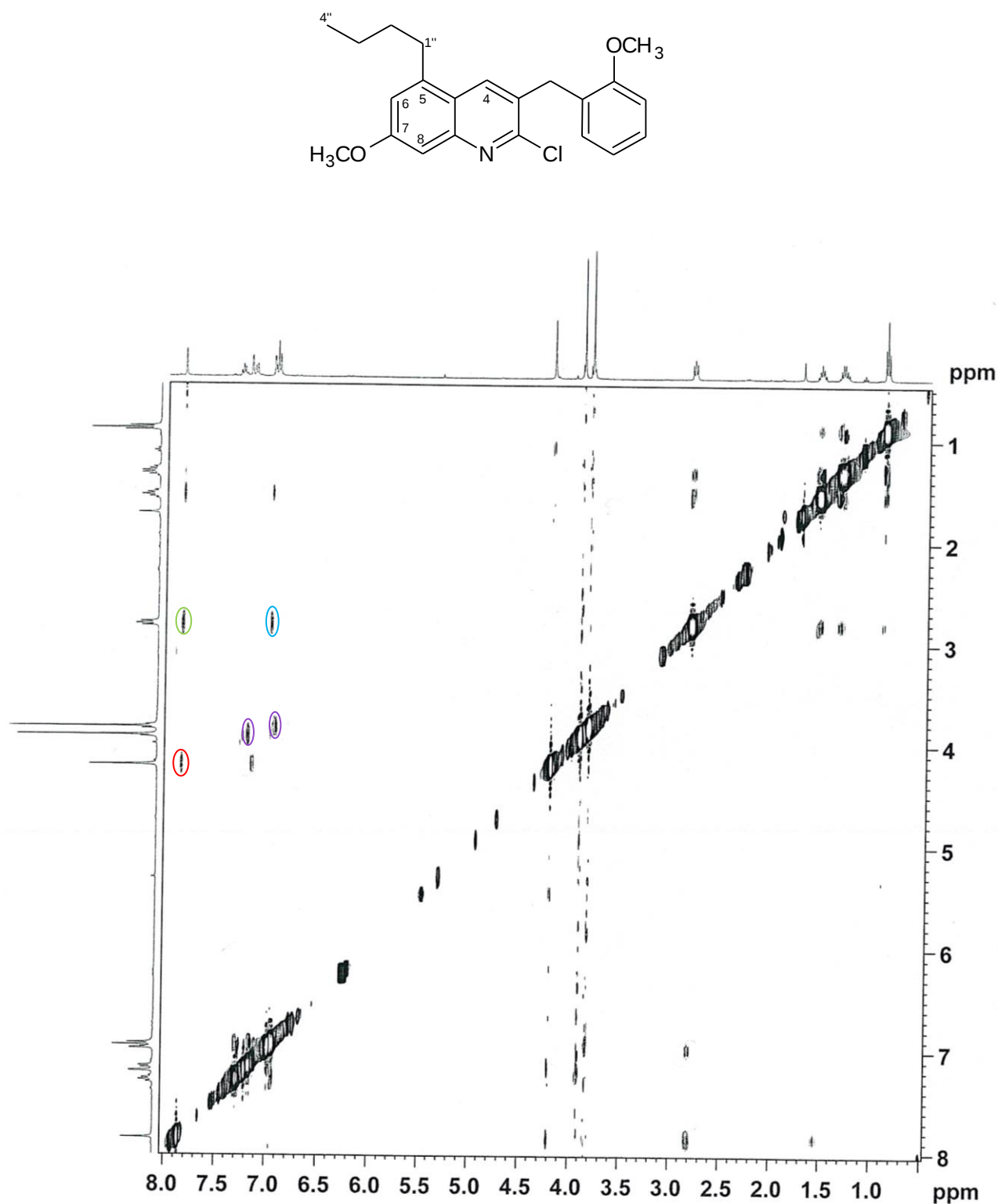
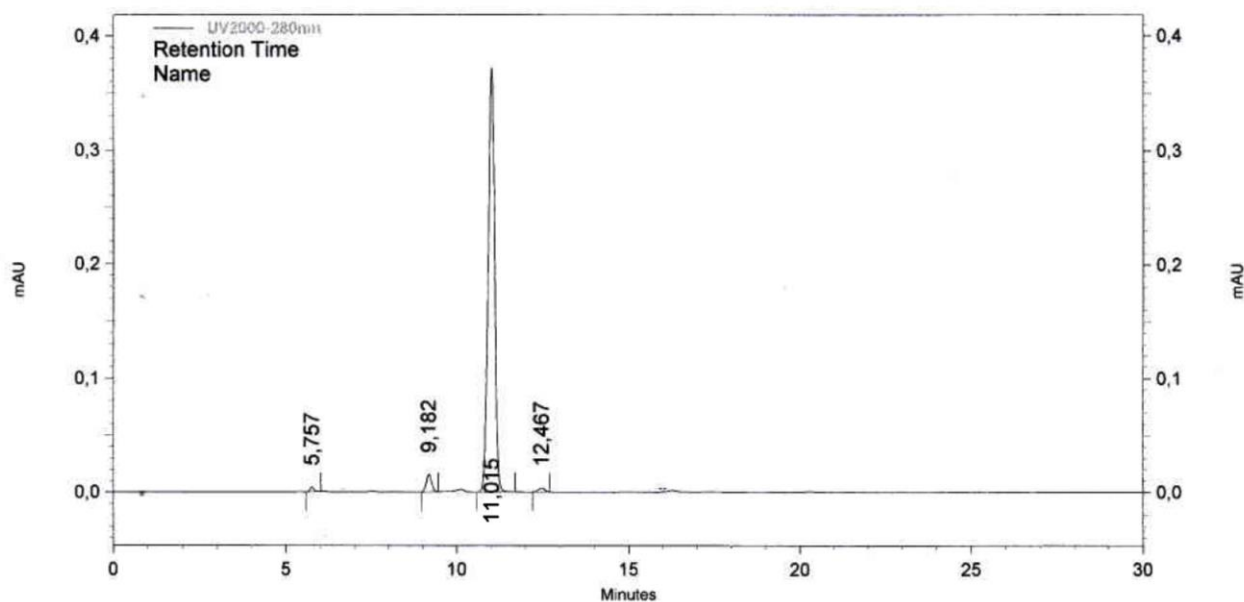


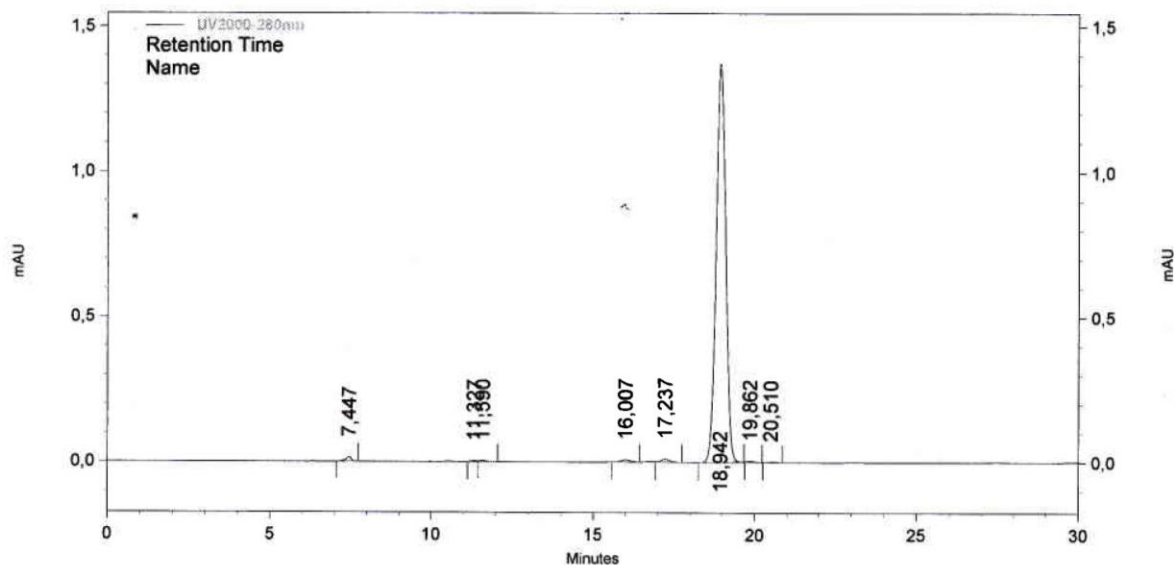
Figure S7. HPLC data of compound 1.



UV2000-280nm
Results (System
(07/09/2021
8.38.21)
(Reprocessed))

Name	Retention Time	Area	Area Percent	Integration Codes
	5,757	30042	0,585	MM
	9,182	169788	3,306	MM
	11,015	4890624	95,214	MM
	12,467	45997	0,896	MM
Totals		5136451	100,000	

Figure S8. HPLC data of compound 2.

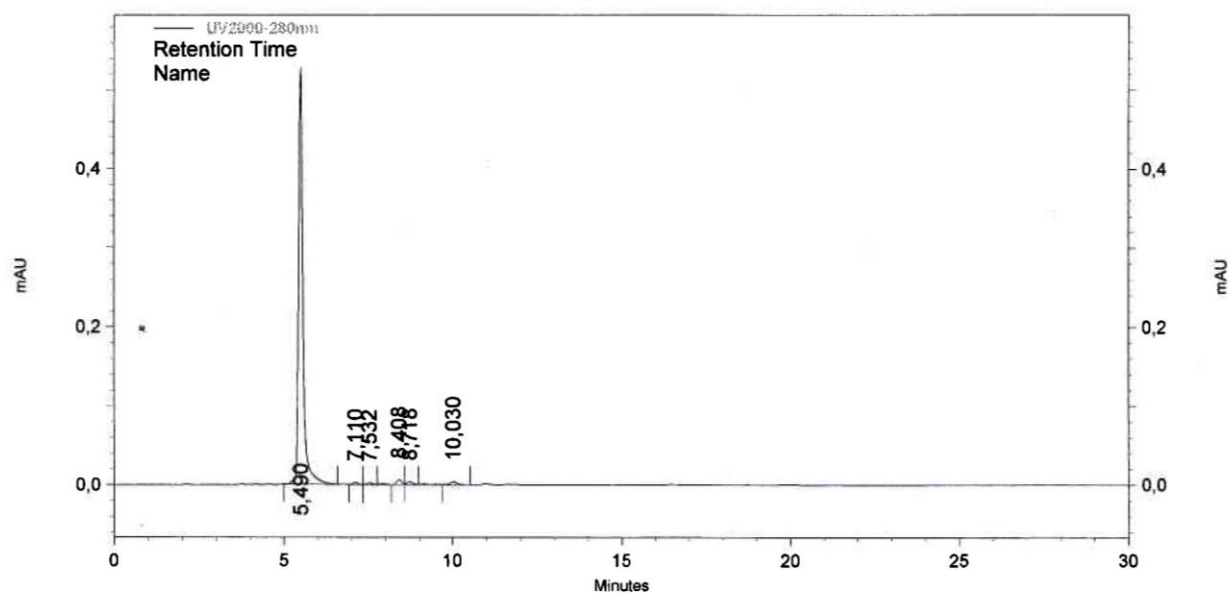


UV2000-280nm
Results (System
(18/11/2021
5.09.01)
(Reprocessed))

Name	Retention Time	Area	Area Percent	Integration Codes
	7,447	177980	0,617	MM
	11,327	39119	0,136	MM
	11,590	61694	0,214	VV
	16,007	135213	0,469	MM
	17,237	165765	0,575	MM
	18,942	28174102	97,705	MM
	19,862	38407	0,133	MM
	20,510	43465	0,151	MM

Totals		28835745	100,000	
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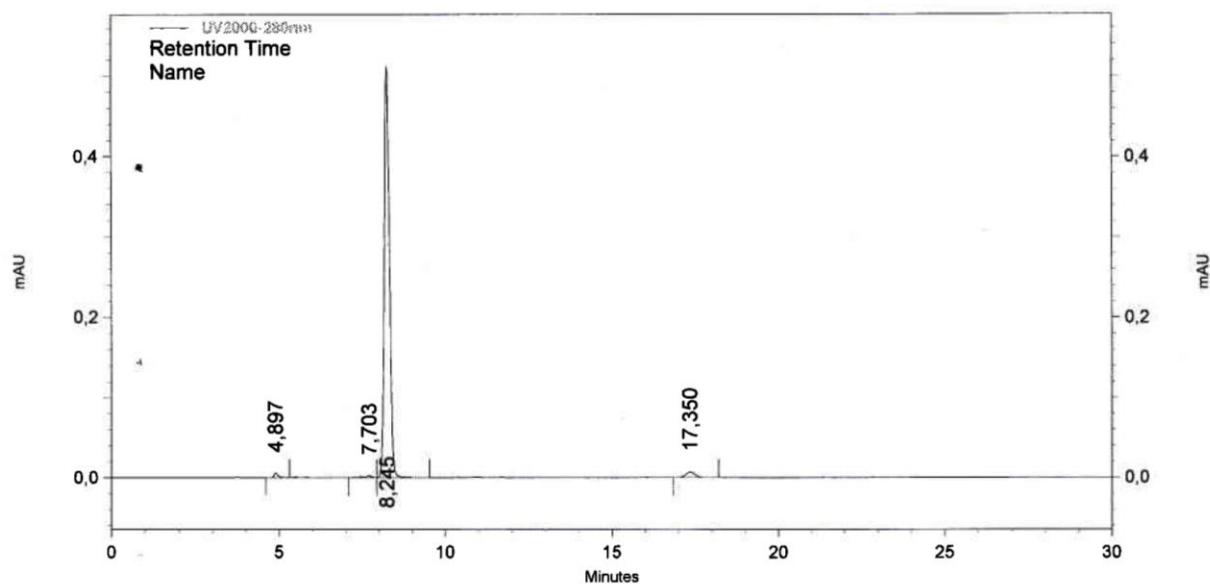
Figure S9. HPLC data of compound 3.



UV2000-280nm
Results (System
(07/09/2021
9.30.42)
(Reprocessed))

Name	Retention Time	Area	Area Percent	Integration Codes
	5,490	4756943	95,194	MM
	7,110	34093	0,682	VV
	7,532	31695	0,634	VV
	8,408	68532	1,371	VV
	8,718	45633	0,913	VV
	10,030	60197	1,205	VV
Totals		4997093	100,000	

Figure S10. HPLC data of compound 4.



UV2000-280nm
Results (System
(07/09/2021
10.10.44)
(Reprocessed))

Name	Retention Time	Area	Area Percent	Integration Codes
	4,897	52323	0,917	VV
	7,703	38417	0,673	VV
	8,245	5485113	96,088	VV
	17,350	132600	2,323	BV
Totals		5708453	100,000	

Table S1. Average ligand root-mean-square deviation (RMSD) calculated during 100 ns of MD simulation for the eight different 2-hGPR55 complexes analyzed.

Complex	Ligand RMSD
C1	4.0
C2	1.3
C3	0.9
C4	2.1
C5	4.9
C6	5.3
C7	2.2
C8	1.2

Table S2. Binding free energy values calculated for the eight different **2**-hGPR55 complexes using the MM-PBSA method (values are expressed in kcal/mol).

Complex	MM-PBSA binding energy (kcal/mol)
C1	-38.5
C2	-48.3
C3	-41.4
C4	-39.6
C5	-37.9
C6	-36.0
C7	-42.4
C8	-41.4