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Synthesis of 3-acylindolizines based on β-nitro-substituted benzochromenes and carbonyl-stabilized pyridinium ylides

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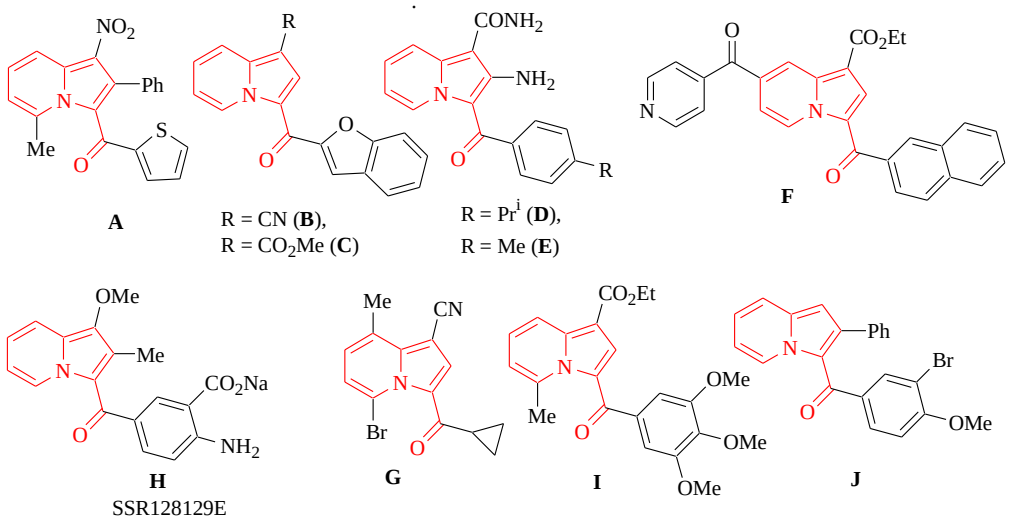
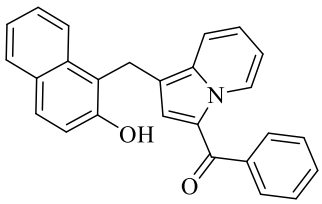


Figure S1 Biologically active 3-acylindolizines. Compound **A** demonstrated diverse pharmacological properties, including antibacterial.[S1] Compounds **B** and **C** showed anticonvulsant and anti-inflammatory effects.[S2] Compounds of type **D** showed antitubercular,[S3] **E** antimalarial[S4] and **F** anti-HIV[S5] activities. One of the most studied aspects of indolizine biological activity is their antitumor potential (compounds **G–J**).[S6]–[S10]

Solvents were purified and dried by standard procedures before use. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively), as well as DEPT-135 spectra were acquired on a JEOL JNM-ECX400 spectrometer in DMSO-d_6 using residual solvent signal (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei) as internal standard. Chemical shifts are reported in δ unit-parts per million (ppm). Splitting patterns are designated as s = singlet; br. s = broad singlet; d = doublet, t = triplet; m = multiplet. Elemental analysis was performed on a Euro Vector EA-3000 CHNS-analyzer. Melting points were determined by the capillary method on an SRS OptiMelt MPA100 apparatus. The starting 2-nitro-1*H*-benzochromenes **1a**–**c**[S11] and 3-nitro-4*H*-benzo[*h*]chromene **1d**[S12] were synthesized according to previously developed procedures.

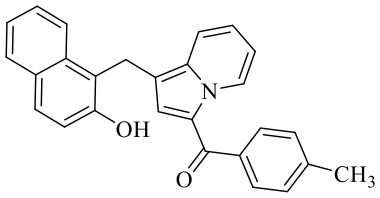
Synthesis of 3-acylindolizines 3a–h (general procedure). To a suspension of 2-nitro-1*H*-benzo[*f*]chromene **1a**–**c** or 3-nitro-4*H*-benzo[*h*]chromene **1d** (0.5 mmol) and pyridinium salt **2a**–**e** (0.5 mmol) MeCN (4 ml), DABCO (112 mg, 1 mmol) was added with stirring, the reaction mixture was stirred for 1 h, the precipitate was filtered off, washed with MeCN, and dried in air. The obtained zwitterionic salt **A** was dissolved in a hot DMF–MeOH mixture (1:5), then the solution was slowly cooled to room temperature and kept at –30°C for 1 h. The precipitated solid was filtered off, washed with ice-cold MeOH, and dried in air to afford products **3**.

{1-[(2-Hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}(phenyl)methanone (3a).



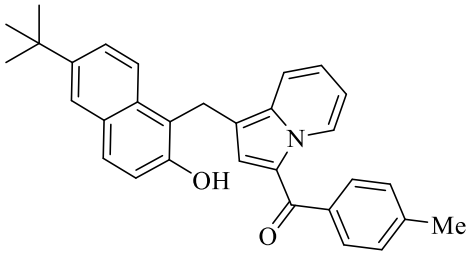
Yield 132 mg (70%), yellow crystals, mp 214–215°C (dec.). IR spectrum, ν, cm^{-1}: 3100–2800 (OH), 1524, 1471, 1429, 1350, 1207, 1200, 1142, 1080, 997, 831, 767, 710. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.47 (2H, s, CH_2); 7.02 (1H, s, H-2); 7.06 (1H, dd, *J* = 7.1, *J* = 1.1, H Ar); 7.20–7.25 (2H, m, H Ar); 7.28–7.46 (4H, m, H Ar); 7.50–7.54 (1H, m, H Ar); 7.58–7.61 (2H, m, H Ar); 7.66 (1H, d, *J* = 8.7, H Ar); 7.74 (1H, d, *J* = 7.8, H Ar); 7.94 (1H, d, *J* = 8.5, H Ar); 8.03 (1H, d, *J* = 8.8, H Ar); 9.80 (1H, d, *J* = 6.9, H-5); 9.87 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 14.6 (CH_2); 108.4 (CH); 110.2 (C); 111.6 (C); 111.7 (CH); 112.2 (CH); 114.4 (C); 116.4 (CH); 117.2 (CH); 118.3 (CH); 119.7 (CH); 120.2 (CH); 121.8 (CH); 121.9 (CH); 122.3 (2CH); 122.4 (C); 122.5 (CH); 122.6 (2CH); 124.9 (CH); 127.3 (C); 131.0 (C); 134.5 (C); 146.3 (C–O); 176.7 (C=O). Found, %: C 82.70; H 5.10; N 3.64. $C_{26}H_{19}NO_2$. Calculated, %: C 82.74; H 5.07; N 3.71.

{1-[(2-Hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}(*p*-tolyl)methanone (3b).



Yield 150 mg (76%), yellow crystals, mp 190–193°C (dec.). IR spectrum, ν, cm^{-1}: 3100–2800 (OH), 1522, 1472, 1433, 1350, 1211, 1198, 1146, 1084, 999, 926, 829, 770, 712. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 4.43 (2H, s, CH_2); 6.98–7.03 (2H, m, H-2, H Ar); 7.18–7.22 (4H, m, H Ar); 7.24–7.28 (1H, m, H Ar); 7.31–7.34 (1H, m, H Ar); 7.46 (2H, d, *J* = 8.0, H *p*-tolyl); 7.62 (1H, d, *J* = 8.9, H Ar); 7.70 (1H, d, *J* = 8.0, H Ar); 7.90 (1H, d, *J* = 8.7, H Ar); 7.99 (1H, d, *J* = 8.9, H Ar); 9.73 (1H, d, *J* = 6.9, H-5); 9.82 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_3); 21.5 (CH_2); 114.7 (CH); 116.4 (C); 118.0 (C); 118.1 (CH); 118.7 (CH); 120.8 (C); 122.8 (CH); 123.6 (CH); 124.5 (CH); 125.8 (CH); 126.6 (CH); 128.2 (CH); 128.3 (CH); 128.8 (C); 128.9 (CH); 129.1 (2CH *p*-tolyl); 129.3 (2CH *p*-tolyl); 133.7 (C); 137.2 (C); 138.2 (C); 141.4 (C); 152.7 (C–O); 183.0 (C=O). Found, %: C 82.76, H 5.39, N 3.67. $C_{27}H_{21}NO_2$. Calculated, %: C 82.84, H 5.41, N 3.58.

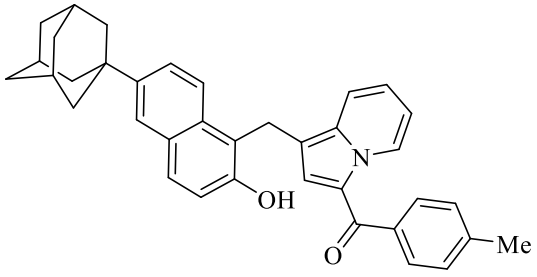
{1-[(6-*tert*-Butyl-2-hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}(*p*-tolyl)methanone (3c).



Yield 130 mg (58%), yellow crystals, mp 229–231°C (dec.). IR spectrum, ν, cm^{-1}: 3400–2800 (OH), 2961 (CH *t*-Bu), 1610, 1578, 1541, 1510, 1470, 1454, 1439, 1423, 1364, 1342, 1298, 1258, 1242, 1182, 1146, 1136, 1090, 1049, 1018, 989, 883, 820, 750, 704. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (9H, s, *t*-Bu); 2.31 (3H, s, CH_3); 4.40 (2H, s, CH_2); 6.98 (1H, s, H-2); 6.99–7.03 (1H, m, H Ar); 7.15 (1H, d, *J* = 8.9, H Ar); 7.20 (2H, d, *J* = 8.0, H *p*-tolyl); 7.24–7.28 (1H, m, H Ar); 7.42 (1H, dd, *J* = 9.1,

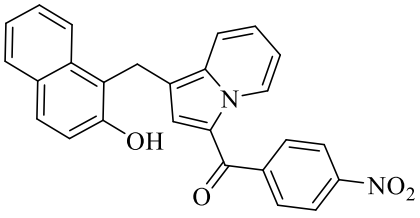
J = 1.8, H Ar); 7.47 (2H, d, *J* = 8.0, H *p*-tolyl); 7.57–7.61 (2H, m, H Ar); 7.81 (1H, d, *J* = 9.1, H Ar); 7.98 (1H, d, *J* = 8.9, H-5); 9.68 (1H, s, OH); 9.74 (1H, d, *J* = 7.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_2); 21.5 (CH_3); 31.5 ($C(\underline{C}H_3)_3$); 34.7 ($\underline{C}(CH_3)_3$); 114.7 (CH); 116.5 (C); 117.8 (C); 118.1 (CH); 118.5 (CH); 120.8 (C); 123.5 (CH); 123.7 (CH); 124.5 (CH); 125.3 (CH); 125.9 (CH); 128.2 (CH); 128.3 (CH); 128.7 (C); 129.19 (2CH *p*-tolyl); 129.25 (2CH *p*-tolyl); 131.9 (C); 137.1 (C); 138.2 (C); 141.4 (C); 144.8 (C); 152.2 (C–O); 183.0 (C=O). Found, %: C 83.27, H 6.57, N 3.04. $C_{31}H_{29}NO_2$. Calculated, %: C 83.19, H 6.53, N 3.13.

(1-{[6-(Adamantan-1-yl)-2-hydroxynaphthalen-1-yl]methyl}indolizin-3-yl)(*p*-tolyl)methanone (3d).



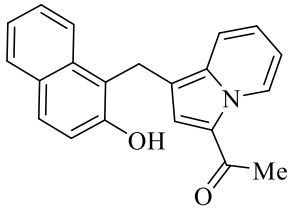
Yield 165 mg (63%), yellow crystals, mp 241–243°C (dec.). IR spectrum, ν, cm^{-1}: 3383 (OH), 2903 (CH Ad), 2845 (CH Ad), 1611, 1587, 1558, 1467, 1449, 1423, 1373, 1346, 1230, 1204, 1180, 1144, 1018, 887, 877, 831, 818, 789, 743. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67 (6H, br. s, CH_2 Ad); 1.83 (6H, br. s, CH_2 Ad); 1.99 (3H, br. s, CH Ad); 2.30 (3H, s, CH_3); 4.39 (2H, s, CH_2); 6.98–7.01 (2H, m, H-2, H Ar); 7.18–7.26 (4H, m, H Ar); 7.39–7.57 (5H, m, H Ar); 7.80 (1H, d, *J* = 8.5, H Ar); 7.97 (1H, d, *J* = 8.2, H Ar); 9.72 (1H, d, *J* = 6.9, H-5); 9.78 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_2); 21.5 (CH_3); 28.8 (3CH Ad); 36.0 (C Ad); 36.8 (3CH_2 Ad); 43.1 (3CH_2 Ad); 114.7 (CH); 116.6 (C); 117.7 (C); 118.1 (CH); 118.5 (CH); 120.8 (C); 123.5 (CH); 123.6 (CH); 124.4 (CH); 124.6 (CH); 125.9 (CH); 128.1 (CH); 128.3 (CH); 128.8 (C); 129.2 (2CH *p*-tolyl); 129.3 (2CH *p*-tolyl); 132.0 (C); 137.1 (C); 138.2 (C); 141.3 (C); 145.1 (C); 152.2 (C–O); 183.0 (C=O). Found, %: C 84.62, H 6.75, N 2.59. $C_{37}H_{35}NO_2$. Calculated, %: C 84.54, H 6.71, N 2.66.

{1-[(2-Hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}(4-nitrophenyl)methanone (3e).



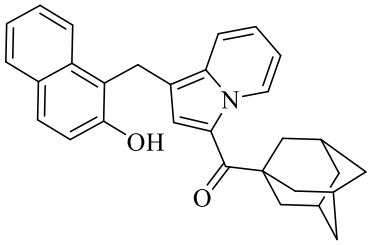
Yield 155 mg (73%), yellow crystals, mp 232–234°C (dec.). IR spectrum, ν, cm^{-1}: 3400–3000 (OH), 1624, 1603, 1558, 1539, 1514, 1472, 1437, 1379, 1202, 1167, 1152, 1123, 1080, 1055, 930, 854, 820, 810, 748, 710, 680. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.42 (2H, s, CH_2); 7.04 (1H, s, H-2); 7.08–7.11 (1H, m, H Ar); 7.15–7.19 (1H, m, H Ar); 7.25 (1H, d, *J* = 8.9, H Ar); 7.30–7.36 (2H, m, H Ar); 7.61 (1H, d, *J* = 8.9, H Ar); 7.69 (1H, d, *J* = 7.6, H Ar); 7.80 (2H, d, *J* = 8.7, H nitrophenyl); 7.90 (1H, d, *J* = 8.5, H Ar); 8.02 (1H, d, *J* = 8.9, H Ar); 8.25 (2H, d, *J* = 8.7, H nitrophenyl); 9.78 (1H, d, *J* = 7.1, H-5); 10.00 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_2); 115.5 (CH); 117.6 (C); 117.7 (C); 118.3 (CH); 118.8 (CH); 120.5 (C); 122.8 (CH); 123.6 (2CH nitrophenyl); 124.0 (CH); 125.7 (CH); 126.3 (CH); 126.6 (CH); 128.4 (C); 128.5 (CH); 128.8 (C); 128.9 (CH); 130.2 (2CH nitrophenyl); 133.7 (C); 138.2 (C); 146.5 (C); 149.0 (C); 152.8 (C–O); 180.6 (C=O). Found, %: C 37.81, H 4.27, N 6.76. $C_{26}H_{18}N_2O_4$. Calculated, %: C 37.92, H 4.30, N 6.63.

{1-[(2-Hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}ethan-1-one (3f).



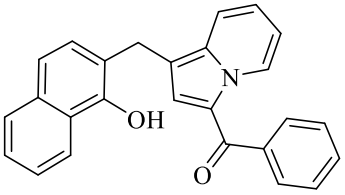
Yield 130 mg (83%), colorless crystals, mp 225–227°C (dec.). IR spectrum, ν, cm^{-1}: 3200–2800 (OH), 1628, 1559, 1510, 1472, 1443, 1433, 1356, 1342, 1327, 1296, 1256, 1244, 1231, 1136, 1125, 1070, 1055, 1024, 1011, 982, 934, 855, 814, 791, 754, 746, 739. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 4.42 (2H, s, CH_2); 6.92 (1H, td, *J* = 6.9, *J* = 1.2, H Ar); 7.14–7.22 (2H, m, H Ar); 7.24 (1H, d, *J* = 8.9, H Ar); 7.28 (1H, s, H-2); 7.32–7.36 (1H, m, H Ar); 7.65 (1H, d, *J* = 8.7, H Ar); 7.73 (1H, d, *J* = 7.8, H Ar); 7.91–7.94 (2H, m, H Ar); 9.64 (1H, d, *J* = 7.1, H-5); 9.85 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_2); 27.4 (CH_3); 114.4 (CH); 115.8 (C); 118.0 (CH); 118.1 (C); 118.8 (CH); 121.2 (C); 122.8 (CH); 123.5 (CH); 123.6 (2CH); 126.7 (CH); 127.8 (CH); 128.3 (CH); 128.9 (C, CH); 133.8 (C); 136.4 (C); 152.8 (C–O); 185.8 (C=O). Found, %: C 79.87, H 5.40, N 4.56. $C_{21}H_{17}NO_2$. Calculated, %: C 79.98, H 5.43, N 4.44.

(Adamantan-1-yl){1-[(2-hydroxynaphthalen-1-yl)methyl]indolizin-3-yl}methanone (3g).



Yield 155 mg (71%), colorless crystals, mp 232–235°C (dec.). IR spectrum, ν, cm^{-1}: 3400–3000 (OH), 2924, 2905, 2884, 2847 (CH Ad), 1628, 1562, 1506, 1462, 1435, 1366, 1339, 1296, 1250, 1209, 1136, 1040, 1030, 976, 907, 816, 741. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60–1.68 (6H, m, CH_2 Ad); 1.90 (6H, br. s, CH_2 Ad); 1.94 (3H, br. s, CH Ad); 4.45 (2H, s, CH_2); 6.85–6.89 (1H, m, H Ar); 7.10–7.14 (1H, m, H Ar); 7.18–7.23 (2H, m, H Ar); 7.32–7.36 (1H, m, H Ar); 7.64 (1H, d, *J* = 8.9, H Ar); 7.64 (1H, d, *J* = 8.9, H Ar); 7.67 (1H, s, H-2); 7.73 (1H, d, *J* = 8.0, H Ar); 7.89 (1H, d, *J* = 8.9, H Ar); 8.07 (1H, d, *J* = 8.5, H Ar); 9.74 (1H, d, *J* = 7.3, H-5); 9.86 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_2); 28.5 (3CH Ad); 36.8 ($3CH_2$ Ad); 40.51 ($3CH_2$ Ad); 46.2 (C Ad); 114.2 (CH); 115.2 (C); 117.8 (CH); 118.5 (C); 118.7 (CH); 122.8 (CH); 123.3 (CH); 123.8 (CH); 124.0 (CH); 126.4 (CH); 128.27 (CH); 128.33 (CH); 128.8 (CH, C); 133.7 (C); 135.2 (C); 152.5 (C–O); 194.4 (C=O). Found, %: C 82.79, H 6.73, N 3.16. $C_{30}H_{29}NO_2$. Calculated, %: C 82.73, H 6.71, N 3.22.

{1-[(1-Hydroxynaphthalen-2-yl)methyl]indolizin-3-yl}(phenyl)methanone (3h).



Yield 130 mg (69%), yellow crystals, mp 299–301°C (dec.). IR spectrum, ν, cm^{-1}: 3100–2800 (OH), 1531, 1469, 1420, 1348, 1203, 1205, 1139, 1077, 997, 830, 767. 1H NMR spectrum, δ, ppm (*J*, Hz): 3.32 (2H, s, CH_2); 6.92 (1H, d, *J* = 8.5, H Ar); 7.32 (1H, d, *J* = 8.5, H Ar); 7.39–7.44 (2H, m, H Ar); 7.52–7.67 (6H, m, H Ar); 7.77–7.92 (1H, m, H Ar); 8.06–8.08 (1H, m, H Ar); 8.30 (1H, t, *J* = 7.9, H

Ar); 8.69–8.73 (3H, m, H Ar); 8.83 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_2); 113.1 (CH); 113.4 (C); 113.5 (C); 114.5 (C); 115.6 (CH); 118.7 (C); 118.8 (CH); 119.2 (CH); 119.6 (CH); 120.9 (2CH); 121.5 (CH); 122.3 (2CH); 122.4 (C); 122.5 (2CH); 124.3 (CH); 126.9 (CH); 129.0 (C); 133.6 (C); 139.2 (CH); 142.2 (CH); 143.2 (C–O); 179.1 (C=O). Found, %: C 82.77; H 5.02; N 3.69. $C_{26}H_{19}NO_2$. Calculated, %: C 82.74; H 5.07; N 3.71.

References

[S1] E. S. Darwish, *Molecules*, 2008, **13**, 1066; https://doi.org/10.3390/molecules13051066.

[S2] Y. M. Shen, P. C. Lv, W. Chen, P. G. Liu, M. Z. Zhang and H. L. Zhu, *Eur. J. Med. Chem.*, 2010, **45**, 3184; https://doi.org/10.1016/j.ejmech.2010.02.056.

[S3] O. Burastero, L. A. Defelipe, G. Gola, N. L. Tateosian, E. D. Lopez, C. B. Martinena, J. P. Arcon, M. D. Traian, D. E. Wetzler, I. Bento, X. Barril, J. Ramirez, M. A. Marti, M. M. Garcia-Alai and A. G. Turjanski, *J. Med. Chem*., 2022, **65**, 9691; https://doi.org/10.1021/acs.jmedchem.1c02012.

[S4] G. Lemercier, A. Fernandez-Montalvan, J. P. Shaw, D. Kugelstadt, J. Bomke, M. Domostoj, M. K. Schwarz, A. Scheer, B. Kappes and D. Leroy, *Biochemistry*, 2009, **48**, 6379; https://doi.org/10.1021/bi9005122.

[S5] W. Huang, T. Zuo, X. Luo, H. Jin, Z. Liu, Z. Yang, X. Yu, L. Zhang and L. Zhang, *Chem. Biol. Drug Des*., 2013, **81**, 730; https://doi.org/10.1111/cbdd.12119.

[S6] K. Dawood, H. Abdel-Gawad, M. Ellithey, H. A. Mohamed and B. Hegazi, *Arch. Pharm.*, 2006, **339**, 133; https://doi.org/10.1002/ardp.200500176.

[S7] A. V. Aksenov, N. A. Arutiunov, N. K. Kirilov, D. A. Aksenov, I. Yu. Grishin, N. A. Aksenov, H. Wang, L. Du, T. Betancourt, S. C. Pelly, A. Kornienko and M. Rubin, *Org. Biomol. Chem*., 2021, **19**, 7234; https://doi.org/10.1039/D1OB01141C.

[S8] F. Bono, F. De Smet, C. Herbert, K. De Bock, M. Georgiadou, P. Fons, M. Tjwa, C. Alcouffe, A. Ny, M. Bianciotto, B. Jonckx, M. Murakami, A. A. Lanahan, C. Michielsen, D. Sibrac, F. Dol-Gleizes, M. Mazzone, S. Zacchigna, J.-P. Herault, C. Fischer, P. Rigon, C. R. Almodovar, F. Claes, I. Blanc, K. Poesen, J. Zhang, I. Segura, G. Gueguen, M.-F. Bordes, D. Lambrechts, R. Broussy, M. van de Wouwer, C. Michaux, T. Shimada, I. Jean, S. Blacher, A. Noel, P. Motte, E. Rom, J.-M. Rakic, S. Katsuma, P. Schaeffer, A. Yayon, A. V. Schepdael, H. Schwalbe, F. L. Gervasio, G. Carmeliet, J. Rozensky, M. Dewerchin, M. Simons, A. Christopoulos, J.-M. Herbert and P. Carmeliet, *Cancer Cell*, 2013, **23**, 477; https://doi.org/10.1016/j.ccr.2013.02.019.

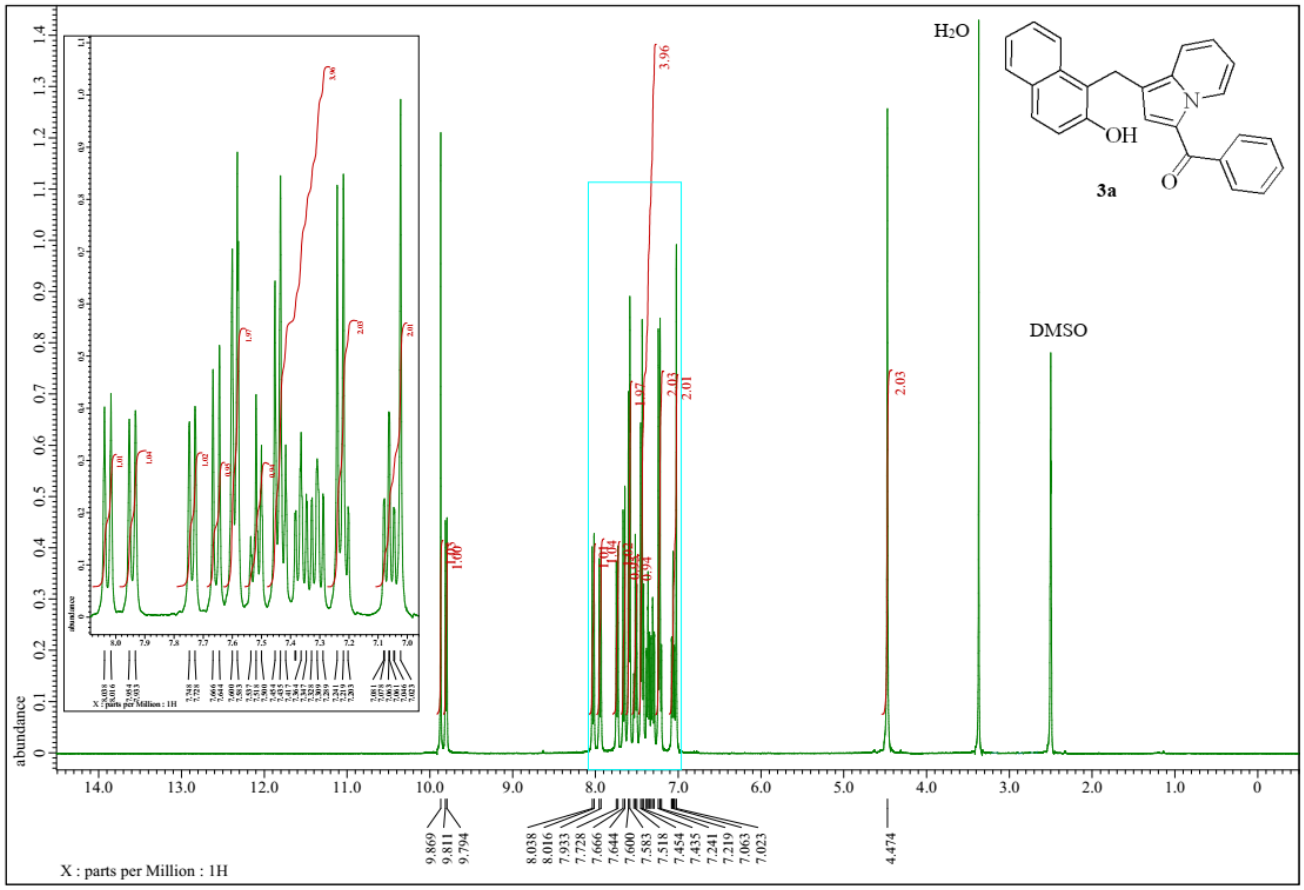
[S9] A. Ghinet, C. M. Abuhaie, P. Gautret, B. Rigo, J. Dubois, A. Farce, D. Belei and E. Bîcu, *Eur. J. Med. Chem.*, 2015, **89**, 115; https://doi.org/10.1016/j.ejmech.2014.10.041.

[S10] S.-H. Moon, Y. Jung, S. H. Kim and Y. Kim, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 110; https://doi.org/10.1016/j.bmcl.2015.11.021.

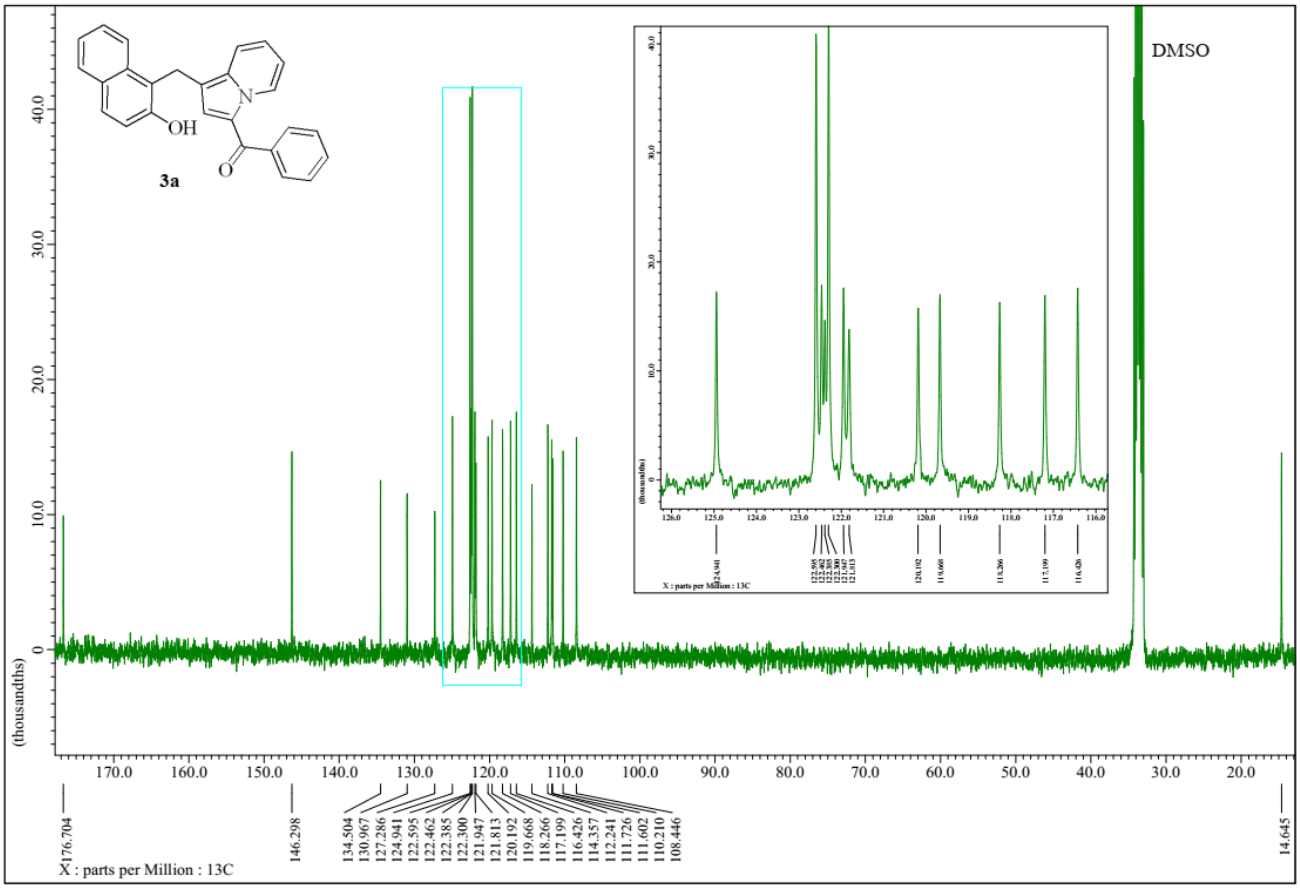
[S11] V. A. Osyanin, A. V. Lukashenko, D. V. Osipov and Yu. N. Klimochkin, *Chem. Heterocycl. Compd.*, 2015, **50**, 1528; https://doi.org/10.1007/s10593-014-1620-2.

[S12] D. V. Osipov, A. A. Artemenko, P. E. Krasnikov and V. A. Osyanin, *Chem. Heterocycl. Compd.*, 2023, **59**, 249; https://doi.org/10.1007/s10593-023-03189-9.

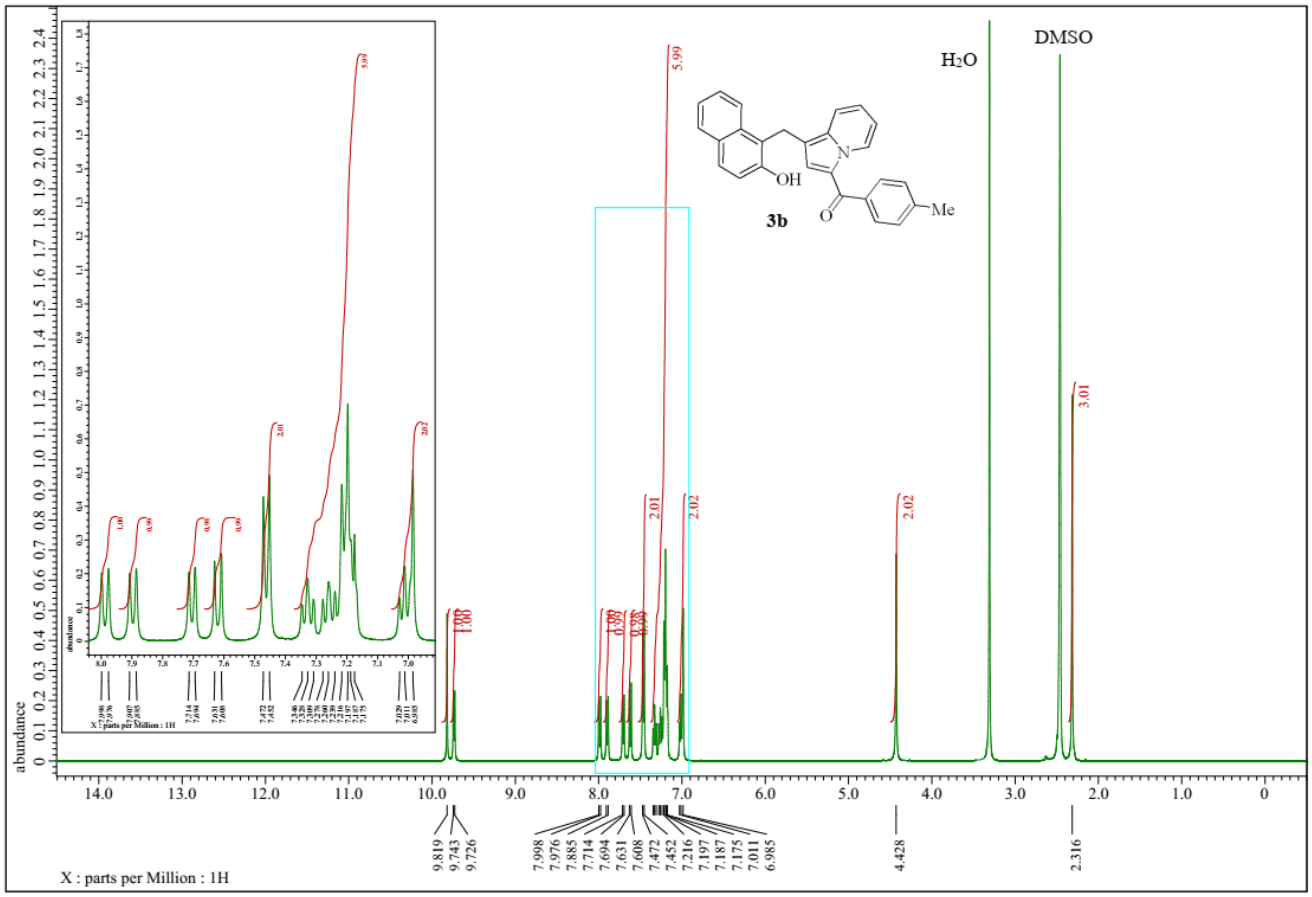
NMR ^{1}H



NMR ^{13}C



NMR ^{1}H



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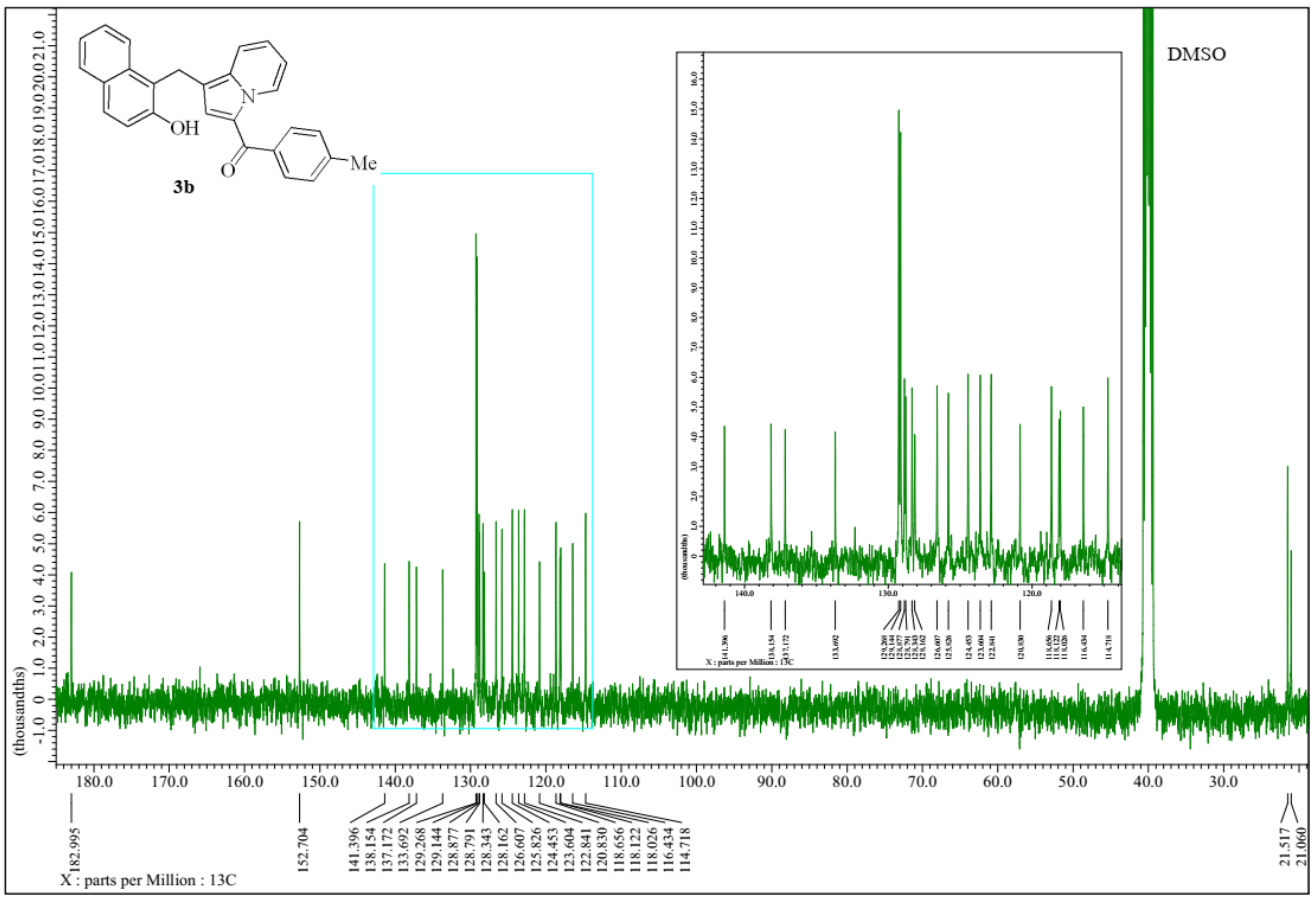

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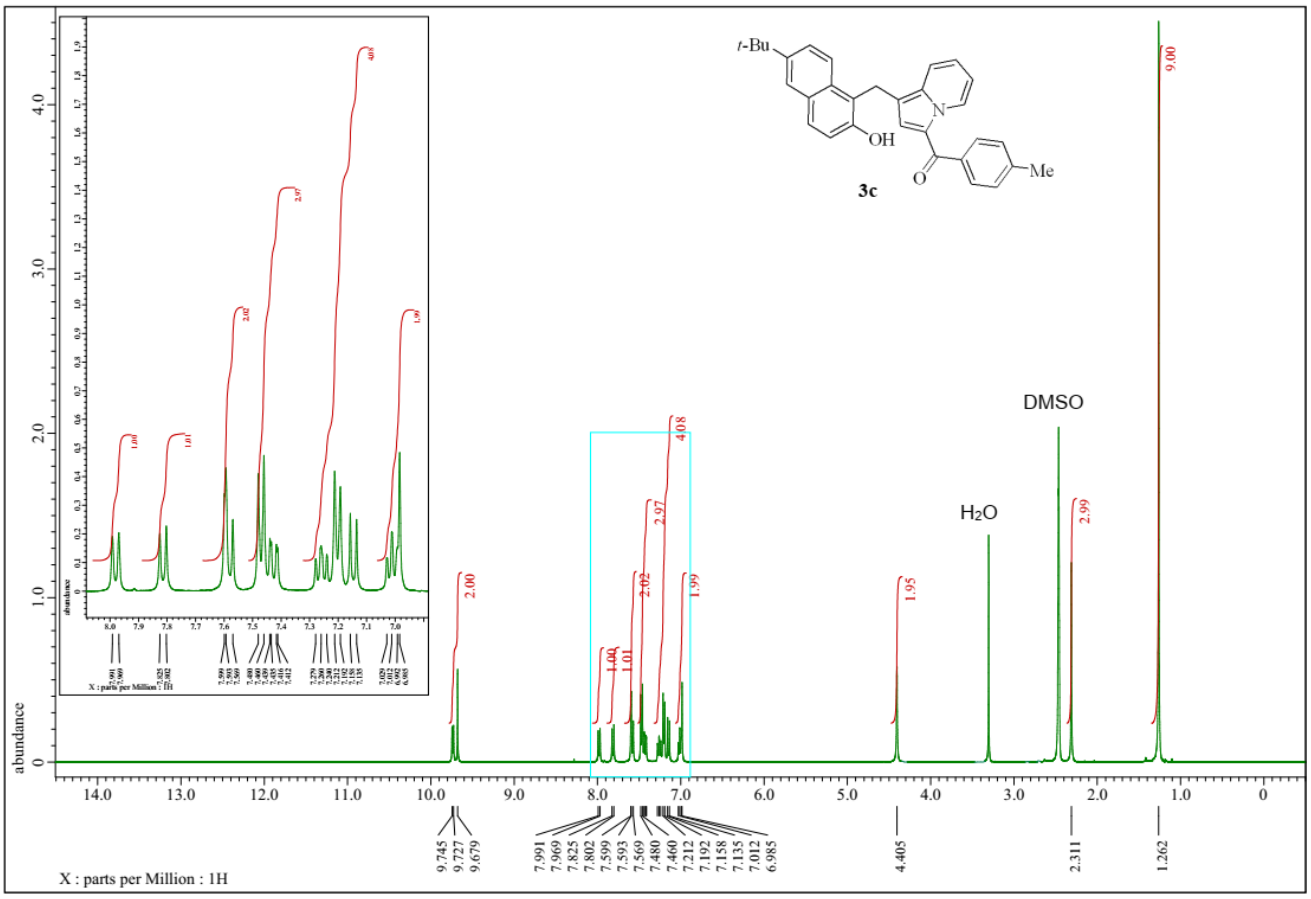

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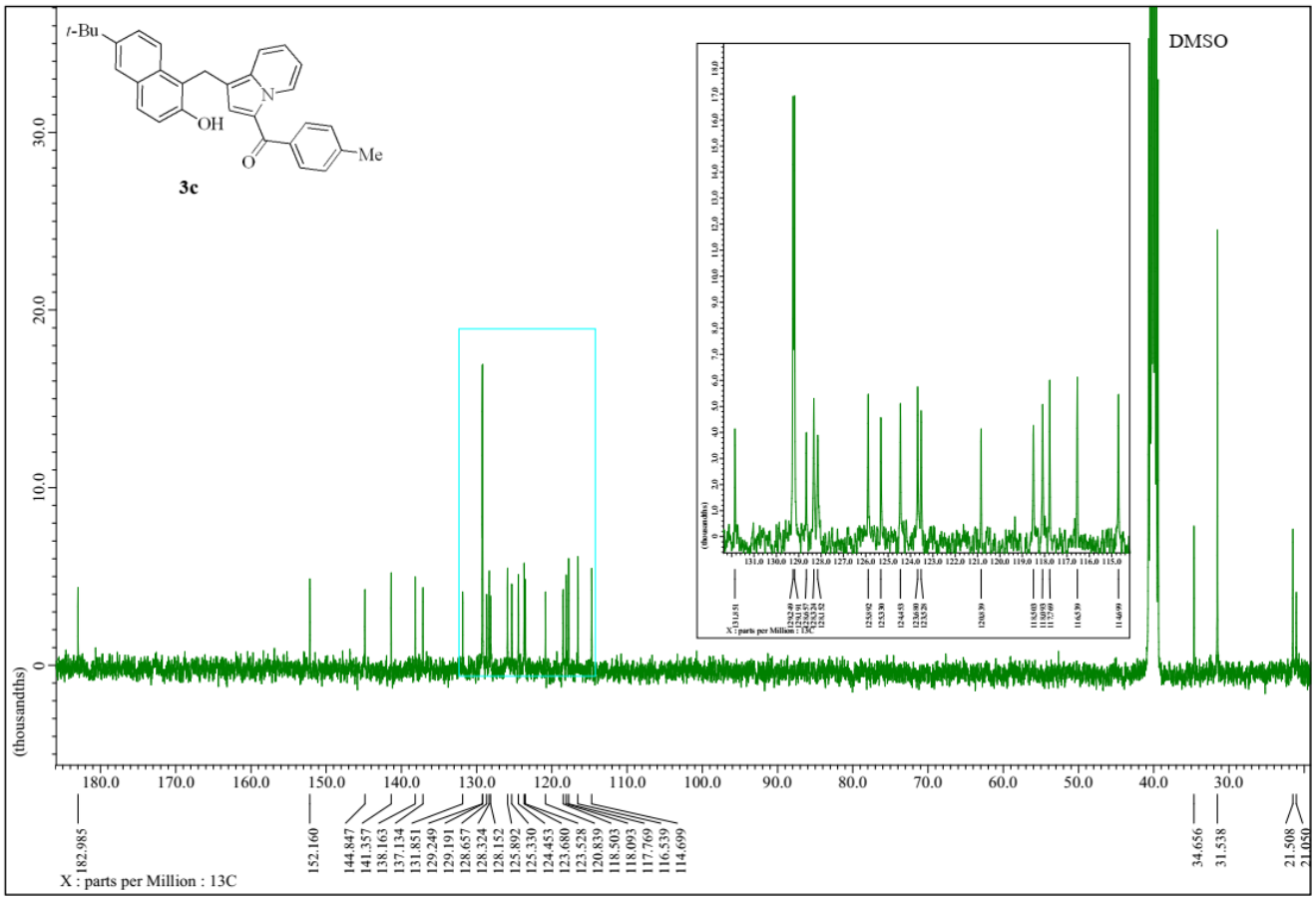

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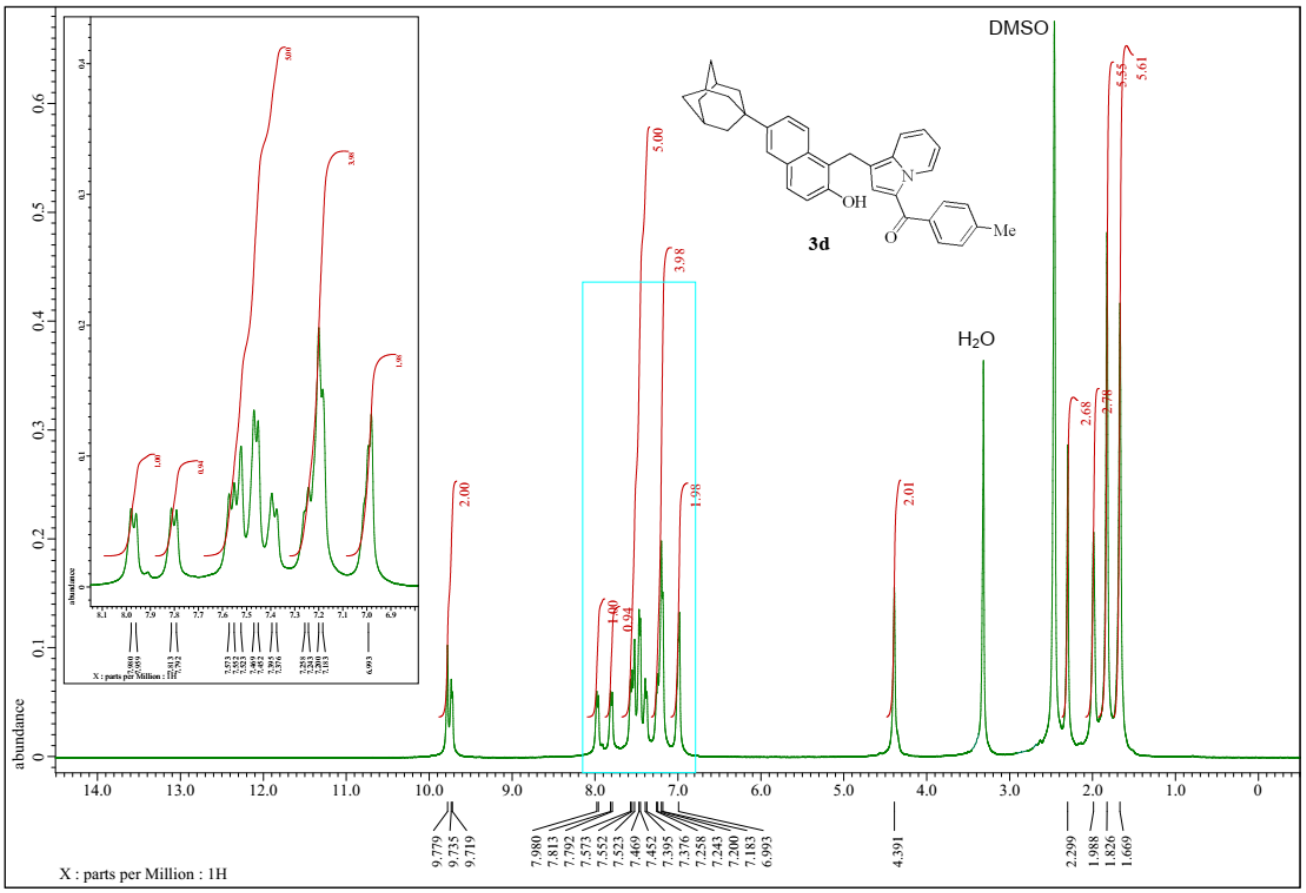

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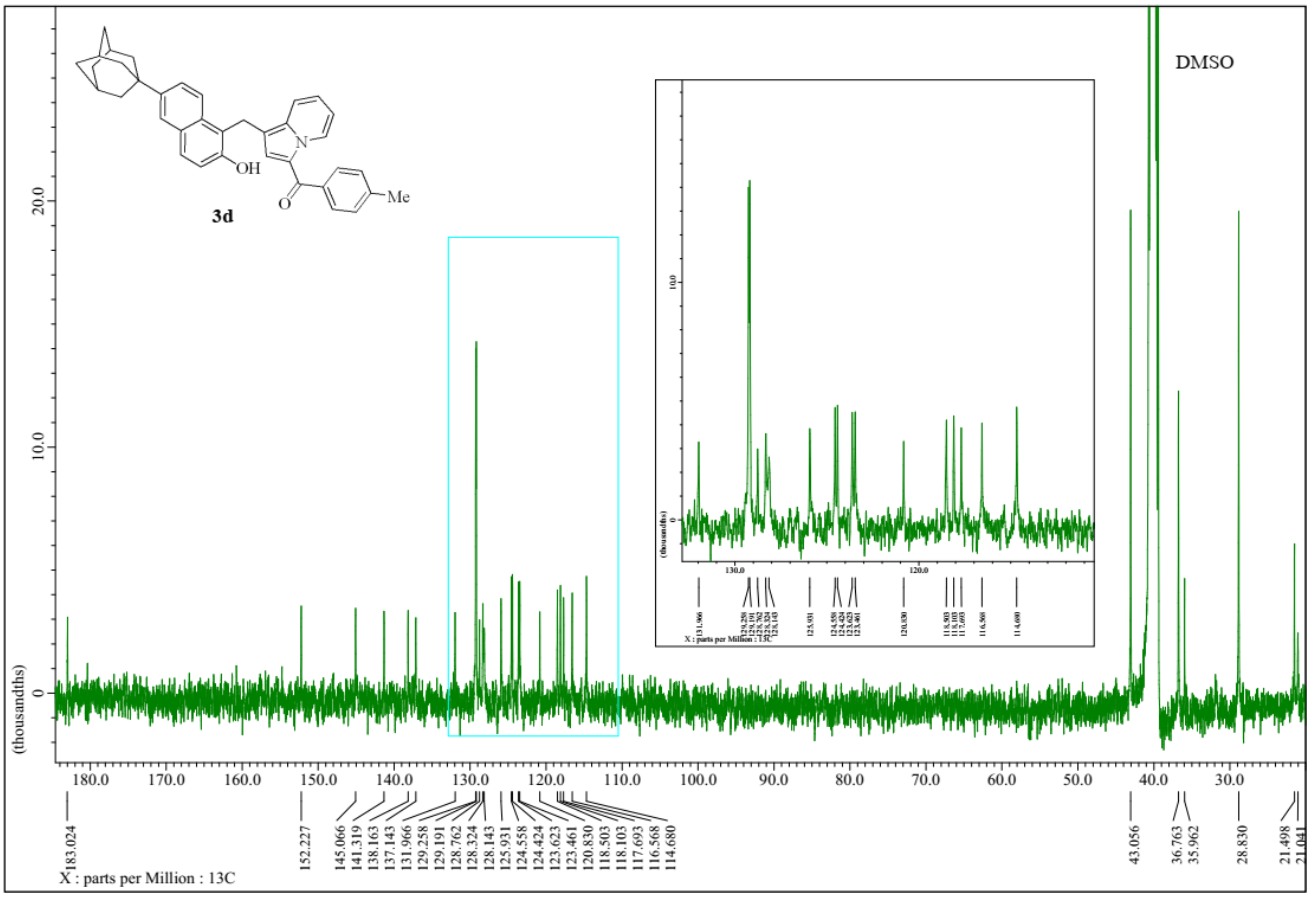

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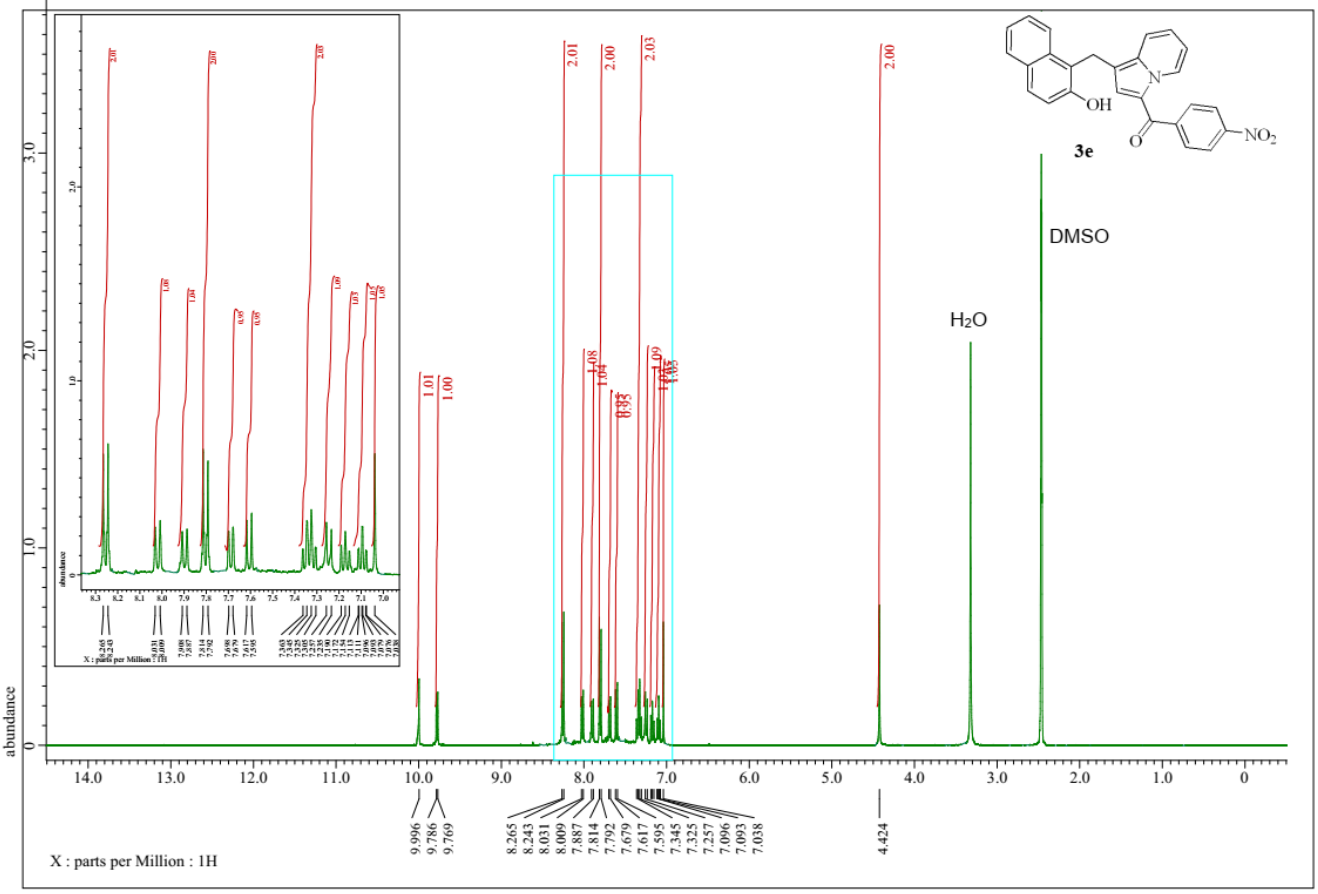

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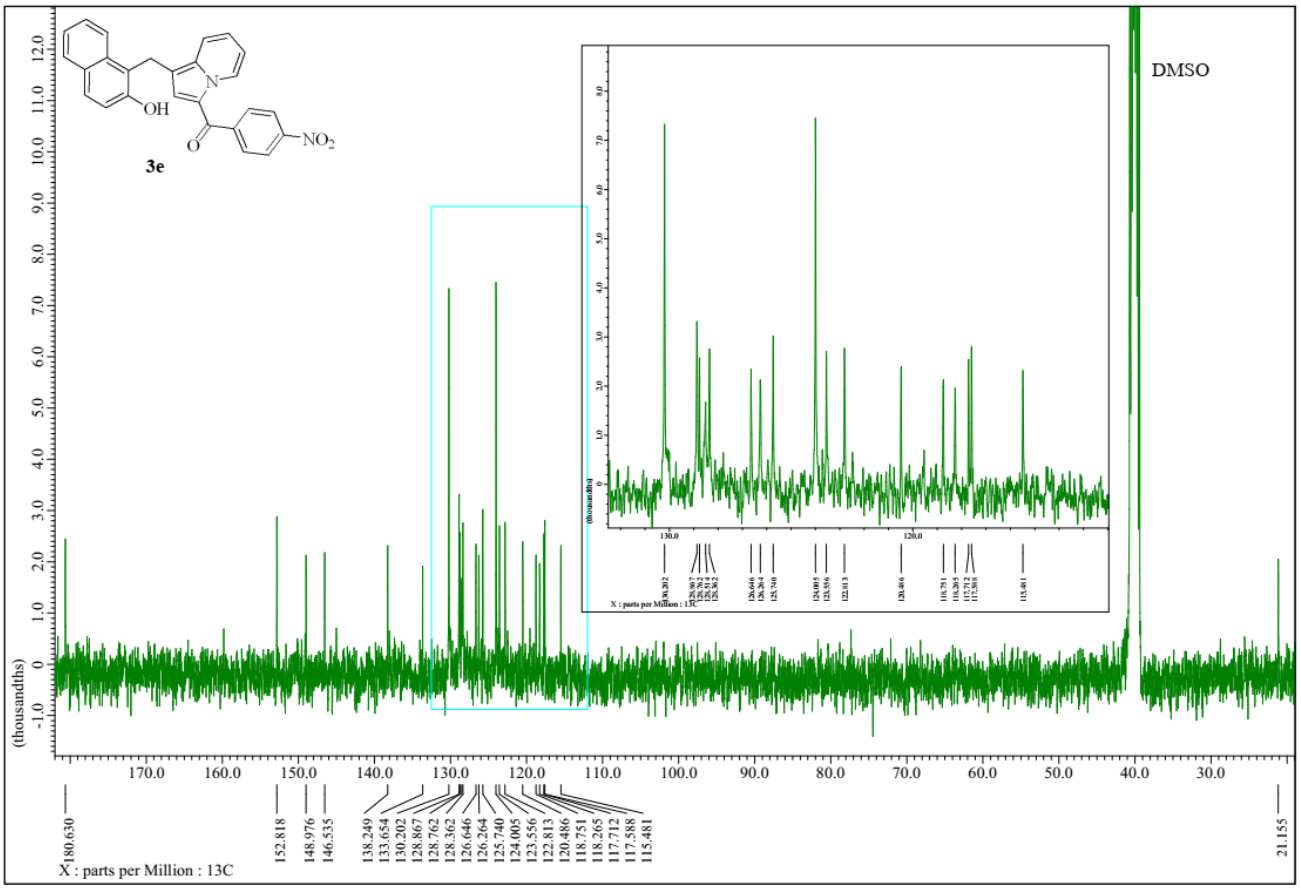

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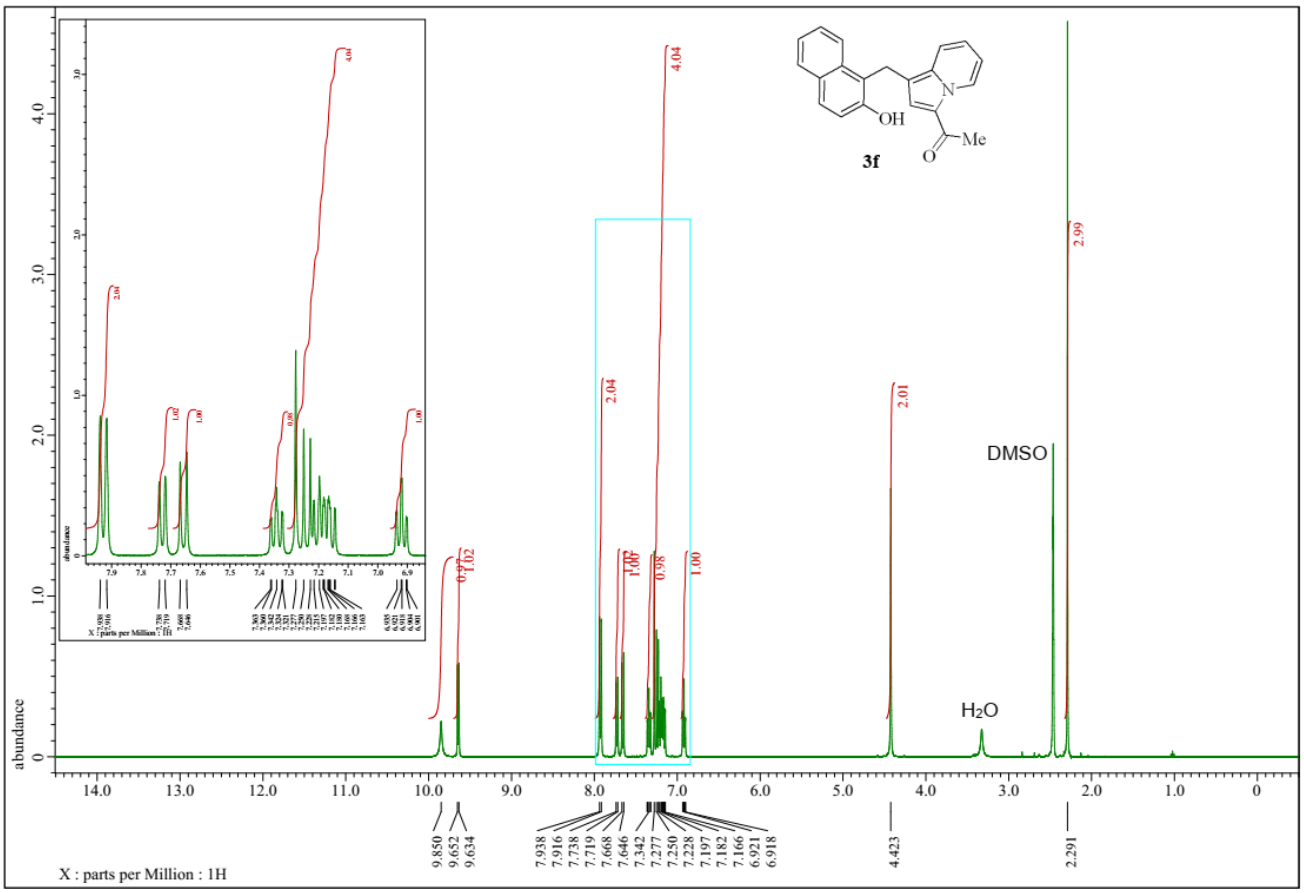

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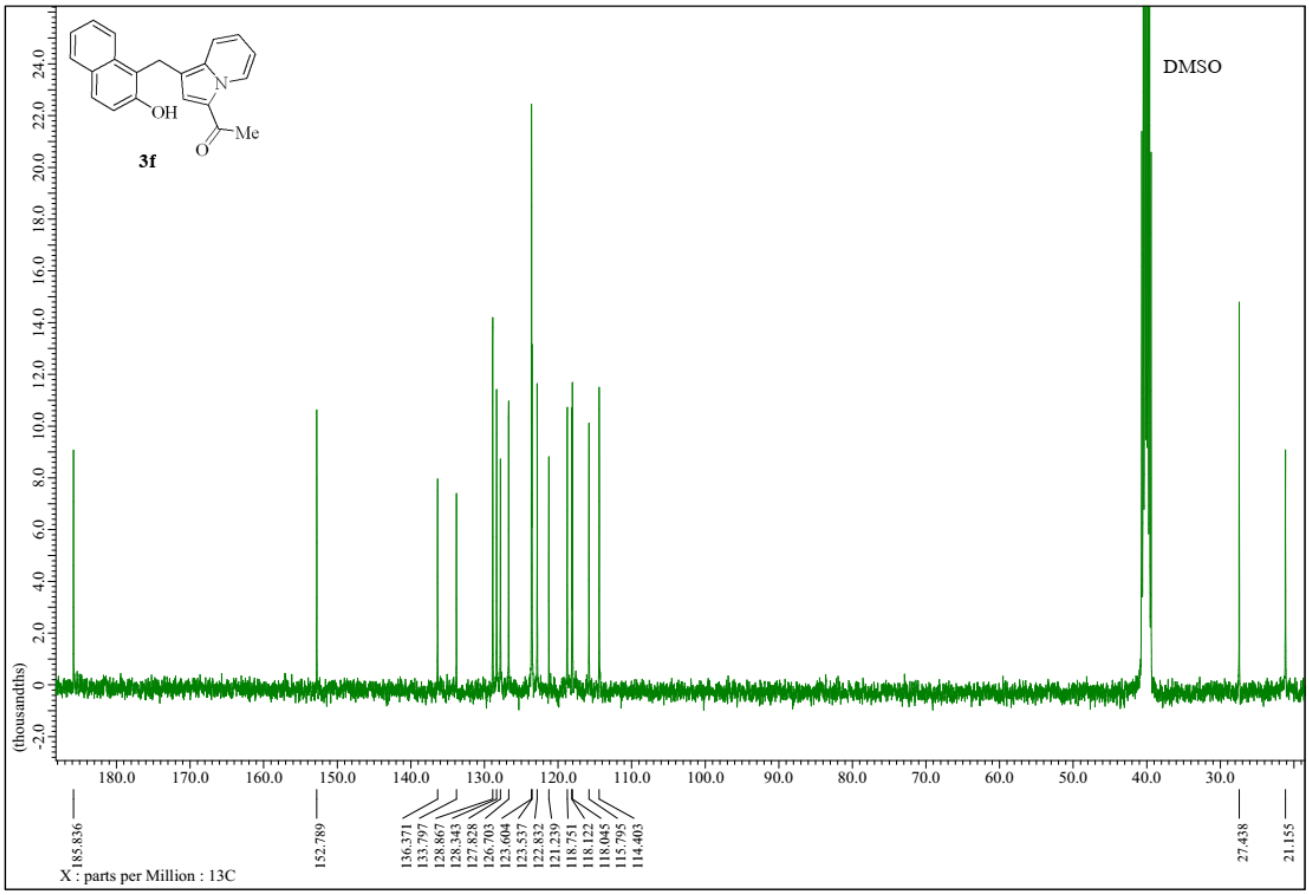

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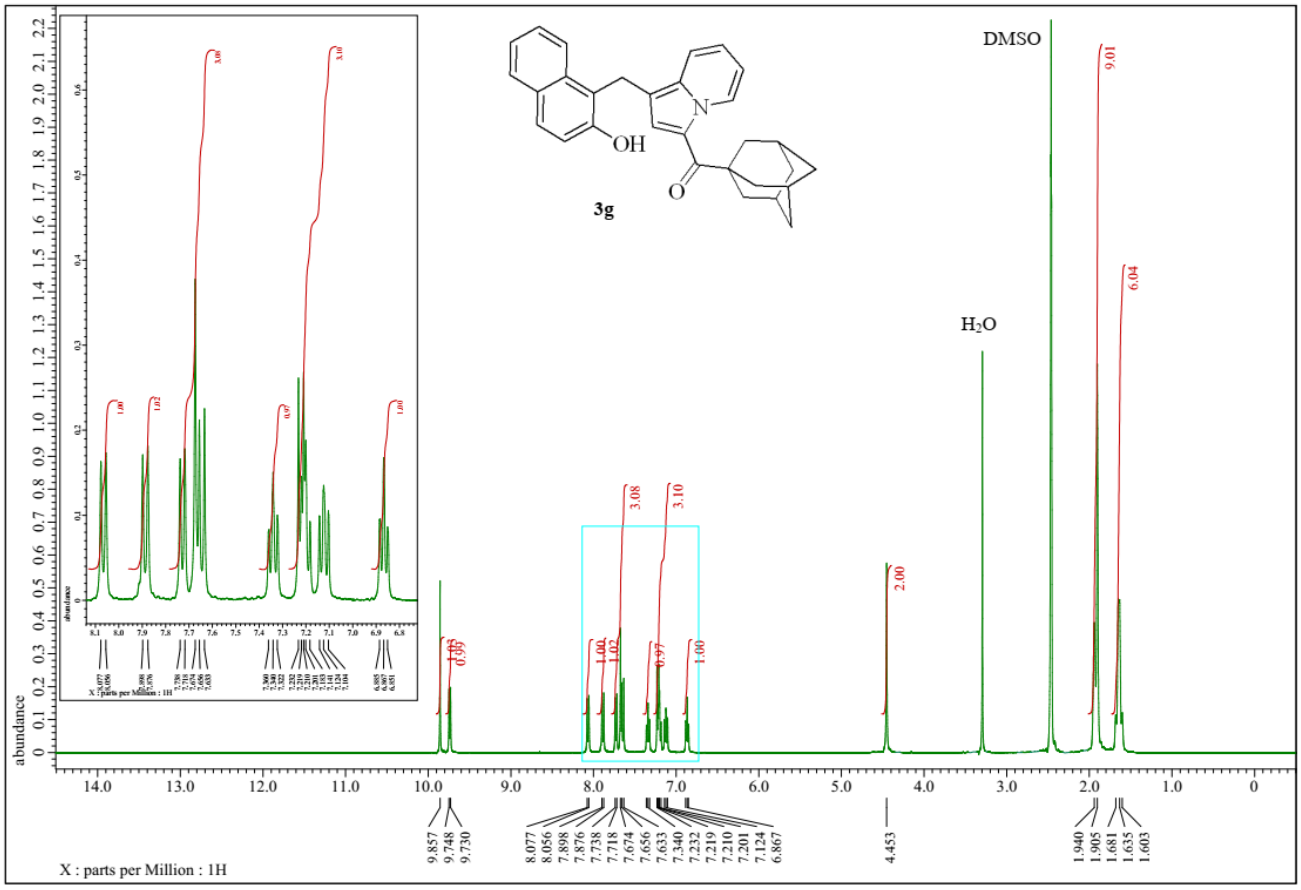

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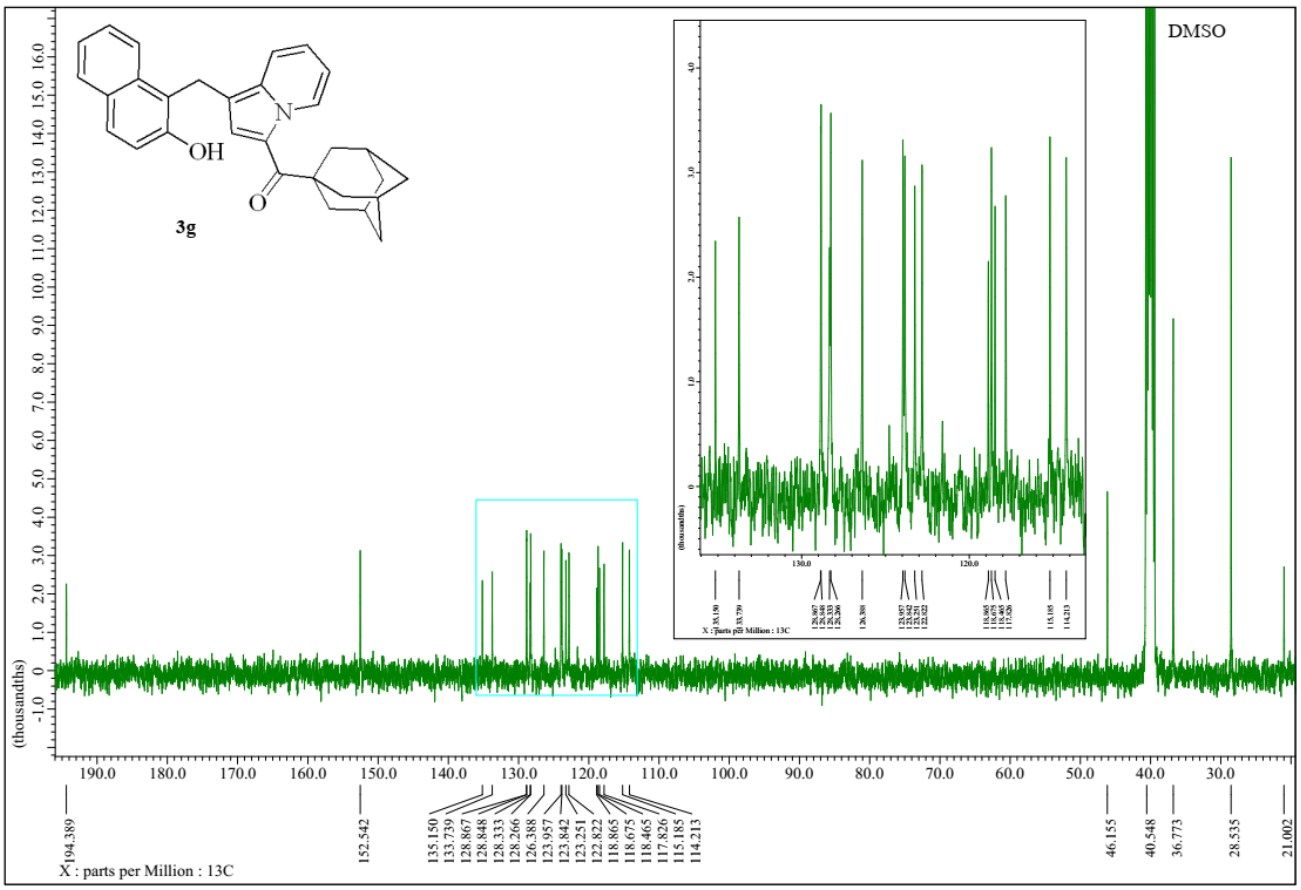

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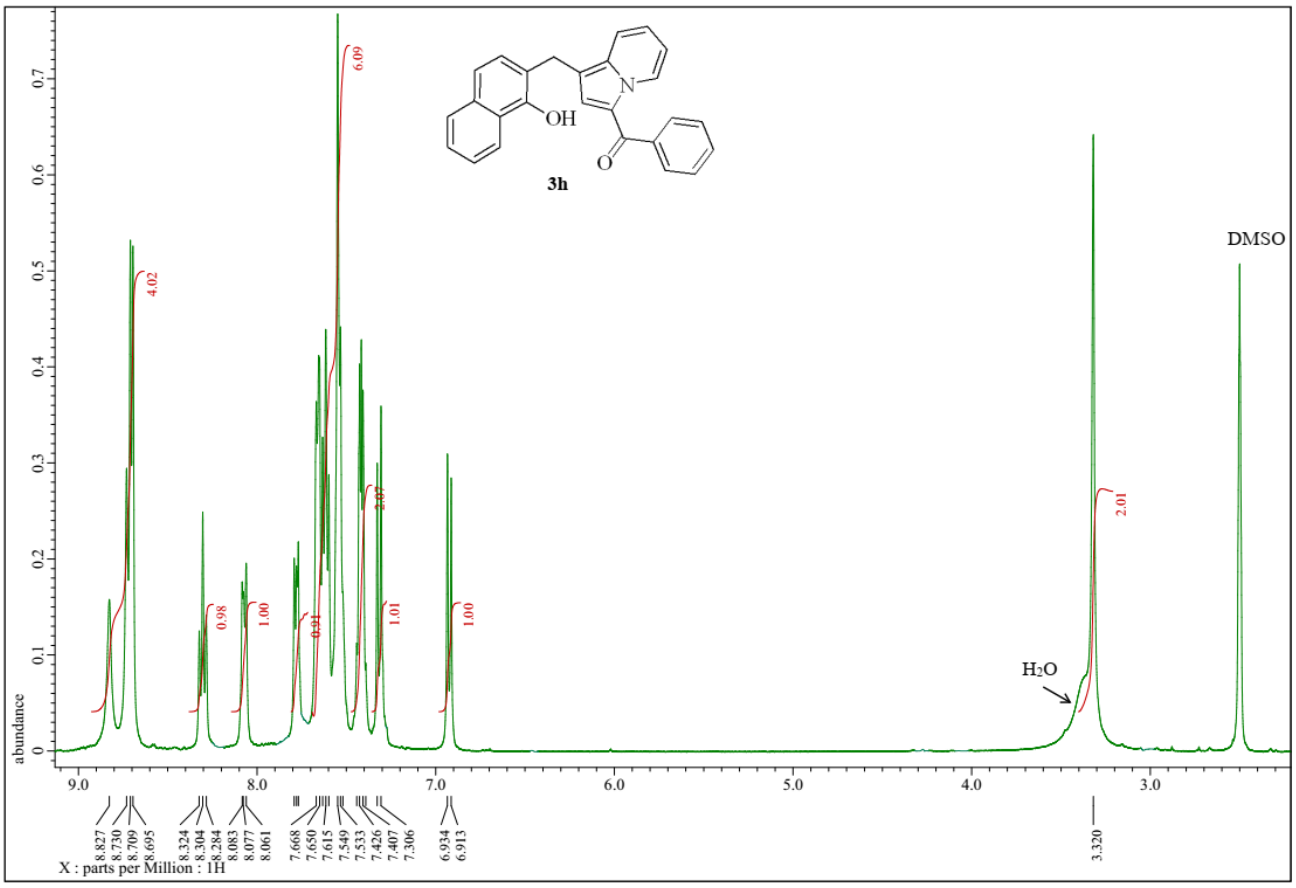

NMR ^{13}C