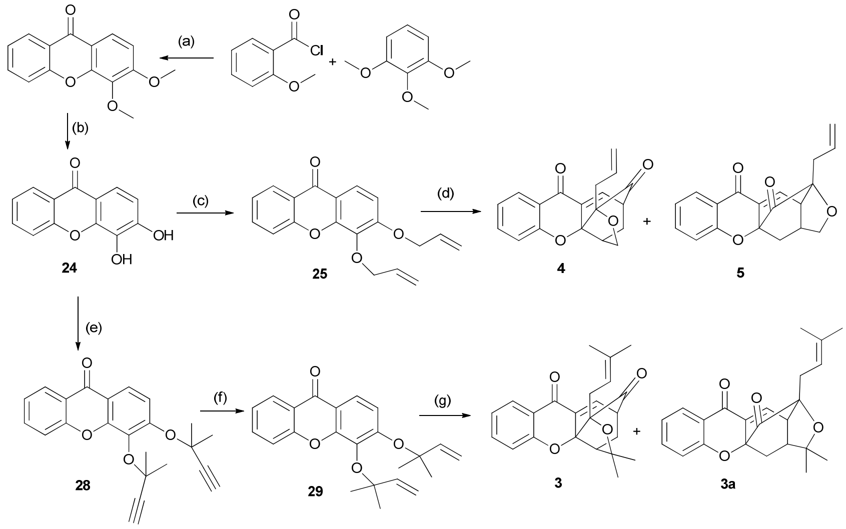
Synthesis and evaluation of novel aza-caged *Garcinia* xanthones

Xiaojin Zhang, [a,1] Xiang Li, [a,1] Haopeng Sun, * [b] Zhengyu Jiang, [b] Lei Tao, [c] Yuan Gao, [c] Qinglong Guo * [c] and Qidong You* [a,c]

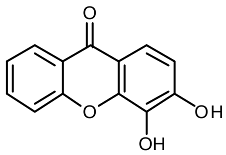
Supplementary Information

Experimental procedure



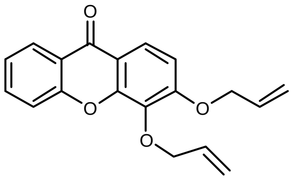
Reagents and conditions: (a) Et_2O, $AlCl_3$, 25°C, 12 h; then NaOH, MeOH, H_2O, 110 °C, 24 h; (b) 40% HBr, HOAc, reflux, 12 h; (c) allyl chloride, DMF, 45 °C, 2 h; (d) decalin, 180 °C, 3 h; (e) 2-chloro-2-methylbut-3-yne, DBU, K_2CO_3, CuI, Acetone, reflux, 6 h; (f) DMF, 120 °C, 1 h.

3,4-Dihydroxy-9*H*-xanthen-9-one (**24**) To a solution of 2-methoxylbenzoyl chloride (1.72 g, 10.1 mmol) and 1,2,3-trimethoxybenzene (1.68 g, 10 mmol) in 20 mL anhydrous ether, aluminum trichloride (3.61 g, 27 mmol) was added at 0 °C. The reaction mixture was stirred for 12 h at room temperature. Then a mixture of 15% hydrochloric acid and ethyl acetate (100 mL, V/V = 1:1) were added. The organic layer was partitioned, washed with brine (30 mL×3), dried over magnesium sulfate and concentrated under reduced pressure. The residue was suspended in a solution that contained methanol (22.4 mL), water (14.9 mL) and sodium hydrate (1.2 g, 30 mmol) at 25 °C. Then the reaction mixture was heated to 110 °C for next 24 h. After cooled to 0 °C, the mixture was acidified with 2 mol/L HCl solution till pH=2~3. The precipitation was formed, filtered, washed with cold water and dried. Then the filter cake was dissolved in a mixture of 40% HBr and acetic acid (150 mL, V/V = 1:2), the reaction mixtre was refluxed for 12 h at 120 °C under N_2 protection. After cooled to 0 °C, the reaction mixture as acidified till pH=3-4 with 10% NaOH solution, the precipitation was filtered, washed with ice water and dried to provide **24** as a yellow solid (1.19 g, 52% combined yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.91 (br, 2H), 8.15 (d, J = 8.2 Hz,1H), 7.83 (t, J = 7.8 Hz,1H), 7.60 (d, J = 8.7 Hz,1H), 7.56 (d, J = 8.7 Hz,1H), 7.46 (t, J =

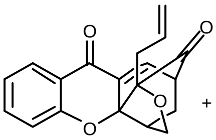


7.5 Hz,1H), 6.95 (d, J = 8.7 Hz,1H); EI-MS (m/z): 228 $(M)^+$ (100), 207(52), 169(54).

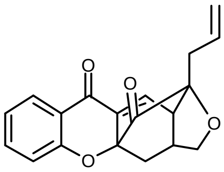
3,4-Bis(allyloxy)-9*H*-xanthen-9-one (**25**) To a solution of compound **14** (1.14 g, 5 mmol) in DMF (15 mL) was added potassium carbonate (1.518 g, 11 mmol) and allyl chloride (912 mg, 12 mmol). The mixture was stirred under nitrogen at 45 °C for 2 h. The reaction mixture was allowed to cool to 25 °C and then partitioned between EtOAc (30 mL) and water (70 mL). The water layer was back-extrated with EtOAc (30 mL × 2) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (10-20% EtOAc-PE) to provide compound **25** (1.53 g, 99%) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.32 (dd, J = 8.4, 1.5 Hz,1H), 8.07 (d, J = 9.0 Hz,1H), 7.72 (dt, J = 8.4, 1.5 Hz,1H), 7.56 (d, J = 7.8 Hz,1H), 7.41-7.35 (m,1H), 6.99 (d, J = 9.0 Hz,1H), 6.24-6.06 (m,2H), 5.51-5.23 (m, 4H), 4.76-4.71 (m, 4H); EI-MS (m/z): 308 $(M)^+$ (42), 267(100).



Caged compounds **4** and **5** A solution of **25** (100 mg, 0.32 mmol) in decalin was stirred under nitrogen at 180 °C for 3 h. The reaction mixture was then cooled to 25 °C and the residue was purified by flash column chromatography (5-10% EtOAc-PE) to yield caged compounds **4** (32mg, 32%) and **5** (29mg, 29%) as white solids. For compound **4,** ^1H NMR ($CDCl_3$, 300 MHz): δ 7.94 (dd, J = 7.8, 1.5 Hz, 1H), 7.58-7.53 (m, 1H), 7.33 (d, J = 6.9 Hz, 1H), 7.10-7.05 (m, 2H), 5.30-5.15 (m, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.56-4.51 (m, 2H), 3.90 (d, J = 7.8 Hz, 1H), 3.54-3.50 (m, 1H), 2.80-2.70 (m, 1H), 2.62 (dd, J = 7.8, 3.3 Hz, 1H), 2.55-2.47 (m, 1H), 1.88-1.77 (m, 2H); EI-MS (m/z): 308 $(M)^+$ (18), 169(100); HRMS (ESI) calc. For $C_{19}H_{16}O_4$ $(M + H)^+$ 309.1127, found 322.1135. For compound **5,** ^1H NMR ($CDCl_3$, 300 MHz): δ 7.91 (dd, J = 7.8, 1.5 Hz, 1H), 7.58-7.53 (m, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.10-7.05 (m, 1H), 5.68-5.52 (m, 1H), 5.15-5.08 (m, 2H), 4.08 (dd, J = 8.1, 3.6 Hz, 1H), 3.97 (d, J = 8.1 Hz, 1H), 3.48 (dd, J = 6.9, 4.2 Hz, 1H), 2.68-2.52 (m, 2H), 2.32-2.22 (m, 3H); EI-MS (m/z): 308 $(M)^+$ (21), 169(100); HRMS (ESI) calc. For $C_{19}H_{16}O_4$ $(M + H)^+$ 309.1127, found 322.1132.

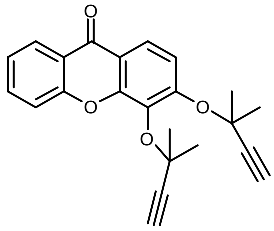


4

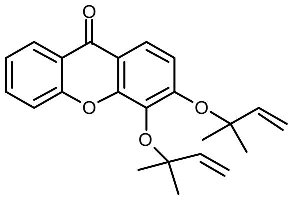


5

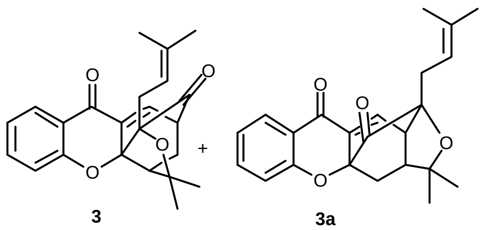
3,4-Bis((2-methylbut-3-yn-2-yl)oxy)-9*H*-xanthen-9-one (**28**) To a solution of **24** (388 mg, 1.7 mmol) in acetone (10 mL), potassium iodide (288 mg, 1.7 mmol), DBU (1.2 mL, 8.16 mmol) and CuI (5 mg, 0.026 mmol) were added. The reaction mixture was stirred at room temperature for 10min, then 2-chloro-2-methylbut-3-yne (1.4 mL, 13.6 mmol) was added and the resulted mixture was refluxed for 6 more hours. Water (50 mL) and EtOAc (20 mL) was added to the mixture and stirred for 30min. The organic layer was separated, dried over sodium sulfate, and evaporated. The residue was purified by flash column chromatography (10-20% EtOAc-PE) to afford **28** (413 mg, 55%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.62 (dd, J= 7.5, 8.4 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 2.50 (s, 1H), 2.22 (s, 1H), 1.77 (s, 6H), 1.70 (s, 6H). EI-MS (m/z): 360 $(M)^+$ (40).



3,4-Bis((2-methylbut-3-en-2-yl)oxy)-9*H*-xanthen-9-one (**29**) To a solution of **28** (221 mg, 0.50 mmol) in ethanol (10 mL) was added 10% Pd/$BaSO_4$ (22 mg). The mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature and filtered through a plug of silica gel, the filtration was concentrated and purified by flash column chromatography (10-20% EtOAc-PE) to afford **29 (188 mg, 85%)** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (d, J = 9 Hz, 1H), 7.93 (d, J = 9 Hz, 1H), 7.71 (t, J = 9 Hz, 1H), 7.50 (d, J = 5.1Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 9 Hz, 1H), 6.30 (dd, J= 17.7, 11.1 Hz, 1H), 6.20 (dd, J= 17.7, 11.1 Hz, 1H), 5.25-5.17 (m, 3H), 5.03 (d, J = 12.1Hz, 1H), 1.61 (s, 6H), 1.58 (s, 6H). EI-MS (m/z) = 364 $(M)^+$ (34).



Caged compounds **3** and **3a** To a solution of **29** (200 mg, 0.55 mmol) in DMF (4.0 mL) was heated at 120 °C under N_2 protection for 1 h. The yellow reaction mixture was cooled to 25°C and the mixture was purified by flash column chromatography (5-10% EtOAc-PE) to yield the caged compounds **3 (114mg,** 57%**) and 3a (56 mg, 28%) as pale-yellow solids**. For compound **3**,



3 + **3a**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 7.2 Hz, 1H), 7. 36 (d, *J* = 6.9 Hz, 1H), 6.97-7.02 (m, 2H), 4.35 (t, 1H), 3.47-3.41 (m, 1H), 2.55 (d, *J* = 9.3Hz, 2H), 2.39 (d, *J* = 9.6Hz, 1H), 2.27 (dd, *J* = 13.5, 4.5Hz, 1H), 1.66 (s, 3H), 1.30-1.15 (m, 7H), 0.84 (s, 3H). HRMS (ESI) calc. For $C_{23}H_{24}O_4$ $(M + H)^+$ 365.1753, found 365.1756. For compound **3a**, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.85 (dd, *J* = 8.1, 1,5 Hz, 1H), 7.49 (m, 1H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H) 6.99 (t, *J* = 7.5 Hz, 1H), 4.95 (m, 1H), 3.71-3.67 (m, 1H), 2.50-2.39 (m, 2H), 2.12-1.98 (m, 2H), 1.84-1.77 (m, 1H), 1.65 (s, 3H), 1.53 (s, 1H), 1.31 (s, 1H), 1.28 (s, 3H); MS (EI): *m/z* 364$(M)^+$ (17); Anal. calcd for $C_{23}H_{24}O_4$: C 75.80, H 6.64. Found: C 75.78, H 6.69.

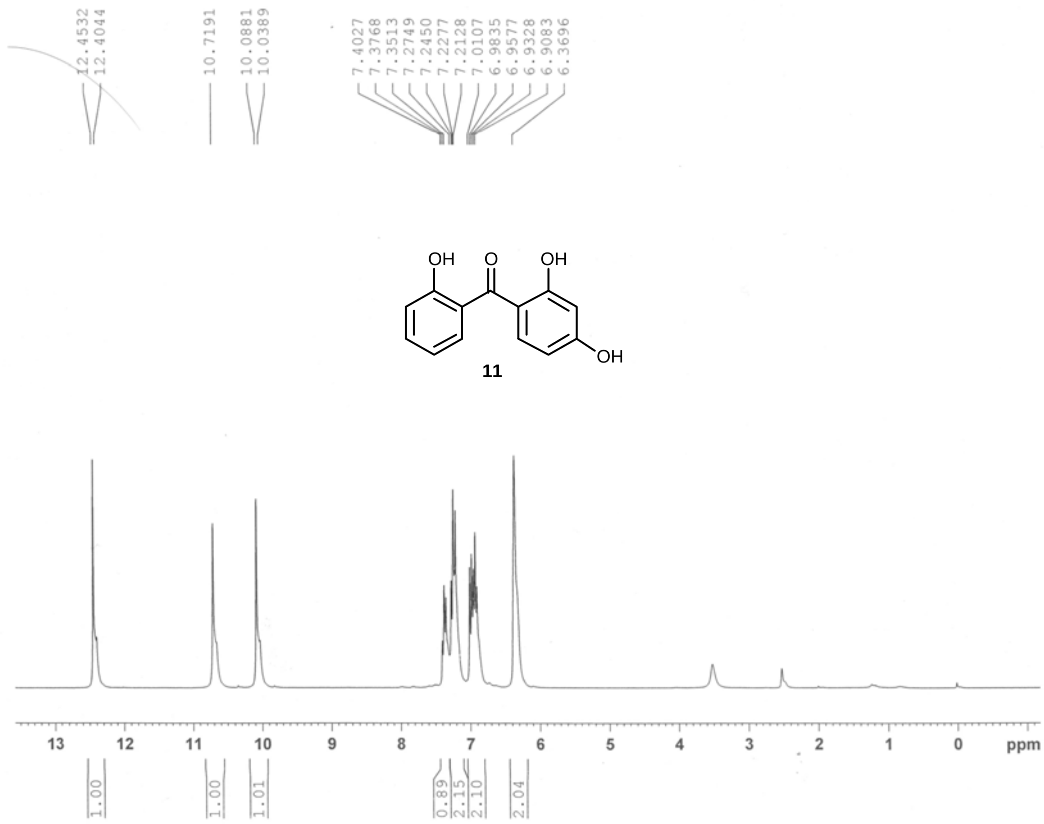
The NMR data of caged compounds **3-5**, **3a** were coordinate with the following references:

1 A. Batova, T. Lam, V. Wascholowski, A. L. Yu, A. Giannis and E. A. Theodorakis, *Org. Biomol. Chem.*, 2007, **5**, 494-500.

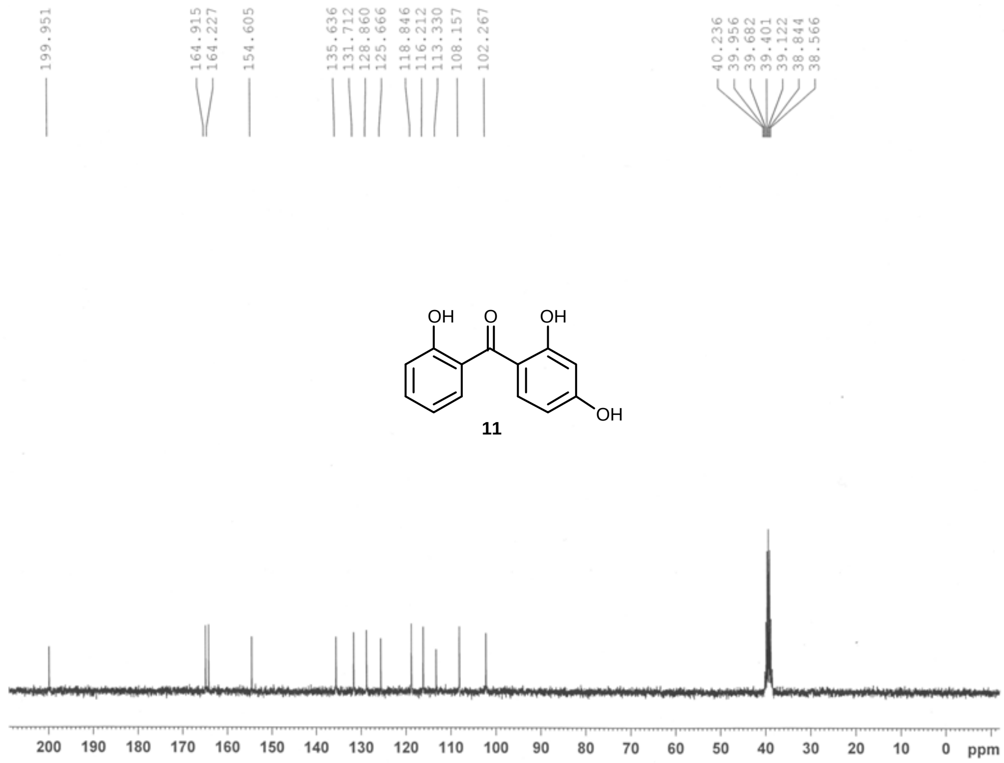
2 X. Wang, N. Lu, Q. Yang, D. Gong, C. Lin, S. Zhang, M. Xi, Y. Gao, L. Wei, Q. Guo and Q. You, *Eur. J. Med. Chem.*, 2011, **46**, 1280-1290.

NMR spectra

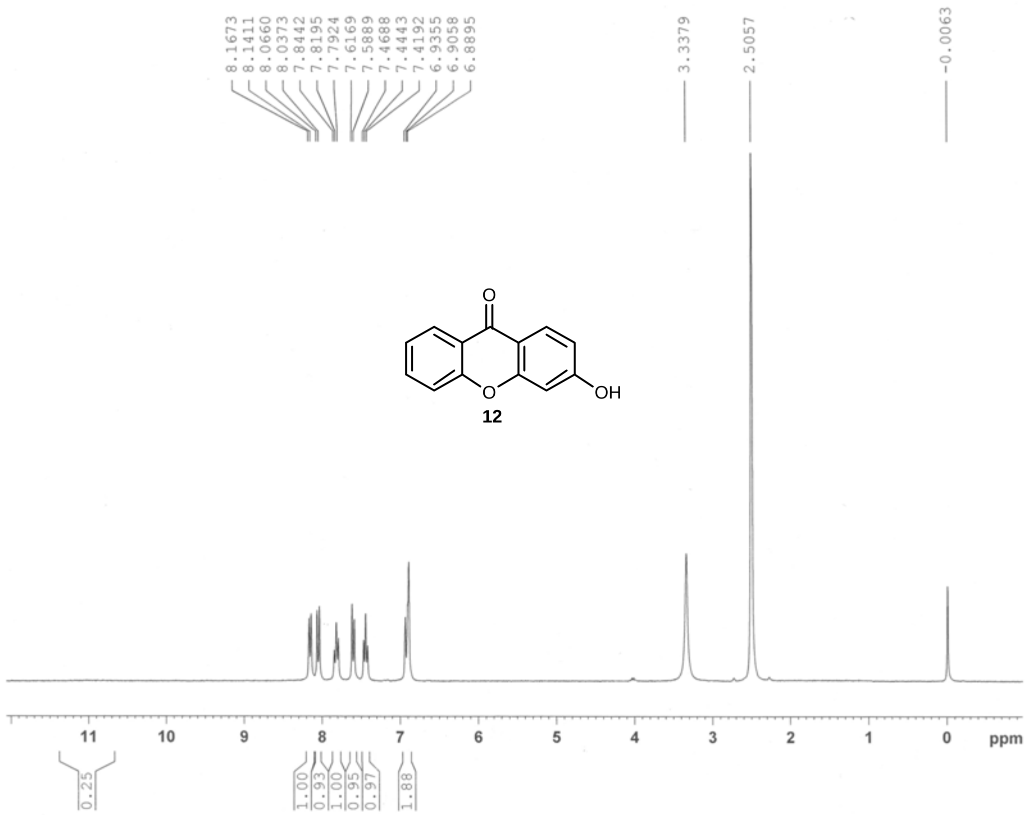
11: [1]H NMR, 300 MHz in DMSO-*d6*



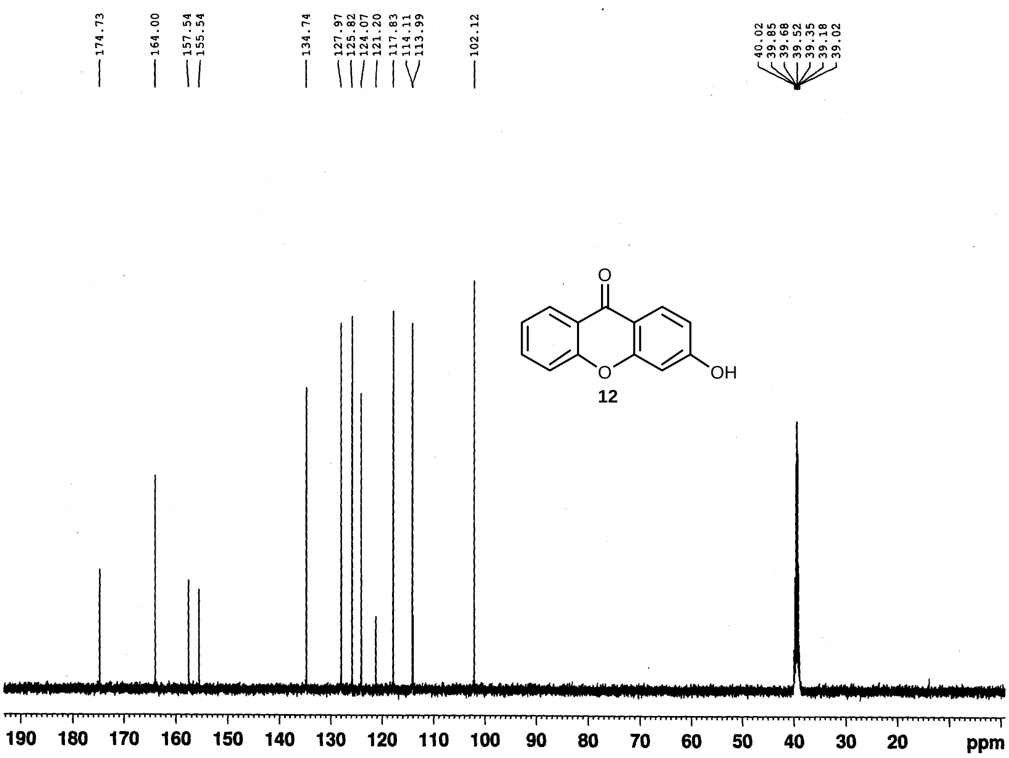
11: [13]C NMR, 300 MHz in DMSO-*d6*



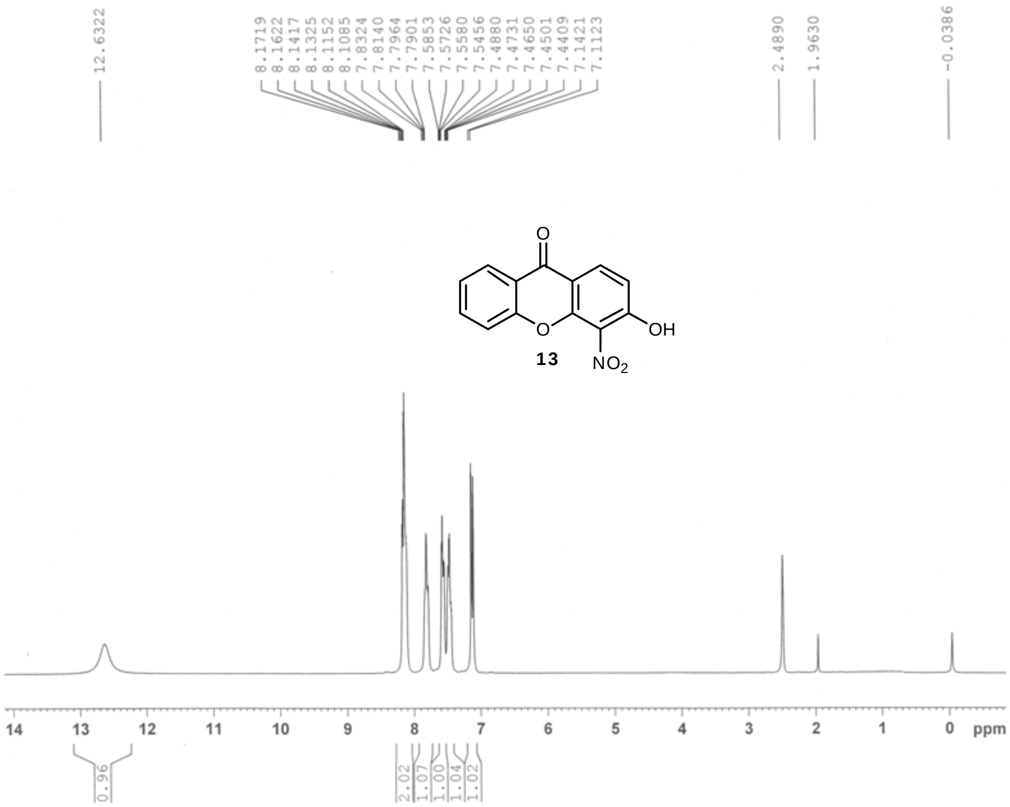
12: ^{1}H NMR, 300 MHz in DMSO-*d6*



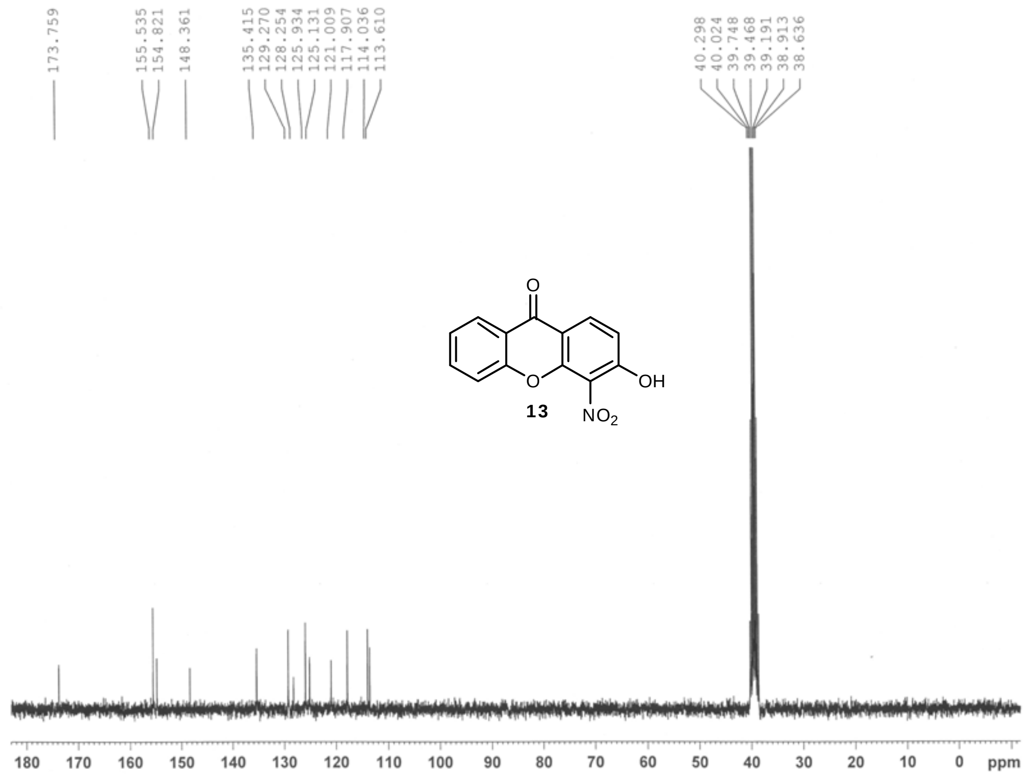
12: ^{13}C NMR, 500 MHz in DMSO-*d6*



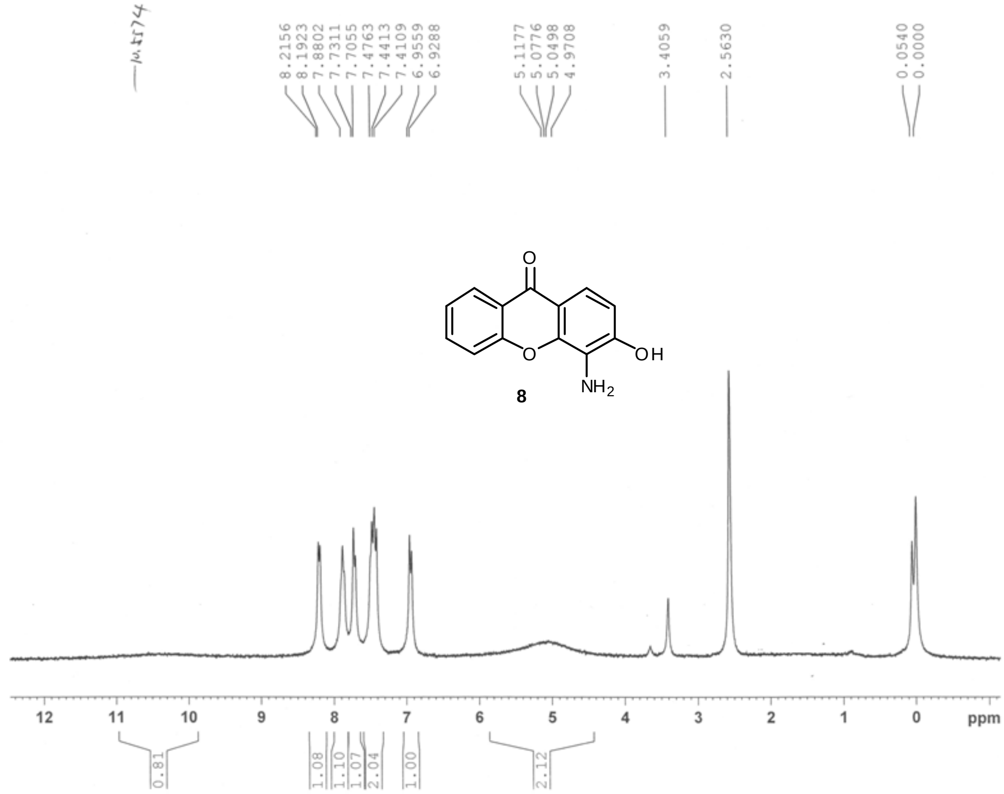
13: [1]H NMR, 300 MHz in DMSO-*d6*



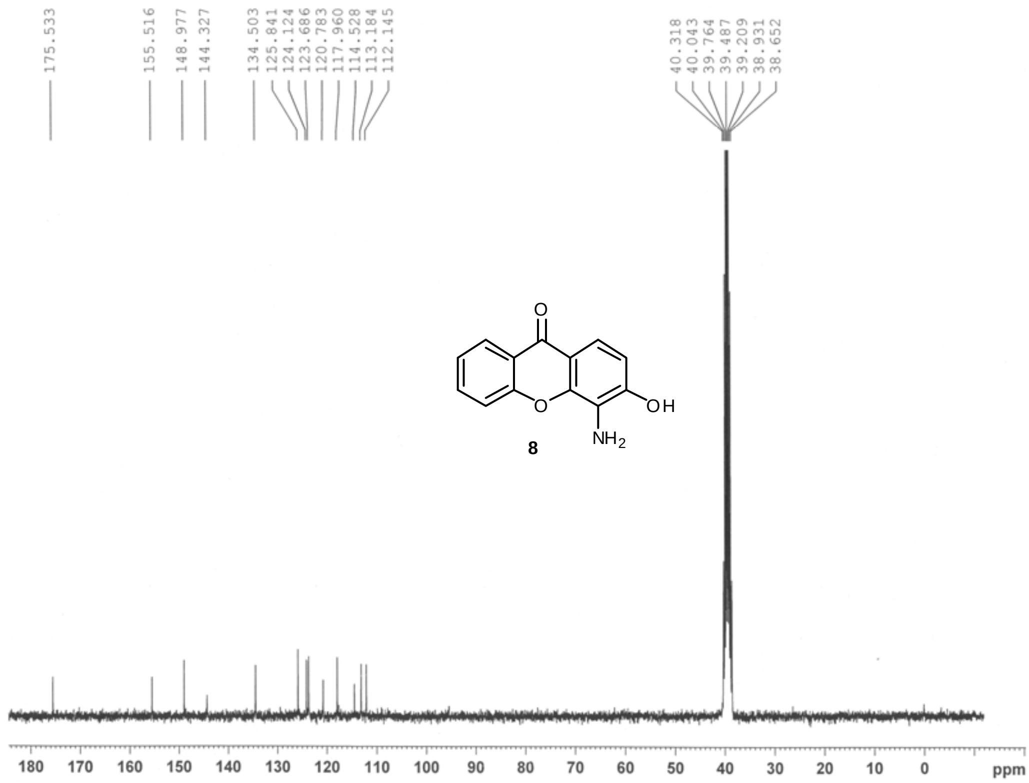
13: [13]C NMR, 300 MHz in DMSO-*d6*



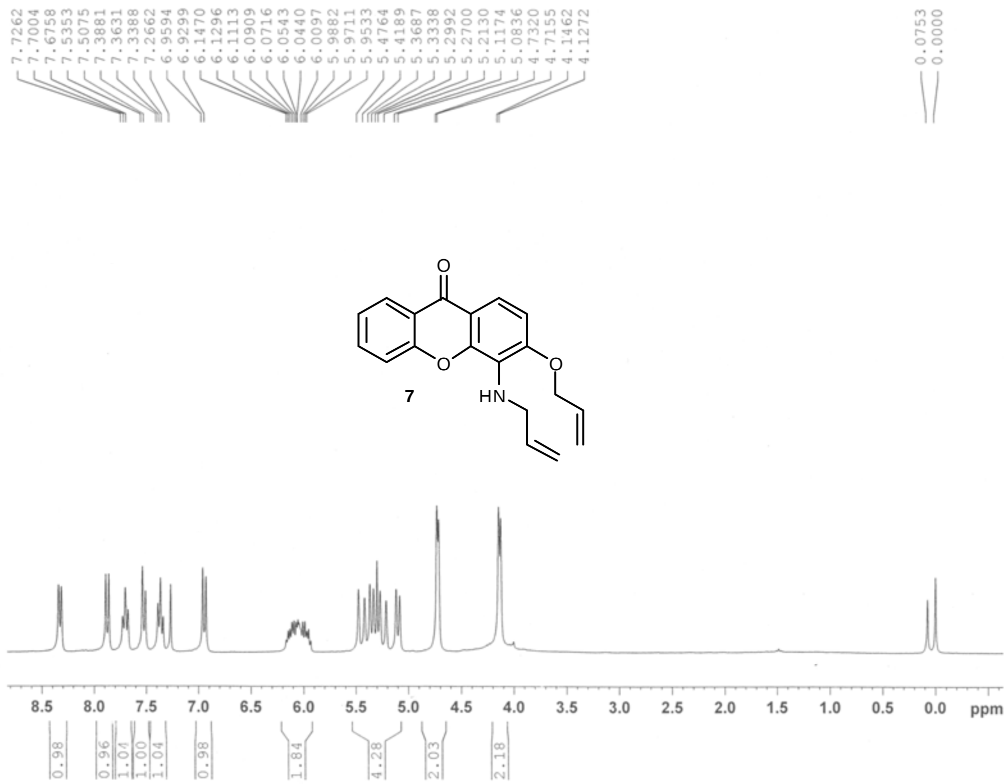
8: ^{1}H NMR, 300 MHz in DMSO-*d6*



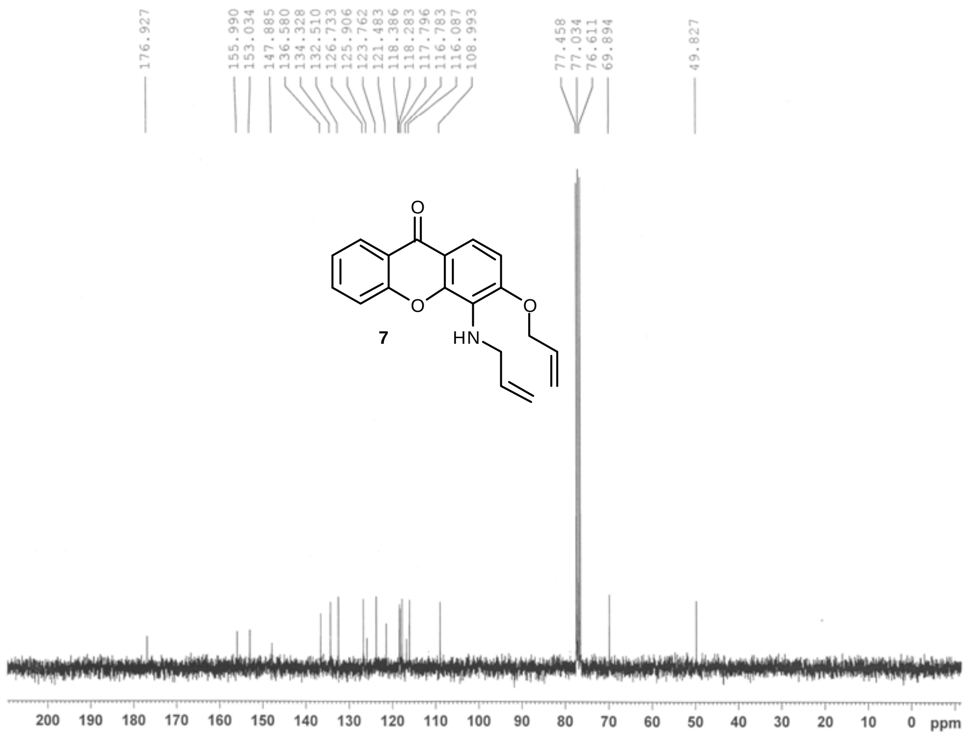
8: ^{13}C NMR, 300 MHz in DMSO-*d6*



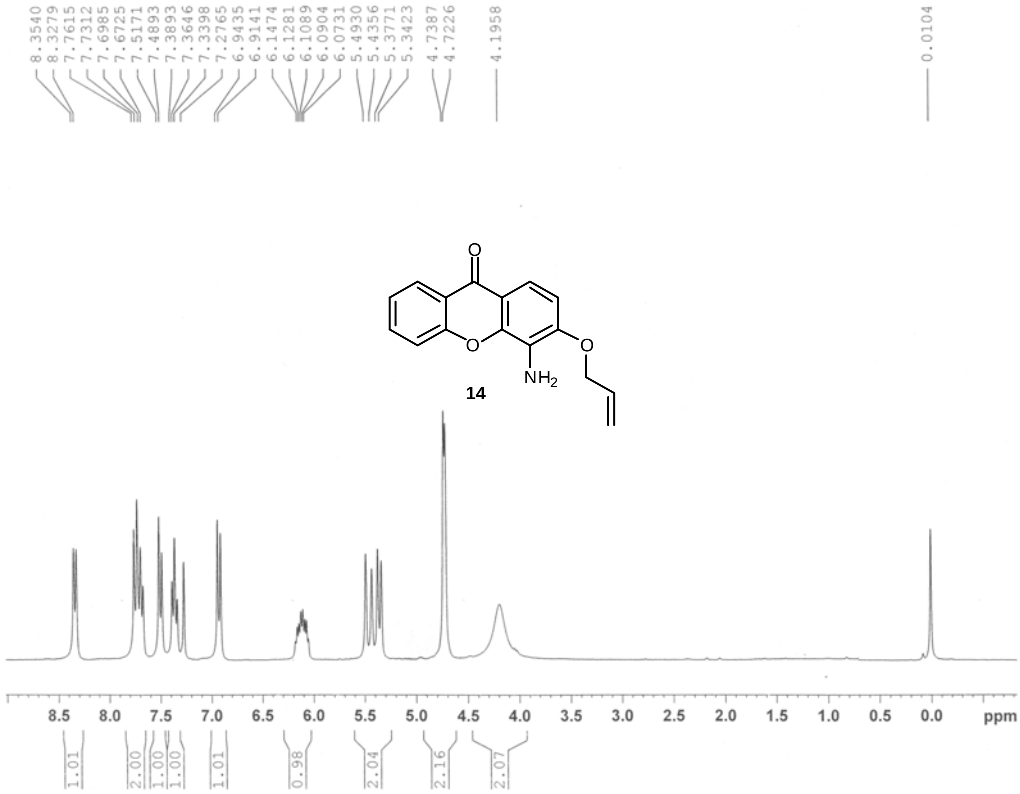
7: ^{1}H NMR, 300 MHz in $CDCl_3$



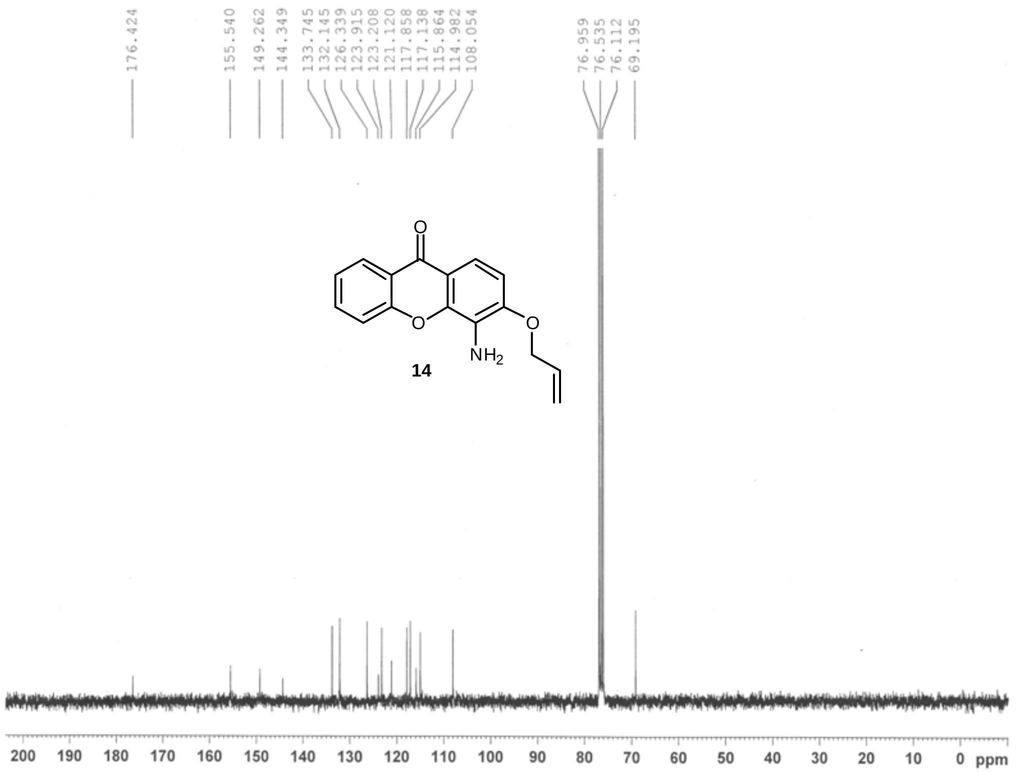
7: ^{1}H NMR, 300 MHz in $CDCl_3$



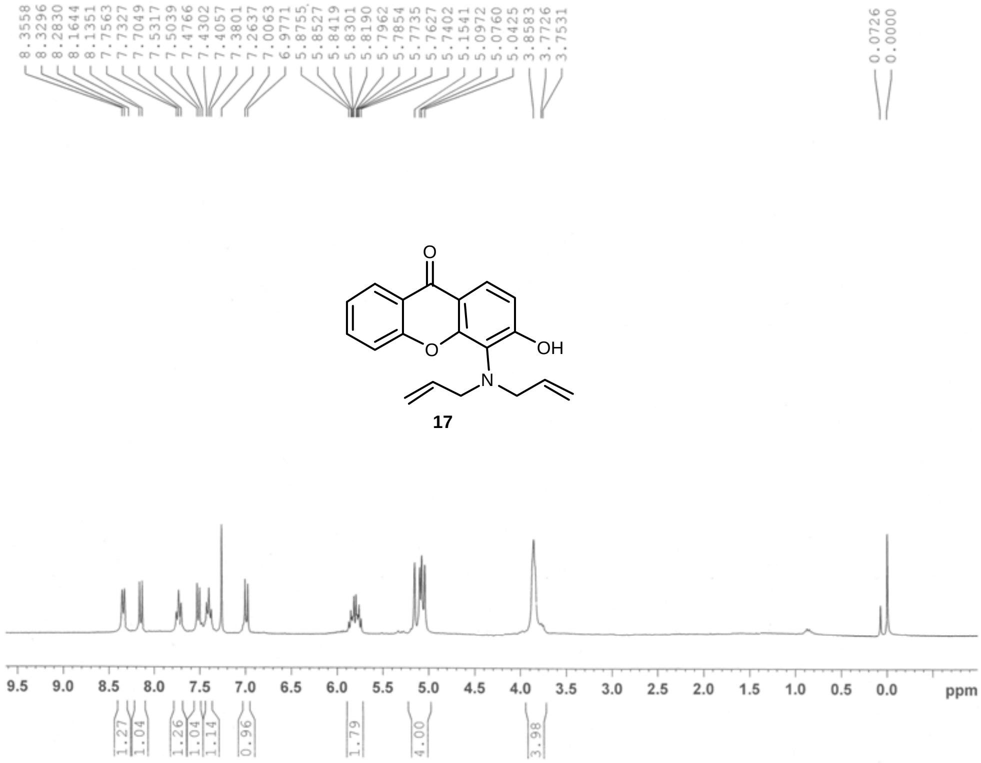
14: ^{1}H NMR, 300 MHz in $CDCl_3$



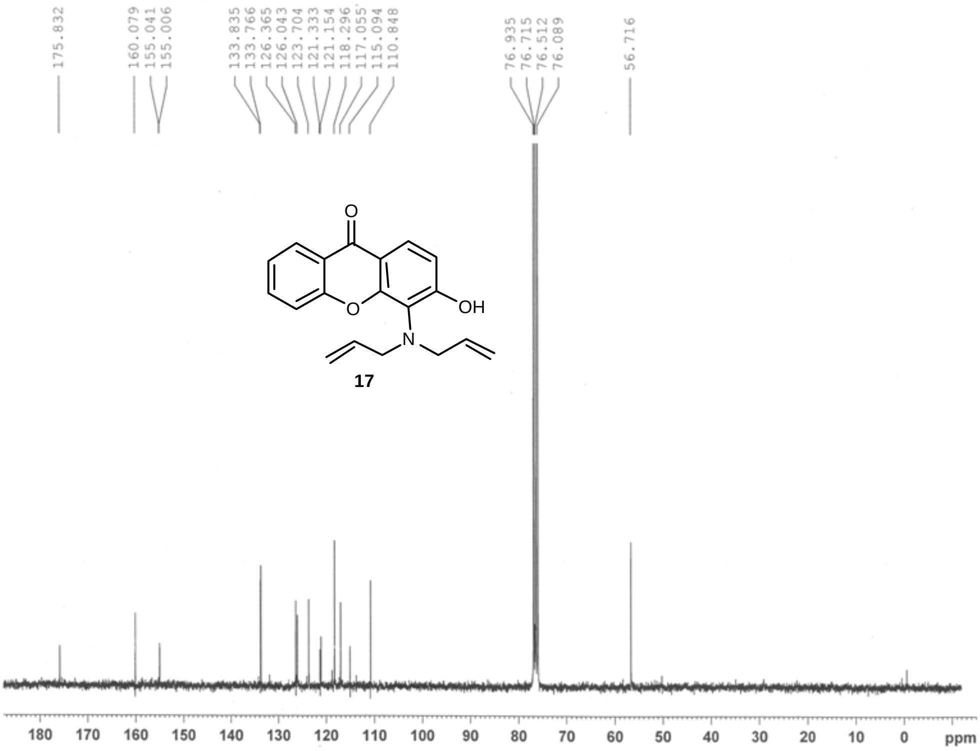
14: ^{13}C NMR, 300 MHz in $CDCl_3$



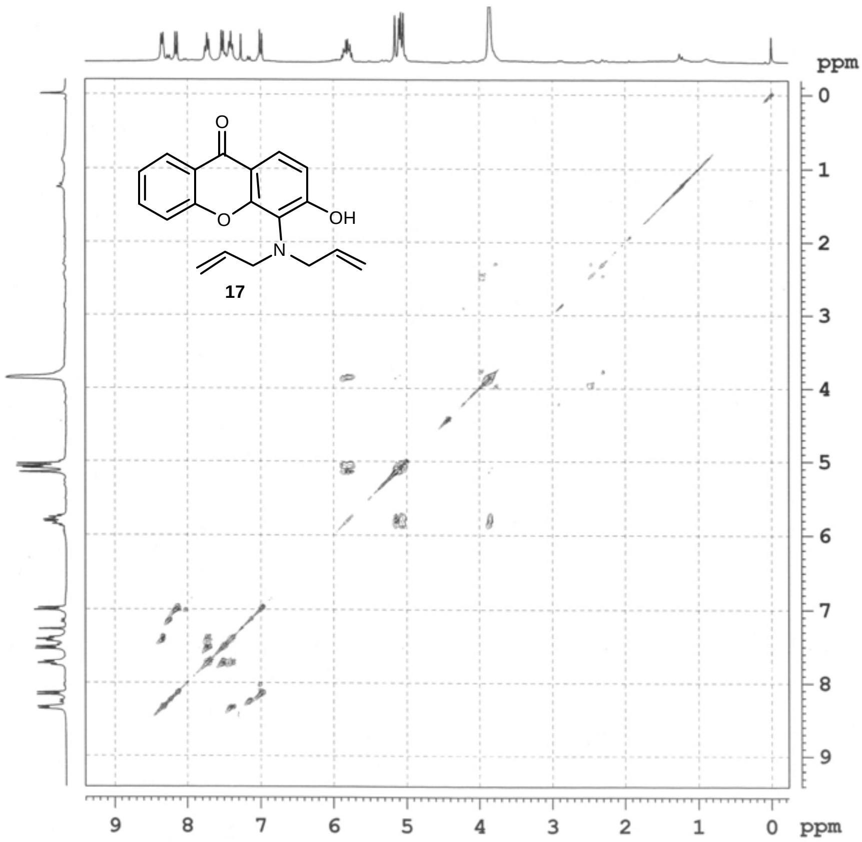
17: ^{1}H NMR, 300 MHz in $CDCl_3$



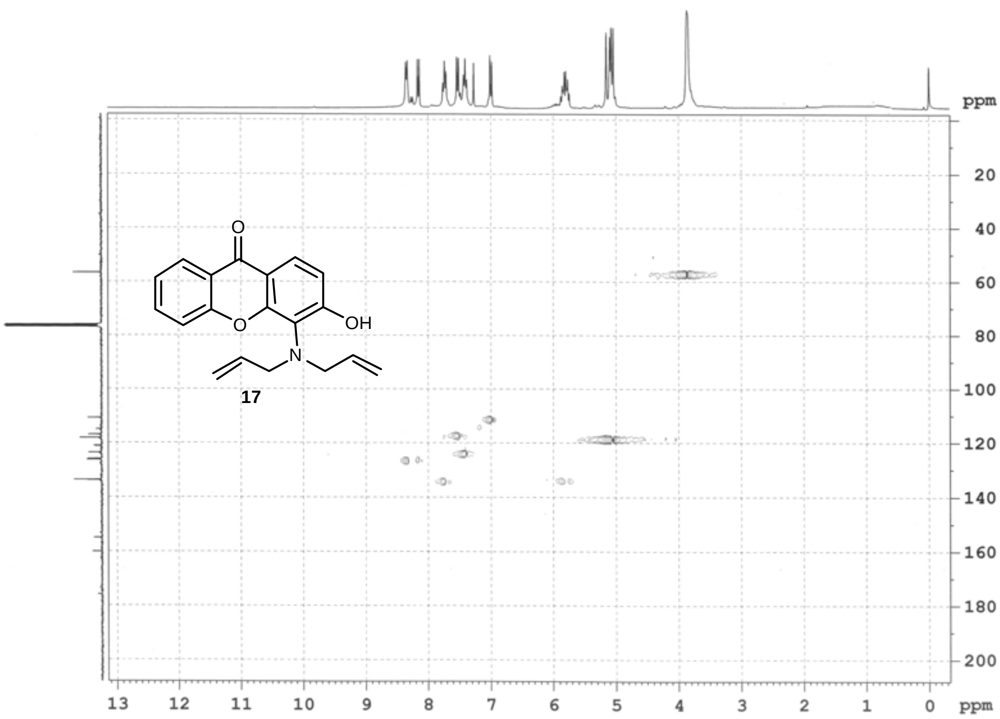
17: ^{13}C NMR, 300 MHz in $CDCl_3$



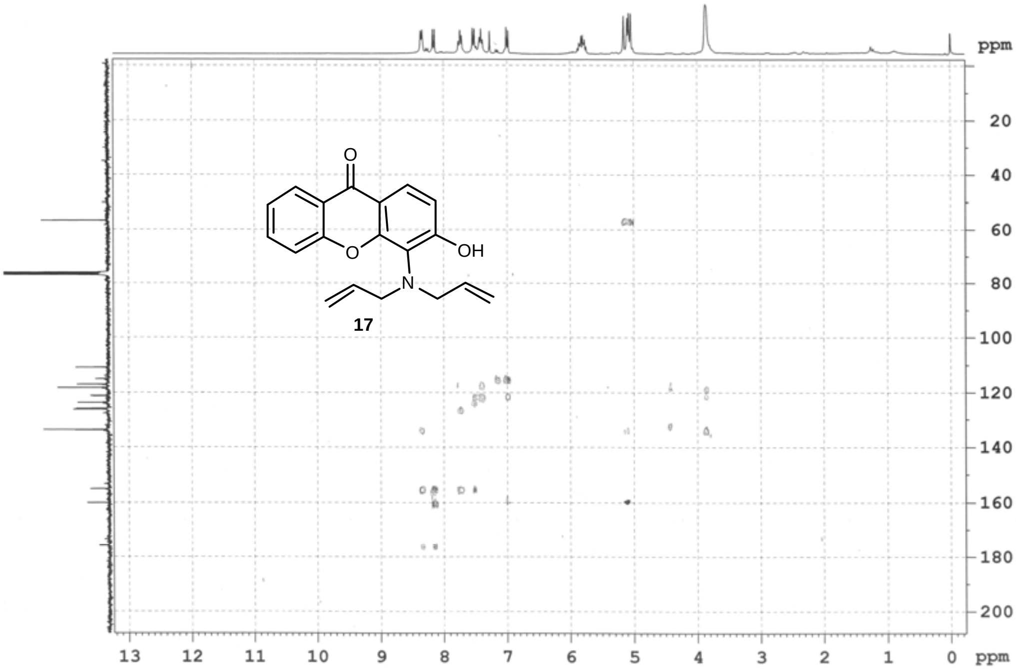
17: ^{1}H-^{1}H COSY, 300 MHz in $CDCl_3$



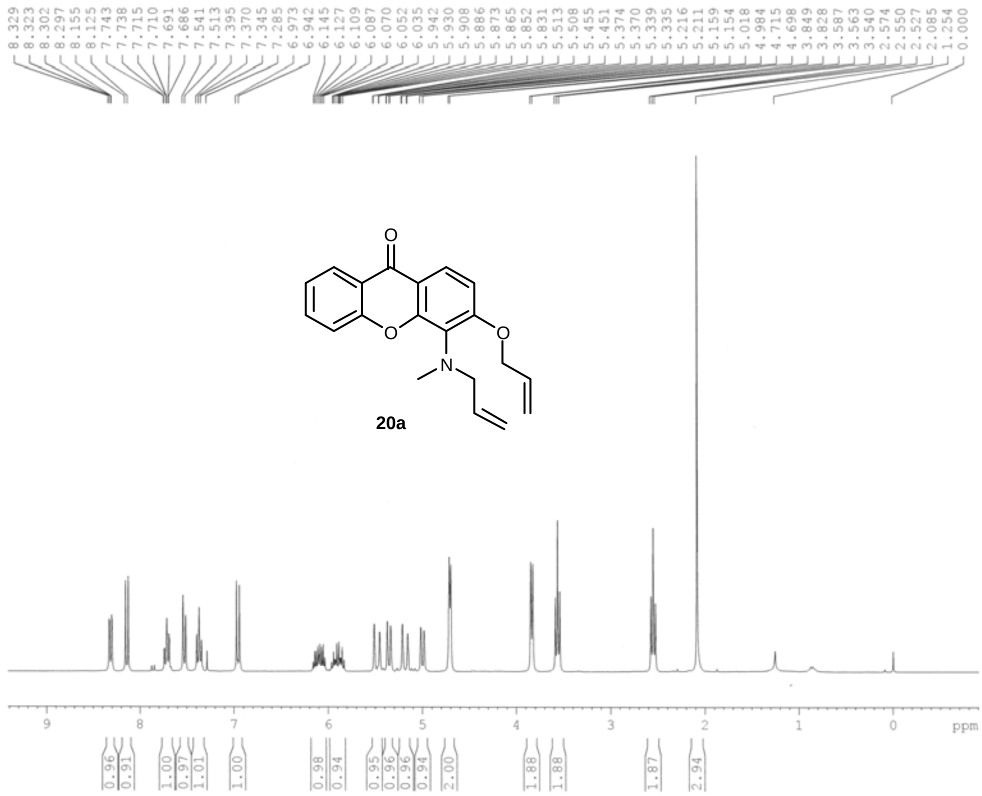
17: HSQC, 300 MHz in $CDCl_3$



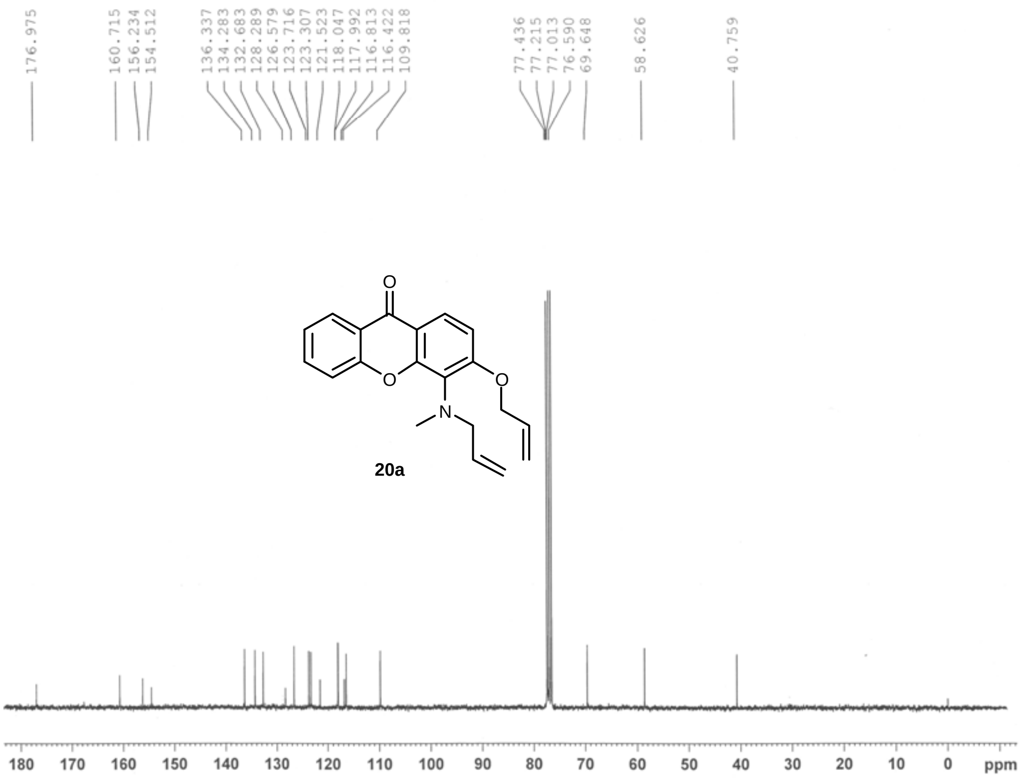
17: HMBC, 300 MHz in $CDCl_3$



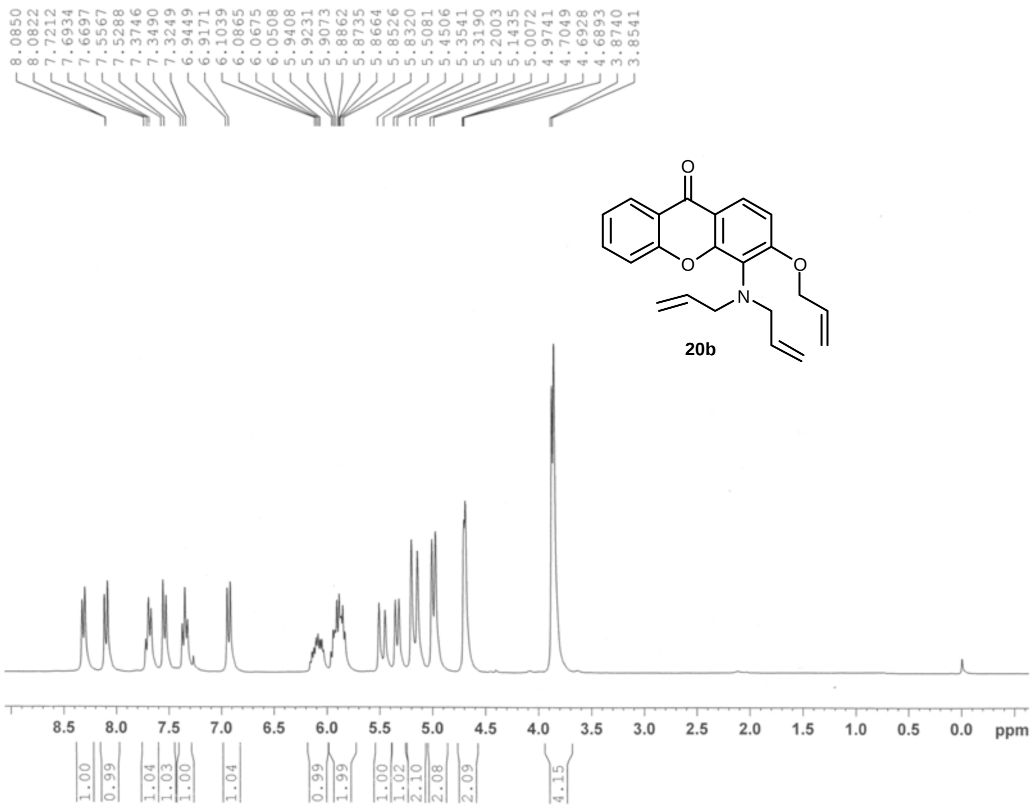
20a: ^{1}H NMR, 300 MHz in $CDCl_3$



20a: ^{13}C NMR, 300 MHz in $CDCl_3$

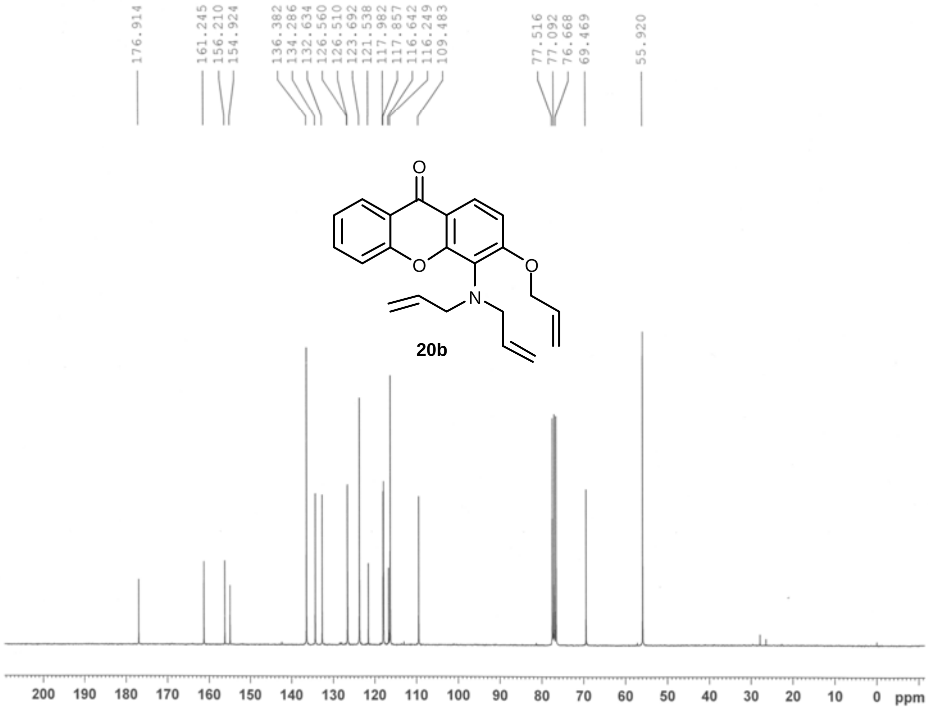


20b: ^{1}H NMR, 300 MHz in $CDCl_3$

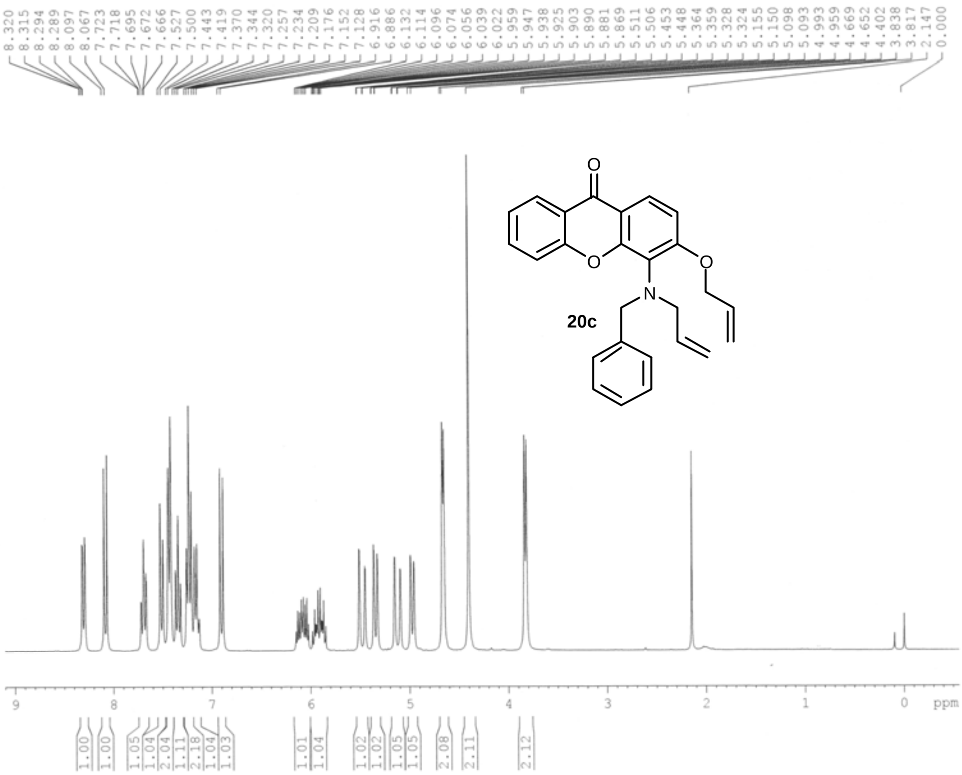


Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

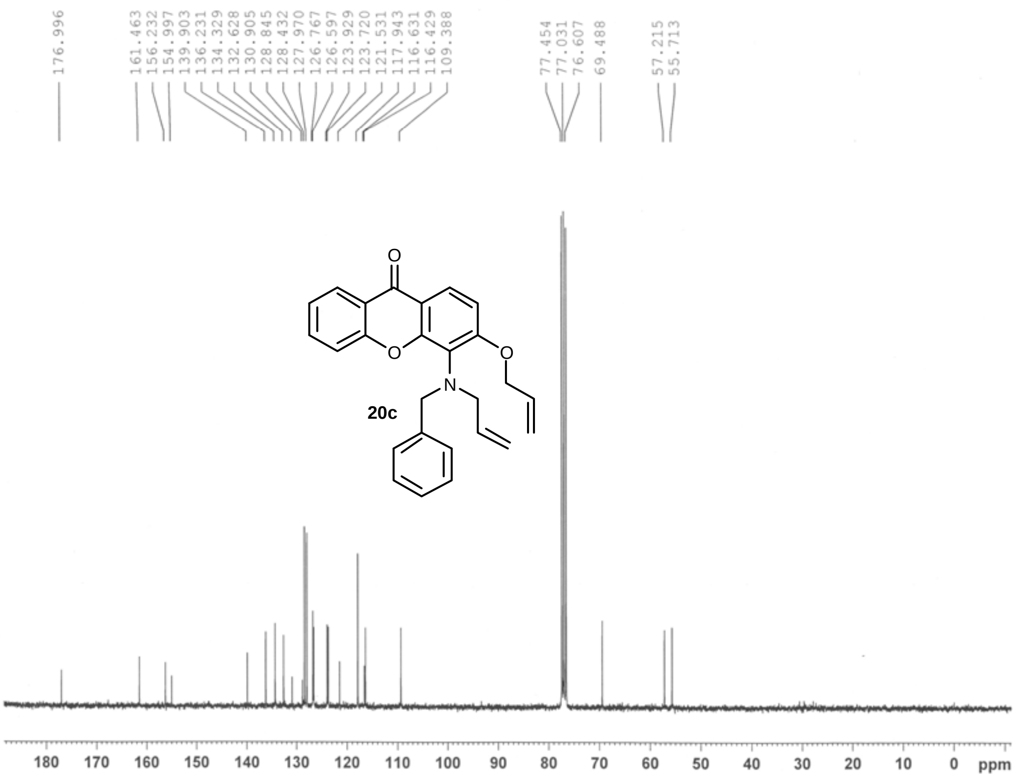
20b: ^{13}C NMR, 300 MHz in $CDCl_3$



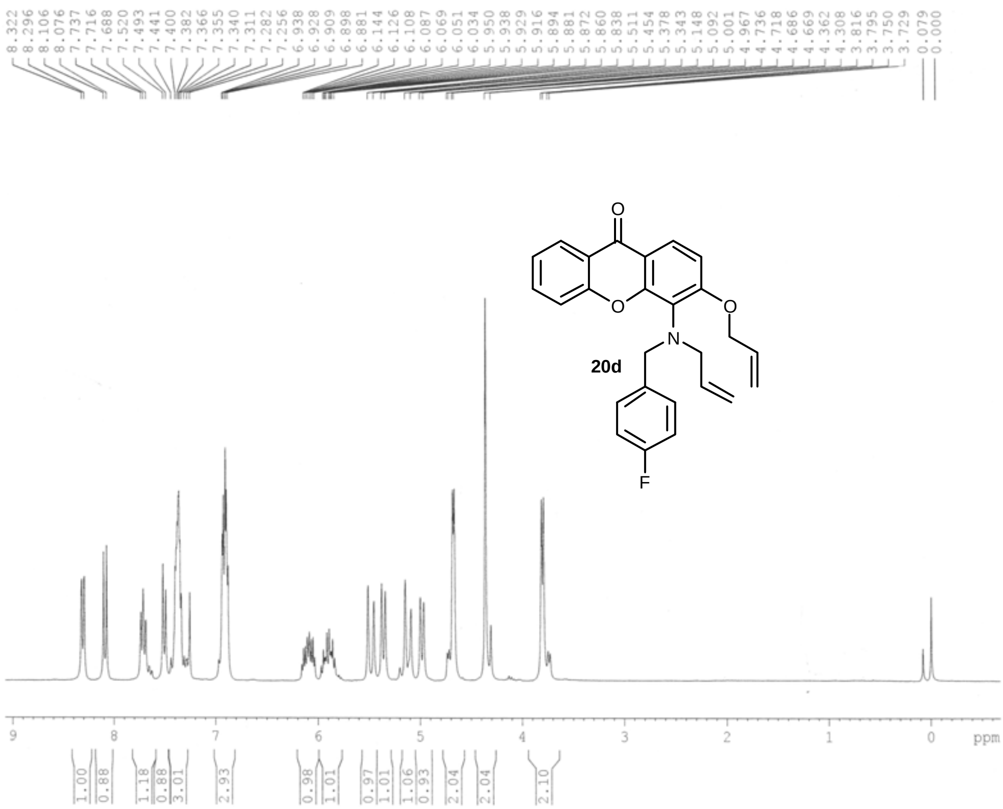
20c: ^{1}H NMR, 300 MHz in $CDCl_3$



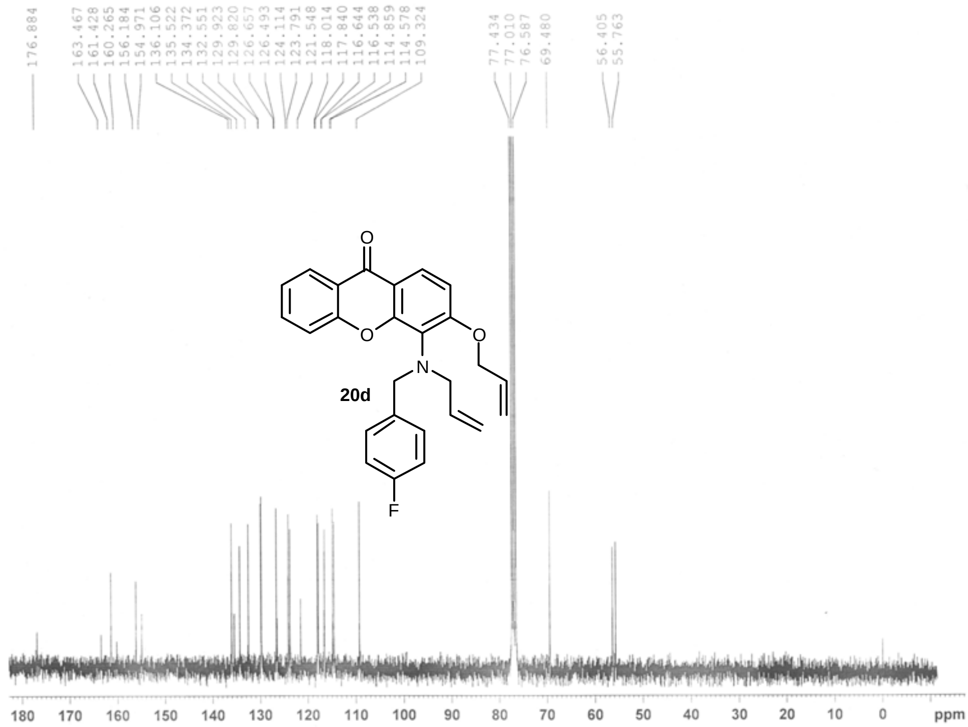
20c: ^{13}C NMR, 300 MHz in $CDCl_3$



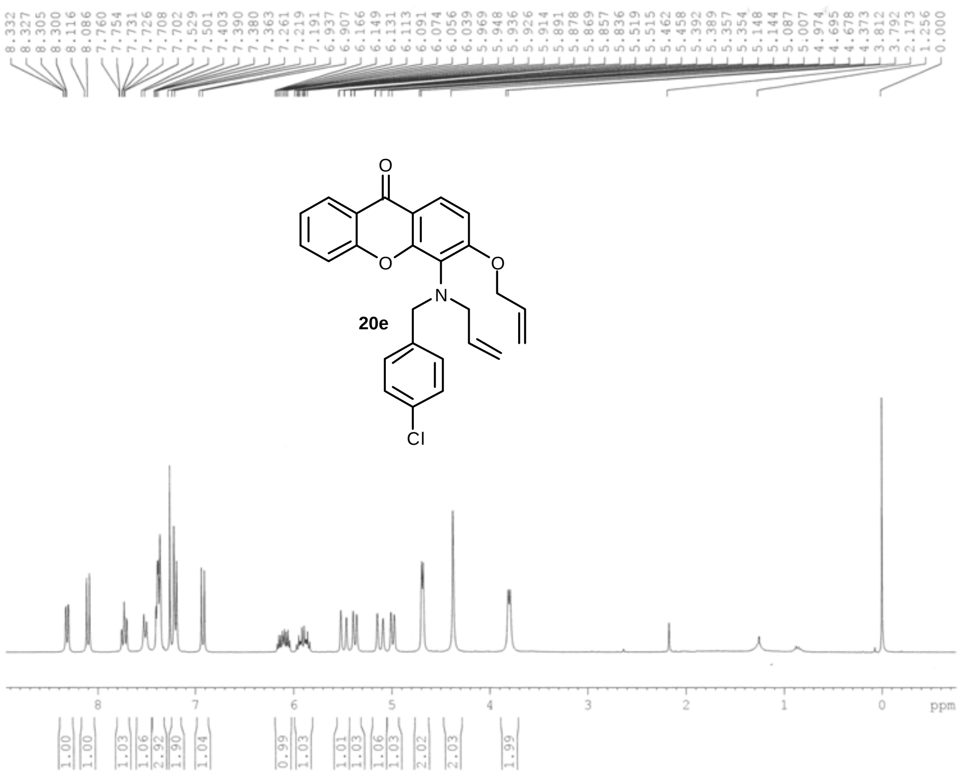
20d: ^{1}H NMR, 300 MHz in $CDCl_3$



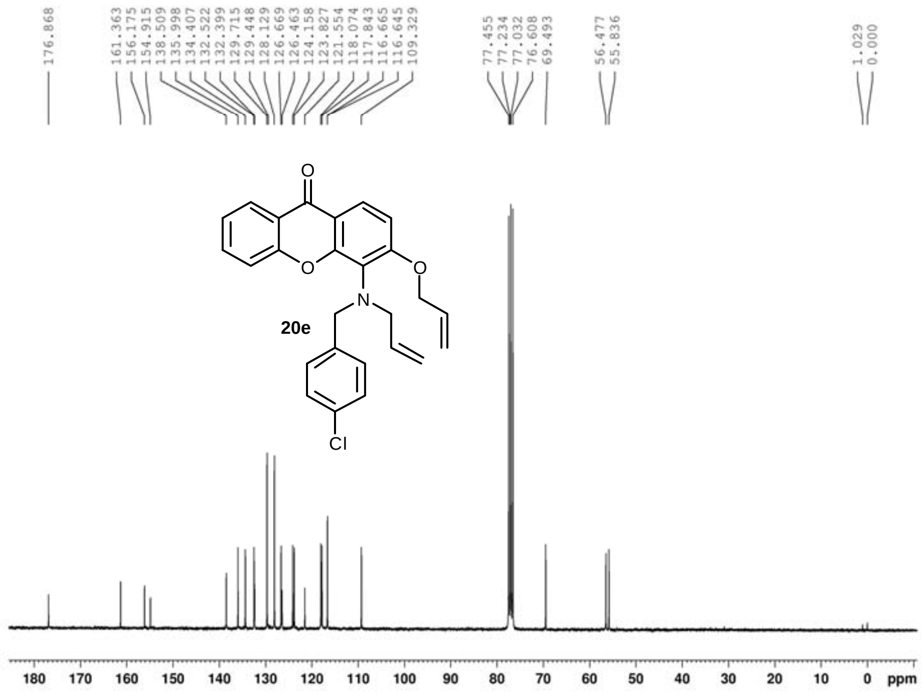
20d: ^{13}C NMR, 300 MHz in $CDCl_3$



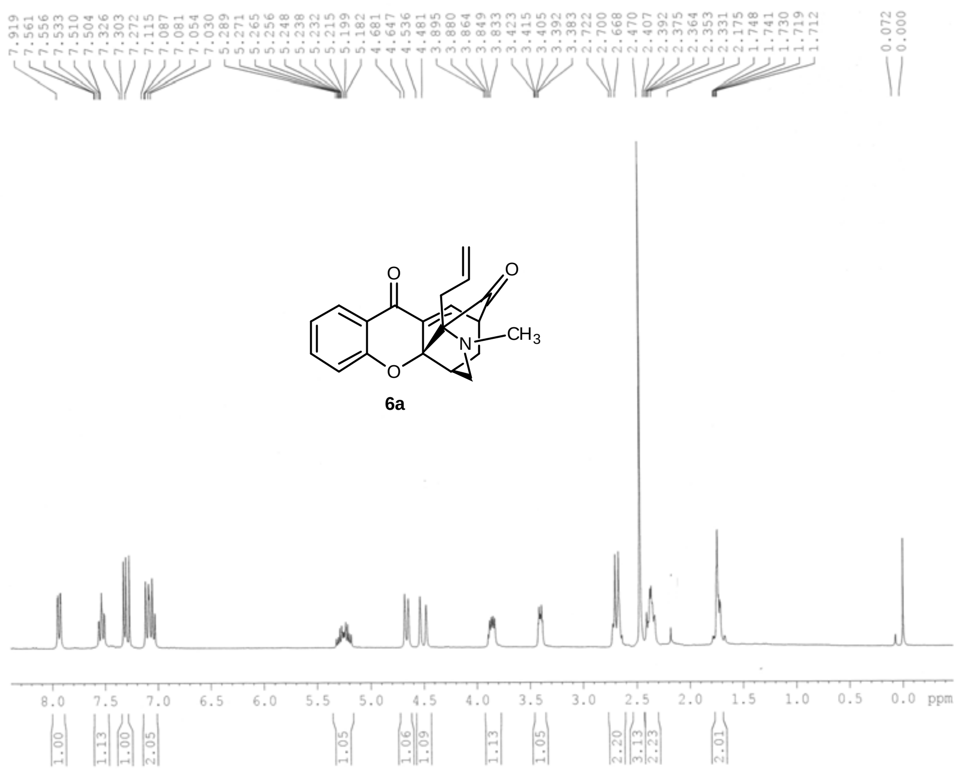
20e: ^{1}H NMR, 300 MHz in $CDCl_3$



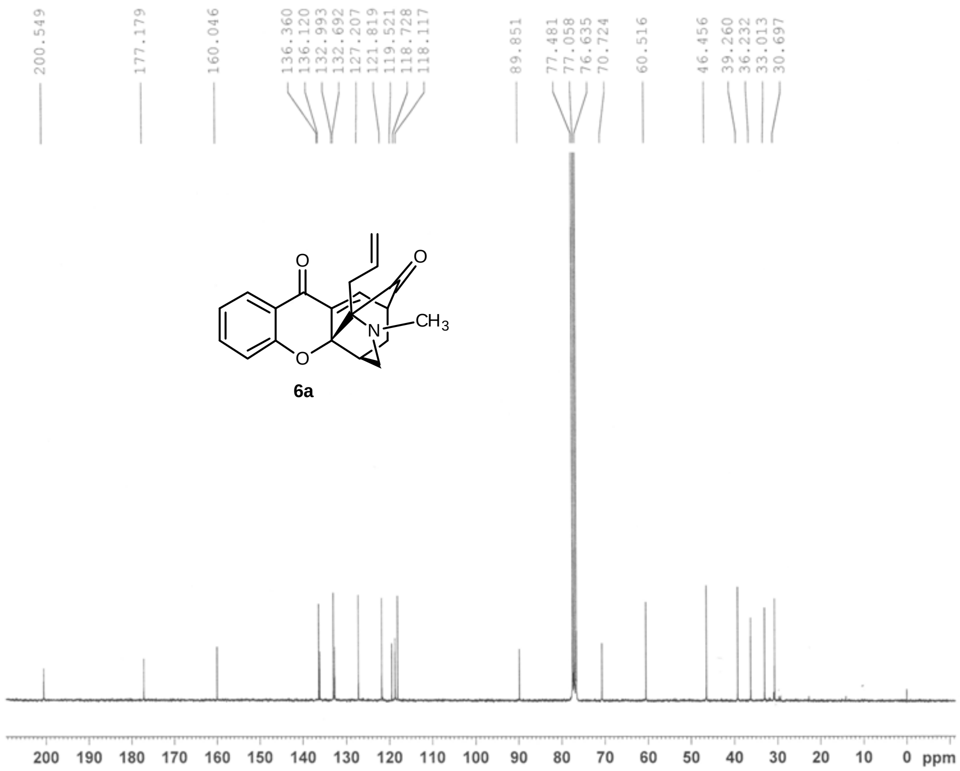
20e: ^{13}C NMR, 300 MHz in $CDCl_3$



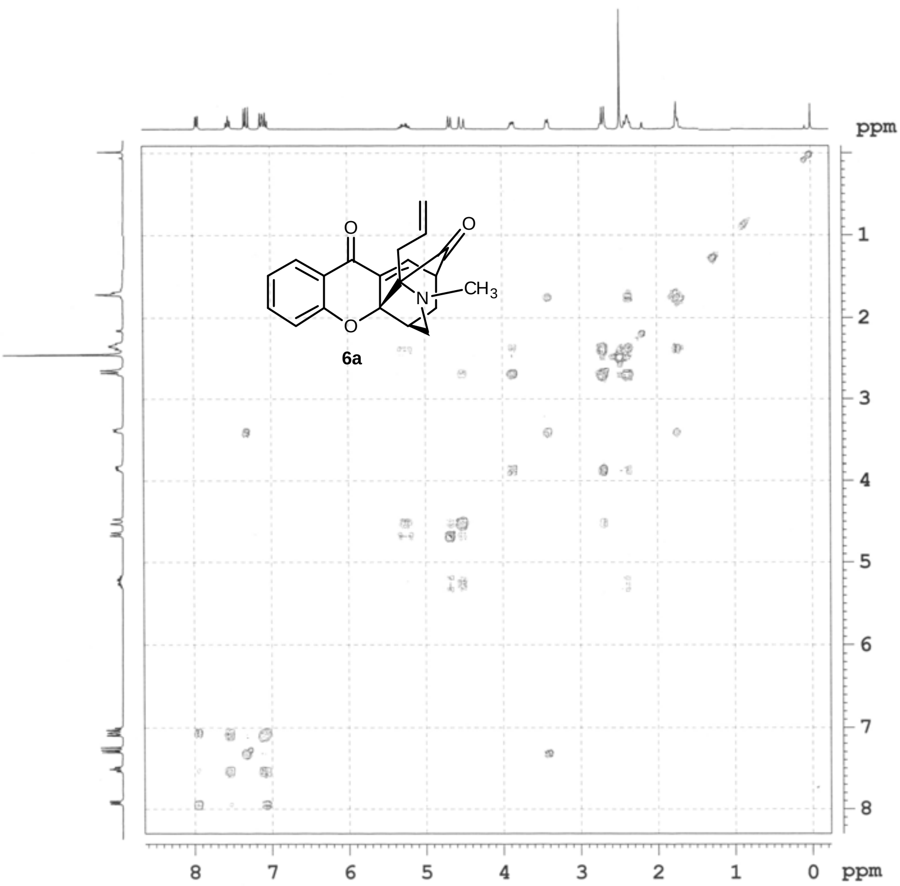
6a: ^{1}H NMR, 300 MHz in $CDCl_3$



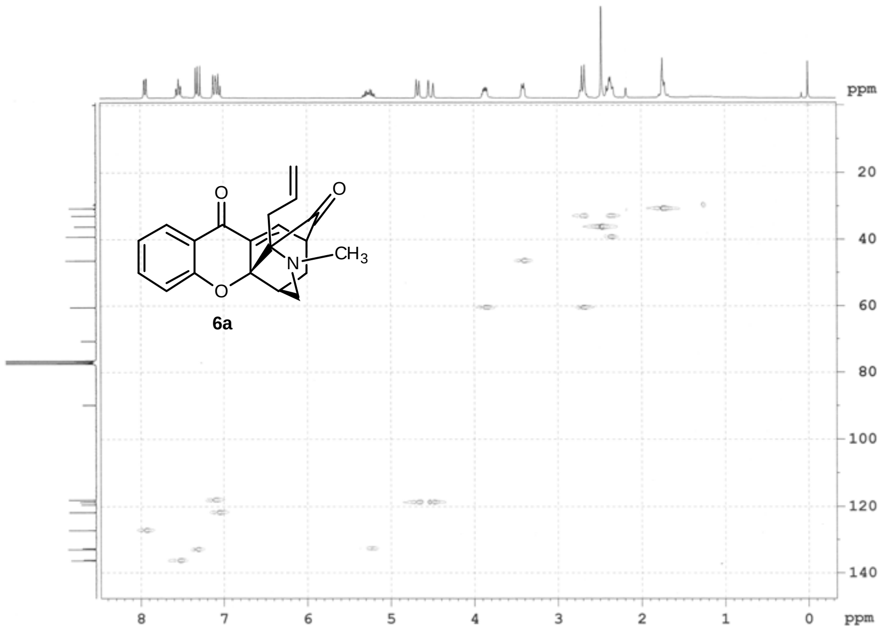
6a: ^{13}C NMR, 300 MHz in $CDCl_3$



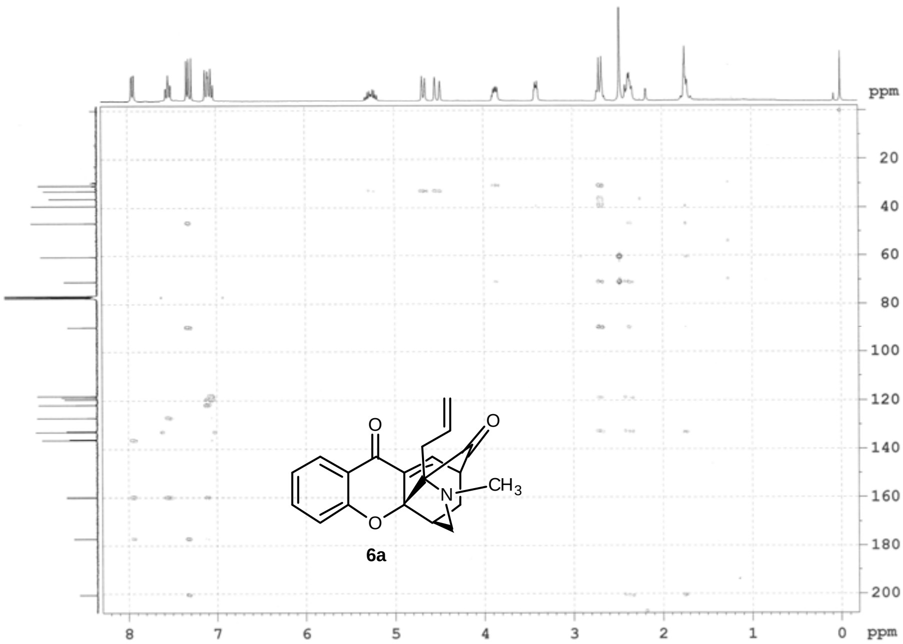
6a: ^{1}H-^{1}H COSY, 300 MHz in $CDCl_3$



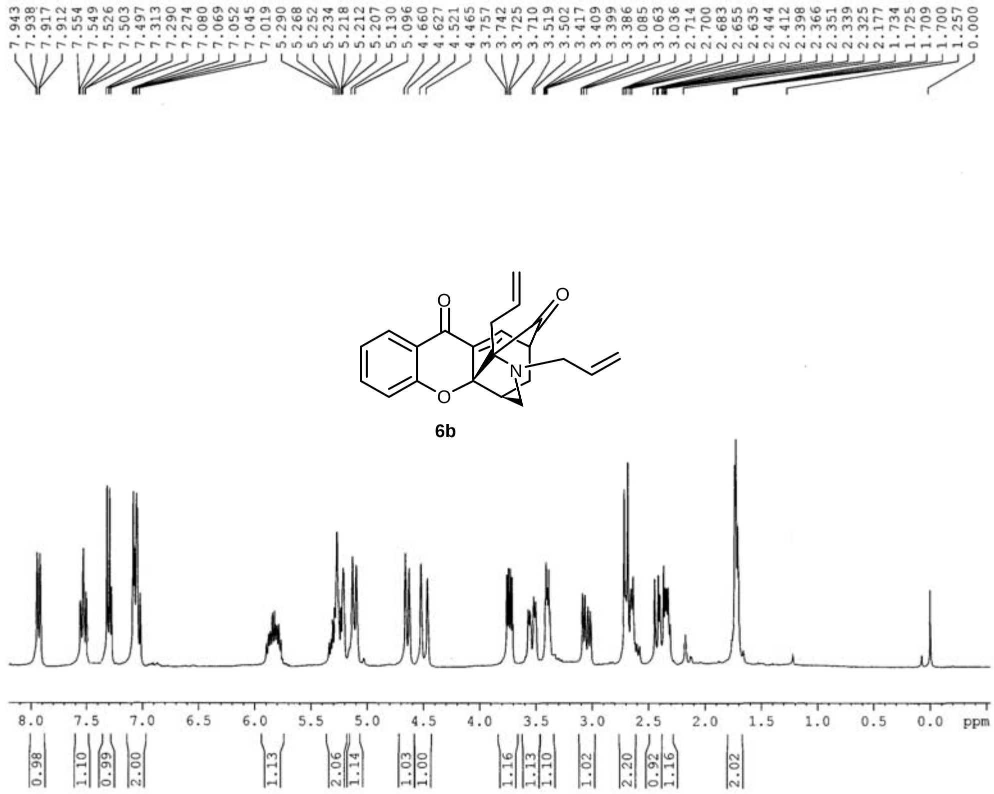
6a: HSQC, 300 MHz in $CDCl_3$



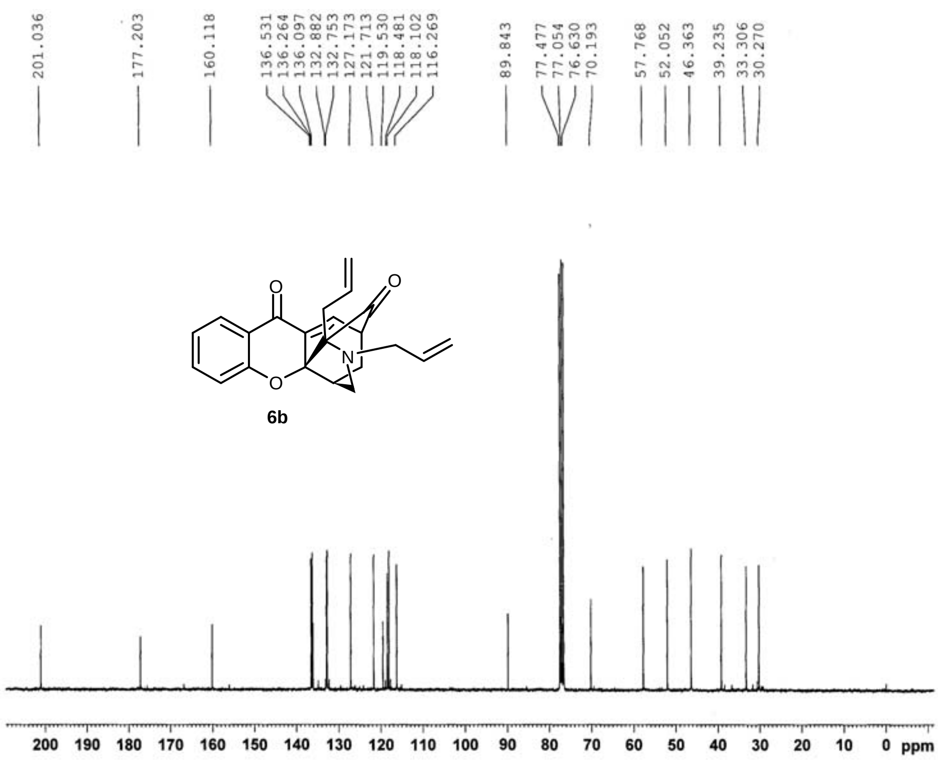
6a: HMBC, 300 MHz in $CDCl_3$



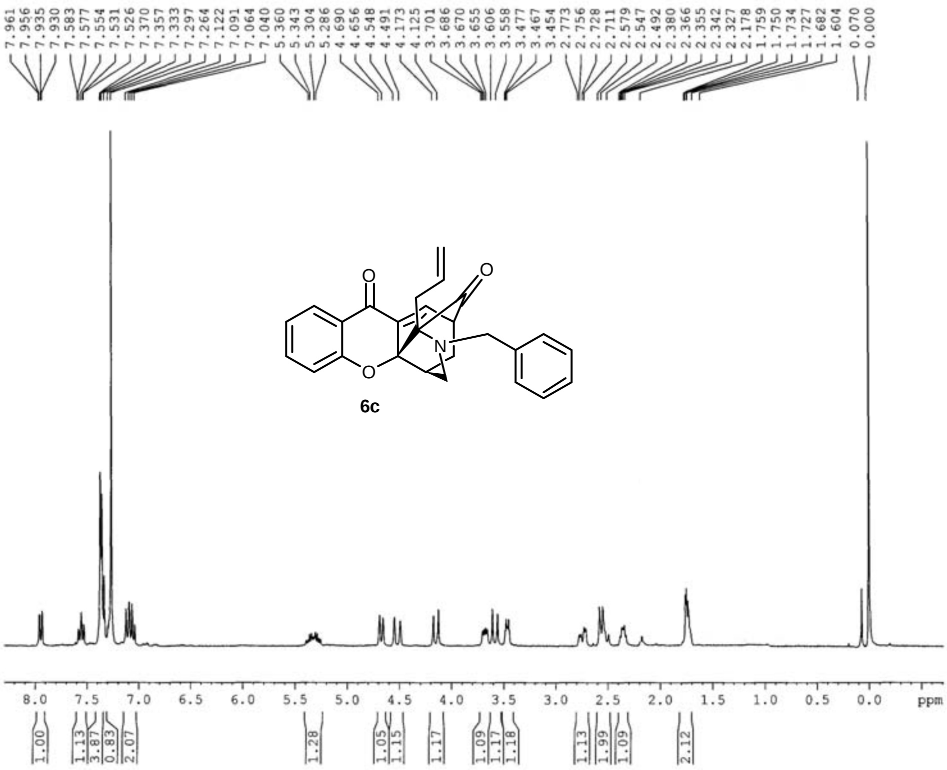
6b: ^{1}H NMR, 300 MHz in $CDCl_3$



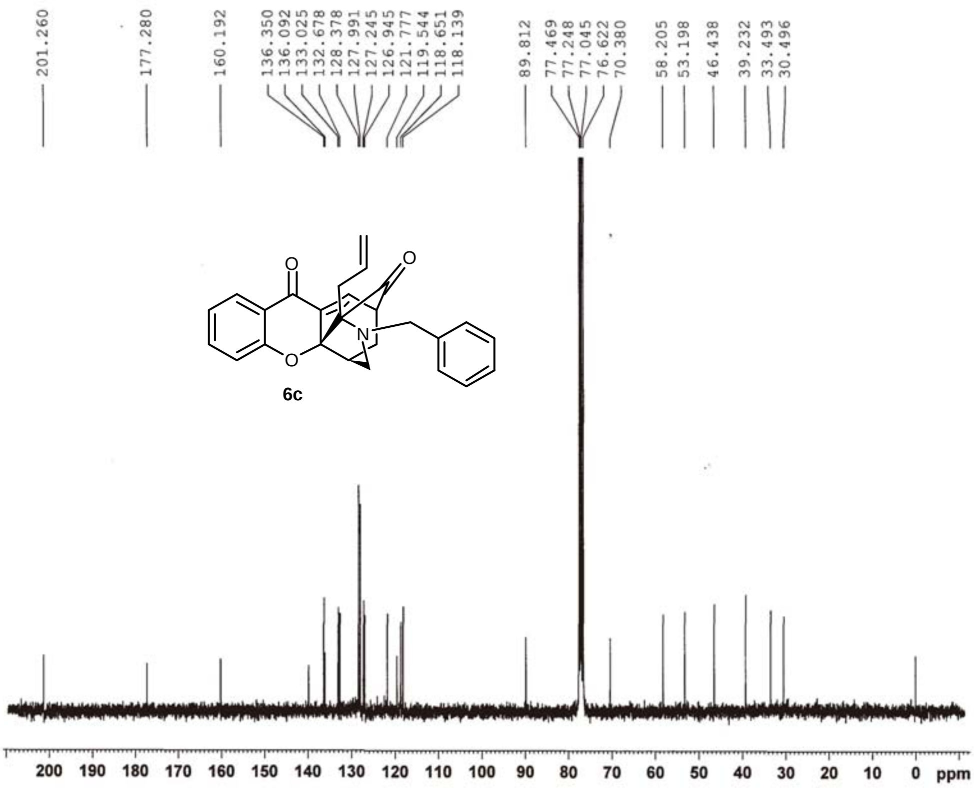
6b: ^{13}C NMR, 300 MHz in $CDCl_3$



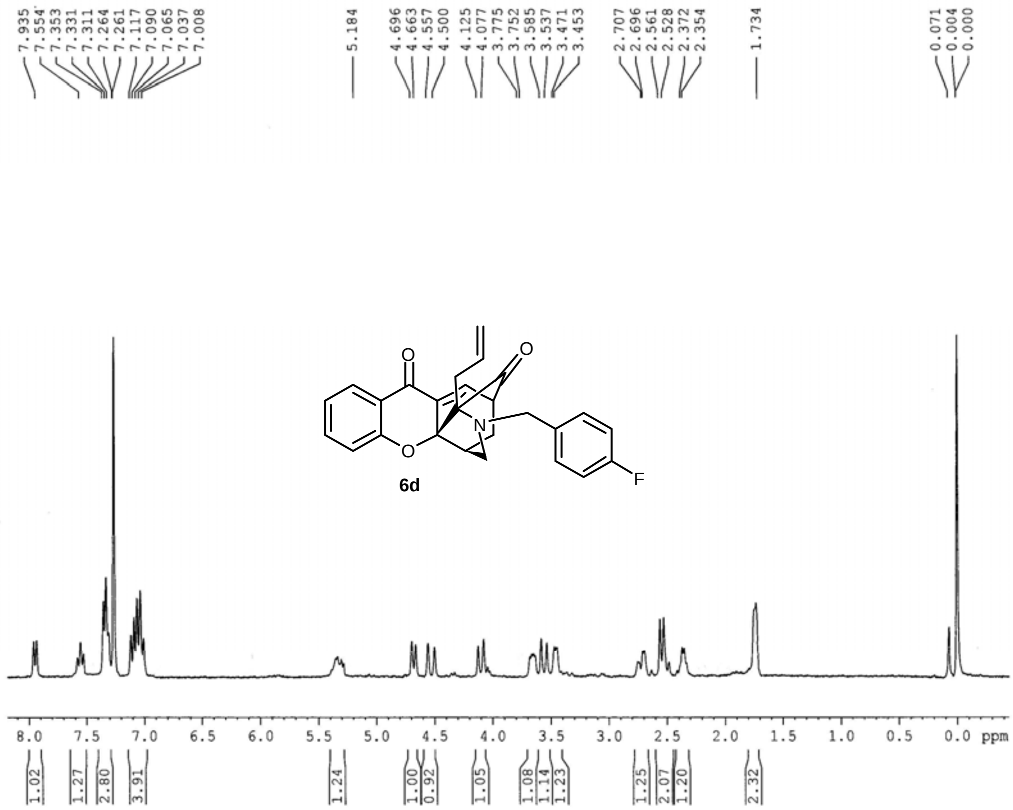
6c: ^{1}H NMR, 300 MHz in $CDCl_3$



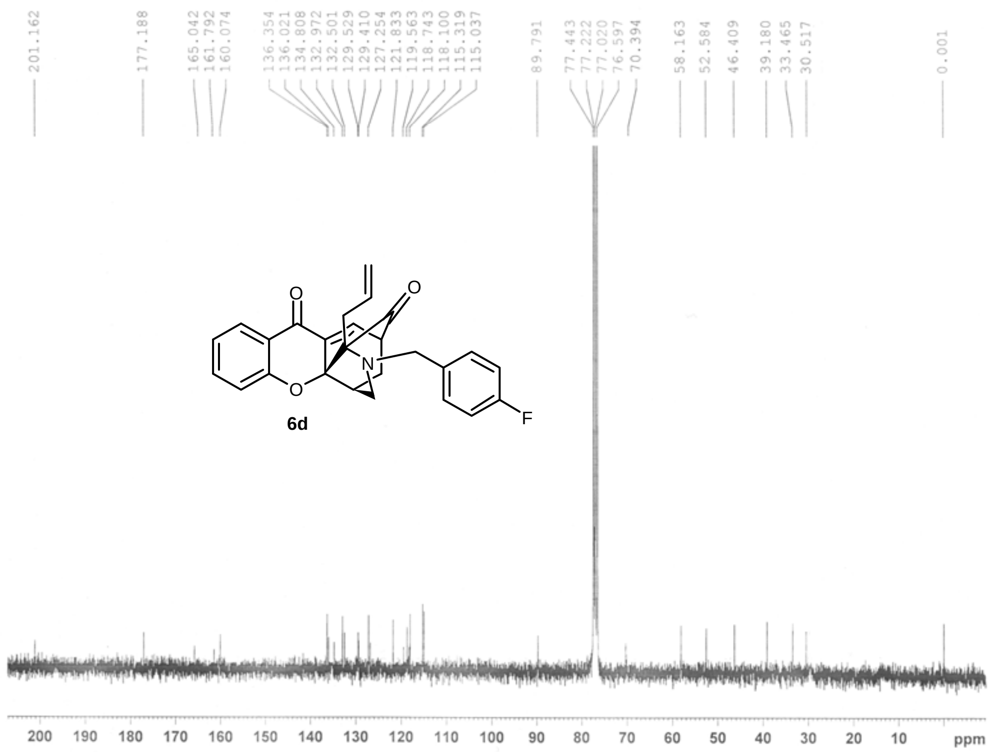
6c: ^{13}C NMR, 300 MHz in $CDCl_3$



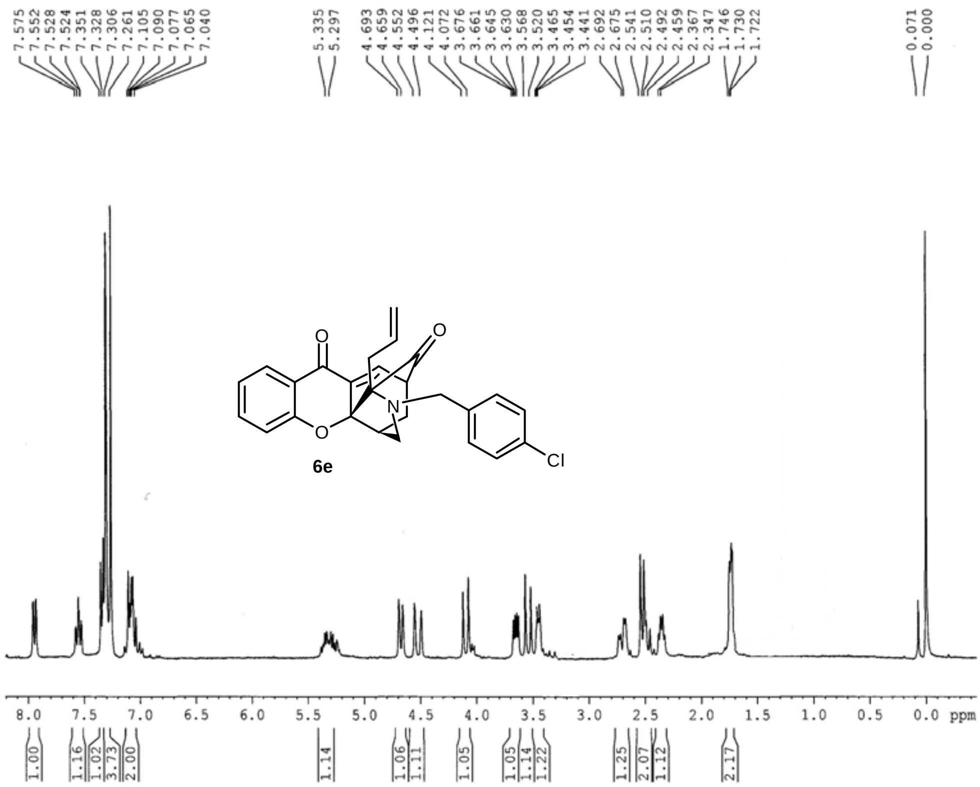
6d: ^{1}H NMR, 300 MHz in $CDCl_3$



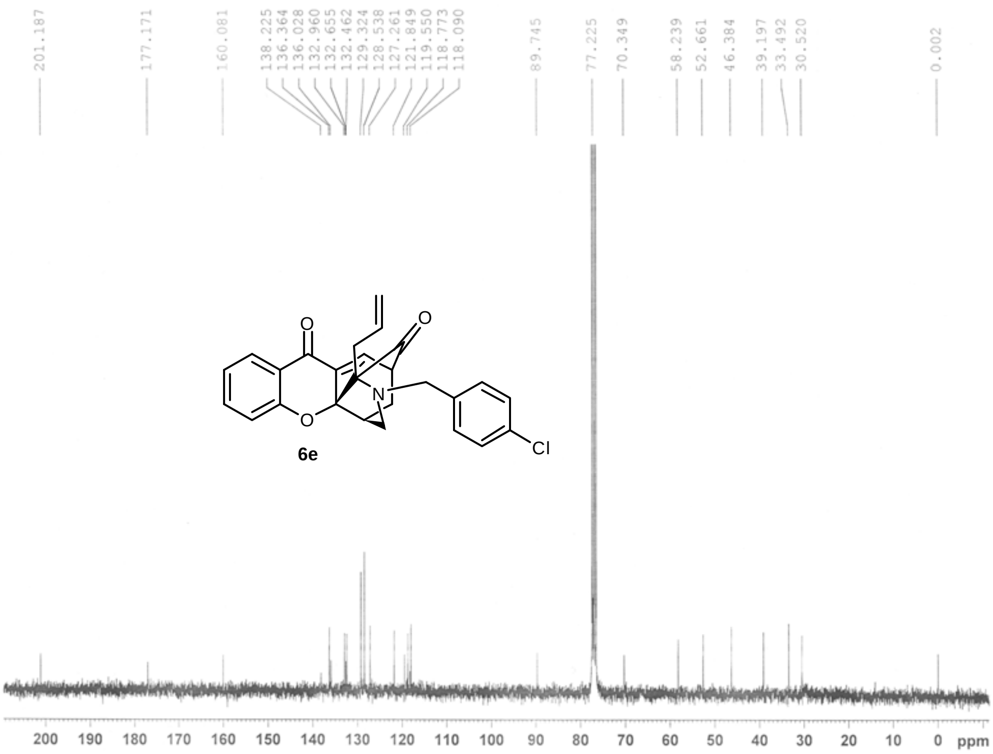
6d: ^{13}C NMR, 300 MHz in $CDCl_3$



6e: ^{1}H NMR, 300 MHz in $CDCl_3$



6e: ^{13}C NMR, 300 MHz in $CDCl_3$



Energy data

All structures were fully optimized at the B3LYP/6-31G(d) level of theory, with Gaussian 03. All structures were validated as minima or first-degree saddle points using frequency analysis. Minima structure geometries and energies. Energies are in Hartrees, distances and coordinates.

Model System

7

C	-5.47923	0.16824	-0.17776
C	-4.93369	1.44107	-0.414
C	-3.55821	1.63082	-0.43786
C	-2.71681	0.53344	-0.22194
C	-3.24012	-0.74627	0.0131
C	-4.63541	-0.91146	0.032
O	-1.37258	0.78375	-0.25351
C	-0.47781	-0.2386	-0.05832
C	-0.89917	-1.56191	0.16782
C	-2.33412	-1.89426	0.22663
C	0.88293	0.11447	-0.10744
C	1.82127	-0.93227	0.03756
C	1.41769	-2.26144	0.23641
C	0.0675	-2.56494	0.31191
O	-2.74873	-3.03407	0.43178
O	3.12568	-0.52919	-0.0455
N	1.32478	1.4213	-0.37298
C	4.16582	-1.50537	0.0877
C	5.48012	-0.78858	0.02152
C	6.46465	-1.11916	-0.81247
C	0.94639	2.51361	0.54142
C	1.43782	3.82508	-0.00496
C	2.22708	4.67063	0.6577
H	2.33184	1.41322	-0.50111
H	-6.55666	0.03337	-0.16182
H	-5.59078	2.29019	-0.58107
H	-3.1185	2.60585	-0.62157
H	-5.01696	-1.91109	0.21458
H	2.1535	-3.04953	0.34323
H	-0.27667	-3.58017	0.47626
H	4.0533	-2.01811	1.05498
H	4.08632	-2.2563	-0.70934
H	5.60567	0.02849	0.7307
H	6.35829	-1.92737	-1.53304
H	7.41802	-0.59856	-0.80442

H	-0.1448	2.5291	0.61155
H	1.33809	2.35876	1.56091
H	1.10665	4.06138	-1.01605
H	2.57984	4.45267	1.66407
H	2.54405	5.61655	0.2268

Sum of Energies = -1014.311908

15

C	-4.49352	-1.37891	-0.01529
C	-3.54089	-2.41031	-0.0167
C	-2.1823	-2.12179	-0.05863
C	-1.77355	-0.78483	-0.10106
C	-2.7071	0.26028	-0.09692
C	-4.07452	-0.05745	-0.05392
C	0.06538	0.71512	-0.1611
C	-0.7898	1.83365	-0.16048
C	-2.25113	1.667	-0.13399
C	1.46343	0.86353	-0.18402
C	1.98056	2.17651	-0.20711
C	1.1444	3.30618	-0.2022
C	-0.22282	3.12159	-0.17817
O	-3.03642	2.61407	-0.13728
O	3.31811	2.34207	-0.23367
O	-0.4213	-0.56174	-0.15188
N	2.44136	-0.1794	-0.16124
C	2.80384	-0.7374	1.15913
C	2.62467	-1.0425	-1.3446
C	1.7287	-1.49145	1.90164
C	1.26262	-1.12205	3.09497
C	1.89182	-2.36311	-1.36924
C	2.50808	-3.54433	-1.43826
H	-5.55241	-1.61742	0.01757
H	-3.86368	-3.44726	0.01666
H	-1.43347	-2.9072	-0.05308
H	-4.77865	0.76859	-0.05193
H	1.59251	4.29379	-0.22144
H	-0.90745	3.96365	-0.17525
H	3.66499	1.42037	-0.27773
H	3.15462	0.09113	1.78805
H	3.66556	-1.39627	0.98485
H	3.70062	-1.2449	-1.44821
H	2.32894	-0.43944	-2.21163

H	1.34242	-2.38471	1.41556
H	1.63065	-0.23103	3.60054
H	0.49819	-1.69247	3.61581
H	0.80651	-2.31258	-1.34714
H	3.59392	-3.62205	-1.46287
H	1.95691	-4.48003	-1.48279

Sum of Energies =-1014.311171

16

C	4.82759	-1.02576	-0.38657
C	4.03896	-1.97747	-1.05438
C	2.66626	-1.80047	-1.17718
C	2.08736	-0.65693	-0.62186
C	2.85071	0.30655	0.04731
C	4.23624	0.10457	0.15789
O	0.72405	-0.52322	-0.76775
C	0.08347	0.55567	-0.26108
C	0.74106	1.5529	0.40488
C	2.19576	1.50256	0.61655
O	2.81602	2.38012	1.21543
C	-1.4419	0.4759	-0.37849
C	-2.09418	1.87098	-0.09
C	-1.33553	2.83799	0.70896
C	-0.00924	2.68836	0.91224
O	-3.22111	2.11183	-0.49074
N	-1.95171	-0.38311	0.71831
C	-1.84842	-0.03487	-1.79145
C	-3.19455	-0.68478	-2.03171
C	-4.31142	-0.65387	-1.3056
H	-1.71731	0.03664	1.6169
C	-1.59939	-1.81003	0.73613
C	-2.40368	-2.49437	1.80789
C	-1.87475	-3.17713	2.8235
H	5.89926	-1.17718	-0.29879
H	4.50234	-2.86245	-1.48097
H	2.03787	-2.52211	-1.68884
H	4.81405	0.8609	0.67942
H	-1.87838	3.71454	1.04832
H	0.57302	3.43122	1.44984
H	-1.75322	0.82191	-2.47422
H	-1.08649	-0.74766	-2.12272
H	-3.21021	-1.24261	-2.97043

H	-4.38263	-0.10819	-0.37392
H	-5.199	-1.18043	-1.64884
H	-1.87154	-2.22407	-0.2411
H	-0.52697	-2.00696	0.89233
H	-3.48402	-2.39284	1.71396
H	-0.7979	-3.28296	2.94247
H	-2.49484	-3.66474	3.57087

Sum of Energies = -1014.278400

17

C	-5.60734	-0.49153	0.29982
C	-5.09431	-1.73091	0.72118
C	-3.72784	-1.97453	0.70565
C	-2.86959	-0.96393	0.26078
C	-3.35672	0.28122	-0.16392
C	-4.74477	0.5011	-0.13804
O	-1.52971	-1.25418	0.26582
C	-0.65368	-0.31081	-0.14101
C	-1.00722	0.93351	-0.58095
C	-2.42349	1.32716	-0.6317
O	-2.79649	2.42886	-1.03372
C	0.7611	-0.75364	-0.23734
C	1.80047	0.38571	-0.09716
C	1.33656	1.57427	-0.92305
C	0.03132	1.83608	-1.08054
O	3.0572	-0.05041	-0.61307
N	1.0046	-1.97789	-0.49104
C	1.84015	0.8038	1.40879
C	2.73563	1.95081	1.81493
C	3.71752	2.53375	1.12526
C	3.9556	-0.76882	0.25227
C	4.9936	-1.407	-0.62224
C	5.34031	-2.69209	-0.55639
H	-6.67879	-0.31537	0.31767
H	-5.77079	-2.5096	1.06208
H	-3.30721	-2.92313	1.02257
H	-5.10541	1.46886	-0.47181
H	2.10249	2.23743	-1.30774
H	-0.31752	2.72828	-1.59001
H	0.8119	1.06177	1.69086
H	2.08708	-0.07507	2.02301
H	2.52933	2.31509	2.82262

H	3.99102	2.22554	0.12101
H	4.28595	3.35383	1.55544
H	4.42093	-0.06582	0.95689
H	3.43431	-1.53647	0.8385
H	5.48031	-0.73929	-1.33196
H	4.86531	-3.3803	0.14033
H	6.11948	-3.10649	-1.18993
H	2.00759	-2.09322	-0.67257

Sum of Energies = -1014.258107

20a

C	5.65548	0.3431	0.07942
C	5.08177	1.58131	0.4132
C	3.70327	1.72399	0.50331
C	2.8877	0.614	0.25605
C	3.43956	-0.63139	-0.07739
C	4.83713	-0.74956	-0.16199
C	0.66883	-0.21369	0.13803
C	1.12002	-1.5019	-0.19919
C	2.55895	-1.79109	-0.32783
C	-0.70101	0.10226	0.26762
C	-1.62105	-0.94507	0.02936
C	-1.18313	-2.25057	-0.26726
C	0.16973	-2.51453	-0.38694
O	2.99492	-2.90425	-0.61851
O	-2.93522	-0.59444	0.099
O	1.53898	0.81929	0.35959
N	-1.0775	1.40985	0.63832
C	-3.93933	-1.59057	-0.129
C	-5.27554	-0.91677	-0.04528
C	-6.27739	-1.34641	0.72009
C	-2.10938	1.61285	1.64595
C	-0.95078	2.47441	-0.36102
C	-2.12119	2.57199	-1.31242
C	-2.88563	3.65388	-1.46423
H	6.73494	0.24503	0.01231
H	5.71929	2.44019	0.60447
H	3.24024	2.67088	0.7613
H	5.2411	-1.72315	-0.42114
H	-1.89996	-3.04669	-0.42814
H	0.5319	-3.50743	-0.63186
H	-3.79044	-2.03024	-1.127

H	-3.85738	-2.39487	0.61417
H	-5.39836	-0.04148	-0.68142
H	-6.17239	-2.21381	1.36857
H	-7.24441	-0.85161	0.7246
H	-1.9075	2.56241	2.1598
H	-2.05364	0.81087	2.38643
H	-3.13162	1.6451	1.24736
H	-0.82667	3.42891	0.16887
H	-0.0251	2.29774	-0.91994
H	-2.33595	1.67183	-1.88906
H	-2.70197	4.56508	-0.89716
H	-3.71717	3.67994	-2.16393

Sum of Energies = -1053.537477

21a

C	4.86678	1.47805	0.27238
C	3.93271	2.50862	0.47037
C	2.56892	2.24421	0.44546
C	2.14578	0.93199	0.22062
C	3.05619	-0.11259	0.01975
C	4.42951	0.18098	0.04935
O	0.78559	0.71508	0.20866
C	0.29752	-0.52652	-0.00875
C	1.09932	-1.61066	-0.21672
C	2.56573	-1.48661	-0.21526
O	3.3184	-2.44345	-0.3901
C	-1.23277	-0.58055	0.09842
C	-1.773	-1.94919	-0.46566
C	-0.84451	-3.08663	-0.51512
C	0.49103	-2.91143	-0.43598
O	-2.93287	-2.06303	-0.82394
N	-1.90941	0.51549	-0.58812
C	-1.4933	-0.63	1.64874
C	-2.89876	-0.59384	2.20284
C	-4.06818	-0.51965	1.56666
C	-1.9667	1.84349	0.03488
C	-3.19186	2.60021	-0.41339
C	-3.17383	3.82722	-0.93451
H	5.92954	1.69985	0.29403
H	4.27521	3.52455	0.64501
H	1.83018	3.02463	0.59578
H	5.12196	-0.63978	-0.10804

H	-1.28675	-4.05232	-0.7393
H	1.18342	-3.7388	-0.56209
H	-1.00725	-1.54713	2.01248
H	-0.92007	0.18614	2.10957
H	-2.90116	-0.63911	3.29401
H	-4.13818	-0.49618	0.48629
H	-4.99541	-0.5073	2.13464
H	-2.02837	1.71458	1.11841
H	-1.06608	2.44568	-0.17176
H	-4.137	2.07847	-0.26808
H	-2.24135	4.36503	-1.09754
H	-4.08719	4.34667	-1.2118
C	-1.6198	0.58282	-2.01814
H	-2.29587	1.30646	-2.48054
H	-0.58426	0.89953	-2.24024
H	-1.79916	-0.38764	-2.48671

Sum of Energies = -1053.511565

22a

C	27.1498	-44.6589	0.5035
C	27.3153	-45.8585	1.0723
C	28.6392	-46.5073	1.047
C	29.6773	-45.9025	0.4582
C	29.4921	-44.5814	-0.1667
C	28.2915	-43.989	-0.1463
O	30.8732	-46.5059	0.443
C	31.962	-45.9695	-0.1337
C	31.9304	-44.7683	-0.7275
C	30.683	-43.993	-0.7867
O	30.6419	-42.9008	-1.3298
C	33.2485	-46.7054	-0.1206
C	34.5159	-45.8796	-0.0195
C	34.366	-44.7519	-1.0169
C	33.1697	-44.2374	-1.3266
O	35.6701	-46.6505	-0.433
N	33.4141	-47.9718	-0.202
C	32.1953	-48.7323	-0.3955
C	34.6126	-45.2507	1.4033
C	35.7954	-44.36	1.7214
C	36.8993	-44.1949	0.9807
C	36.2162	-47.5556	0.5509
C	37.2858	-48.357	-0.1476

C	37.2426	-49.6887	-0.2796
H	26.1753	-44.1693	0.5157
H	26.4786	-46.3638	1.556
H	28.7664	-47.4852	1.5119
H	28.139	-43.0118	-0.6045
H	35.2509	-44.3287	-1.4926
H	33.1068	-43.408	-2.0321
H	32.5111	-49.7325	-0.7264
H	31.53	-48.3281	-1.1758
H	31.6521	-48.8532	0.5545
H	33.7135	-44.6324	1.5593
H	34.5794	-46.0511	2.1584
H	35.7376	-43.7998	2.6572
H	37.0832	-44.7012	0.0374
H	37.6831	-43.5183	1.3225
H	36.7079	-47.0015	1.3641
H	35.4625	-48.219	0.9986
H	38.1339	-47.8121	-0.5659
H	36.4168	-50.2783	0.1176
H	38.0436	-50.219	-0.7952

Sum of Energies = -1053.461860

6a

C	-4.72106	-0.47843	-0.15472
C	-4.18942	-1.77557	-0.0776
C	-2.81741	-1.98853	-0.12327
C	-1.9486	-0.89491	-0.24715
C	-2.46695	0.41099	-0.32358
C	-3.85908	0.60002	-0.27587
O	-0.62114	-1.19442	-0.26358
C	0.37626	-0.19847	-0.51523
C	-0.12484	1.22231	-0.58305
C	-1.56202	1.56627	-0.45455
C	1.17247	-0.60782	-1.80485
C	2.1261	0.55802	-2.18165
C	2.20878	1.59	-1.01114
C	0.82529	2.14272	-0.82387
O	-1.95472	2.72859	-0.48967
C	1.52638	-0.3577	0.53603
C	1.0761	-0.443	2.00627
C	0.34979	0.7606	2.54323
C	-0.87974	0.73146	3.06079

C	2.50709	0.8163	0.28525
O	3.44741	1.05716	1.01545
N	2.16607	-1.6189	0.11111
C	1.9346	-1.85108	-1.32093
H	-5.7952	-0.32424	-0.11908
H	-4.85534	-2.62917	0.01829
H	-2.39337	-2.98574	-0.06378
H	-4.2252	1.62019	-0.33622
H	0.48149	-0.83649	-2.62044
H	3.12664	0.17773	-2.41321
H	1.76251	1.08222	-3.07042
H	2.97441	2.34915	-1.1786
H	0.59195	3.20041	-0.89349
H	0.46331	-1.34345	2.10812
H	1.9866	-0.58936	2.60238
H	0.89741	1.70285	2.52842
H	-1.46142	-0.1871	3.10213
H	-1.35116	1.6242	3.46241
H	2.87715	-1.97889	-1.87134
H	1.33903	-2.76263	-1.467
C	3.4675	-1.99693	0.63164
H	3.48863	-1.88729	1.71876
H	3.64019	-3.05481	0.40238
H	4.31005	-1.41337	0.22069

Sum of Energies = -1053.538988

23a

C	5.10999	0.61751	-0.43534
C	4.97776	-0.77036	-0.2717
C	3.74479	-1.33965	0.021
C	2.61497	-0.5202	0.15647
C	2.73234	0.87367	-0.00424
C	3.99169	1.42464	-0.29949
O	1.45093	-1.16397	0.44923
C	0.2087	-0.46599	0.55835
C	0.29055	1.04289	0.45012
C	1.55607	1.74998	0.15178
O	1.61096	2.97244	0.05075
C	-0.38741	-0.8132	1.95605
C	-1.8037	-0.20727	2.10912
C	-2.05374	0.76966	0.91391
C	-0.88733	1.66198	0.64712

C	-2.21483	-0.3074	-0.2023
O	-2.9803	-1.36334	0.42251
C	-2.91209	-1.23014	1.84649
C	-0.81511	-0.88765	-0.53098
C	-2.95423	0.15915	-1.46229
C	-4.36712	0.60048	-1.20325
C	-4.85657	1.80661	-1.4975
H	6.07827	1.05184	-0.66447
H	5.84745	-1.41381	-0.37504
H	3.63065	-2.41072	0.15292
H	4.04811	2.50266	-0.41391
H	-0.4026	-1.90233	2.0683
H	0.29901	-0.4126	2.70846
H	-1.92142	0.28565	3.07789
H	-2.9909	1.31687	1.04094
H	-0.97026	2.74325	0.59978
H	-3.87839	-0.87351	2.23235
H	-2.70749	-2.21297	2.28657
H	-2.37614	0.96661	-1.92812
H	-2.93563	-0.68638	-2.16035
H	-5.01599	-0.14706	-0.74893
H	-4.24185	2.579	-1.95652
H	-5.89488	2.06519	-1.30605
C	0.53322	-2.2615	-1.99798
H	0.91775	-2.94645	-1.23581
H	1.33052	-1.54877	-2.24199
H	0.30894	-2.83566	-2.90204
N	-0.68937	-1.58588	-1.57799

Sum of Energies = -1053.524400

25

C	-5.4792	0.1682	-0.1778
C	-4.9337	1.4411	-0.414
C	-3.5582	1.6308	-0.4379
C	-2.7168	0.5334	-0.2219
C	-3.2401	-0.7463	0.0131
C	-4.6354	-0.9115	0.032
O	-1.3726	0.7837	-0.2535
C	-0.4778	-0.2386	-0.0583
C	-0.8992	-1.5619	0.1678
C	-2.3341	-1.8943	0.2266
C	0.8829	0.1145	-0.1074

C	1.8213	-0.9323	0.0376
C	1.4177	-2.2614	0.2364
C	0.0675	-2.5649	0.3119
O	-2.7487	-3.0341	0.4318
O	3.1257	-0.5292	-0.0455
C	4.1658	-1.5054	0.0877
C	5.4801	-0.7886	0.0215
C	6.4647	-1.1192	-0.8125
C	0.9464	2.5136	0.5414
C	1.4378	3.8251	-0.005
C	2.2271	4.6706	0.6577
H	-6.5567	0.0334	-0.1618
H	-5.5908	2.2902	-0.5811
H	-3.1185	2.6059	-0.6216
H	-5.017	-1.9111	0.2146
H	2.1535	-3.0495	0.3432
H	-0.2767	-3.5802	0.4763
H	4.0533	-2.0181	1.055
H	4.0863	-2.2563	-0.7093
H	5.6057	0.0285	0.7307
H	6.3583	-1.9274	-1.533
H	7.418	-0.5986	-0.8044
H	-0.1448	2.5291	0.6115
H	1.3381	2.3588	1.5609
H	1.1067	4.0614	-1.0161
H	2.5798	4.4527	1.6641
H	2.544	5.6165	0.2268
O	1.3248	1.4213	-0.373

Sum of Energies = -1034.133278

26

C	4.83531	-1.1213	-0.28642
C	4.03444	-2.09993	-0.89904
C	2.66466	-1.91213	-1.03473
C	2.10072	-0.73009	-0.54833
C	2.87632	0.26053	0.06539
C	4.25911	0.04674	0.1899
O	0.74079	-0.58555	-0.70461
C	0.11657	0.52847	-0.25504
C	0.78035	1.55107	0.35503
C	2.23768	1.49571	0.5636
O	2.86842	2.40025	1.10745

C	-1.40498	0.47606	-0.4069
C	-2.04889	1.88175	-0.14362
C	-1.27625	2.87985	0.59668
C	0.0465	2.72372	0.80416
O	-3.18683	2.09838	-0.52803
C	-1.80694	-0.06324	-1.81632
C	-3.09299	-0.85363	-1.96416
C	-4.25375	-0.69048	-1.32855
C	-1.59729	-1.65398	0.82332
C	-2.60125	-2.28018	1.74321
C	-2.28112	-2.94321	2.85372
H	5.90465	-1.28208	-0.18781
H	4.48639	-3.0145	-1.27207
H	2.02704	-2.65402	-1.50428
H	4.84677	0.82407	0.66765
H	-1.80953	3.77601	0.8971
H	0.64053	3.48362	1.30315
H	-1.84501	0.80672	-2.48632
H	-0.9925	-0.68799	-2.19168
H	-3.02794	-1.63447	-2.72351
H	-4.40051	0.07825	-0.57984
H	-5.10192	-1.32829	-1.56664
H	-1.63938	-2.1339	-0.16327
H	-0.58116	-1.77314	1.22157
H	-3.64024	-2.17702	1.43533
H	-1.2486	-3.04633	3.18173
H	-3.03686	-3.41206	3.4779

Sum of Energies = -1034.111473

27

C	5.56963	0.43406	-0.21
C	5.13188	1.54306	0.53636
C	3.79143	1.69566	0.86091
C	2.88037	0.72454	0.43145
C	3.29284	-0.39052	-0.31498
C	4.65734	-0.5205	-0.62928
O	1.57129	0.91908	0.77963
C	0.64483	0.01649	0.38241
C	0.91917	-1.10266	-0.34826
C	2.30855	-1.39711	-0.75471
O	2.60865	-2.39812	-1.40254
C	-0.72682	0.31876	0.86394
C	-1.89944	-0.55269	0.32964

C	-1.43997	-1.77211	-0.43632
C	-0.1561	-2.01092	-0.73192
O	-2.57305	0.25772	-0.65835
C	-2.77279	-0.95762	1.54218
C	-4.07548	-1.67735	1.29131
C	-4.77244	-1.77138	0.15642
C	-3.34158	1.391	-0.21263
C	-3.87963	2.0631	-1.44082
C	-3.751	3.36469	-1.69497
H	6.62206	0.32913	-0.45597
H	5.84802	2.29105	0.86455
H	3.42937	2.54153	1.43577
H	4.95936	-1.38835	-1.20677
H	-2.21951	-2.45578	-0.75466
H	0.14873	-2.89193	-1.28736
H	-2.14343	-1.59234	2.18306
H	-2.96031	-0.05772	2.14398
H	-4.48061	-2.15425	2.1852
H	-4.43697	-1.31796	-0.77028
H	-5.71265	-2.31574	0.12794
H	-4.16934	1.04098	0.42119
H	-2.72661	2.08172	0.37376
H	-4.42157	1.41868	-2.13227
H	-3.20744	4.02736	-1.02472
H	-4.1886	3.82046	-2.57901
O	-0.93504	1.25033	1.62514

Sum of Energies = -1034.110549

4

C	4.56979	0.09289	-0.23551
C	4.19419	1.39173	0.14183
C	2.85512	1.75713	0.20586
C	1.86437	0.81718	-0.10884
C	2.22475	-0.48899	-0.48674
C	3.58638	-0.83346	-0.54503
O	0.57831	1.25523	-0.0017
C	-0.53169	0.44447	-0.39874
C	-0.2022	-0.97085	-0.79802
C	1.18985	-1.48444	-0.81861
C	-1.3321	1.20958	-1.50999
C	-2.44098	0.27084	-2.05384
C	-2.58103	-0.99413	-1.14834
C	-1.2599	-1.71151	-1.17612

O	1.44538	-2.64487	-1.12459
C	-1.62686	0.4885	0.71693
C	-1.16108	0.34848	2.16656
C	-0.52519	-0.974	2.50199
C	0.7227	-1.12289	2.94936
C	-2.71371	-0.54714	0.31787
O	-3.56768	-0.94139	1.07932
C	-1.90061	2.3618	-0.68184
H	5.61924	-0.18113	-0.28278
H	4.95627	2.12647	0.38778
H	2.55151	2.75756	0.49696
H	3.8309	-1.84938	-0.83909
H	-0.66095	1.55202	-2.30174
H	-3.40008	0.79757	-2.1008
H	-2.19911	-0.06189	-3.06744
H	-3.43024	-1.61789	-1.43085
H	-1.15138	-2.74834	-1.47793
H	-0.47768	1.17535	2.38056
H	-2.06118	0.48818	2.77912
H	-1.15923	-1.85278	2.38784
H	1.38808	-0.27319	3.08749
H	1.12528	-2.10052	3.19985
H	-2.78695	2.82329	-1.12879
H	-1.14487	3.13739	-0.50746
O	-2.27981	1.76805	0.57005

Sum of Energies = -1034.144058

5

C	5.04522	0.6689	-0.55513
C	4.8846	-0.66521	-0.96325
C	3.67368	-1.32317	-0.79183
C	2.59491	-0.64842	-0.20566
C	2.73936	0.6905	0.20891
C	3.97702	1.33331	0.02485
O	1.46131	-1.38263	-0.02771
C	0.24188	-0.76093	0.33844
C	0.33229	0.66608	0.83399
C	1.61271	1.41472	0.82265
O	1.69845	2.55425	1.27077
C	-0.43971	-1.62165	1.43819
C	-1.86889	-1.09379	1.72743
C	-2.04255	0.2955	1.02808
C	-0.85292	1.18834	1.19916

C	-2.13897	-0.21726	-0.43975
O	-2.89377	-1.44604	-0.36929
C	-2.94791	-1.89362	0.99373
C	-0.71357	-0.64797	-0.87885
C	-2.78533	0.7263	-1.45754
C	-4.22503	1.03506	-1.15475
C	-4.71481	2.25969	-0.95348
H	5.99642	1.17308	-0.69573
H	5.71504	-1.19454	-1.42285
H	3.53367	-2.35241	-1.105
H	4.05741	2.36458	0.35413
H	-0.45676	-2.66528	1.10733
H	0.18964	-1.56718	2.33139
H	-2.05976	-1.03938	2.80233
H	-2.98078	0.77244	1.32236
H	-0.93098	2.20801	1.56316
H	-3.94513	-1.68822	1.40838
H	-2.77991	-2.97558	1.01278
H	-2.19346	1.64864	-1.50578
H	-2.6941	0.23883	-2.43695
H	-4.89012	0.17395	-1.10847
H	-4.08342	3.14529	-0.99755
H	-5.7697	2.42722	-0.75247
O	-0.38349	-0.86405	-2.01978

Sum of Energies = -1034.14358

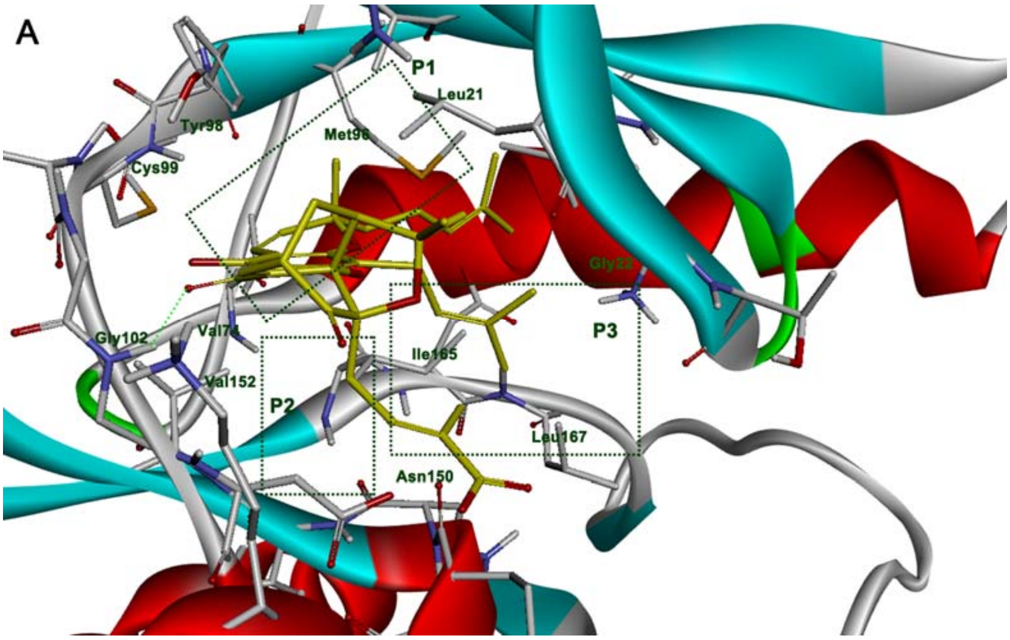


Fig. 3A-1 Molecular docking simulations for GA (**1**).

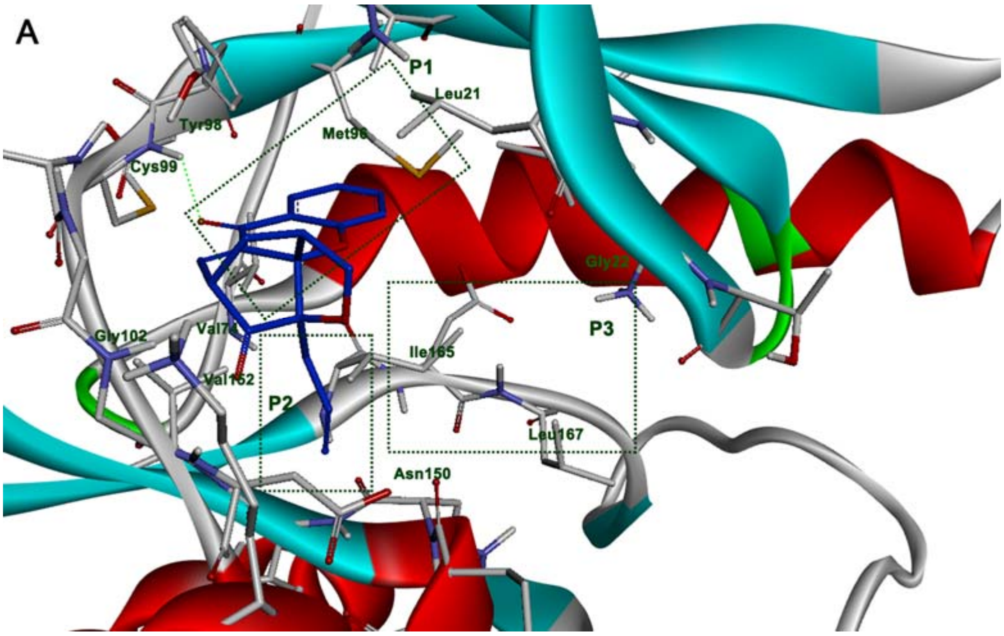


Fig. 3A-2 Molecular docking simulations for **4.**

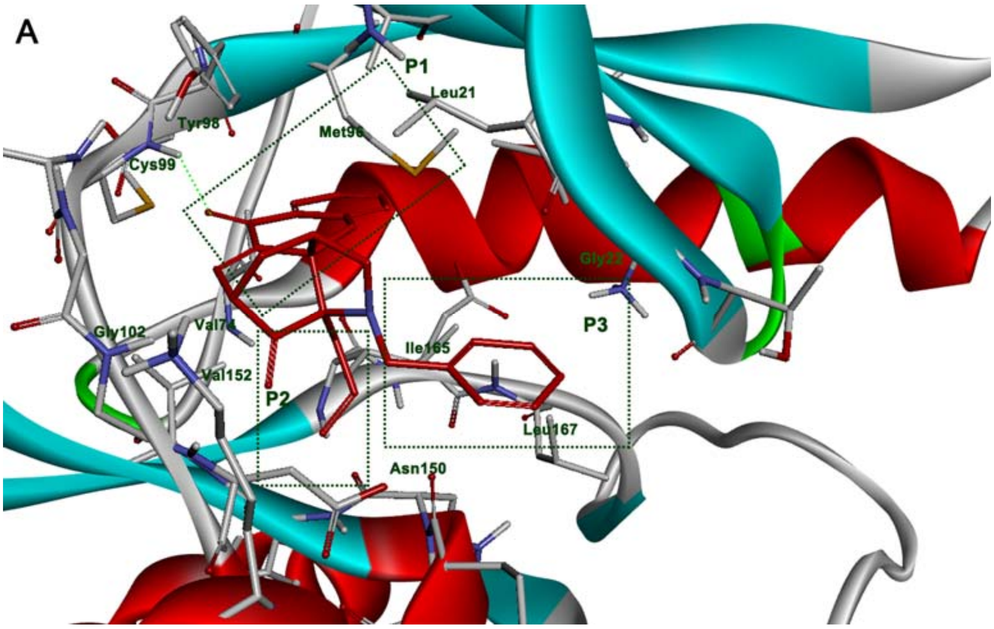


Fig. 3A-3 Molecular docking simulations for **6c.**