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Synthesis of 2-sulfamoylquinoxaline 1,4-dioxide derivatives

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General Information

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) with TMS as internal standard. The signals in the ^{13}C NMR spectra were assigned using the APT method. High-resolution mass spectra (electrospray ionization) were recorded on a micrOTOF-Q II spectrometer (Bruker Daltonics GmbH). The measurement accuracy was 0.25–0.38 ppm in the mass range 118.086255–2721.894829. Solutions of samples (0.1 mg ml^{-1}) in a MeCN–HCOOH, 2000:1 mixture were directly injected into the ion source (electrospray ionization). Conditions for determining positively and negatively charged ions: capillary voltage 4 kV, nitrogen pressure in the nebulizer 0.4 bar, drying gas flow rate 4 dm^3 min^{-1} and source temperature 180°C. Elemental analysis was performed on a PerkinElmer 2400 CHN automatic microanalyzer. The OMNIC-7.0 software package was used for processing. The reaction progress and the purity of the obtained compounds were monitored by TLC on Silufol and Silica Gel 60 F_{254} (Merck) plates. Preparative chromatography was performed on Merck silica gel 60 (SiO_2). The extracts were dried over anhydrous Na_2SO_4.

All solvents and reagents from Sigma-Aldrich were used without additional purification; freshly distilled solvents were used for the reactions. The starting *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide was synthesized according to a published procedure[S1] and used without purification. Benzofuroxan derivatives (compounds **5**, **10**[S2],[S3]) were obtained by oxidation of the corresponding *o*-nitroanilines according to methods described earlier.[S2],[S4]

6,7-Dichloro-3-phenyl-2-sulfamoylquinoxaline 1,4-dioxide (6). Method 1. A solution of *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide (0.2 g, 0.98 mmol) in EtOH (5 m) was added to a mixture of 5,6-dichlorobenzofuroxan[S2] (**5**, 0.1 g,0.48 mmol), K_2CO_3 (0.14 g,1 mmol) and $CaCl_2$ (0.05 g, 0.45 mmol) in THF (2 ml). The mixture was stirred for 8 h at 50°C and concentrated under reduced pressure after completion of the reaction (TLC monitoring). The residue was purified by column chromatography on silica gel (PhMe–EtOAc, 4:1) and crystallized from a mixture of dichloromethane–*n*-hexane. Yield of compound **6** 9 mg (5%), yellow powder.

Method 2. A solution of 2-(*N*-(*tert*-butyl)sulfamoyl)-3-phenyl-6,7-dichloroquinoxaline-1,4-dioxide (**7**, 0.1 g, 0.22 mmol) in 2 ml of TFA was stirred under argon flow for 18 h and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (PE – EOAc, 6:1) and

crystallized from *n*-hexane–CH_2Cl_2 mixture. Yield of compound **6** 71 mg (84%), yellow powder, mp > 250°C. ^{1}H NMR (DMSO-d_6), δ, ppm: 8.43 (1H, br. s, H-8); 8.21 (1H, br. s, H-5); 7.65 (2H, br. s, SO_2NH_2); 7.47–7.41 (5H, br. m, H_{Ph}). ^{13}C NMR (DMSO-d_6), δ, ppm: 155.4; 140.1; 136.8; 134.9; 132.2; 130.6; 129.6; 129.2; 128.7; 127.5; 121.4; 116.9. Found, m/z: 385.9747 [M+H]+. $C_{14}H_{10}Cl_2N_3O_4S$. Calculated, m/z: 385.9764. Found, %: C, 43.68; H, 2.19; N, 10.66; calculated for $C_{14}H_9Cl_2N_3O_4S$, %: C, 43.54; H, 2.35; N, 10.88.

2-[*N*-(*tert*-Butyl)sulfamoyl]-6,7-dichloro-3-phenylquinoxaline 1,4-dioxide (7). A solution of *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide[S1] 1.2 g (4.9 mmol) in EtOH (5 ml) was added to a solution of 5,6-dichlorobenzofuroxan (**5**, 0.5 g, 2.4 mmol), K_2CO_3 (0.14 g,1 mmol) and $CaCl_2$ (0.05 g,0.45 mmol) in THF (5 ml) at room temperature. The mixture was stirred for 5–8 h at 50°C and after completion of the reaction (TLC control) was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PhMe–EtOAc, 5:1) and crystallized from *n*-hexane–CH_2Cl_2 mixture. Yield of compound **7** 389 mg (39%), yellow powder, mp 153–155°C. ^{1}H NMR (DMSO-d_6), δ, ppm: 8.75 (1H, br s, H-8); 8.66 (1H, br. s, H-5); 7.97 (1H, br. s, NH); 7.52–7.50 (3H, br. m, H_{Ph}); 7.40–7.39 (2H, br. m, H_{Ph}); 1.10 (9H, s, $3CH_3$). ^{13}C NMR (DMSO-d_6), δ, ppm: 143.8; 142.5; 137.6; 137.0; 136.6; 136.4; 129.8; 129.7; 129.6; 128.1; 122.3; 121.8; 86.4; 29.6. Found, m/z: 442.0377 $[M+H]^+$. $C_{18}H_{18}Cl_2N_3O_4S$. Calculated, m/z: 442.0390. Found, %: C, 48.97; H, 3.72; N, 9.35; calculated for $C_{18}H_{17}Cl_2N_3O_4S$, %: C, 48.88; H, 3.87; N, 9.50.

6-[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]-2-[*N*-(*tert*-butyl)sulfamoyl]-7-chloro-3-phenyl-quinoxaline 1,4-dioxide (8). *N*-Boc-piperazine (0.17 g, 0.9 mmol) was added to a solution of 2-[*N*-(*tert*-butyl)sulfamoyl]-6,7-dichloro-3-phenyl-quinoxaline 1,4-dioxide (**7**, 0.2 g, 0.45 mmol) in THF (10 ml). The mixture was stirred for 14 h at room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE – EtOAc, 8:1) and crystallized from *n*-hexane–CH_2Cl_2 mixture. Yield of compound **8** 210 mg (81%), yellow powder, mp 224–226°C. ^{1}H NMR ($CDCl_3$), δ, ppm: 8.70 (1H, s, H-8); 8.04 (1H, s, H-5); 7.58–7.56 (3H, m, H_{Ph}); 7.45–7.44 (2H, m, H_{Ph}); 6.92 (1H, s, NH); 3.68–3.65 (4H, m, $2CH_2$); 3.25–3.22 (4H, m, $2CH_2$); 1.50 (9H, s, $3CH_3$); 1.20 (9H, s, $3CH_3$). ^{13}C NMR ($CDCl_3$), δ, ppm: 154.4; 153.8; 141.9; 141.7; 137.5; 135.4; 132.3; 130.1; 129.0; 128.2; 128.1; 122.1; 108.9; 80.0; 55.5; 50.7; 50.6; 29.4; 28.0. Found, m/z: 592.1991 $[M+H]^+$. $C_{27}H_{35}ClN_5O_6S$. Calculated, m/z: 592.1986. Found, %: C, 54.53; H, 5.64; N, 11.66; calculated for $C_{27}H_{34}ClN_5O_6S$, %: C, 54.77; H, 5.79; N, 11.83.

7-Chloro-3-phenyl-6-(piperazin-1-yl)-2-sulfamoylquinoxaline 1,4-dioxide hydrochloride (9·HCl**)**. A solution of Boc-intermediate **8** (0.1 g, 0.17 mmol) in TFA (2 ml) was stirred for 18 h at room temperature under argon flow and then concentrated under reduced pressure. The residue was dissolved in THF (1 ml) and 3M HCl in MeOH (2 mL) was added. The mixture was stirred at room temperature for 10 min. The solvent was concentrated in a rotary evaporator, and the residue was dissolved in H_2O (3 mL). The hot solution was filtered and concentrated to ~ 1 ml. The product was precipitated by adding a mixture of MeOH (3 mL) and Et_2O (10 mL). The formed precipitate was filtered off, washed with Me_2CO (3 × 3 ml), Et_2O (3 × 3 ml), *n*-hexane (3 × 3 ml) and dried under reduced pressure. Yield of compound **9**·HCl 52 mg (63%), orange powder, mp 260–262°C (decomp.). ^{1}H NMR (DMSO-d_6), δ, ppm: 8.57 (1H, s, H-8); 7.98 (1H, s, H-5); 7.49–7.47 (5H, m, H_{Ph}); 7.41–7.38 (2H, m, SO_2NH_2); 3.45–3.44 (4H, m, $2CH_2$); 3.36–3.35 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6), δ, ppm: 152.5; 142.5; 141.9; 138.1; 134.0; 133.6; 130.5; 130.2; 129.7; 128.0; 121.9; 109.9; 48.2; 43.3. Found, m/z: 436.0844 $[M+H]^+$. $C_{18}H_{19}ClN_5O_4S$. Calculated, m/z: 436.0835. Found, %: C, 43.85; H, 4.50; N, 14.07; calculated for $C_{18}H_{18}ClN_5O_4S$*HCl*H_2O, %: C, 44.09; H, 4.32; N, 14.28.

6-[(4-*tert*-Butoxycarbonyl)piperazin-1-yl]-5-chlorobenzofuroxan (10). This compound was prepared from 5-[(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-chloro-2-nitroaniline as described.[S2] Yield 0.9 g (85%), yellow powder, mp 154-155 °C. ^{1}H NMR (400 MHz, DMSO-d_6; Me_4Si) δ 7.90 (1H, s, H-7); 7.01 (1H, s, H-4); 3.51 (4H, t, J = 4.7, CH_2); 3.05 (4H, t, J = 4.7, CH_2); 1.44 (9H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4; 151.7; 136.5; 116.7; 101.9 (m, 9-C); 79.6; 51.6; 43.7; 28.6. HRMS (ESI) calculated for $C_{15}H_{20}ClN_4O_4^+$ $(M + H)^+$ 355.1168, found 355.1155.

7-[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]-2-[*N*-(*tert*-butyl)sulfamoyl]-6-chloro-3-phenylquinoxaline 1,4-dioxide (**11**). A solution of *N*-(*tert*-butyl)-2-oxo-2-phenylethane-1-sulfonamide[S1] (0.43 g, 1.7 mmol)

in EtOH (3 ml) was added to a solution of benzofuroxan **10**[S4] (0.3 g, 0.85 mmol), K_2CO_3 (0.14 g, 1 mmol) and (0.05 g, 0.45 mmol) $CaCl_2$ in dioxane (5 ml) at room temperature. The mixture was stirred for 5–8 h at 50°C and after completion of the reaction (TLC control) was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$–EtOAc, 3:1) and crystallized from *n*-hexane–CH_2Cl_2 mixture. Yield of compound **11** 182 mg (35%), orange powder, mp 249–251°C. ^{1}H NMR ($CDCl_3$), δ, ppm: 8.62 (1H, s, H-8); 8.03 (1H, s, H-5); 7.56–7.54 (3H, m, H_{Ph}); 7.45–7.43 (2H, m, H_{Ph}); 6.92 (1H, s, NH); 3.67–3.65 (4H, m, $2CH_2$); 3.26–3.22 (4H, m, $2CH_2$); 1.49 (9H, s, $3CH_3$); 1.19 (9H, s, $3CH_3$). ^{13}C NMR ($CDCl_3$), δ, ppm: 154.6; 154.1; 142.2; 142.1; 136.6; 135.7; 133.9; 130.5; 129.5; 128.7; 128.4; 122.8; 109.3; 80.3; 55.8; 51.0; 50.9; 29.7; 28.3. Found, m/z: 592.1949 [M+H]+. $C_{27}H_{35}ClN_5O_6S$. Calculated, m/z: 592.1991. Found, %: C, 54.31; H, 5.50; N, 11.92; calculated for $C_{27}H_{34}ClN_5O_6S$, %: C, 54.77; H, 5.79; N, 11.83.

6-Chloro-7-(piperazin-1-yl)-2-sulfamoylquinoxaline 1,4-dioxide hydrochloride (**12**·HCl) was obtained from derivative **11** according to the procedure for regioisomer **9**·HCl. Yield of compound **12** 58 mg (70%), orange powder, mp > 265°C (decomp.). ^{1}H NMR (DMSO-*d*$_6$), δ, ppm: 8.49 (1H, s, H-5); 8.02 (1H, s, H-8); 7.51–7.50 (2H, m, H_{Ph}); 7.48–7.47 (3H, m, H_{Ph}); 7.41–7.40 (2H, m, SO_2NH_2); 3.51–3.35 (8H, m, $4CH_2$, partially overlapped by the signal of H_2O). ^{13}C NMR (DMSO-*d*$_6$), δ, ppm: 152.0; 143.6; 140.9; 137.1; 134.9; 134.7; 130.4; 130.1; 129.7; 128.1; 122.5; 109.5; 48.2; 43.3. Found, m/z: 436.0890 $[M+H]^+$. $C_{18}H_{19}ClN_5O_4S$. Calculated, m/z: 436.0841. Found, %: C, 43.87; H, 4.12; N, 14.06; calculated for $C_{18}H_{18}ClN_5O_4S*HCl*H_2O$, %: C, 44.09, H, 4.32; N, 14.28.

References

[S1] S. K. Krymov, D. I. Salnikova, L. G. Dezhenkova, F. B. Bogdanov, A. A. Korlyukov, A. M. Scherbakov and A. E. Shchekotikhin, *Pharmaceuticals*, 2024, **17**, 32; https://doi.org/10.3390/ph17010032.

[S2] G. I. Buravchenko, A. M. Scherbakov, L. G. Dezhenkova, L. Monzote and A. E. Shchekotikhin, *RSC Adv*., 2021, **11**, 38782; https://doi.org/10.1039/D1RA07978F.

[S3] G. I. Buravchenko, D. A. Maslov, M. S. Alam, N. E. Grammatikova, S. G. Frolova, A. A. Vatlin, X. Tian, I. V. Ivanov, O. B. Bekker, M. A. Kryakvin, O. A. Dontsova, V. N. Danilenko, T. Zhang and A. E. Shchekotikhin, *Pharmaceuticals*, 2022, **15**, 155; https://doi.org/10.3390/ph15020155.

[S4] Y. Hu, Q. Xia, S. Shangguan, X. Liu, Y. Hu and R. Sheng, *Molecules*, 2012, **17**, 9683; https://doi.org/10.3390/molecules17089683.

Copies of NMR Spectra

Figure S1. Copy of ^{1}H NMR spectrum of the derivative **6**.

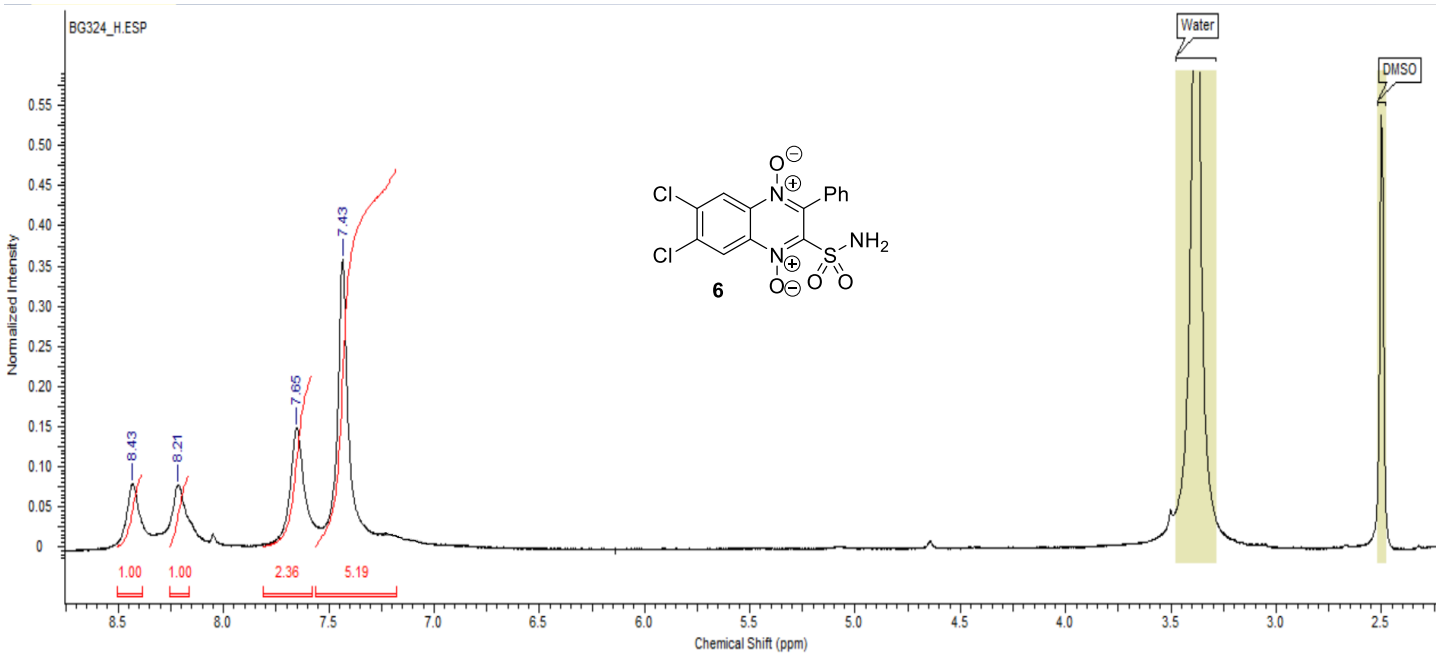


Figure S2. Copy of ^{13}C NMR spectrum of the derivative **6**.

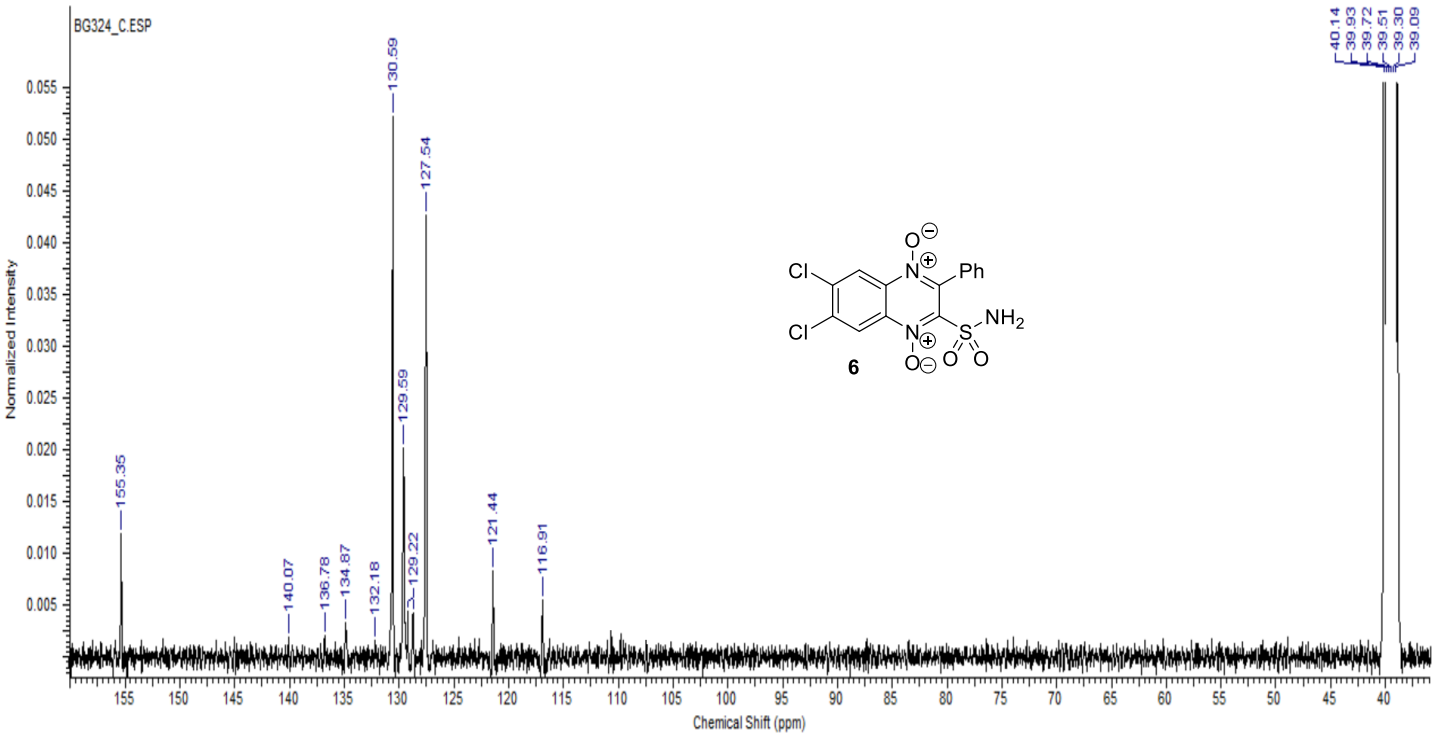


Figure S3. Copy of ^{1}H NMR spectrum of the derivative **7**.

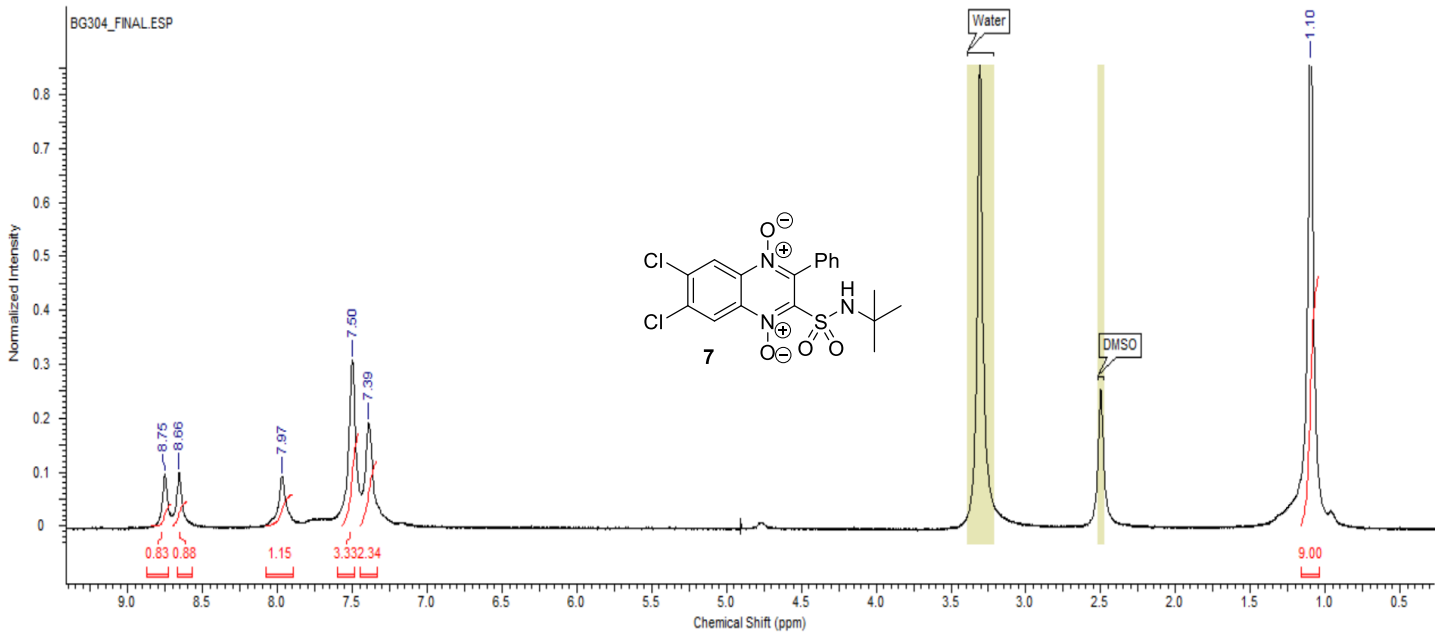


Figure S4. Copy of ^{13}C NMR spectrum of the derivative**7**.

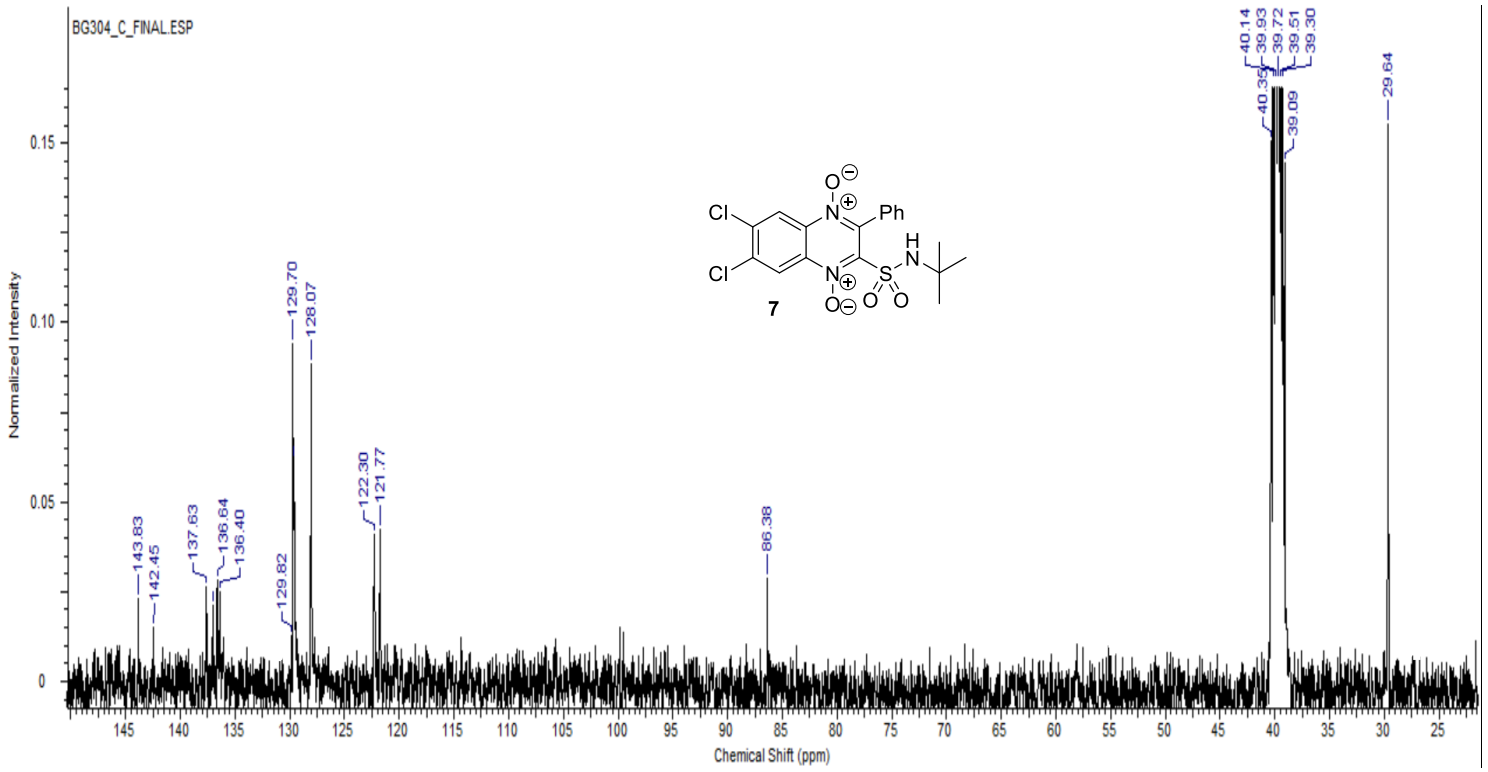


Figure S5. Copy of ^{1}H NMR spectrum of the derivative **8**.

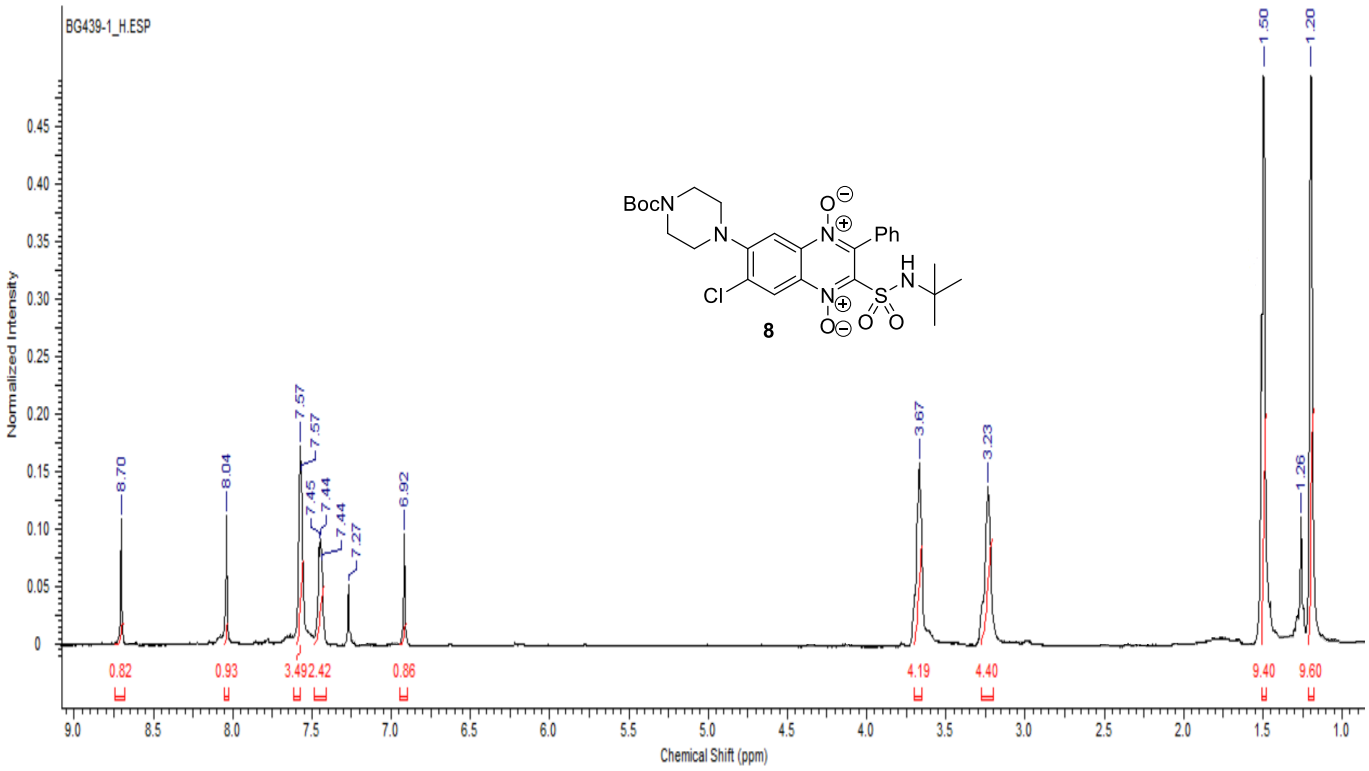


Figure S6. Copy of ^{13}C NMR spectrum of the derivative **8**.

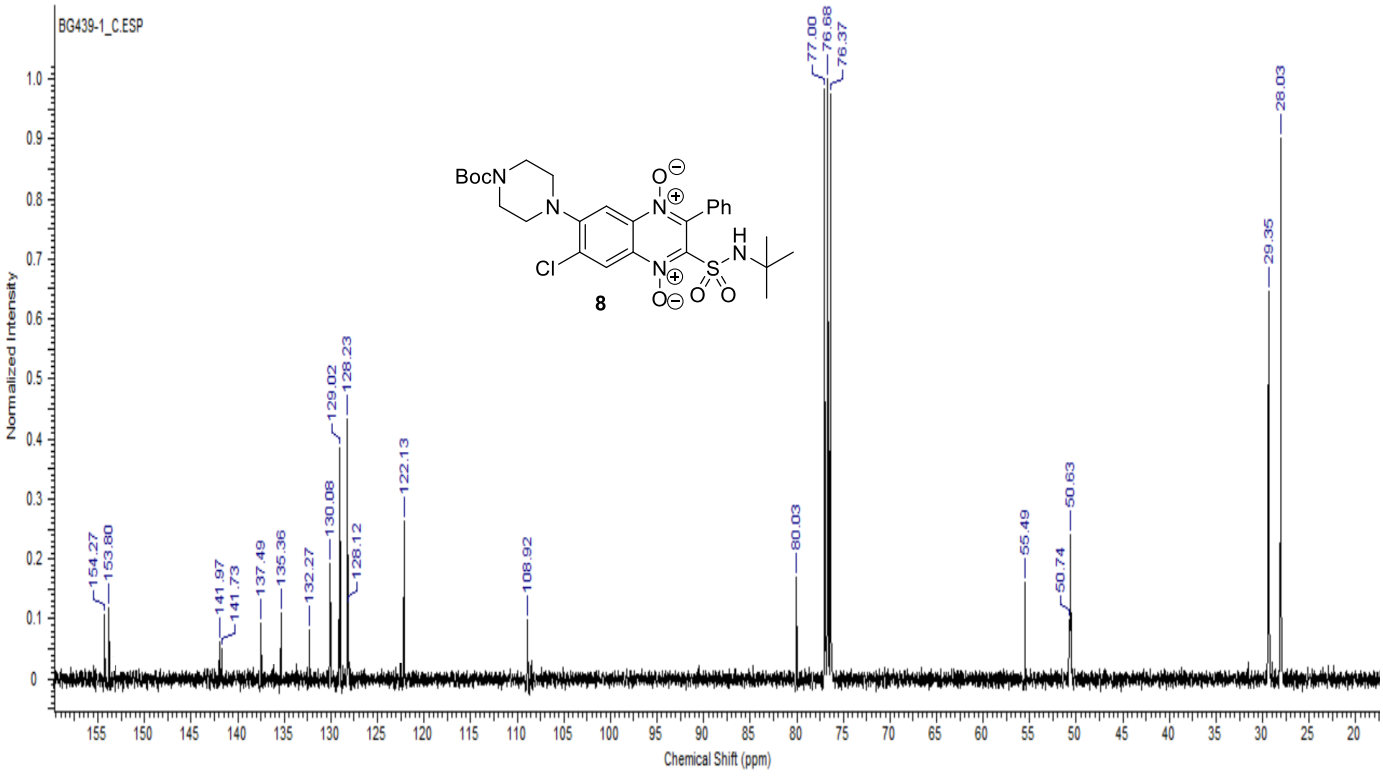


Figure S7. Copy of ^{1}H NMR spectrum of the derivative **9**·HCl.

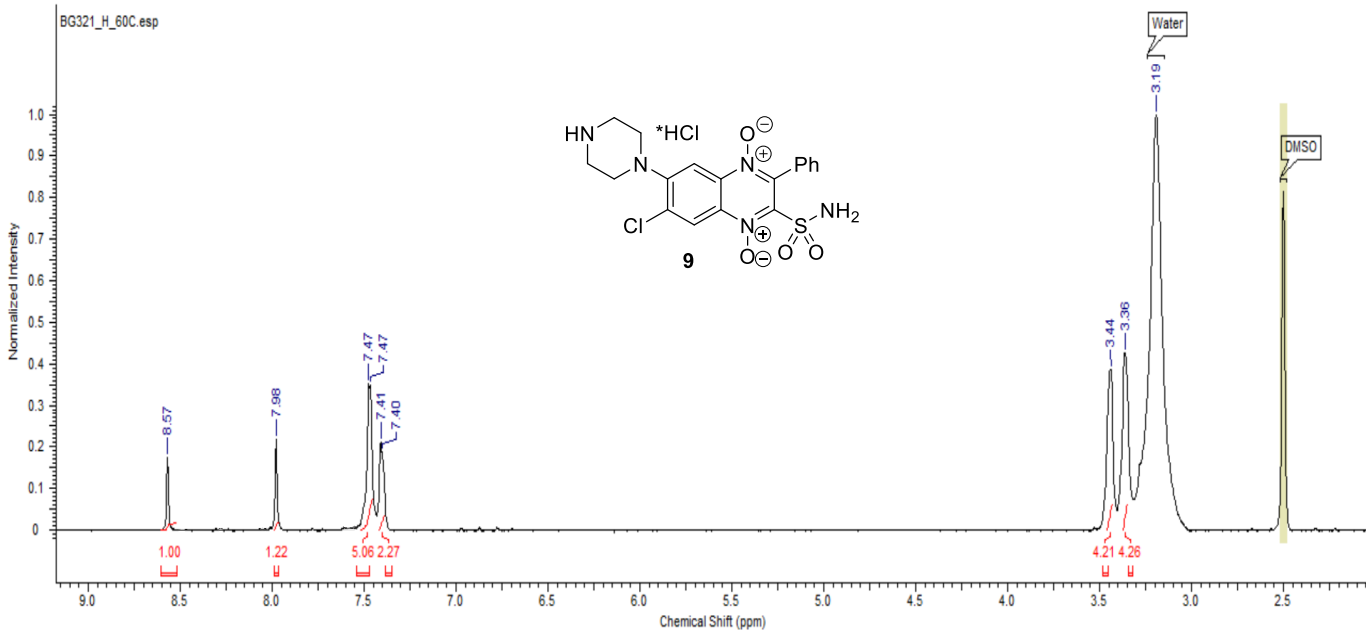


Figure S8. Copy of ^{13}C NMR spectrum of the derivative **9**·HCl.

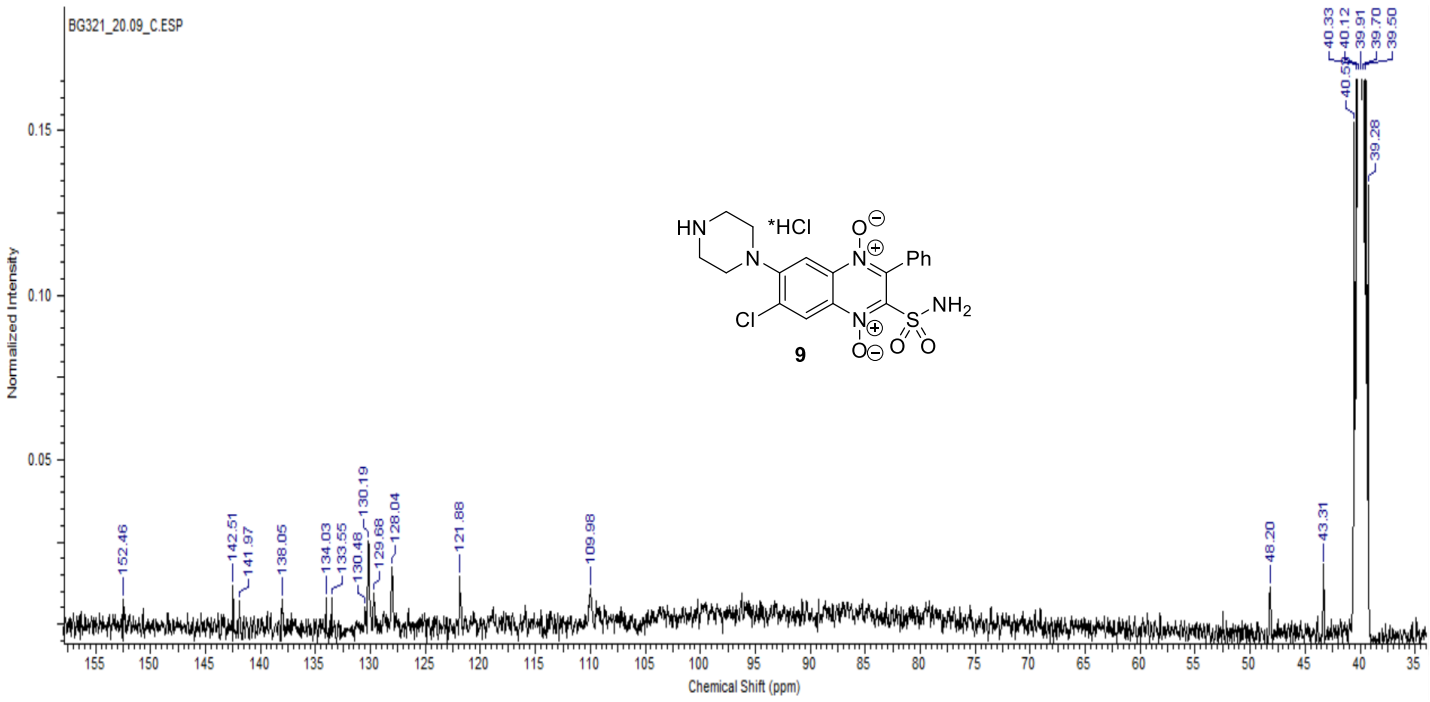


Figure S9. Copy of ^{1}H NMR spectrum of the derivative **10**.

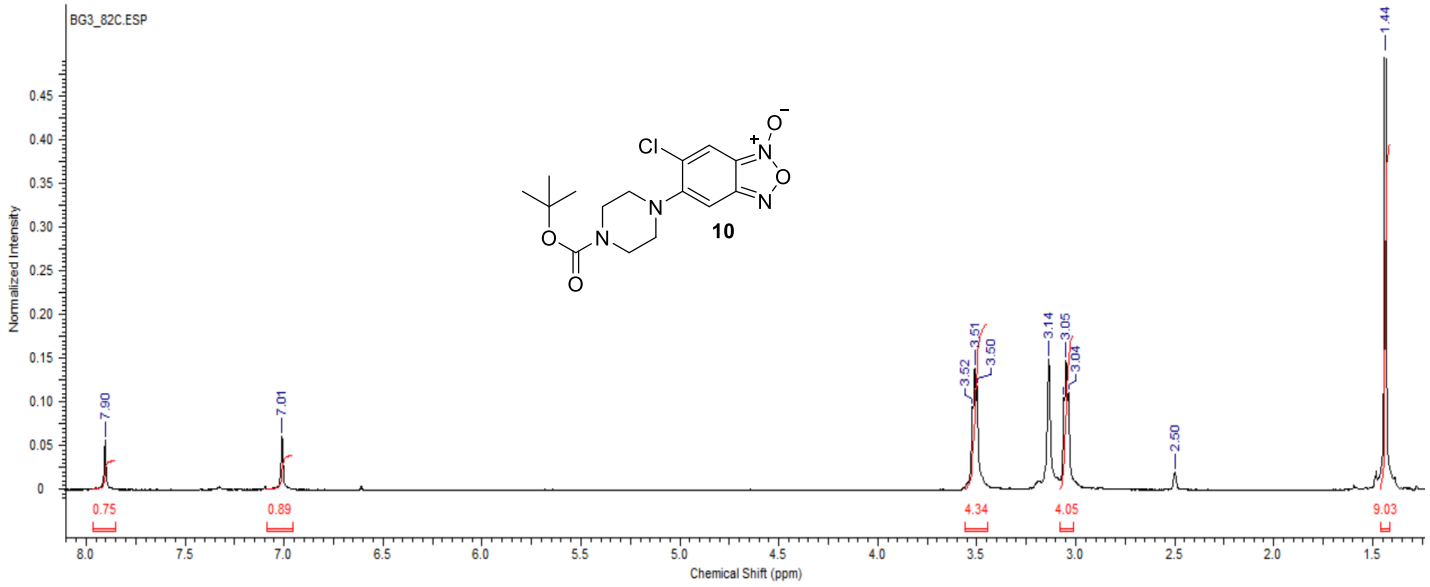


Figure S10. Copy of ^{13}C NMR spectrum of the derivative **10**.

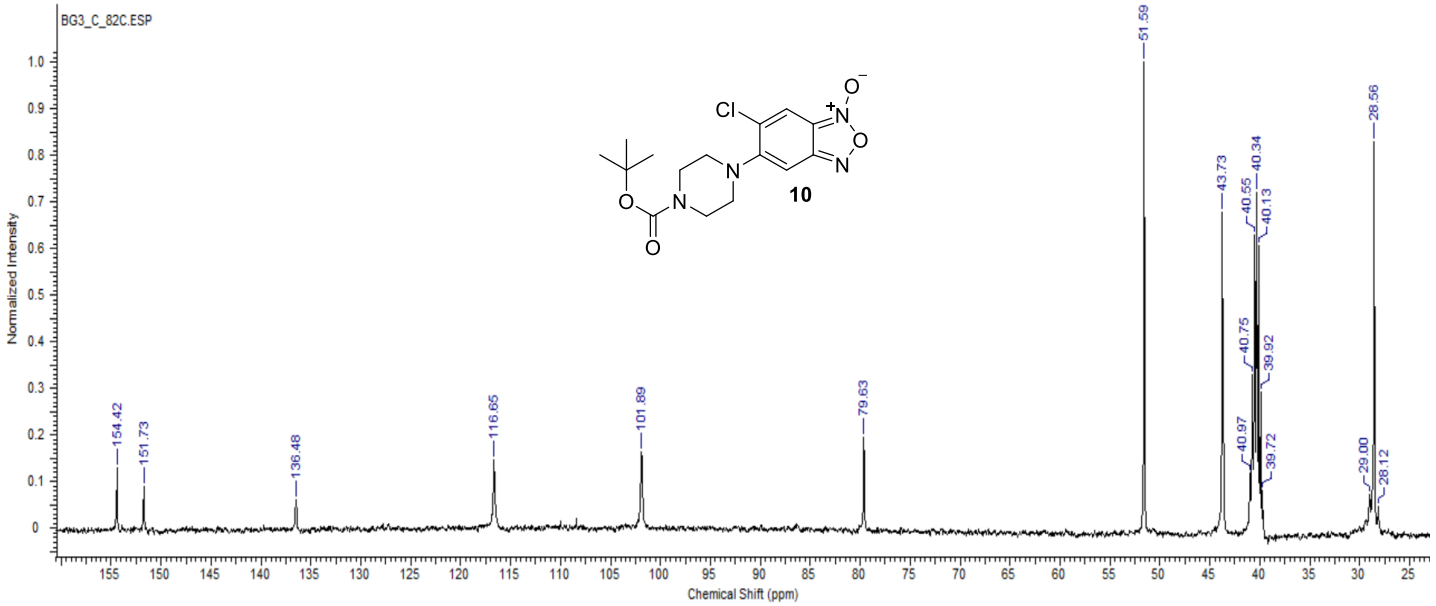


Figure S11. Copy of ^{1}H NMR spectrum of the derivative **11**.

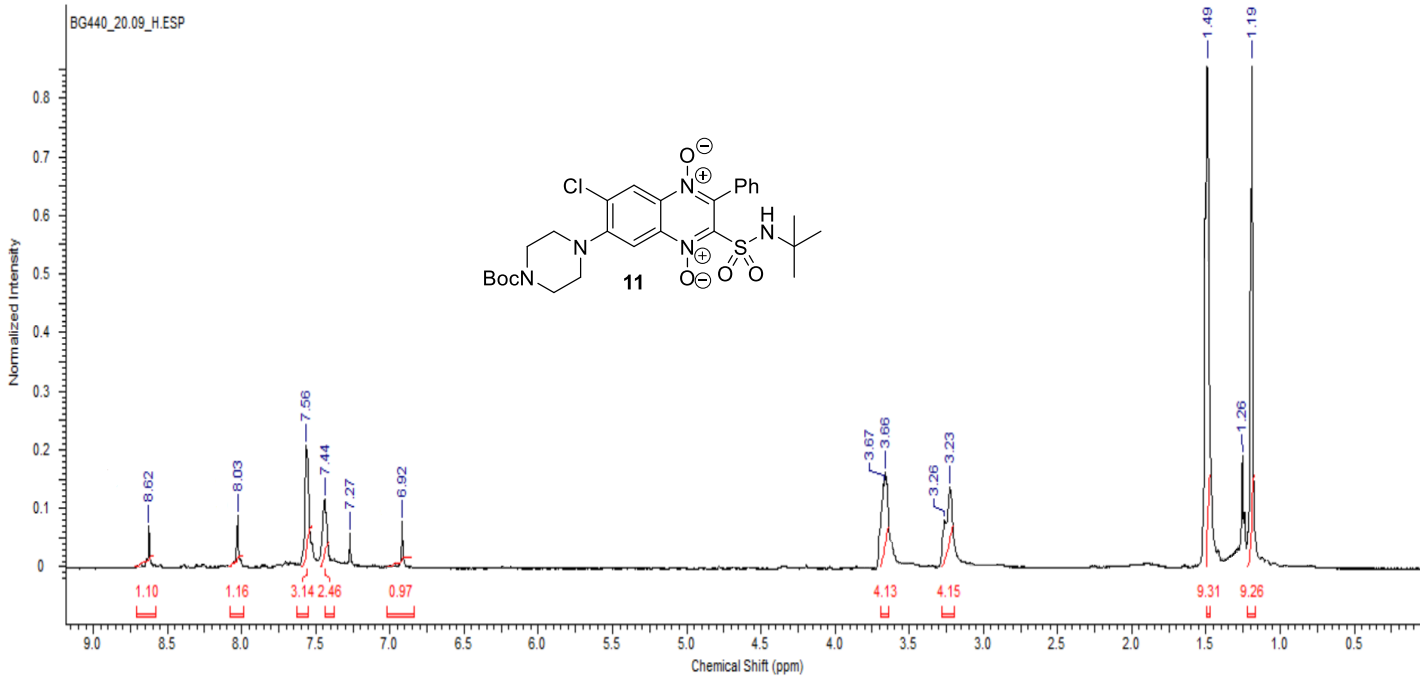


Figure S12. Copy of ^{13}C NMR spectrum of the derivative **11**.

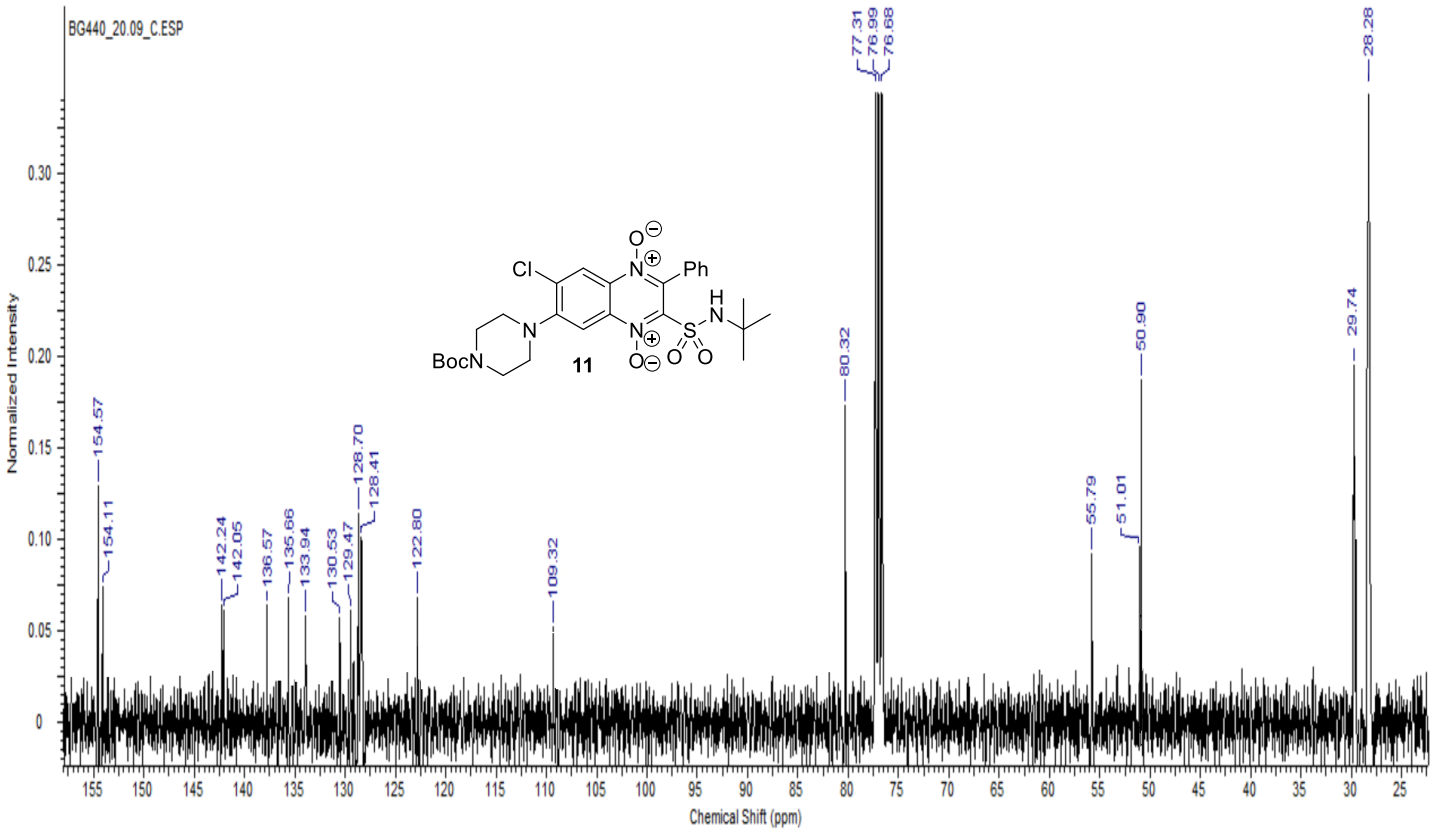


Figure S13. Copy of ^{1}H NMR spectrum of the derivative **12**·HCl.

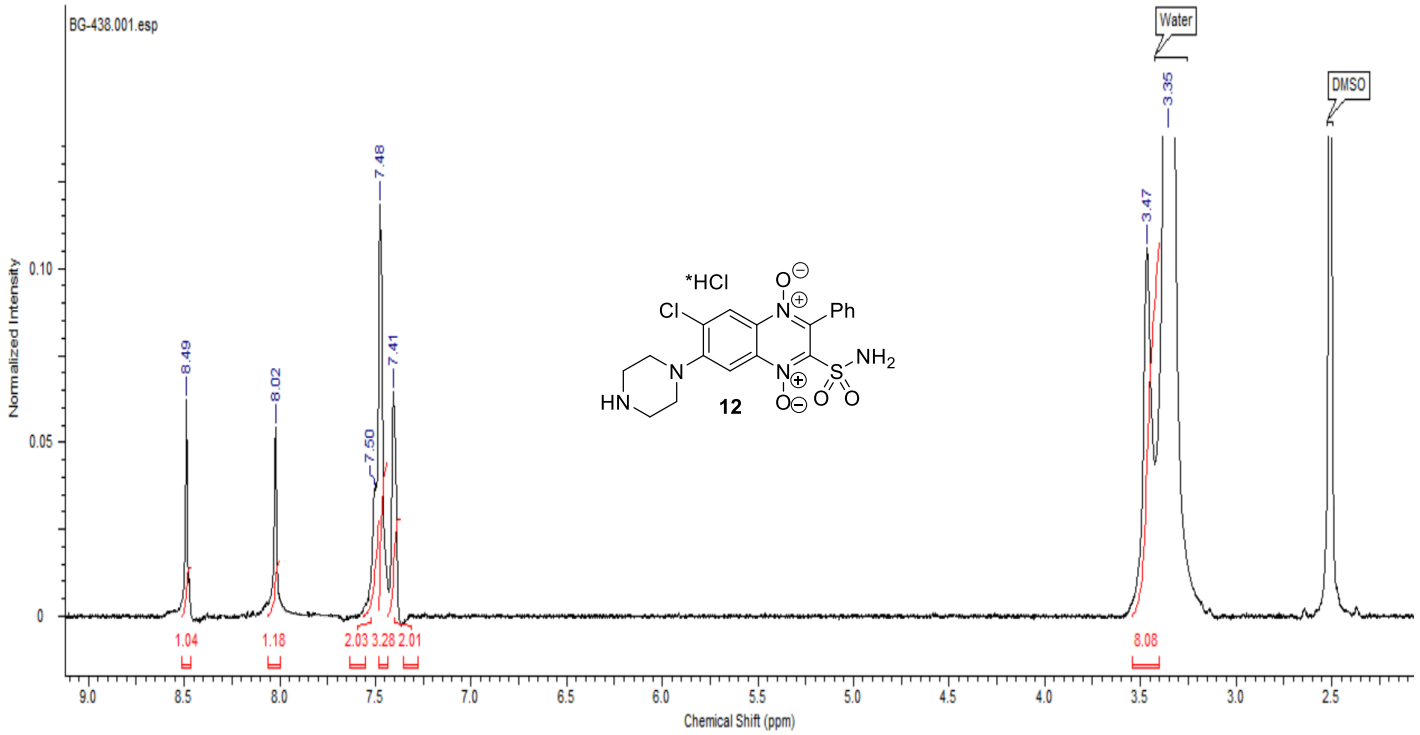
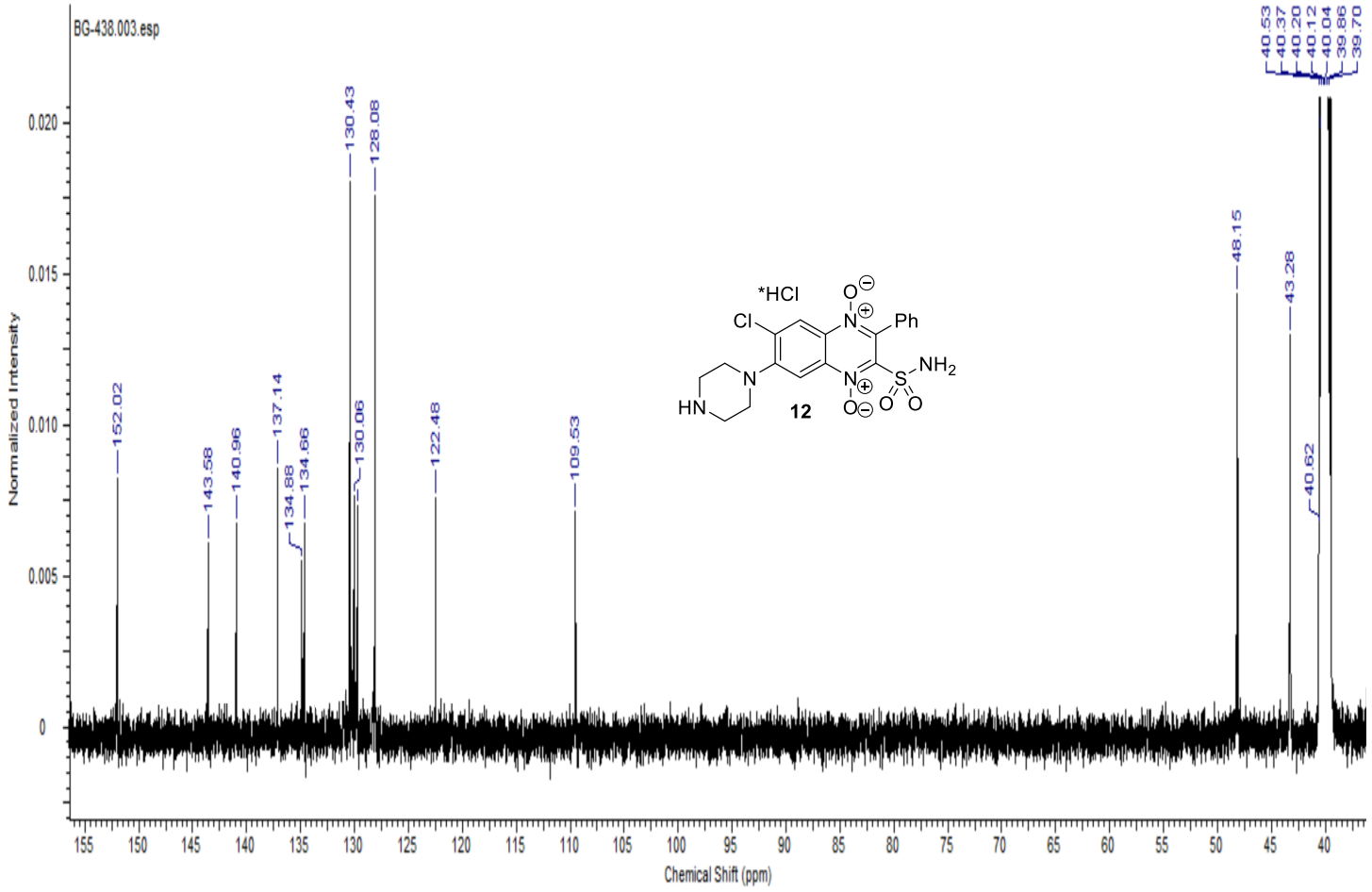
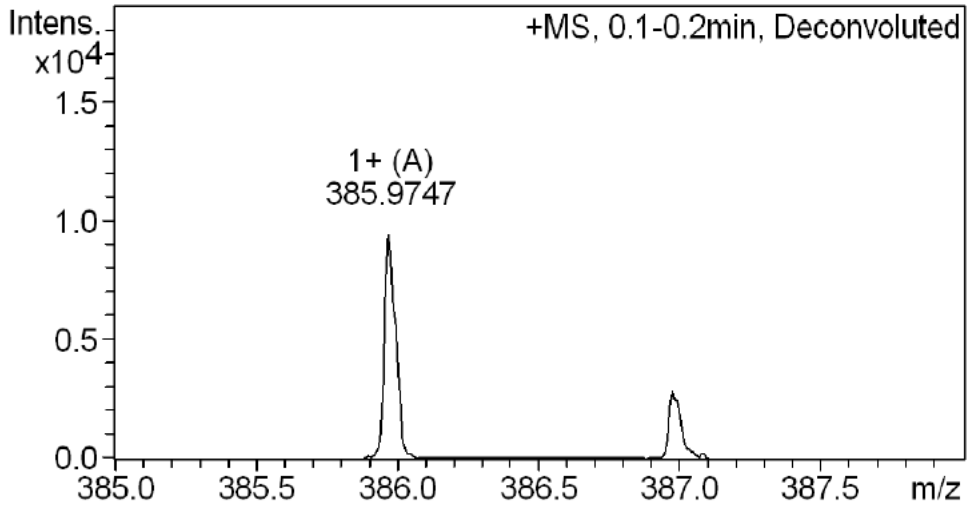


Figure S14. Copy of ^{13}C NMR spectrum of the derivative **12**·HCl.



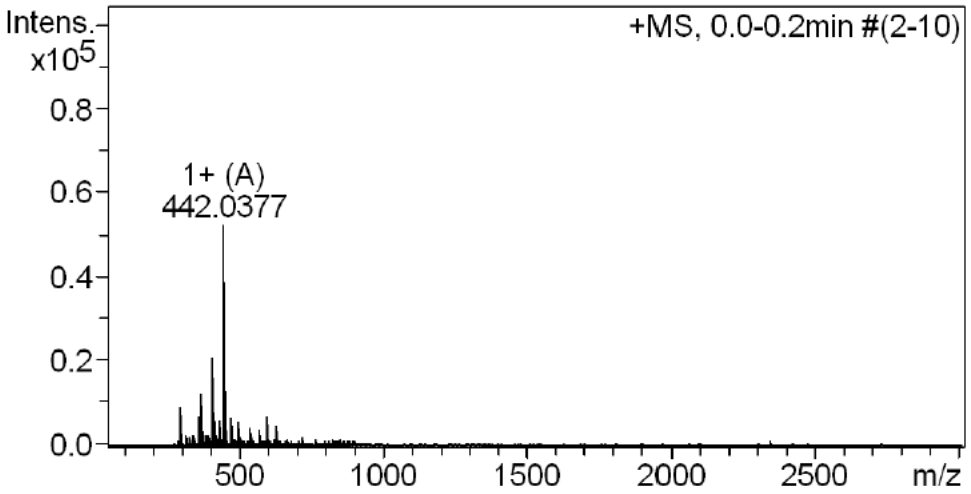
Copies of HRMS ESI Analysis

Figure S15. Copy of HRMS ESI analysis of the derivatives **6**.



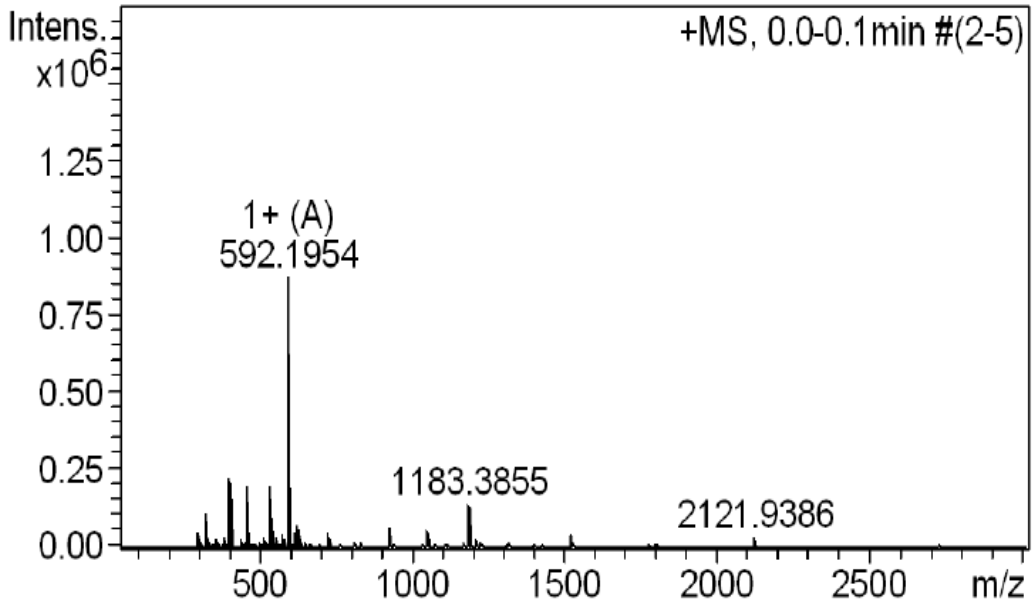
#	m/z	Res.	S/N	I	I %
1	385.9747			10327	100.0

Figure S16. Copy of HRMS ESI analysis of the derivatives **7**.



#	m/z	Res.	S/N	I	I %
1	294.0575	7121	213.3	8995	17.3
2	369.3825	7791	198.0	12095	23.2
3	402.6201	7924	291.4	20711	39.7
4	403.1224	8163	129.0	9213	17.7
5	415.2105	7928	101.2	7614	14.6
6	442.0377	8455	628.9	52109	100.0
7	443.0408	8484	136.9	11436	21.9
8	444.0355	8280	433.9	36231	69.5
9	445.0374	8471	92.8	7833	15.0
10	446.0333	8382	91.8	7779	14.9

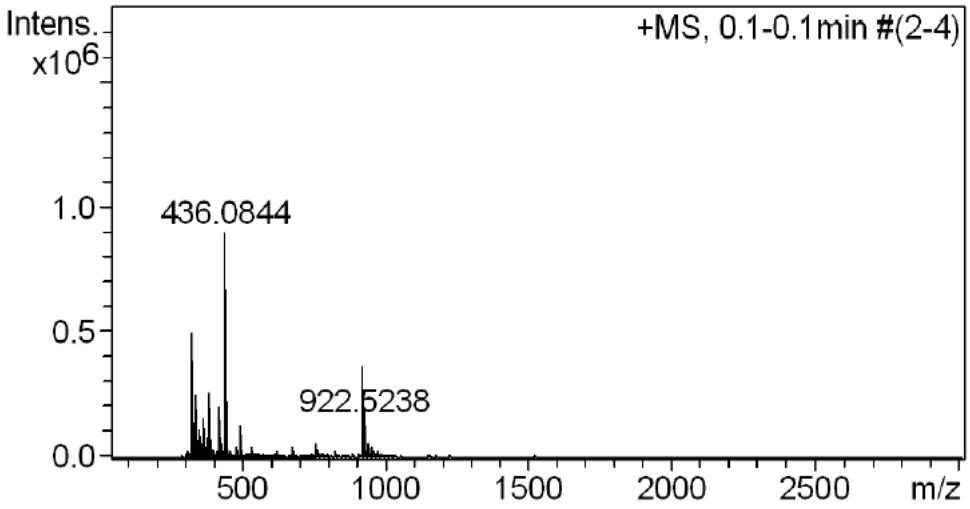
Figure S17. Copy of HRMS ESI analysis of the derivatives **8**.



#	m/z	Res.	S/N	I	I %
1	326.1001	5327	1054.4	107514	12.4
2	401.0973	5312	1196.4	217397	25.0
3	457.1583	5481	801.5	199283	22.9
4	536.1326	5604	574.1	196889	22.6
5	592.1954	5302	2882.2	870248	100.0
6	593.1970	5828	1060.7	319708	36.7
7	594.1923	5756	1365.3	410318	47.1
8	595.1940	5731	396.4	119132	13.7
9	1183.3855	6659	655.2	136516	15.7
10	1185.3824	6651	630.4	130608	15.0

Figure S18. Copy of HRMS ESI analysis of the derivative **9**·HCl.

+MS, 0.1-0.1min #(2-4)

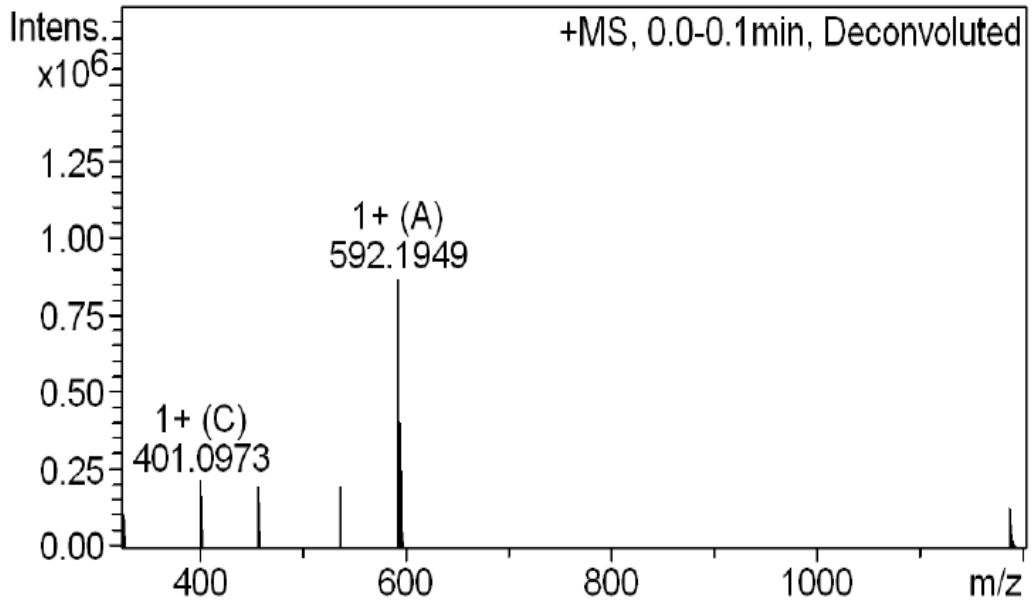


#	m/z	Res.	S/N	I	I %
1	326.1026	5271	1404.9	493842	55.0
2	338.3409	5397	655.0	245498	27.3
3	361.2214	5283	405.1	156368	17.4
4	383.2033	5422	655.7	257200	28.6
5	420.0876	5657	504.7	203651	22.7
6	436.0844	5033	2205.1	898517	100.0
7	437.0849	5619	567.0	231585	25.8
8	438.0806	5480	965.6	394338	43.9
9	492.1442	6066	296.7	126444	14.1
10	922.5238	6518	253.4	150534	16.8

Figure S19. Copy of HRMS ESI analysis of the derivatives **10**.

#	m/z	Res.	S/N	I	I %
1	355.1155			69565	100.0
2	357.1136			25547	36.7
3	374.1391			24889	35.8
4	377.0968			16095	23.1

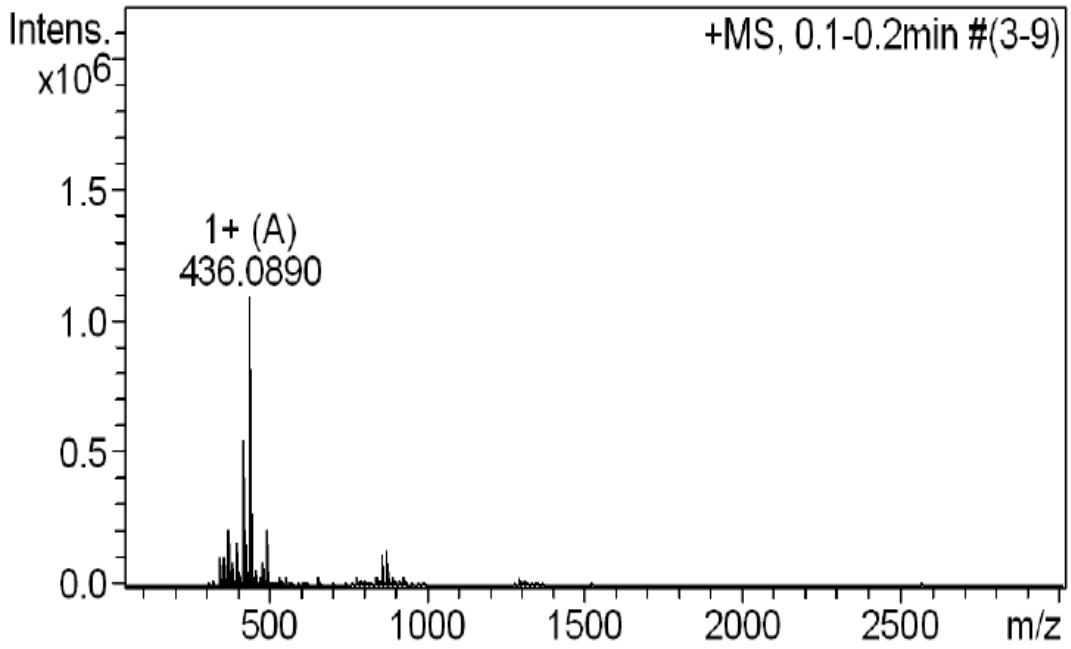
Figure S20. Copy of HRMS ESI analysis of the derivatives **11**.



#	m/z	Res.	S/N	I	I %
1	326.0999			107513	12.4
2	401.0973			217396	25.0
3	457.1580			199282	22.9
4	536.1319			196888	22.6
5	592.1949			870247	100.0
6	594.1914			410317	47.1
7	1185.3793			130608	15.0

Figure S21. Copy of HRMS ESI analysis of the derivatives **12**·HCl.

+MS, 0.1-0.2min #(3-9)



#	m/z	Res.	S/N	I	I %
1	369.1501	5454	915.4	212324	19.4
2	399.1637	5319	669.8	158063	14.4
3	420.0935	5347	2311.5	551341	50.4
4	421.0954	5555	549.4	131315	12.0
5	422.0896	5587	890.3	212755	19.4
6	436.0890	4764	4551.9	1094968	100.0
7	437.0895	5616	1360.4	327641	29.9
8	438.0849	5430	2312.5	557028	50.9
9	492.1494	5841	840.8	208749	19.1
10	871.1710	6345	404.1	127764	11.7