

Supporting Information

AI promoted virtual screening, structure-based hit optimization and synthesis of novel COVID-19 S-RBD domain inhibitors

Ioannis Gkekas^{1, #}, Sotirios Katsamakas^{2, 3, 4, #}, Stelios Mylonas^{3, #}, Theano Fotopoulou², George E. Magoulas², Alia Cristina Tenchiu², Marios Dimitriou⁵, Apostolos Axenopoulos³, Simona Kostova⁶, Erich E. Wanker⁶, Demetris Papahatjis², Vassilis G Gorgoulis⁷, Maria Koufaki^{2*}, Ioannis Karakasiliotis⁵, Theodora Calogeropoulou^{2*}, Petros Daras³ and Spyros Petrakis^{1*}.

¹ Institute of Applied Biosciences, Centre for Research and Technology Hellas, Thessaloniki, Greece

² Institute of Chemical Biology, National Hellenic Research Foundation, Leof. Vassileos Constantinou 48, Athens 11635, Greece

³ Information Technologies Institute, Centre for Research and Technology Hellas, Thessaloniki, Greece

⁴ Laboratory of Pharmaceutical Chemistry, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, Campus, Thessaloniki 54124, Greece

⁵ Laboratory of Biology, Department of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

⁶ Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany

⁷ Molecular Carcinogenesis Group, Department of Histology and Embryology, Medical School, National and Kapodistrian University of Athens, Athens

equal contribution

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Supplementary Tables

Table S1. Spike (RBD)/ACE2(19-615) inhibitors identified through AI-enabled VS.

Name	ChemBridge ID	IUPAC NAME	Binding scores
#1	5609384	4-(1-naphthyl)-3,4-dihydrobenzo[h]quinolin-2(1H)-one	0.972
#2	5979742	4-(2-naphthyl)-3,4-dihydrobenzo[h]quinolin-2(1H)-one	0.897
#3	6238693	3'-[(9H-fluoren-2-ylcarbonyl)amino]-4-biphenyl acetate	0.902
#4	5635769	2-[2-oxo-2-(10H-phenothiazin-10-yl)ethyl]-1H-isoindole-1,3(2H)-dione	0.875
#5	6954709	5-(4-biphenyl)-4-phenyl-1,3-thiazol-2-amine	0.874
#6	7226620	2-(4-biphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline	0.857
#7	6384272	1-[(4-methoxy-1-naphthyl)sulfonyl]-1H-1,2,3-benzotriazole	0.864
#8	6431096	1-benzofuran-2-yl(4-biphenyl)methanone	0.894
#9	6996505	2-[4-(2,2-dimethyl-4-oxo-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-5-yl)phenoxy]acetamide	0.881
#10	5260662	1-(4-biphenylcarbonyl)-1H-benzimidazole	0.916
#11	5668688	2,2,4-trimethyl-1,2-dihydro-6-quinolinyl (1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetate	0.868
#12	5837562	5-(1,3-benzodioxol-5-yl)-1-benzoyl-3-phenyl-4,5-dihydro-1H-pyrazole	0.9
#13	7262001	N-[2-(4-morpholinyl)phenyl]-2-naphthamide	0.857
#14	5315079	1-[2-(9H-fluoren-2-yl)-2-oxoethyl]-2,3-dimethylpyridinium bromide	0.891
#15	6085984	N-2-naphthyl-2-(2-naphthyloxy)acetamide	0.871
#16	6541298	1,1'-(1,4-phenylene)bis[3-(1,3-benzodioxol-5-yl)-2-propen-1-one]	0.877
#17	5465521	(1,3-benzodioxol-5-ylmethyl)(4-methoxy-3-biphenyl)amine	0.857
#18	5733393	1,3-dioxo-2-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-5-isoindolinecarboxylic acid	0.884
#19	7306847	N-(4-[(4,5-diphenyl-1,3-oxazol-2-yl)amino]sulfonyl)phenylacetamide	0.91
#20	5524376	2-[(2-naphthylamino)(4-pyridinyl)methyl]cycloheptanone	0.895
#21	7113299	5-[(8-quinolinylloxy)acetyl]-10,11-dihydro-5H-dibenzo[b,f]azepine	0.866
#22	5755483	2'-([4-(3-oxo-3-phenyl-1-propen-1-yl)phenyl]amino)carbonyl)-2-biphenylcarboxylic acid	0.865
#23	5979349	1-(2-naphthylmethyl)-1H-benzimidazole	0.871
#24	6038144	[4-(benzyloxy)phenyl](1-methyl-1H-benzimidazol-2-yl)methanol	0.885

#25	6104275	1,3-dimethyl-5-phenyl-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione	0.896
#26	7154899	N-(4-methoxy-1-naphthyl)-4-biphenylcarboxamide	0.85
#27	5160674	2-dibenzo[b,d]furan-3-yl-1,3-dioxo-5-isoindolinecarboxylic acid	0.862
#28	6048589	4-{4-[(diphenylacetyl)amino]benzoyl}phthalic acid	0.905
#29	6659989	3-(4-biphenyloxy)-7-hydroxy-4H-chromen-4-one	0.889
#30	6052953	2-({[4-(2-naphthyloxy)phenyl]amino}carbonyl)benzoic acid	0.924
#31	6573636	N-(4-anilinophenyl)-2-naphthamide	0.884

Table S2. RMSD values of the aligned protein structures of various SARS-CoV-2 strains.

PDB entries	6m0j Å
6m0j	0
7ekf	0.248
7ekg	0.210
7ekc	0.229
7wbq	0.298
7tez	0.521
7u0n	0.518
7xo9	0.492
7xb1	0.475
7zxu	0.377

Supplementary Figures

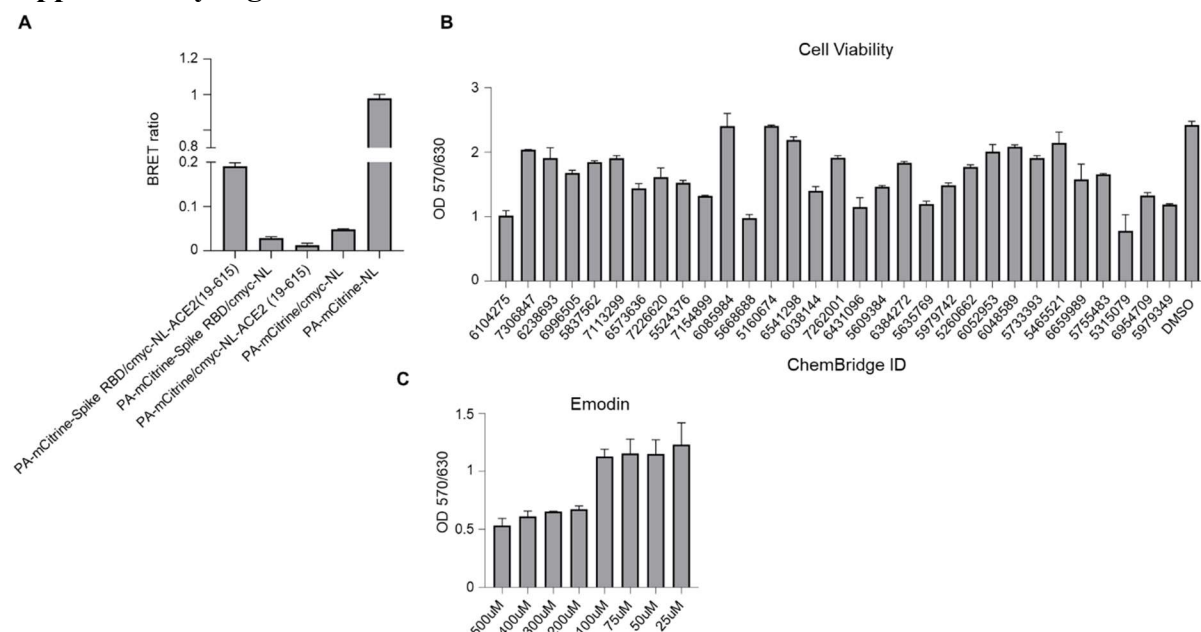


Figure S1. Quantification of Spike-RBD/ACE2 (19-615) interaction, cytotoxicity of computationally-predicted compounds in HEK293T cells **A)** Establishment of cell-based LuThy assay for the quantification of Spike-RBD/ACE2 (19-615) interaction. The positive control PA-mCitrine-NL and the interacting proteins PA-mCitrine-Spike-RBD and NL-ACE2 (aa 19-615) show high corrected BRET (cBRET) ratios. Data are presented as mean \pm SD. **B-C)** Viability of HEK293T cells treated with **(B)** hit compounds in a concentration of 100 μ M or **(C)** the commercial inhibitor Emodin. Cell viability was measured 48 h later using an MTT assay Cells treated with DMSO were used as control. **C)** dvc sdcvsvd

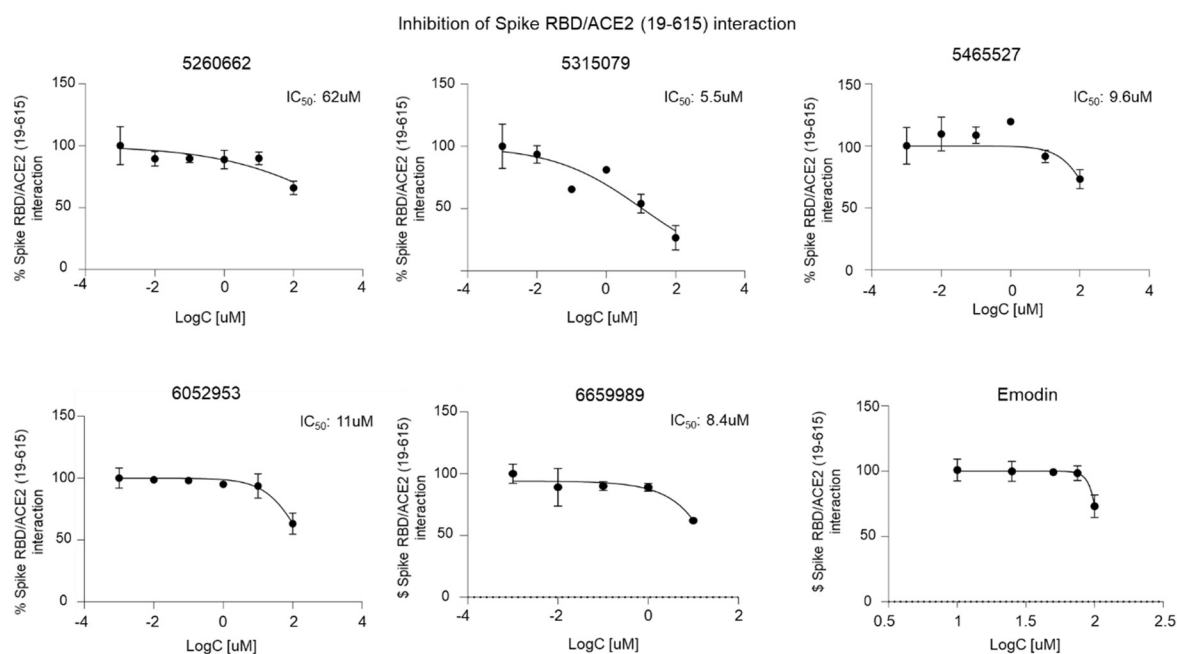


Figure S2. Concentration-dependent inhibition of Spike RBD/ACE2 (19-615) interaction by the active compounds and the positive control (Emodin), as determined by LuTHy assay. Data were presented as mean \pm SD and fitted with standard sigmoid curves for IC₅₀ determination.

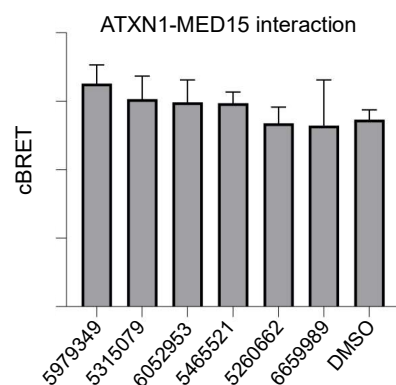


Figure S3. Effect of compounds in ATXN1/MED15 interaction. Validation of six compounds' specificity as inhibitors to Spike RBD/ACE2 interaction. Compounds were checked for their inhibitory activity against ATXN1/MED15 interaction in LuTHy assay. cBRET ratios as compared to control DMSO are shown in diagram, confirming their interaction-based specificity.

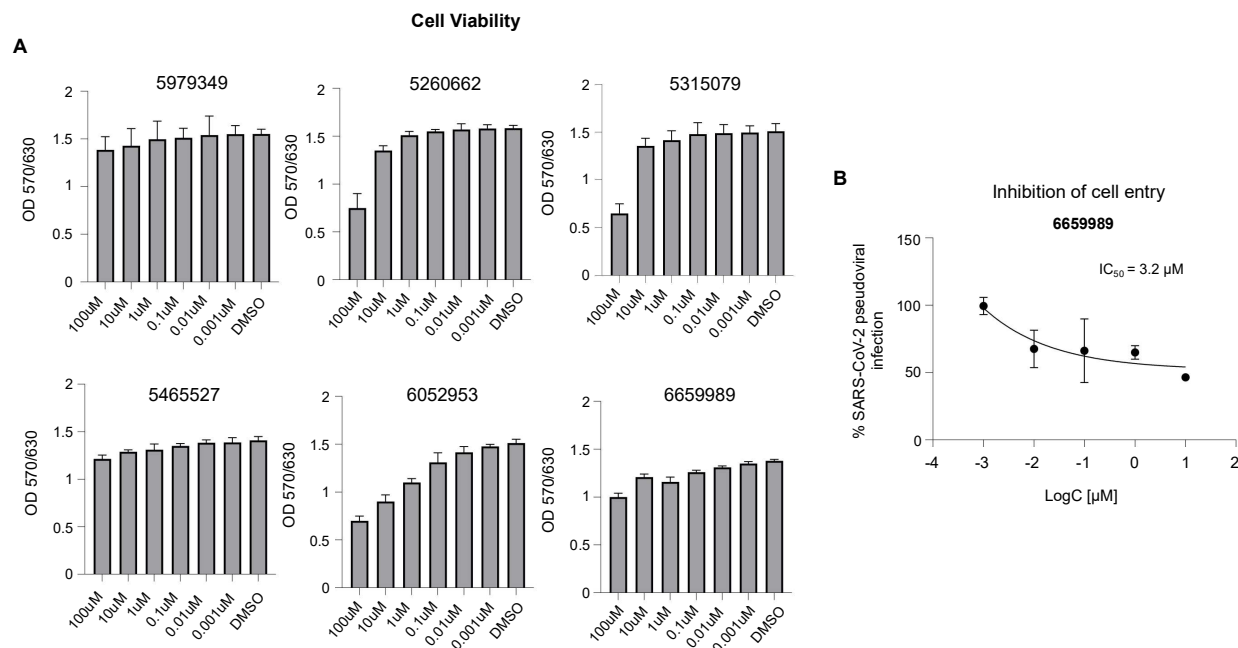


Figure S4. A) Cytotoxicity of the active six compounds in SH-SY5Y cells. Cells were incubated with gradient concentrations of compounds for 48 h. Cell viability was measured by MTT assay. **B)** Concentration-response curve obtained for the inhibition of SARS-CoV-2 pseudovirus entry in a cell-based assay. Compound 6659989 blocks the entry of SARS-COV-2 pseudovirus with an IC_{50} of $3.2 \mu M$. Data are mean \pm SD and fitted with standard sigmoid curves for IC_{50} determination.

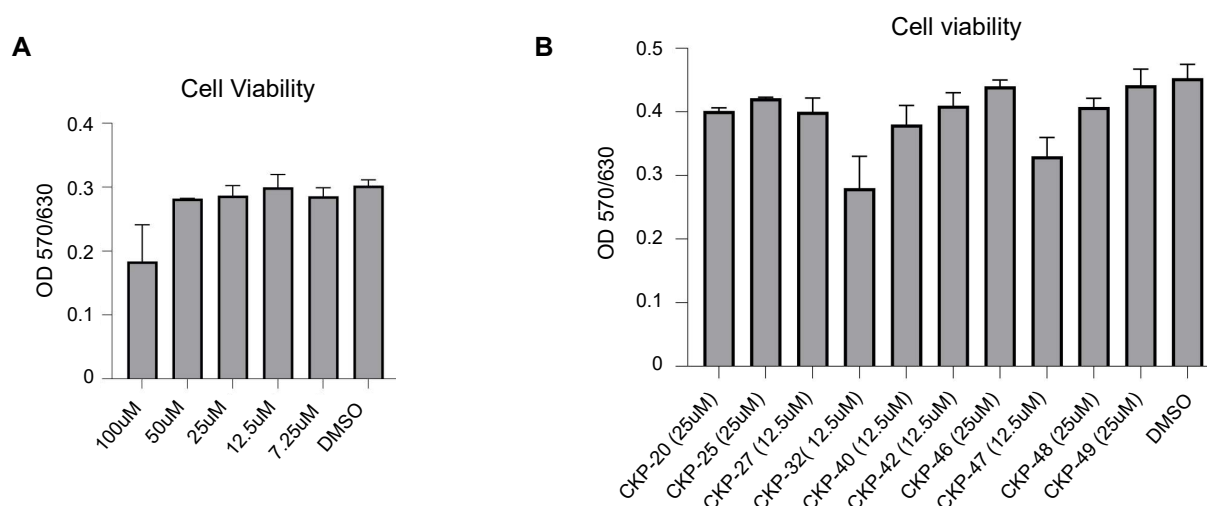
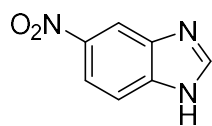


Figure S5. Toxicity assessment of A) CKP-22 (7.25-100 μM final concentration) and B) its derivatives in Vero E6 cells. Cell viability was monitored at 48hrs post treatment using MTT assay.

Experimental procedures

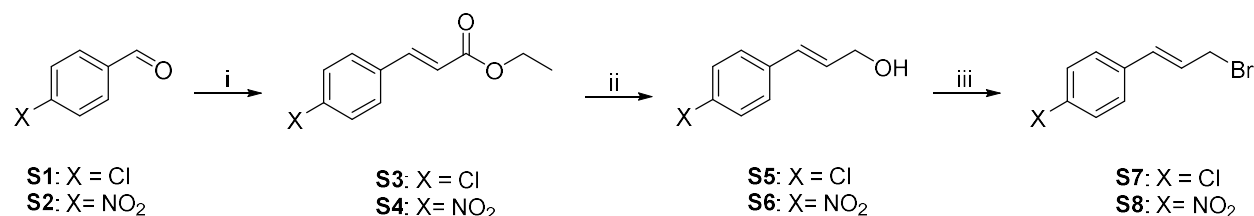
5-nitro-1*H*-benzo[*d*]imidazole (2) [1]



To an ice-cold mixture of benzimidazole (1.0 g, 8.46 mmol) in conc. H₂SO₄ (6 mL), fuming HNO₃ (6 mL) was added dropwise and the resulting solution was stirred at 0 °C for 3h. Then, reaction mixture was poured slowly to ice-water

with stirring. The precipitated product was filtered, washed with cold water and dried. White solid, 1.38 g (quant.); *R*_f = 0.29 (DCM/MeOH 9:1 v/v); ¹H-NMR (300 MHz, DMSO-*d*₆): δ 12.35 (s, 1H), 9.39 (unresolved d, 1H), 8.65 (s, 1H), 8.32 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ 145.7, 144.6, 136.5, 132.6, 120.3, 115.5, 111.8.

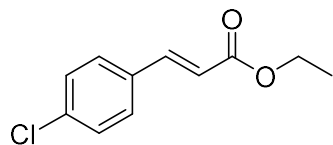
Synthesis of bromides S7 and S8



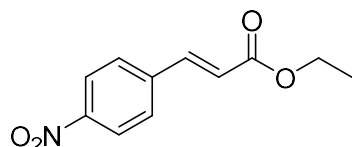
Scheme S1. Synthesis of bromides **S7** and **S8**. *Reagents and conditions.* (i) triethyl phosphonoacetate, LiCl, DBU, MeCN, rt, overnight; (ii) DIBAL-H (1.2 M in PhMe), PhMe, -78 °C, 0.5-1 h; (iii) PBr₃, Et₂O, 0 °C, 0.5 h.

General procedure for the Horner-Emmons reaction [2].

To an ice-cold suspension of LiCl (0.47 g, 11 mmol) in MeCN (30 mL), triethyl phosphonoacetate (1.98 mL, 10 mmol) and the appropriate benzaldehyde **S1** or **S2** (10 mmol) were added. After 5 min, DBU (1.49 mL, 10 mmol) was added dropwise and the resulting mixture was allowed to attend slowly rt and stirred overnight. Upon completion, solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether and brine. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was subjected to FCC to afford the desired ethyl ester **S3** or **S4** respectively, in pure form.

Ethyl (*E*)-3-(4-chlorophenyl)acrylate (S3). [3]

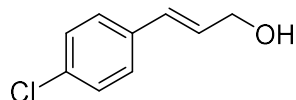
Prepared according to the above general procedure using 4-chlorobenzaldehyde (**S1**) (1.41 g, 10 mmol) as starting material. 2.04 g (97 %), colorless oil; R_f = 0.29 (Hexane/EtOAc 20:1); ^1H NMR (300 MHz, CDCl_3): δ 7.60 (d, J = 16.1 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 6.39 (d, J = 16.1 Hz, 1H), 4.25 (q, J = 6.6 Hz, 1H), 1.32 (t, J = 6.6 Hz, 1H) ppm.

Ethyl (*E*)-3-(4-nitrophenyl)acrylate (S4). [3]

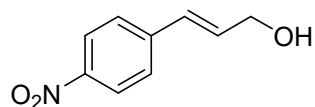
Prepared according to the above general procedure using 4-nitrobenzaldehyde (**S2**) (1.51 g, 10 mmol) as starting material. 1.94 g (88%), yellow solid; mp. 136–138 °C; R_f = 0.25 (Hexane/EtOAc 5:1); ^1H NMR (300 MHz, CDCl_3): δ 8.25 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 16.1 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 16.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 1H), 1.35 (t, J = 7.1 Hz, 1H) ppm.

General procedure for the synthesis of cinnamyl alcohols. [2]

To a solution of the appropriate α,β -unsaturated ester **S3** or **S4** (8 mmol) in PhMe (65 mL) at -78 °C, DIBAL-H (13.5 mL, 16 mmol, 1.2 M in PhMe) was added dropwise. When starting material was fully consumed (0.5 – 1h), the reaction was quenched with MeOH (3 mL) and a sat. aqueous NH_4Cl solution (15 mL), it was allowed to warm slowly at rt and it was stirred for additional 20 min. The resulting salts were passed through a Celite pad and the filtrate was transferred to a separatory funnel. The aqueous phase was extracted thrice with DCM and the combined organic layers washed with brine, dried over Na_2SO_4 , filtered and evaporated. The desired allylic alcohols **S5** or **S6** respectively, were obtained in pure form after FCC purification.

(*E*)-3-(4-chlorophenyl)prop-2-en-1-ol (S5) [4]

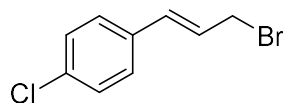
Prepared according to the above general procedure using ethyl ester **S3** (1.69 g, 8 mmol) as starting material. 1.35 g (quant.), yellow solid; mp. 62–65 °C; R_f = 0.20 (petroleum ether/Ethyl acetate 4:1); ^1H NMR (300 MHz, CDCl_3): δ 7.31–7.26 (m, 4H), 6.58 (d, J = 15.9 Hz, 1H), 6.38–6.31 (m, 1H), 4.33 (dd, J = 5.6 and 1.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 135.3, 133.4, 129.9, 129.3; 128.9 (two C), 127.8 (two C), 63.7 ppm

(E)-3-(4-nitrophenyl)prop-2-en-1-ol (S6) [5]

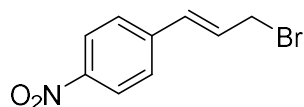
Prepared according to the above general procedure using ethyl ester **S4** (1.77 g, 8 mmol) as starting material. 1.12 g (78%), yellow solid; mp. 123–125 °C; R_f = 0.14 (petroleum ether/Ethyl acetate 3:1); ^1H NMR (300 MHz, CDCl_3): δ 8.18 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 16.1 Hz, 1H), 6.54 (dt, J = 16.1 and 5.0 Hz, 1H), 4.40 (d, J = 5.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 146.4, 143.6, 133.7; 128.4; 127.1 (two C), 124.2 (two C), 63.3 ppm.

General procedure for the synthesis of cinnamyl bromides. [6]

To an ice-cold solution of cinnamyl alcohol **S5** or **S6** (5 mmol) in diethyl ether (12.5 mL), PBr_3 (0.62 mL, 6.5 mmol) was added. The reaction mixture was stirred at 0 °C until the full consumption of starting material (20-30 min), it was diluted with diethyl ether (12.5 mL) and it was carefully quenched with a sat. aqueous NaHCO_3 solution (2-3 mL). The mixture was allowed to attain rt, stirred for additional 15 min and transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted thrice with diethyl ether. The combined organic layers were washed with a sat. aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine, dried over Na_2SO_4 , filtered and evaporated to afford cinnamyl bromides **S7** and **S8** respectively.

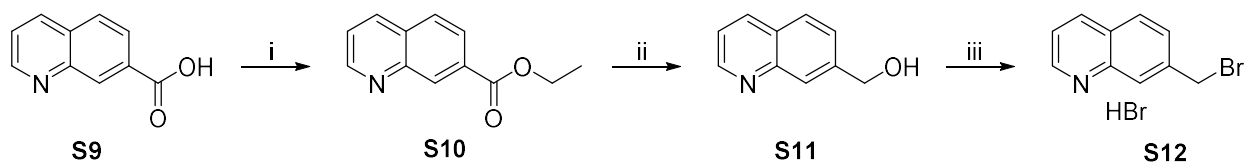
(E)-1-(3-bromoprop-1-en-1-yl)-4-chlorobenzene (S7) [6]

Prepared according to the above general procedure using cinnamyl alcohol **S5** (0.84 g, 5 mmol) as starting material. 0.83 g (72%), white solid; mp. 60–61 °C; ^1H NMR (600 MHz, CDCl_3): δ 7.35–7.28 (m, 4H), 6.60 (d, J = 15.6 Hz, 1H), 6.41–6.32 (m, 1H), 4.14 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 134.3, 134.0, 133.2, 128.9 (two C), 127.9 (two C), 125.8, 33.0 ppm.

(E)-1-(3-bromoprop-1-en-1-yl)-4-nitrobenzene (S8). [6]

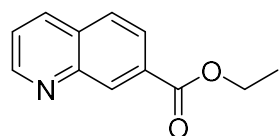
Prepared according to the above general procedure using cinnamyl alcohol **S6** (0.90 g, 5 mmol) as starting material. 0.64 g (53%), yellow solid (recrystallized from Et_2O /Hex 95:5); m.p. 76–78 °C; ^1H NMR (600 MHz, CDCl_3): δ 8.19 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 15.6 Hz, 1H), 6.58 – 6.56 (m, 1H), 4.16 (dd, J = 7.8 and 0.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 147.6, 142.2, 132.1, 129.9 (two C), 127.3, 124.0 (two C), 31.8 ppm.

Synthesis of bromide **S12**.



Scheme S2. Synthesis of bromide **S12**. *Reagents and conditions.* (i) conc. H₂SO₄, EtOH, reflux, 72 h; (ii) DIBAL-H (1.0 M in DCM), THF, -78 to 0 °C, 1.5 h; (iii) 33% HBr solution in CH₃CO₂H, reflux, overnight.

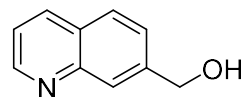
Ethyl quinoline-7-carboxylate (**S10**)



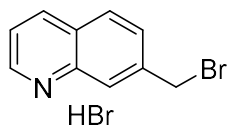
To a solution of quinoline-7-carboxylic acid (**S9**) (0.5 g, 2.88 mmol) in EtOH (20 mL), conc. H₂SO₄ (1.1 mL) was added and the resulting mixture was refluxed for 72 h. The mixture was left to attain rt and all the volatile components were evaporated under vacuo. The residue was taken up in EtOAc and washed with a sat. aqueous NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to furnish **S10** which was used to the next step without further purification.

0.6 g (quant.); off-white solid, mp. 55–56 °C; ¹H NMR (300 MHz, acetone-*d*₆): δ 9.05 (unresolved dd, 1H), 8.74 m, 1H), 8.50 (m, 1H), 8.15 (m, 2H), 7.69 (m, 1H), 4.45 (q, *J* = 7.0 Hz 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ESI-MS: 424.63 (2M+Na), 202.25 (M+H).

Quinolin-7-ylmethanol (**S11**)



A solution of ester **S10** (0.5 g, 2.5 mmol) in THF (12.5 mL) was cooled to –78 °C and then a solution of DIBAL-H (1M in DCM, 7.5 mL) in THF (12.5 mL) was added dropwise. Upon addition, the reaction mixture was stirred at 0 °C for 1.5 h, quenched with MeOH (12.5 mL) and CH₃COOH (2.1 mL), stirred for 5 min and then a sat. aqueous sodium potassium tartrate solution (25 mL) was added. The resulting mixture was stirred for further 20 min and the EtOAc was added. The aqueous phase was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was subjected to FCC (petroleum ether/EtOAc 1:1 to EtOAc) to afford alcohol **S11** in pure form which was used directly to the next step. 0.16 g (40% or 84% brsm); white solid, m.p 58–60 °C

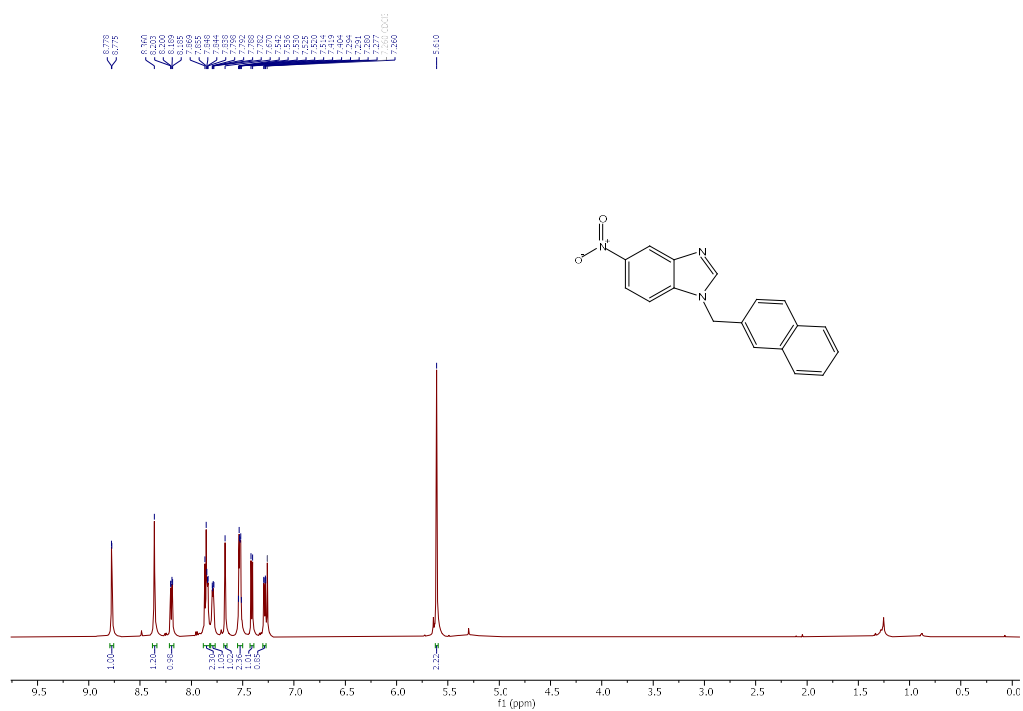
7-(bromomethyl)quinoline hydrobromide salt (S12)

To a rb-flask containing alcohol **S11** (0.16 g, 1.0 mmol) a 33% HBr solution in $\text{CH}_3\text{CO}_2\text{H}$ (1.2 mL) was added and the mixture was heated at 70 °C overnight. The reaction mixture was evaporated to dryness and co-evaporated three times with

PhMe to remove excess $\text{CH}_3\text{CO}_2\text{H}$ until an off-white solid was formed.

0.28 g (92%), off-white solid, m.p. 67–70 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 9.22 (dd, $J = 5.0$ and 1.6 Hz, 1H), 8.95 (d, $J = 8.4$ Hz, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 8.25 – 8.23 (m, 1H), 7.95 (dd, $J = 8.4$ and 5.0 Hz, 1H), 7.90 (dd, $J = 8.4$ and 1.6 Hz, 1H), 5.02 (s, 2H).

Copies of ^1H -NMR, ^{13}C -NMR and HRMS spectra of final compounds.



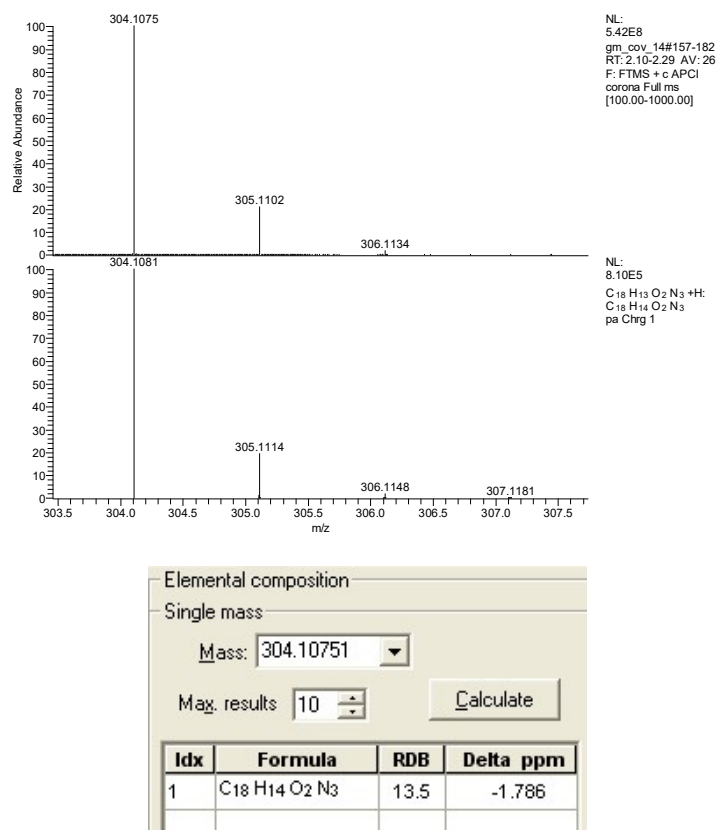


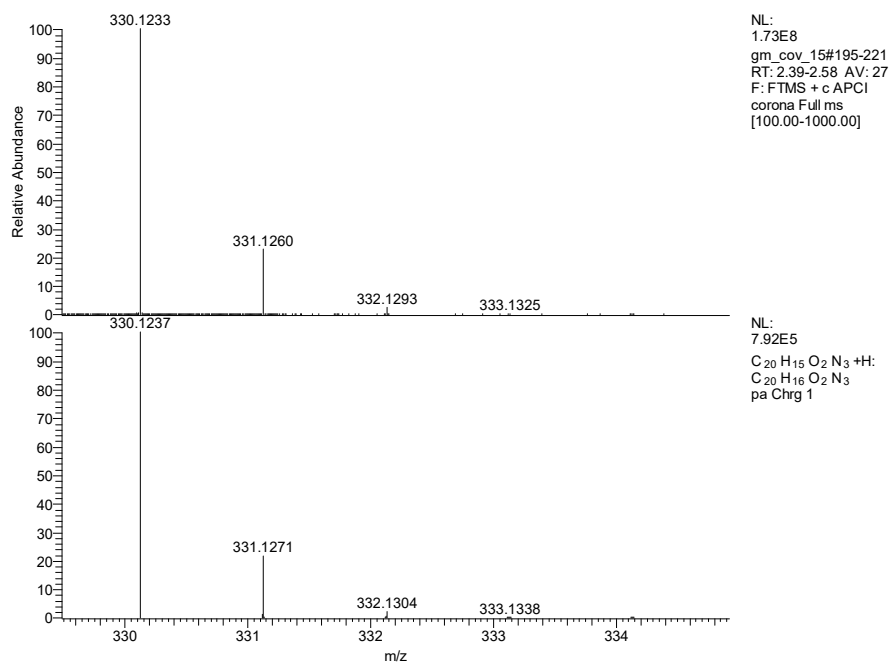
Figure S8. HRMS of compound **3**.

Chemical structure of the compound is shown above the spectrum. The spectrum displays peaks corresponding to the chemical structure, with the following chemical shifts (ppm) labeled above the peaks:

- 146.534
- 142.067
- 140.091
- 137.279
- 132.061
- 129.892
- 129.881
- 127.817
- 127.254
- 119.361
- 117.166
- 110.521
- 49.449

The x-axis is labeled f1 (ppm) and ranges from 190 to 0.

Figure S10. ^{13}C -NMR of compound **4**.



Elemental composition

Single mass

Mass: 330.12332

Max. results 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₀ H ₁₆ O ₂ N ₃	14.5	-1.161

Figure S11. HRMS of compound 4.

Chemical structure: Nc1ccc2c(c1)n(c2)CNc3cccc4ccccc34

¹H NMR spectrum (CDCl₃) showing peaks in the aromatic region (6.5-8.5 ppm) and an NH₂ peak (7.8 ppm). The x-axis is labeled f1 (ppm) and ranges from -10 to 230.

Peak list (ppm): 8.372, 8.361, 8.351, 8.341, 8.331, 8.321, 8.311, 8.301, 8.291, 8.281, 8.271, 8.261, 8.251, 8.241, 8.231, 8.221, 8.211, 8.201, 8.191, 8.181, 8.171, 8.161, 8.151, 8.141, 8.131, 8.121, 8.111, 8.101, 8.091, 8.081, 8.071, 8.061, 8.051, 8.041, 8.031, 8.021, 8.011, 8.001, 7.991, 7.981, 7.971, 7.961, 7.951, 7.941, 7.931, 7.921, 7.911, 7.901, 7.891, 7.881, 7.871, 7.861, 7.851, 7.841, 7.831, 7.821, 7.811, 7.801, 7.791, 7.781, 7.771, 7.761, 7.751, 7.741, 7.731, 7.721, 7.711, 7.701, 7.691, 7.681, 7.671, 7.661, 7.651, 7.641, 7.631, 7.621, 7.611, 7.601, 7.591, 7.581, 7.571, 7.561, 7.551, 7.541, 7.531, 7.521, 7.511, 7.501, 7.491, 7.481, 7.471, 7.461, 7.451, 7.441, 7.431, 7.421, 7.411, 7.401, 7.391, 7.381, 7.371, 7.361, 7.351, 7.341, 7.331, 7.321, 7.311, 7.301, 7.291, 7.281, 7.271, 7.261, 7.251, 7.241, 7.231, 7.221, 7.211, 7.201, 7.191, 7.181, 7.171, 7.161, 7.151, 7.141, 7.131, 7.121, 7.111, 7.101, 7.091, 7.081, 7.071, 7.061, 7.051, 7.041, 7.031, 7.021, 7.011, 7.001, 6.991, 6.981, 6.971, 6.961, 6.951, 6.941, 6.931, 6.921, 6.911, 6.901, 6.891, 6.881, 6.871, 6.861, 6.851, 6.841, 6.831, 6.821, 6.811, 6.801, 6.791, 6.781, 6.771, 6.761, 6.751, 6.741, 6.731, 6.721, 6.711, 6.701, 6.691, 6.681, 6.671, 6.661, 6.651, 6.641, 6.631, 6.621, 6.611, 6.601, 6.591, 6.581, 6.571, 6.561, 6.551, 6.541, 6.531, 6.521, 6.511, 6.501, 6.491, 6.481, 6.471, 6.461, 6.451, 6.441, 6.431, 6.421, 6.411, 6.401, 6.391, 6.381, 6.371, 6.361, 6.351, 6.341, 6.331, 6.321, 6.311, 6.301, 6.291, 6.281, 6.271, 6.261, 6.251, 6.241, 6.231, 6.221, 6.211, 6.201, 6.191, 6.181, 6.171, 6.161, 6.151, 6.141, 6.131, 6.121, 6.111, 6.101, 6.091, 6.081, 6.071, 6.061, 6.051, 6.041, 6.031, 6.021, 6.011, 6.001, 5.991, 5.981, 5.971, 5.961, 5.951, 5.941, 5.931, 5.921, 5.911, 5.901, 5.891, 5.881, 5.871, 5.861, 5.851, 5.841, 5.831, 5.821, 5.811, 5.801, 5.791, 5.781, 5.771, 5.761, 5.751, 5.741, 5.731, 5.721, 5.711, 5.701, 5.691, 5.681, 5.671, 5.661, 5.651, 5.641, 5.631, 5.621, 5.611, 5.601, 5.591, 5.581, 5.571, 5.561, 5.551, 5.541, 5.531, 5.521, 5.511, 5.501, 5.491, 5.481, 5.471, 5.461, 5.451, 5.441, 5.431, 5.421, 5.411, 5.401, 5.391, 5.381, 5.371, 5.361, 5.351, 5.341, 5.331, 5.321, 5.311, 5.301, 5.291, 5.281, 5.271, 5.261, 5.251, 5.241, 5.231, 5.221, 5.211, 5.201, 5.191, 5.181, 5.171, 5.161, 5.151, 5.141, 5.131, 5.121, 5.111, 5.101, 5.091, 5.081, 5.071, 5.061, 5.051, 5.041, 5.031, 5.021, 5.011, 5.001, 4.991, 4.981, 4.971, 4.961, 4.951, 4.941, 4.931, 4.921, 4.911, 4.901, 4.891, 4.881, 4.871, 4.861, 4.851, 4.841, 4.831, 4.821, 4.811, 4.801, 4.791, 4.781, 4.771, 4.761, 4.751, 4.741, 4.731, 4.721, 4.711, 4.701, 4.691, 4.681, 4.671, 4.661, 4.651, 4.641, 4.631, 4.621, 4.611, 4.601, 4.591, 4.581, 4.571, 4.561, 4.551, 4.541, 4.531, 4.521, 4.511, 4.501, 4.491, 4.481, 4.471, 4.461, 4.451, 4.441, 4.431, 4.421, 4.411, 4.401, 4.391, 4.381, 4.371, 4.361, 4.351, 4.341, 4.331, 4.321, 4.311, 4.301, 4.291, 4.281, 4.271, 4.261, 4.251, 4.241, 4.231, 4.221, 4.211, 4.201, 4.191, 4.181, 4.171, 4.161, 4.151, 4.141, 4.131, 4.121, 4.111, 4.101, 4.091, 4.081, 4.071, 4.061, 4.051, 4.041, 4.031, 4.021, 4.011, 4.001, 3.991, 3.981, 3.971, 3.961, 3.951, 3.941, 3.931, 3.921, 3.911, 3.901, 3.891, 3.881, 3.871, 3.861, 3.851, 3.841, 3.831, 3.821, 3.811, 3.801, 3.791, 3.781, 3.771, 3.761, 3.751, 3.741, 3.731, 3.721, 3.711, 3.701, 3.691, 3.681, 3.671, 3.661, 3.651, 3.641, 3.631, 3.621, 3.611, 3.601, 3.591, 3.581, 3.571, 3.561, 3.551, 3.541, 3.531, 3.521, 3.511, 3.501, 3.491, 3.481, 3.471, 3.461, 3.451, 3.441, 3.431, 3.421, 3.411, 3.401, 3.391, 3.381, 3.371, 3.361, 3.351, 3.341, 3.331, 3.321, 3.311, 3.301, 3.291, 3.281, 3.271, 3.261, 3.251, 3.241, 3.231, 3.221, 3.211, 3.201, 3.191, 3.181, 3.171, 3.161, 3.151, 3.141, 3.131, 3.121, 3.111, 3.101, 3.091, 3.081, 3.071, 3.061, 3.051, 3.041, 3.031, 3.021, 3.011, 3.001, 2.991, 2.981, 2.971, 2.961, 2.951, 2.941, 2.931, 2.921, 2.911, 2.901, 2.891, 2.881, 2.871, 2.861, 2.851, 2.841, 2.831, 2.821, 2.811, 2

Figure S13. ^{13}C -NMR of compound **5**.

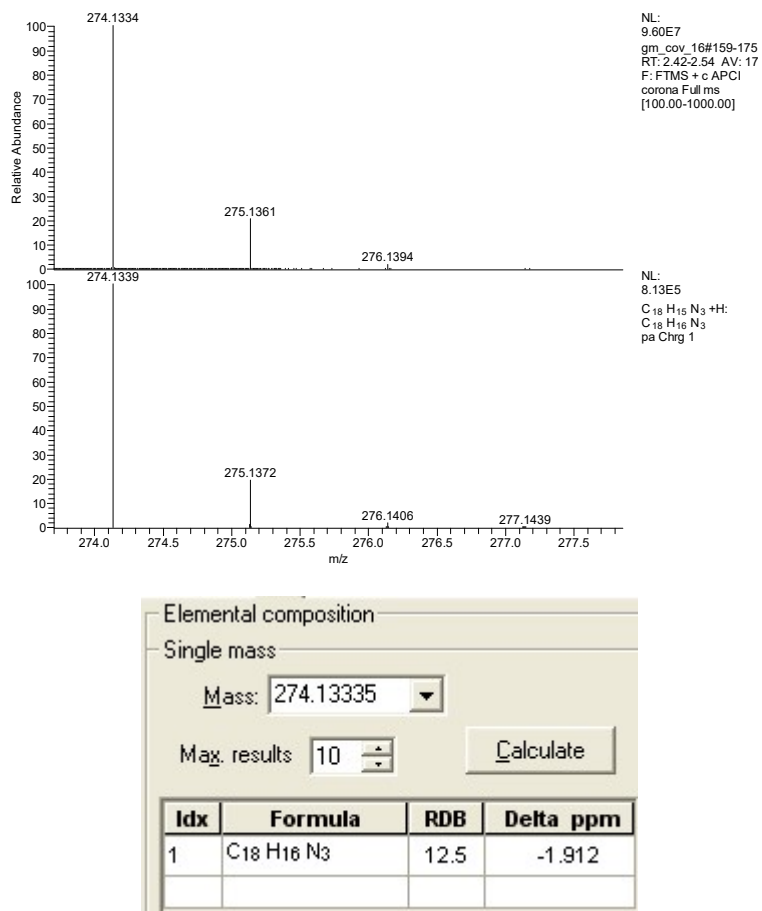


Figure S14. HRMS of compound **5**.

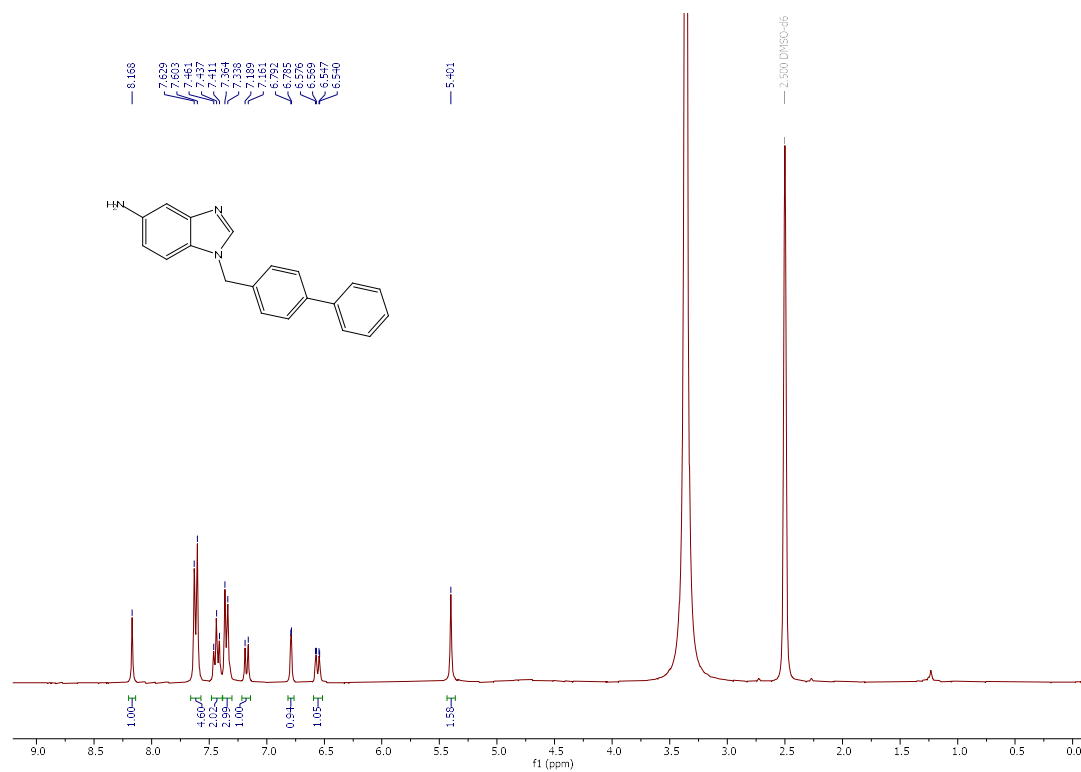


Figure S15. ¹H-NMR of compound 6.

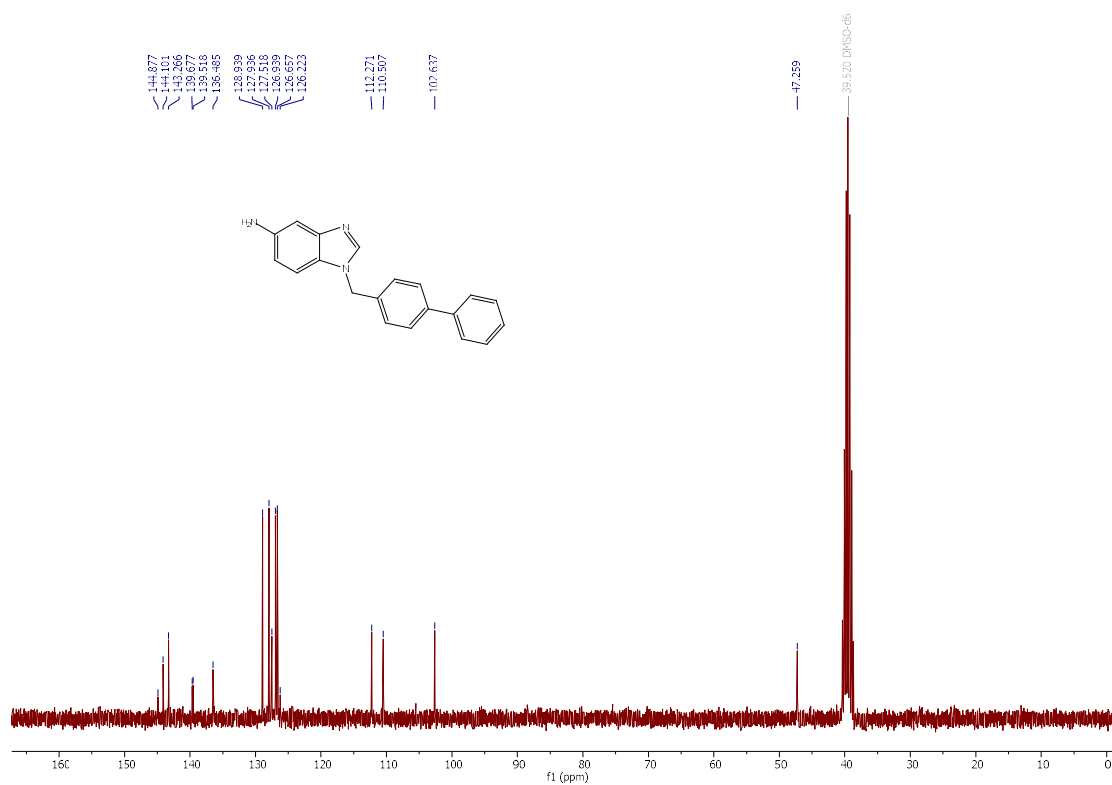
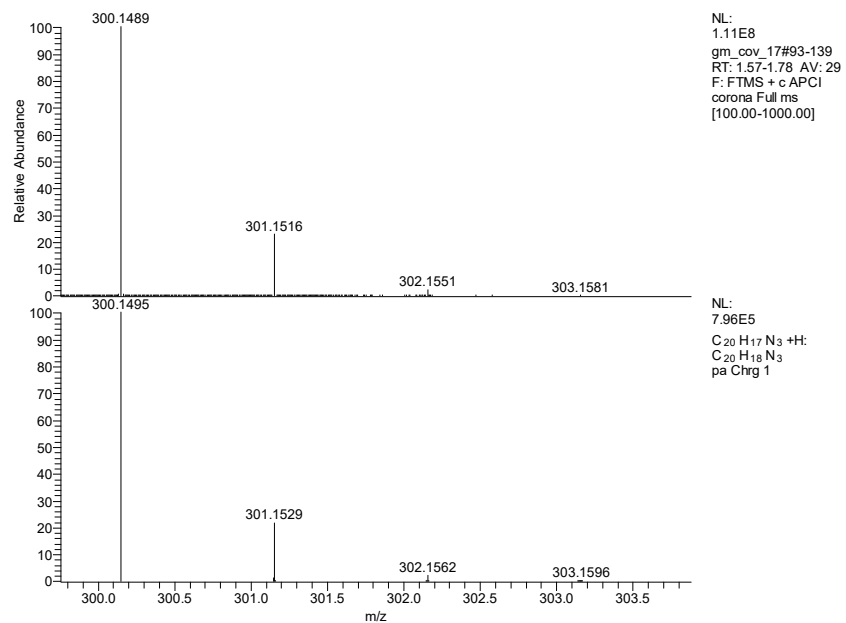


Figure S16. ¹³C-NMR of compound 6.



Elemental composition

Single mass

Mass: 300.14886

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₀ H ₁₈ N ₃	13.5	-2.213

Figure S17. HRMS of compound 6.

Chemical structure: c1ccc2ccccc2c1CNc3c[nH]c4ccccc4c3[N+](=O)[O-]

¹³C NMR peaks (ppm): 158.235, 157.772, 157.770, 157.768, 157.766, 157.764, 157.762, 157.760, 157.758, 157.756, 157.754, 157.752, 157.750, 157.748, 157.746, 157.744, 157.742, 157.740, 157.738, 157.736, 157.734, 157.732, 157.730, 157.728, 157.726, 157.724, 157.722, 157.720, 157.718, 157.716, 157.714, 157.712, 157.710, 157.708, 157.706, 157.704, 157.702, 157.700, 157.698, 157.696, 157.694, 157.692, 157.690, 157.688, 157.686, 157.684, 157.682, 157.680, 157.678, 157.676, 157.674, 157.672, 157.670, 157.668, 157.666, 157.664, 157.662, 157.660, 157.658, 157.656, 157.654, 157.652, 157.650, 157.648, 157.646, 157.644, 157.642, 157.640, 157.638, 157.636, 157.634, 157.632, 157.630, 157.628, 157.626, 157.624, 157.622, 157.620, 157.618, 157.616, 157.614, 157.612, 157.610, 157.608, 157.606, 157.604, 157.602, 157.600, 157.598, 157.596, 157.594, 157.592, 157.590, 157.588, 157.586, 157.584, 157.582, 157.580, 157.578, 157.576, 157.574, 157.572, 157.570, 157.568, 157.566, 157.564, 157.562, 157.560, 157.558, 157.556, 157.554, 157.552, 157.550, 157.548, 157.546, 157.544, 157.542, 157.540, 157.538, 157.536, 157.534, 157.532, 157.530, 157.528, 157.526, 157.524, 157.522, 157.520, 157.518, 157.516, 157.514, 157.512, 157.510, 157.508, 157.506, 157.504, 157.502, 157.500, 157.498, 157.496, 157.494, 157.492, 157.490, 157.488, 157.486, 157.484, 157.482, 157.480, 157.478, 157.476, 157.474, 157.472, 157.470, 157.468, 157.466, 157.464, 157.462, 157.460, 157.458, 157.456, 157.454, 157.452, 157.450, 157.448, 157.446, 157.444, 157.442, 157.440, 157.438, 157.436, 157.434, 157.432, 157.430, 157.428, 157.426, 157.424, 157.422, 157.420, 157.418, 157.416, 157.414, 157.412, 157.410, 157.408, 157.406, 157.404, 157.402, 157.400, 157.398, 157.396, 157.394, 157.392, 157.390, 157.388, 157.386, 157.384, 157.382, 157.380, 157.378, 157.376, 157.374, 157.372, 157.370, 157.368, 157.366, 157.364, 157.362, 157.360, 157.358, 157.356, 157.354, 157.352, 157.350, 157.348, 157.346, 157.344, 157.342, 157.340, 157.338, 157.336, 157.334, 157.332, 157.330, 157.328, 157.326, 157.324, 157.322, 157.320, 157.318, 157.316, 157.314, 157.312, 157.310, 157.308, 157.306, 157.304, 157.302, 157.300, 157.298, 157.296, 157.294, 157.292, 157.290, 157.288, 157.286, 157.284, 157.282, 157.280, 157.278, 157.276, 157.274, 157.272, 157.270, 157.268, 157.266, 157.264, 157.262, 157.260, 157.258, 157.256, 157.254, 157.252, 157.250, 157.248, 157.246, 157.244, 157.242, 157.240, 157.238, 157.236, 157.234, 157.232, 157.230, 157.228, 157.226, 157.224, 157.222, 157.220, 157.218, 157.216, 157.214, 157.212, 157.210, 157.208, 157.206, 157.204, 157.202, 157.200, 157.198, 157.196, 157.194, 157.192, 157.190, 157.188, 157.186, 157.184, 157.182, 157.180, 157.178, 157.176, 157.174, 157.172, 157.170, 157.168, 157.166, 157.164, 157.162, 157.160, 157.158, 157.156, 157.154, 157.152, 157.150, 157.148, 157.146, 157.144, 157.142, 157.140, 157.138, 157.136, 157.134, 157.132, 157.130, 157.128, 157.126, 157.124, 157.122, 157.120, 157.118, 157.116, 157.114, 157.112, 157.110, 157.108, 157.106, 157.104, 157.102, 157.100, 157.098, 157.096, 157.094, 157.092, 157.090, 157.088, 157.086, 157.084, 157.082, 157.080, 157.078, 157.076, 157.074, 157.072, 157.070, 157.068, 157.066, 157.064, 157.062, 157.060, 157.058, 157.056, 157.054, 157.052, 157.050, 157.048, 157.046, 157.044, 157.042, 157.040, 157.038, 157.036, 157.034, 157.032, 157.030, 157.028, 157.026, 157.024, 157.022, 157.020, 157.018, 157.016, 157.014, 157.012, 157.010, 157.008, 157.006, 157.004, 157.002, 157.000, 156.998, 156.996, 156.994, 156.992, 156.990, 156.988, 156.986, 156.984, 156.982, 156.980, 156.978, 156.976, 156.974, 156.972, 156.970, 156.968, 156.966, 156.964, 156.962, 156.960, 156.958, 156.956, 156.954, 156.952, 156.950, 156.948, 156.946, 156.944, 156.942, 156.940, 156.938, 156.936, 156.934, 156.932, 156.930, 156.928, 156.926, 156.924, 156.922, 156.920, 156.918, 156.916, 156.914, 156.912, 156.910, 156.908, 156.906, 156.904, 156.902, 156.900, 156.898, 156.8

Figure S19. ^{13}C -NMR of compound **11**.

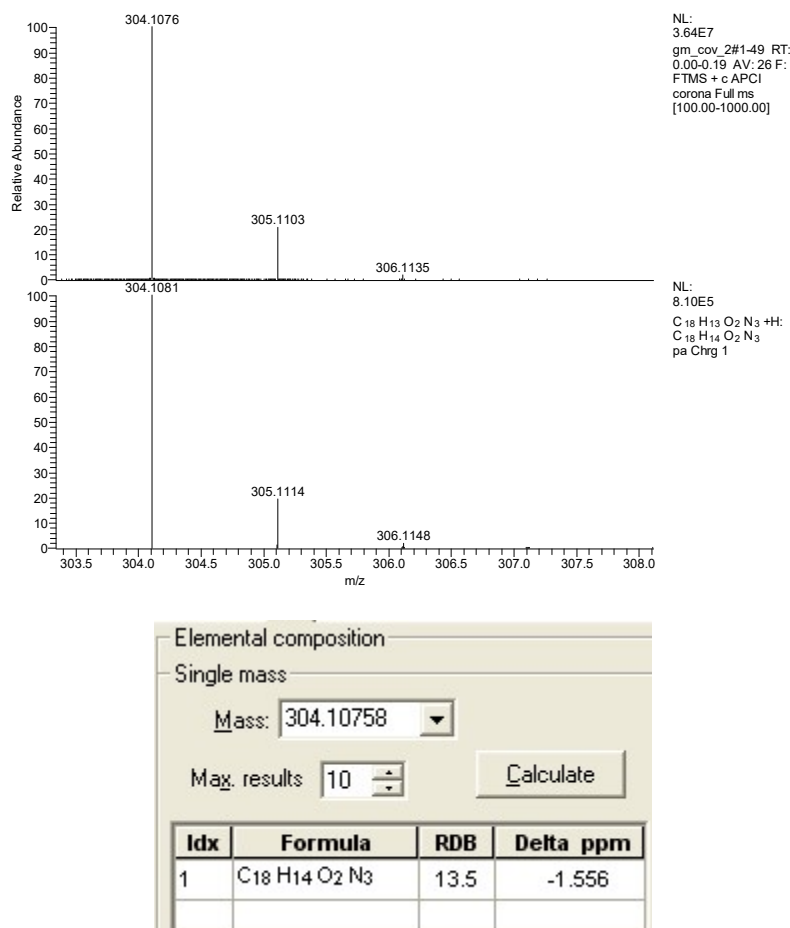


Figure S20. HRMS of compound **11**.

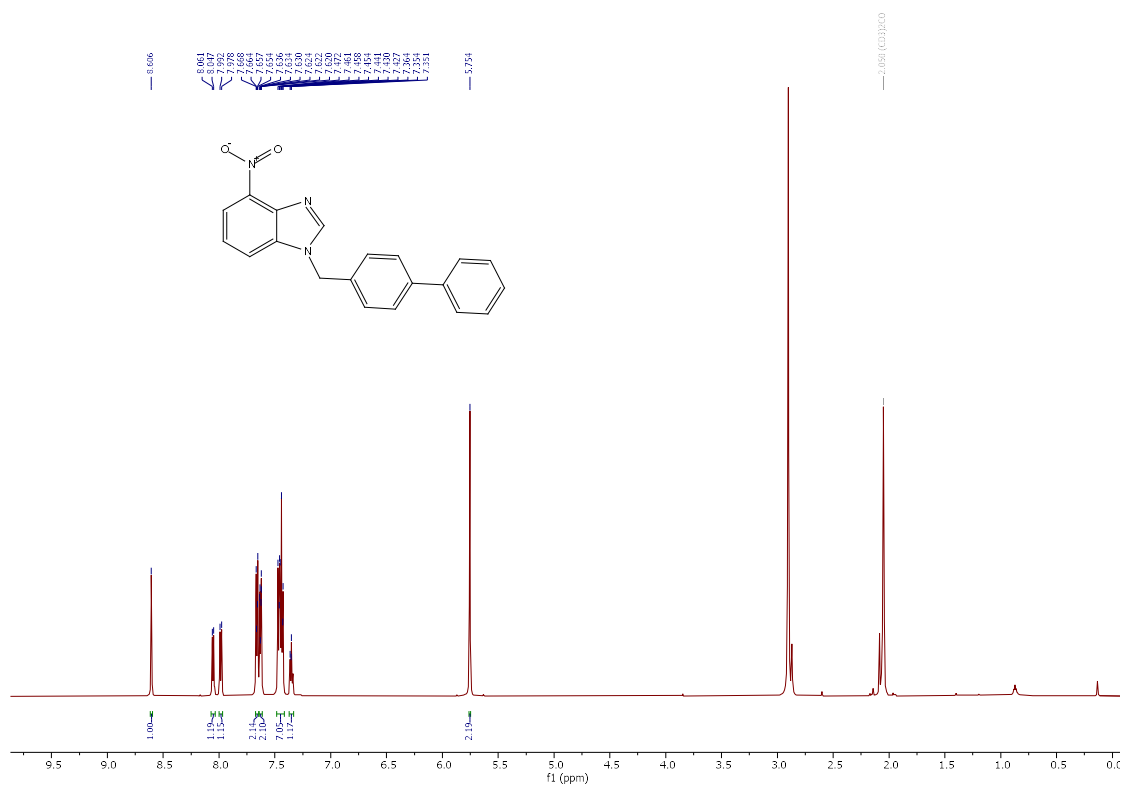


Figure S21. ¹H-NMR of compound 12.

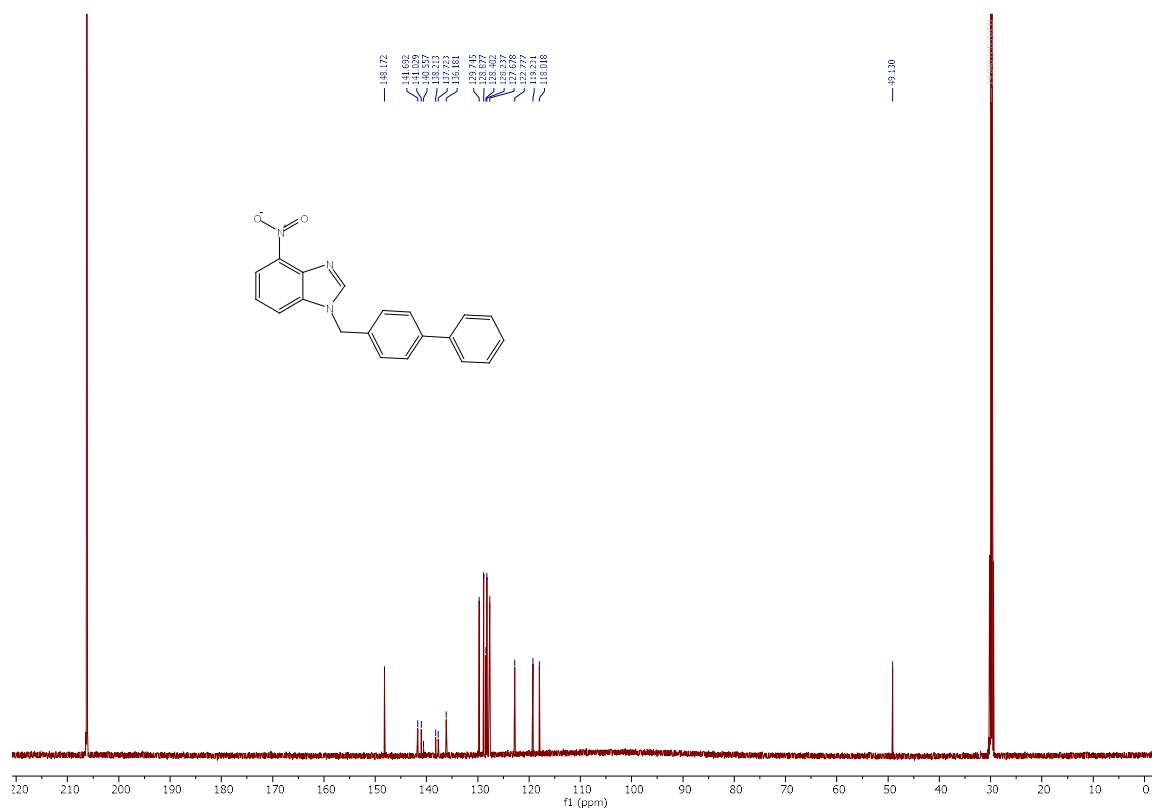
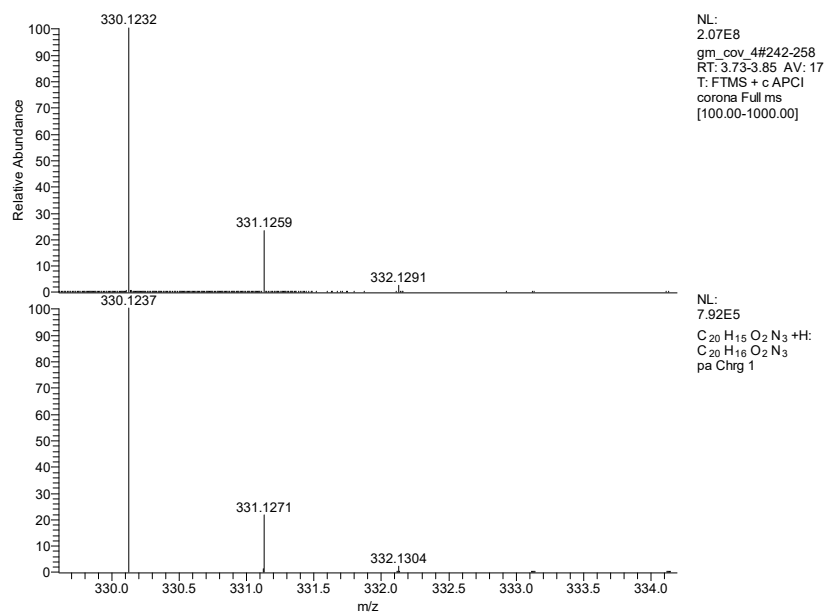


Figure S22. ¹³C-NMR of compound 12.



Elemental composition

Single mass

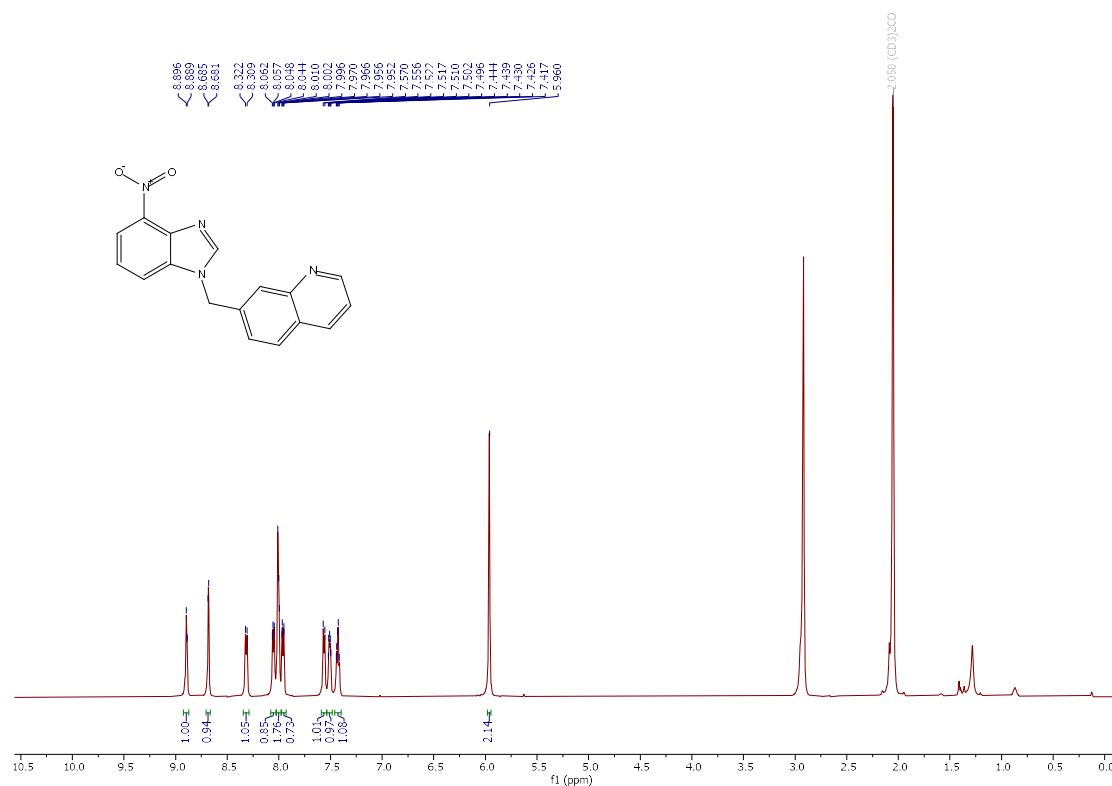
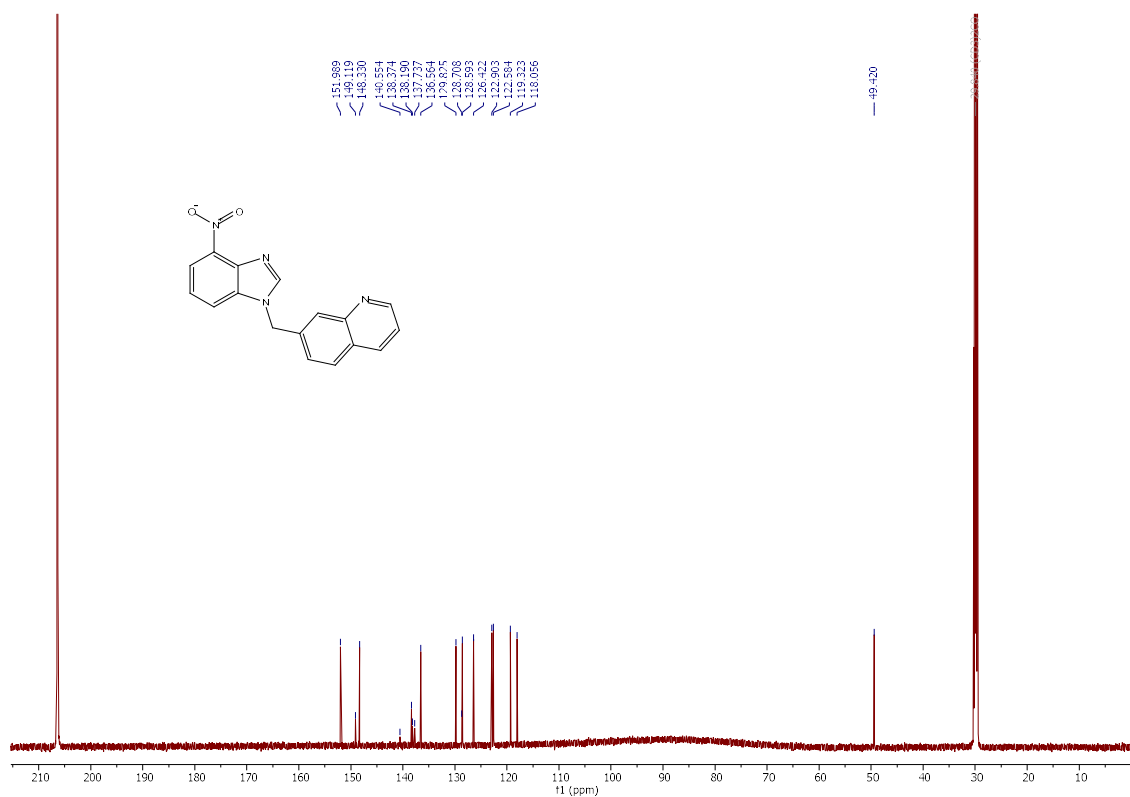
Mass: 330.12323

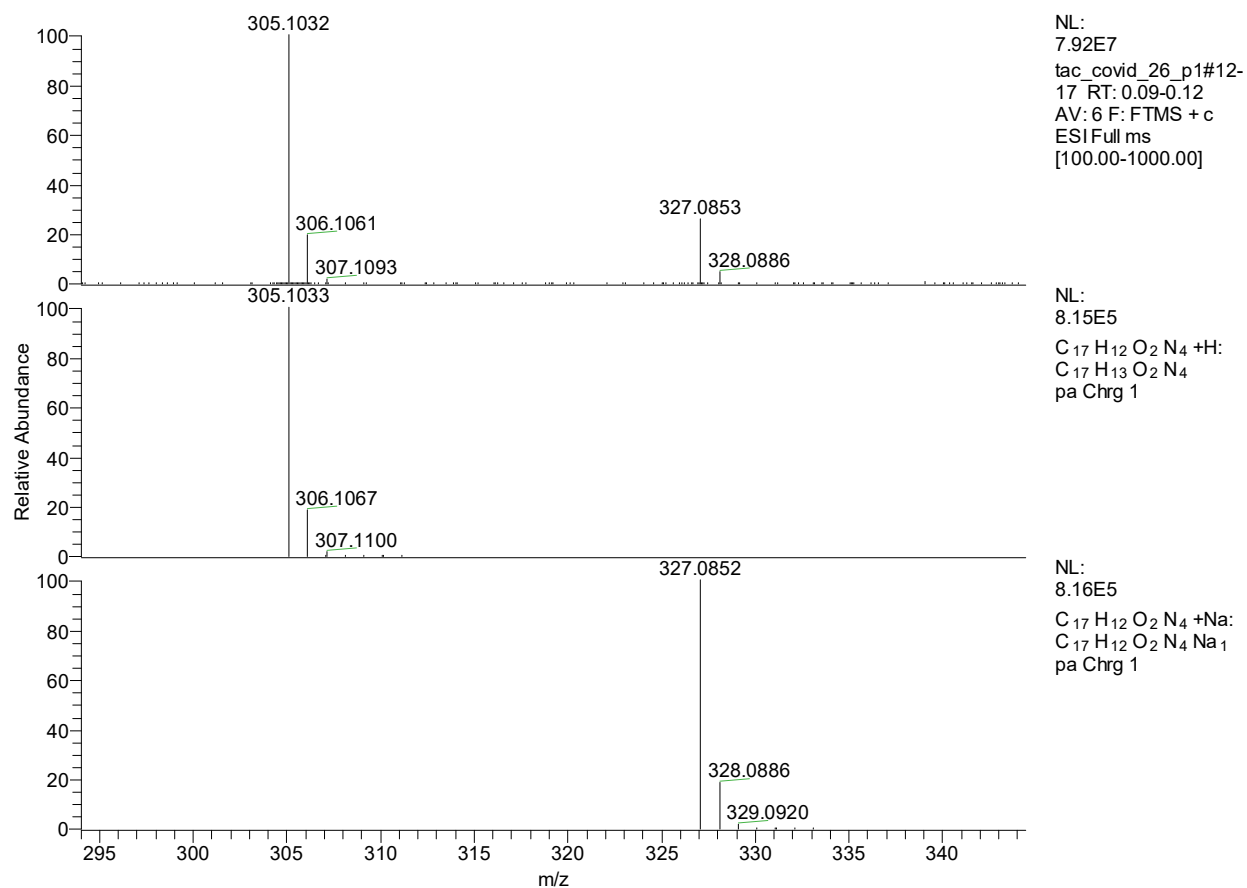
Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₀ H ₁₆ O ₂ N ₃	14.5	-1.434

Figure S23. HRMS of compound 12.

Figure S24. ¹H-NMR of compound 13.Figure S25. ¹³C-NMR of compound 13.



Elemental composition				Elemental composition			
Single mass				Single mass			
Mass: 305.10320				Mass: 327.08529			
Max. results 10				Max. results 10			
Calculate				Calculate			
Idx	Formula	RDB	Delta ppm	Idx	Formula	RDB	Delta ppm
1	C ₁₇ H ₁₃ O ₂ N ₄	13.5	-0.335	1	C ₁₇ H ₁₂ O ₂ N ₄ Na	13.5	0.132

Figure S26. HRMS of compound **13**.

Chemical structure of 1-(2-(naphthalen-1-ylmethyl)-1H-indol-3-yl)pyrrolidine:

C1CCN1c2cnc3ccccc3c2Cc4ccc5ccccc45

¹³C NMR peaks (ppm):

- 142.519
- 141.588
- 141.586
- 141.584
- 135.681
- 135.681
- 134.283
- 134.283
- 133.613
- 133.613
- 132.981
- 132.981
- 132.671
- 132.671
- 132.544
- 132.544
- 132.523
- 132.523
- 132.249
- 132.249
- 132.082
- 132.082
- 126.962
- 126.962
- 126.940
- 126.940
- 126.700
- 126.690
- 126.690
- 123.786
- 123.786
- 123.610
- 123.610
- 105.519

Chemical shift range: 100.000 to 145.000 ppm.

Figure S28. ^{13}C -NMR of compound **14**.

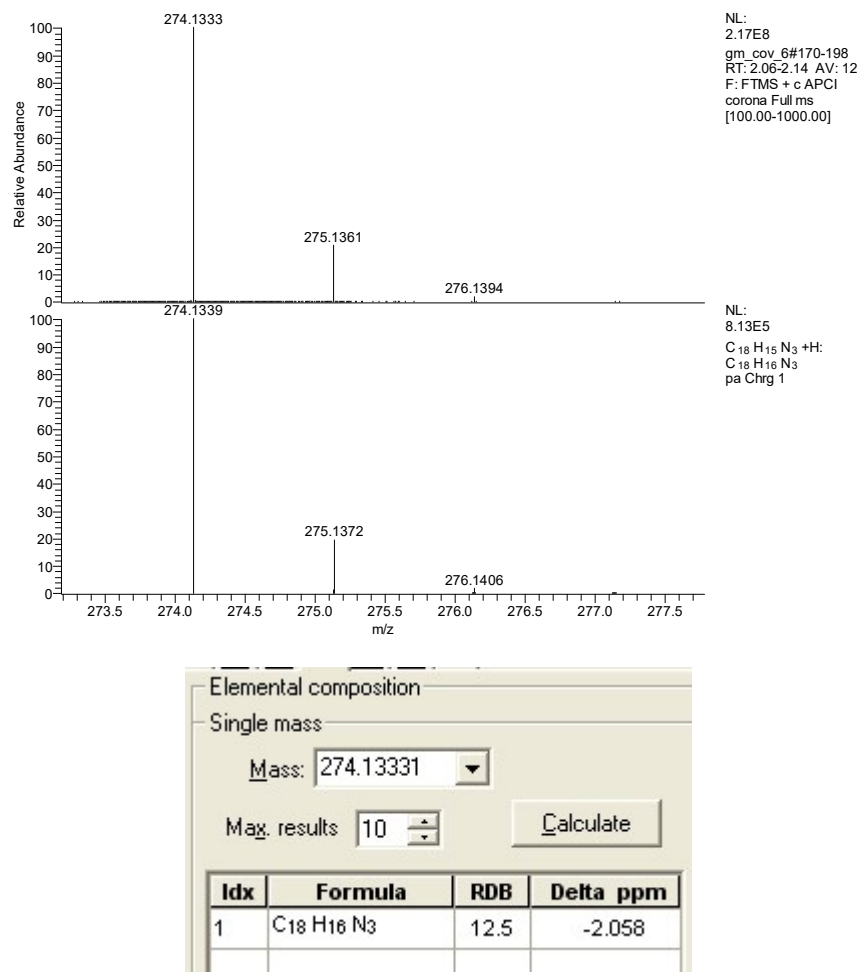
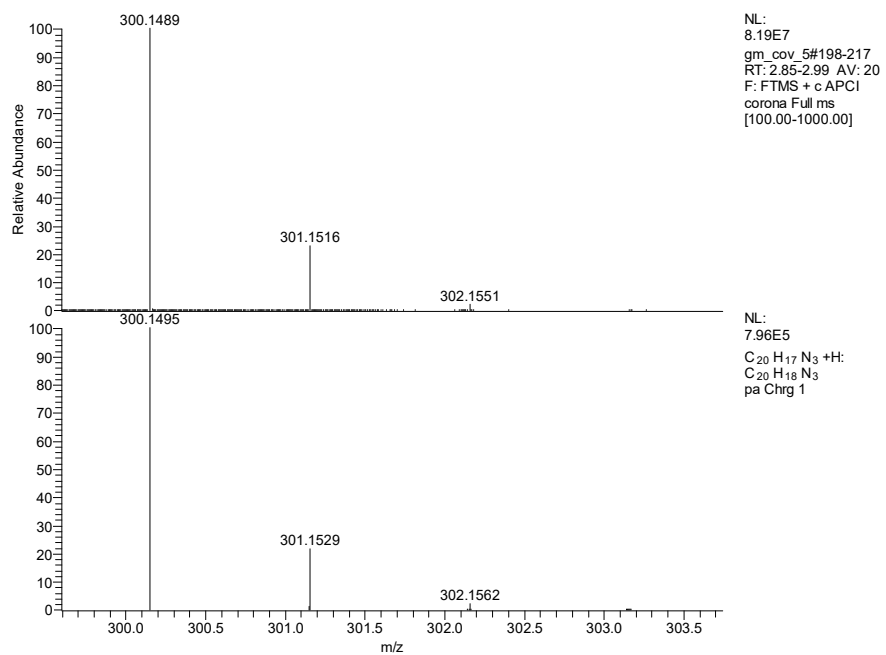


Figure S29. HRMS of compound 14.

Figure S31. ^{13}C -NMR of compound **15**.



Elemental composition

Single mass

Mass: 300.14890

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₀ H ₁₈ N ₃	13.5	-2.079

Figure S32. HRMS of compound 15.

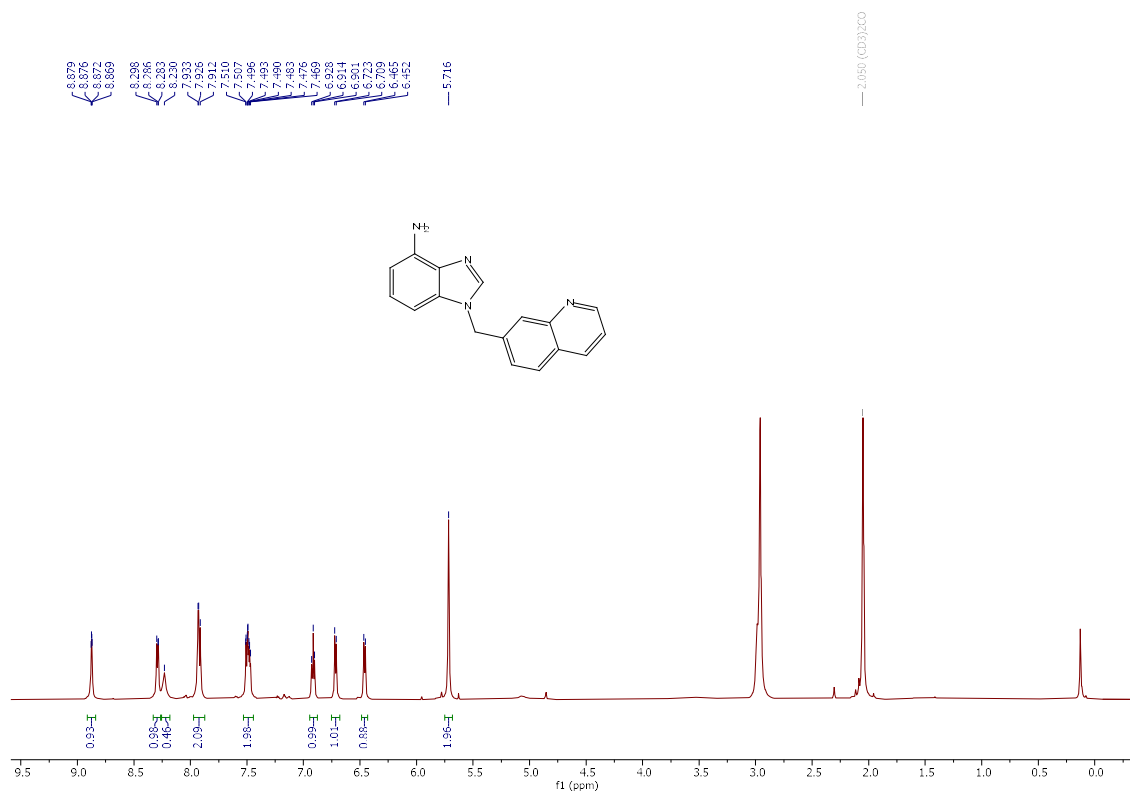


Figure S33. ¹H-NMR of compound 16.

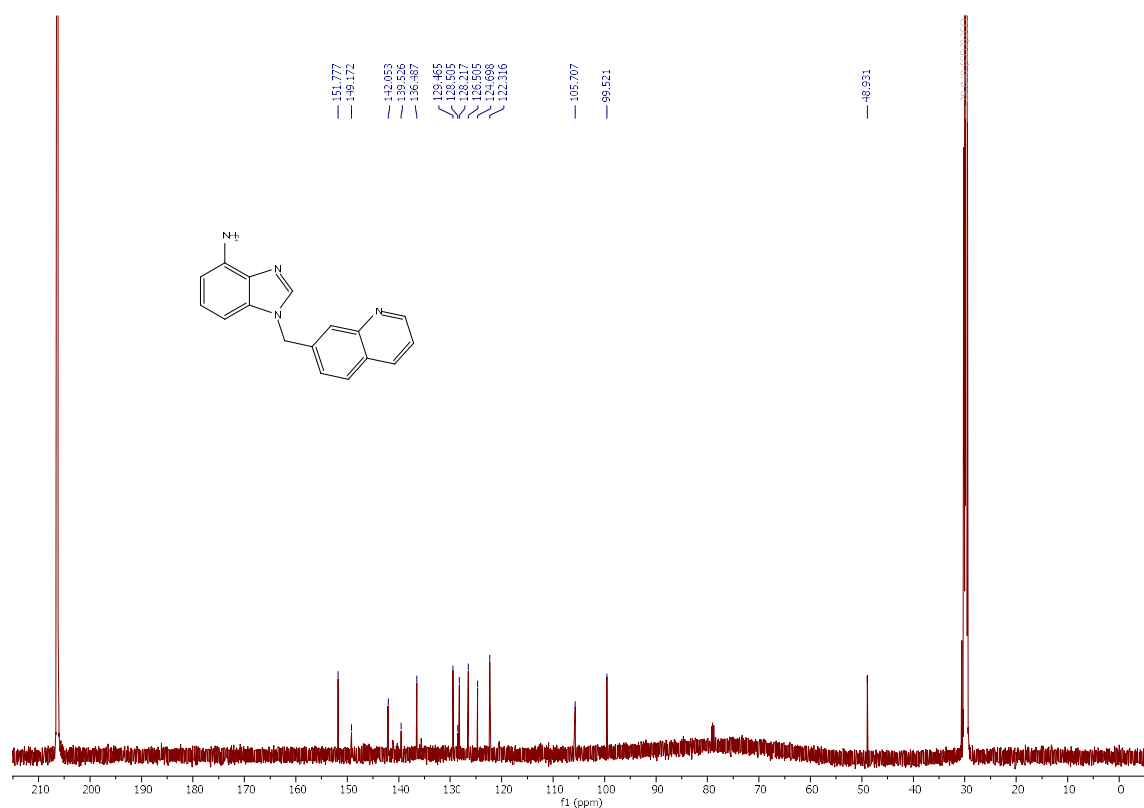
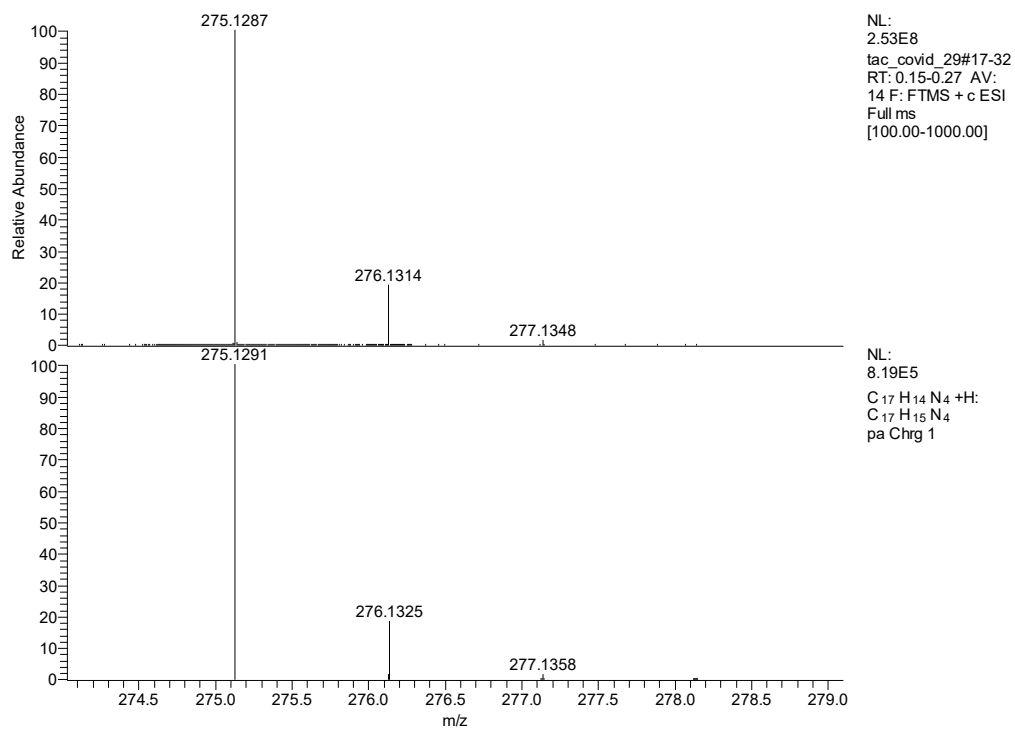


Figure S34. ¹³C-NMR of compound 16.



Elemental composition			
Single mass			
Mass:	275.12873		
Max. results	10	Calculate	
Idx	Formula	RDB	Delta ppm
1	C17 H15 N4	12.5	-1.429

Figure S35. HRMS of compound **16**.

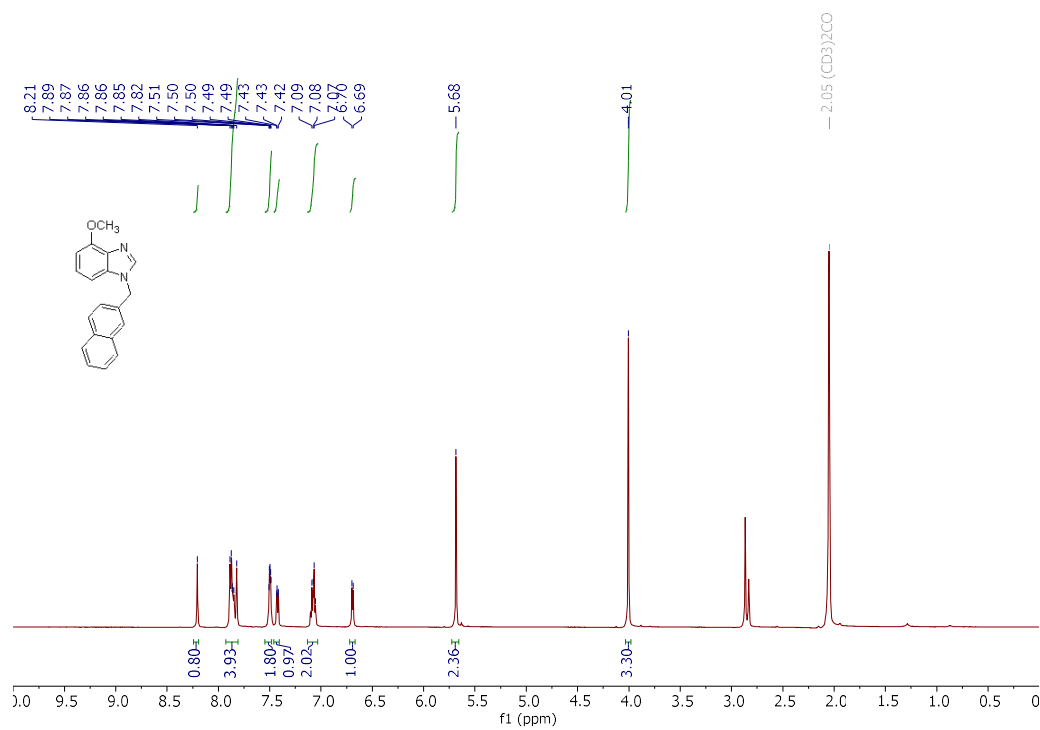


Figure S36. ¹H-NMR of compound 28.

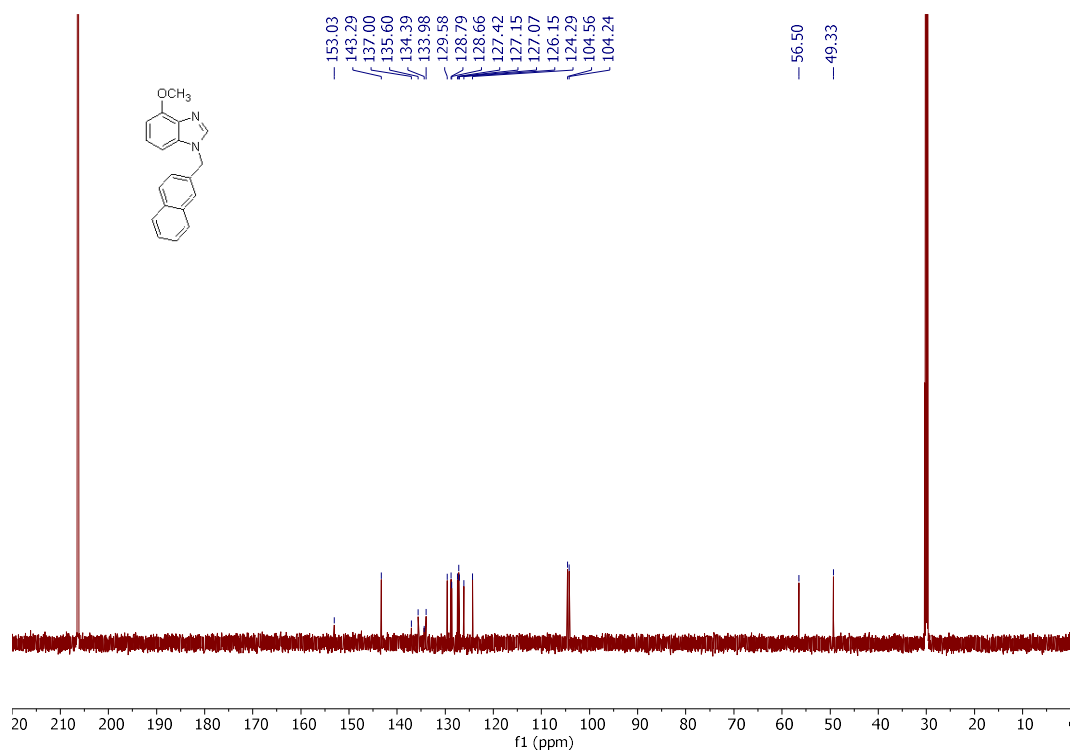
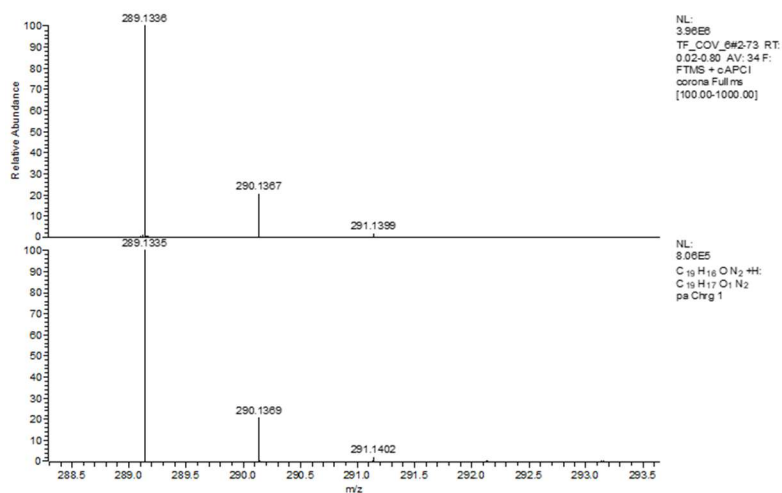


Figure S37. ¹³C-NMR of compound 28.



Elemental composition

Single mass

Mass: 289.13359

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₁₉ H ₁₇ O ₂ N ₂	12.5	0.174

Figure S38. HRMS of compound **28**.

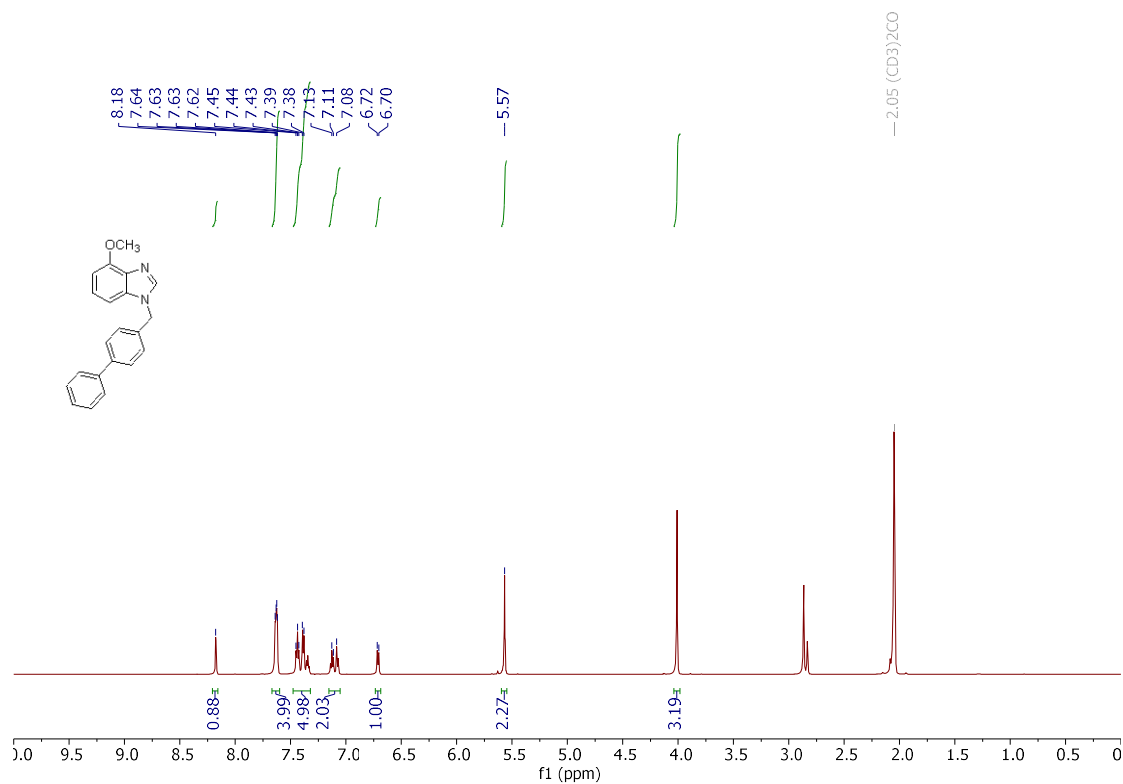


Figure S39. ¹H-NMR of compound 29.

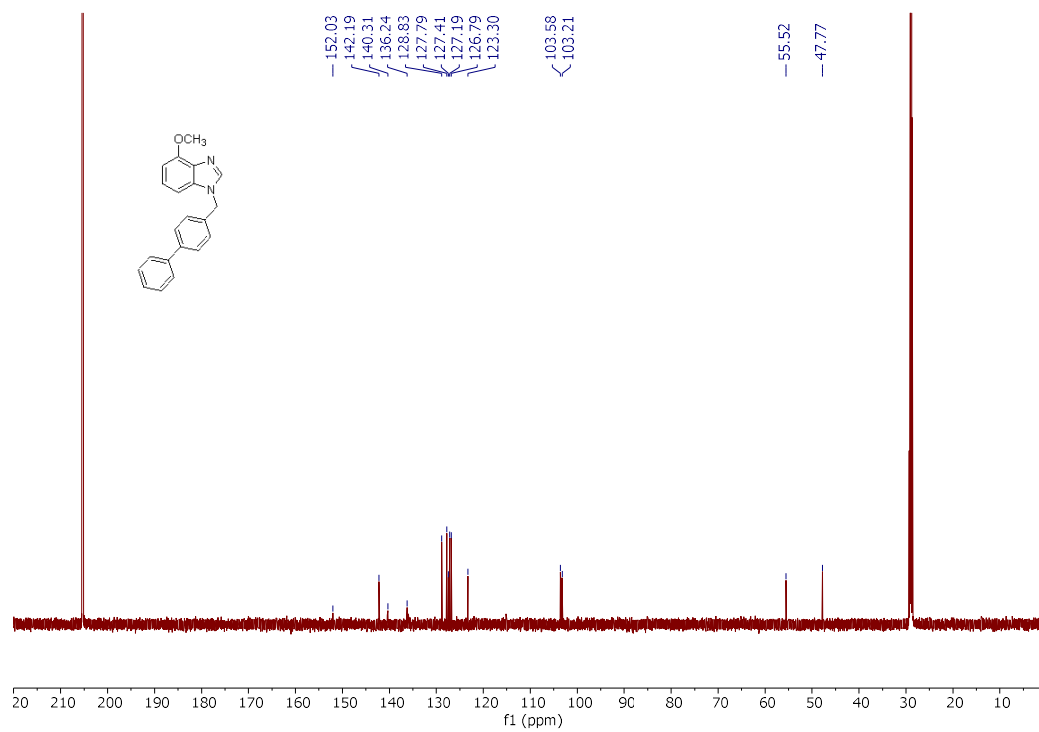
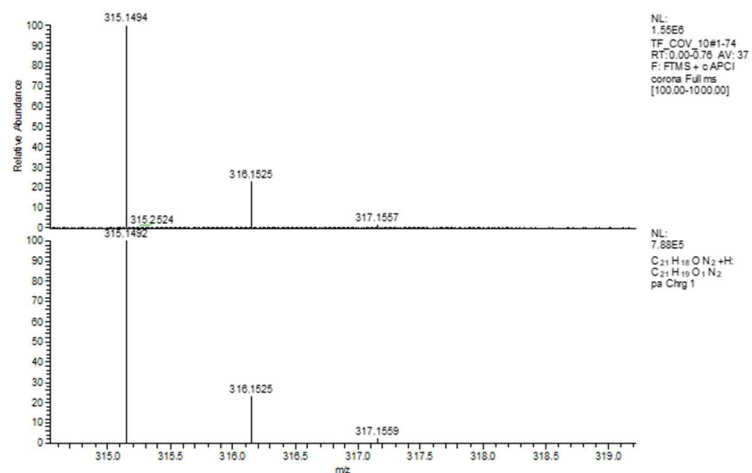


Figure S40. ¹³C-NMR of compound 29.



Elemental composition

Single mass

Mass: 315.14940

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₁ H ₁₉ O ₂ N ₂	13.5	0.667

Figure S41. HRMS of compound **29**.

Chemical structure of 1-(4-(7-methoxy-1H-indol-2-ylmethyl)phenyl)pyrrole is shown above the spectrum.

Peak list (ppm):

- 152.86
- 151.80
- 149.13
- 143.23
- 139.30
- 136.76
- 136.56
- 129.57
- 128.57
- 128.23
- 126.48
- 124.40
- 122.39
- 104.59
- 104.11
- 56.40
- 49.01
- 30.84

Figure S43. ^{13}C -NMR of compound **30**.

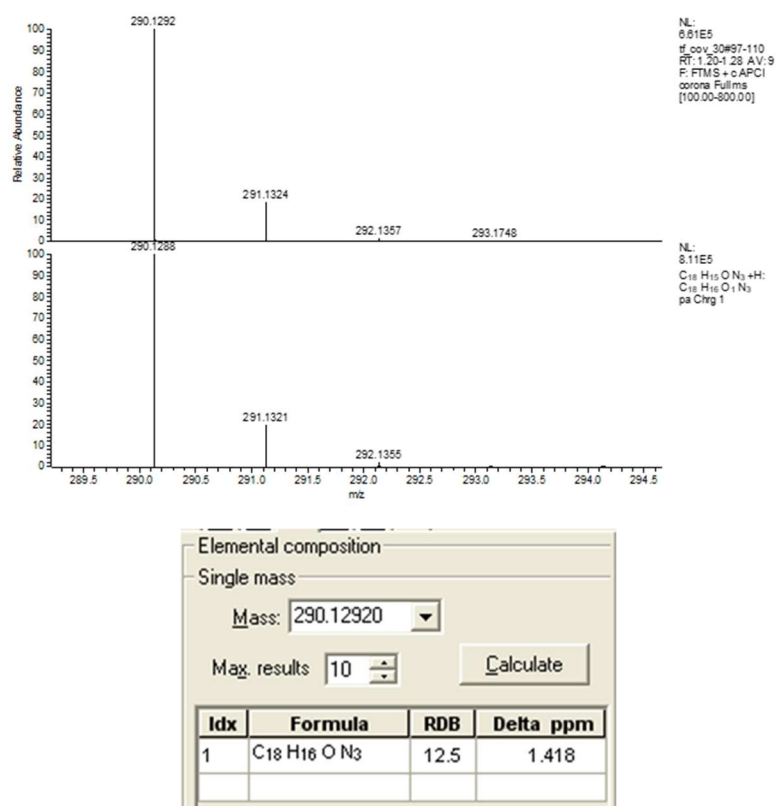


Figure S44. HRMS of compound **30**.

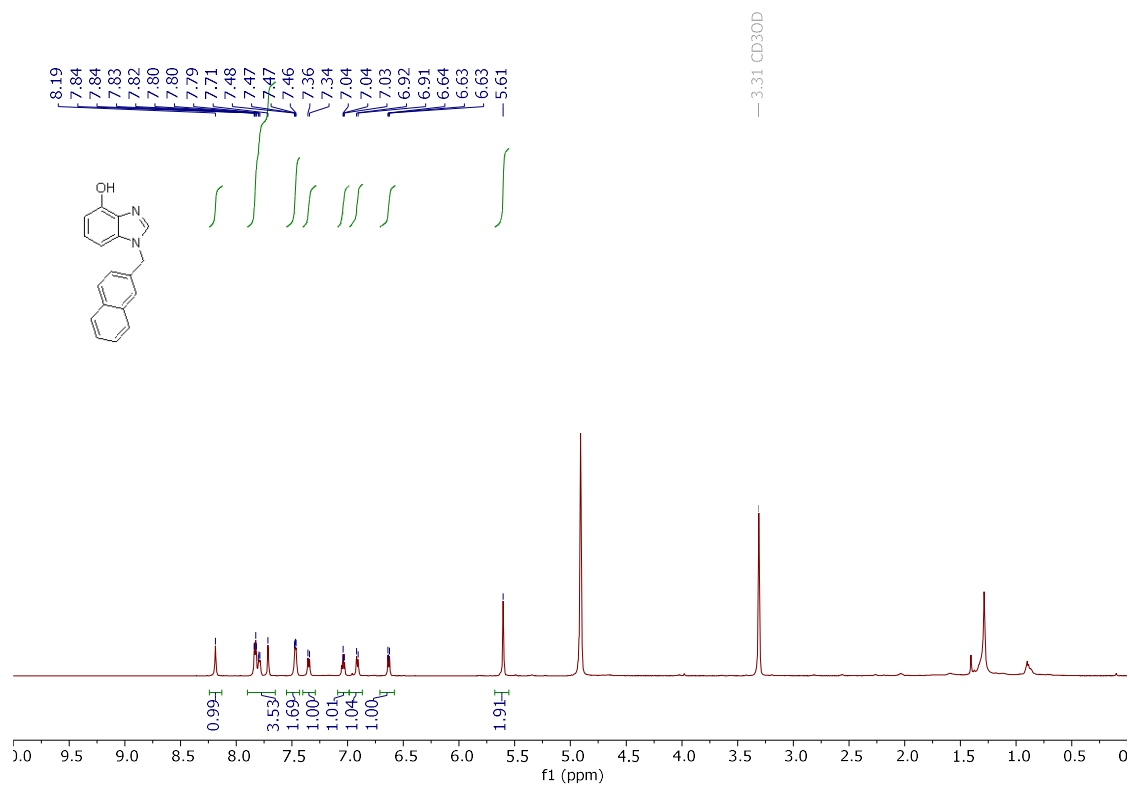


Figure S45. ¹H-NMR of compound 31.

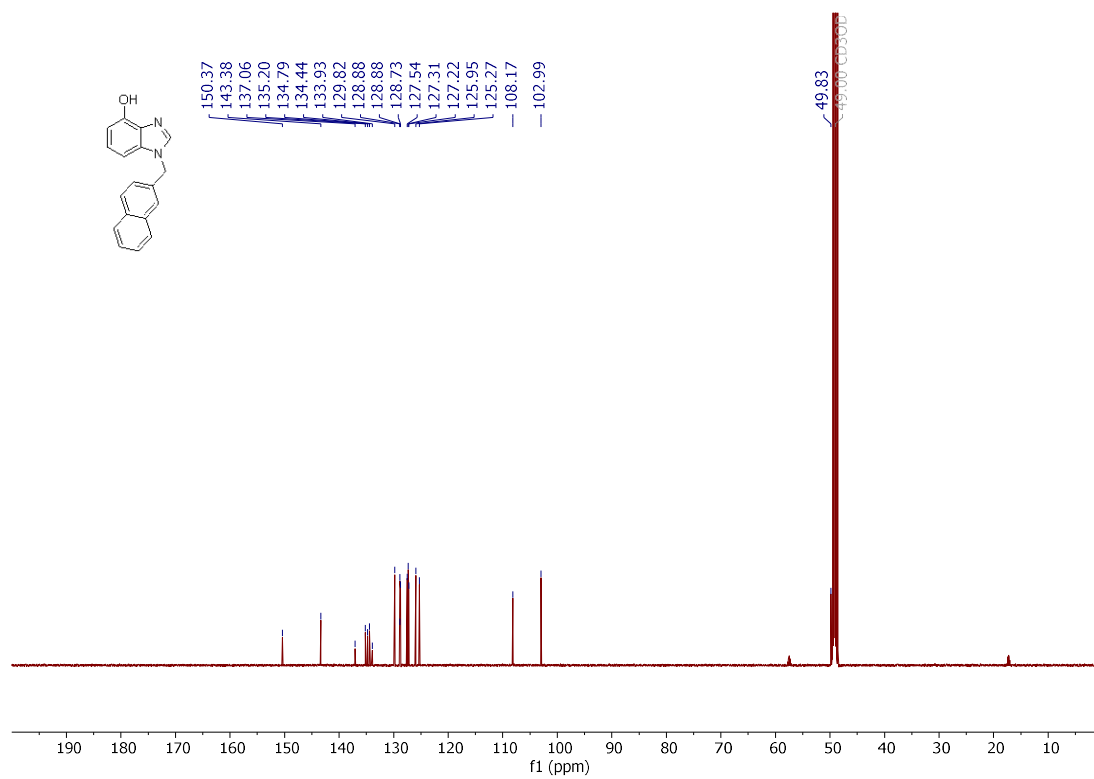


Figure S46. ¹³C-NMR of compound 31.

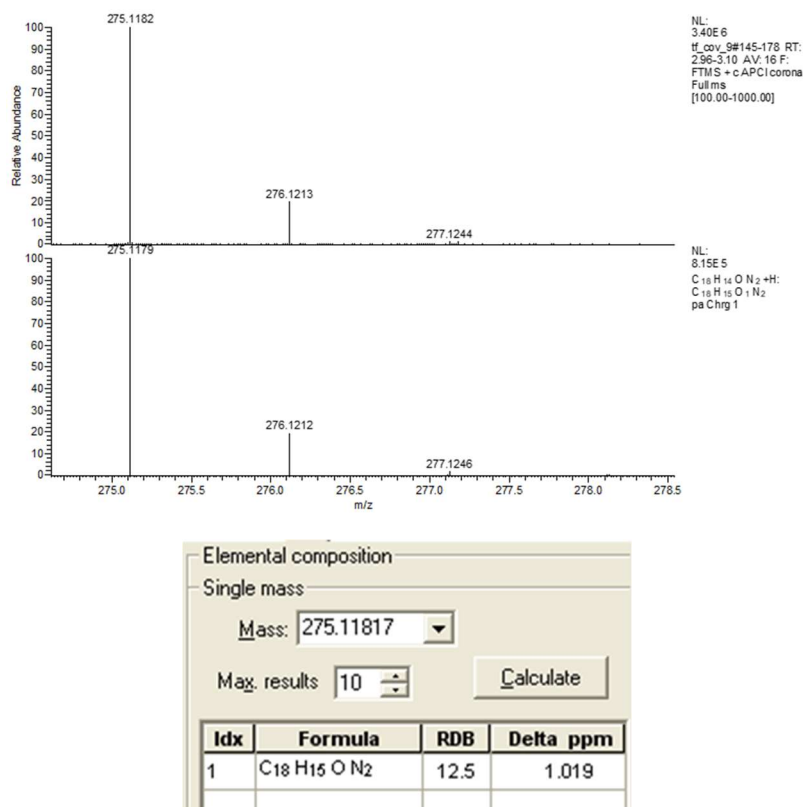


Figure S47. HRMS of compound **31**.

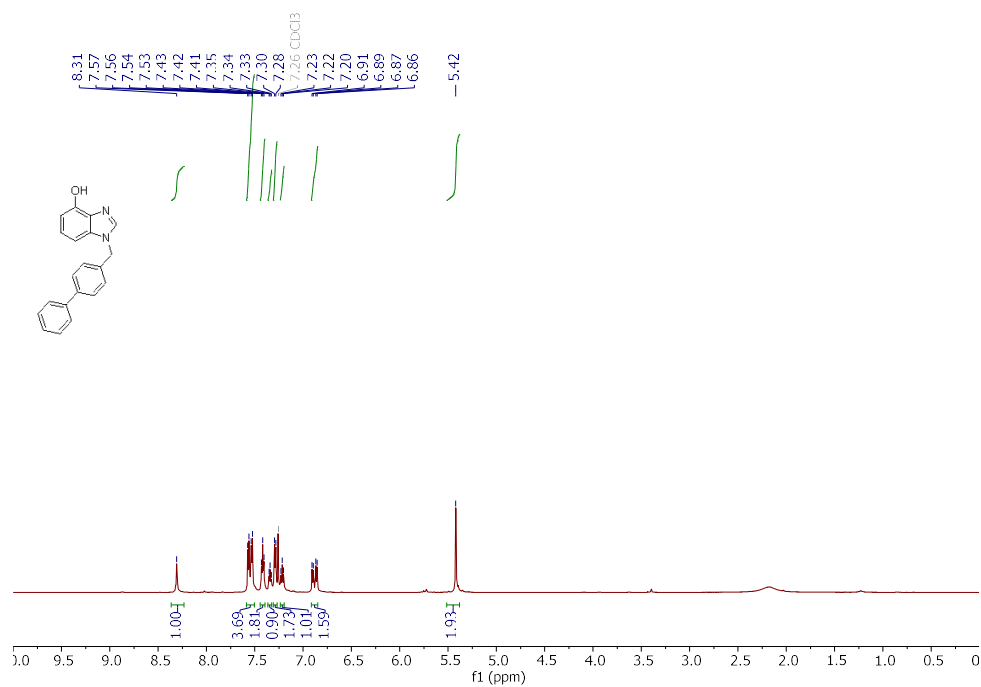


Figure S48. ¹H-NMR of compound **32**.

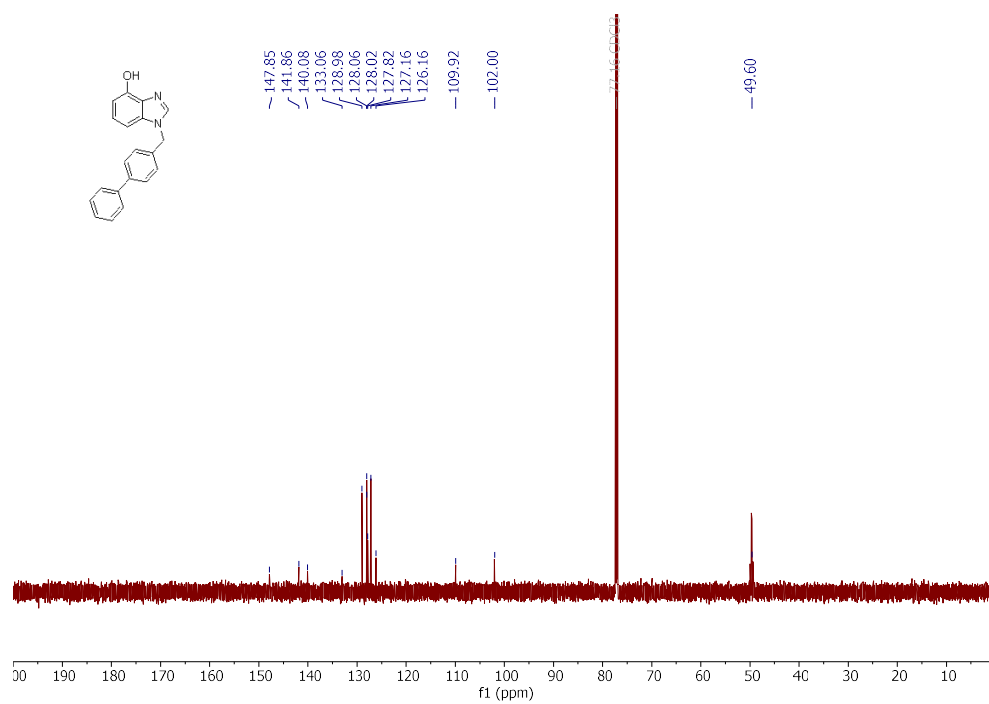


Figure S49. ¹³C-NMR of compound **32**.

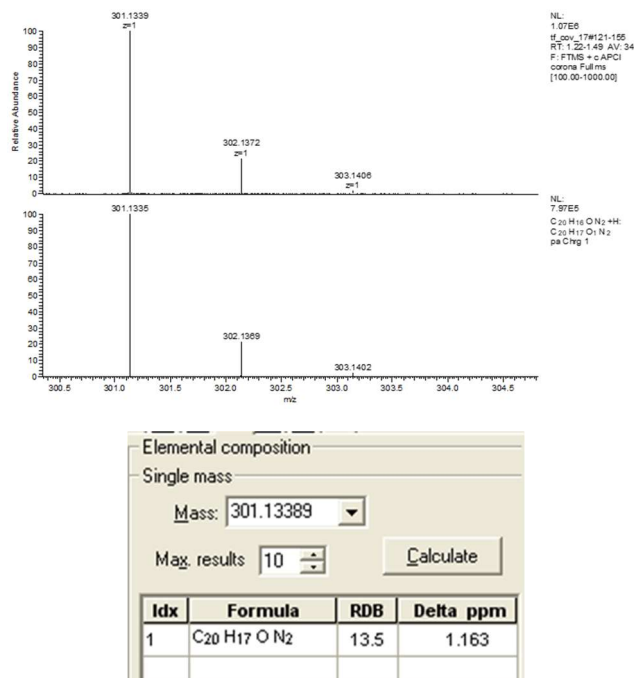


Figure S50. HRMS of compound **32**.

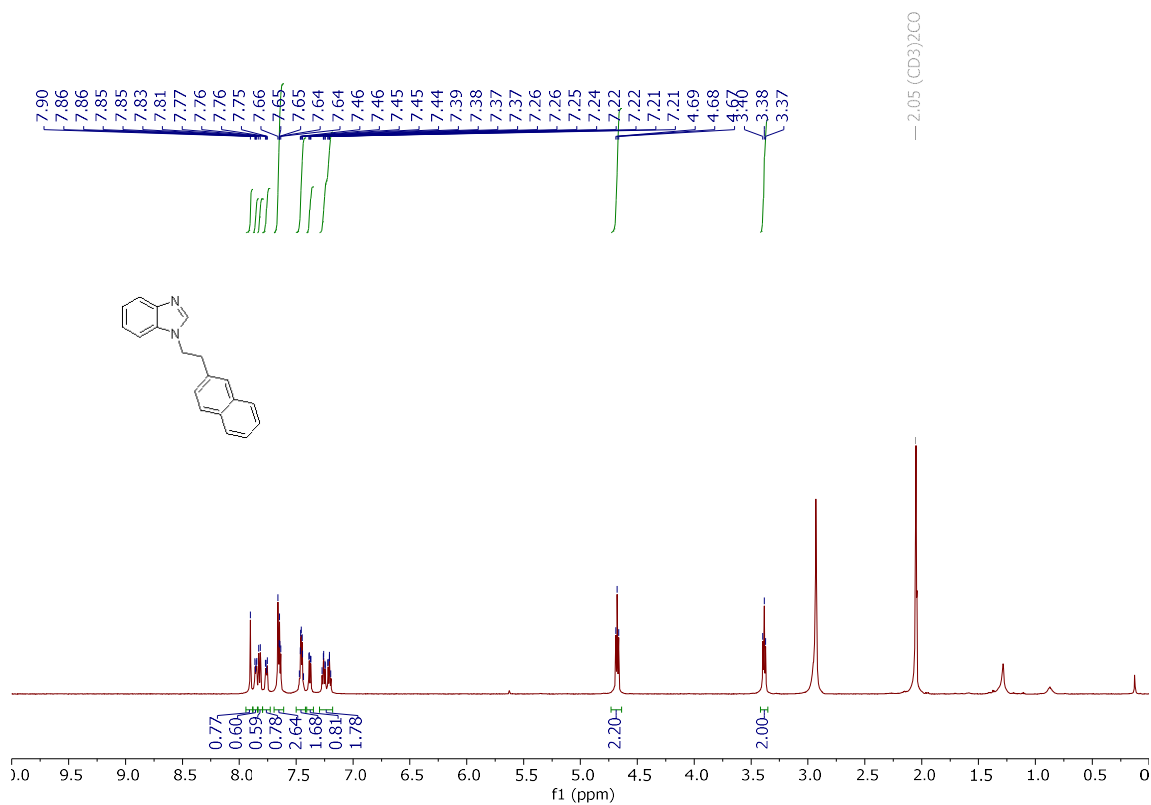


Figure S51. ¹H-NMR of compound **33**.

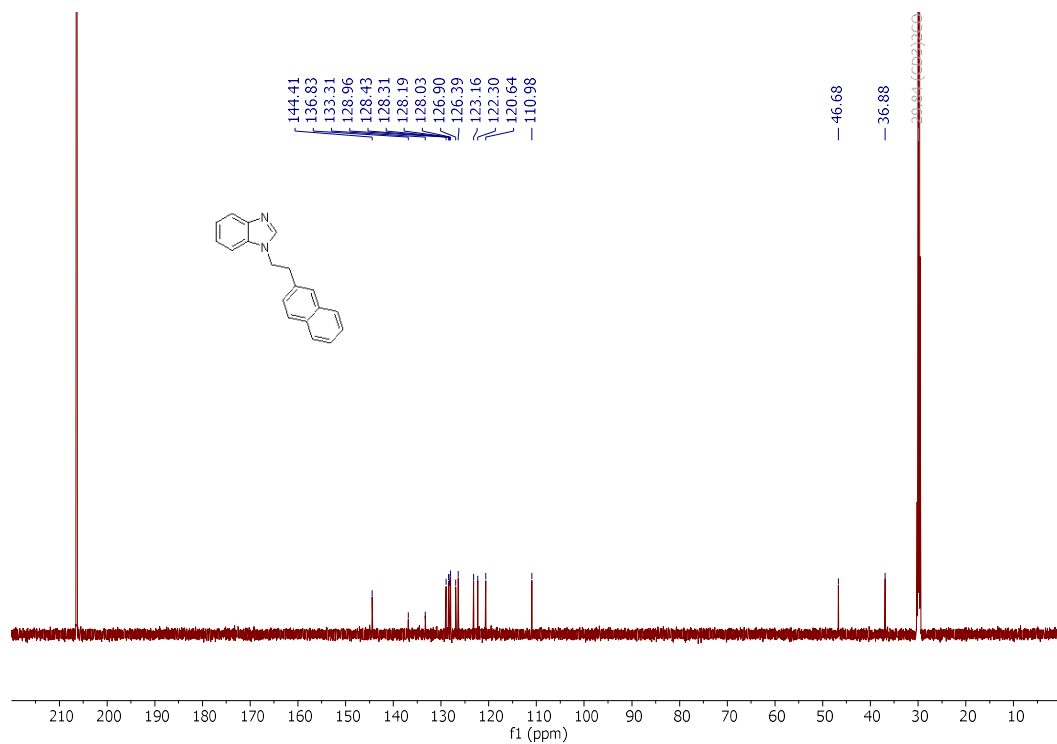


Figure S52. ¹³C-NMR of compound **33**.

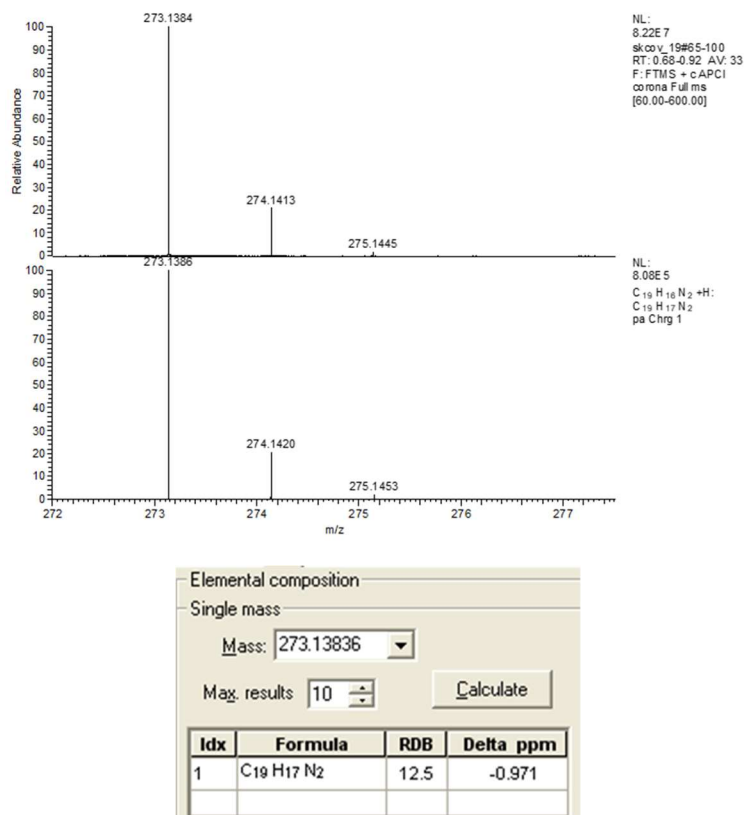


Figure S53. HRMS of compound **33**.

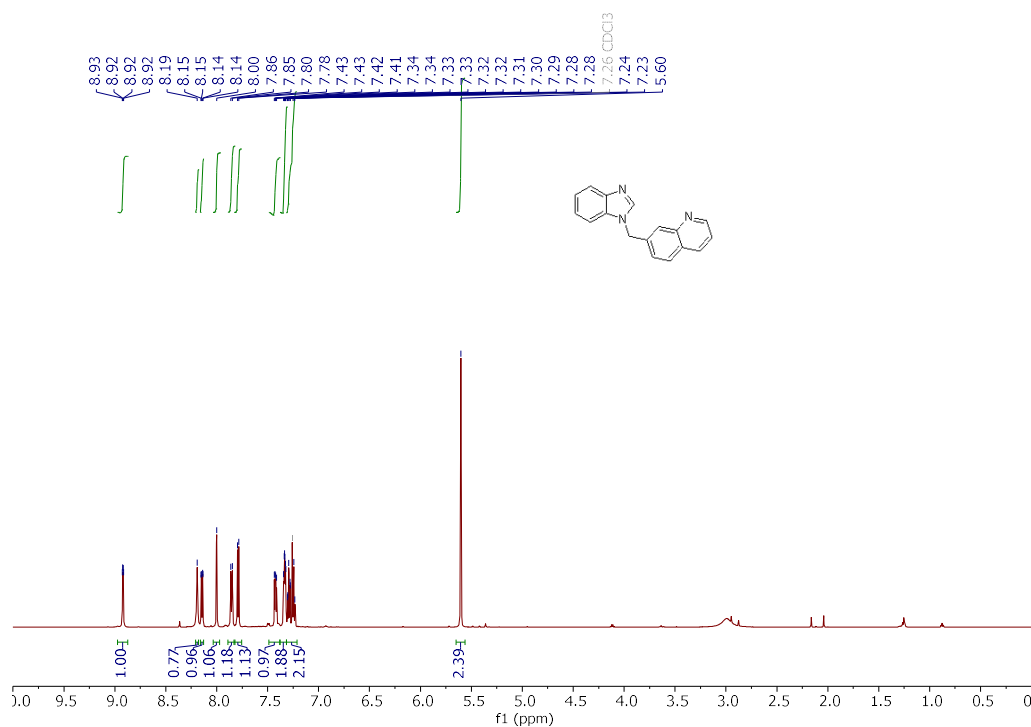


Figure S54. ¹H-NMR of compound **35**.

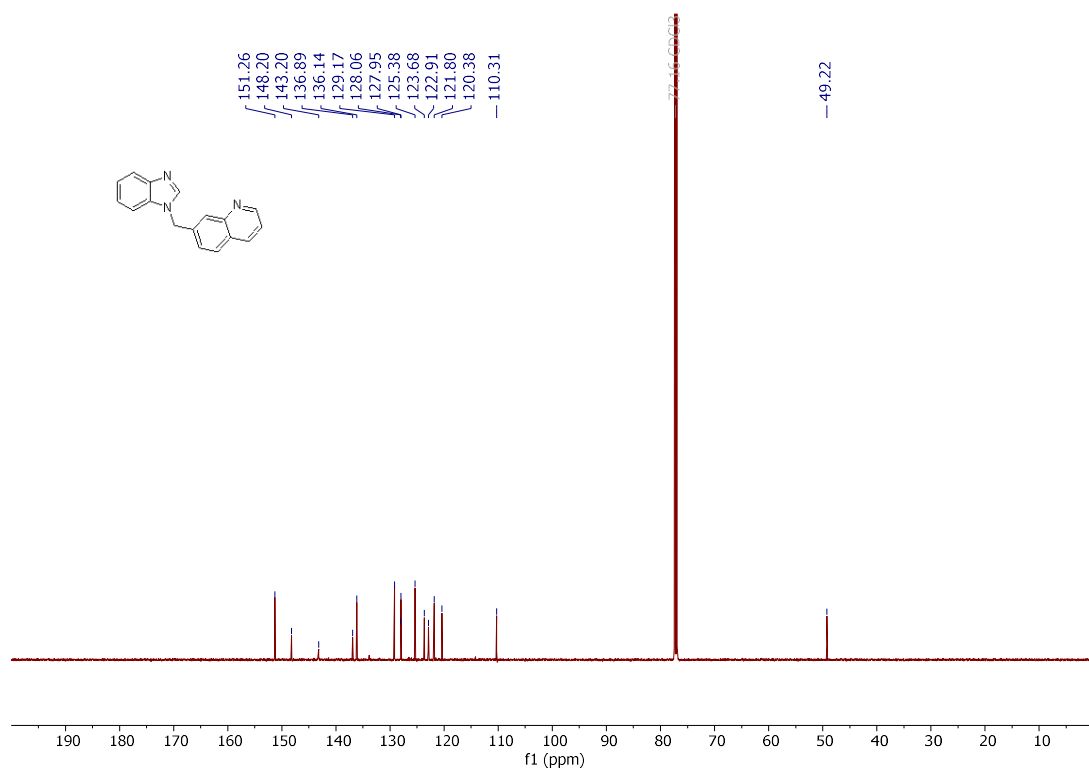
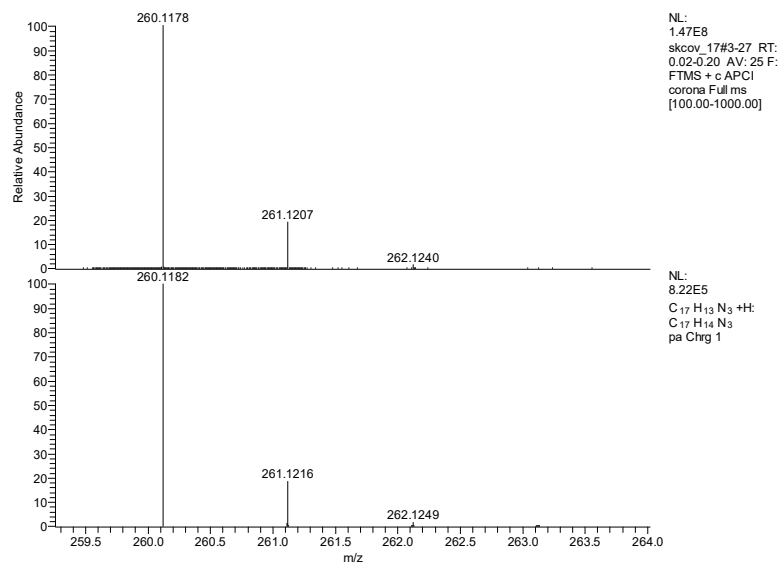


Figure S55. ¹³C-NMR of compound **35**.



Elemental composition

Single mass

Mass: 260.11777

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₁₇ H ₁₄ N ₃	12.5	-1.745

Figure S56. HRMS of compound **35**.

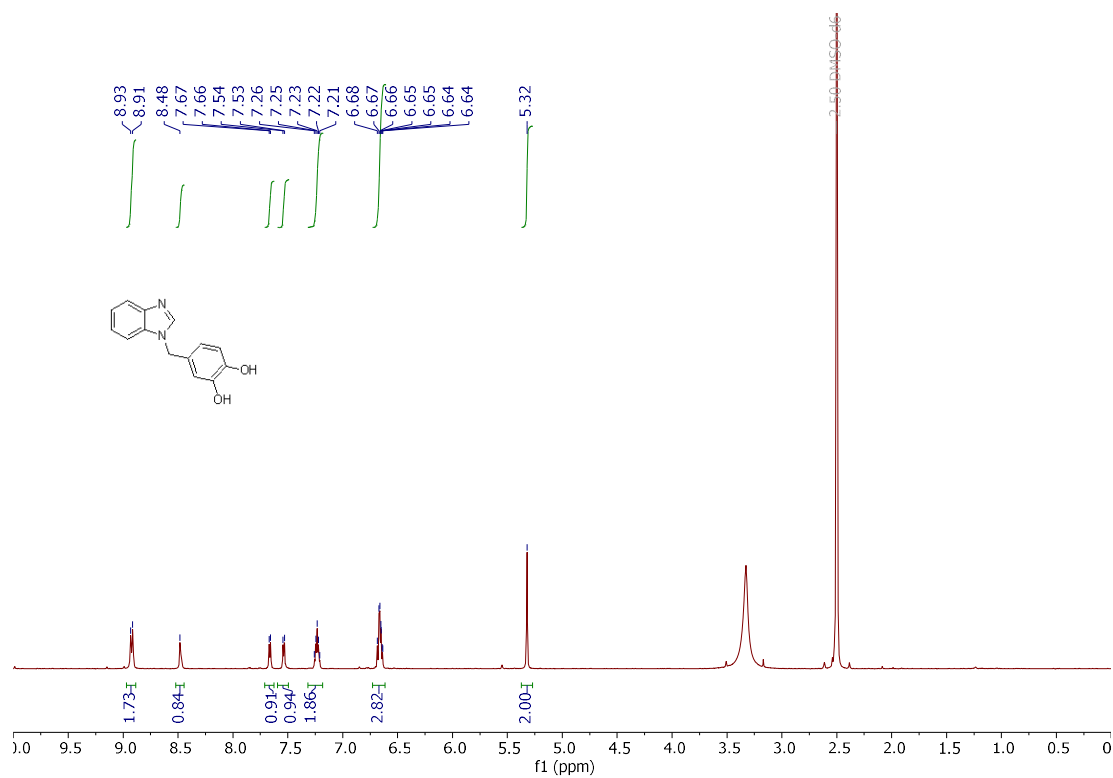


Figure S57. ¹H-NMR of compound **37**.

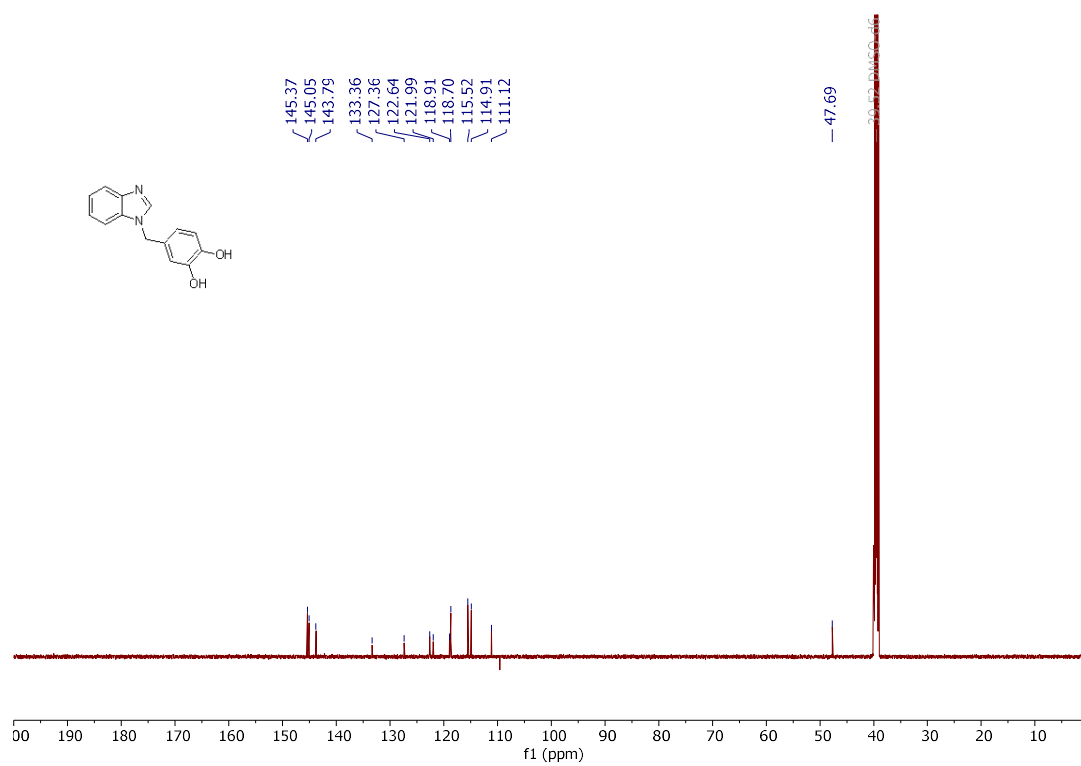


Figure S58. ¹³C-NMR of compound **37**.

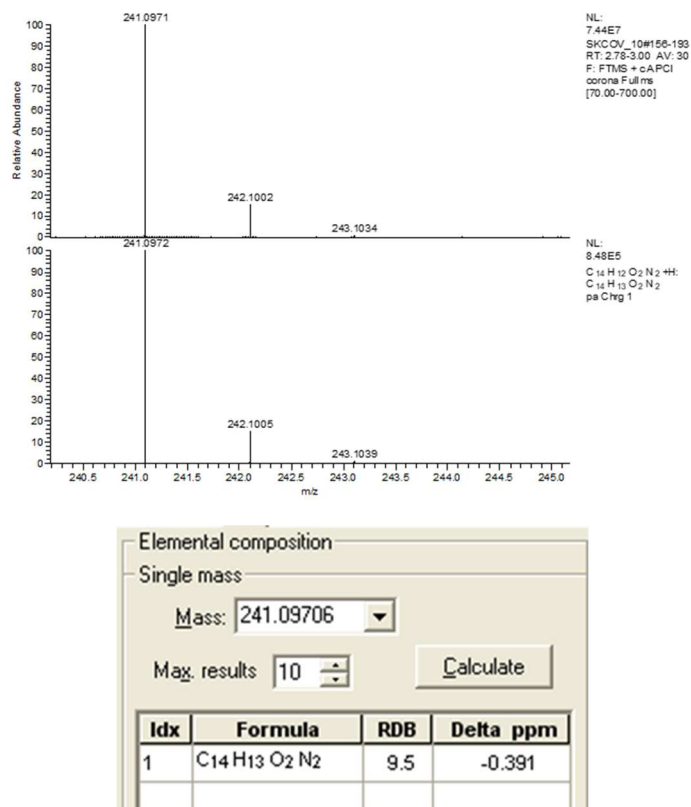


Figure S59. HRMS of compound **37**.

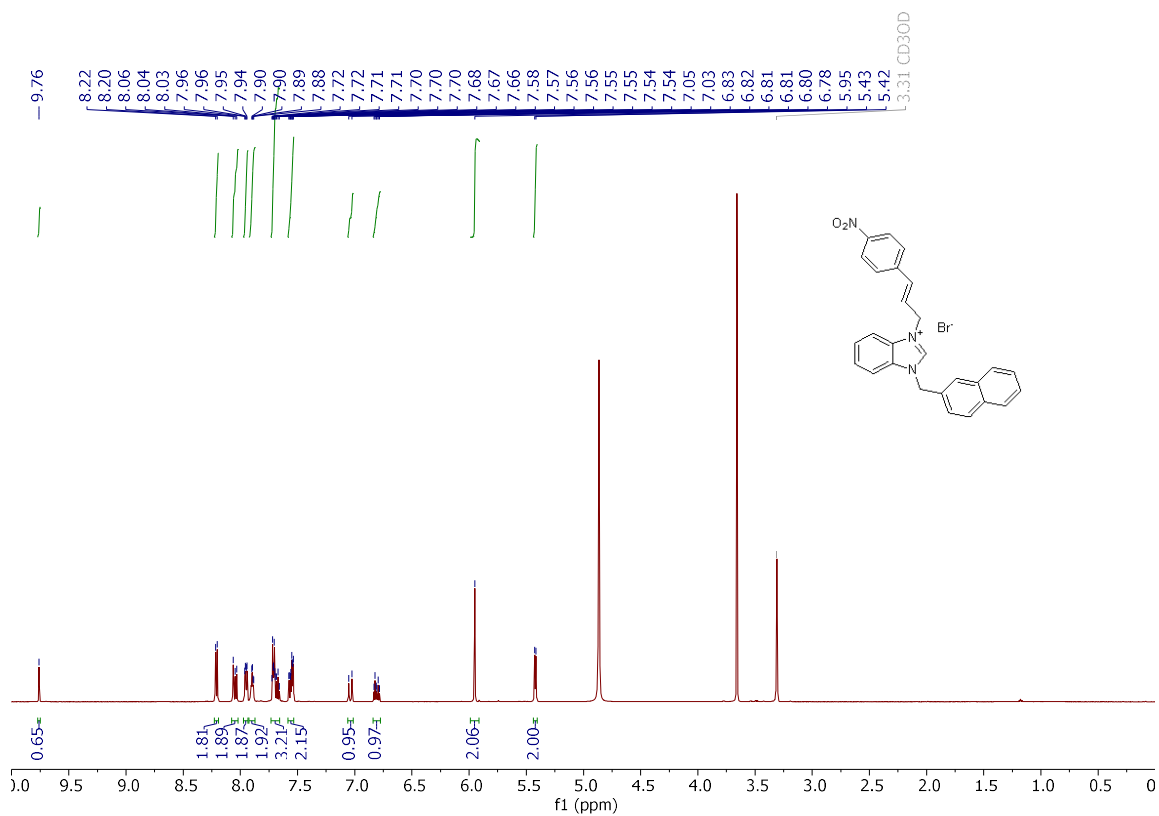


Figure S60. ¹H-NMR of compound **38**.

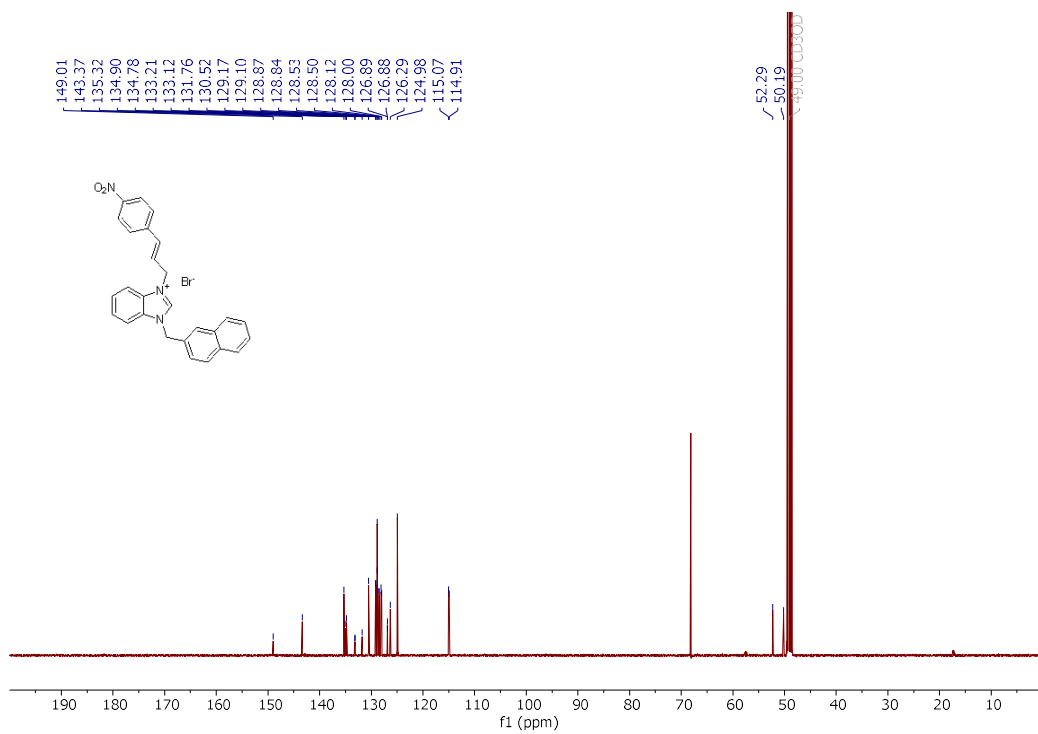


Figure S61. ¹³C-NMR of compound **38**.

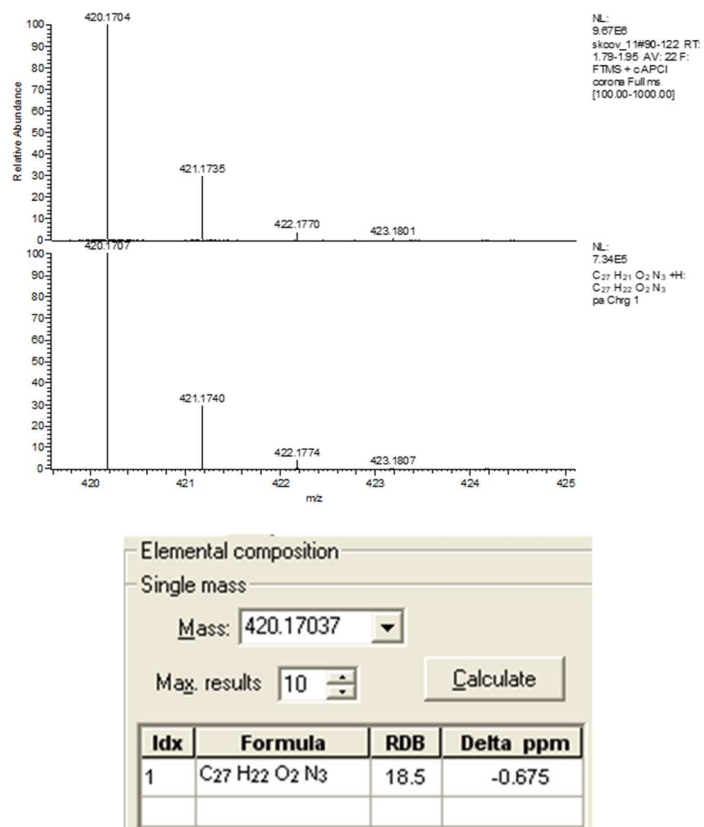


Figure S62. HRMS of compound **38**.

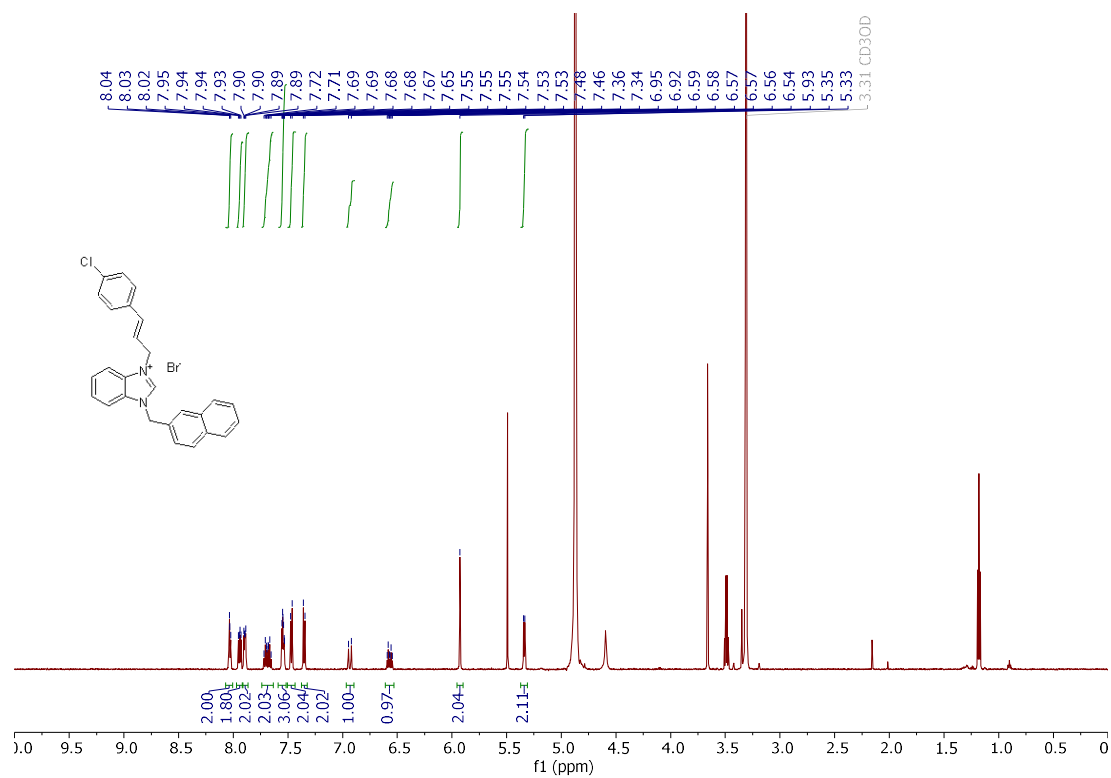


Figure S63. ¹H-NMR of compound **39**.

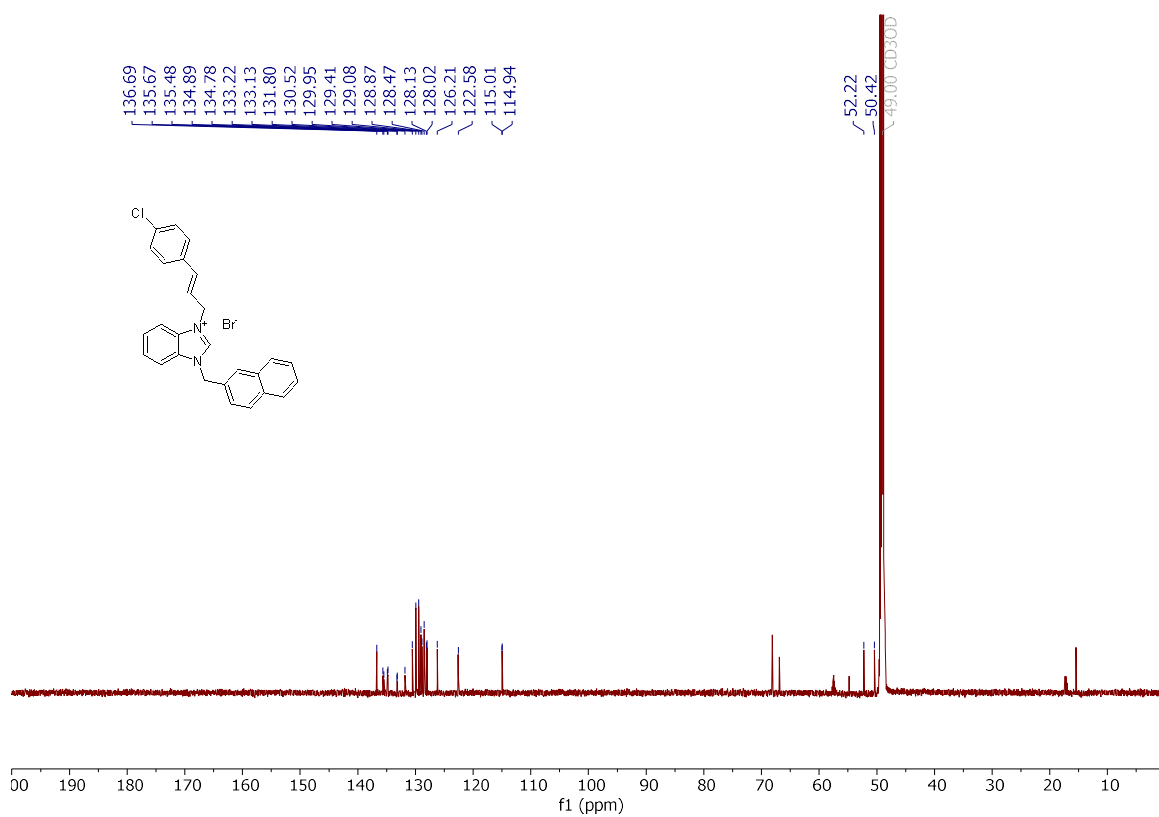


Figure S64. ¹³C-NMR of compound **39**.

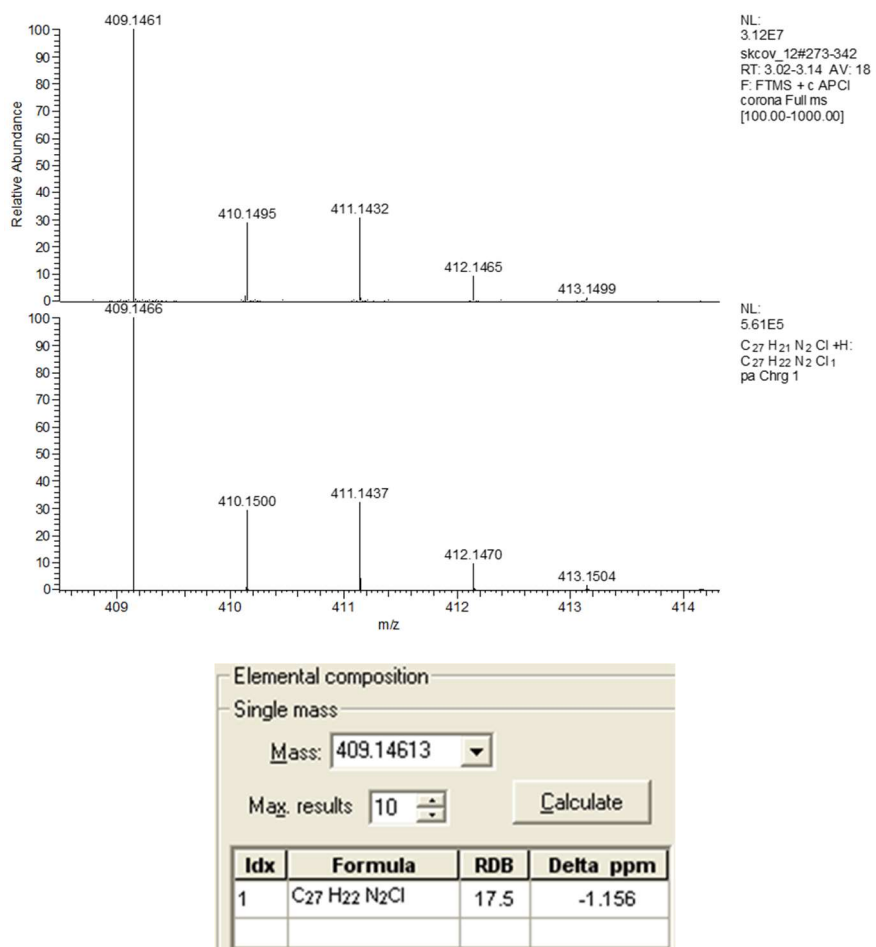
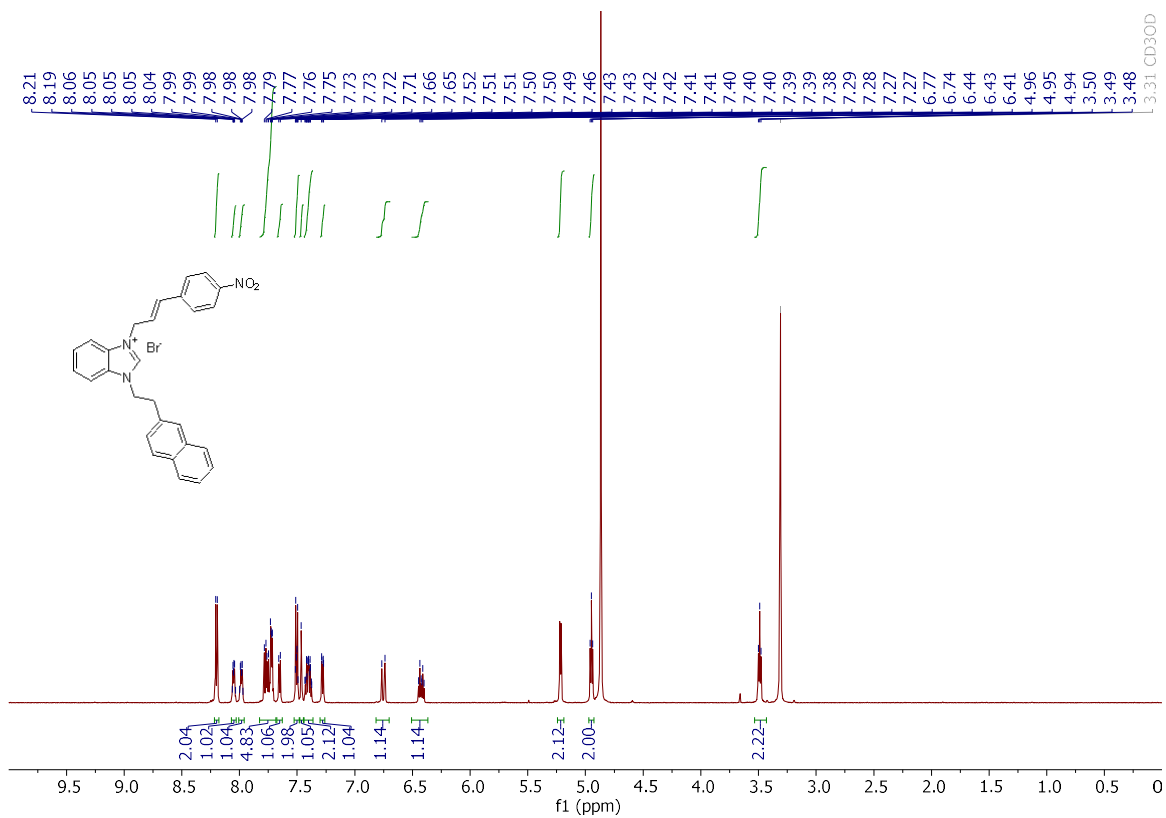
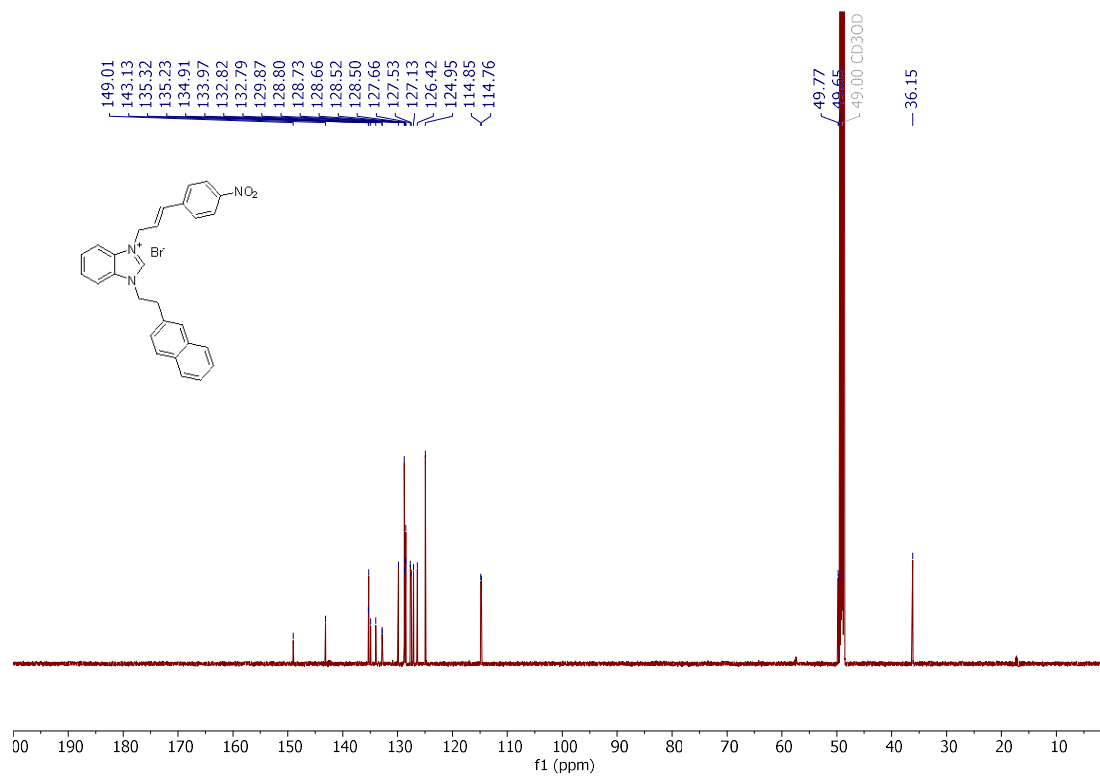
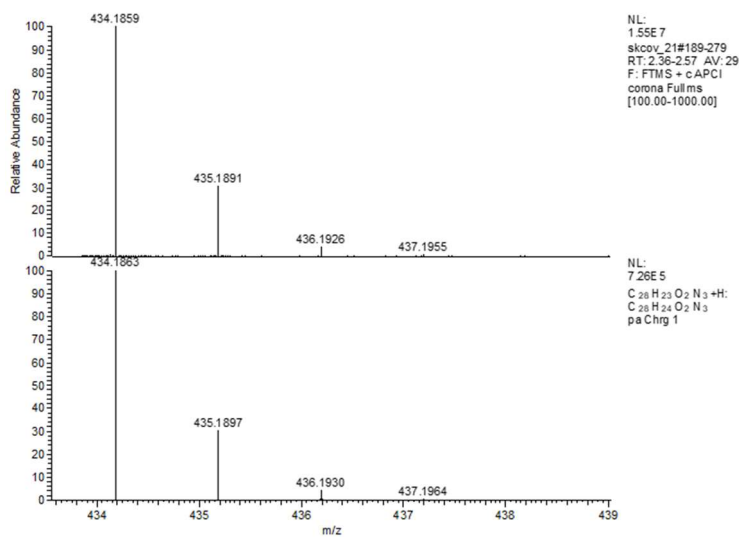


Figure S65. HRMS of compound 39.

Figure S66. ¹H-NMR of compound **40**.Figure S67. ¹³C-NMR of compound **40**.



Elemental composition

Single mass

Mass: 434.18593

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₂₈ H ₂₄ O ₂ N ₃	18.5	-0.860

Figure S68. HRMS of compound 40.

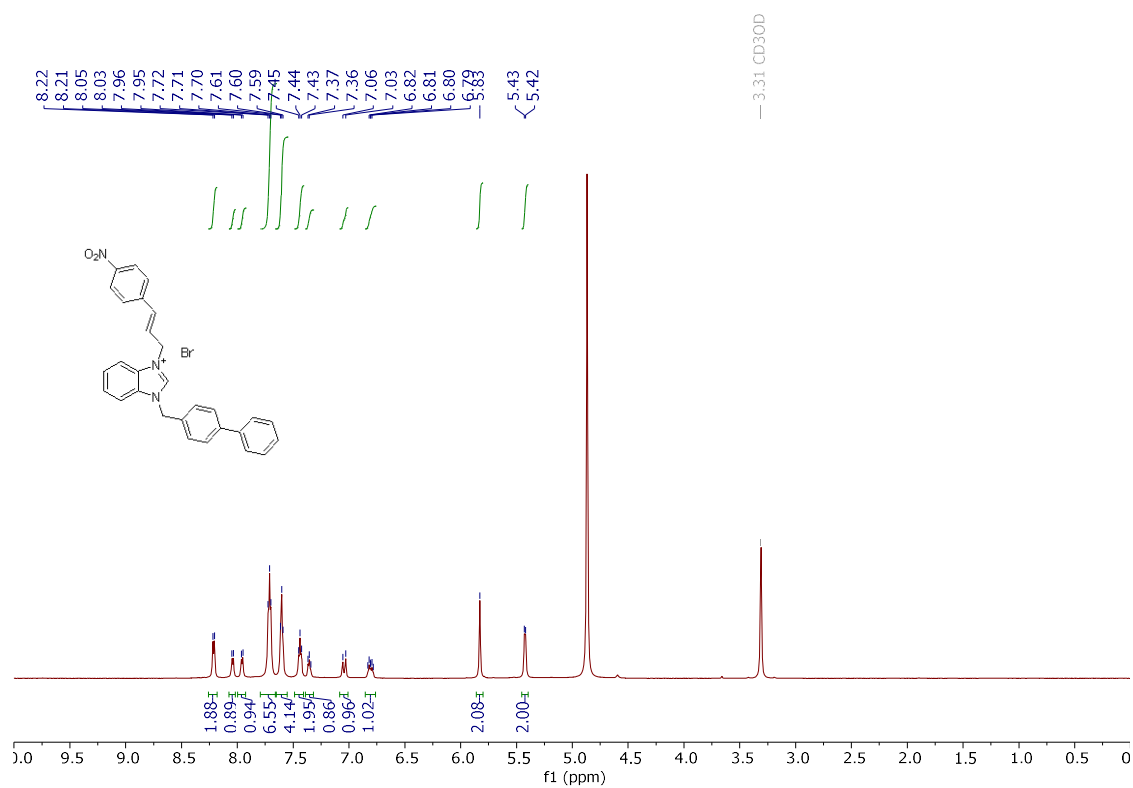


Figure S69. ¹H-NMR of compound 41.

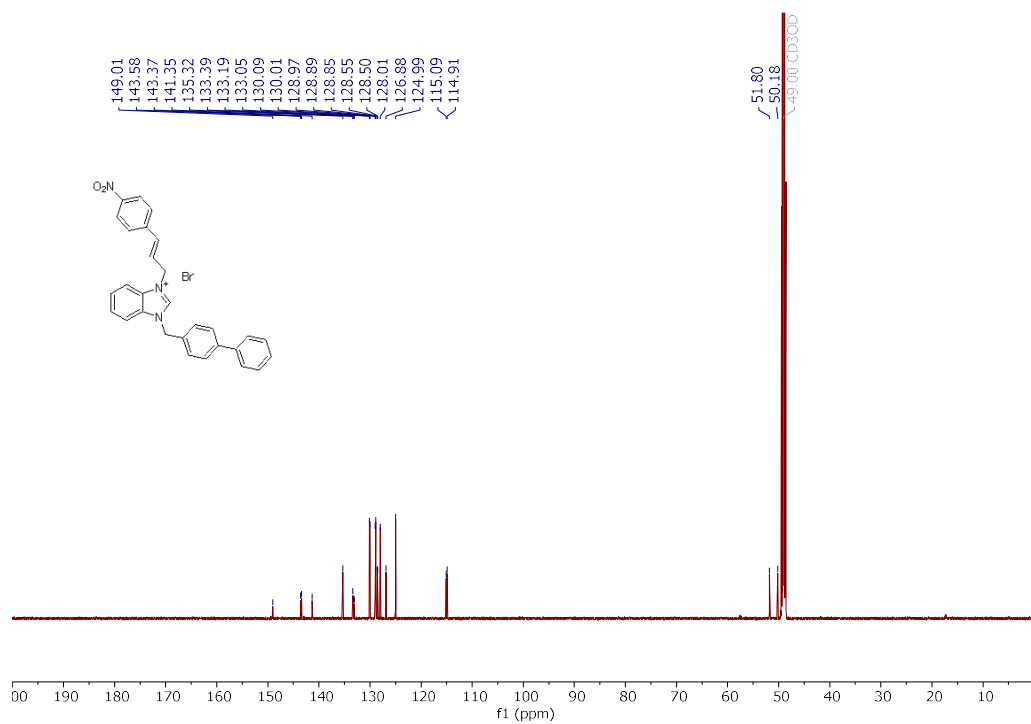


Figure S70. ¹³C-NMR of compound 41.

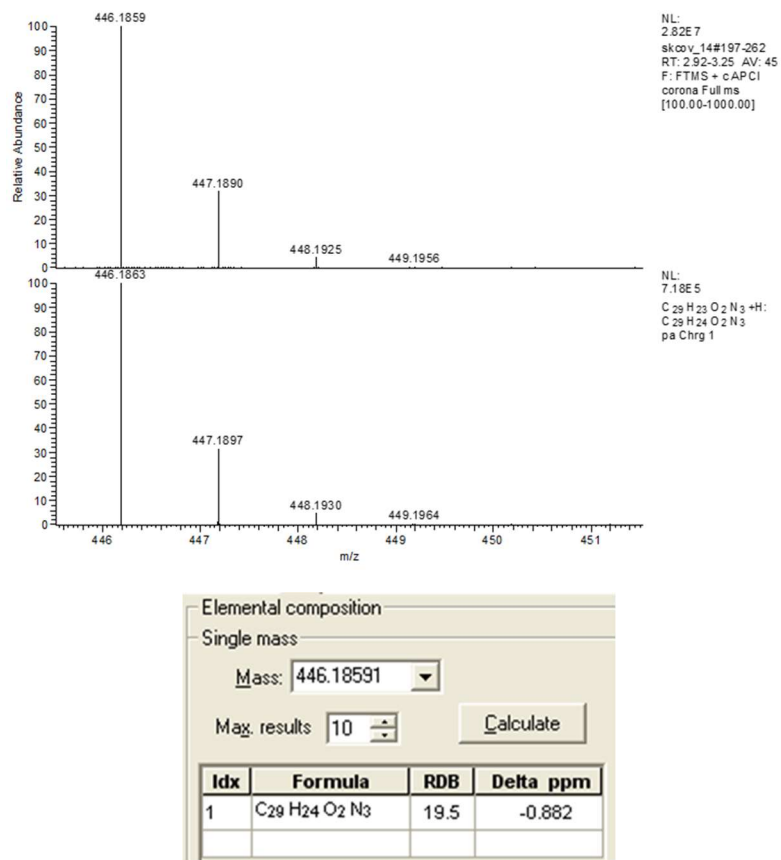


Figure S71. HRMS of compound **41**.

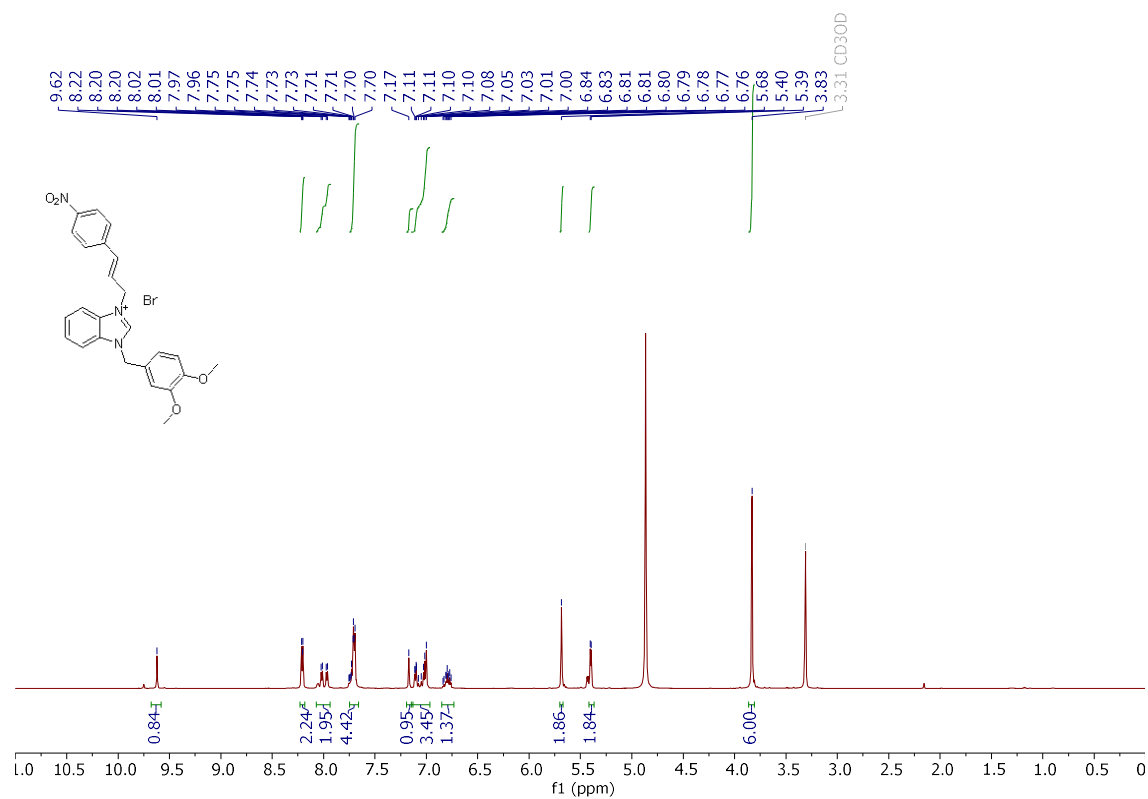


Figure S72. ¹H-NMR of compound 42.

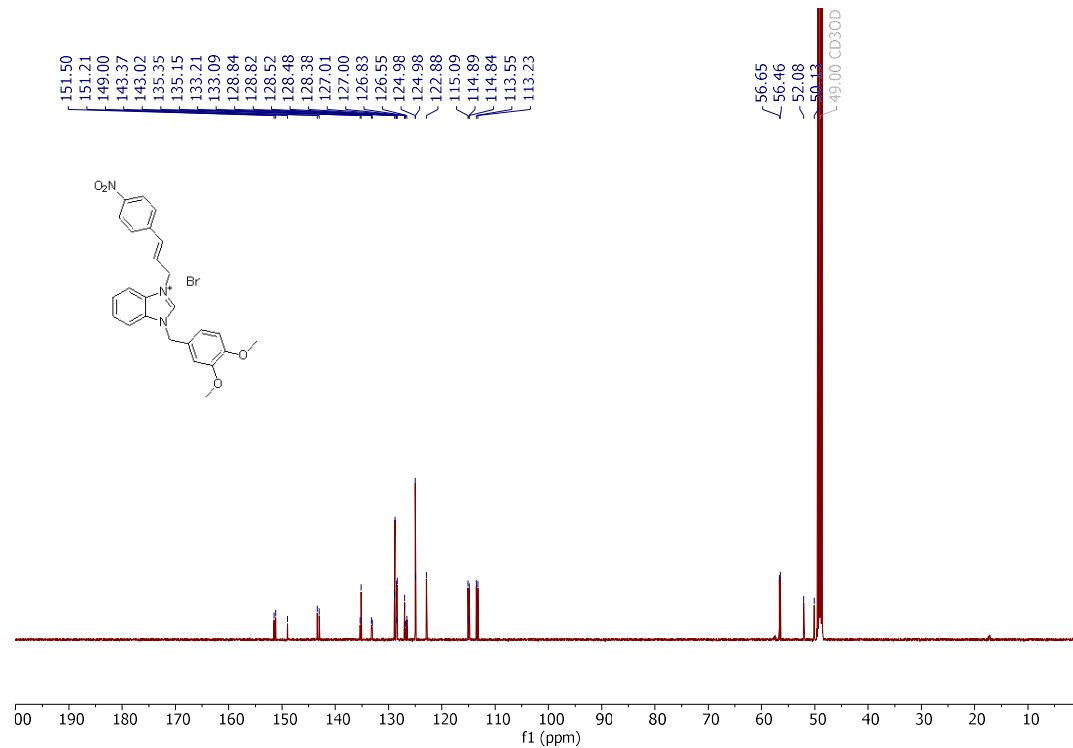


Figure S73. ¹³C-NMR of compound 42.

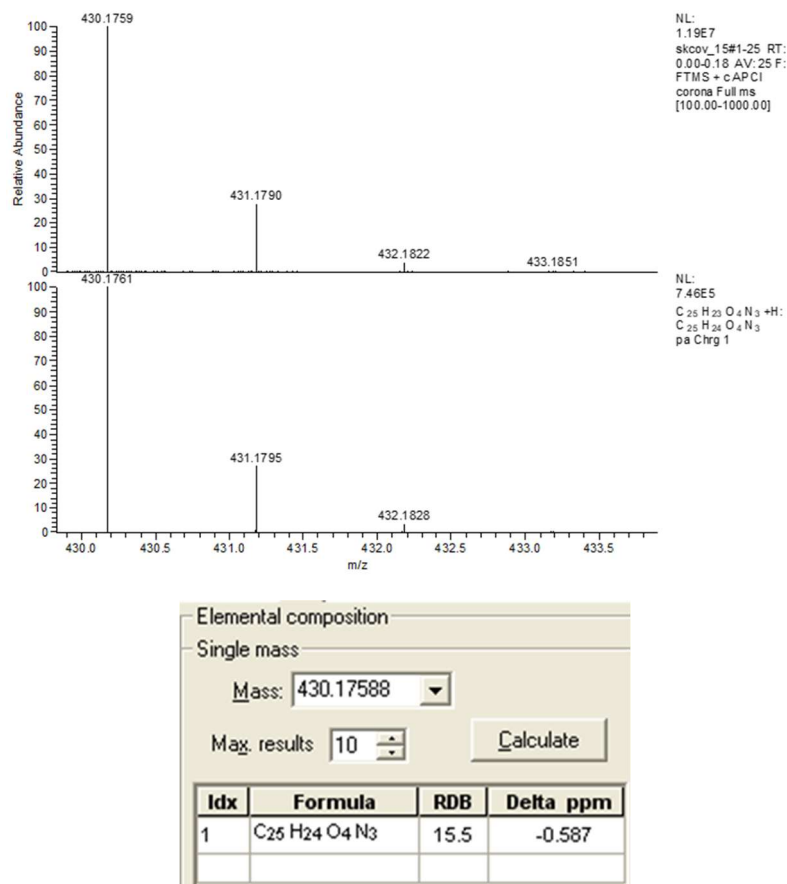


Figure S74. HRMS of compound **42**.

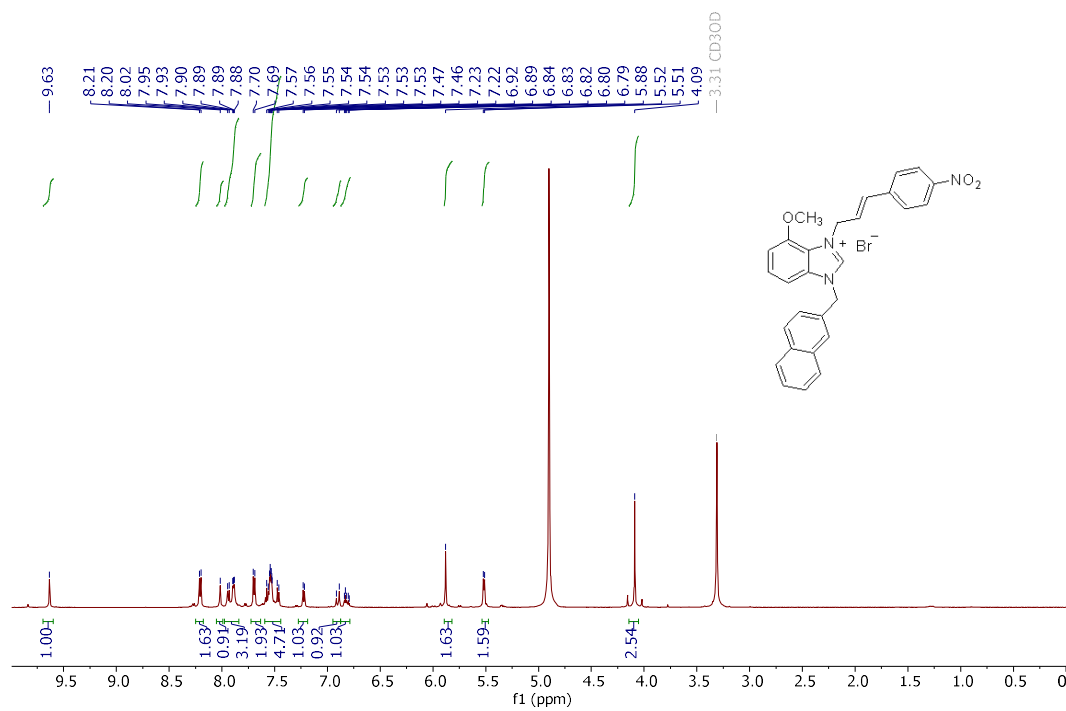


Figure S75. ¹H-NMR of compound 43.

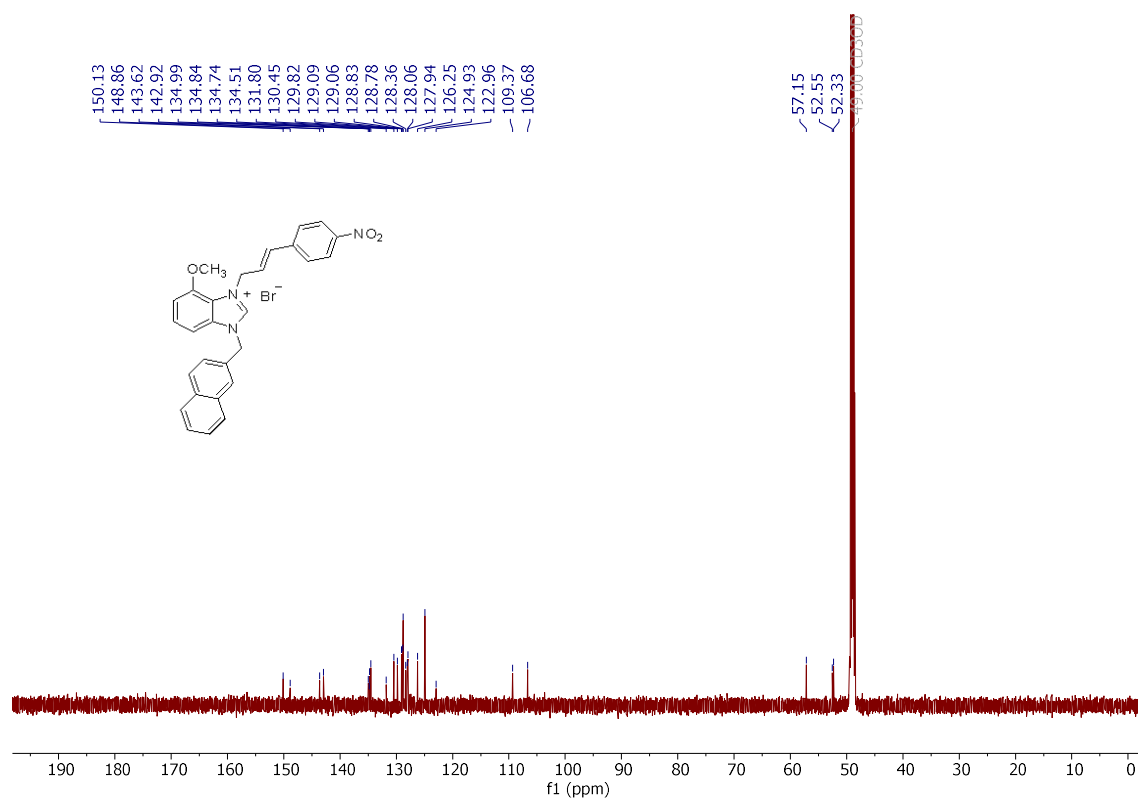


Figure S76. ¹³C-NMR of compound 43.

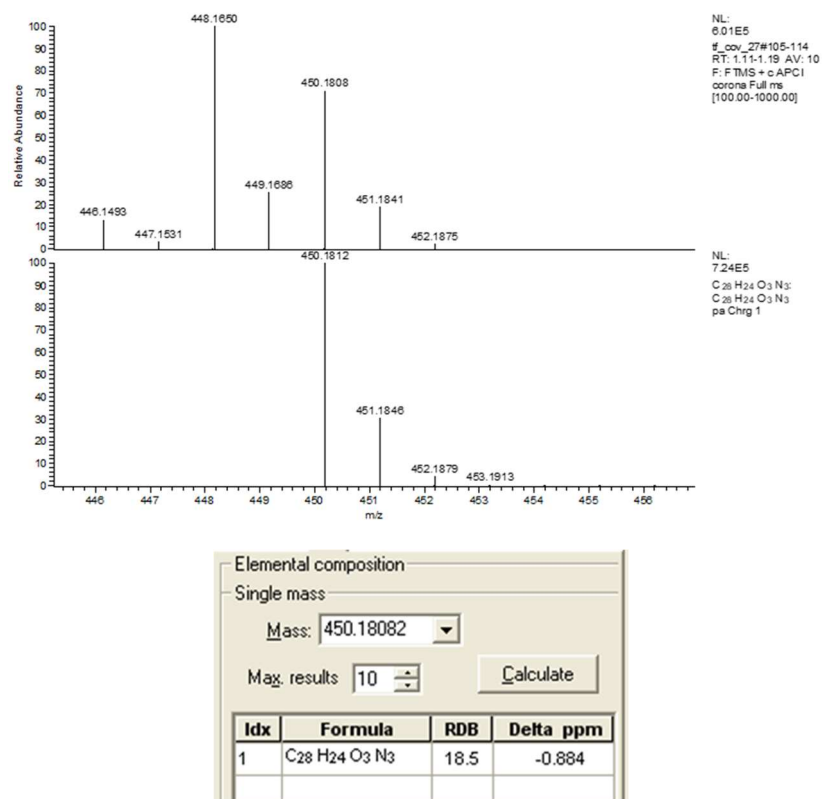


Figure S77. HRMS of compound **43**.

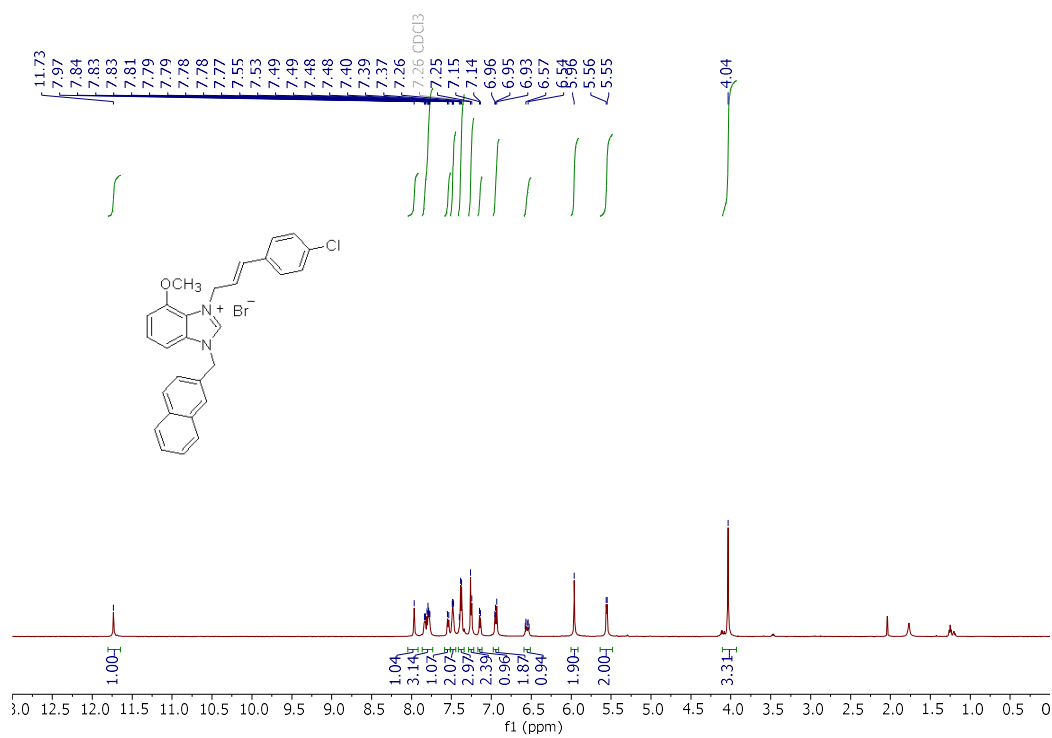


Figure S78. ¹H-NMR of compound 44.

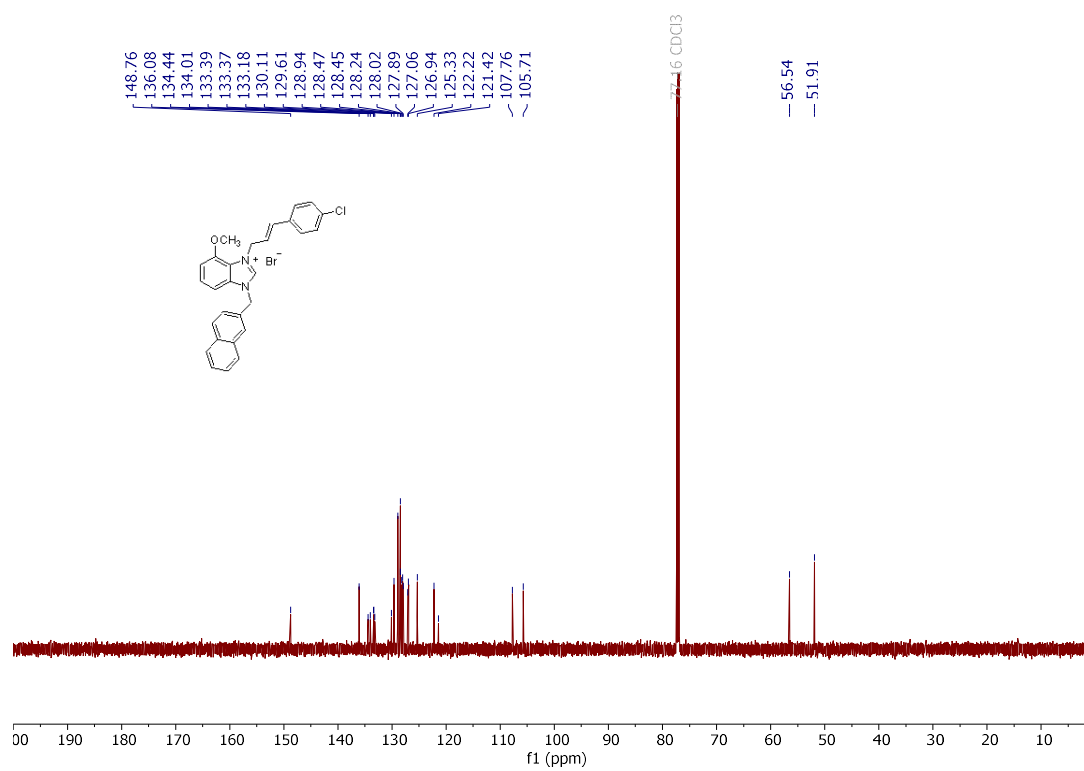


Figure S79. ¹³C-NMR of compound 44.

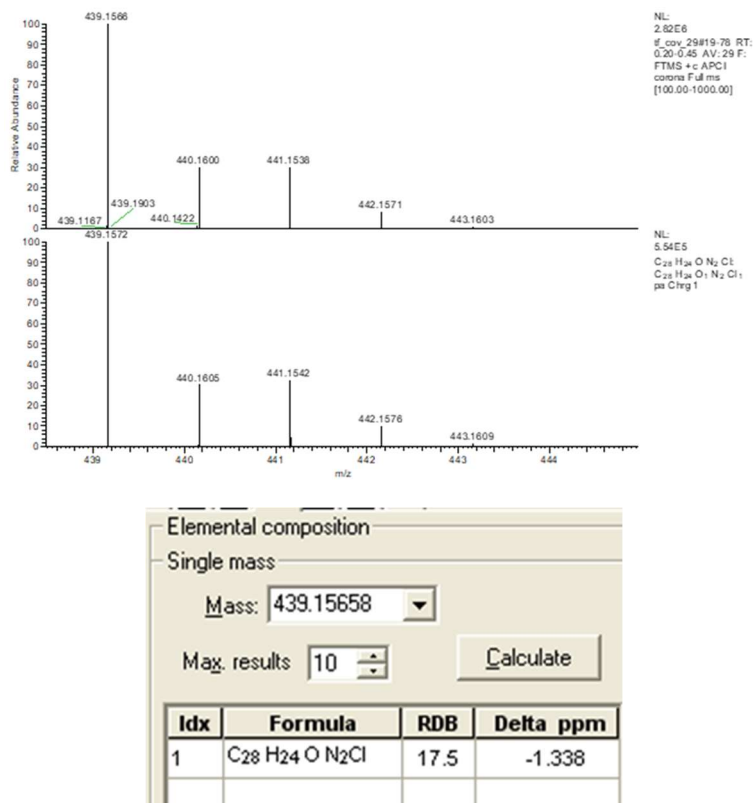


Figure S80. HRMS of compound 44.

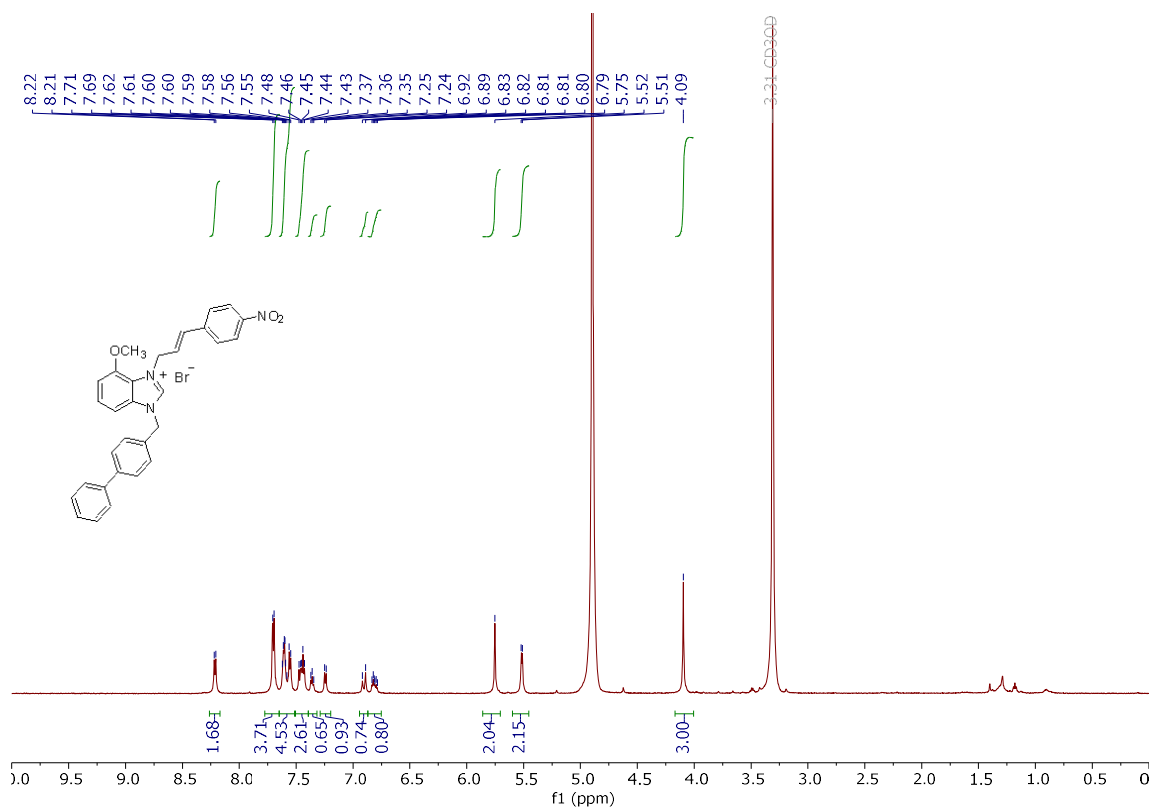


Figure S81. ¹H-NMR of compound 45.

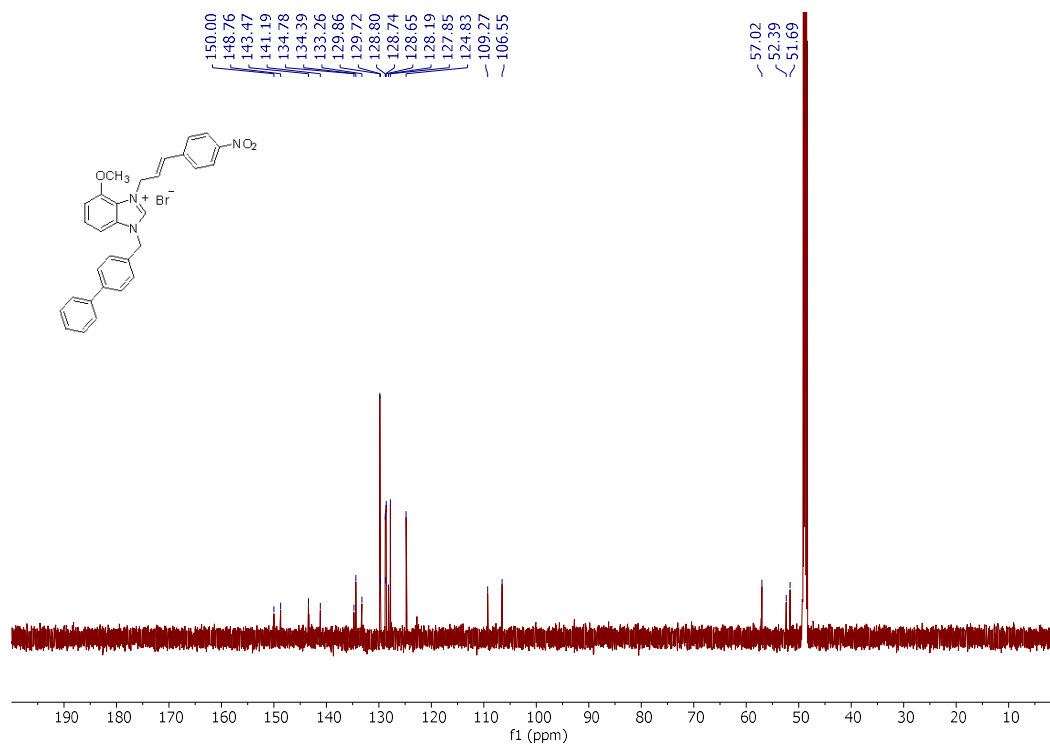


Figure S82. ¹³C-NMR of compound 45.

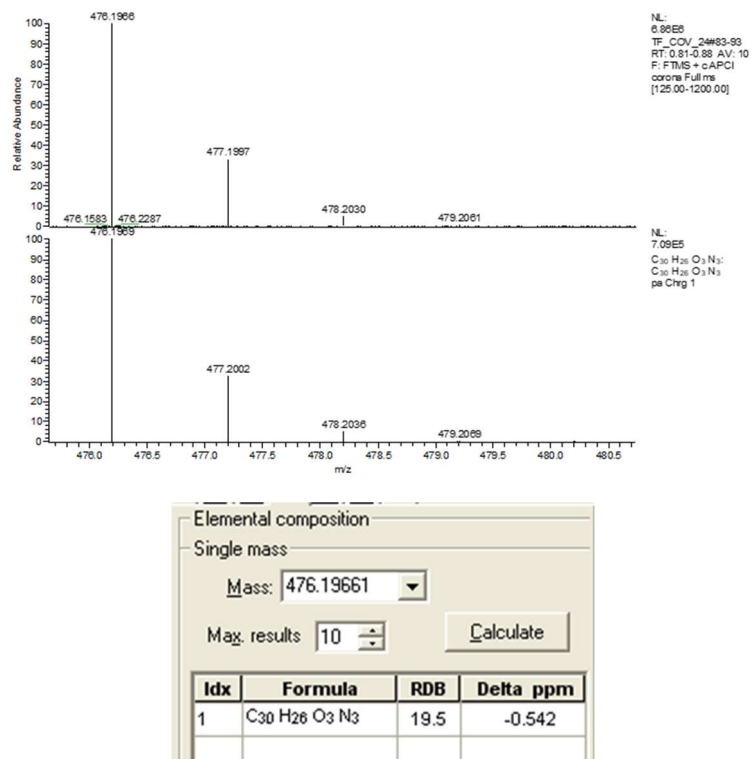


Figure S83. HRMS of compound **45**.

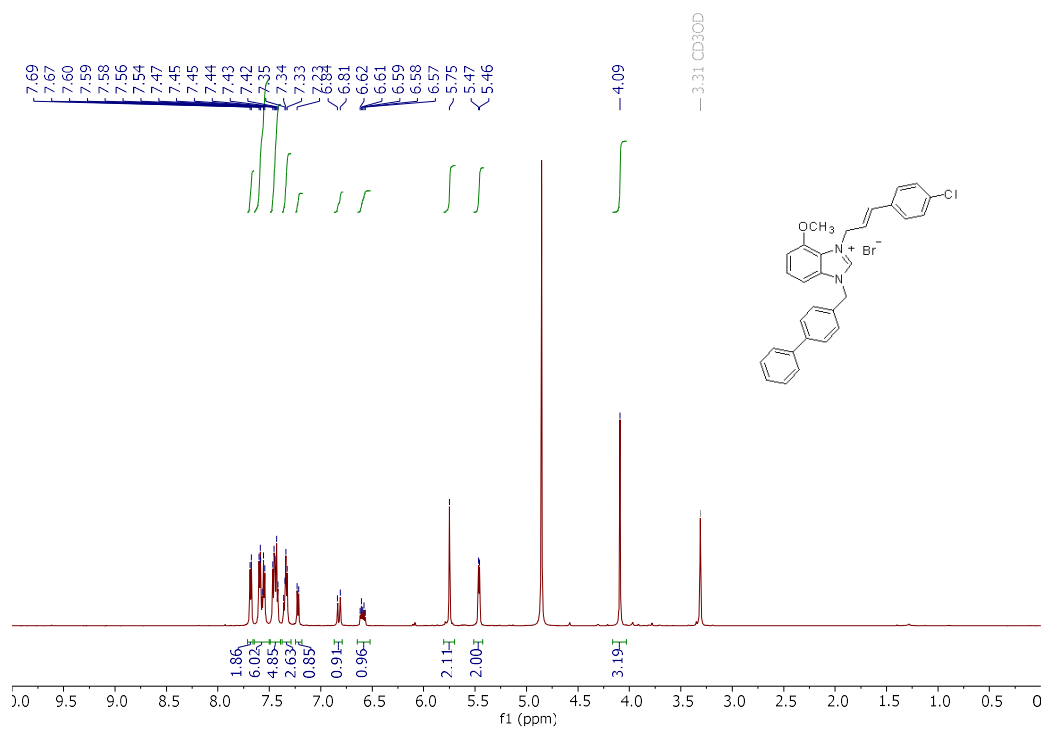


Figure S84. ¹H-NMR of compound 46.

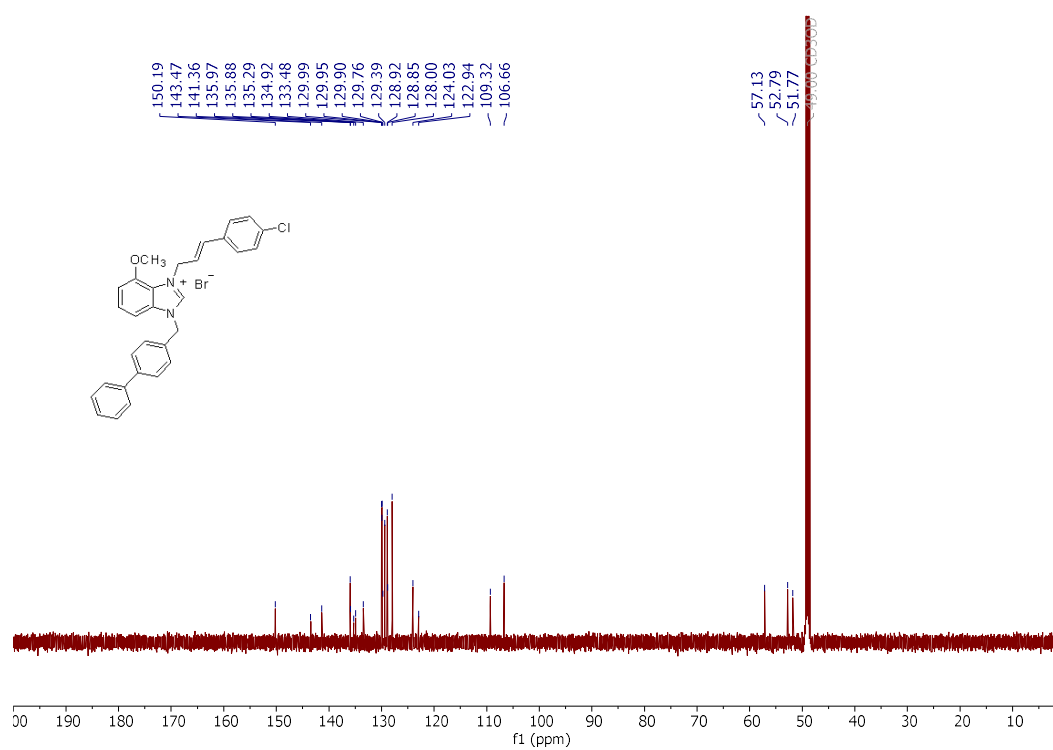
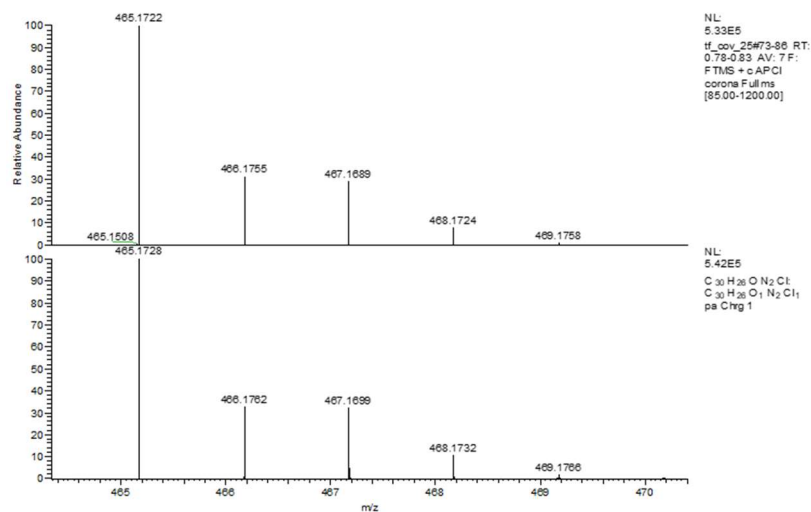


Figure S85. ¹³C-NMR of compound 46.



Elemental composition

Single mass

Mass: 465.17222

Max. results: 10

Calculate

Idx	Formula	RDB	Delta ppm
1	C ₃₀ H ₂₆ O ₁ N ₂ Cl	18.5	-1.285

Figure S86. HRMS of compound **46**.

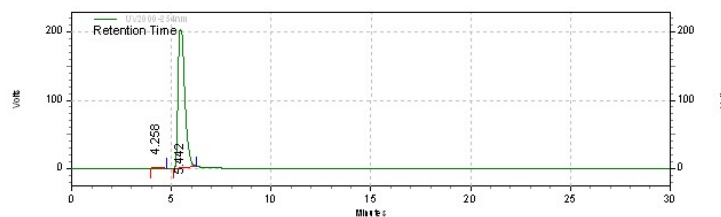
HPLC chromatograms of final compounds

Compound 3

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\data\Covid Project\CKP37_.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/30/2023 4:00:02 PM
 Printed: 10/31/2023 5:43:41 PM



UV2000-254nm
 Results (System
 (10/31/2023
 5:43:37 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
4.258	37637	0.78	1700	0.83
5.442	4759276	99.22	202418	99.17
Totals	4796913	100.00	204118	100.00

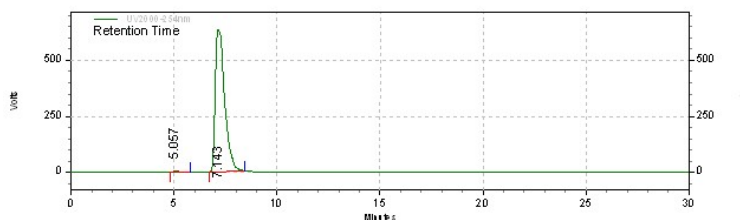
Figure S87. HPLC of compound 3.

Compound 4

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\data\Covid Project\CKP38.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/30/2023 2:38:57 PM
 Printed: 10/31/2023 5:46:29 PM



UV2000-254nm
 Results (System
 (10/31/2023
 5:46:26 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
5.057	108028	0.54	4733	0.74
7.143	20082872	99.46	634225	99.26
Totals	20190900	100.00	638958	100.00

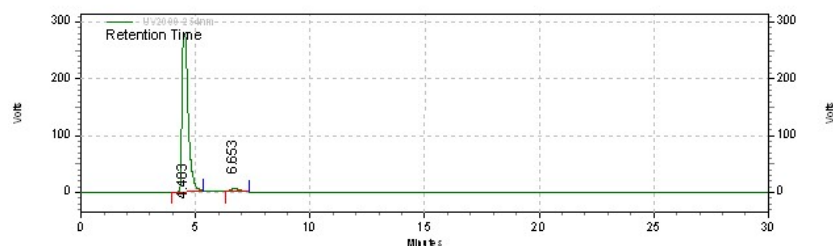
Figure S88. HPLC of compound 4.

Compound 5

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP39.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/30/2023 3:12:36 PM
 Printed: 10/31/2023 5:48:21 PM



UV2000-254nm

Results (System

(10/31/2023

5:48:19 PM)

(Reprocessed))

Retention Time	Area	Area %	Height	Height %
4.483	5167965	97.18	278479	98.07
6.653	149770	2.82	5487	1.93

Totals	5317735	100.00	283966	100.00
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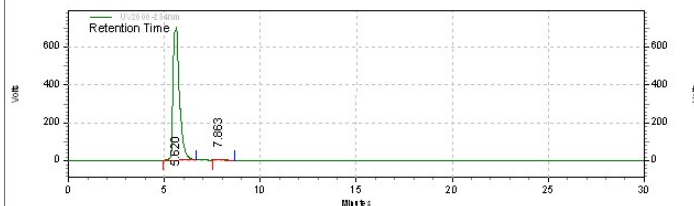
Figure S89. HPLC of compound 5.

Compound 6

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP45_.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/30/2023 2:03:56 PM
 Printed: 10/31/2023 5:50:45 PM



UV2000-254nm

Results (System

(10/31/2023

5:50:41 PM)

(Reprocessed))

Retention Time	Area	Area %	Height	Height %
5.620	16335588	99.27	703101	99.44
7.863	120591	0.73	3959	0.56

Totals	16456179	100.00	707060	100.00
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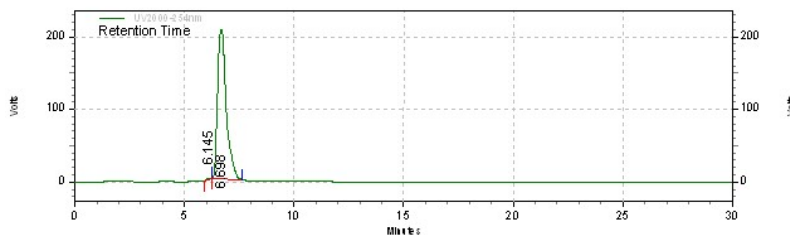
Figure S90. HPLC of compound 6.

Compound 11

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\data\Covid Project\CKP20.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/26/2023 2:36:01 PM
 Printed: 10/26/2023 3:31:55 PM



UV2000-254nm
 Results (System
 (10/26/2023
 3:31:52 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
6.145	17736	0.31	1353	0.65
6.698	5649294	99.69	205356	99.35
Totals	5667030	100.00	206709	100.00

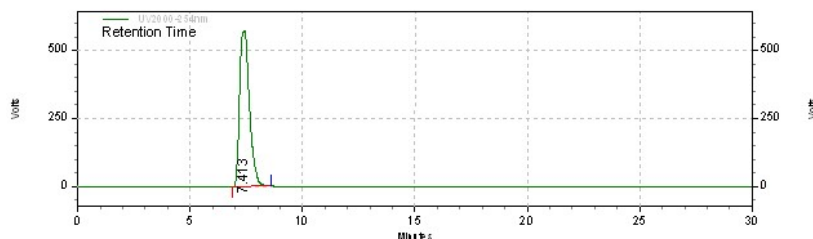
Figure S91. HPLC of compound 11.

Compound 12

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\data\Covid Project\CKP21_.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/26/2023 3:38:44 PM
 Printed: 10/26/2023 4:23:27 PM



UV2000-254nm
 Results (System
 (10/26/2023
 4:23:26 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
7.413	17527345	100.00	572896	100.00
Totals	17527345	100.00	572896	100.00

Figure S92. HPLC of compound 12.

Compound 13

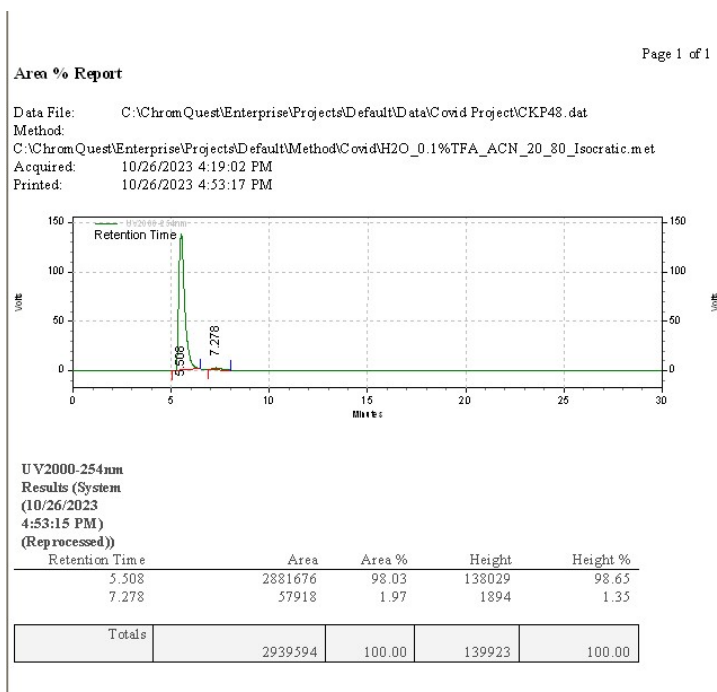


Figure S93. HPLC of compound 13.

Compound 14

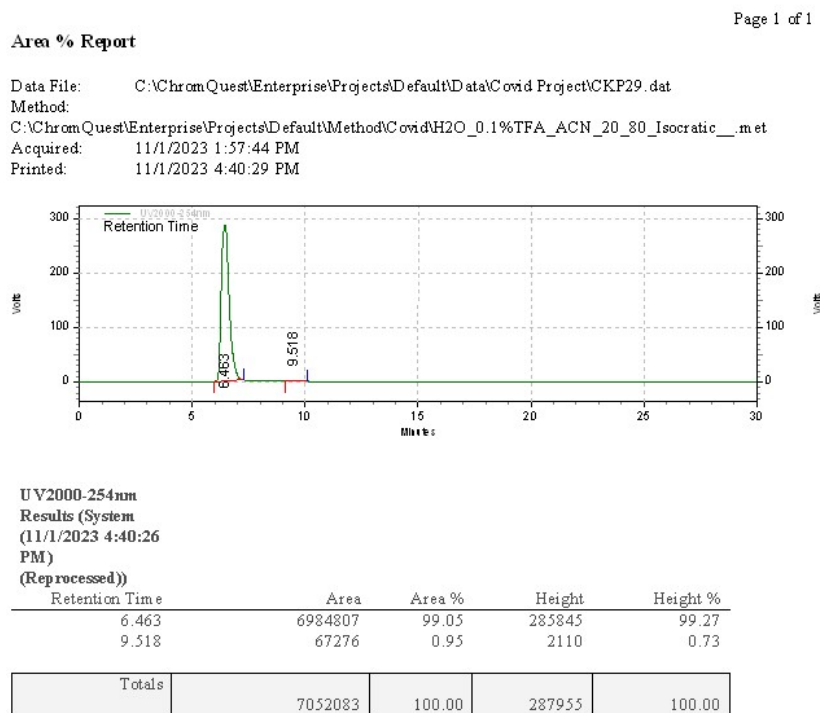


Figure S94. HPLC of compound 14.

Compound 15

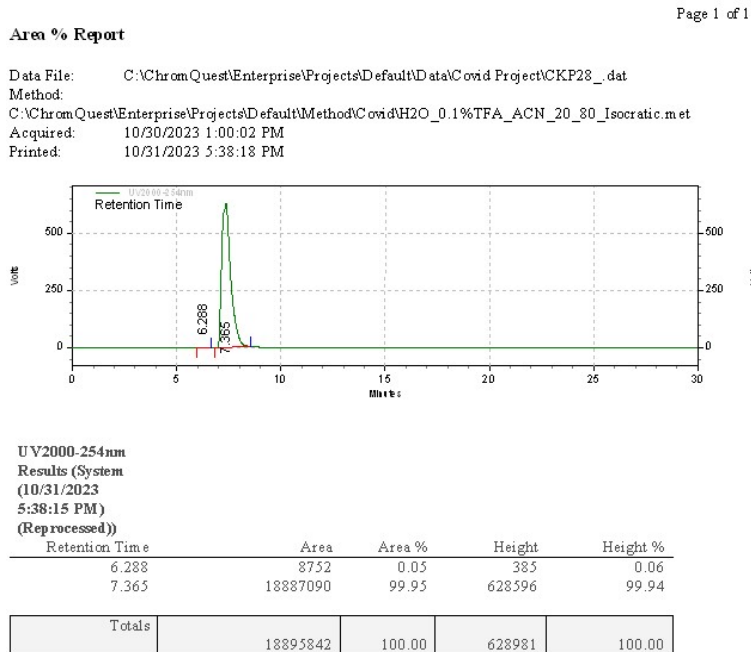


Figure S95. HPLC of compound 15.

Compound 16

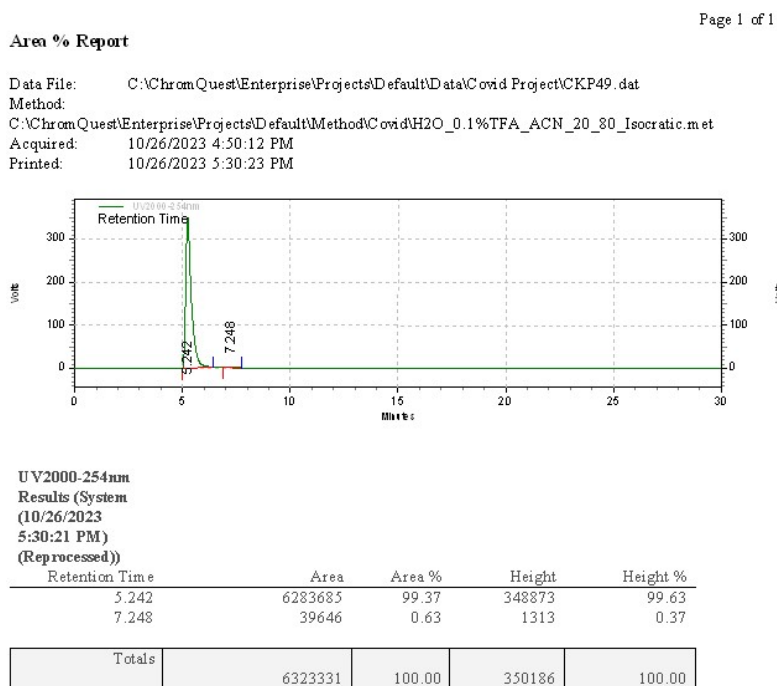


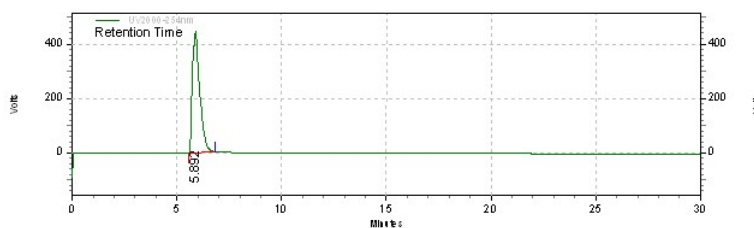
Figure S96. HPLC of compound 16.

Compound 28

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP25_251023_TFA.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/25/2023 2:47:13 PM
 Printed: 10/26/2023 12:51:13 PM



UV2000-254nm
 Results (System
 (10/25/2023
 3:52:06 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
5.892	10806884	100.00	447104	100.00
Totals				
	10806884	100.00	447104	100.00

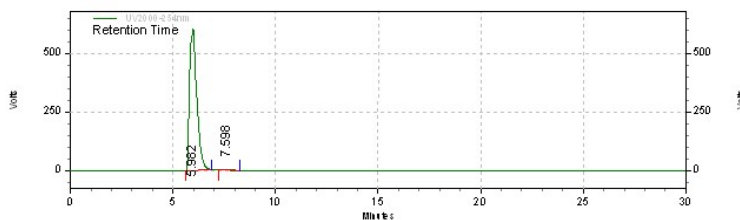
Figure S97. HPLC of compound 28.

Compound 29

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP27_1.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/25/2023 4:00:22 PM
 Printed: 10/26/2023 3:40:36 PM



UV2000-254nm
 Results (System
 (10/26/2023
 3:40:33 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
5.982	14636128	99.25	602166	99.37
7.598	110597	0.75	3792	0.63
Totals				
	14746725	100.00	605958	100.00

Figure S98. HPLC of compound 29.

Compound 30

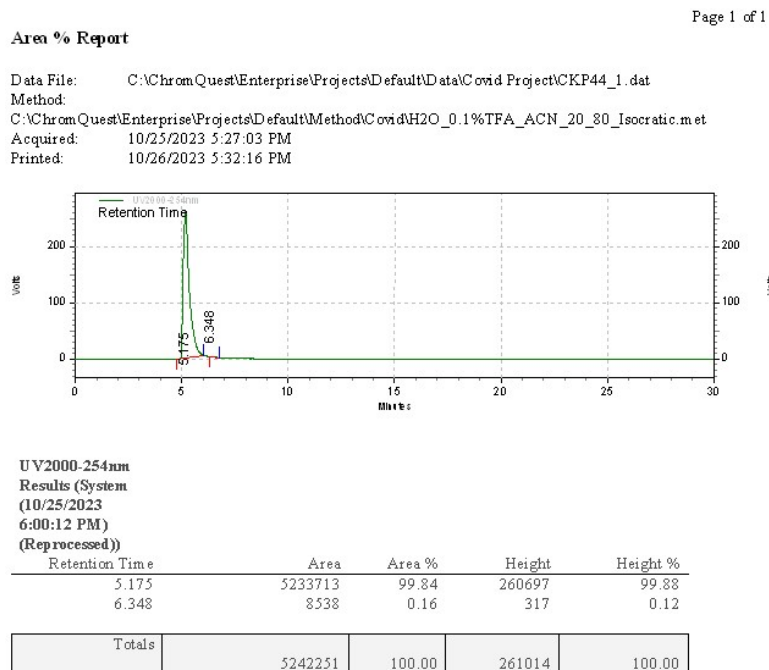


Figure S99. HPLC of compound 30.

Compound 31

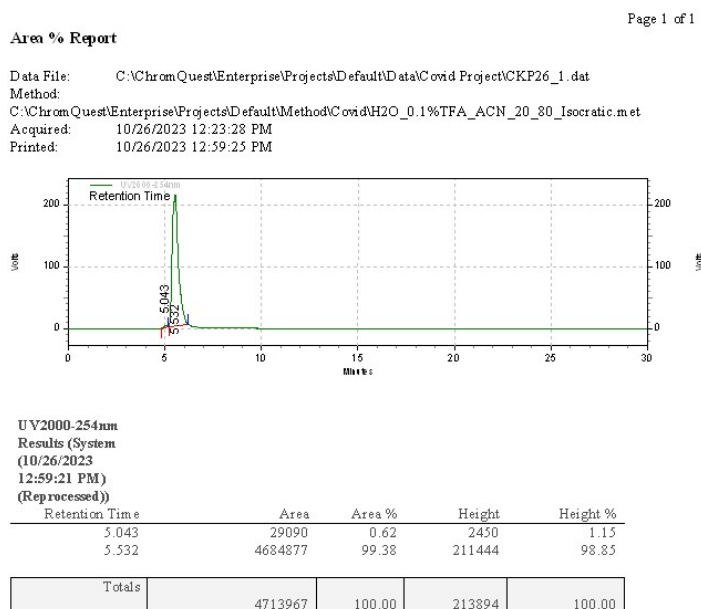


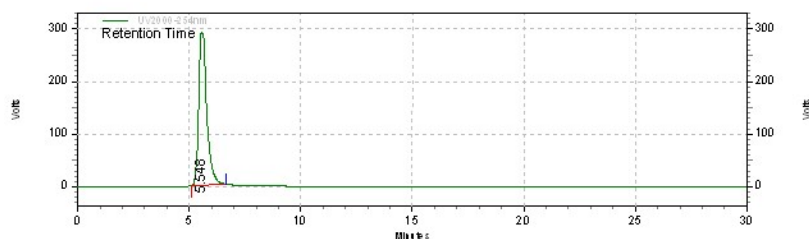
Figure S100. HPLC of compound 31.

Compound 32

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP30.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/26/2023 1:08:29 PM
 Printed: 10/26/2023 3:44:17 PM



UV2000-254nm
 Results (System
 (10/26/2023
 3:43:59 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
5.548	7357293	100.00	291779	100.00
Totals	7357293	100.00	291779	100.00

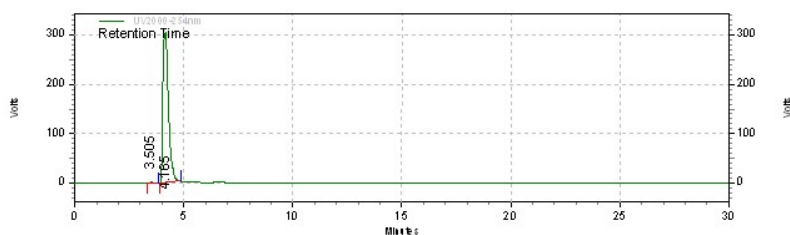
Figure S101. HPLC of compound 32.

Compound 33

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP46.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
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 Printed: 10/31/2023 5:53:11 PM



UV2000-254nm
 Results (System
 (10/31/2023
 5:53:08 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
3.505	21085	0.39	1525	0.50
4.165	5369981	99.61	303581	99.50
Totals	5391066	100.00	305106	100.00

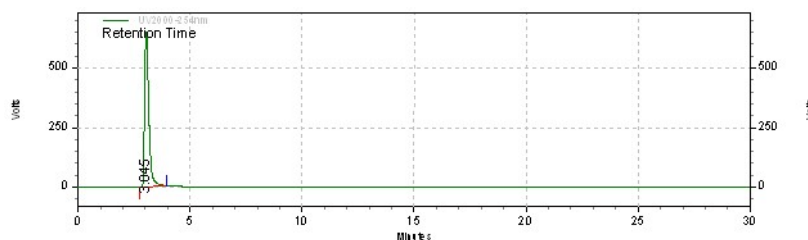
Figure S102. HPLC of compound 33.

Compound 35

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP36_.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 2/13/2024 6:36:50 PM
 Printed: 2/13/2024 7:11:30 PM



UV2000-254nm
 Results (System
 (2/13/2024 7:11:25
 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
3.045	8654473	100.00	651293	100.00
Totals				
	8654473	100.00	651293	100.00

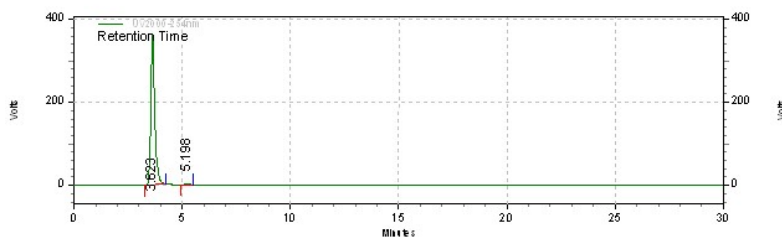
Figure S103. HPLC of compound 35.

Compound 37

Area % Report

Page 1 of 1

Data File: C:\ChromQuest\Enterprise\Projects\Default\Data\Covid Project\CKP35_.dat
 Method: C:\ChromQuest\Enterprise\Projects\Default\Method\Covid\H2O_0.1%TFA_ACN_20_80_Isocratic.met
 Acquired: 10/30/2023 4:34:23 PM
 Printed: 10/31/2023 6:04:11 PM



UV2000-254nm
 Results (System
 (10/31/2023
 6:04:09 PM)
 (Reprocessed))

Retention Time	Area	Area %	Height	Height %
3.623	4641126	99.56	360922	99.68
5.198	20467	0.44	1167	0.32
Totals				
	4661593	100.00	362089	100.00

Figure S104. HPLC of compound 37.

Compound 38

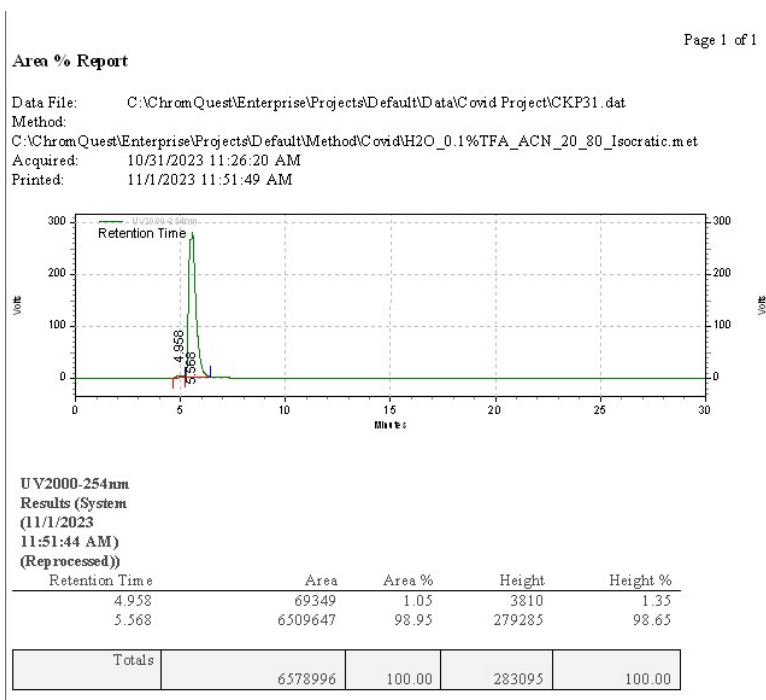


Figure S105. HPLC of compound 38.

Compound 39

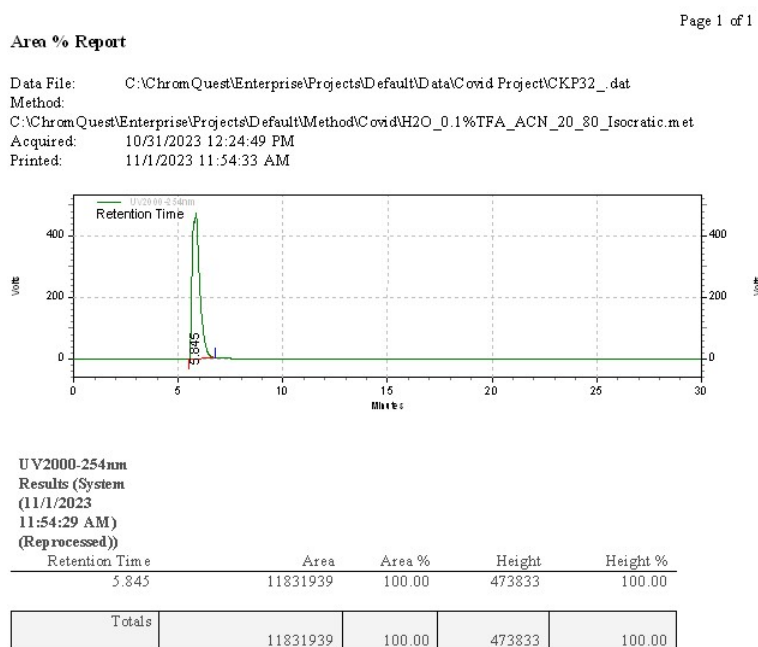


Figure S106. HPLC of compound 39.

Compound 40

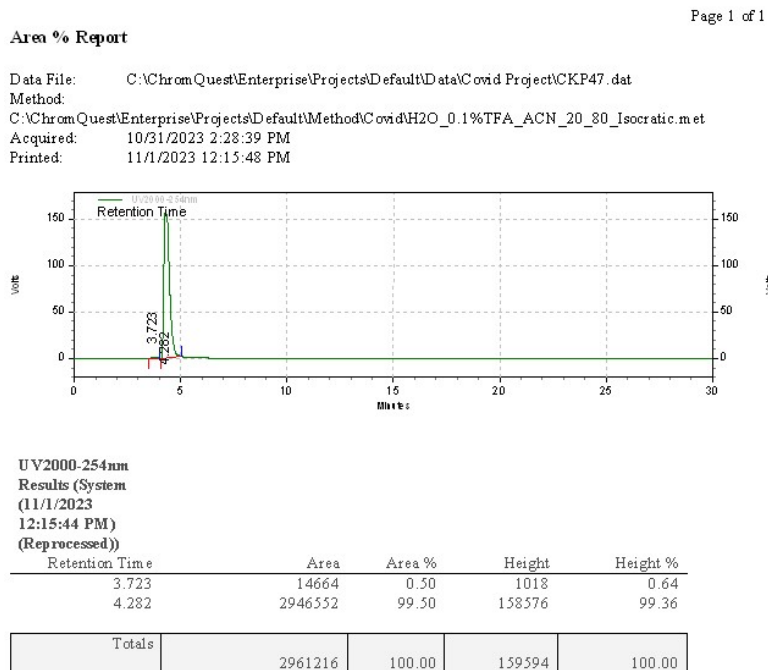


Figure S107. HPLC of compound 40.

Compound 41

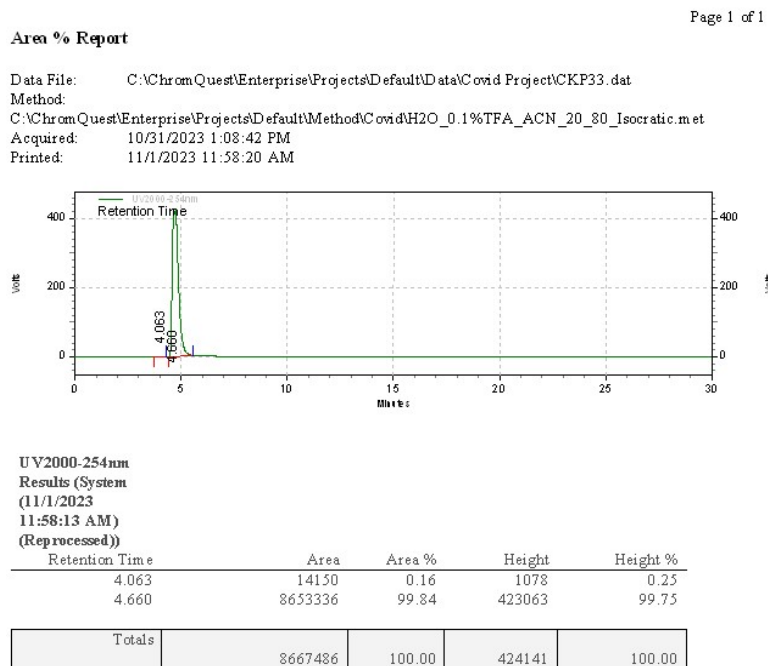


Figure S108. HPLC of compound 41.

Compound 42

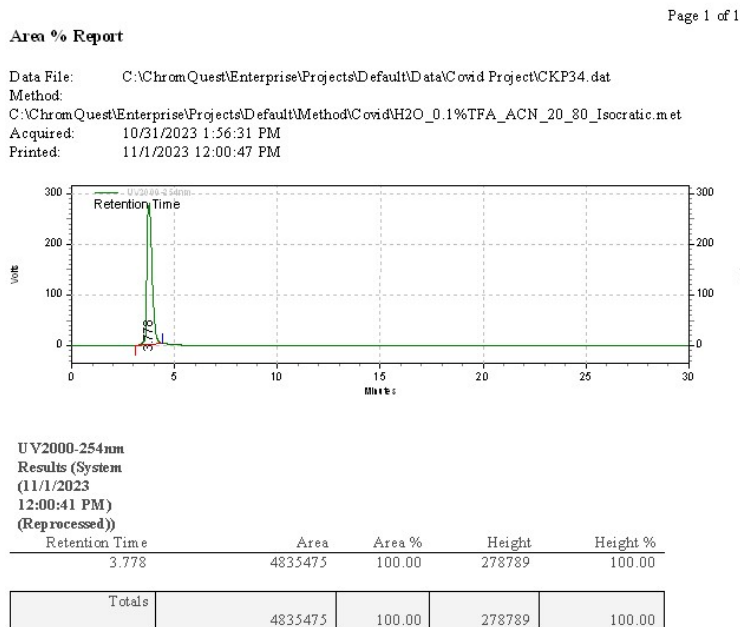


Figure S109. HPLC of compound 42.

Compound 43

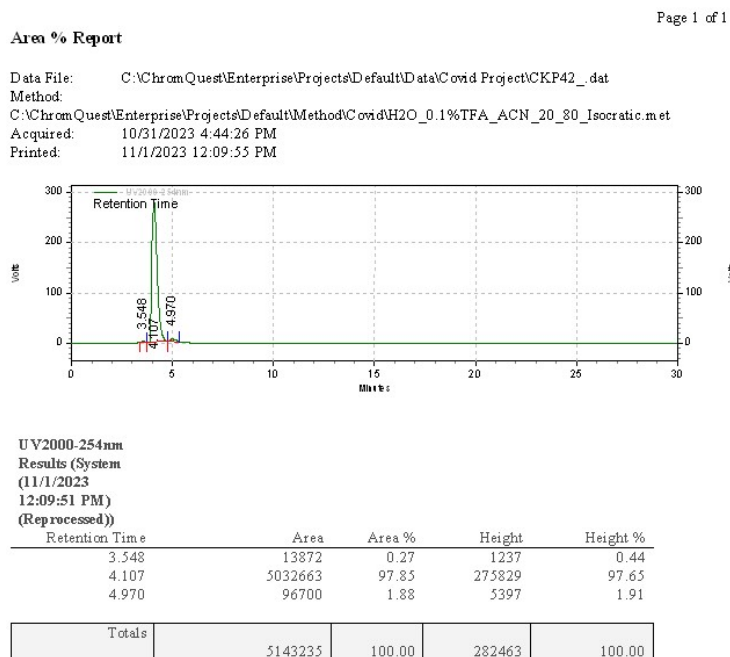


Figure S110. HPLC of compound 43.

Compound 44

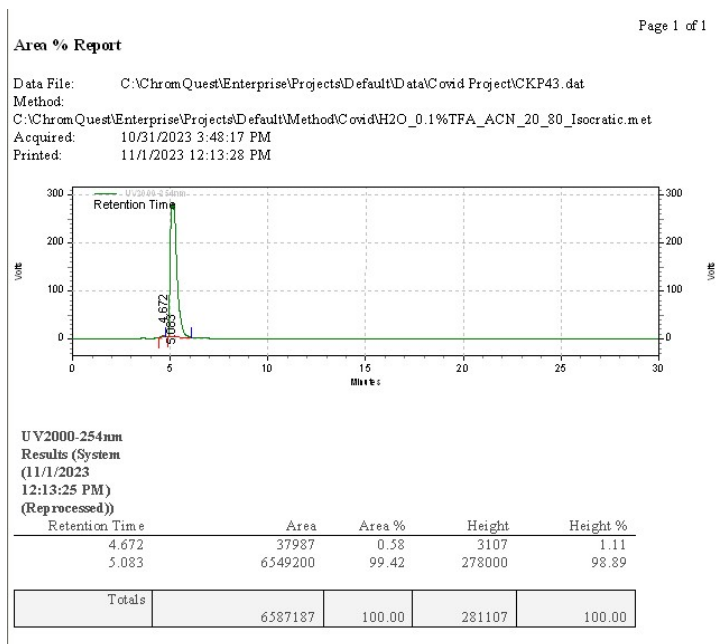


Figure S111. HPLC of compound 44.

Compound 45

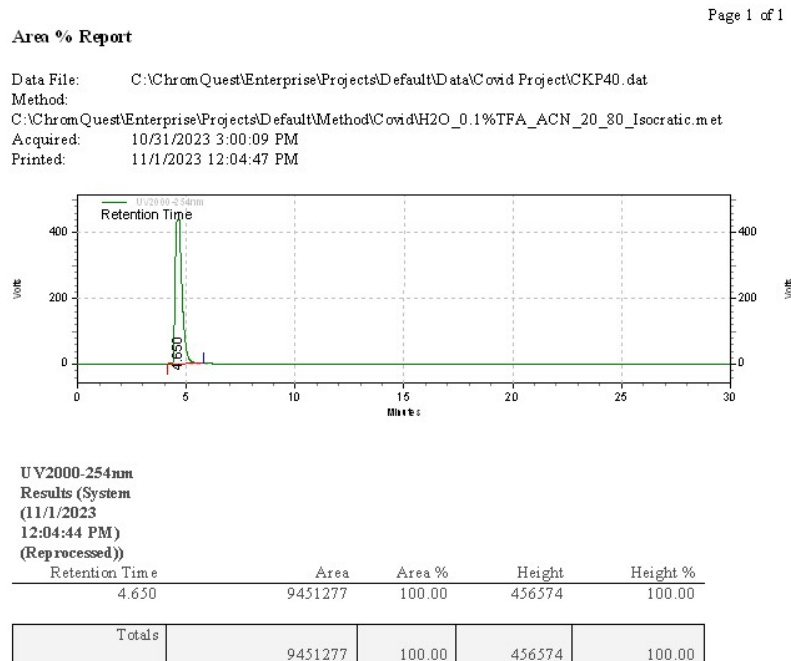


Figure S112. HPLC of compound 45.

Compound 46

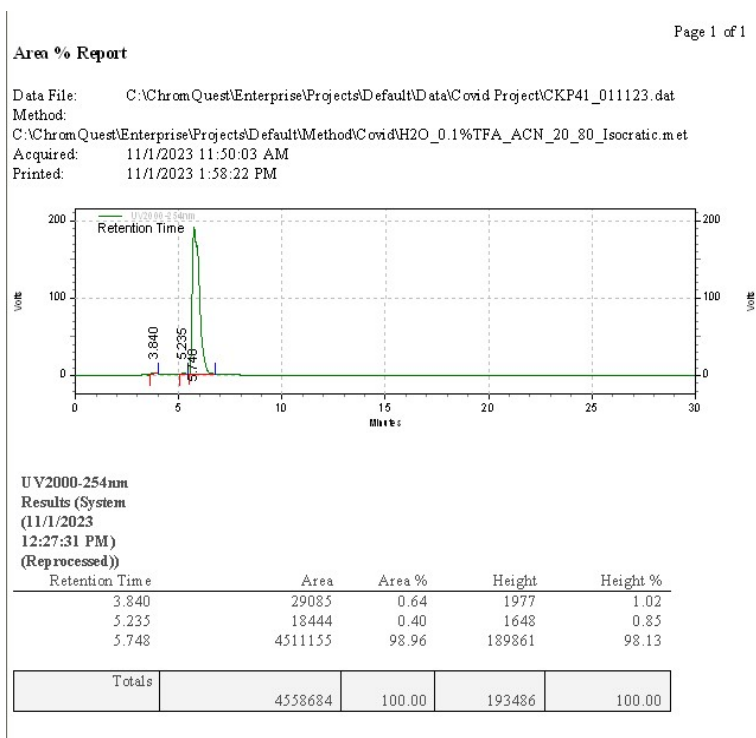


Figure S113. HPLC of compound 46.

Supplementary Charts

Chart S1

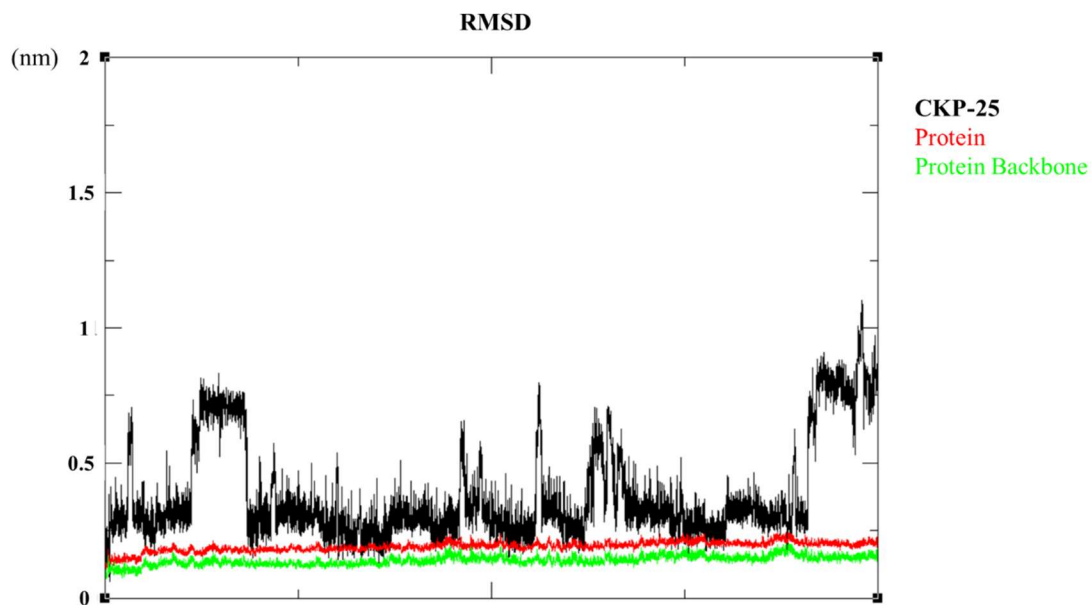
Chart S1, RMSD plot of the MD simulation results for **CKP-25**, the protein and the protein backbone with respective coloring provided.

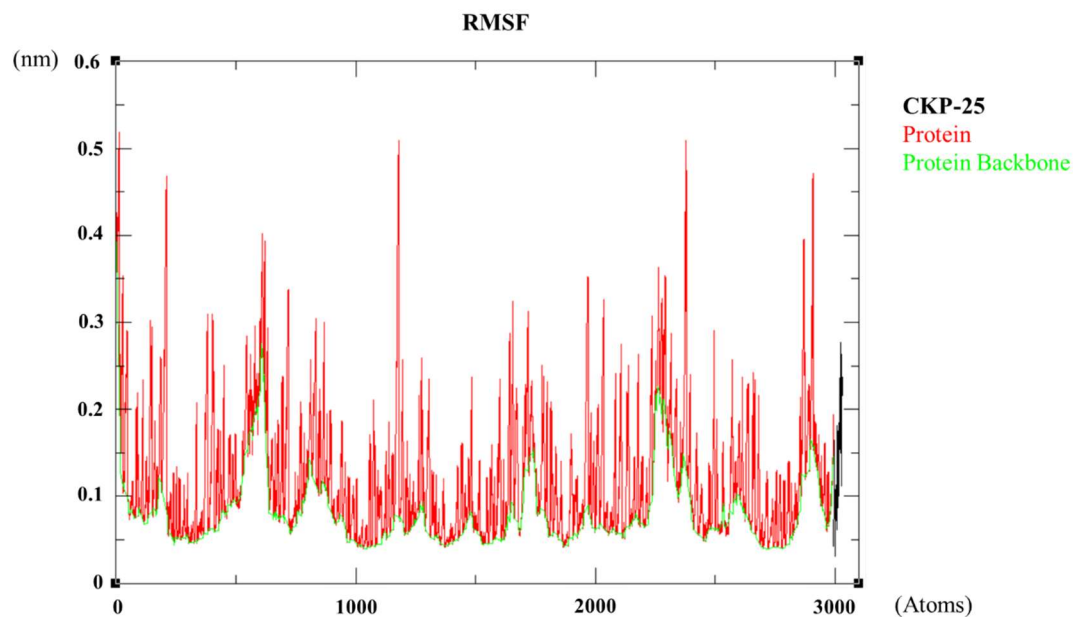
Chart S2

Chart S2. Atom fluctuation plot of the MD simulation results for CKP-25, the protein and the protein backbone with respective coloring provided.

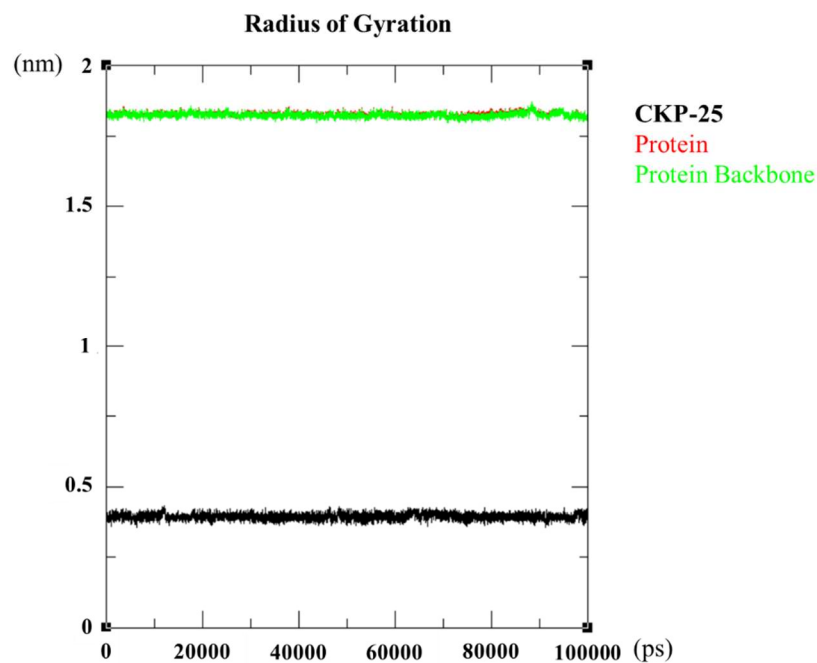
Chart S3

Chart S3. Radius of gyration plot of the MD simulation results for CKP-25, the protein and the protein backbone with respective coloring provided.

Chart S4

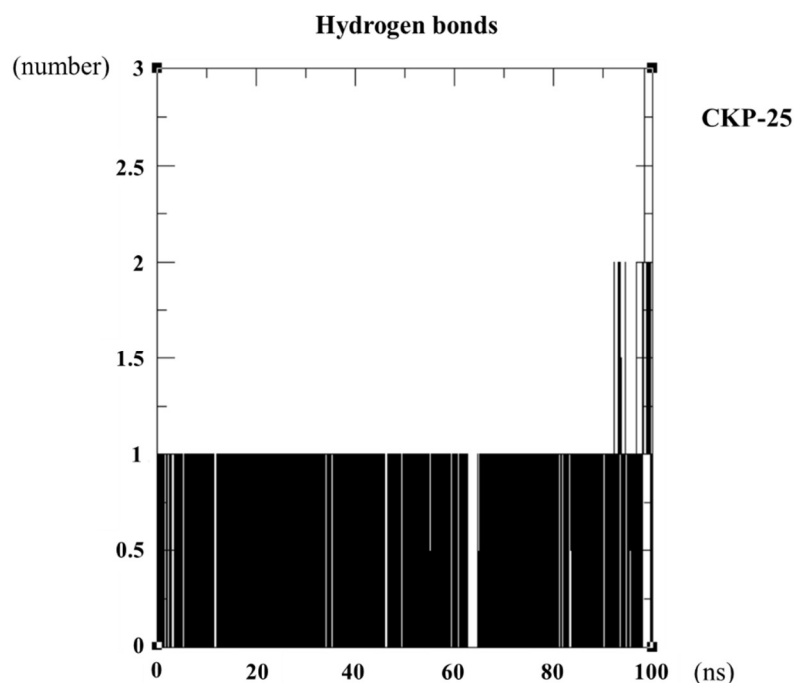


Chart S4. Number of hydrogen bonds plot for the MD simulation results regarding compound CKP-25.

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