Supplementary Information

A Versatile and Practical One-Pot Strategy for a Greener, Waste-Minimized Synthesis of Aryloxy- and Alkyloxy-Substituted Metallophthalocyanines via Tandem S_NAr-cyclotetramerization

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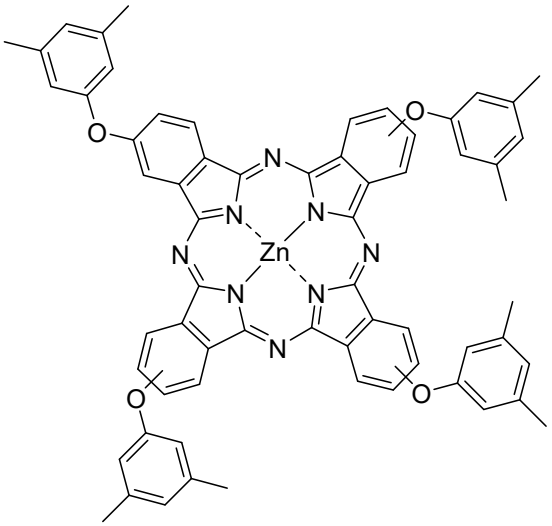
General procedure for solvent recovery

Regarding the use of methanol and methanol/water mixtures during the workup: To minimize the amount of DMF and DBU in the recoverable mixture, we removed it separately during the filtration of the quenched reaction (with 1 N HCl), followed by washings with water. Then, the mixed water-methanol waste generated from crude and product washings in several reactions was collected into a single flask to reach a working volume of approximately 150–200 mL, suitable for distillation. Methanol does not form binary azeotropes with water and was therefore recovered using a standard distillation setup (atmospheric pressure) equipped with a Vigreux column to improve separation efficiency.

Regarding the organic solvents used as eluents: The solvent mixtures were recovered individually for the filtration on silica pad of each reaction by collecting the packing solvent (hexane), deposition solvent (THF), and eluted fractions. We then recovered the solvent mixtures using a rotary evaporator until dryness, discarding only a small fraction collected at the beginning of the evaporation process, and re-used the recovered mixtures several times for subsequent silica-pad filtrations, supplementing the volume when necessary with freshly prepared solvent at the initially set polarity. Since the separation is relatively simple, phthalocyanines being the only macrocyclic products and polar impurities remaining at the baseline (Rf ~ 0), the choice of eluent does not require a narrow polarity window, provided that it is not so polar as to co-elute the polar impurities with the target compound.

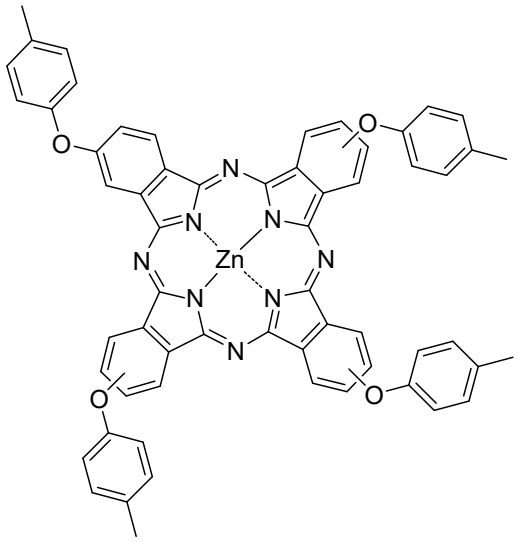
Spectroscopic and Analytical Data of target compounds

Tetra-(3,5-dimethylphenoxy)-zinc-phthalocyanine (1).



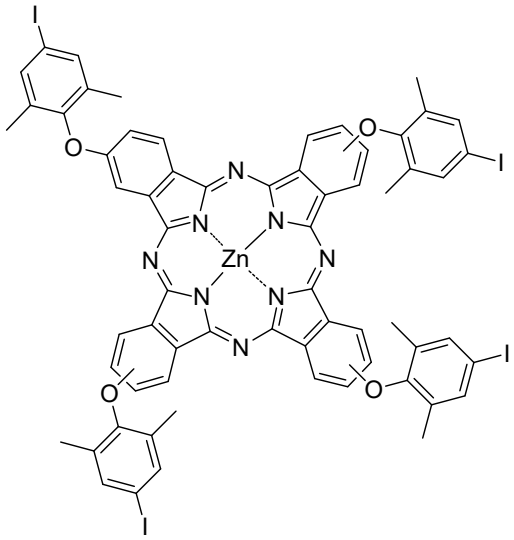
Purification of the crude was carried out by short pad filtration on silica gel, using THF for sample loading and a 3:1 hexane:THF mixture as the eluent. The target compound was obtained as a blue solid in 48% yield. ^{1}H NMR (600 MHz, THF-d_8): δ = 9.01 – 8.91 (m, 4H), 8.65 – 8.60 (m, 4H), 7.72 – 7.70 (m, 4H), 7.12 – 6.93 (m, 12H), 2.44 – 2.41 (m, 24H, CH_3) ppm; ^{13}C NMR (150 MHz, THF-d_8): δ = 160.62, 160.58, 160.54, 160.48, 160.40, 160.37, 158.99, 158.93, 158.89, 158.84, 158.81, 141.28, 141.24, 141.23, 141.19, 140.88, 140.86, 140.82, 140.80, 134.43, 134.33, 134.27, 126.59, 126.57, 126.53, 126.51, 126.49, 126.42, 126.41, 124.89, 124.74, 124.71, 121.38, 121.34, 118.49, 118.47, 118.39, 118.37, 118.36, 118.26, 118.23, 112.92, 112.87, 112.83, 21.75 ppm. FT-IR: ν = 2918, 2849, 2828, 1611, 1584, 1456, 1393, 1335, 1292, 1256, 1217, 1173, 1134, 1084, 1043, 1022, 951, 999, 820, 559, 534 cm^{-1}. UV-vis (THF): λ_{max} = 675, 352 nm. MALDI-TOF $[M]^{\bullet+}$: m/z = 1056.41, (Calcd: 1056.31).

Tetra-(p-tolyloxy)-zinc-phthalocyanine (2).



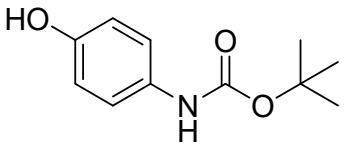
Purification of the crude was carried out by short pad filtration on silica gel, using THF for sample loading and a 3:1 hexane:THF mixture as the eluent. The target compound was obtained as a blue solid in 43% yield. ^{1}H NMR (600 MHz, THF-d_8): δ = 8.94 – 8.77 (m, 4H), 8.64 – 8.50 (m, 4H) 7.69 – 7.61 (m, 4H), 7.45 – 7.35 (m, 16H), 2.49 – 2.47 (m, 12H) ppm; ^{13}C NMR (150 MHz, THF-d_8): δ = 160.70, 160.66, 160.62, 160.54, 156.60, 156.58, 156.51, 156.44, 156.38, 156.34, 153.49, 152.46, 141.14, 141.08, 141.06, 134.47, 134.45, 134.31, 134.30, 134.24, 134.22, 134.08, 134.03, 134.00, 131.61, 131.54, 124.87, 124.84, 124.64, 124.59, 120.92, 120.88, 120.81, 120.77, 120.71, 120.68, 120.60, 120.57, 112.47, 112.38, 112.32, 111.95, 111.87, 111.78, 21.17 ppm. FT-IR: ν = 3024, 2922, 2860, 1602, 1504, 1472, 1393, 1335, 1259, 1227, 1205, 1161, 1115, 1086, 1043, 1016, 945, 889, 868, 816, 743, 668, 498 cm^{-1}. UV-vis (THF): λ_{max} = 675, 352 nm. MALDI-TOF $[M]^{\bullet+}$: m/z = 1000.37, (Calcd: 1000.25).

Tetra-(4-iodo-2,6-dimethylphenoxy)-zinc-phthalocyanine (3).



Purification of the crude was performed by short pad filtration on silica gel, using THF for sample loading and a gradient elution with increasing polarity (from 4:1 to 1:1 petroleum ether:THF). The target compound was obtained as a blue solid in 37% yield. ^{1}H NMR (600 MHz, Pyr-d_5) δ = 9.36 – 9.68 (m, 4H), 8.87 – 9.19 (m, 4H), 7.74 (m, 4H), 7.60 – 7.67 (m, 8H), 2.19 (m, 24H) ppm; ^{13}C NMR (150 MHz, Pyr-d_5): δ = 159.92, 159.75, 159.60, 151.66, 151.64, 151.54, 151.54, 151.50, 142.92, 142.92, 138.41, 138.39, 138.35, 134.18, 134.18, 125.68, 125.68, 117.55, 117.49, 117.02, 116.88, 114.87, 114.86, 90.73, 90.71, 90.70, 90.64, 90.61, 79.53, 79.09, 34.77, 34.71, 30.55, 30.24, 29.34, 24.15, 24.15, 21.15, 16.53, 16.50, 15.99, 15.96, 15.96 ppm. FT-IR: ν = 2926, 2850, 1607, 1460, 1392, 1337, 1268, 1213, 1179, 1115, 1084, 1038, 944, 852, 813, 764, 743 cm^{-1}. UV-vis (THF): λ_{max} = 677, 351 nm. MALDI-TOF $[M]^{\bullet+}$: m/z = 1559.83, (Calcd: 1559.90).

***Tert*-butyl(4-hydroxyphenyl)carbamate (4a).**

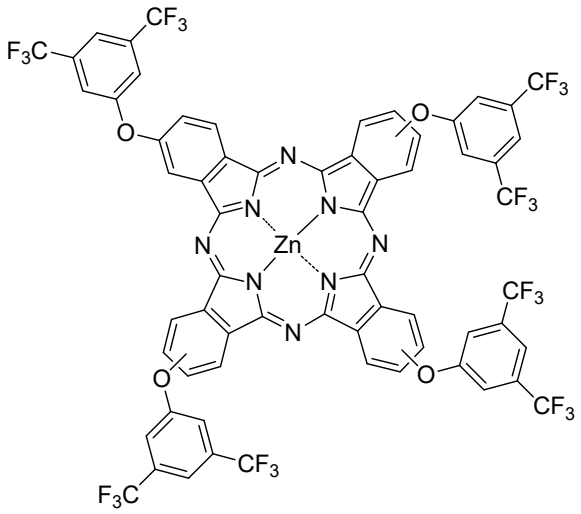


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.17 – 7.16 (m, 2H), 6.74 – 6.73 (m, 2H), 6.35 (bs , 1H), 5.33 (bs, 1H), 1.51 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.56, 152.04, 130.99, 121.4, 115.74, 80.46, 28.38.

Phthalocyanine (4).

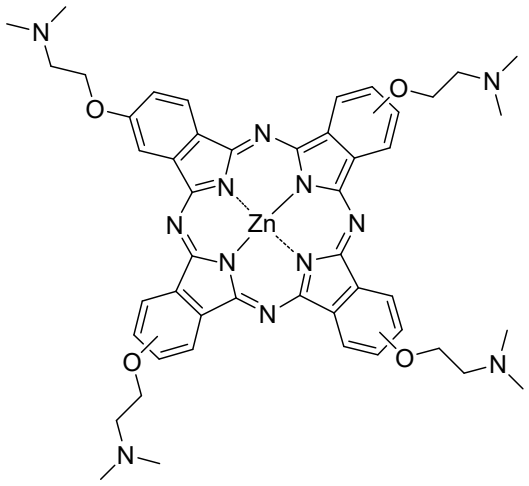
Purification of the crude by Soxhlet extraction with methanol gave a phthalocyanine-based product as a green solid. FT-IR: ν = 3309, 2930, 2860, 1721, 1593, 1484, 1466, 1395, 1362, 1333, 1314, 1267, 1220, 1112, 1092, 1041, 1007, 946, 885, 832, 743, 724, 696 cm^{-1}. UV-vis (Pyridine): λ_{max} = 685, 355 nm.

Tetra-(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine (5).



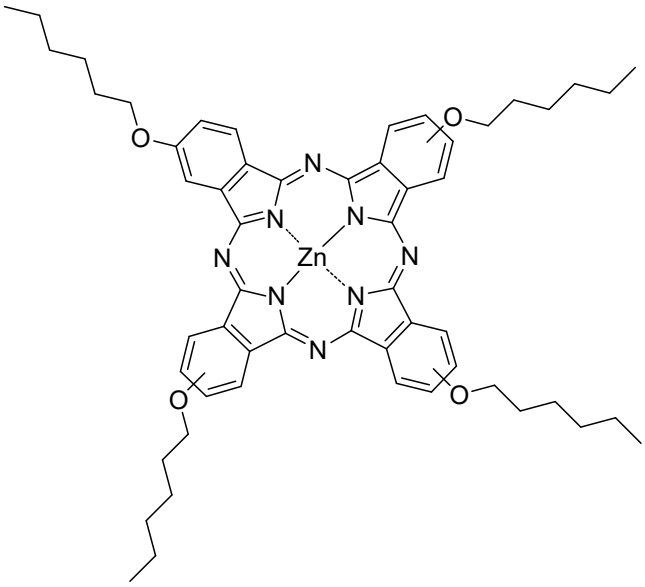
Purification of the crude was performed by short pad filtration on silica gel, using a 5:3 hexane:ethyl acetate mixture for both sample loading and elution. The target compound was obtained as a blue solid in 27% yield. ^{1}H NMR (600 MHz, THF-d_8): δ = 9.17 – 9.06 (m, 4H), 8.80-8.75 (m, 4H), 8.05-7.84 (m, 16H) ppm; ^{13}C NMR (150 MHz, THF-d_8): δ = 160.59, 160.57, 160.54, 157.96, 157.94, 157.86, 157.78, 157.76, 141.32, 141.29, 141.25, 141.20, 141.18, 141.13, 135.94, 135.92, 135.86, 135.84, 134.67, 134.65, 134.63, 134.61, 134.45, 134.43, 134.41, 134.39, 134.32, 125.52, 125.49, 125.46, 124.44 (q, CF3, J = 272 Hz), 122.21, 122.17, 119.88, 119.84, 119.81, 118.07, 118.02, 117.96, 117.93, 117.91, 117.85, 114.43, 114.40, 114.37, 114.33 ppm. FT-IR: ν = 1607, 1487, 1460, 1337, 1275, 1231, 1171, 1125, 1105, 1084, 1045, 961, 945, 914, 885, 847, 735, 700, 681, 617, 449, 436 cm^{-1}. UV-vis (THF): λ_{max} = 670, 349 nm. MALDI-TOF $[M]^{\bullet+}$: m/z = 1488.20, (Calcd: 1488.08).

Tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (6).



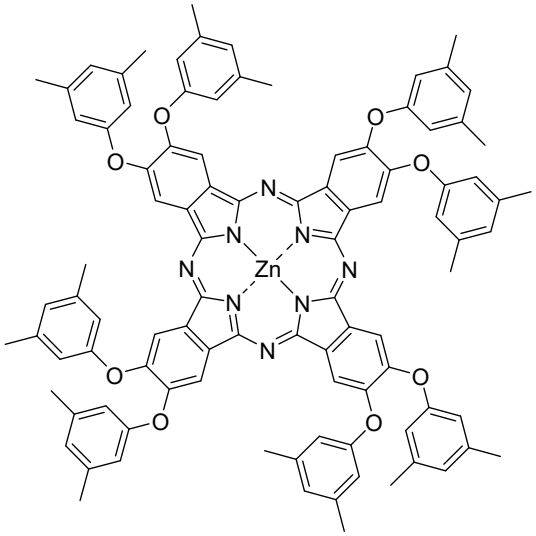
Purification of the crude by several washings with a 3:1 water:methanol mixture gave the target product in 49% yield as a green solid. ^{1}H NMR (600 MHz, Pyr-d_5) δ = 9.56 (m, 4H), 9.30 (d, J = 8.1 Hz, 4H), 7.84 – 7.92 (m, 4H), 4.56 (m, 8H), 2.92 (m, 8H), 2.40 (s, 12H), 2.35 (s, 12H) ppm; ^{13}C NMR (150 MHz, Pyr-d_5): δ = 161.49, 161.27, 153.54, 141.12, 132.08, 132.06, 118.67, 118.63, 115.87, 113.99, 112.54, 108.54, 106.59, 106.52, 67.47, 67.45, 67.37, 67.35, 58.56, 58.52, 57.95, 57.88, 45.90, 45.84, 45.63, 45.50, 37.20, 29.79, 29.75, 23.49, 23.45 ppm. FT-IR: ν = 2935, 2859, 2830, 2781, 2370, 2322, 2212, 1606, 1508, 1488, 1456, 1436, 1388, 1337, 1278, 1229, 1112, 1089, 1040, 952, 836, 827, 770, 746, 727 cm^{-1}. UV-vis (THF): λ_{max} = 677, 351 nm. MALDI-TOF $[M]^{\bullet+}$: m/z = 924.32, (Calcd: 924.35).

Tetra-(hexyloxy)-zinc-phthalocyanine (7).



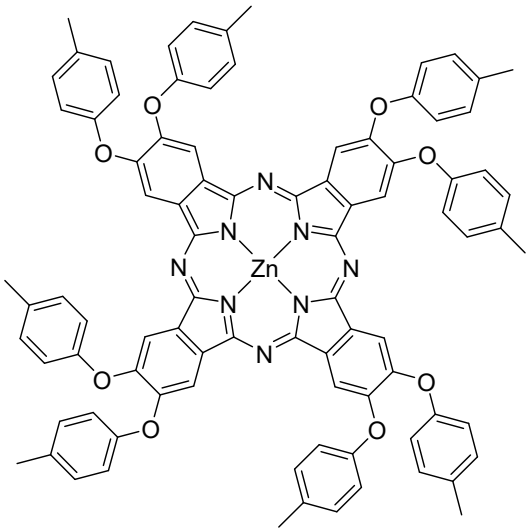
Purification of the crude was carried out by short pad filtration on silica gel, using THF for sample loading and a 2:1 hexane:THF mixture as the eluent. The target compound was obtained as a blue solid in 22% yield. ^{1}H NMR (600 MHz, THF-d_8): δ = 8.98 – 8.88 (m, 4H), 8.55 – 8.51 (m, 4H), 7.57 – 7.49 (m, 4H), 4.49 (bs, 8H), 2.14 – 2.09 (m, 8H), 1.82 – 1.78 (m, 8H), 1.61 – 1.53 (m, 16H), 1.08 – 1.04 (m, 12H) ppm; ^{13}C NMR (150 MHz, THF-d_8): δ = 161.94, 132.52, 125.90, 124.03, 69.41, 32.87, 30.74, 27.05, 23.73, 14.55 ppm. FT-IR: ν = 2954, 2925, 2859, 2361, 2341, 2321, 1603, 1495, 1460, 1384, 1335, 1277, 1228, 1112, 1083, 1046, 946, 874, 846, 818, 770, 746, 726, 658 cm^{-1}. UV-vis (THF): λ_{max} = 676, 349 nm. MALDI-TOF $[M+H]^+$: m/z = 977.522, (Calcd: 976.43).

Octakis(3,5-dimethylphenoxy)-zinc-phthalocyanine (8).



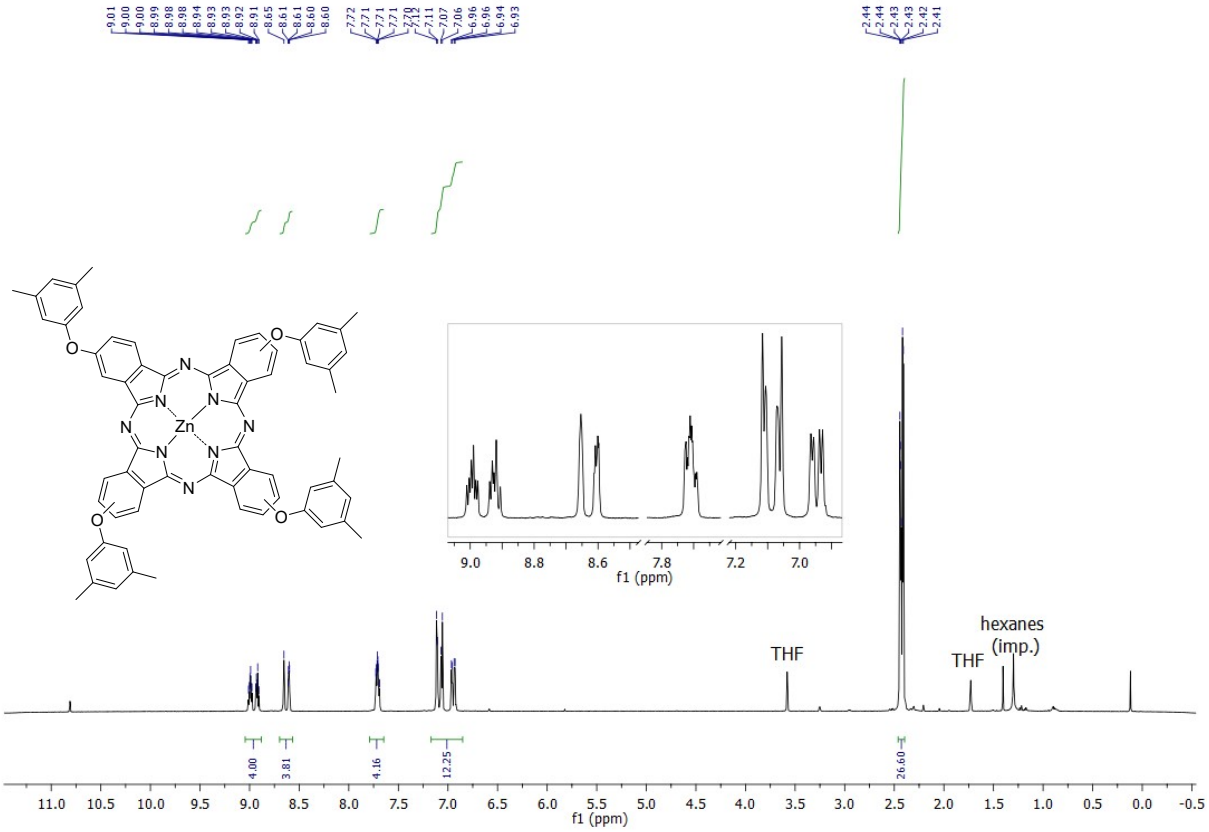
Purification of the crude was carried out by short pad filtration on silica gel, using THF for sample loading and a 2:1 petroleum ether:THF mixture as the eluent. The target compound was obtained as a green solid in 30% yield. ^{1}H NMR (600 MHz, THF-d_8): 8.75 (s, 8H), 6.89 (s, 16H), 6.79 (m, 8H), 2.31 (s, 48H) ppm; ^{13}C NMR (150 MHz, THF-d_8): 159.03, 151.29, 140.23, 135.58, 125.80, 116.82, 115.53, 21.58 ppm. FT-IR: ν = 3011, 2918, 2853, 1614, 1587, 1445, 1396, 1389, 1261, 1177, 1132, 1086, 1038, 1022, 947, 868, 833, 744, 723, 683 cm^{-1}. UV-vis (THF): λ_{max} = 679, 357 nm. MALDI-TOF $[M+H]^+$: m/z =1536.639, (Calcd: 1539.124).

Octakis(p-tolyloxy)-zinc-phthalocyanine (9).

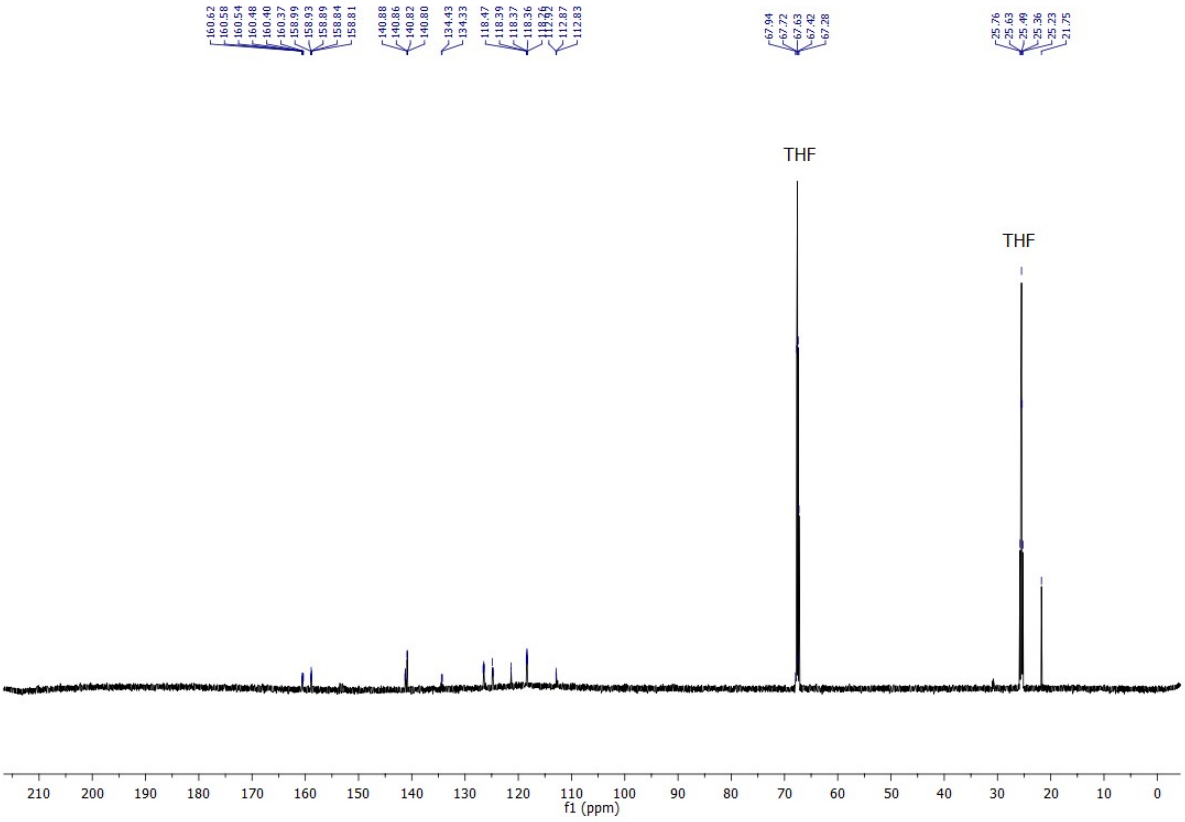


Purification of the crude was performed by short pad filtration on silica gel, using THF for sample loading and gradient elution with increasing polarity, from 7:1 to 3:1 to 2:1 petroleum ether:THF. The target compound was obtained as a green solid in 31% yield. ^{1}H NMR (600 MHz, THF-d_8): 8.72 (s, 8H), 7.20 – 7.17 (m, 32H), 2.35 (s, 24H) ppm; ^{13}C NMR (150 MHz, THF-d_8): 156.95, 152.86, 151.27, 135.53, 133.41, 131.15, 119.06, 115.28, 21.05. FT-IR: ν = 3028, 2918, 2855, 1605, 1504, 1485, 1447, 1398, 1337, 1265, 1202, 1173, 1138, 1090, 1028, 953, 890, 860, 810, 725, 698, 486, 473 cm^{-1}. UV-vis (THF): λ_{max} = 676, 356 nm. MALDI-TOF $[M+H]^+$: m/z =1425.052, (Calcd: 1426.908).

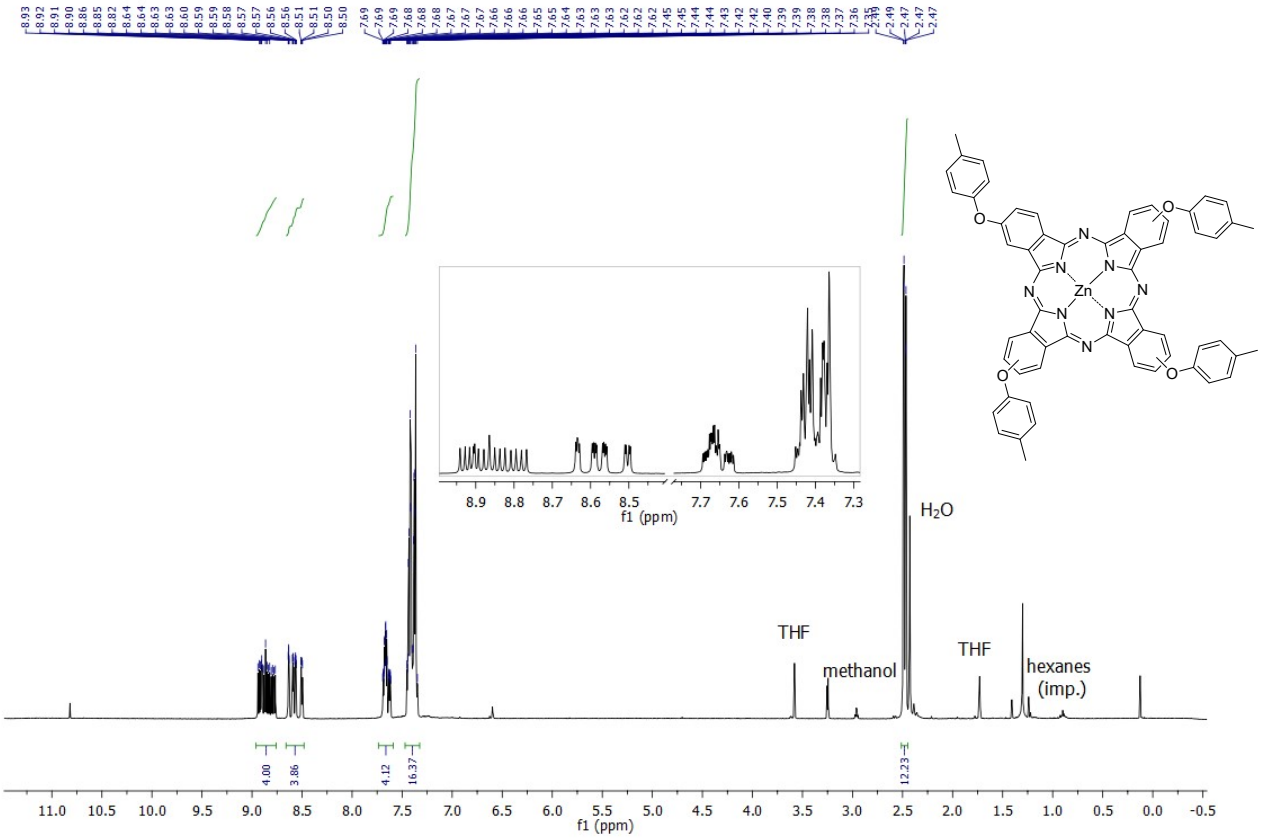
^{1}H NMR spectrum of tetra-(3,5-dimethylphenoxy)-zinc-phthalocyanine (1) in THF-d_8.



^{13}C NMR spectrum of tetra- (3,5-dimethylphenoxy)-zinc-phthalocyanine (1) in THF-d_8.



^{1}H NMR spectrum of tetra-(p-tolyloxy)-zinc-phthalocyanine (2) in THF-d_8.



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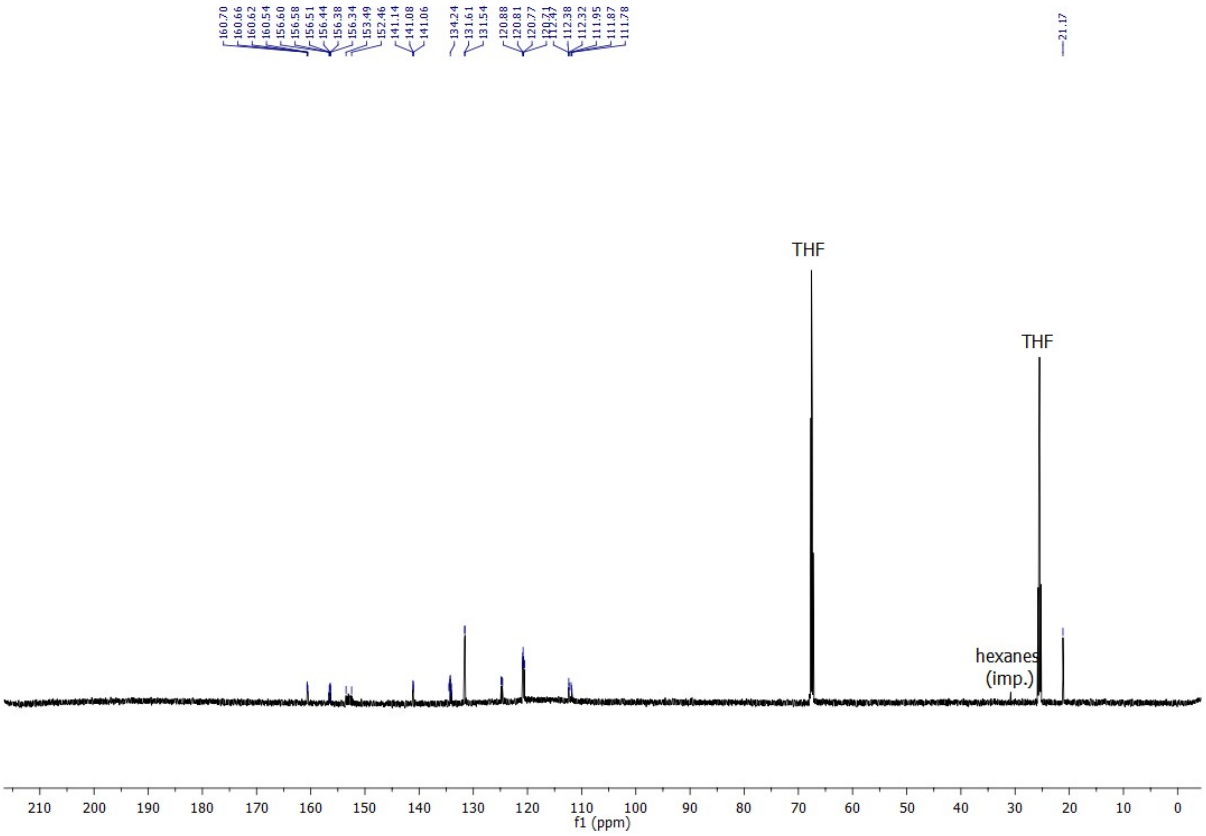
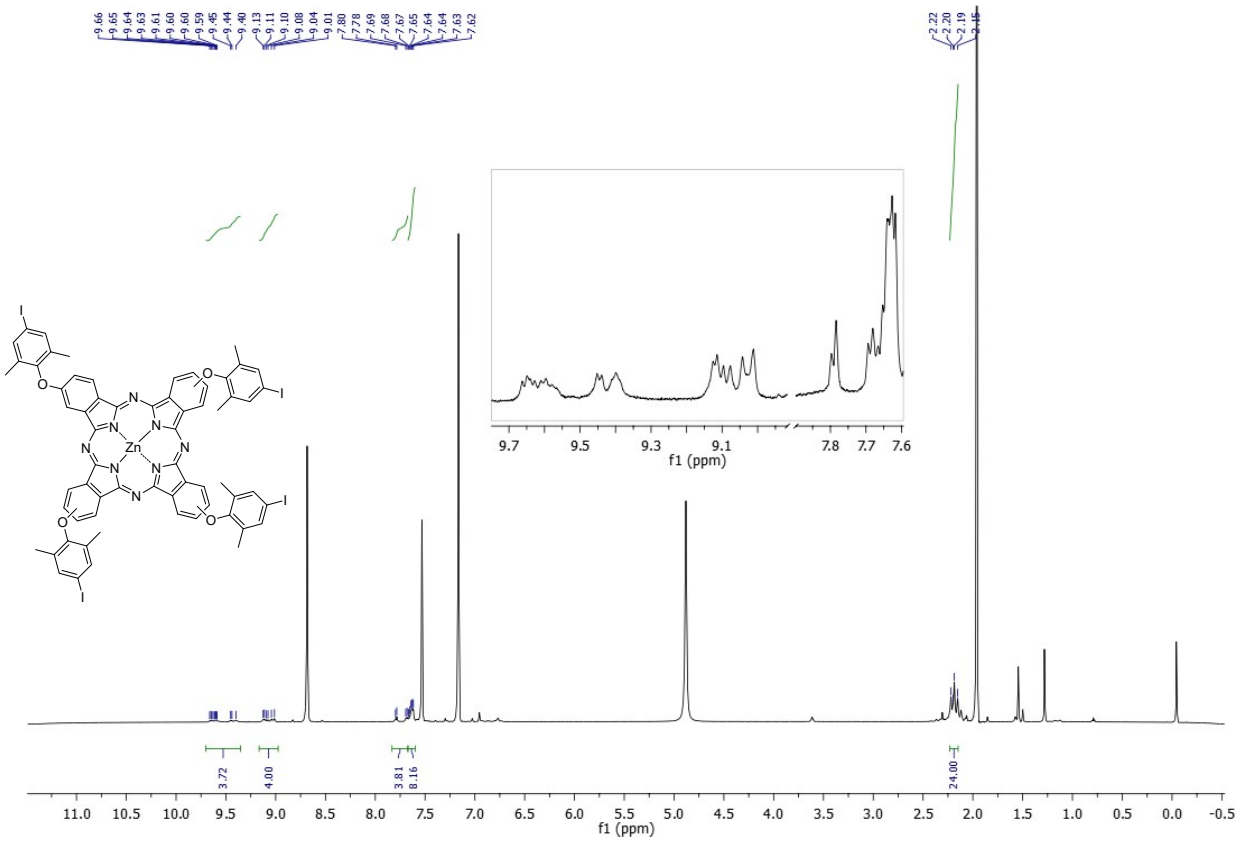
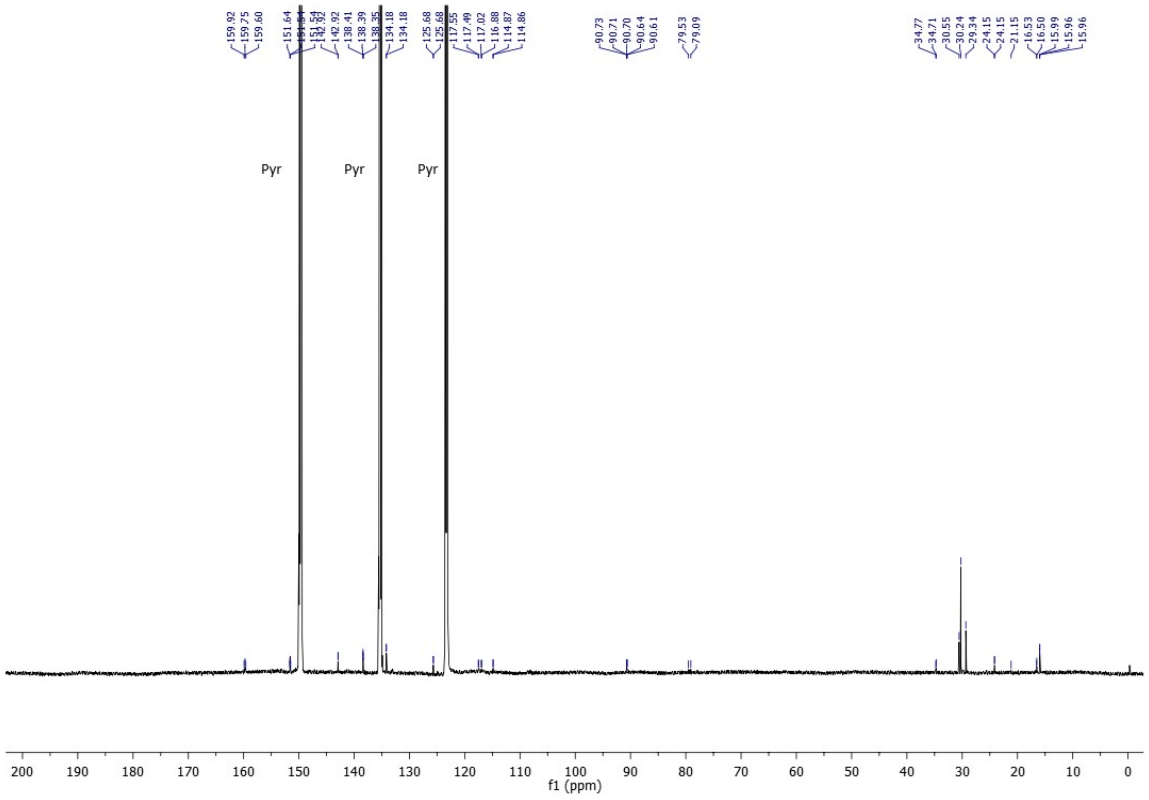


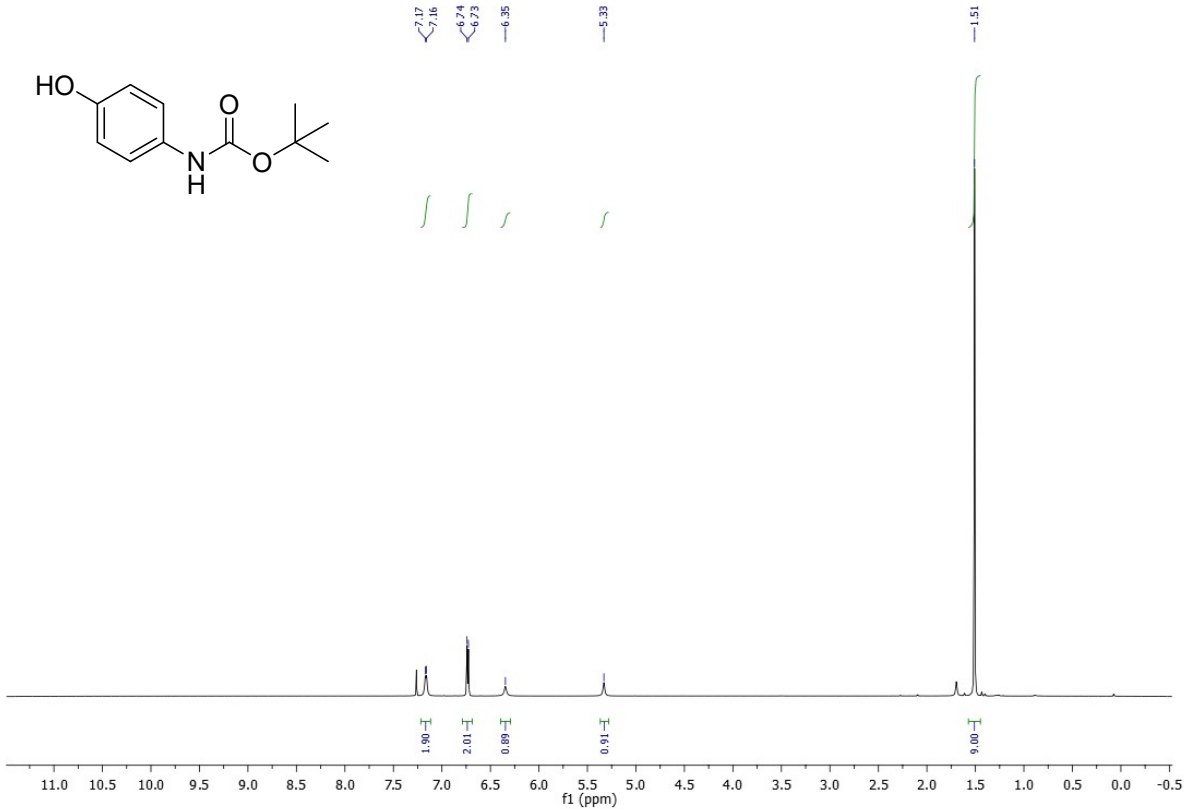
^{1}H NMR spectrum of tetra-(4-iodo-2,6-dimethylphenoxy)-zinc-phthalocyanine (3) in Pyr-d_5.



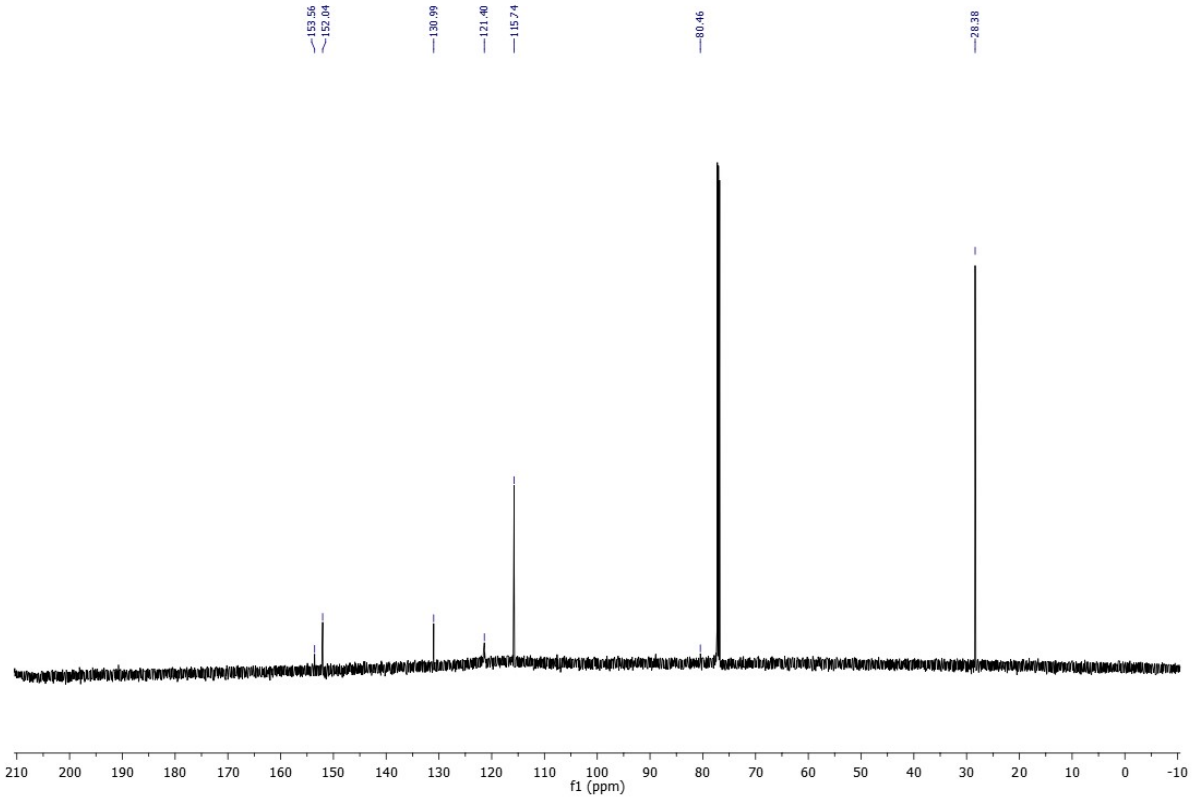
^{13}C NMR spectrum of tetra-(4-iodo-2,6-dimethylphenoxy)-zinc-phthalocyanine (3) in Pyr-d_5.



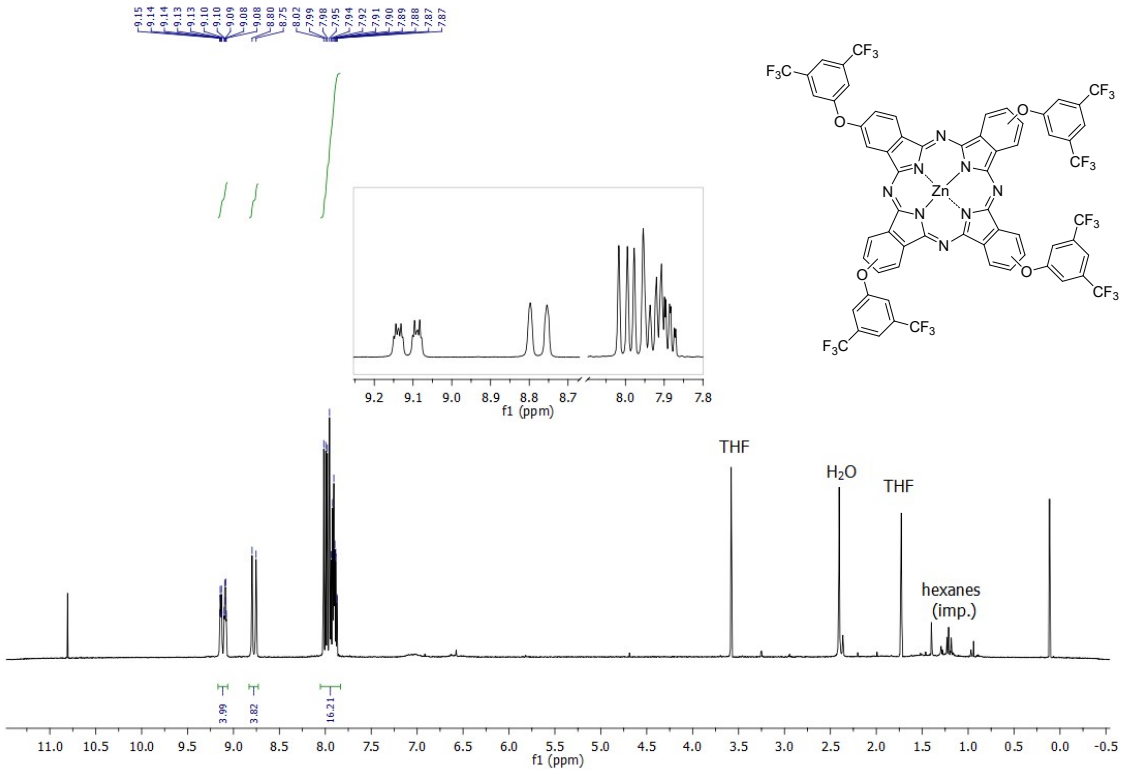
^{1}H NMR spectrum of *tert*-butyl(4-hydroxyphenyl)carbamate (4a) in $CDCl_3$.



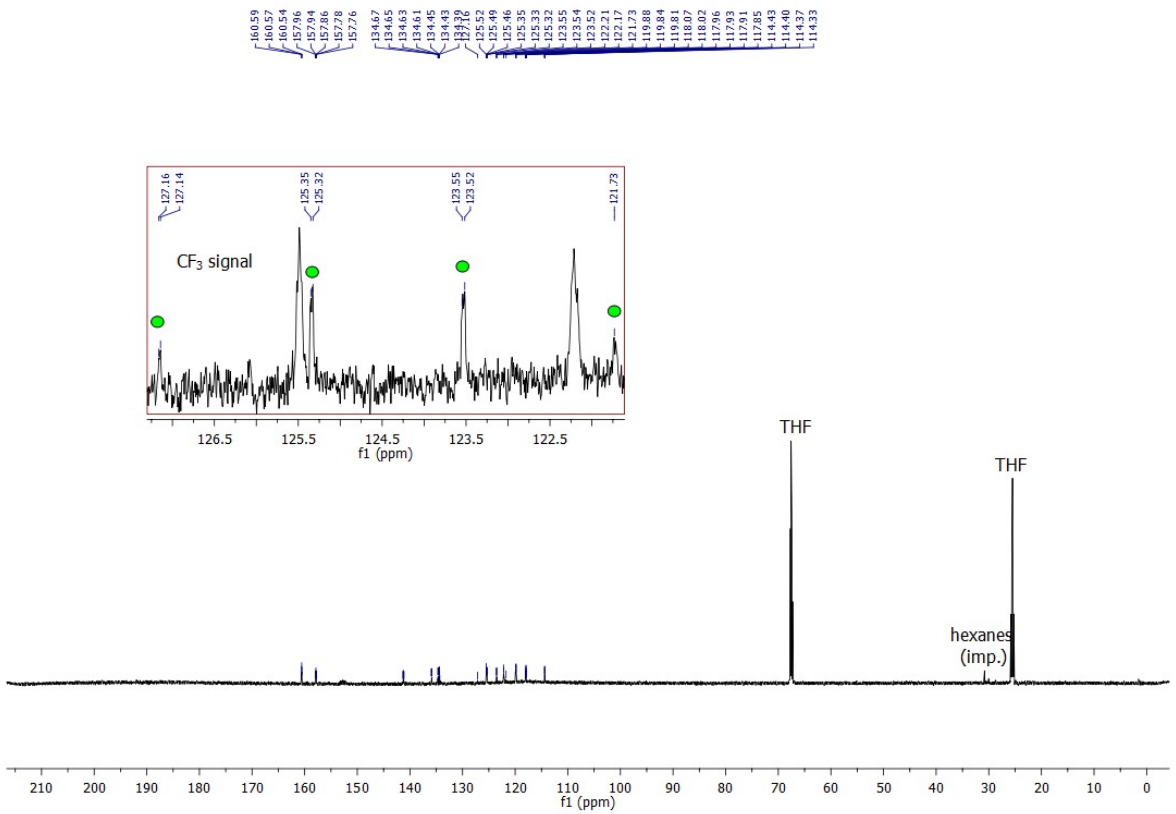
^{13}C NMR spectrum of *tert*-butyl(4-hydroxyphenyl)carbamate (4a) in $CDCl_3$.



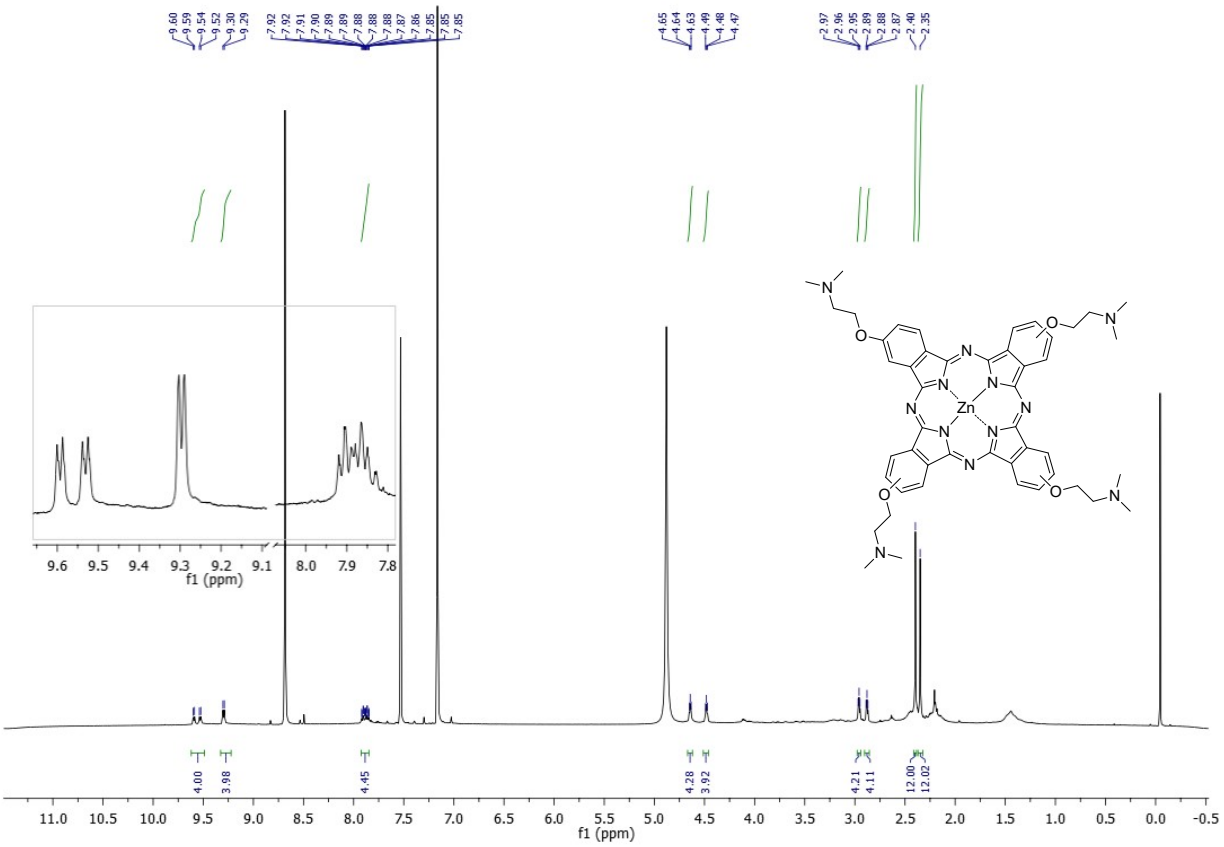
^{1}H NMR spectrum of tetra-(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine (5) in THF-d_8.



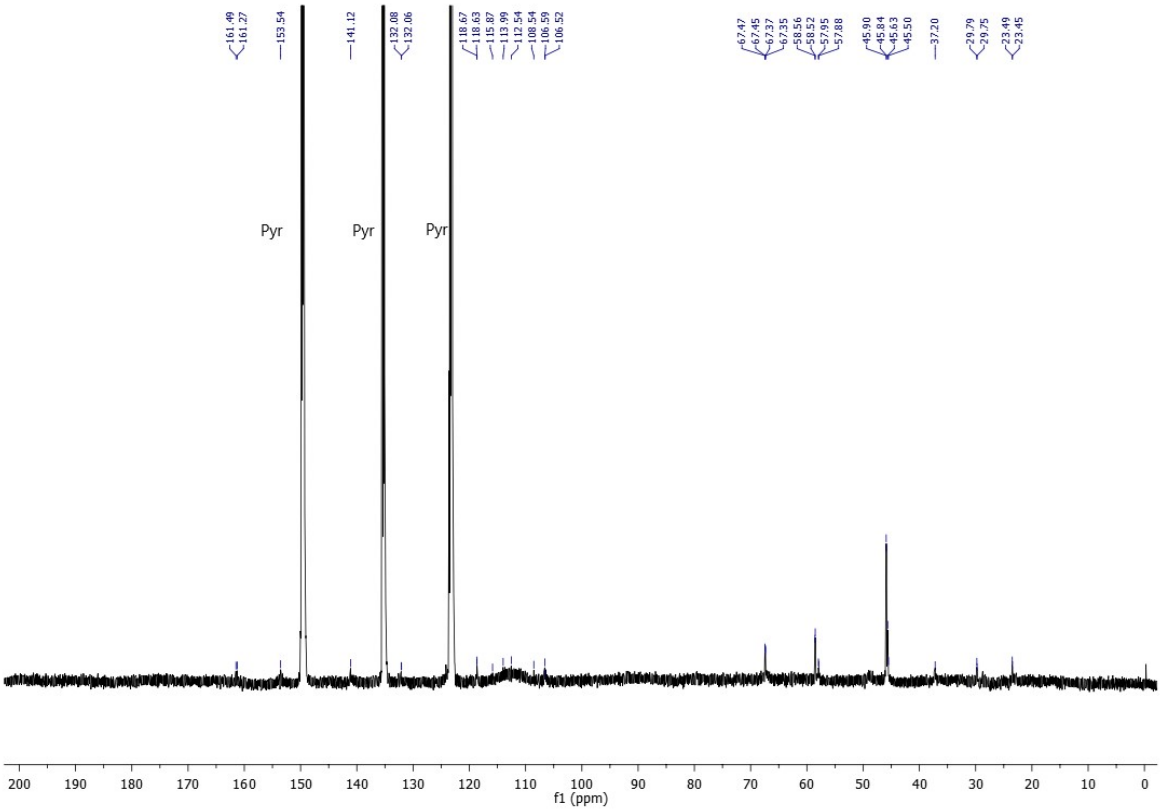
^{13}C NMR spectrum of tetra-(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine (5) in THF-d_8.



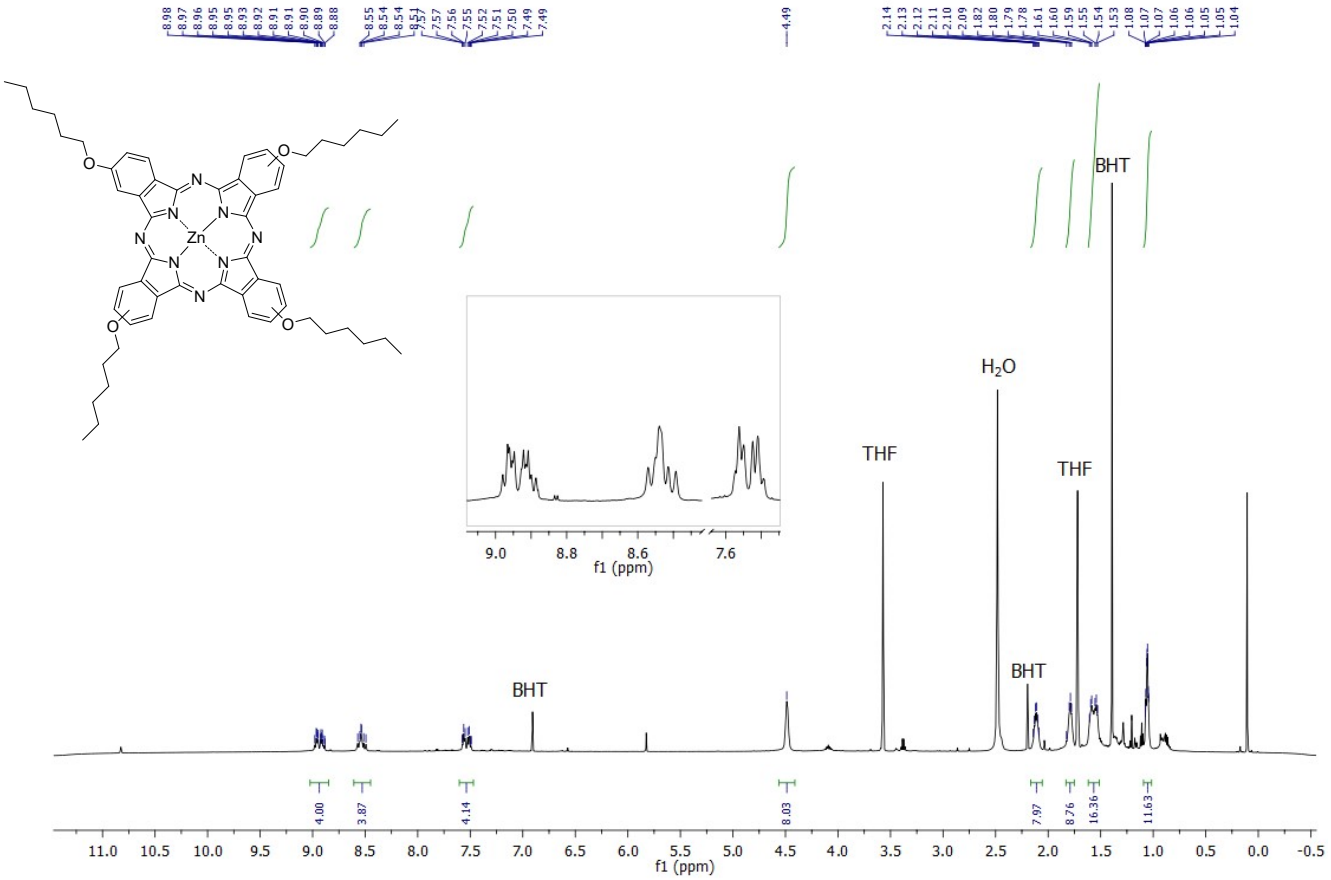
^{1}H NMR spectrum of tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (6) in Pyr-d_5.



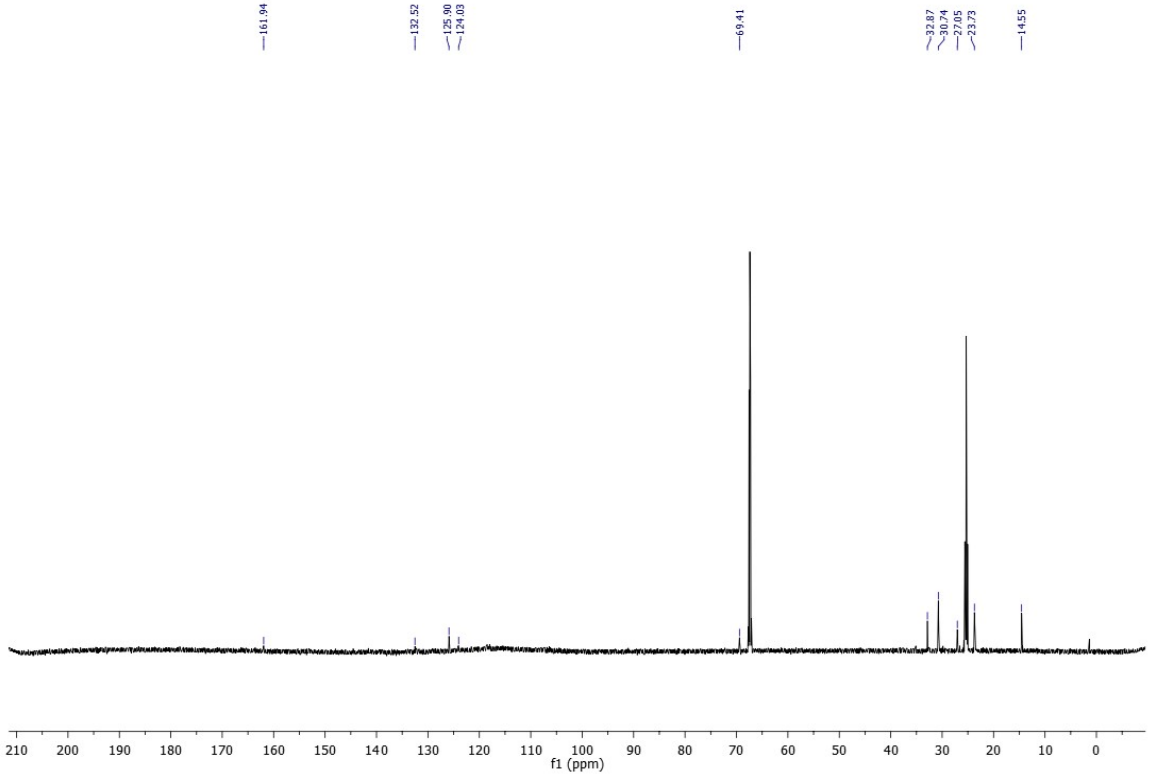
^{13}C NMR spectrum of tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (6) in Pyr-d_5.



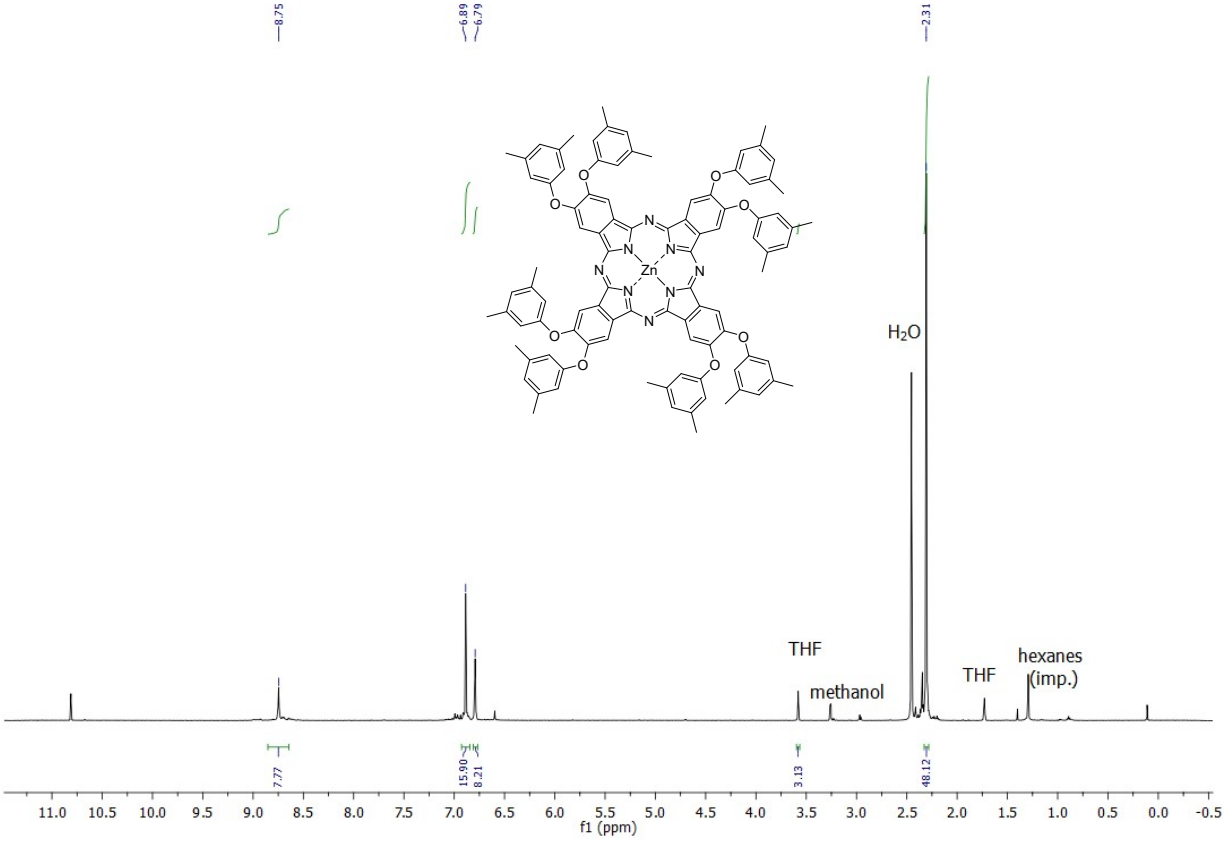
^{1}H NMR spectrum of tetra-(hexyloxy)-zinc-phthalocyanine (7) in THF-d_8.



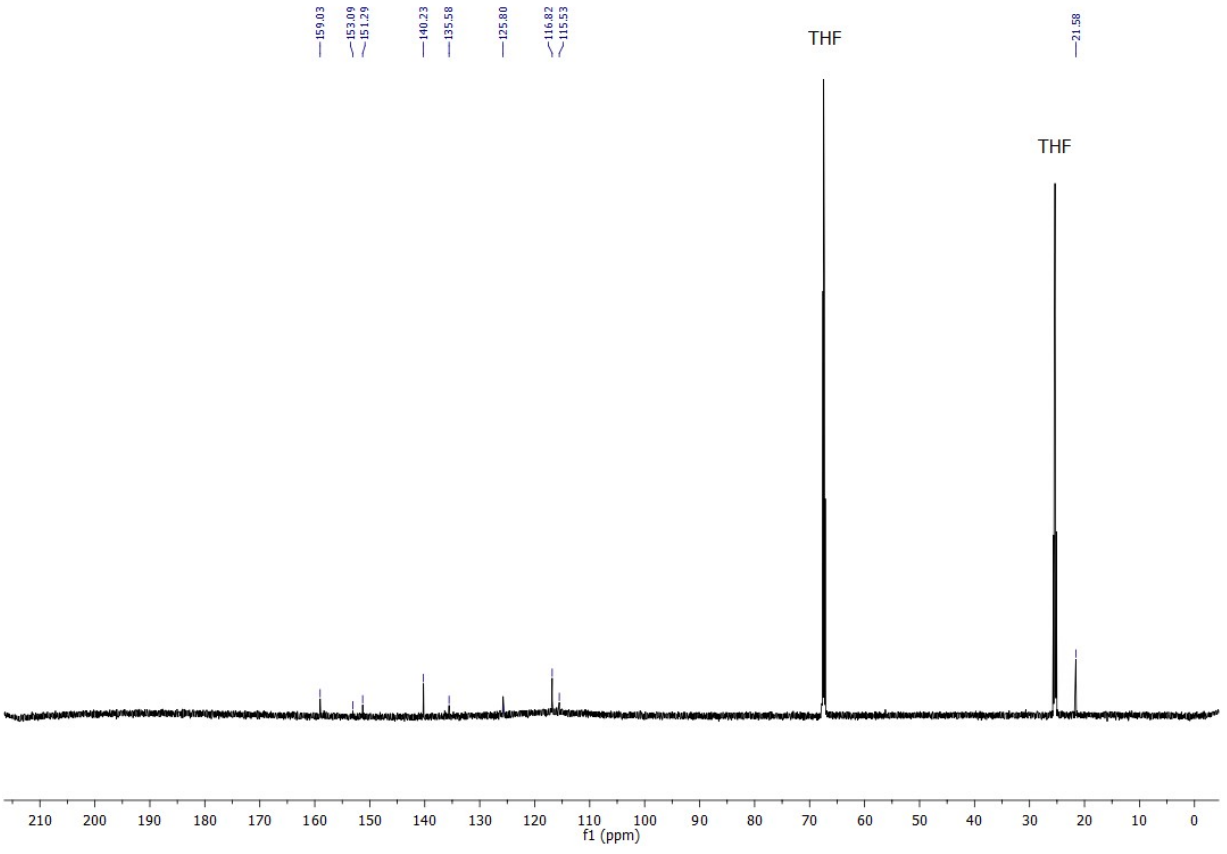
^{13}C NMR spectrum of tetra-(hexyloxy)-zinc-phthalocyanine (7) in THF-d_8.



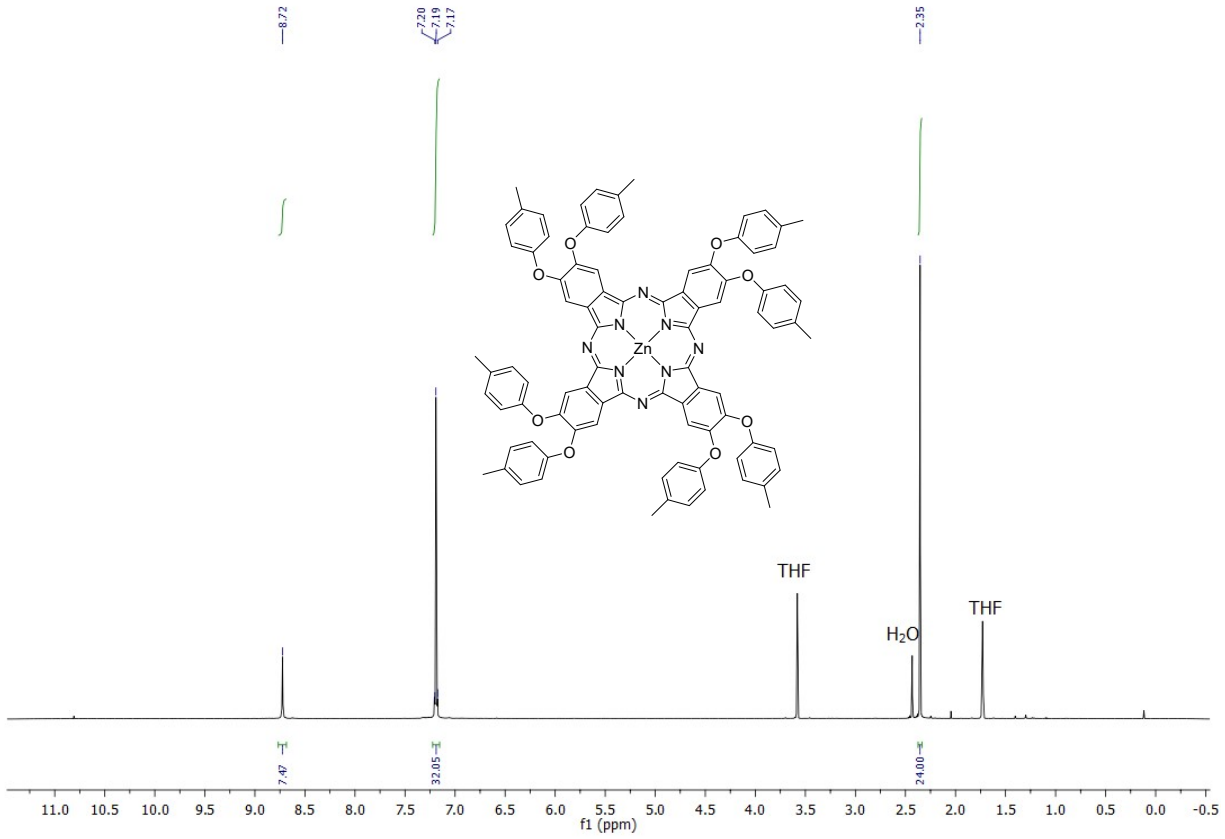
^{1}H NMR spectrum of octakis(3,5-dimethylphenoxy)-zinc-phthalocyanine (8) in THF-d_8.



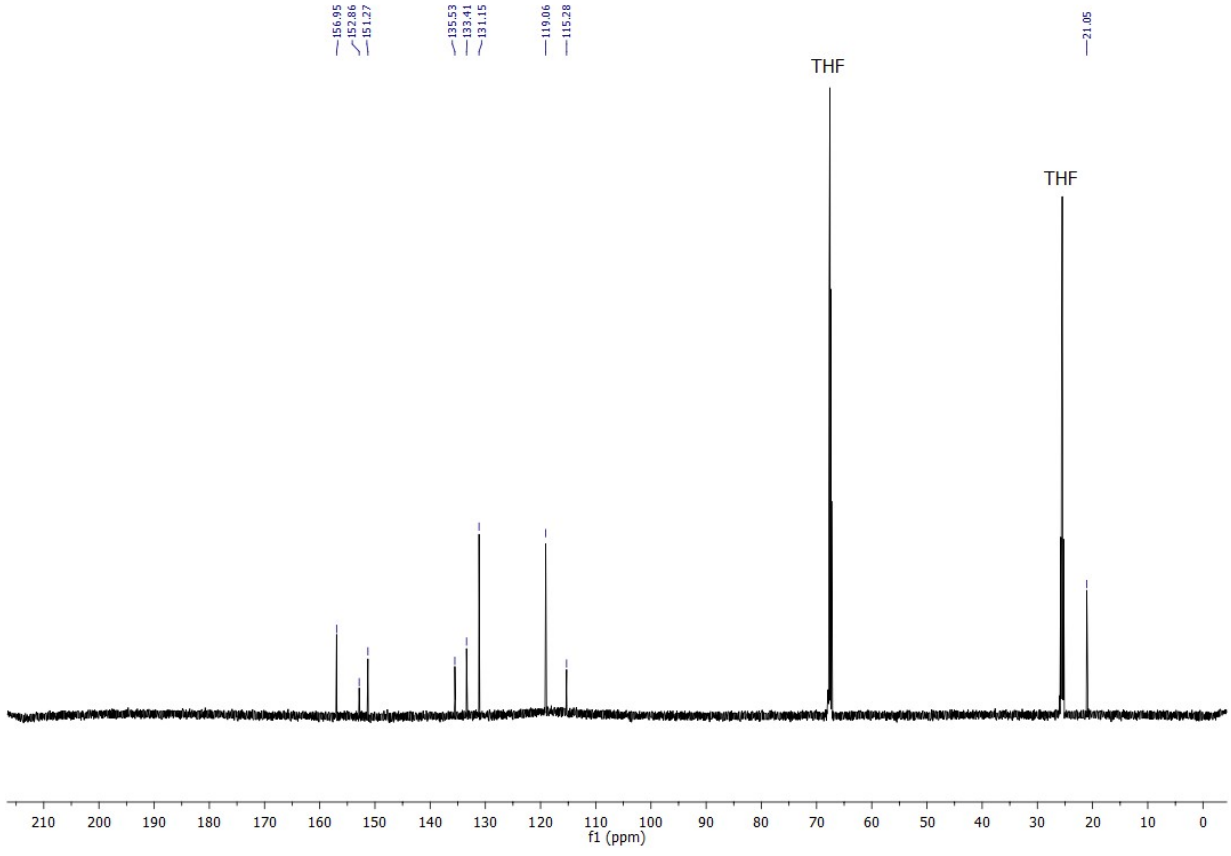
^{13}C NMR spectrum of octakis(3,5-dimethylphenoxy)-zinc-phthalocyanine (8) in THF-d_8.



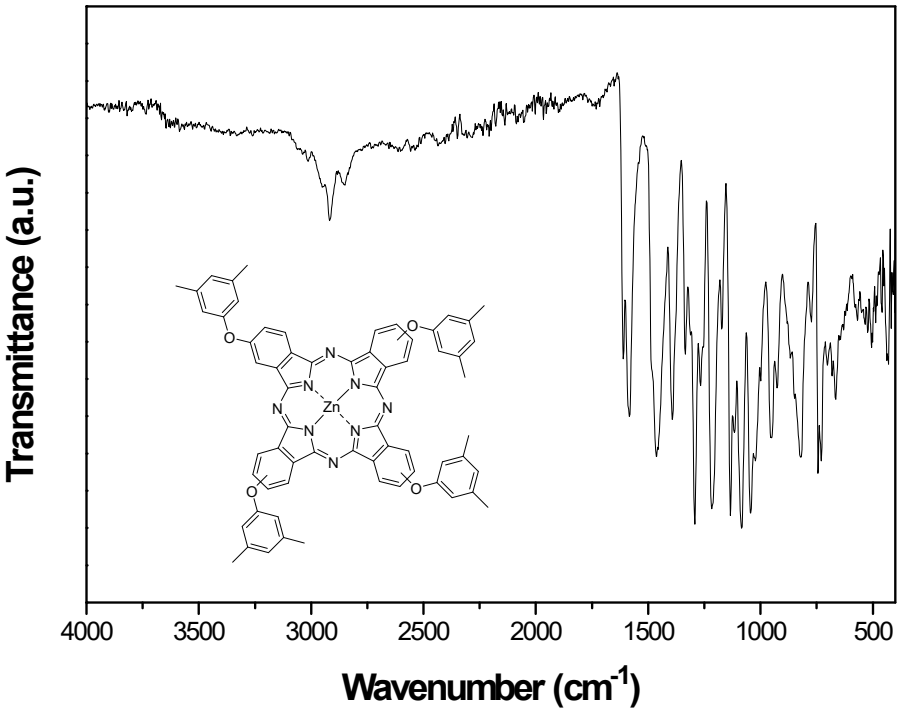
^{1}H NMR spectrum of octakis(p-tolyloxy)-zinc-phthalocyanine (9) in THF-d_8.



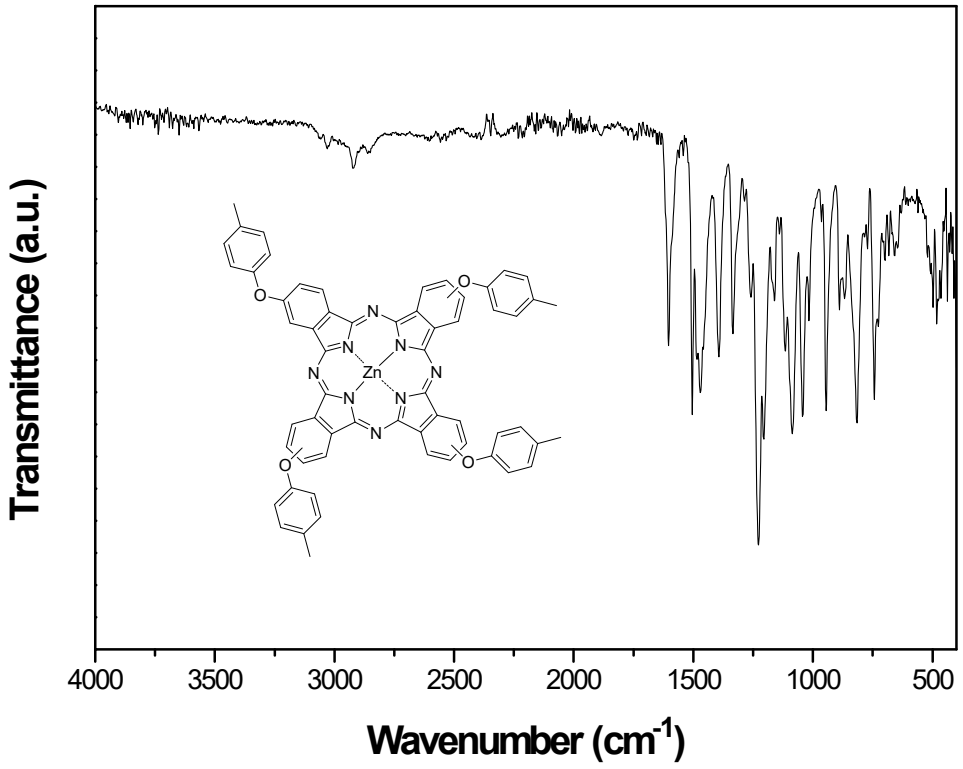
^{13}C NMR spectrum of octakis(p-tolyloxy)-zinc-phthalocyanine (9) in THF-d_8.



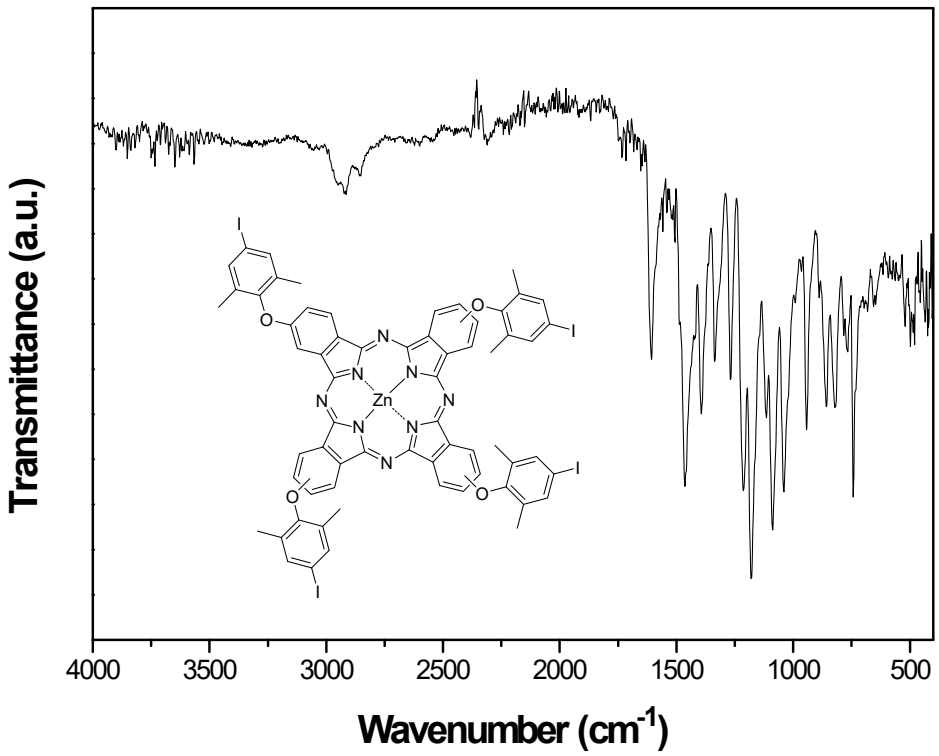
ATR spectrum of tetra-(3,5-dimethylphenoxy)-zinc-phthalocyanine (1).



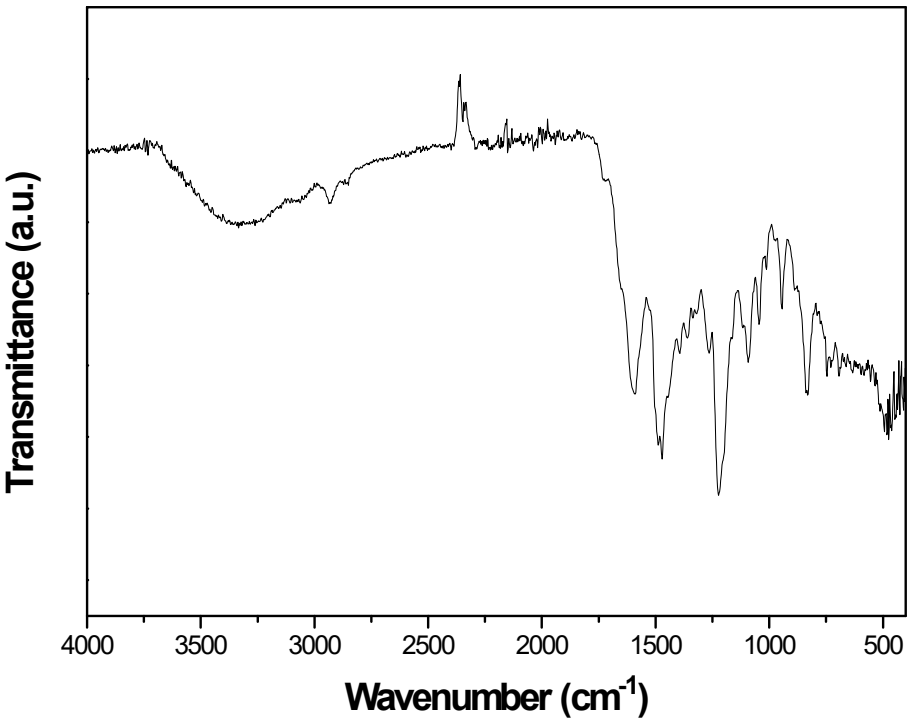
ATR spectrum of tetra-(p-tolyloxy)-zinc-phthalocyanine (2).



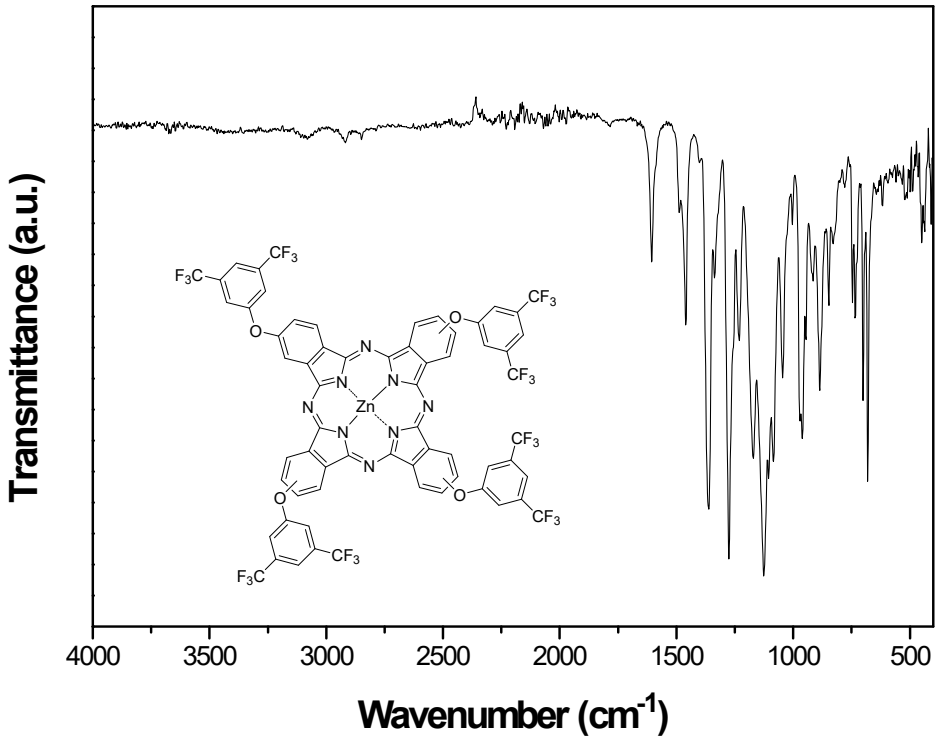
ATR spectrum of tetra-(4-iodo-2,6-dimethylphenoxy)-zinc-phthalocyanine (3).



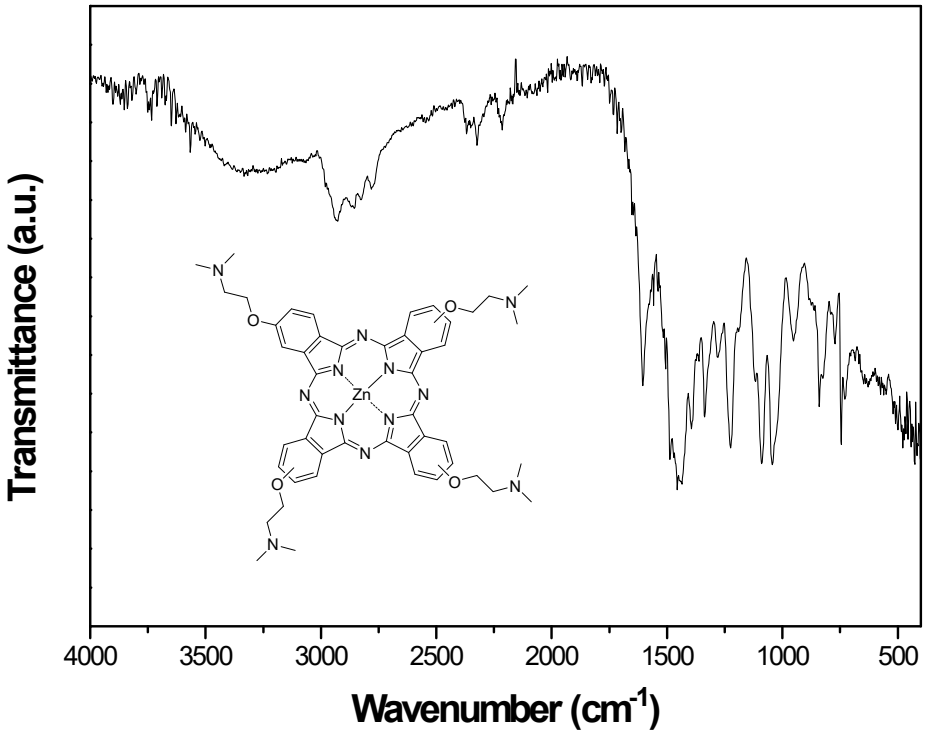
ATR spectrum of phthalocyanine (4).



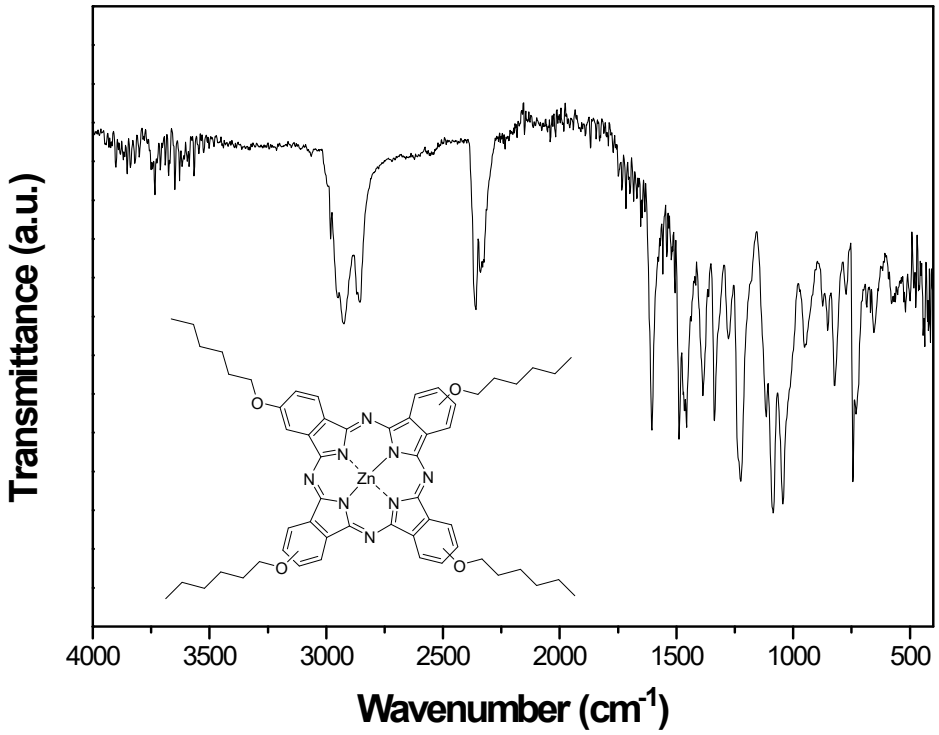
ATR spectrum of tetra-(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine (5).



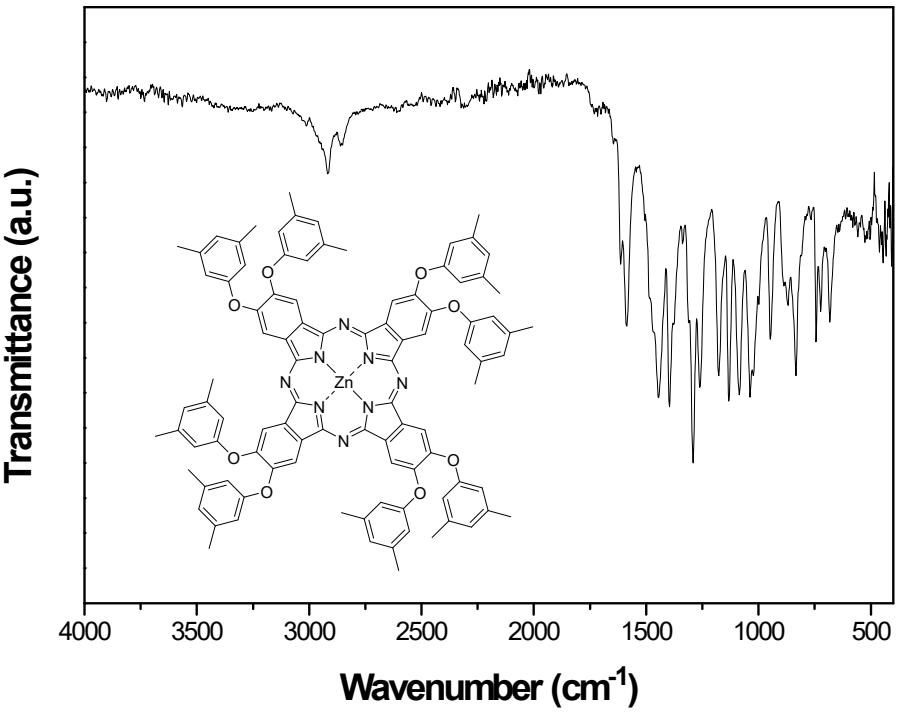
ATR spectrum of tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (6).



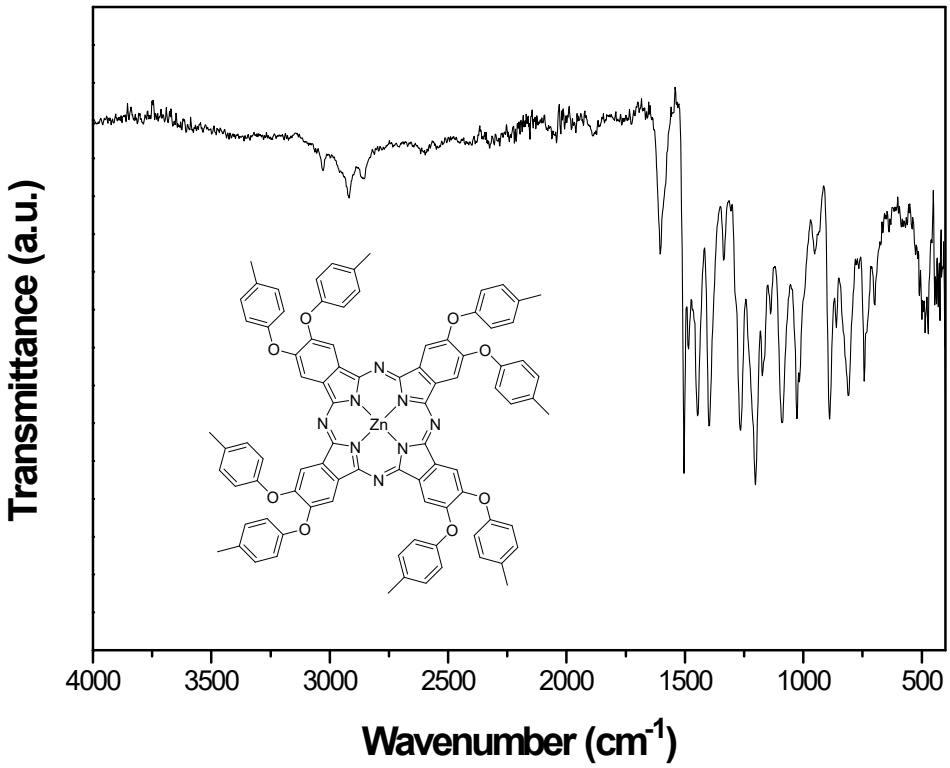
ATR spectrum of tetra-(hexyloxy)-zinc-phthalocyanine (7).



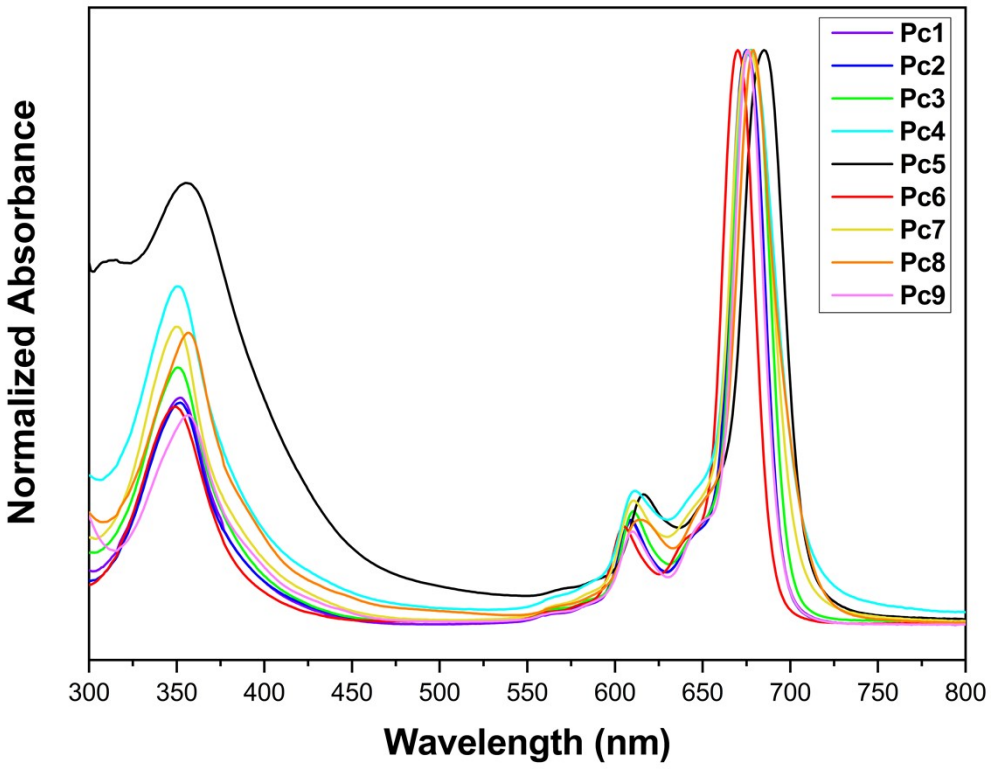
ATR spectrum of octakis(3,5-dimethylphenoxy)-zinc-phthalocyanine (8).



ATR spectrum of octakis(p-tolyloxy)-zinc-phthalocyanine (9).

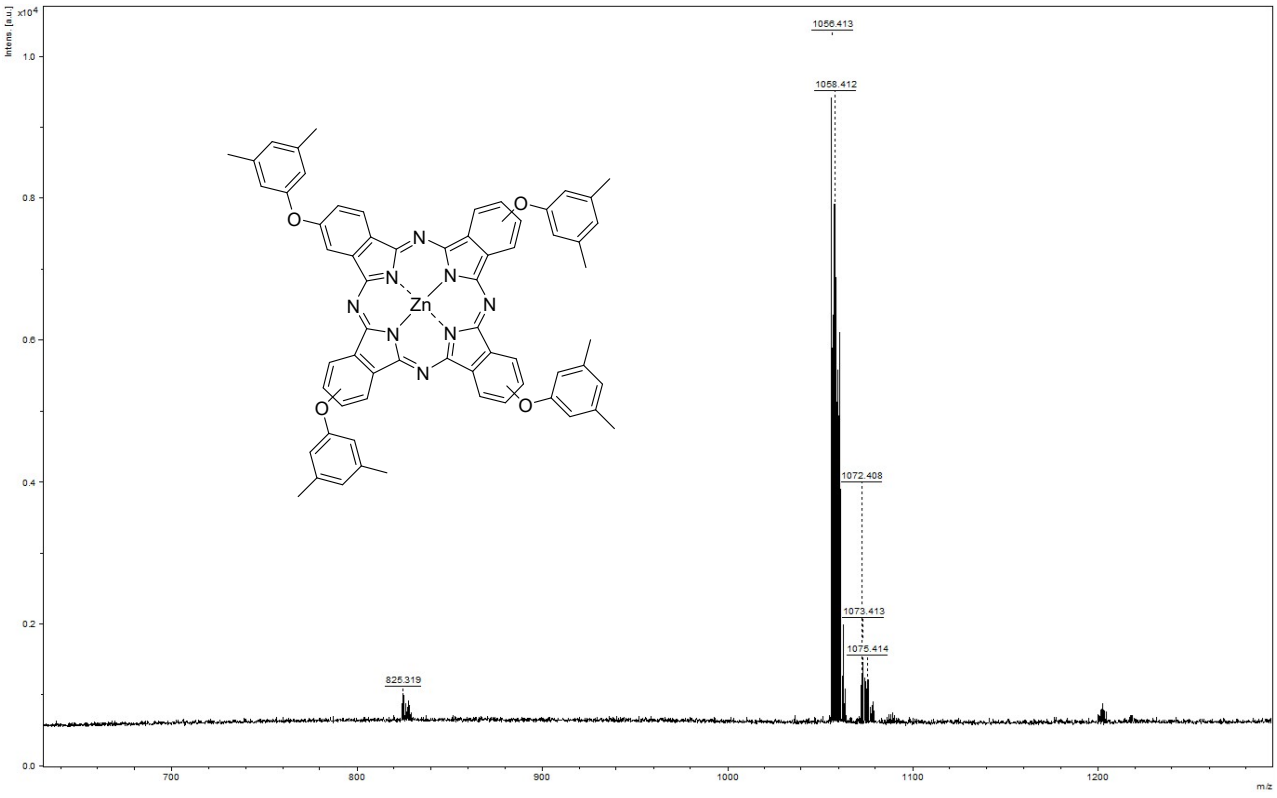


UV-vis spectra of the synthesized zinc phthalocyanines (1-9).

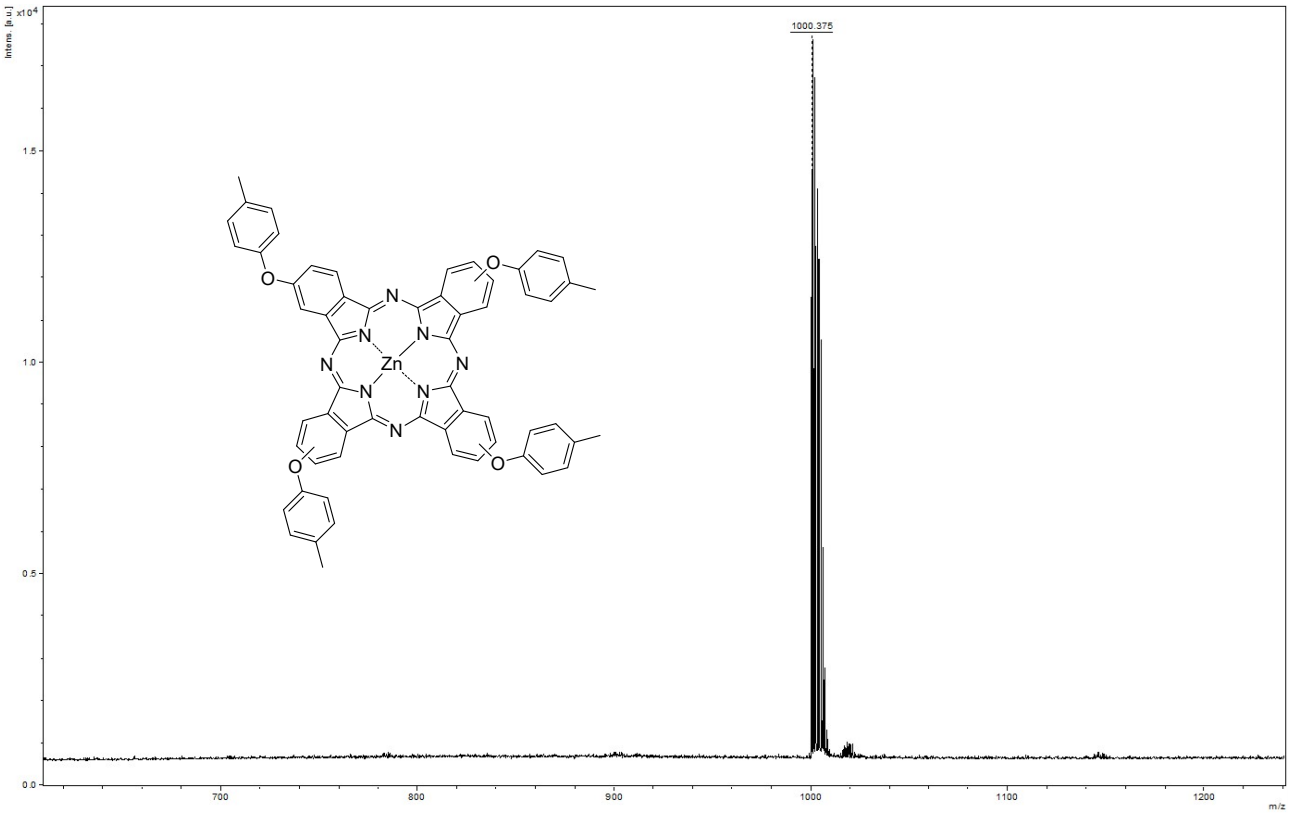


Absorption spectra of zinc phthalocyanines (**1-9**) in THF, except for **4** in pyridine.

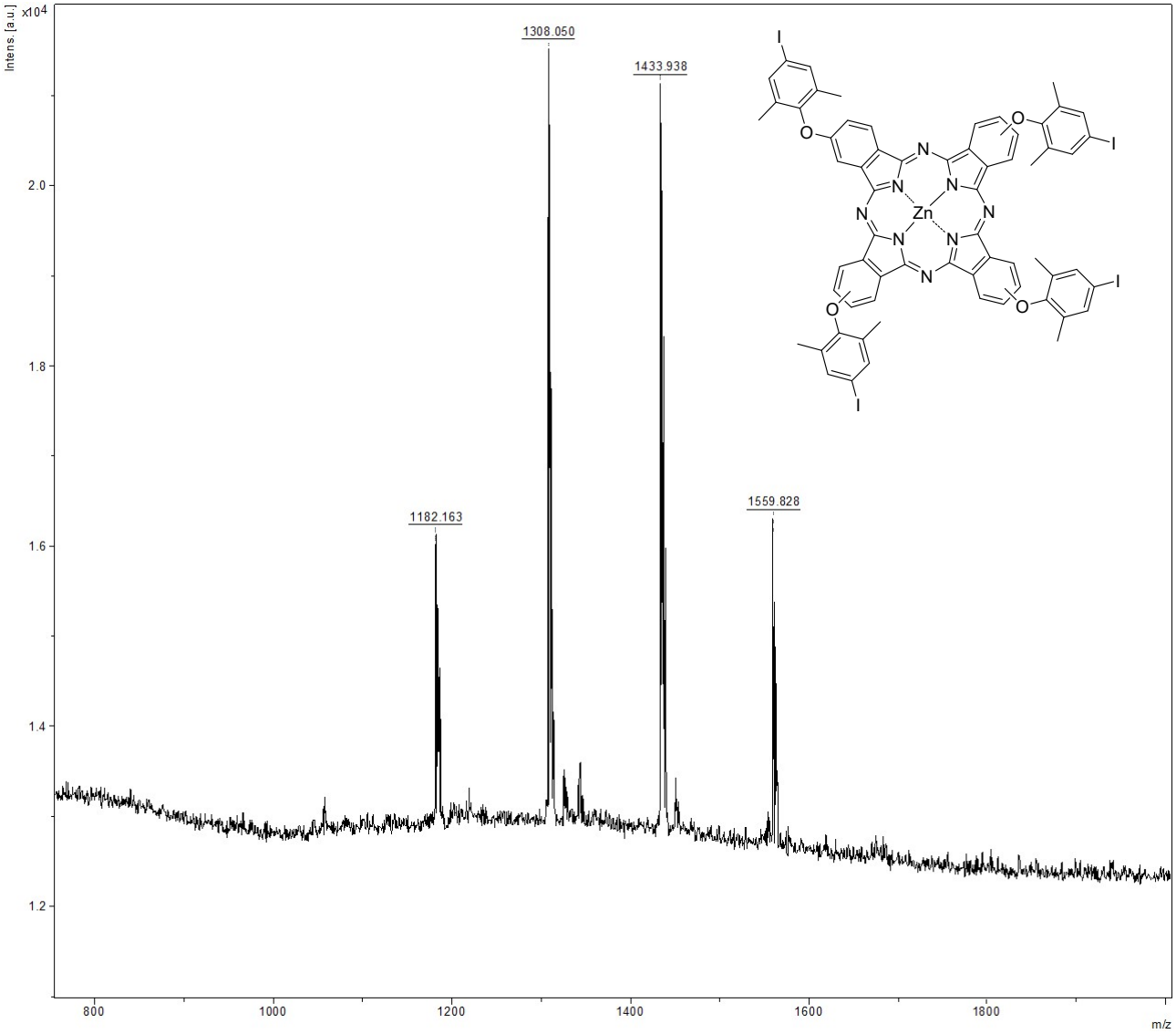
MALDI-TOF spectrum of tetra-(3,5-dimethylphenoxy)-zinc-phthalocyanine (1).



MALDI-TOF spectrum of tetra-(*p*-tolyloxy)-zinc-phthalocyanine (2).

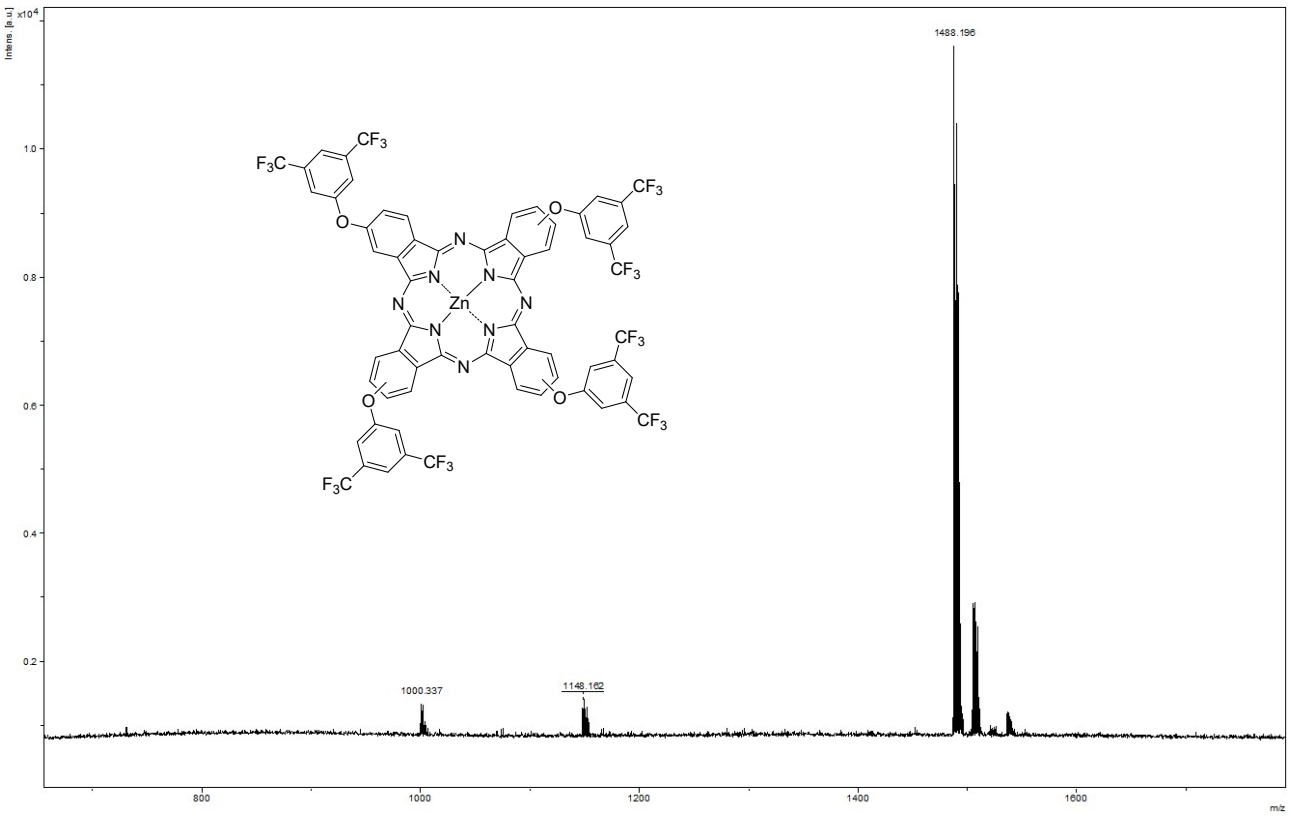


MALDI-TOF spectrum of tetra-(4-iodo-2,6-dimethylphenoxy)-zinc-phthalocyanine (3).

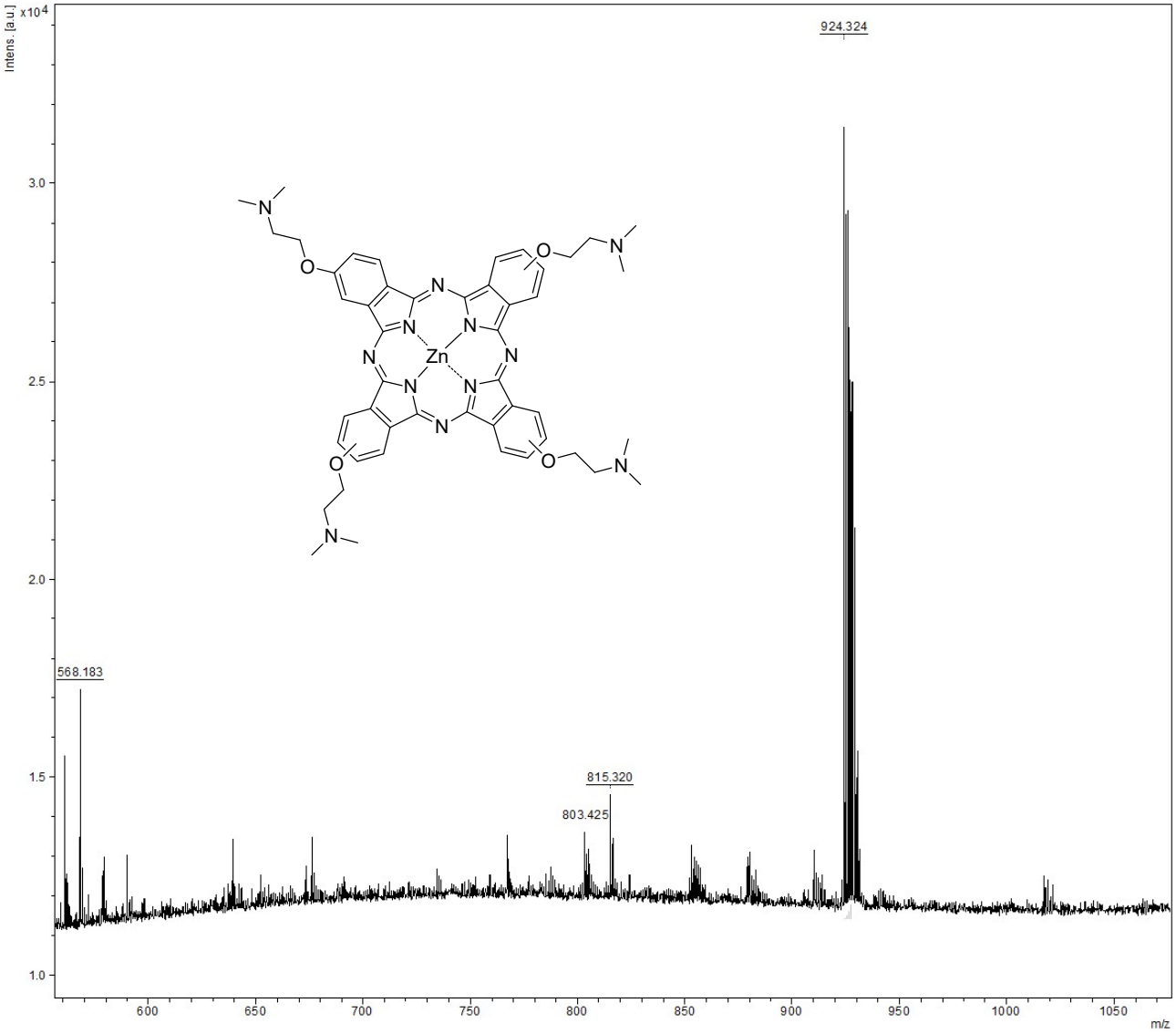


The peaks at m/z 1433.938, 1308.050, and 1182.163 are compatible with the loss of 1, 2, and 3 iodine atoms respectively.

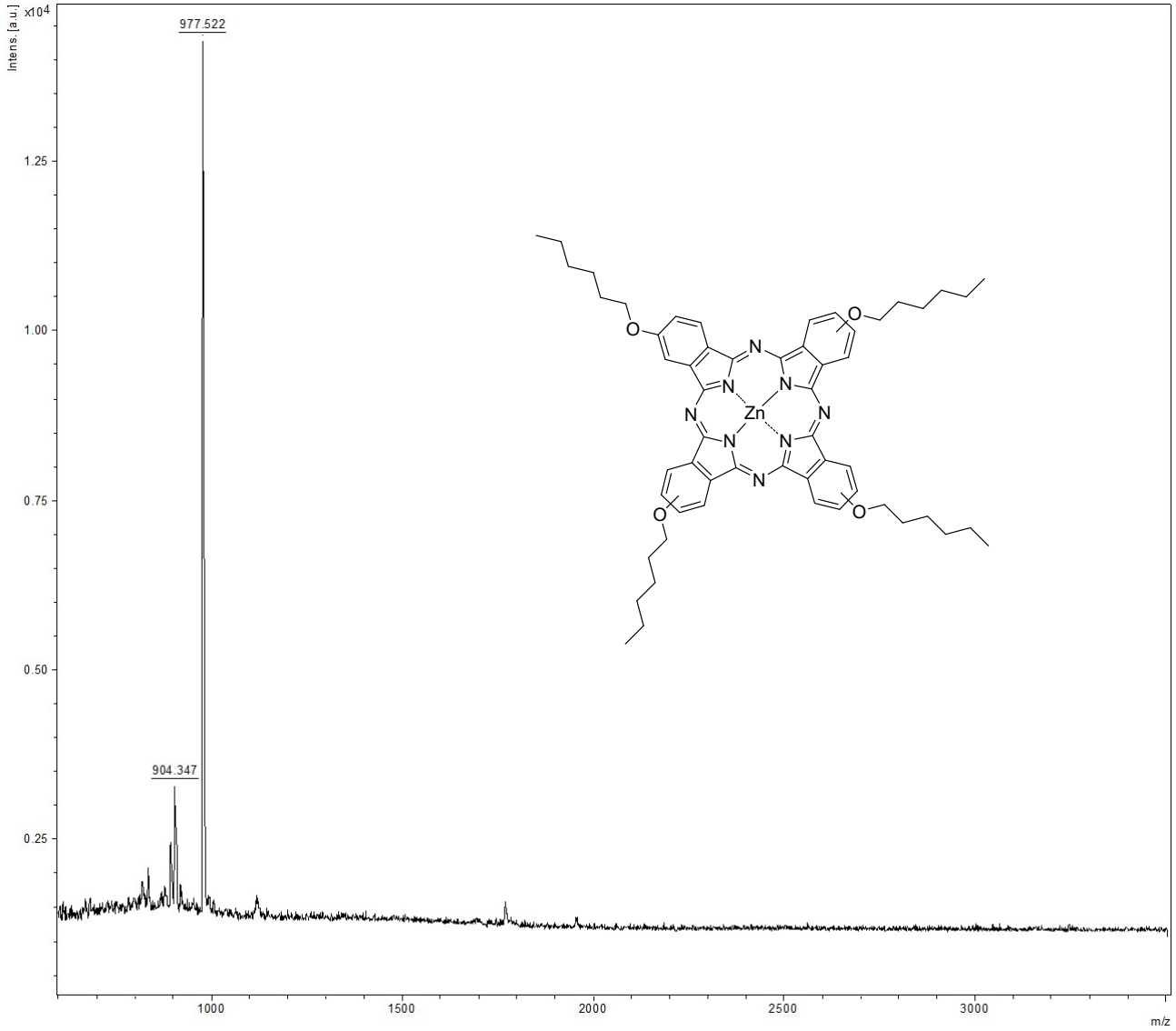
MALDI-TOF spectrum of tetra-(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine (5).



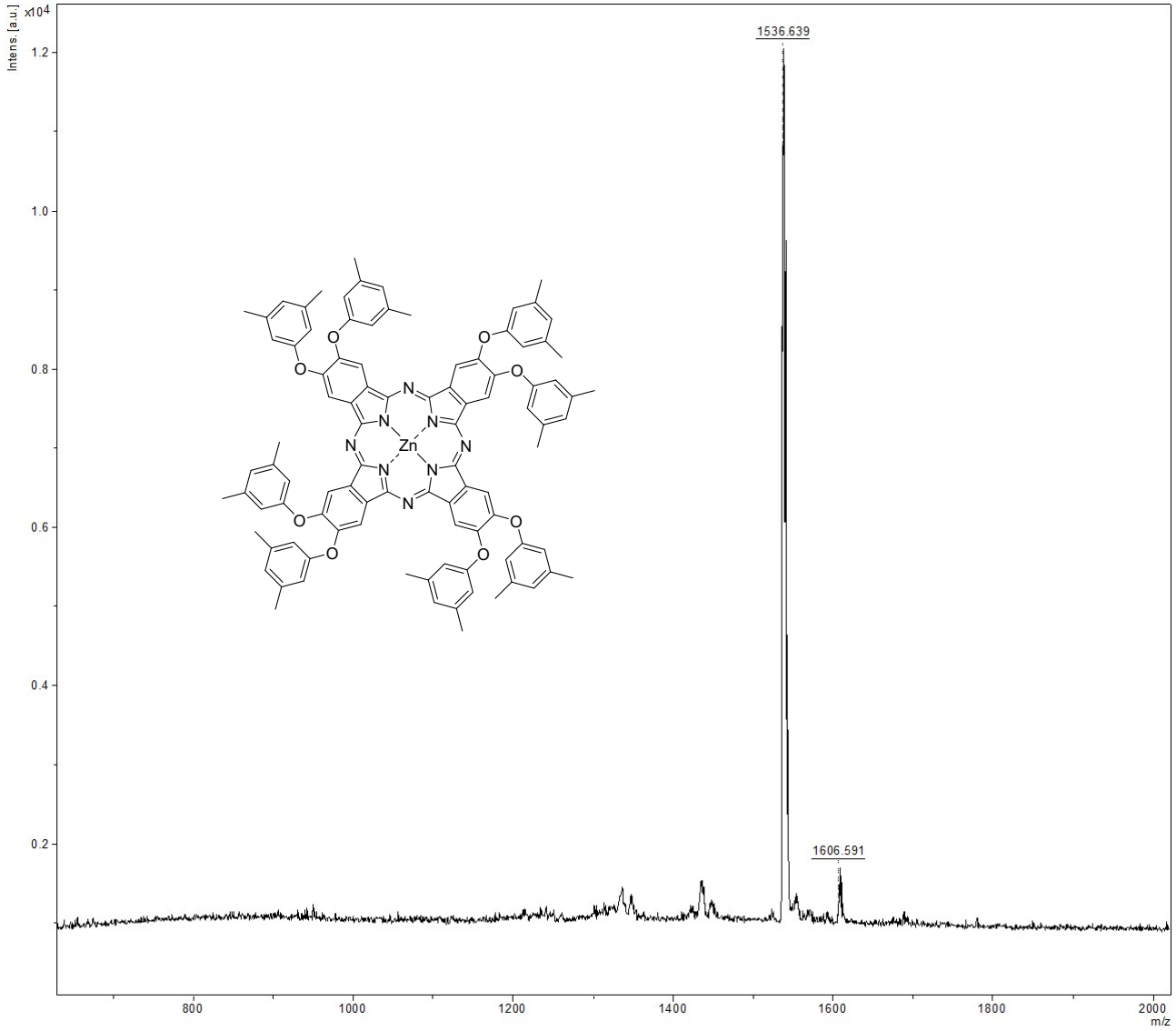
MALDI-TOF spectrum of tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (6).



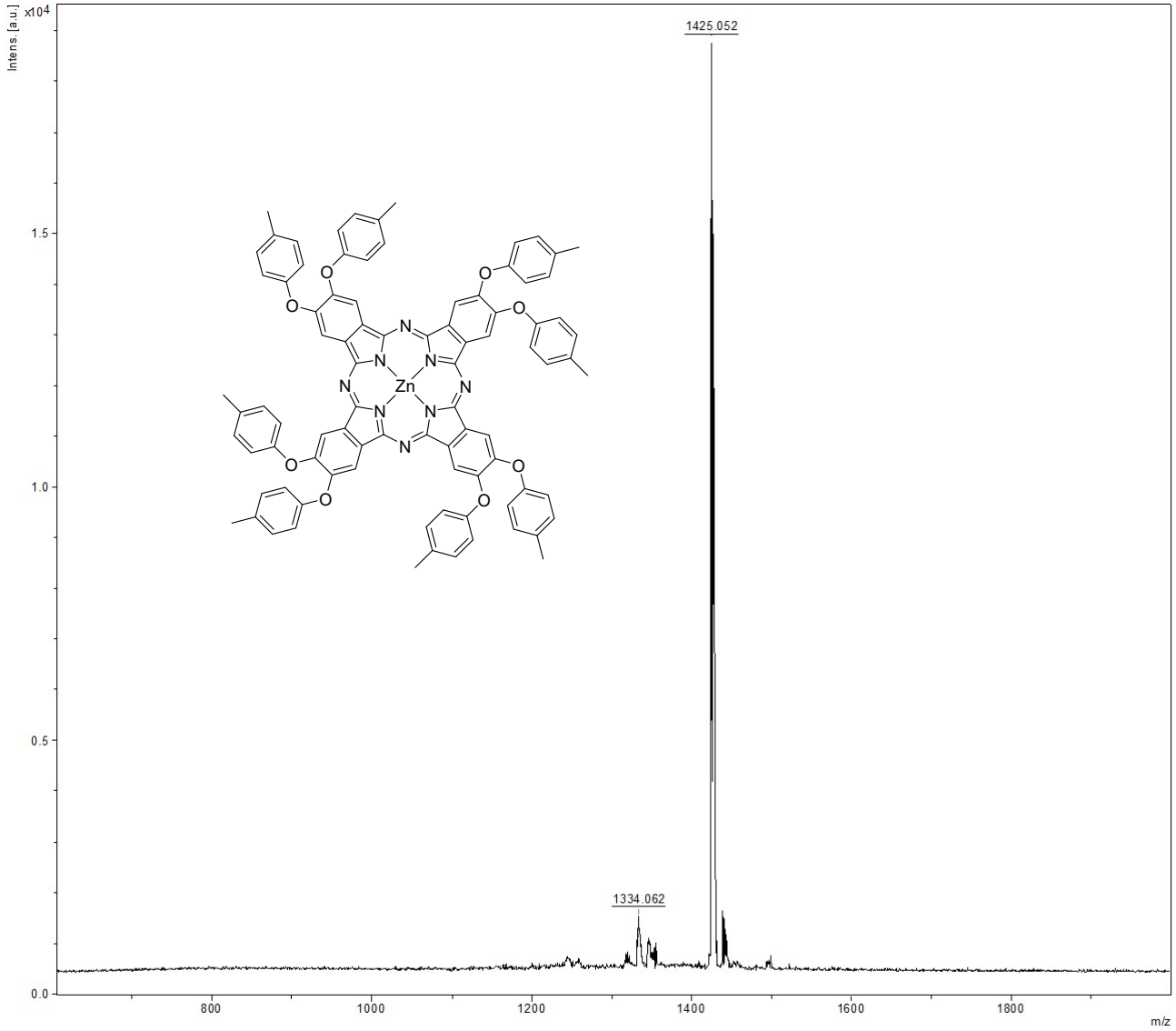
MALDI-TOF spectrum of tetra-(hexyloxy)-zinc-phthalocyanine (7).



MALDI-TOF spectrum of octakis(3,5-dimethylphenoxy)-zinc-phthalocyanine (8).



MALDI-TOF spectrum of octakis(p-tolyloxy)-zinc-phthalocyanine (9).



E-factor calculation

The E-factor (Environmental factor) is used to assess the environmental impact of a chemical process and is defined as the ratio of the total mass of waste generated to the mass of the isolated product.

General equation for the calculation of E-factor:

$$E\text{-}factor = \frac{Mass\ of\ total\ waste\ (g)}{Mass\ of\ product\ (g)}$$

In all calculations, water is excluded from the waste count. This exclusion is consistent with standard practices in green chemistry, where water is typically not considered a harmful by-product.[1]

An estimated 80% of the organic solvents used in the processes described in our paper are recovered and reused, thanks to careful work-up and purification procedures. In particular, solvent mixtures employed in silica pad filtrations are collected and reused multiple times. Although slight variations in polarity may occur upon reuse, the recycled eluents remained suitable for similar separations. This solvent recovery significantly reduces the amount of waste attributed to the process, leading to a more accurate and representative E-factor. The approach reflects an emphasis on sustainability through the minimization of solvent waste and the efficient use of resources.

For literature-reported procedures in which complete experimental details were not available, reasonable approximations were employed to estimate the E-factor, most of which were derived from established sources:[2,3]

- It was assumed that crude products obtained from 1.0 g of starting material would require two washes with 20 mL of water or aqueous solvent mixtures, as well as two washes with 15 mL of organic solvents.
- In cases involving solvent extraction, it was estimated that three separate extractions with 50 mL of organic solvent (totaling 150 mL), along with 1 g of a drying agent such as Na_2SO_4 or $MgSO_4$, would be necessary to isolate 1 g of crude product from the reaction mixture.
- For crystallization steps, it is assumed that 100 mL of solvent are required to isolate 1 g of product, with the procedure performed only once.
- For purifications involving column chromatography, the processing of 1 g of product was assumed to require 400 mL of eluent and a silica gel column packed with 263 g of 60 μm silica gel, as previously reported under ideal conditions (i.e., efficient separation with Rf > 0.3 and optimal sample loading).[4]
- The density of all aqueous solutions (e.g. HCl 1N or aqueous salt solutions) was approximated to 1.0 g/mL.

These standardized approximations were consistently applied across all procedures to facilitate direct comparison while preserving realistic estimates of material consumption and waste production.

- E-factor calculation for compound **1**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
3,5-dimethylphenol			*0.36*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*1.2*	
4-nitrophthalonitrile			*0.5*	
Zinc acetate dihydrate			*0.172*	
DBU	0.4	1.018	*0.407*	
Water	30.0		30.0	
HCl 1N			*2.0*	
Silica gel			*8.0*	
THF	19.5	0.888	17.32	*3.463*
Hexane	37.5	0.661	24.79	*4.958*
Methanol	45.0	0.792	35.64	*7.128*

Amount of product = 0.364 g (48% yield)

Total E-Factor = 257.7

E-factor 80% solvent recovery = 86.9

- E-factor calculation for compound **2**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
4-methylphenol			*0.319*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*1.2*	
4-nitrophthalonitrile			*0.5*	
Zinc acetate dihydrate			*0.172*	
DBU	0.4	1.018	*0.407*	
Water	28.0		28.0	
HCl 1N			*2.0*	
Silica gel			*10.0*	
THF	28.75	0.888	25.53	*5.106*
Hexane	76.25	0.661	50.40	*10.08*
Methanol	10.0	0.792	7.92	1.584

Amount of product = 0.313 g (43% yield)

Total E-factor = 326.2

E-factor 80% solvent recovery = 111.3

- E-factor calculation for compound **3**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
4-iodo-2,6-dimethylphenol			*0.365*	
DMF	2.5	0.948	*2.37*	
K_2CO_3			*0.6*	
4-nitrophthalonitrile			*0.25*	
Zinc acetate dihydrate			*0.086*	
DBU	0.2	1.018	*0.204*	
Water	4.5		4.5	
HCl 1N			*0.5*	
Silica gel			*13.0*	
THF	40.5	0.888	35.96	*7.193*
Petroleum ether	66.0	0.666	43.96	*8.791*
Methanol	25.0	0.792	19.8	*3.96*

Amount of product = 0.210 g (37% yield)

Total E-factor = 556.6

E-factor 80% solvent recovery = 176.7

- E-factor calculation for compound **5**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
3,5-bis(trifluoromethyl)phenol			*0.678*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*1.2*	
4-nitrophthalonitrile			*0.5*	
Zinc acetate dihydrate			*0.172*	
DBU	0.4	1.018	*0.407*	
Water	29.0		29.0	
Silica gel			*10.0*	
Hexane	31.4	0.661	20.755	*4.151*
Ethyl acetate	20.6	0.902	18.501	*3.716*

Amount of product = 0.290 g (27% yield)

Total E-factor = 192.1

E-factor 80% solvent recovery = 83.9

- E-factor calculation for compound **6**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
2-(dimethylamino)ethanol	0.4	0.89	*0.356*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*1.2*	
4-nitrophthalonitrile			*0.5*	
Zinc acetate dihydrate			*0.172*	
DBU	0.4	1.018	*0.407*	
Water	34.0		4.5	
HCl 1N	4.0		*4.0*	
Methanol	7.0	0.792	5.544	*1.109*

Amount of product = 0.330 g (49% yield)

Total E-factor: 47.4

E-factor 80% solvent recovery = 34.0

- E-factor calculation for compound **7**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
Hexan-1-ol	0.4	0.814	*0.326*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*1.2*	
4-nitrophthalonitrile			*0.5*	
Zinc acetate dihydrate			*0.172*	
DBU	0.4	1.018	*0.407*	
HCl 1N	2.0		*2.0*	
Water	22.0		22.0	
Silica gel			*10.0*	
THF	20.0	0.888	17.76	*3.552*
Hexane	30.0	0.661	19.83	*3.966*
Methanol	19.0	0.792	15.048	*3.010*

Amount of product = 0.16 g (22% yield)

Total E-factor = 443.0

E-factor 80% solvent recovery = 179.8

- E-factor calculation for compound **8**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
3,5-dimethylphenol			*0.368*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*0.423*	
4,5-dichlorophthalonitrile			*0.2*	
Zinc acetate dihydrate			*0.06*	
DBU	0.152	1.018	*0.155*	
HCl 1N	5.0		*5.0*	
Water	10.0		10.0	
Silica gel			*10.0*	
THF	30.0	0.888	26.64	*5.328*
Hexane	60.0	0.661	39.66	*7.932*
Methanol	10.0	0.792	7.92	*1.584*

Grams of product = 0.118 g (30% yield)

Total E-factor = 797.4

E-factor 80% solvent recovery = 294.3

- E-factor calculation for compound **9**.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considered toward E-factor (after 80% solvent recovery) (g)
4-methylphenol			*0.34*	
DMF	4.0	0.948	*3.792*	
K_2CO_3			*0.423*	
4,5-dichlorophthalonitrile			*0.2*	
Zinc acetate dihydrate			*0.061*	
DBU	0.152	1.018	*0.155*	
HCl 1N	5.0		*5.0*	
Water	10.0		10.0	
Silica gel			*10.0*	
THF	17.7	0.888	15.73	*3.146*
Hexane	57.3	0.661	38.16	*7.630*
Methanol	15.0	0.792	11.88	*2.376*

Amount of product = 0.114 g (31% yield)

Total E-factor = 751.1

E-factor 80% solvent recovery = 289.5

E-factor calculation for compound **2** synthesized according to the literature method.[5]

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-methylphenol			6.92	
4-nitrophthalonitrile			5.41	
DMSO	60.0	1.100	66.0	
K_2CO_3			10.35	
Dichloromethane	200.0	1.327	265.4	53.08
Na_2CO_3 5% solution in water	200.0		200.0	
Sodium sulfate			7.0	
Hexane	680.0	0.661	449.48	89.90

Amount of product = 6.83 g (73% yield)

E-factor = 147.0

E-factor assuming 80% solvent recovery = 63.2

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-(p-methylphenoxy)phthalonitrile			2.34	
Zinc powder			1.308	
Ammonium molibdate			0.2	
Neutral alumina			263.0	
Toluene	3.0	0.862	2.586	0.52
THF	1025.0	0.888	910.2	182.04
Chloroform	30.0	1.489	44.67	8.93
Methanol	450.0	0.792	356.4	71.28

Amount of product = 1.22 g (52% yield)

E-factor =1294.7

E-factor assuming 80% solvent recovery = 433.1

Total yield: 38%, total E-factor: 1441.7, total E-factor assuming 80% solvent recovery = 496.3

E-factor calculation for compound **5** synthesized according to the literature method.[6]

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-nitrophthalonitrile			1.0	
3,5-bis(trifluoromethyl)phenol			1.66	
DMF	40.0	0.948	37.92	
K_2CO_3			7.98	
Ethanol	130.0	0.789	102.57	20.514

Amount of product = 1.3 g (63% yield)

E-factor = 115.2

E-factor assuming 80% solvent recovery = 52.1

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
3,5-bis(trifluoromethyl)phenoxy]phthalonitrile			0.06	
Zinc acetate			0.01	
Dimethylaminoethanol	2.0		1.78	
Hexane	4.5	0.661	2.97	0.594
Silica gel			2.89	
Dichloromethane	4.26	1.327	5.65	1.13
Methanol	0.14	0.792	0.11	0.022

Amount of product = 0.012 g (11% yield)

E-factor = 1121.5

E-factor assuming 80% solvent recovery = 539.5

Total yield: 7%, total E-factor: 1236.7, total E-factor assuming 80% solvent recovery = 591.6.

E-factor calculation for compound **6** synthesized according to the literature.

Synthetic procedure with 13% total yield:[7]

- The amount of DMF was estimated to be 4 mL. To calculate the quantity of solvent required for extraction, a crude product mass of 0.75 g was assumed.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-nitrophthalonitrile			0.5	
1,2-(dimethylamino)-ethanol			0.356	
K_2CO_3			4.0	
DMF	4.0	0.948	3.792	
Chloroform (extraction)	398.2	1.489	592.92	118.584
Na_2SO_4			0.75	
Silica gel			197.25	
Methanol	14.3	0.792	11.326	2.265

Amount of product = 0.565 g (91% yield)

E-factor = 1434.2

E-factor assuming 80% solvent recovery = 579.0

- A crude product mass of 250 mg was assumed.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-(2-(dimethylamino)ethoxy)phthalonitrile			0.215	
DBU			0.152	
Pentanol	8.0		6.488	
Zinc acetate			0.064	
Aqueous acetic acid	6.45	1.0	6.45	
Diethyl ether	6.45	0.713	4.599	0.92
Ethyl acetate	6.45	0.902	5.818	1.164
Dichloromethane	6.45	1.327	8.559	1.712
Chloroform	83.95	1.489	125.001	25.00
K_2CO_3	37.5		37.5	
Silica gel			65.75	
Methanol	40.0		31.68	6.336

Product obtained = 0.032 g (14% yield)

E-factor = 9132.6

E-factor assuming 80% solvent recovery = 4741.2

Total yield: 13%, total E-factor: 10566.8, Total E-factor assuming 80% solvent recovery = 5320.2.

Synthetic procedure with 55% total yield:[8]

The corresponding phthalonitrile precursor for this synthesis was prepared according to reference [7].

- For the calculation of extraction solvent volumes, it was assumed that 0.6 g of crude product was obtained.

Chemical	Volume (mL)	Density (g/mL)	Mass (g)	Mass of solvents considering a 80% recovery (g)
4-(2-(dimethylamino)ethoxy)phthalonitrile			0.5	
DMAE	0.7	0.890	0.623	
Butan-1-ol	0.7	0.810	0.567	
Zinc acetate			0.15	
Dichloromethane	90.0	1.327	119.43	23.886
Na_2SO_4			0.6	
Al_2O_3			50.0	
Chloroform	240.0	1.489	357.36	71.472

Amount of product = 0.32 g (60% yield)

E-factor = 1652.8

E-factor assuming 80% solvent recovery = 460.9

Total yield: 55%, total E-factor: 3087.0, total E-factor assuming 80% solvent recovery: 1039.9.

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