

Supporting Information

One-pot acid-catalysed synthesis of bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes and evaluation of anticancer activities

Tran Quang Hung,^{*a} Ban Van Phuc,^a Ha Nam Do,^b Thu Hue Tran,^b Hai Yen Nguyen,^b Nguyen Truong Phuoc,^c Truong Mai Chi,^c Dang Van Do,^b Hien Nguyen,^d Truong Thi Thanh Nga,^a Van Tuyen Nguyen^a and Tuan Thanh Dang^{*b}

^a *Institute of Chemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Hanoi, Vietnam. Email : tqhung@ich.vast.vn*

^b *Faculty of Chemistry, VNU-Hanoi University of Science, 19 Le Thanh Tong, Hanoi, Vietnam. Email : dangthanhtuan@hus.edu.vn*

^c *Hanoi-Amsterdam high school for gifted, Hoang Minh Giam, Cau Giay, Hanoi, Vietnam.*

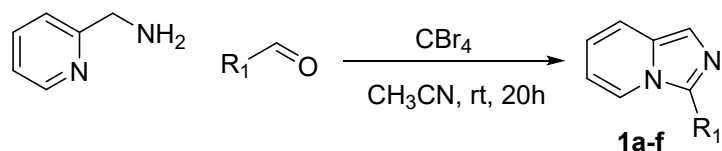
^d *Faculty of Chemistry, Hanoi National University of Education, 136 Xuan Thuy, Cau Giay, Hanoi, Vietnam.*

Table of Contents

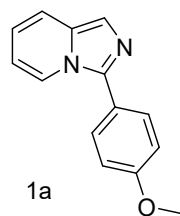
- 1. Experimental procedures**
- 2. Materials and methods in anticancer studies**
- 3. Copies of NMR spectra**
- 4. References**

1. Experimental procedures

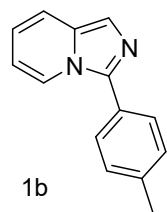
General Procedure A for the synthesis of compound 1a-f [1]



A 50 mL round-bottom flask fitted with a magnetic stir bar was filled with 2-picolylamine (0.60 g, 5.65 mmol), the corresponding aldehyde (1.885 mmol), and acetonitrile (MeCN, 10 mL). Carbon tetrabromide (0.94 g, 2.83 mmol) was added to the solution and stirred at room temperature for 20 hours. The reaction mixture was then diluted with ethyl acetate and rinsed with water. The organic layer was separated and dried on anhydrous sodium sulfate. The solvent was evaporated under reduced pressure using a rotary evaporator, and the crude residue was purified using flash column chromatography on silica gel with a gradient eluent system of n-hexane/ethyl acetate to provide the desired product.

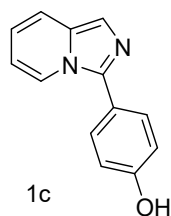


3-(4-methoxyphenyl)imidazo[1,5-a]pyridine 1a prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and 4-methoxybenzaldehyde (257 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (2:1)) to yield **1a** (80%) as a brown solid [2]. ¹H NMR (600 MHz, CDCl₃) δ 8.13 (dq, *J* = 7.4, 1.2 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.49 (s, 1H), 7.41 (dt, *J* = 9.2, 1.3 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.63 (ddd, *J* = 9.2, 6.3, 0.9 Hz, 1H), 6.47 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 1H), 3.83 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 159.9, 138.2, 131.3, 129.4, 122.8, 121.3, 120.1, 118.7, 118.5, 114.4, 112.9, 55.4.

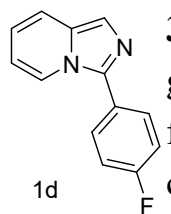


3-(p-tolyl)imidazo[1,5-a]pyridine 1b prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and 4-methylbenzaldehyde (226 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (5:1)) to yield **1b** (79%) as a brown solid [1]. ¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.52 (s, 1H), 7.43 (dt, *J* = 9.2, 1.3 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.71 – 6.61 (m, 1H), 6.49 (ddd, *J* = 7.5, 4.5, 1.3 Hz, 1H),

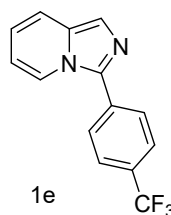
2.41 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 138.6, 138.4, 131.5, 129.6, 127.8, 127.6, 121.5, 120.4, 118.7, 118.5, 112.9, 21.4.



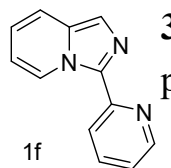
4-(imidazo[1,5-a]pyridin-3-yl)phenol 1c prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and 4-hydroxybenzaldehyde (230 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (1:1)) to yield **1c** (75%) as a brown solid [1]. ¹H NMR (600 MHz, DMSO) δ 9.81 (s, 1H), 8.31 (d, *J* = 7.4 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.60 – 7.52 (m, 1H), 7.46 (s, 1H), 6.95 (tt, *J* = 6.4, 2.0 Hz, 2H), 6.81 – 6.70 (m, 1H), 6.64 (tdd, *J* = 8.5, 3.8, 2.1 Hz, 1H). ¹³C NMR (151 MHz, DMSO) δ 157.7, 137.8, 130.8, 129.2, 121.6, 121.0, 119.7, 118.5, 118.4, 115.7, 115.7, 112.9.



3-(4-fluorophenyl)imidazo[1,5-a]pyridine 1d prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and 4-fluorobenzaldehyde (234 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (5:1)) to yield **1d** (82%) as a brown solid [2]. ¹H NMR (500 MHz, CDCl₃) δ 8.10 (d, *J* = 7.3 Hz, 1H), 7.75 – 7.65 (m, 2H), 7.49 (s, 1H), 7.41 (dt, *J* = 9.2, 1.2 Hz, 1H), 7.20 – 7.08 (m, 2H), 6.69 – 6.59 (m, 1H), 6.49 (ddd, *J* = 7.4, 6.3, 1.3 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 163.0 (d, *J* = 248.9 Hz), 137.5, 131.8, 130.0 (d, *J* = 8.2 Hz), 126.9 (d, *J* = 3.4 Hz), 121.3, 120.8, 119.0 (d, *J* = 2.4 Hz), 116.4, 116.2, 113.4.



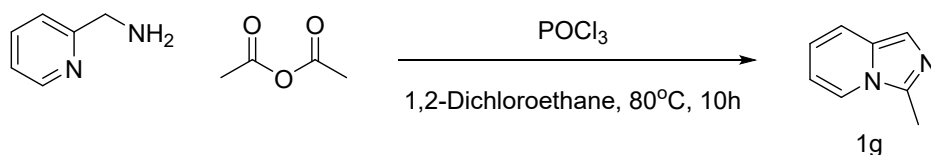
3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine 1e prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and 4-(trifluoromethyl)benzaldehyde (328 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (5:1)) to yield **1e** (80%) as a brown solid [1]. ¹H NMR (600 MHz, CDCl₃) δ 8.27 (dq, *J* = 7.3, 1.0 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.79 – 7.71 (m, 2H), 7.59 (s, 1H), 7.51 (dt, *J* = 9.2, 1.2 Hz, 1H), 6.77 (ddd, *J* = 9.1, 6.4, 0.9 Hz, 1H), 6.62 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 136.7, 133.9, 132.3, 130.2 (q, *J* = 32.5 Hz), 126.0 (q, *J* = 3.8 Hz), 124.0 (d, *J* = 272.2 Hz), 121.4, 121.2, 119.3, 119.0, 113.8.



3-(pyridin-2-yl)imidazo[1,5-a]pyridine 1f prepared following general procedure A using 2-Picolylamine (612 mg; 5.65 mmol) and

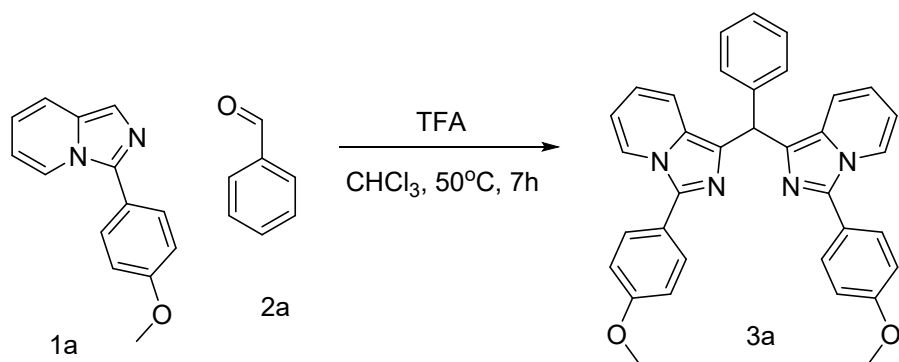
picolinaldehyde (202 mg, 1.885 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (2:1)) to yield **1f** (90%) as a brown solid [3]. ¹H NMR (600 MHz, CDCl₃) δ 9.96 (dq, *J* = 7.3, 1.1 Hz, 1H), 8.63 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 8.34 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.77 (td, *J* = 7.8, 1.8 Hz, 1H), 7.59 (s, 1H), 7.53 (dt, *J* = 9.1, 1.3 Hz, 1H), 7.18 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 6.85 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.72 (ddd, *J* = 7.5, 6.4, 1.3 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 151.2, 148.1, 136.5, 135.5, 133.0, 126.0, 121.7, 121.5, 121.0, 120.1, 118.0, 113.5.

Procedure for preparing 3-methylimidazo[1,5-*a*]pyridine **1g**



2-Picolylamine (0.5 g; 4.62 mmol), acetic anhydride (0.472 g; 4.62 mmol) and 1,2-dichloroethane (2 ml) were introduced to a flask fitted with a magnetic stir bar. The flask was added POCl₃ 0.52 ml. After that, the reaction temperature gradually increased to 80°C using an oil bath under stirring for 10 hours. After completion, the reaction mixture was cooled to room temperature and quenched with aqueous sodium bicarbonate (NaHCO₃, 3M) solution until the pH reached 7. The reaction mixture was then extracted using ethyl acetate and water. The organic layer was separated, dried over anhydrous sodium sulfate (Na₂SO₄), filtered, and the solvent was evaporated under low pressure with a rotary evaporator. The resulting brown residue was purified by column chromatography (silica gel, DCM/ethyl acetate (1/1)) to yield **1g** (0.593 g, 97 %) as a brown oil. ¹H NMR (600 MHz, CDCl₃) δ 7.64 (dq, *J* = 7.19, 1.10 Hz, 1H), 7.38 (dt, *J* = 9.15, 1.24 Hz, 1H), 7.31 (s, 1H), 6.63 (ddd, *J* = 9.14, 6.33, 0.96 Hz, 1H), 6.53 (ddd, *J* = 7.41, 6.37, 1.18 Hz, 1H), 2.63 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 134.9, 130.3, 120.6, 118.5, 118.2, 117.5, 112.2, 12.5.

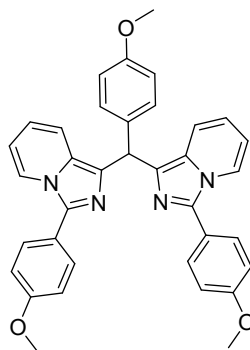
General procedure B for preparation of 1,1'-(phenylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine) **3a** and derivatives



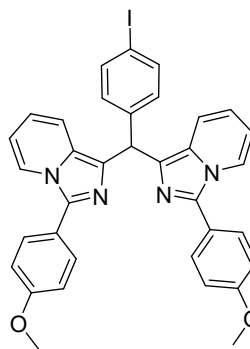
Compound **1a** (150 mg; 0.67 mmol) and benzaldehyde **2a** (71 mg; 0.67 mmol) were introduced to a flask fitted with a magnetic stir bar. The flask was added with a 6 μ L solution of trifluoroacetic acid (TFA) and 0.3 mL of chloroform. After that, the reaction temperature gradually increased to 50°C using an oil bath and stirred for 7 hours. After completion, the reaction mixture was cooled to room temperature and quenched with aqueous sodium bicarbonate (NaHCO_3 , 3M) solution until the pH reached neutral. The mixture was then extracted using ethyl acetate and water. The organic layer was separated, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and the solvent evaporated under low pressure with a rotary evaporator. The resulting brown residue was purified by column chromatography (silica gel, hexane/DCM/ethyl acetate (9/4/2)) to yield **3a** (352 mg, 98 %) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.07 (dt, $J = 7.3, 1.1$ Hz, 2H), 7.73 – 7.64 (m, 4H), 7.52 – 7.46 (m, 2H), 7.41 (dt, $J = 9.3, 1.2$ Hz, 2H), 7.28 (t, $J = 7.7$ Hz, 2H), 7.22 – 7.16 (m, 1H), 7.04 – 6.95 (m, 4H), 6.50 (ddd, $J = 9.3, 6.3, 1.0$ Hz, 2H), 6.41 (ddd, $J = 7.4, 6.3, 1.3$ Hz, 2H), 6.34 (s, 1H), 3.84 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.7, 143.2, 136.7, 133.6, 129.6, 128.9, 128.2, 128.2, 126.2, 123.1, 121.1, 119.7, 117.4, 114.3, 112.7, 55.4, 45.0.

1,1'-(p-tolylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3b prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4- methylbenzaldehyde **2b** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3b** (98%) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.07 (dt, $J = 7.2, 1.1$ Hz, 2H), 7.71 – 7.64 (m, 4H), 7.44 (dt, $J =$

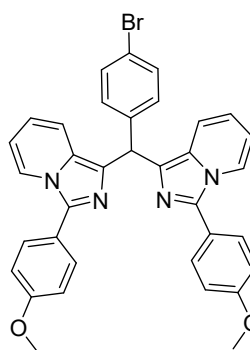
9.3, 1.3 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.11 – 7.05 (m, 2H), 7.03 – 6.97 (m, 4H), 6.50 (ddd, $J = 9.3, 6.3, 0.9$ Hz, 2H), 6.42 (ddd, $J = 7.5, 6.3, 1.3$ Hz, 2H), 6.29 (s, 1H), 3.85 (d, $J = 0.6$ Hz, 6H), 2.30 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.7, 140.2, 136.6, 135.6, 133.8, 129.7, 128.9, 128.7, 128.1, 123.2, 121.0, 119.8, 117.3, 114.3, 112.7, 55.4, 44.6, 21.1.



1,1'-((4-methoxyphenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3c prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4-methoxybenzaldehyde **2c** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3c** (97%) as a bright green solid [4]. ^1H NMR (600 MHz, CDCl_3) δ 8.06 (dt, $J = 7.3, 1.1$ Hz, 2H), 7.70 – 7.64 (m, 4H), 7.45 – 7.37 (m, 4H), 7.03 – 6.96 (m, 4H), 6.86 – 6.79 (m, 2H), 6.48 (ddd, $J = 9.3, 6.3, 1.0$ Hz, 2H), 6.39 (ddd, $J = 7.4, 6.3, 1.2$ Hz, 2H), 6.29 (s, 1H), 3.83 (s, 6H), 3.75 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.7, 158.0, 136.6, 135.5, 134.0, 129.8, 129.6, 128.1, 123.2, 121.1, 119.7, 117.3, 114.3, 113.6, 112.7, 55.4, 55.2, 44.3.

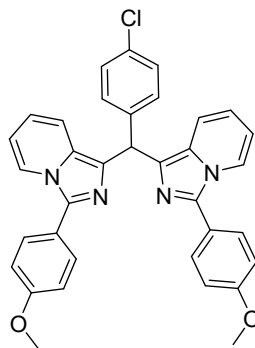


1,1'-((4-iodophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3d prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4-iodobenzaldehyde **2d** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3d** (95%) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.09 (dt, $J = 7.3, 1.1$ Hz, 2H), 7.71 – 7.64 (m, 4H), 7.60 – 7.55 (m, 2H), 7.48 (dt, $J = 9.3, 1.2$ Hz, 2H), 7.25 – 7.21 (m, 2H), 7.05 – 6.97 (m, 4H), 6.54 (ddd, $J = 9.3, 6.3, 1.0$ Hz, 2H), 6.44 (ddd, $J = 7.4, 6.3, 1.2$ Hz, 2H), 6.24 (s, 1H), 3.86 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.8, 143.2, 137.2, 136.8, 133.0, 131.0, 129.6, 128.2, 123.0, 121.2, 119.4, 117.6, 114.4, 112.8, 91.6, 55.4, 44.5.



1,1'-((4-bromophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3e prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and

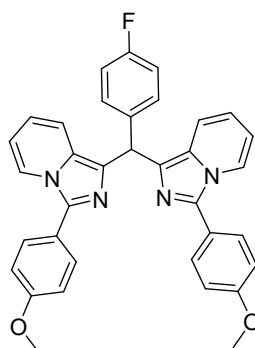
4-bromobenzaldehyde **2e** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3e** (95%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.06 (dt, *J* = 7.3, 1.1 Hz, 2H), 7.71 – 7.63 (m, 4H), 7.48 (dt, *J* = 9.3, 1.3 Hz, 2H), 7.39 (s, 4H), 7.03 – 6.95 (m, 4H), 6.51 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 2H), 6.39 (ddd, *J* = 7.4, 6.3, 1.3 Hz, 2H), 6.28 (s, 1H), 3.82 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 159.8, 142.4, 136.8, 133.0, 131.2, 130.7, 129.6, 128.2, 123.0, 121.2, 120.1, 119.4, 117.7, 114.4, 112.8, 55.4, 44.3.



1,1'-((4-chlorophenyl)methylene)bis(3-(4-

methoxyphenyl)imidazo[1,5-a]pyridine) **3f prepared following**

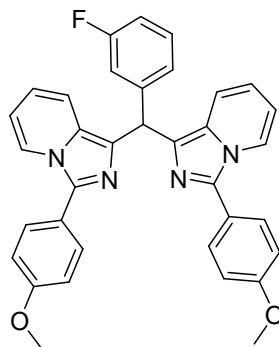
general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4-chlorobenzaldehyde **2f** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3f** (97%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.07 (dt, *J* = 7.3, 1.1 Hz, 2H), 7.71 – 7.64 (m, 4H), 7.47 (dt, *J* = 9.3, 1.2 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.26 – 7.22 (m, 2H), 7.04 – 6.95 (m, 4H), 6.51 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 2H), 6.40 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 2H), 6.29 (s, 1H), 3.82 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 159.8, 141.9, 136.8, 133.1, 131.9, 130.2, 129.6, 128.2, 128.1, 123.0, 121.2, 119.4, 117.6, 114.4, 112.8, 55.4, 44.3.



1,1'-((4-fluorophenyl)methylene)bis(3-(4-

methoxyphenyl)imidazo[1,5-a]pyridine) **3g prepared following**

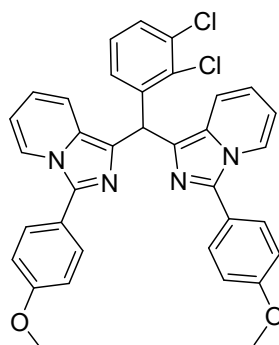
general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4-fluorobenzaldehyde **2g** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3g** (98%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.07 (dt, *J* = 7.3, 1.1 Hz, 2H), 7.71 – 7.64 (m, 4H), 7.49 – 7.40 (m, 4H), 7.03 – 6.98 (m, 4H), 6.99 – 6.93 (m, 2H), 6.51 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 2H), 6.41 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 2H), 6.31 (s, 1H), 3.84 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 161.5 (d, *J* = 244.0 Hz), 159.8, 139.1 (d, *J* = 3.0 Hz), 136.8, 133.5, 130.4 (d, *J* = 8.0 Hz), 129.7, 128.2, 123.1, 121.2, 119.5, 117.6, 114.9 (d, *J* = 21.2 Hz), 114.4, 112.8, 55.4, 44.3.



1,1'-((3-fluorophenyl)methylene)bis(3-(4-

methoxyphenyl)imidazo[1,5-*a*]pyridine) 3h prepared

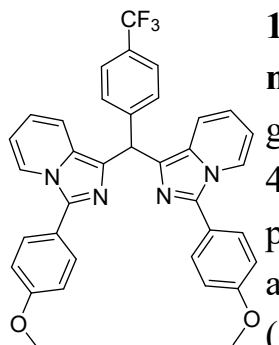
following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 3-fluorobenzaldehyde **2h** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3h** (98%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.05 (dt, *J* = 7.3, 1.1 Hz, 2H), 7.69 – 7.63 (m, 4H), 7.49 (dt, *J* = 9.3, 1.2 Hz, 2H), 7.27 – 7.17 (m, 3H), 7.00 – 6.95 (m, 4H), 6.86 (tdd, *J* = 8.4, 3.1, 1.1 Hz, 1H), 6.49 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 2H), 6.38 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 2H), 6.31 (s, 1H), 3.80 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 162.9 (d, *J* = 244.7 Hz), 159.8, 146.1 (d, *J* = 6.9 Hz), 136.8, 132.9, 129.6, 129.5 (d, *J* = 8.1 Hz), 128.2, 124.6 (d, *J* = 2.6 Hz), 123.0, 121.2, 119.5, 117.7, 115.8 (d, *J* = 21.8 Hz), 114.4, 113.0 (d, *J* = 21.1 Hz), 112.8, 55.4, 44.6.



1,1'-((2,3-dichlorophenyl)methylene)bis(3-(4-

methoxyphenyl)imidazo[1,5-*a*]pyridine) 3i prepared following

general procedure B using compound **1a** (150 mg; 0.67 mmol), and 2,3-dichlorobenzaldehyde **2i** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3i** (95%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.01 (dt, *J* = 7.3, 1.1 Hz, 2H), 7.61 (dd, *J* = 9.1, 2.4 Hz, 5H), 7.30 – 7.23 (m, 3H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.96 – 6.90 (m, 4H), 6.73 (s, 1H), 6.44 (ddd, *J* = 9.4, 6.3, 1.0 Hz, 2H), 6.32 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 2H), 3.74 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 159.8, 143.1, 137.0, 132.9, 132.4, 131.7, 129.6, 129.5, 128.5, 128.4, 126.9, 122.9, 121.3, 118.9, 117.9, 114.3, 112.7, 55.3, 42.7.

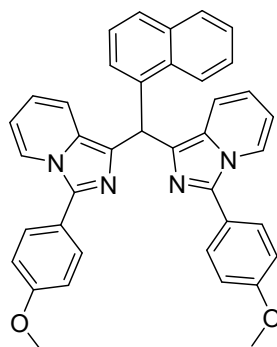


1,1'-((4-(trifluoromethyl)phenyl)methylene)bis(3-(4-

methoxyphenyl)imidazo[1,5-*a*]pyridine) 3j prepared following

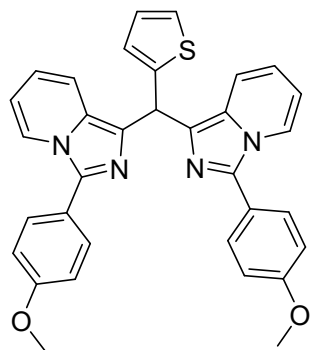
general procedure B using compound **1a** (150 mg; 0.67 mmol), and 4-(trifluoromethyl)benzaldehyde **2j** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3j** (96%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.11 – 8.05 (m, 2H), 7.69 (dt, *J* = 9.6, 2.3 Hz, 4H), 7.65 (d, *J* = 5.0 Hz, 2H), 7.58 – 7.52 (m, 4H), 7.05 – 6.98 (m,

4H), 6.57 – 6.50 (m, 2H), 6.45 – 6.34 (m, 3H), 3.82 (d, $J = 3.8$ Hz, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.8, 147.5, 136.9, 132.7, 129.6, 129.2, 128.3 (q, $J = 32.1$ Hz), 128.2, 125.1 (q, $J = 3.7$ Hz), 124.5 (q, $J = 271.9$ Hz), 123.0, 121.2, 119.3, 117.8, 114.4, 112.8, 55.3, 44.7.



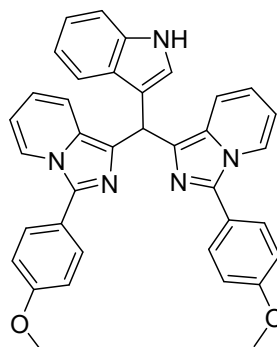
1,1'-(naphthalen-1-ylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3k prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 1-naphthaldehyde **2k** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3k** (80%) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.45 – 8.37 (m, 1H), 8.07 (dt, $J = 6.7$, 1.3 Hz, 2H), 7.85 – 7.79 (m, 1H), 7.74 (d, $J = 8.2$ Hz, 1H), 7.72 –

7.66 (m, 4H), 7.59 (dt, $J = 7.2$, 1.0 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.11 (dt, $J = 9.2$, 1.5 Hz, 2H), 7.07 (s, 1H), 7.04 – 6.97 (m, 4H), 6.43 – 6.33 (m, 4H), 3.85 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 159.7, 138.7, 136.7, 134.0, 133.3, 132.2, 129.7, 128.5, 128.5, 127.3, 126.4, 125.9, 125.3, 124.8, 123.1, 121.1, 119.4, 117.4, 114.3, 112.6, 55.4, 29.7.



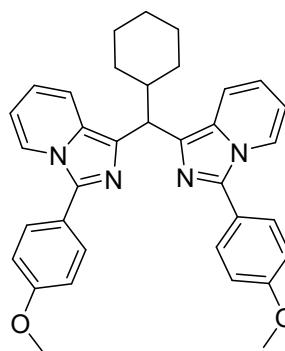
1,1'-(thiophen-2-ylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3l prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and thiophene-2-carbaldehyde **2l** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3l** (98%) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.04 (dt, $J = 7.3$, 1.1 Hz, 2H), 7.71 – 7.64 (m, 4H), 7.60 (dt, $J = 9.4$, 1.2 Hz, 2H),

7.16 (dd, $J = 5.1$, 1.2 Hz, 1H), 7.05 (dt, $J = 3.6$, 1.3 Hz, 1H), 7.01 – 6.95 (m, 4H), 6.91 (dd, $J = 5.1$, 3.6 Hz, 1H), 6.54 (s, 1H), 6.51 (ddd, $J = 9.4$, 6.3, 1.0 Hz, 2H), 6.37 (ddd, $J = 7.5$, 6.3, 1.2 Hz, 2H), 3.80 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.7, 147.4, 136.5, 133.4, 129.6, 127.8, 126.4, 125.6, 124.2, 123.1, 121.1, 119.6, 117.6, 114.3, 112.8, 55.3, 40.8.



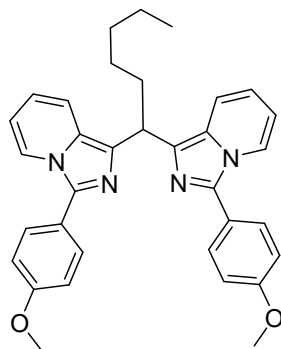
1,1'-((1H-indol-3-yl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3m prepared

following general procedure B using compound **1a** (150 mg; 0.67 mmol), and 1*H*-indole-3-carbaldehyde **2m** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/2)) to yield **3m** (88%) as a purple solid. ¹H NMR (600 MHz, CDCl₃) δ 8.81 (s, 1H), 8.02 (dt, *J* = 7.2, 1.1 Hz, 2H), 7.68 – 7.63 (m, 4H), 7.58 (dt, *J* = 9.3, 1.3 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.17 – 7.10 (m, 2H), 7.01 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.98 – 6.90 (m, 5H), 6.54 (d, *J* = 1.2 Hz, 1H), 6.40 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 2H), 6.34 (ddd, *J* = 7.4, 6.3, 1.3 Hz, 2H), 3.80 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 159.6, 136.7, 136.4, 136.3, 134.0, 129.6, 127.7, 127.4, 123.7, 123.1, 121.4, 120.9, 119.7, 119.6, 118.8, 117.2, 114.3, 112.8, 111.2, 55.3, 36.5.



1,1'-(cyclohexylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine) 3n prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and cyclohexanecarbaldehyde **2n** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/1)) to yield **3n** (55%) as a brown oil.

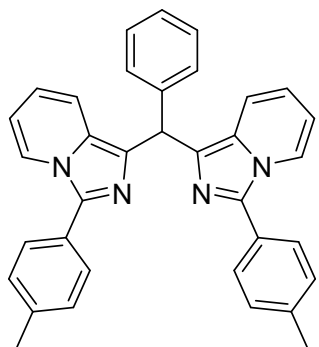
¹H NMR (600 MHz, CDCl₃) δ 8.06 – 7.99 (m, 4H), 7.73 – 7.66 (m, 4H), 7.05 – 7.00 (m, 4H), 6.56 (ddd, *J* = 9.5, 6.2, 0.9 Hz, 2H), 6.43 – 6.37 (m, 2H), 4.48 (d, *J* = 10.6 Hz, 1H), 3.86 (s, 5H), 2.69 (qt, *J* = 10.9, 3.2 Hz, 1H), 1.64 (tdt, *J* = 11.7, 7.9, 3.7 Hz, 5H), 1.30 – 1.13 (m, 4H), 1.11 – 1.01 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 159.7, 136.0, 129.5, 127.9, 120.8, 120.1, 116.7, 114.4, 112.8, 55.4, 41.6, 32.1, 26.7, 26.3.



1,1'-(hexane-1,1-diyl)bis(3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine) 3o prepared following general procedure B using compound **1a** (150 mg; 0.67 mmol), and hexanal **2o** (0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/1)) to yield **3o** (60%) as a brown oil.

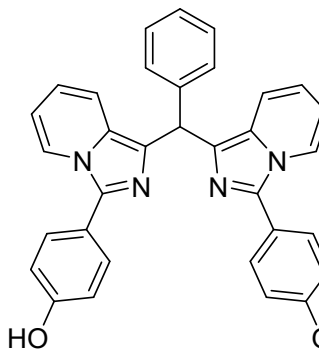
¹H NMR (600 MHz, CDCl₃) δ 8.04 (dt, *J* = 7.2, 1.1 Hz, 2H), 7.75 (dt, *J* = 9.3, 1.2 Hz, 2H), 7.72 – 7.67 (m, 4H), 7.06 – 7.00 (m, 4H), 6.51 (ddd, *J* = 9.3, 6.3, 0.9 Hz, 2H), 6.38 (ddd, *J* = 7.4, 6.3, 1.2 Hz, 2H), 4.79 (t, *J* = 7.9 Hz, 1H), 3.85 (s, 6H), 2.50 (q, *J* = 7.7 Hz, 2H), 1.41 –

1.33 (m, 4H), 1.30 – 1.24 (m, 2H), 0.83 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 159.7, 136.0, 135.1, 129.5, 127.4, 123.2, 120.9, 119.7, 116.8, 114.4, 112.8, 55.4, 39.0, 34.9, 31.8, 28.0, 22.6, 14.1.



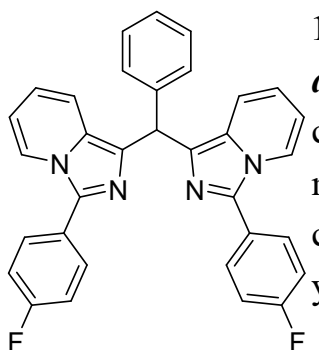
1,1'-(phenylmethylene)bis(3-(p-tolyl)imidazo[1,5-a]pyridine) 3p prepared following general procedure B using compound **1b** (140 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/1)) to yield **3p** (98%) as a bright green solid. ^1H NMR (600 MHz, CDCl_3) δ 8.13 (dt, $J = 7.3, 1.1$ Hz, 2H), 7.69 – 7.63 (m, 4H), 7.53 – 7.49 (m, 2H), 7.47 (dt, $J = 9.3, 1.2$ Hz, 2H), 7.31 – 7.27

(m, 6H), 7.23 – 7.15 (m, 1H), 6.52 (ddd, $J = 9.3, 6.3, 1.0$ Hz, 2H), 6.43 (ddd, $J = 7.4, 6.3, 1.2$ Hz, 2H), 6.36 (s, 1H), 2.41 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 138.3, 136.8, 133.8, 129.5, 128.8, 128.4, 128.2, 128.1, 127.8, 126.2, 121.2, 119.8, 117.5, 112.8, 45.0, 21.4.



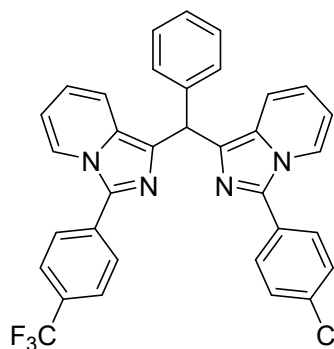
4,4'-((phenylmethylene)bis(imidazo[1,5-a]pyridine-1,3-diyl))diphenol 3q prepared following general procedure B using compound **1c** (141 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol). The product was purified by filter and wash with ethyl acetate to yield **3q** (82%) as a bright blue solid. ^1H NMR (600 MHz, DMSO) δ 8.23 (dd, $J = 7.2, 1.3$ Hz, 2H), 7.62 – 7.53 (m, 4H), 7.53 – 7.44 (m, 4H), 7.28 (t, $J = 7.7$ Hz, 2H), 7.22 – 7.14 (m, 1H), 6.97 – 6.88 (m, 4H),

6.66 – 6.58 (m, 2H), 6.56 (ddd, $J = 7.5, 6.3, 1.3$ Hz, 2H), 6.24 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 157.8, 143.3, 136.3, 133.2, 129.2, 128.7, 128.0, 127.2, 126.0, 121.5, 120.8, 118.6, 117.6, 115.8, 112.8, 43.4.



1,1'-(phenylmethylene)bis(3-(4-fluorophenyl)imidazo[1,5-a]pyridine) 3r prepared following general procedure B using compound **1d** (142 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/1)) to yield **3r** (90%) as a bright green solid. ^1H NMR (600 MHz,

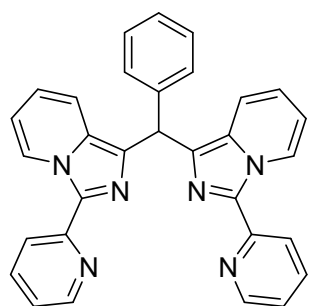
CDCl₃) δ 8.07 (dt, $J = 7.2, 1.1$ Hz, 2H), 7.76 – 7.70 (m, 4H), 7.51 – 7.47 (m, 2H), 7.43 (dt, $J = 9.3, 1.3$ Hz, 2H), 7.32 – 7.27 (m, 2H), 7.23 – 7.19 (m, 1H), 7.19 – 7.13 (m, 4H), 6.54 (ddd, $J = 9.3, 6.3, 1.0$ Hz, 2H), 6.45 (ddd, $J = 7.4, 6.3, 1.2$ Hz, 2H), 6.34 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 162.7 (d, $J = 248.6$ Hz), 143.0, 135.8, 133.9, 130.1 (d, $J = 8.1$ Hz), 128.8, 128.5, 128.3, 126.8 (d, $J = 3.3$ Hz), 126.4, 120.9, 119.7, 117.8, 116.0 (d, $J = 21.8$ Hz), 113.1, 45.0.



1,1'-(phenylmethylene)bis(3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine) 3s

prepared following general procedure B using compound **1e** (176 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/1)) to yield **3s** (85%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 8.20 (dt, $J = 7.3, 1.1$ Hz, 2H), 7.92 (d, $J = 8.1$ Hz,

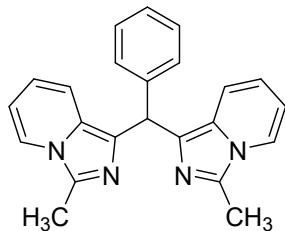
4H), 7.74 (d, $J = 8.2$ Hz, 4H), 7.56 (dt, $J = 9.3, 1.3$ Hz, 2H), 7.53 – 7.48 (m, 2H), 7.31 (t, $J = 7.7$ Hz, 2H), 7.25 – 7.18 (m, 1H), 6.63 (ddd, $J = 9.3, 6.4, 1.0$ Hz, 2H), 6.54 (ddd, $J = 7.4, 6.3, 1.3$ Hz, 2H), 6.39 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 142.7, 135.1, 134.7, 134.0, 129.9 (q, $J = 32.7$ Hz), 129.3, 128.7, 128.3, 128.0, 126.5, 125.9 (q, $J = 3.8$ Hz), 124.1 (q, $J = 272.2$ Hz), 121.0, 119.8, 118.5, 113.8, 44.9.



1,1'-(phenylmethylene)bis(3-(pyridin-2-yl)imidazo[1,5-a]pyridine) 3t

prepared following general procedure B using compound **1f** (131 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, hexane/ethyl acetate (9/4/3)) to yield **3t** (85%) as a bright green solid. ¹H NMR (600 MHz, CDCl₃) δ 9.90 (dt, $J = 7.6, 1.1$ Hz, 2H), 8.59 (ddd, $J = 4.9, 1.8,$

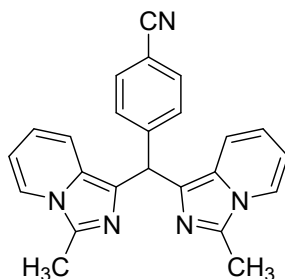
0.9 Hz, 2H), 8.32 (dt, $J = 8.2, 1.1$ Hz, 2H), 7.70 (tdd, $J = 8.2, 1.9, 0.8$ Hz, 2H), 7.58 (dt, $J = 9.1, 1.3$ Hz, 2H), 7.44 (dt, $J = 8.2, 1.0$ Hz, 2H), 7.29 (dd, $J = 8.4, 7.0$ Hz, 2H), 7.24 – 7.19 (m, 1H), 7.11 (ddt, $J = 7.1, 4.8, 1.1$ Hz, 2H), 6.72 (ddd, $J = 9.2, 6.4, 1.0$ Hz, 2H), 6.66 (ddd, $J = 7.5, 6.3, 1.2$ Hz, 2H), 6.43 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 151.3, 148.0, 142.8, 136.3, 134.3, 133.8, 130.2, 128.8, 128.2, 126.3, 125.8, 122.1, 121.2, 119.2, 118.9, 113.5, 44.9.



1,1'-(phenylmethylene)bis(3-methylimidazo[1,5-a]pyridine)

3u prepared following general procedure B using compound **1g** (89 mg; 0.67 mmol), and benzaldehyde **2a** (71 mg; 0.67 mmol).

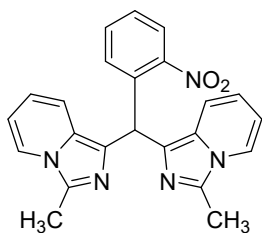
The product was purified by column chromatography (silica gel, DCM/ethyl acetate (1/2)) to yield **3u** (95%) as a dark purple solid. ¹H NMR (600 MHz, CDCl₃) δ 7.51 (ddd, *J* = 5.79, 2.53, 1.26 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.28 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 7.00 (dtd, *J* = 7.46, 2.76, 1.23 Hz, 2H), 6.45 – 6.37 (m, 4H), 6.21 (s, 1H), 2.58 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 142.8, 133.6, 131.4, 128.9, 128.2, 127.0, 126.4, 120.4, 119.1, 116.7, 112.2, 44.1, 12.3.



4-(bis(3-methylimidazo[1,5-a]pyridin-1-yl)methyl)benzotrile

3v prepared following general procedure B using compound **1g** (89 mg; 0.67 mmol), and 4-formylbenzotrile **2p** (88 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, DCM/ethyl acetate (1/2)) to yield **3v** (94%) as a dark purple solid. ¹H NMR

(600 MHz, CDCl₃) δ 7.56 (dt, *J* = 6.63, 1.34 Hz, 2H), 7.55 – 7.51 (m, 2H), 7.49 – 7.44 (m, 2H), 7.16 (dt, *J* = 9.05, 1.44 Hz, 2H), 6.54 – 6.44 (m, 4H), 6.23 (s, 1H), 2.60 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 148.8, 133.9, 132.0, 130.0, 129.7, 127.2, 120.5, 119.2, 118.6, 117.3, 112.4, 109.9, 44.0, 12.4.



1,1'-((2-nitrophenyl)methylene)bis(3-methylimidazo[1,5-

a]pyridine) 3x prepared following general procedure B using

compound **1g** (89 mg; 0.67 mmol), and 2-nitro benzaldehyde **2q** (101 mg; 0.67 mmol). The product was purified by column chromatography (silica gel, DCM/ethyl acetate (1/2)) to yield **3x**

(83%) as a green solid. ¹H NMR (600 MHz, CDCl₃) δ 7.83 (dd, *J* = 8.10, 1.38 Hz, 1H), 7.70 (dd, *J* = 7.96, 1.44 Hz, 1H), 7.53 (dt, *J* = 6.98, 1.19 Hz, 2H), 7.47 (td, *J* = 7.64, 1.41 Hz, 1H), 7.31 (ddd, *J* = 8.63, 7.36, 1.46 Hz, 1H), 7.05 (dt, *J* = 9.20, 1.28 Hz, 2H), 6.92 (s, 1H), 6.50 – 6.38 (m, 4H), 2.57 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 149.1, 137.7, 133.9, 132.5, 132.4, 129.6, 127.5, 127.1, 124.3, 120.5, 118.3, 117.3, 112.3, 38.4, 12.4.

2. Materials and methods in anticancer studies

2.1. Materials and chemicals

Human cancer cell lines

- MCF-7: human breast carcinoma
- SK-LU-1: human lung carcinoma
- HepG2: human hepatocellular carcinoma

Cell culture medium: DMEM (Dulbecco s Modified Eagle Medium) or MEME (Minimum Esental Medium with Eagle salt), with the addition of L-glutamine, sodium pyruvate, NaHCO₃, penicillin/streptomycin, 10% FBS (Fetal Bovine). Serum), Trypsin-EDTA (0.05%)

Basic tools and equipment: Inverted microscope (Axiovert 40 CFL); Cell Counting Chamber (Fisher, USA); Spectrometer (BioTek); CO₂ incubator, -80°C deep refrigerator, liquid nitrogen tank, analytical balance, pH meter and common laboratory instruments.

Other basic chemicals: DMSO (Dimethyl sulfoxide), TCA (Trichloroacetic acid), Tris base, PBS (phosphate buffered saline), Ellipticine, SRB (Sulforhodamine B), Acetic acid etc.

Cell Line Origin: The cell lines were kindly provided by Prof. Dr. J. M. Pezzuto, University of Long-Island, US and Prof. J. Maier, University of Milan, Italy.

2.2. Method for determination of cytotoxicity (cytotoxic assay) for cells cultured monolayer

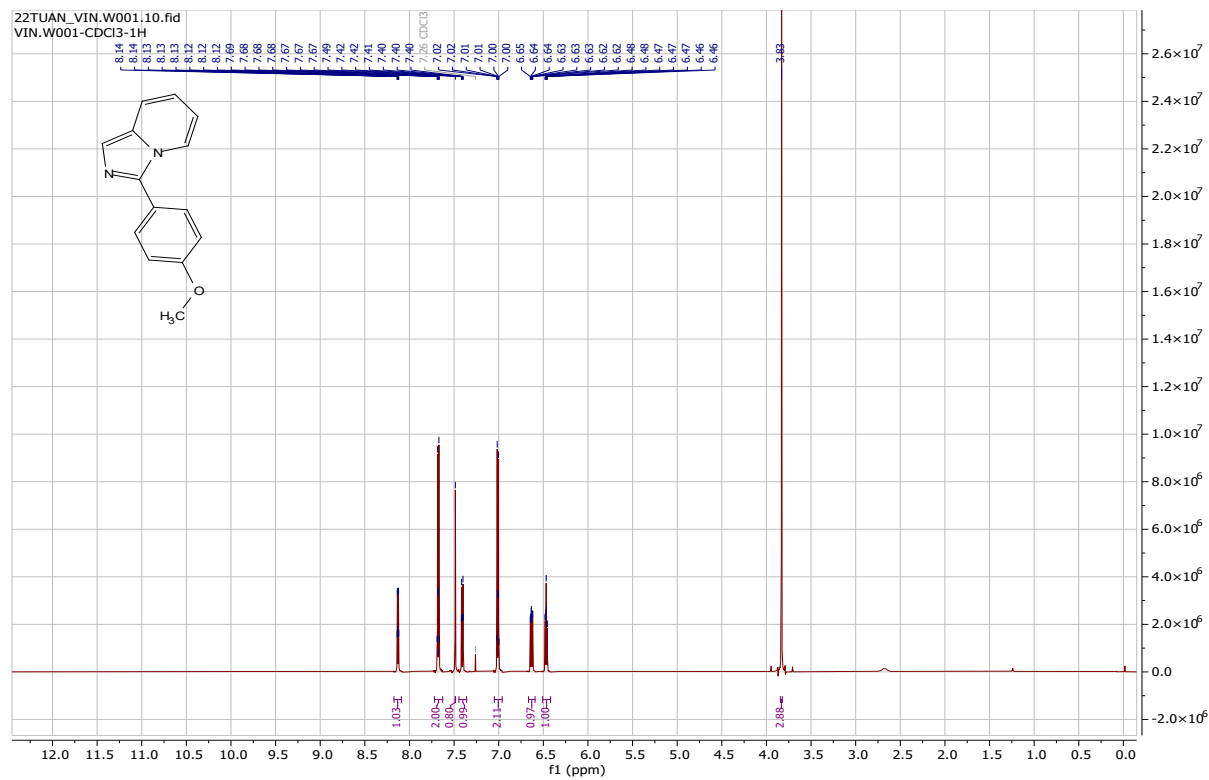
The in vitro cytotoxicity test method was confirmed by the US National Cancer Institute (NCI) as a standard cytotoxicity test to screen and detect substances capable of inhibiting growth or kill TBUT under in vitro conditions. This test was performed according to the method of Skekan et al. (1990) [5]. The test was carried out to determine the total cellular protein content basing on the optical density (OD) measurement when the protein composition of the cells was stained by Sulforhodamine B (SRB). The measured OD value is directly proportional to the amount of SRB attached to the protein molecule, so the more cells (the more

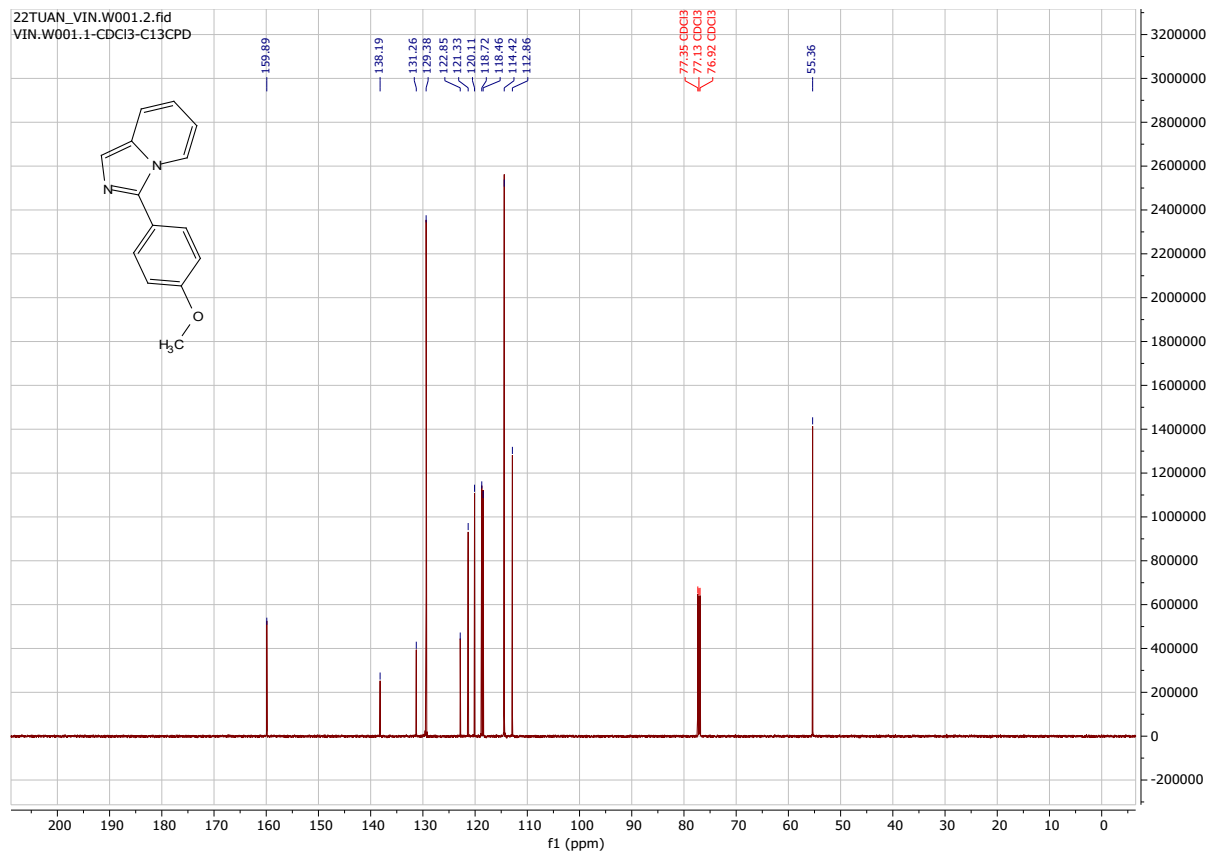
protein) the larger OD value. The test is carried out under the following specific conditions:

- Cell Preparation: Cells were harvested using trypsin-EDTA solution and counted using a hemocytometer. Performing the introduce of 190 μL of cells in 96-wells plate for testing.
- Sample Preparation: the test sample was dissolved in 100% DMSO to prepare a 20 mM stock solution. Serial dilutions were performed in culture medium (without FBS) to obtain four different concentrations ranges from high to low. Diluted reagents at different concentrations (10 μL) were introduced into the wells of the cell-prepared 96-wells plate above. Wells without reagent but containing TBUT (190 μL) + DMSO 1% (10 μL) will be used as day 0 control. After 1 hour, the day 0 control wells of cells will be fixed with TCA 20% (Trichloroacetic acid).
- Incubation: Plates were incubated for 72 hours. After 72 h, cells were fixed with TCA for 1 h, stained with SRB for 30 min at 37 $^{\circ}\text{C}$, washed 3 times with acetic acid, and then dried at room temperature.
- Data Analysis: The experiment was repeated three times. Ellipticine was used as a positive control at concentrations of 10, 2, 0.4, and 0.08 $\mu\text{g}/\text{mL}$. The IC_{50} values (concentration required to inhibit cell growth by 50%) were calculated using TableCurve 2Dv4 software.
- Bioactivity Criteria: According to the standards of the US National Cancer Institute (NCI) [6], the extract is considered to have good activity with $\text{IC}_{50} \leq 20 \mu\text{g}/\text{ml}$, while the purified substance is considered to have good activity when $\text{IC}_{50} \leq 5 \mu\text{M}$

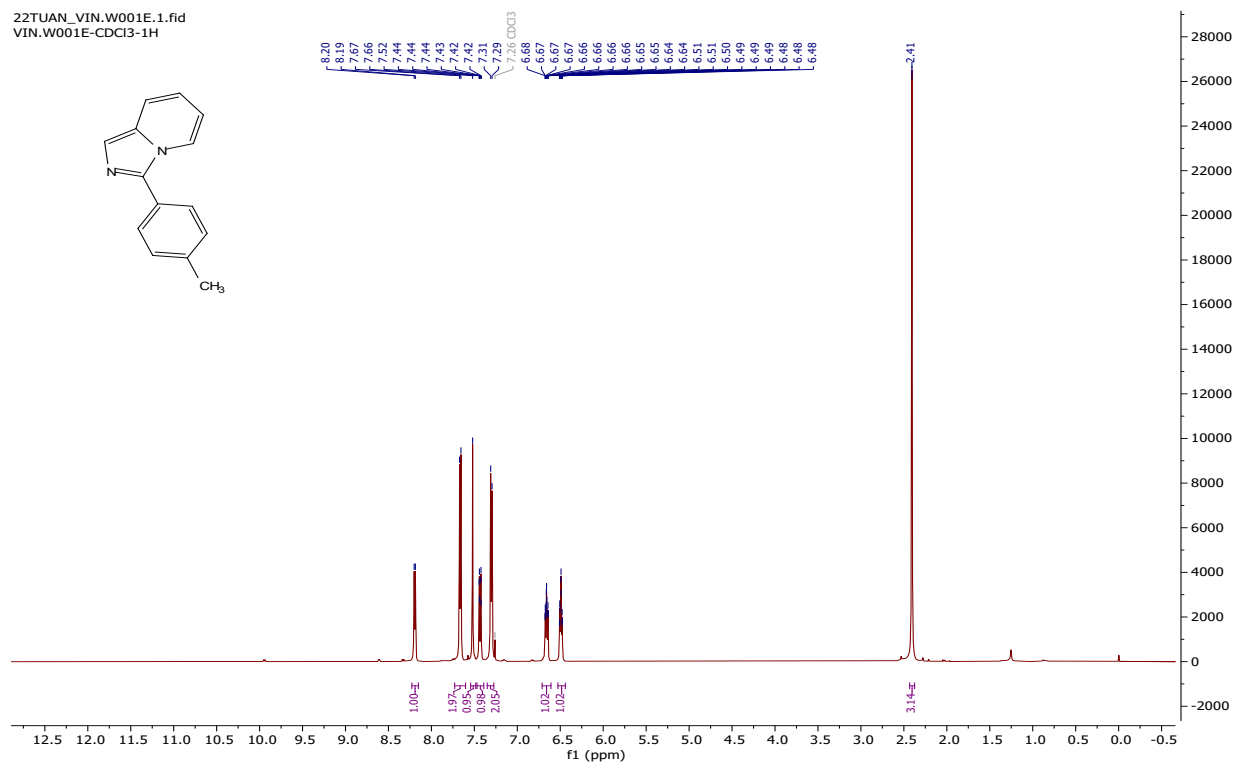
3. Copies of NMR spectra

3-(4-methoxyphenyl)imidazo[1,5-a]pyridine 1a

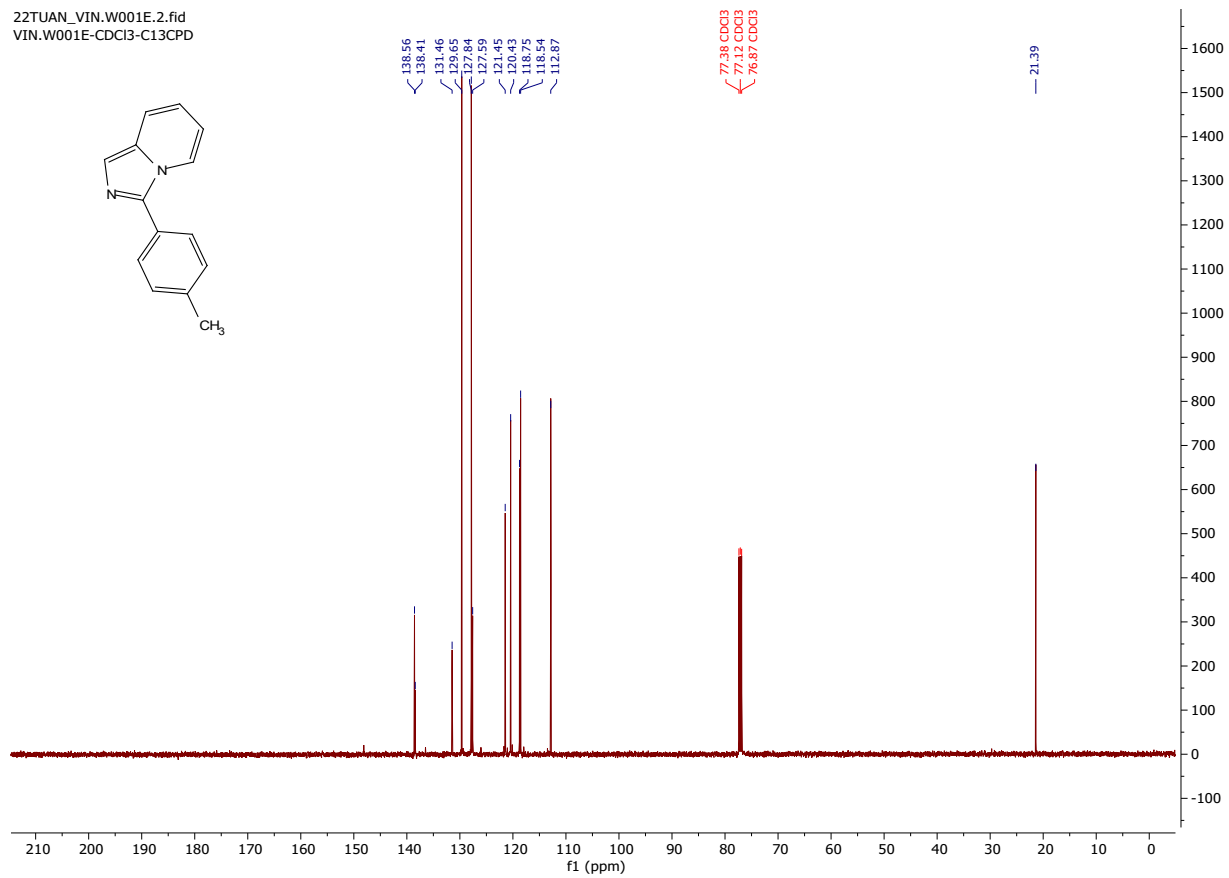




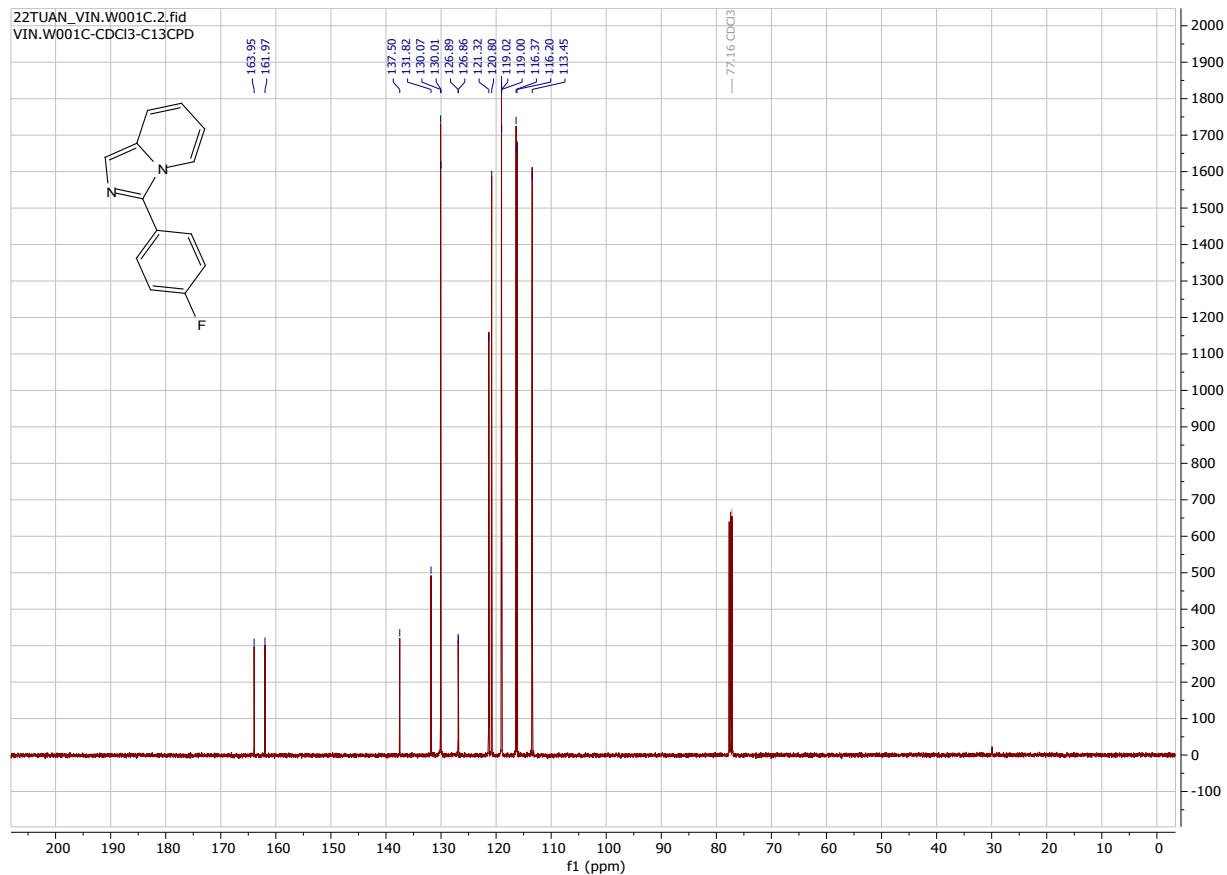
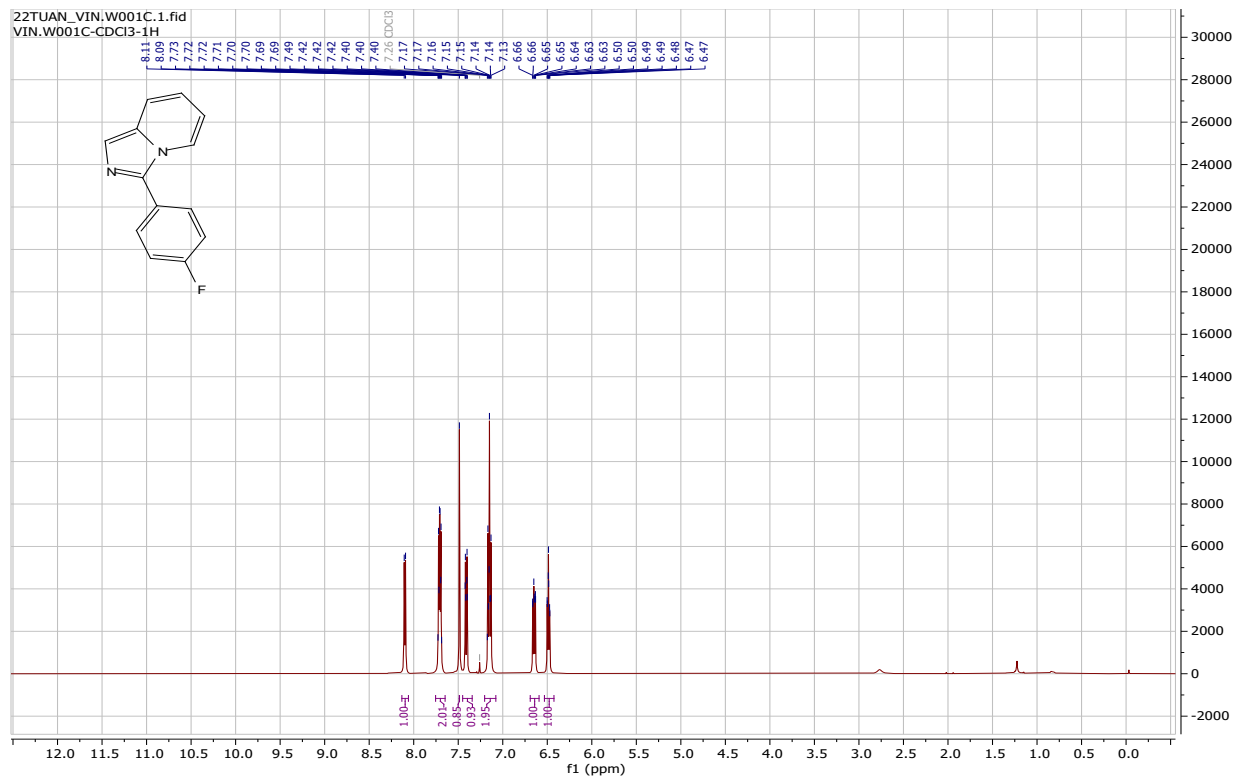
3-(p-tolyl)imidazo[1,5-a]pyridine 1b



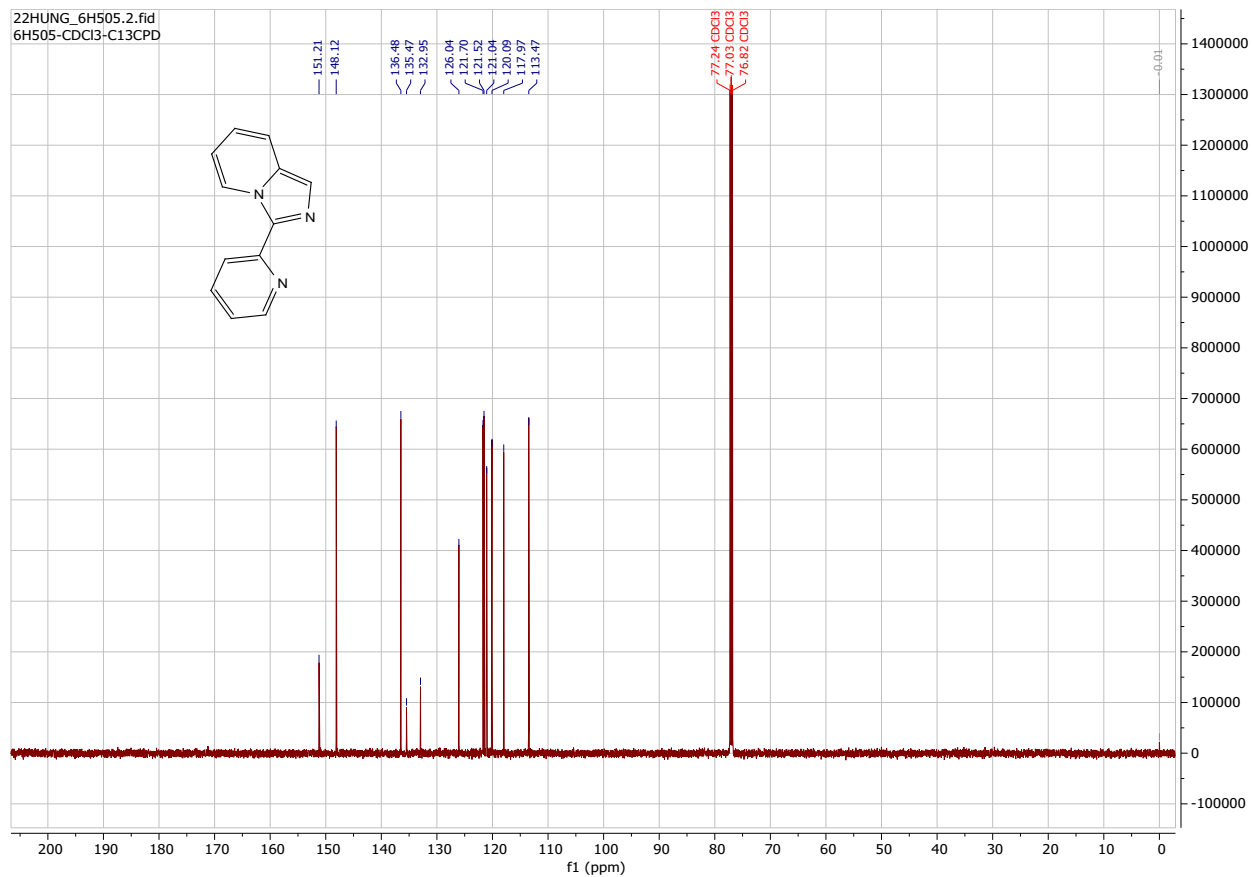
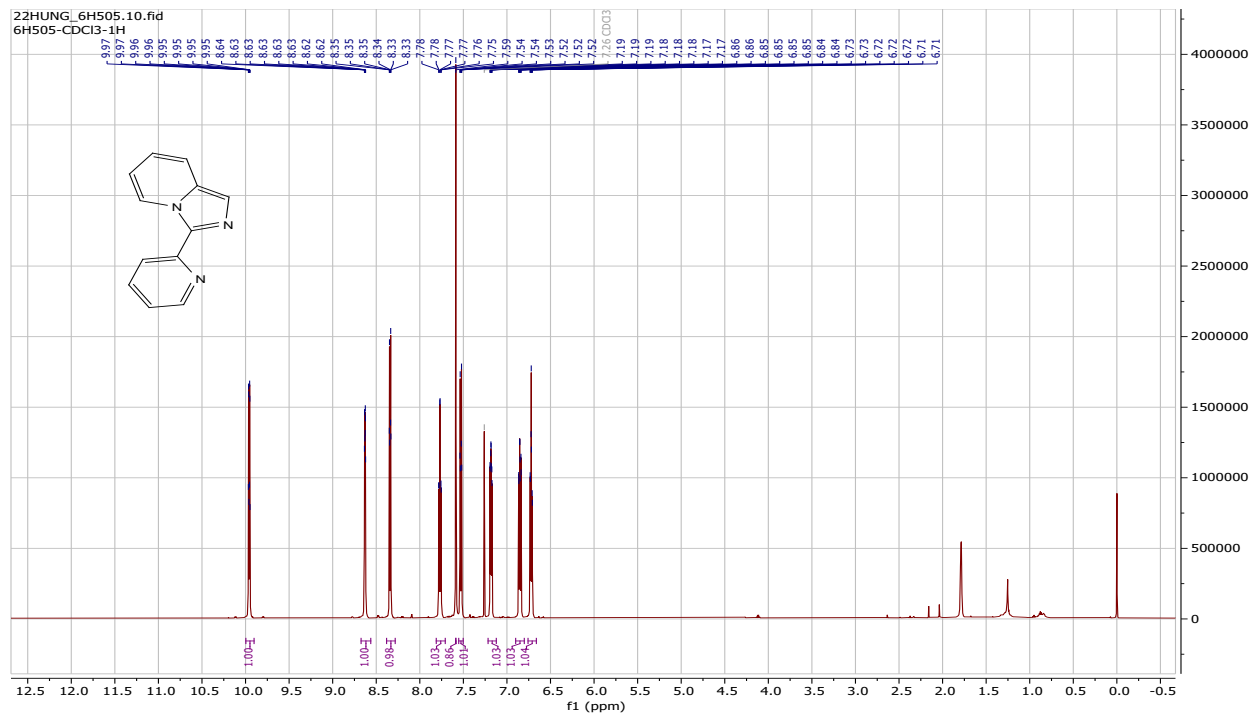
22TUAN_VIN.W001E.2.fid
VIN.W001E-CDCl3-C13CPD



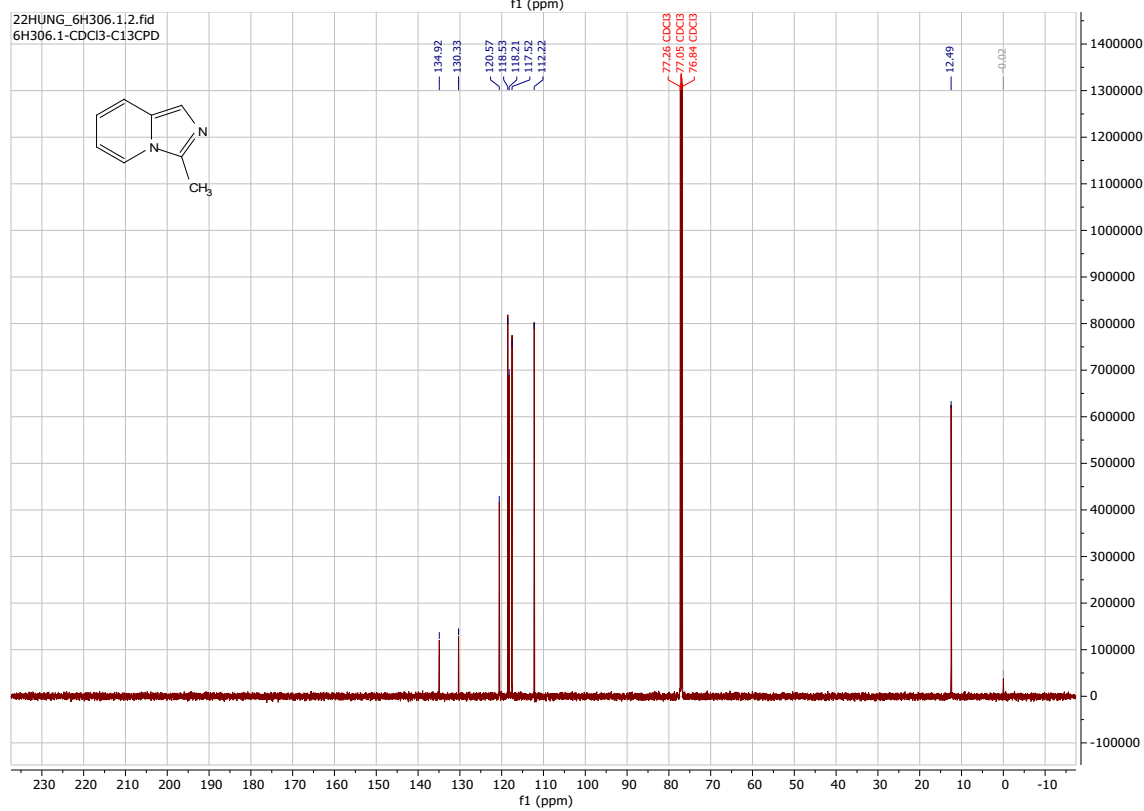
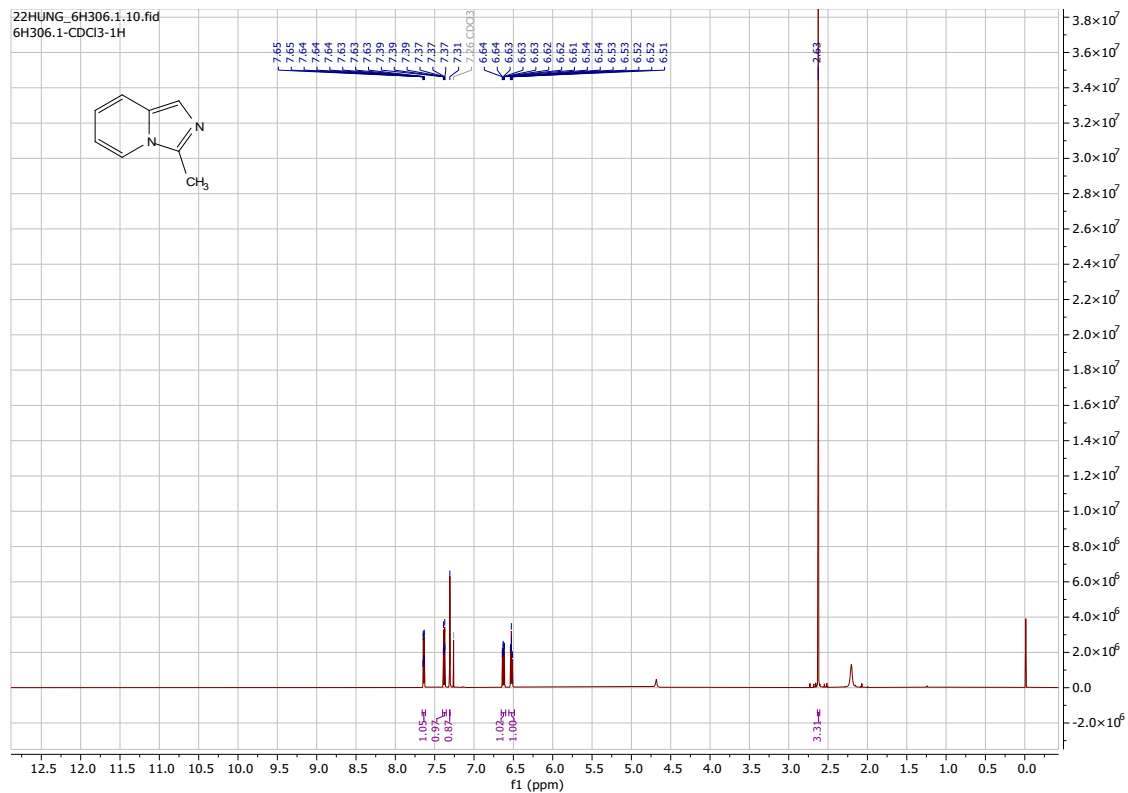
4-(imidazo[1,5-a]pyridin-3-yl)phenol 1c



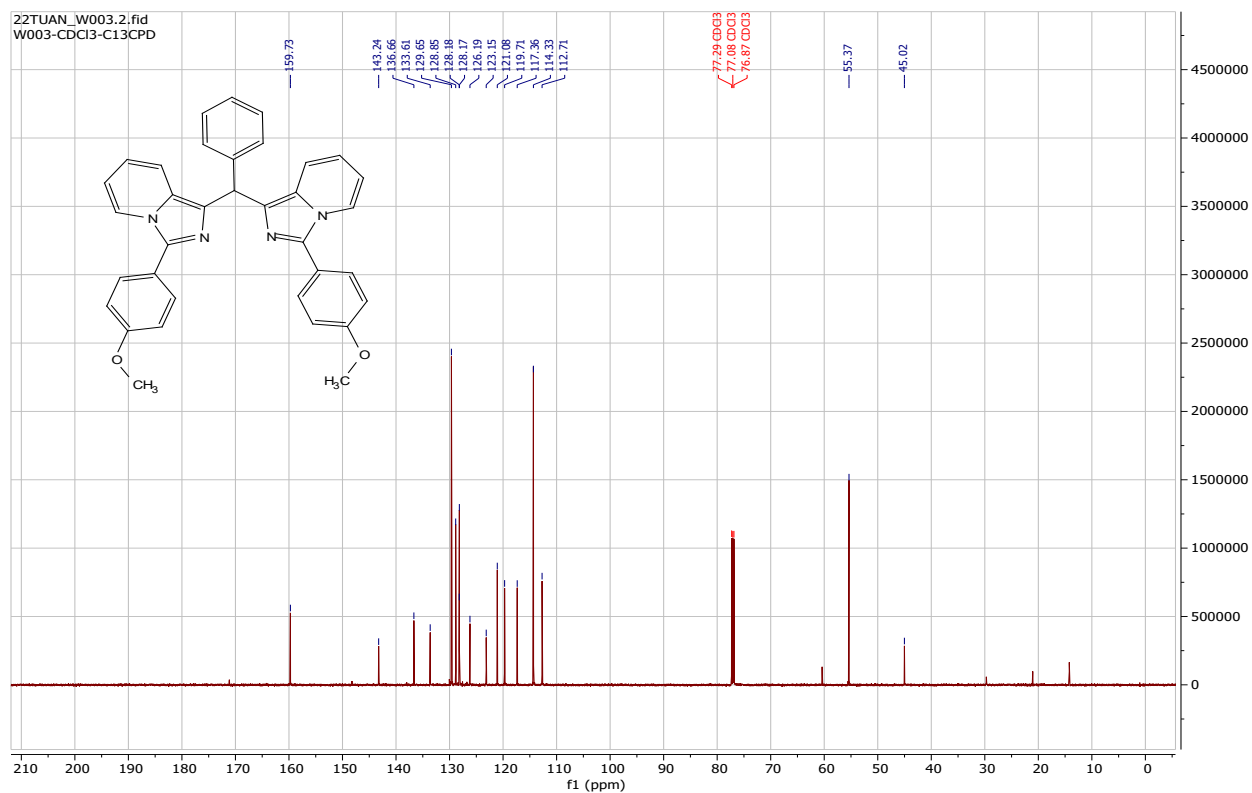
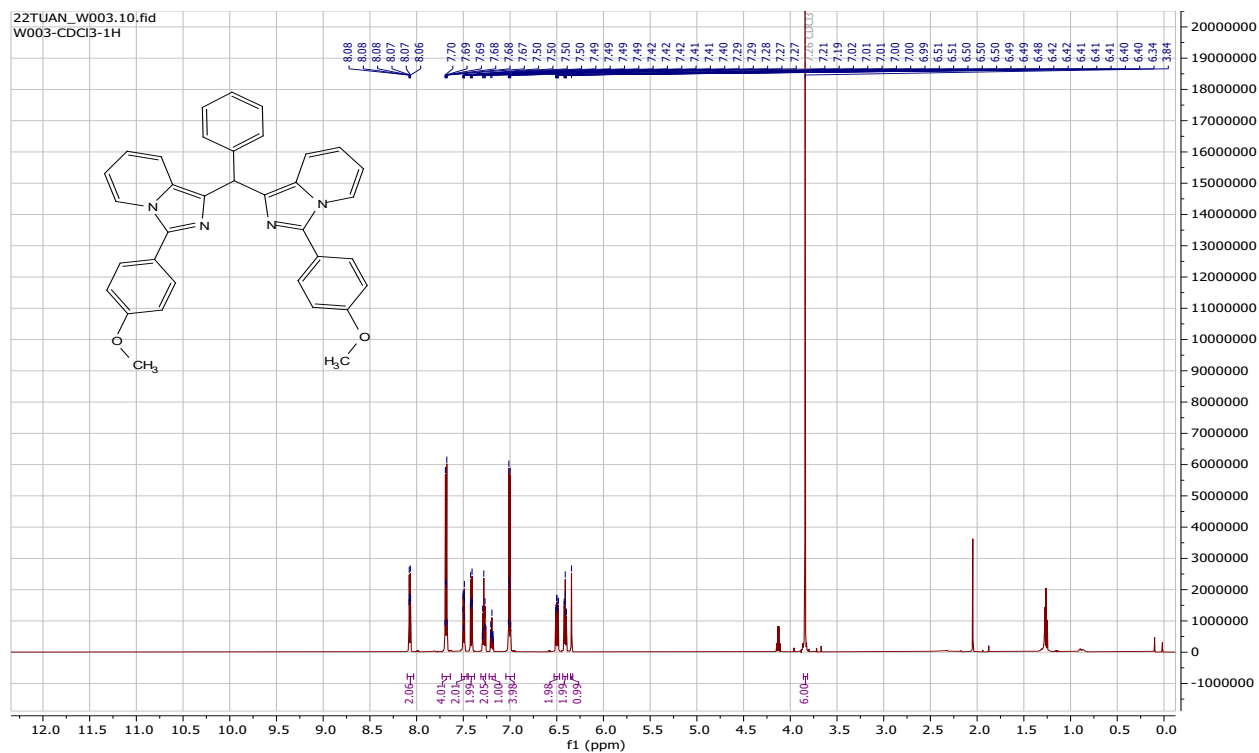
3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine 1e



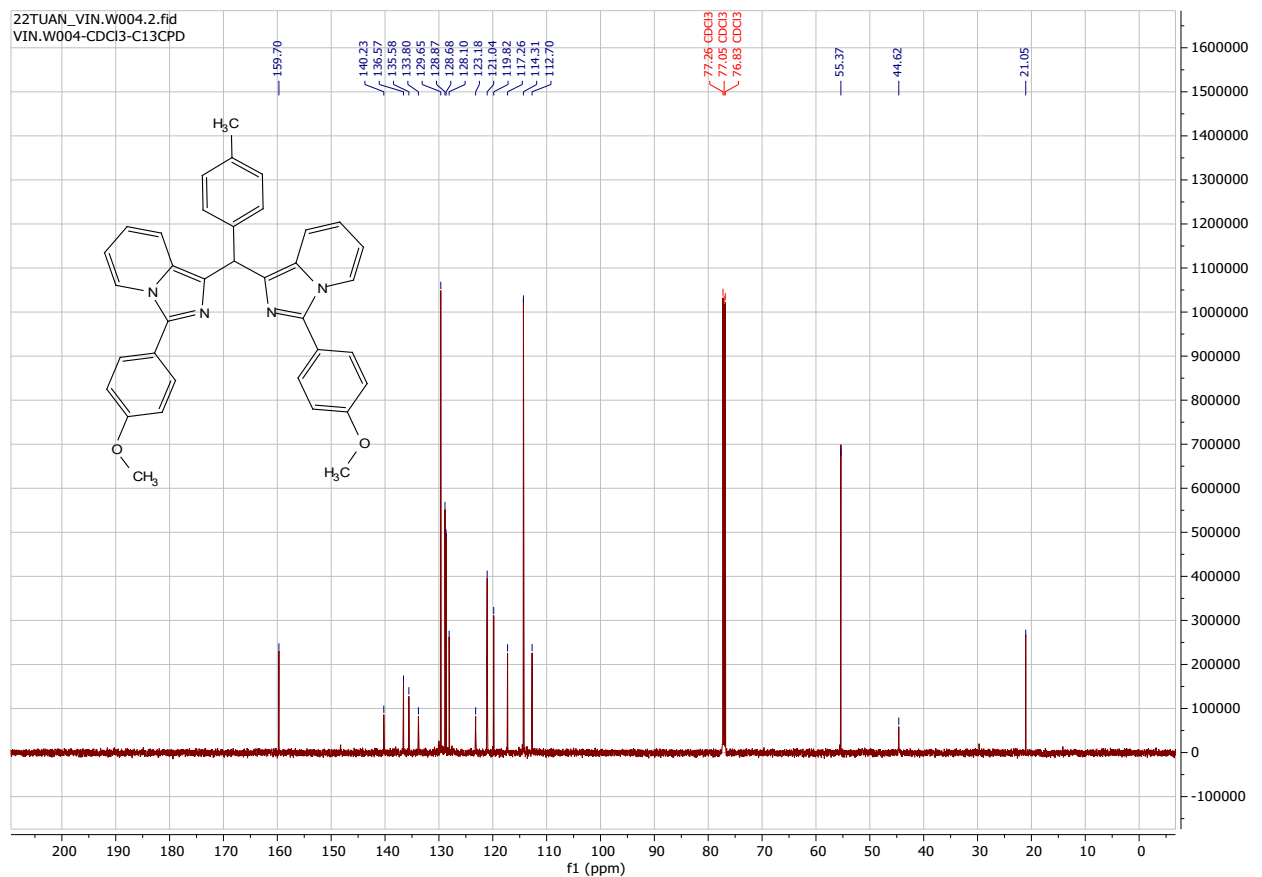
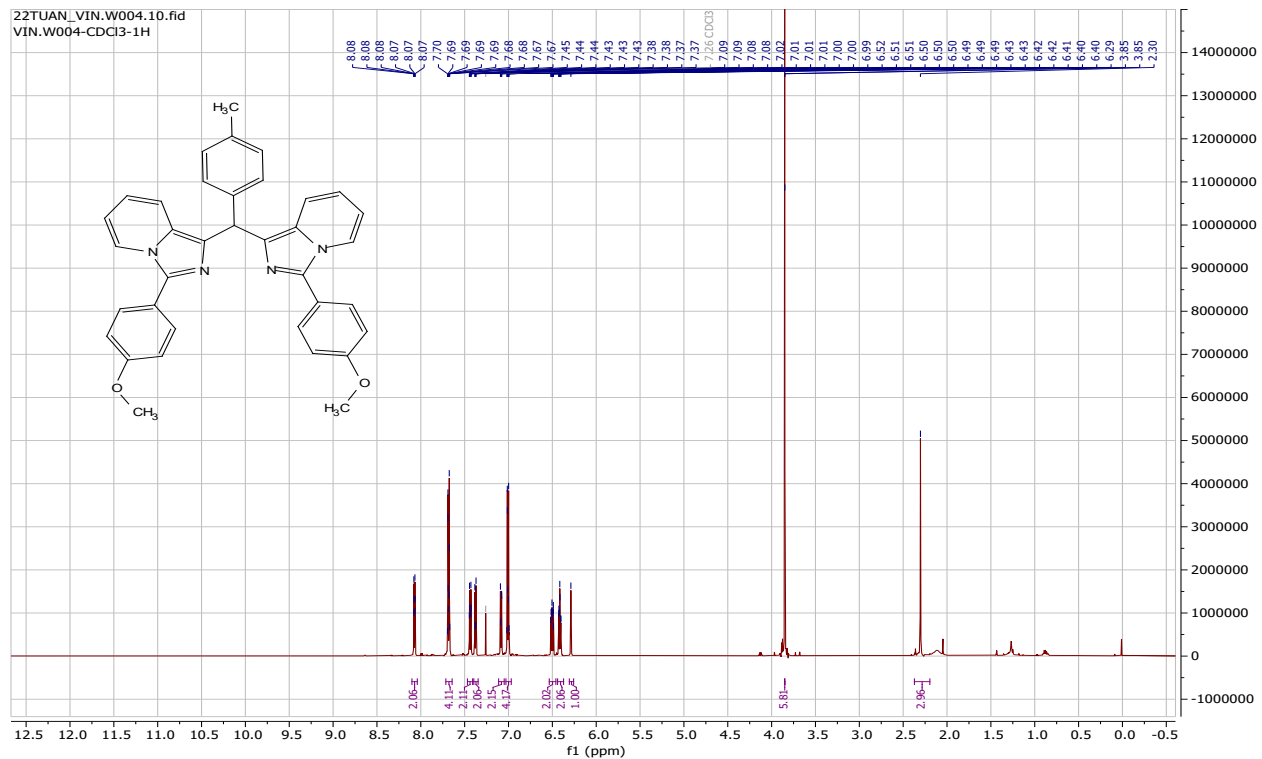
3-methylimidazo[1,5-a]pyridine 1g



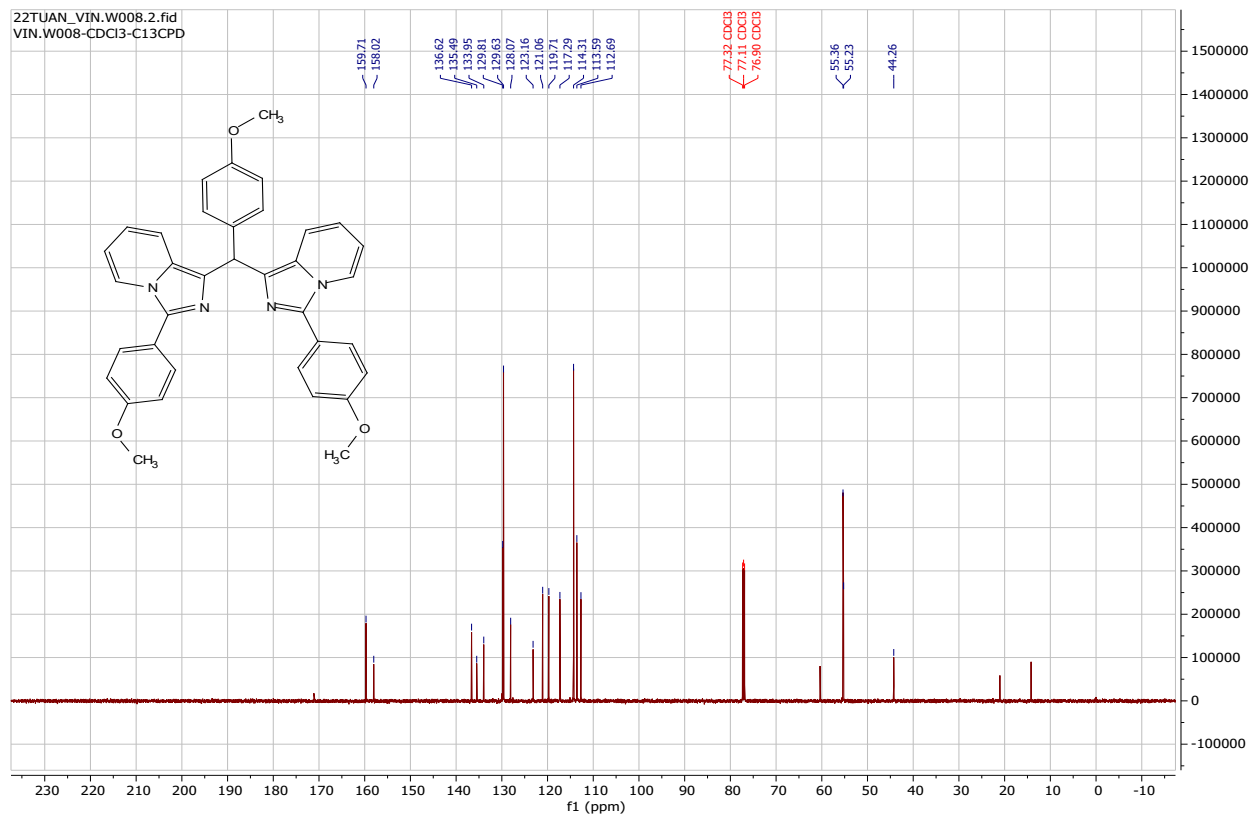
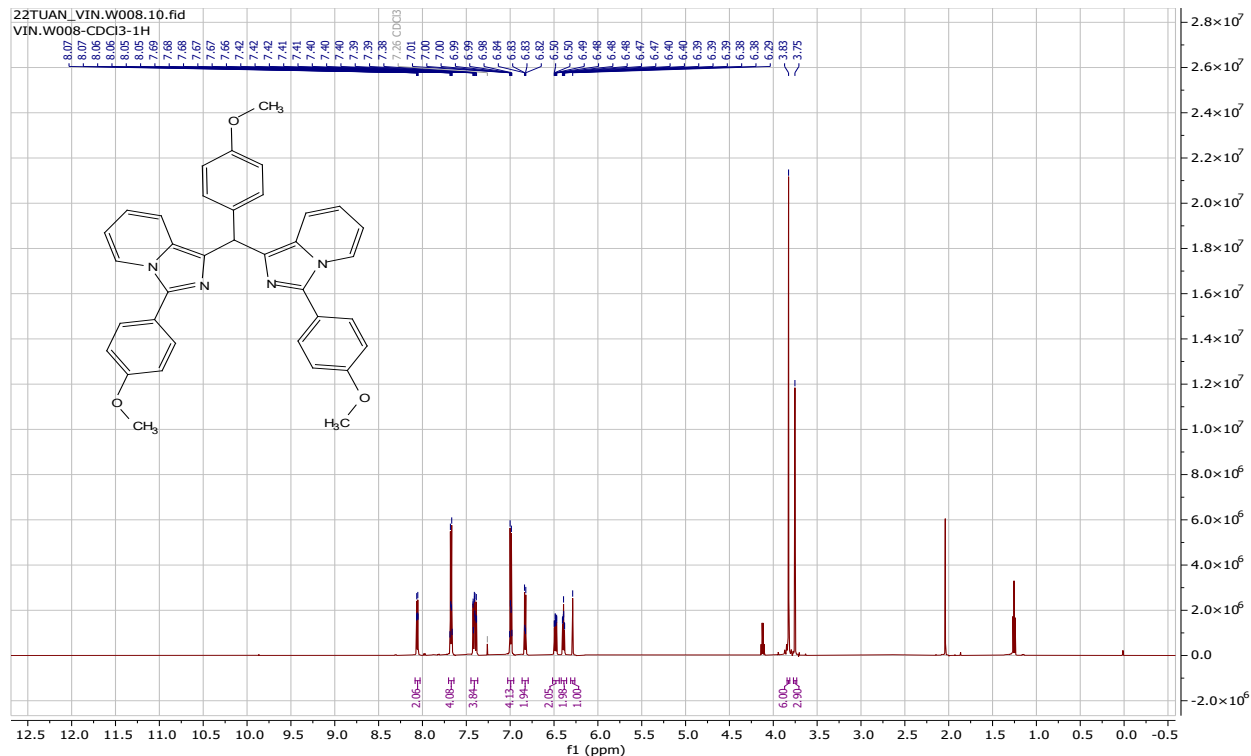
1,1'-(phenylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3a



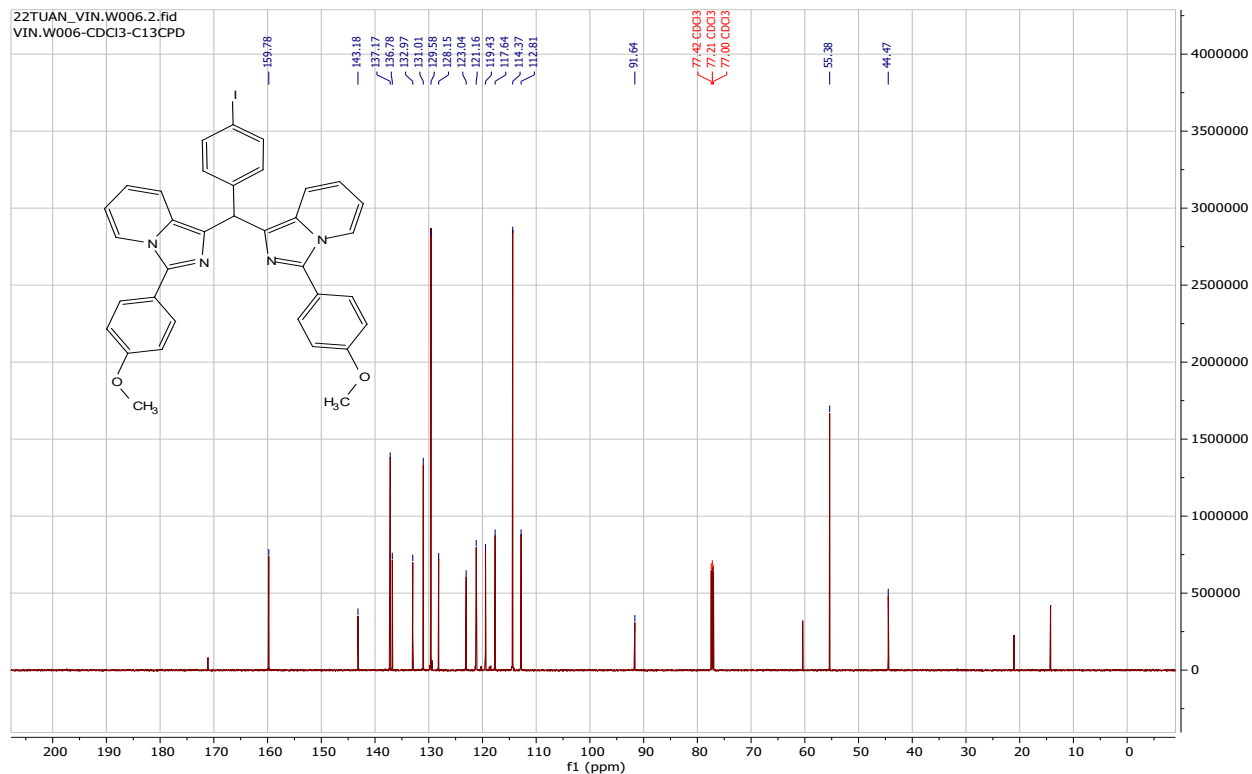
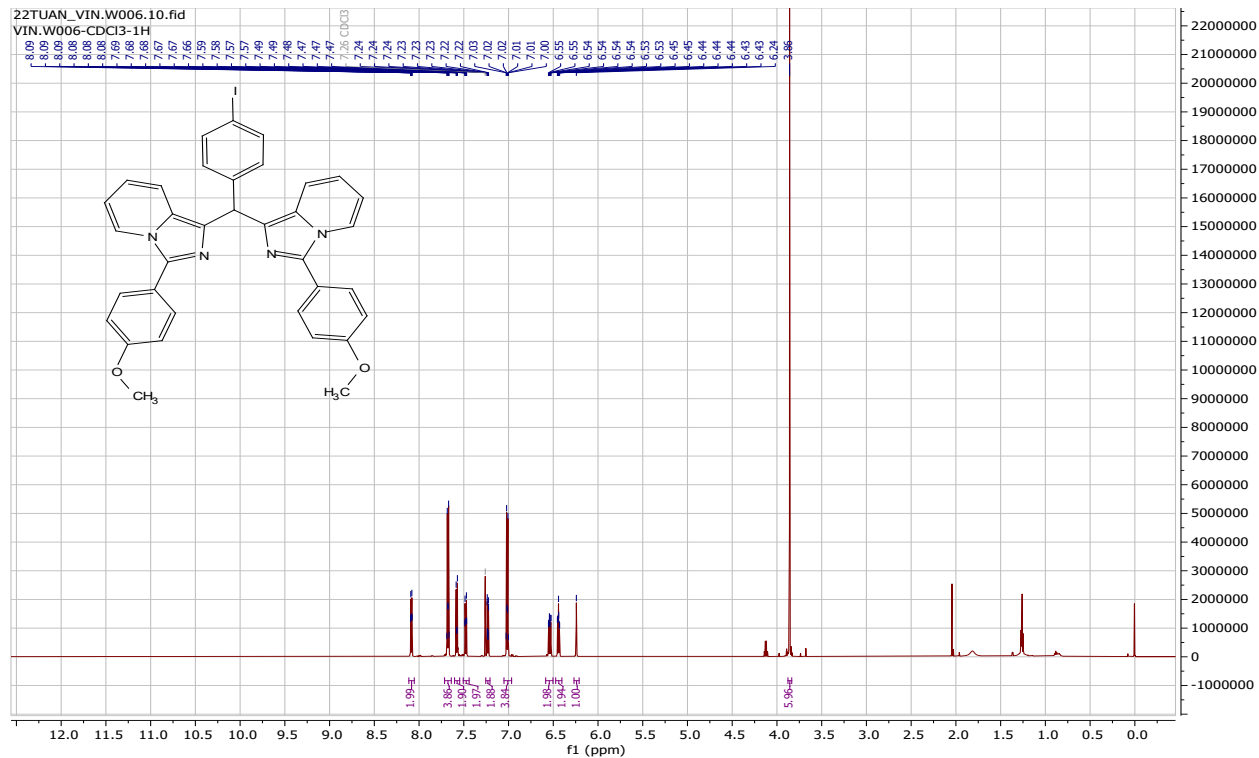
1,1'-(p-tolylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3b



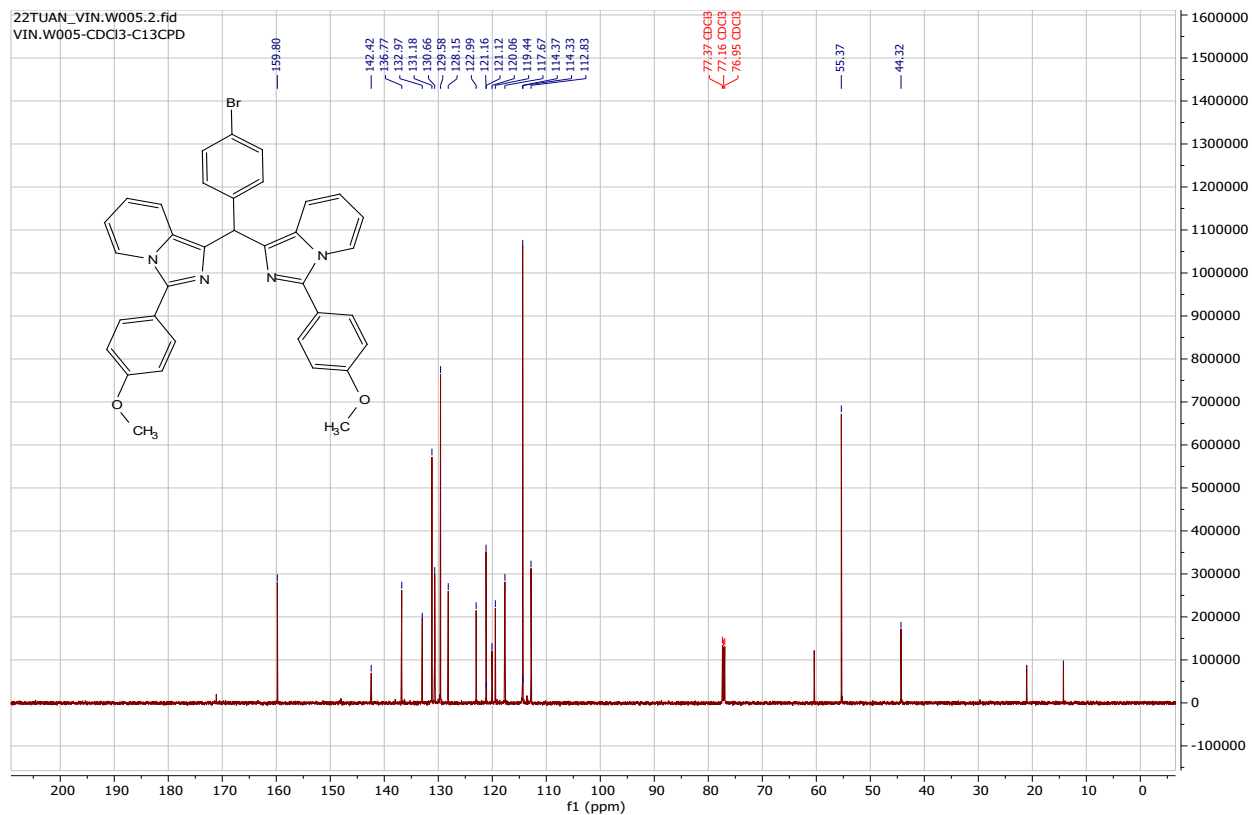
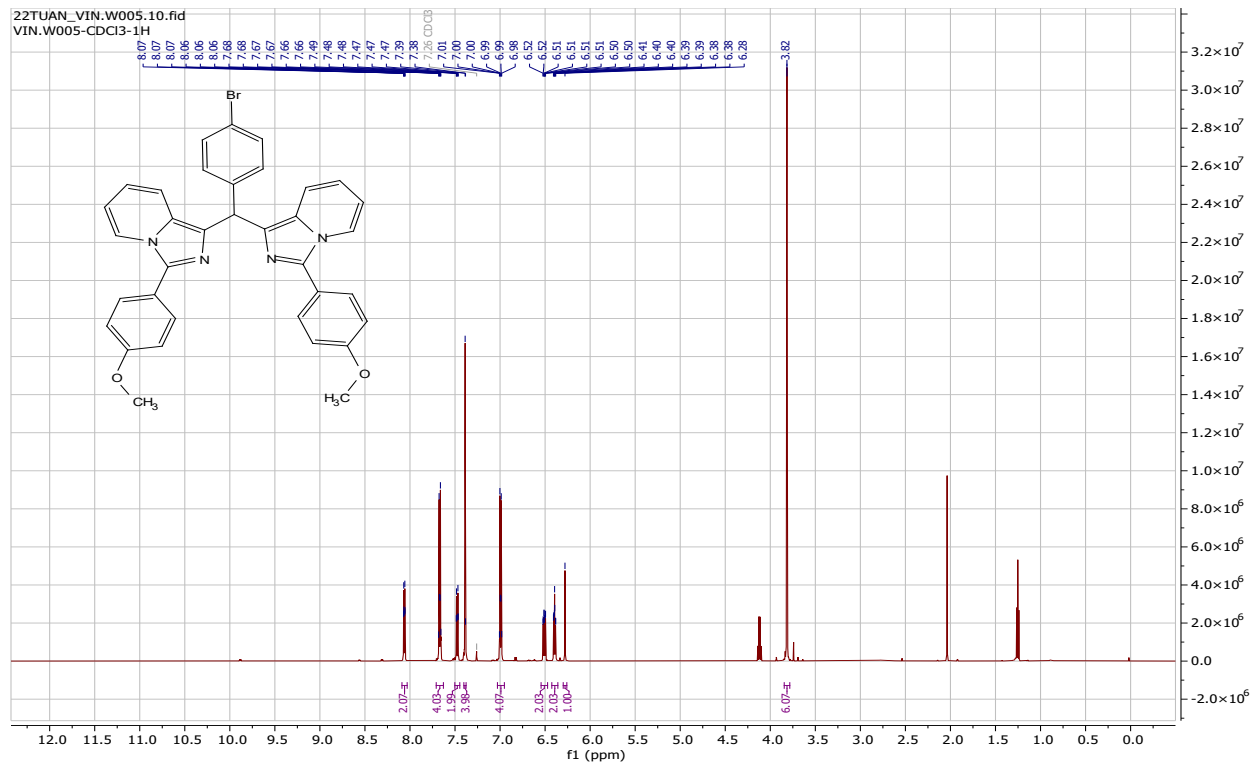
1,1'-((4-methoxyphenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3c



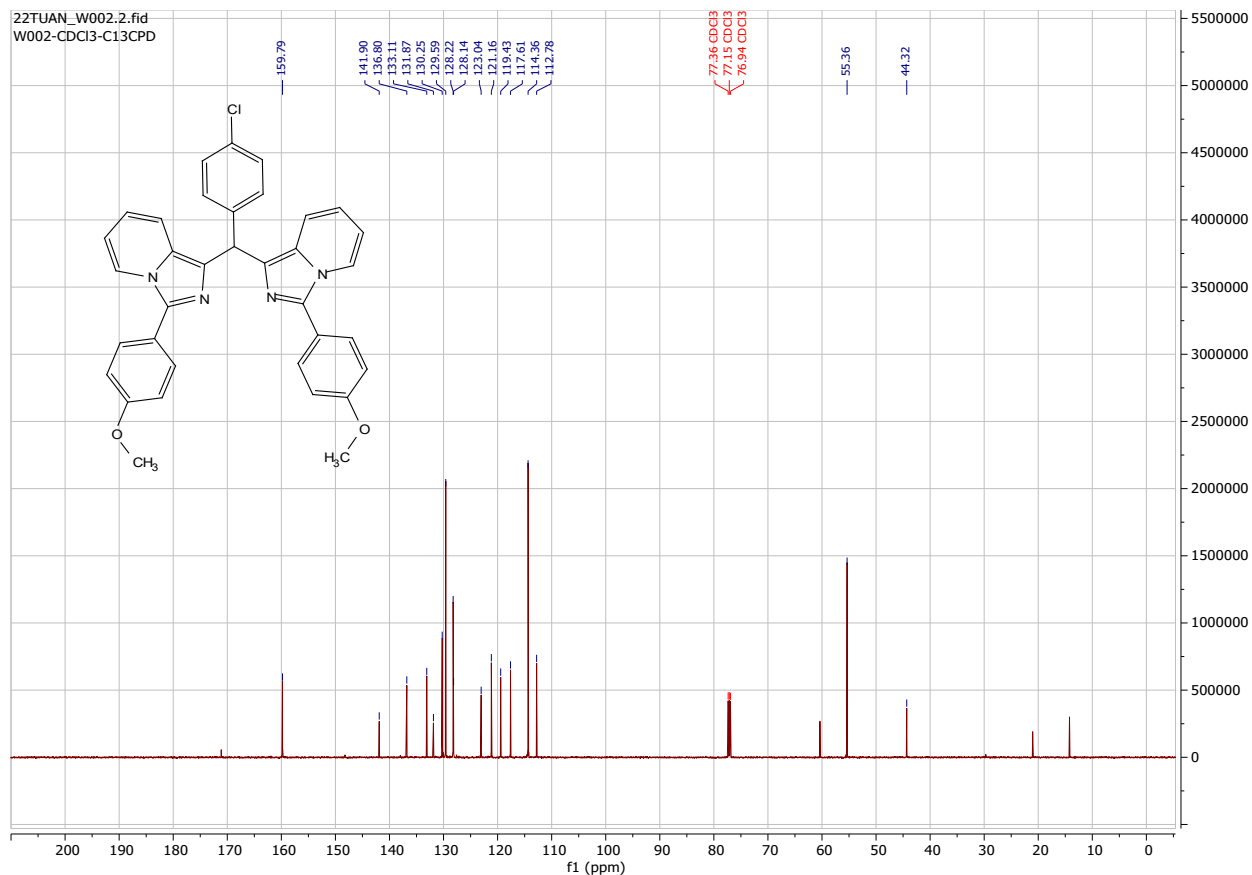
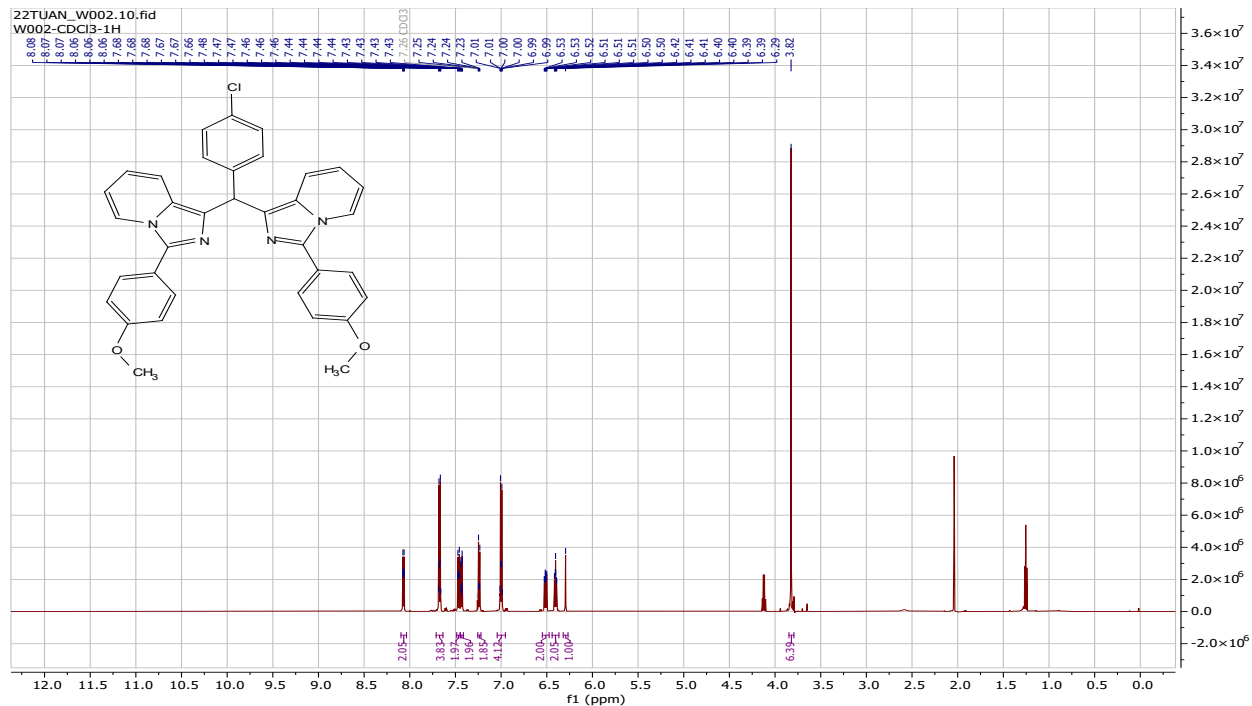
1,1'-((4-iodophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3d



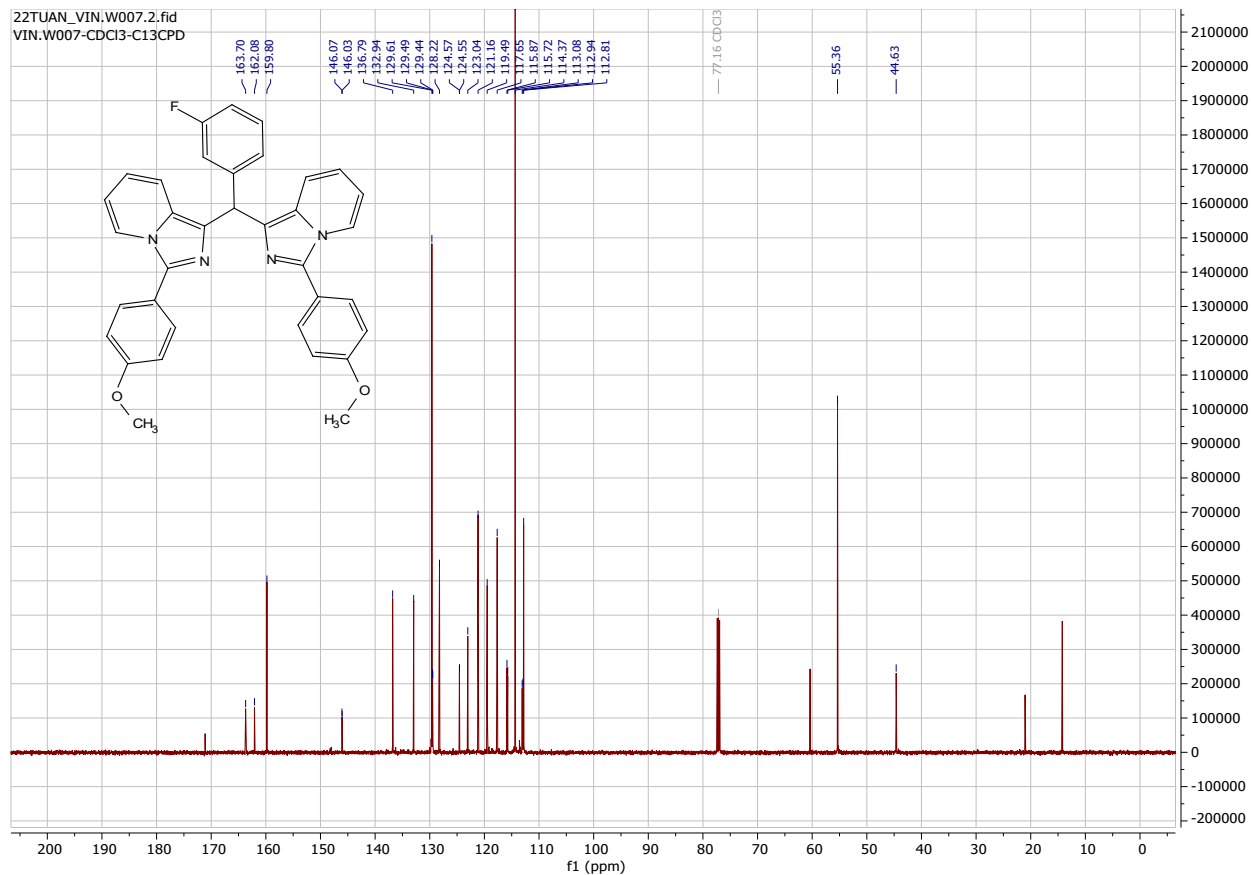
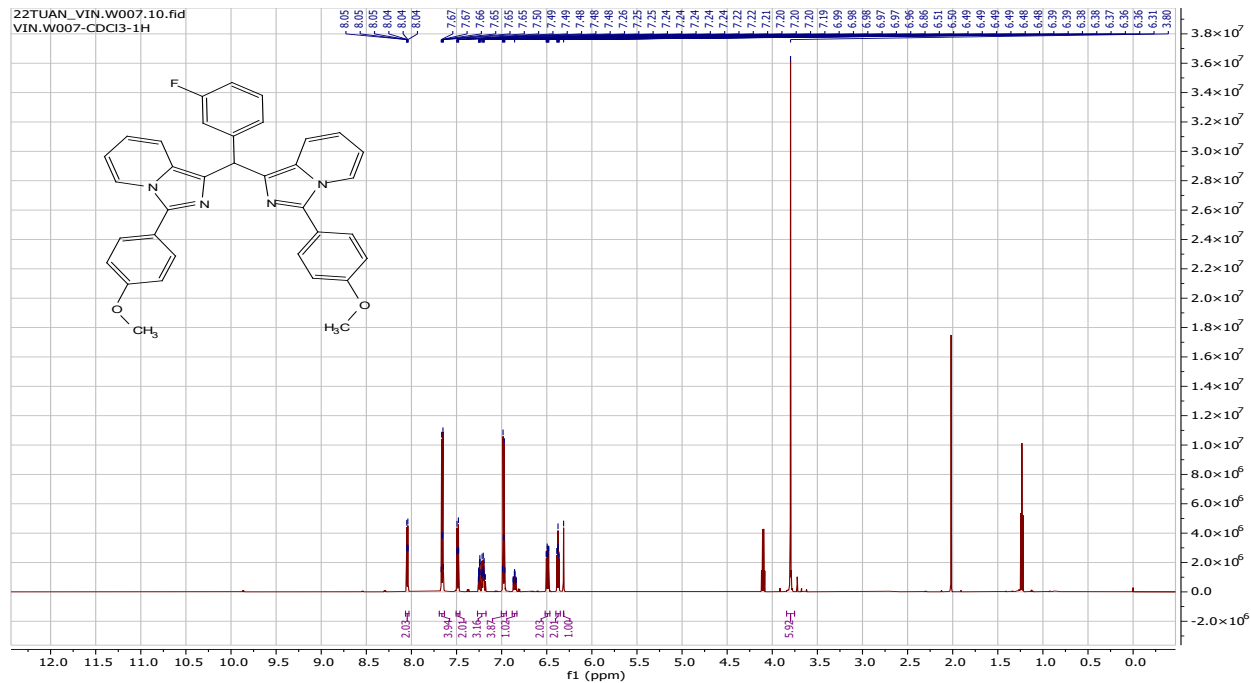
1,1'-((4-bromophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3e



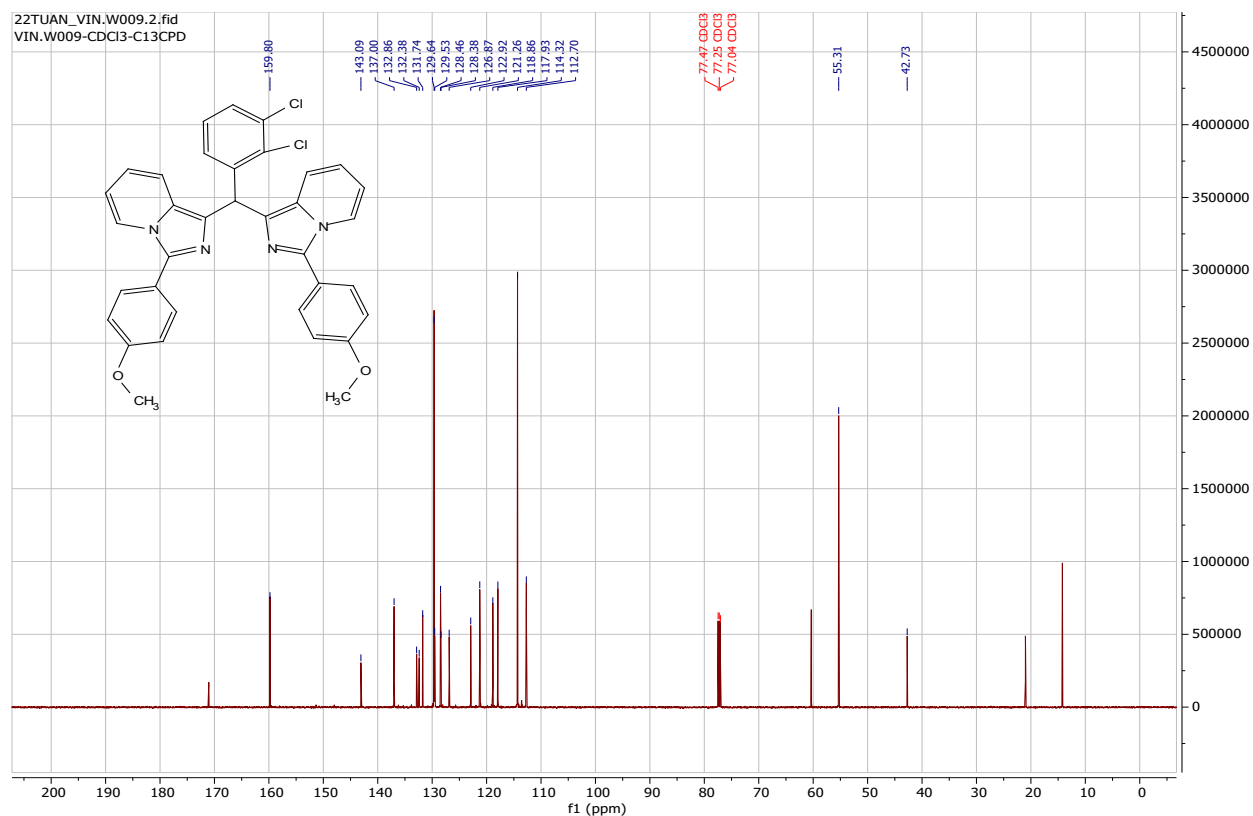
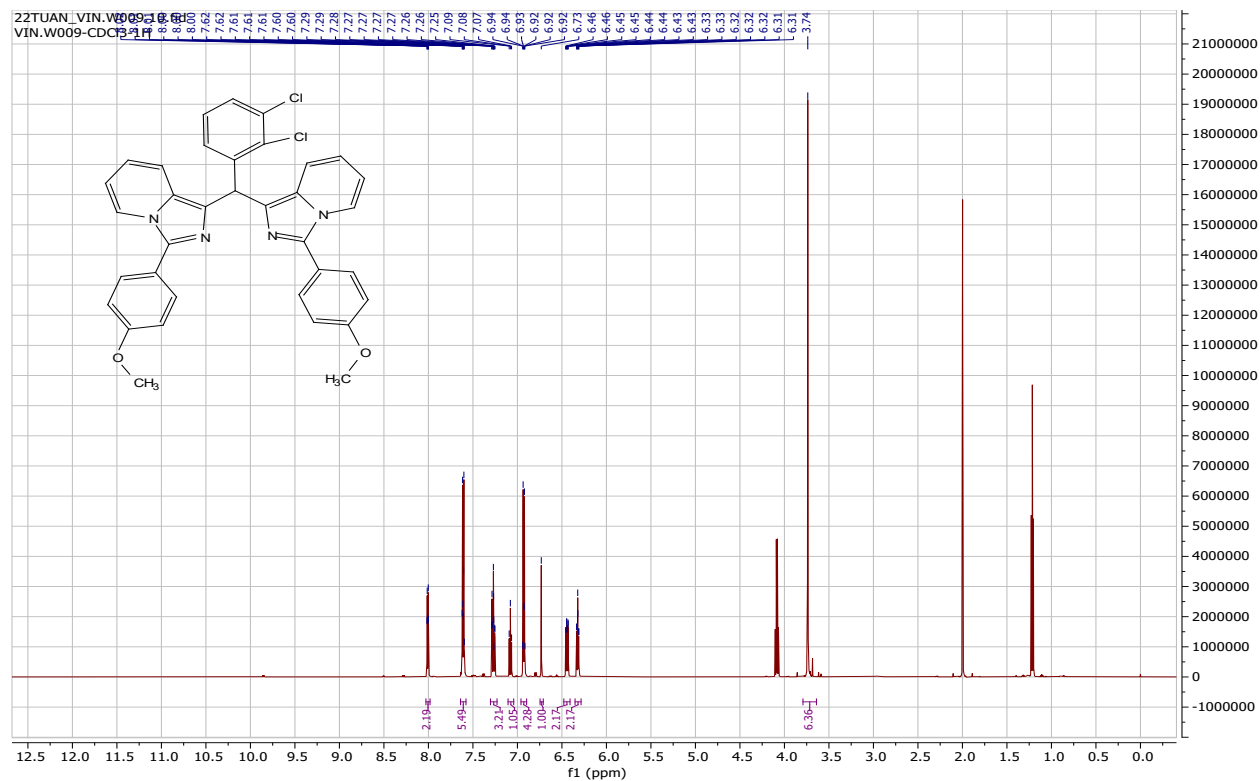
1,1'-((4-chlorophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3f



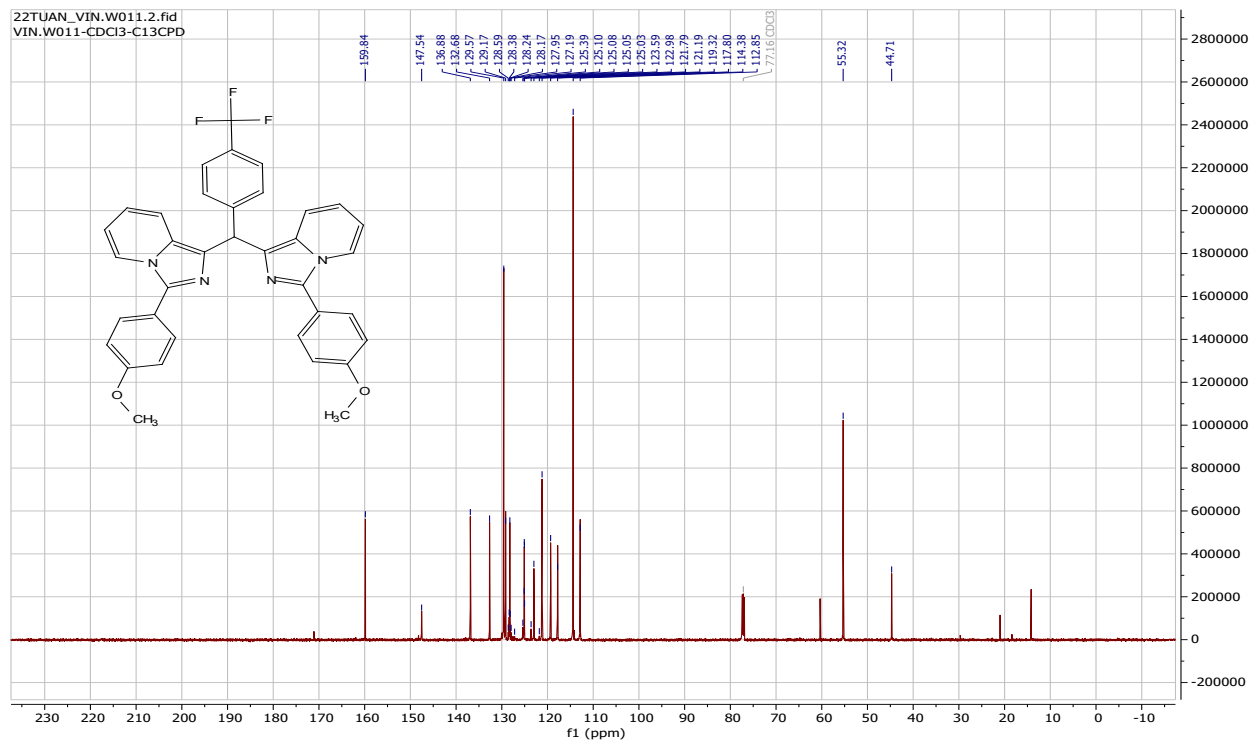
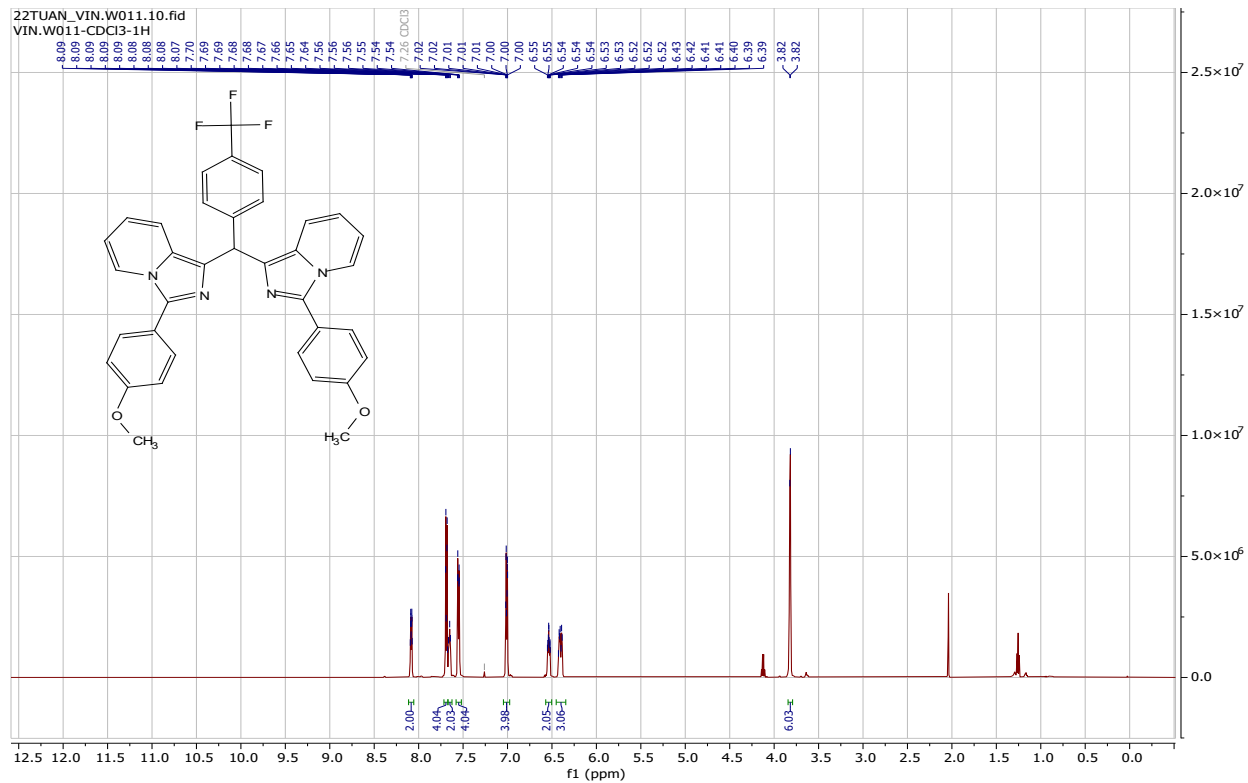
1,1'-((3-fluorophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3h



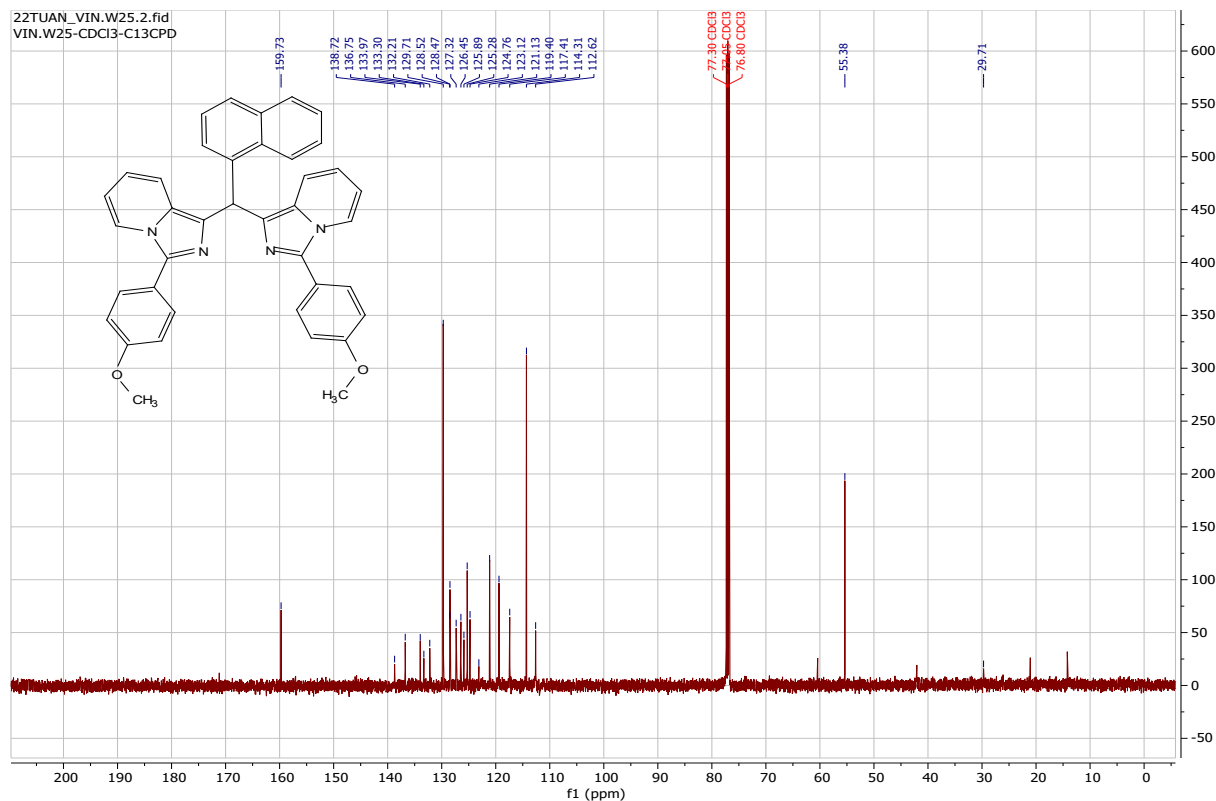
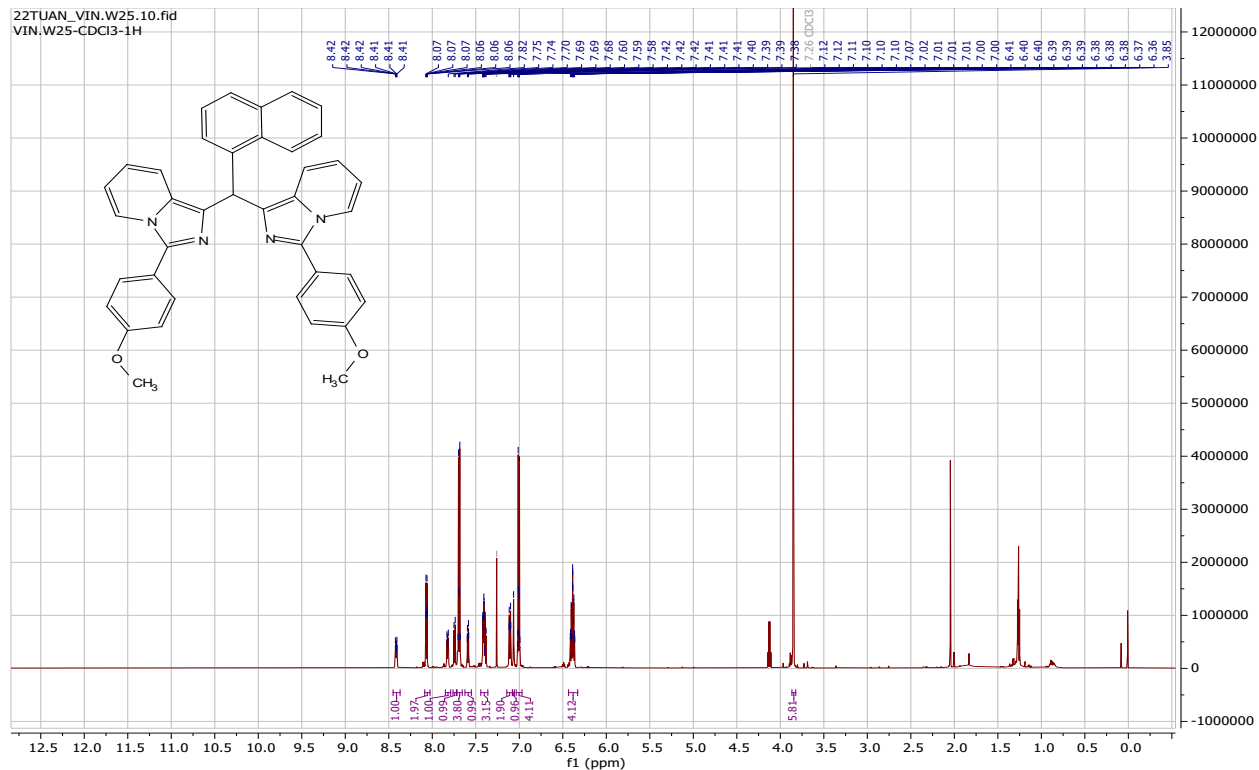
1,1'-((2,3-dichlorophenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3i



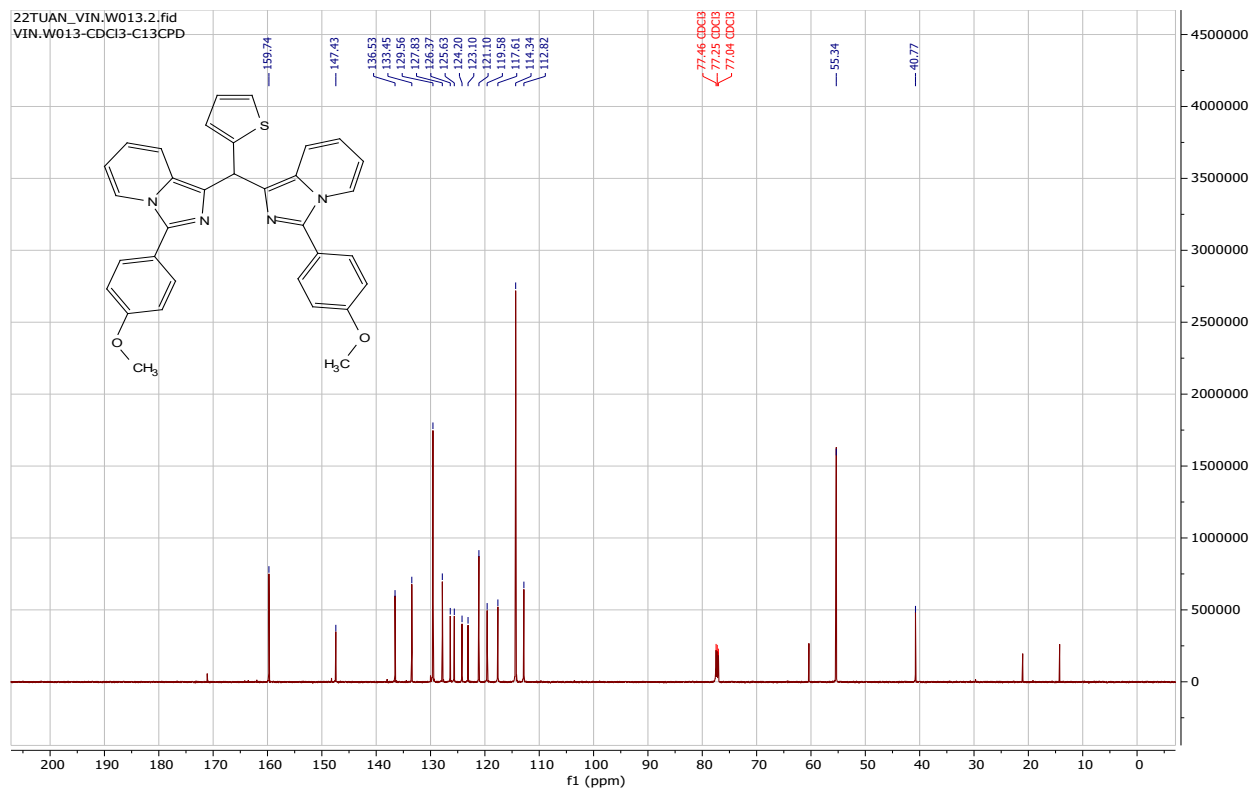
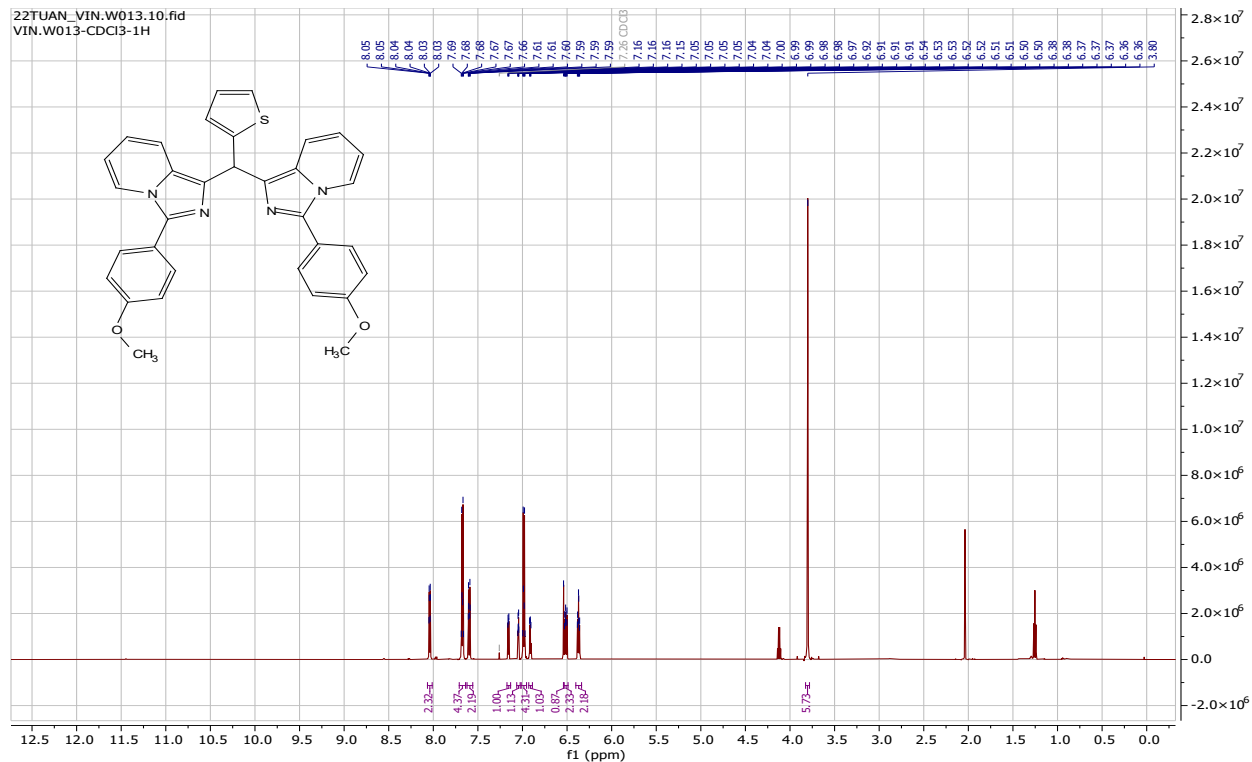
1,1'-((4-(trifluoromethyl)phenyl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3j



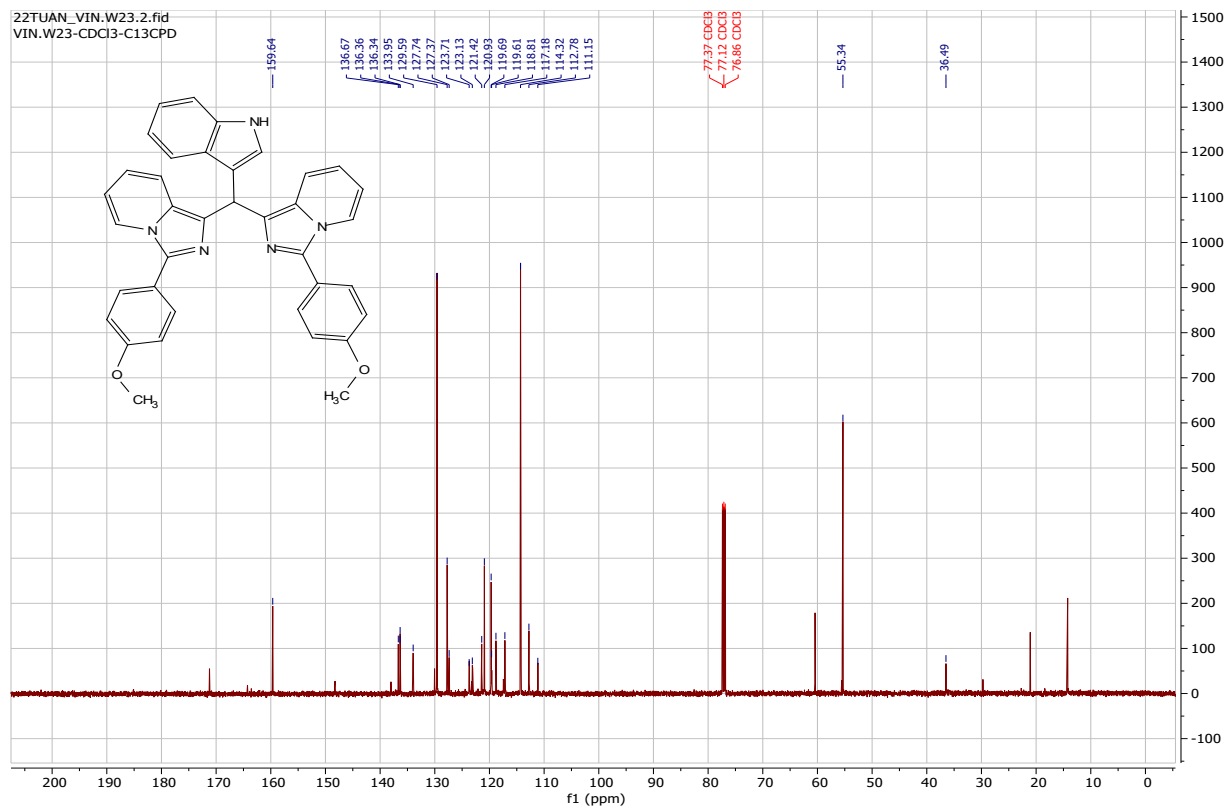
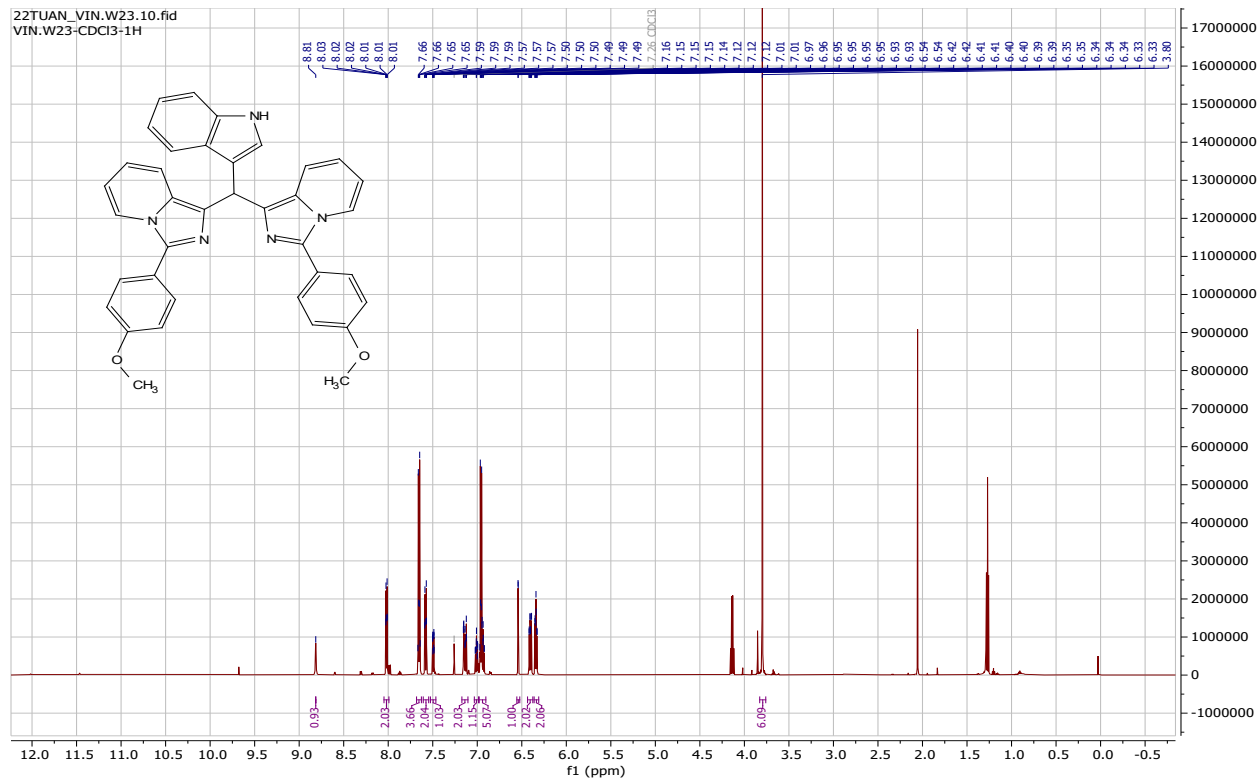
1,1'-(naphthalen-1-ylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3k



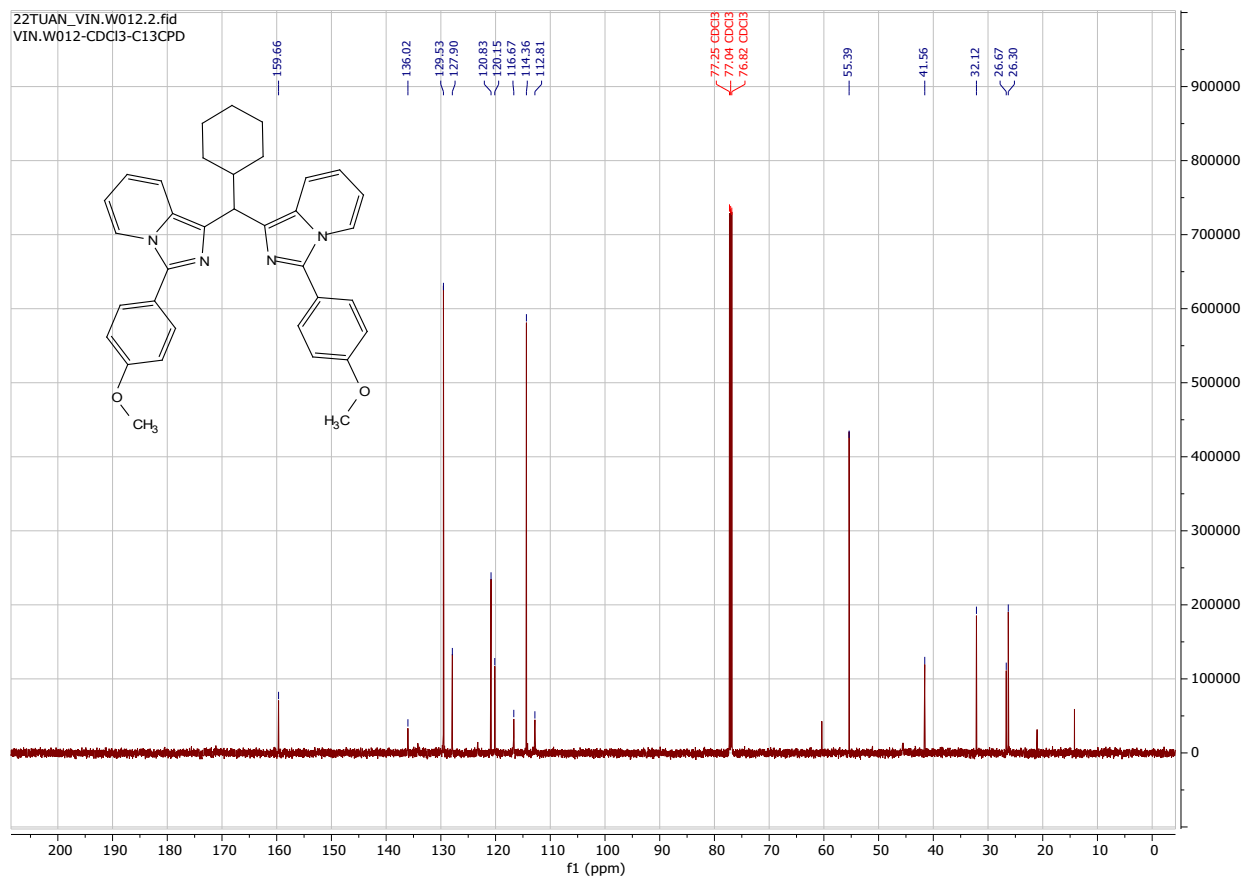
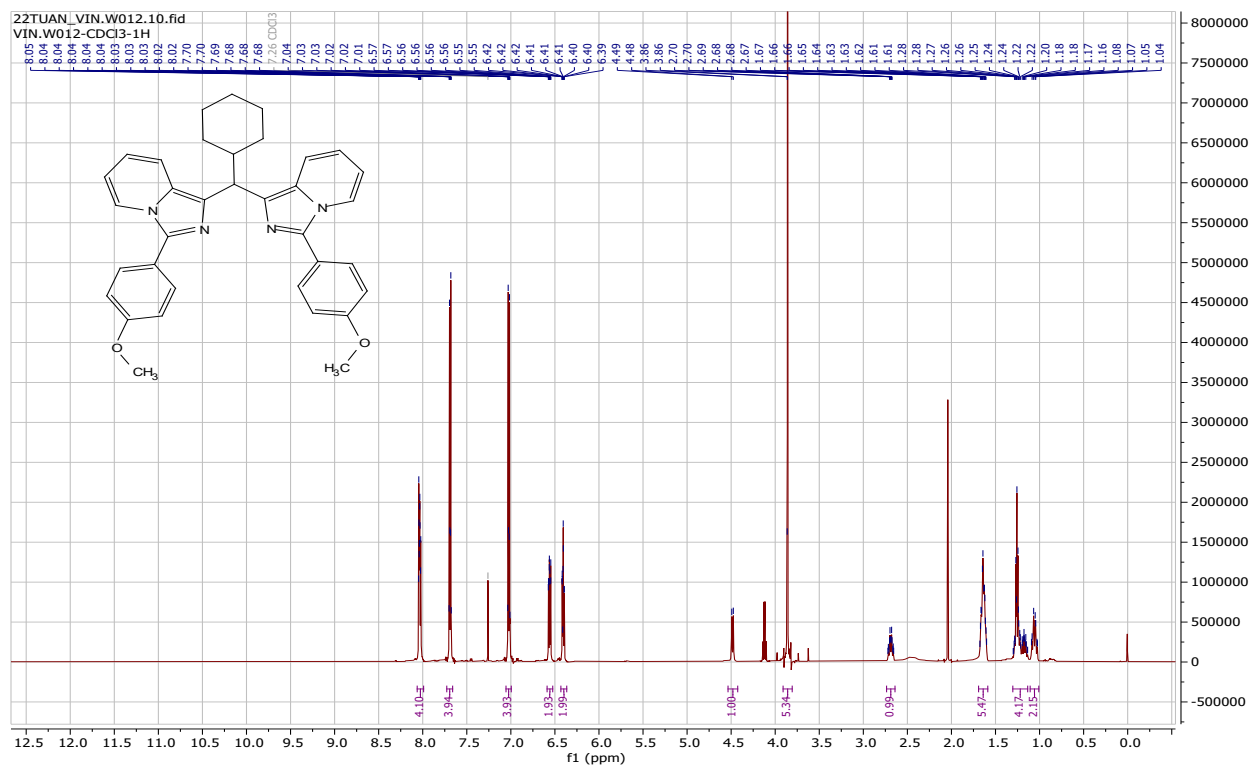
1,1'-(thiophen-2-ylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3I



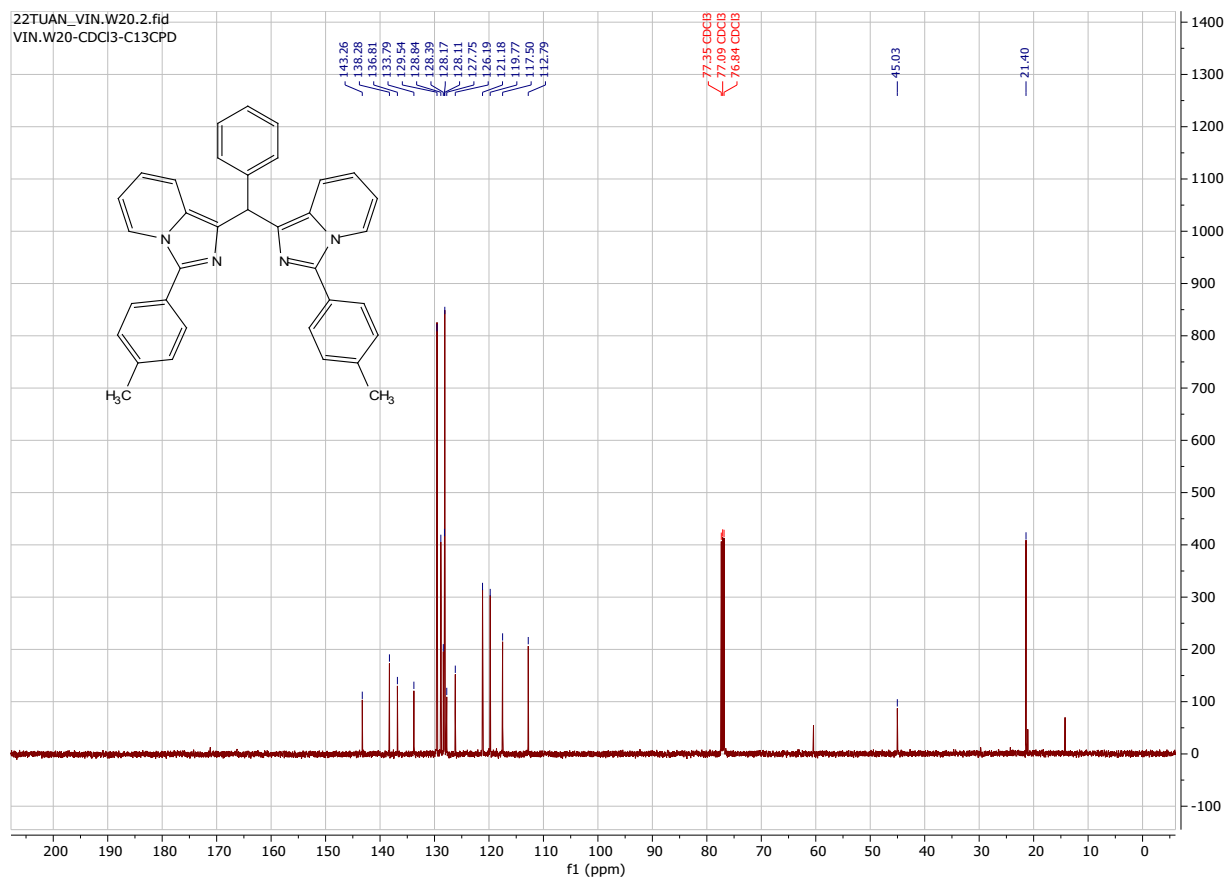
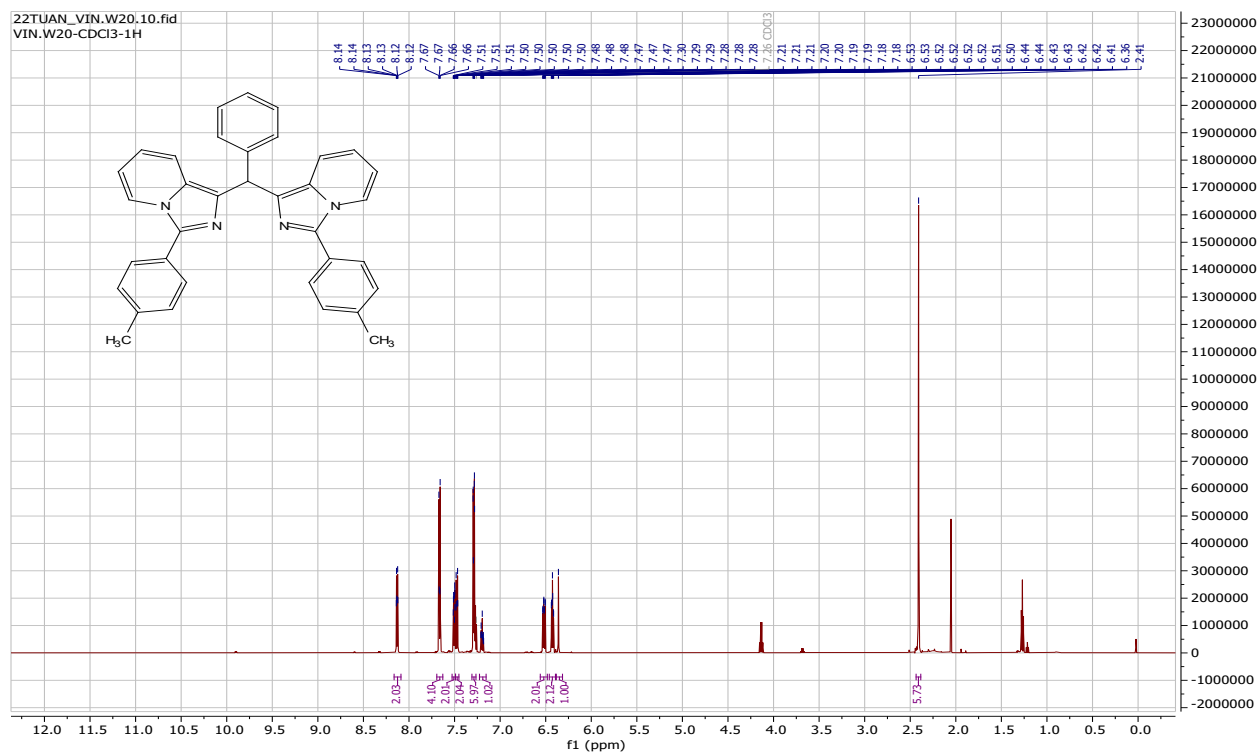
1,1'-((1H-indol-3-yl)methylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3m



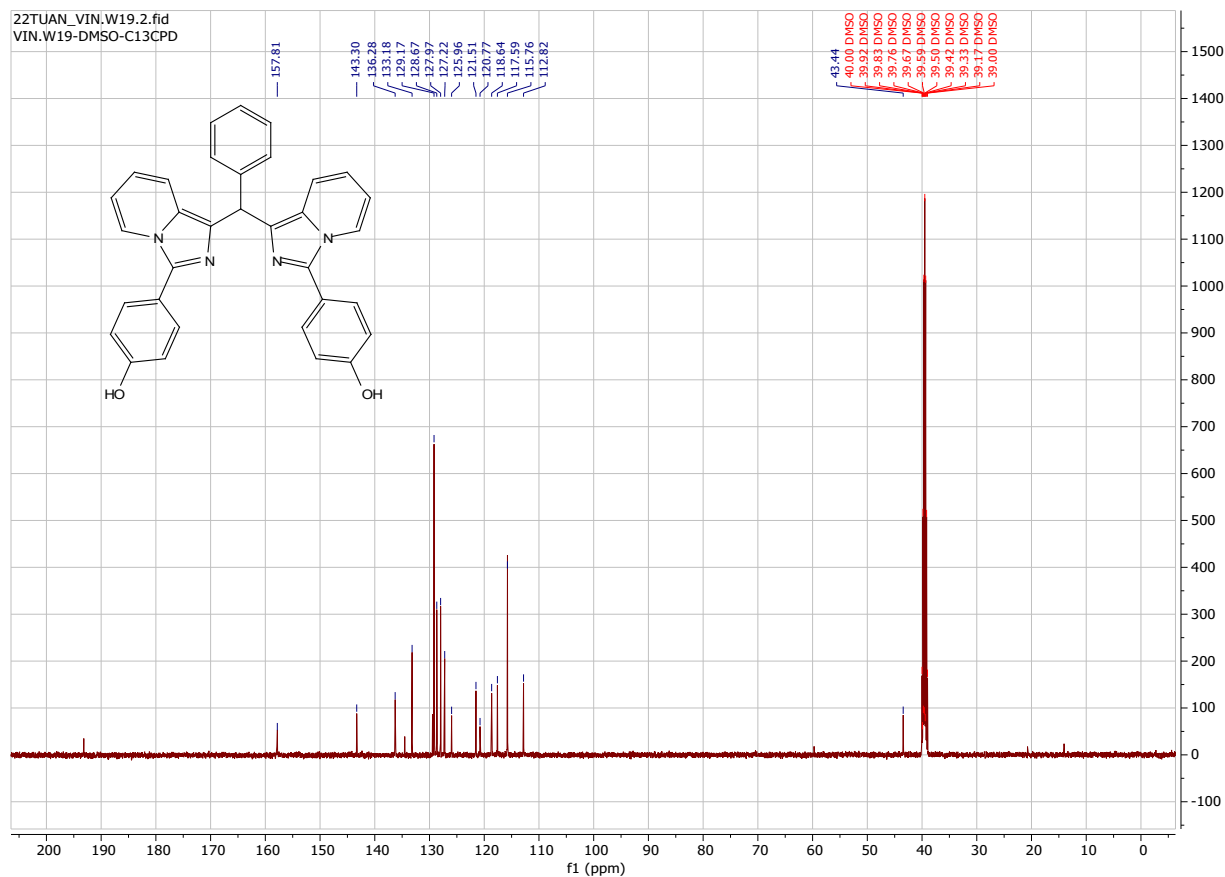
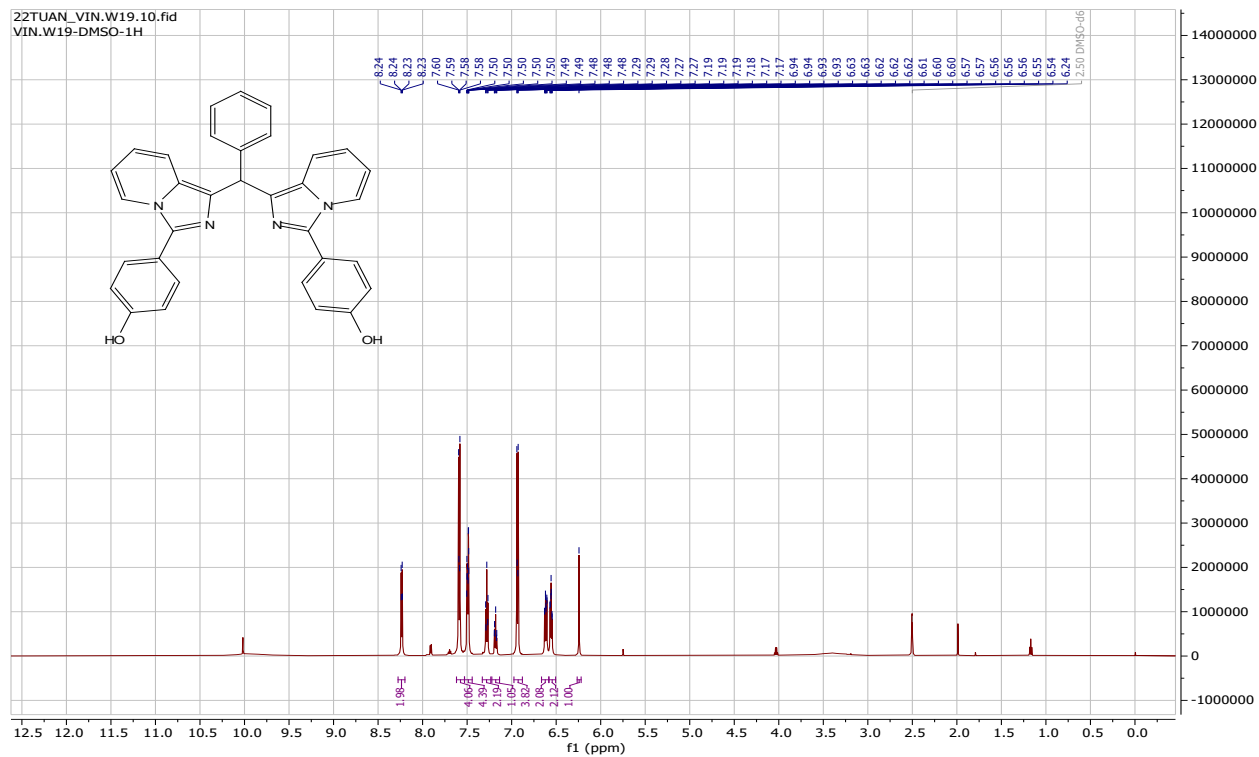
1,1'-(cyclohexylmethylene)bis(3-(4-methoxyphenyl)imidazo[1,5-a]pyridine) 3n



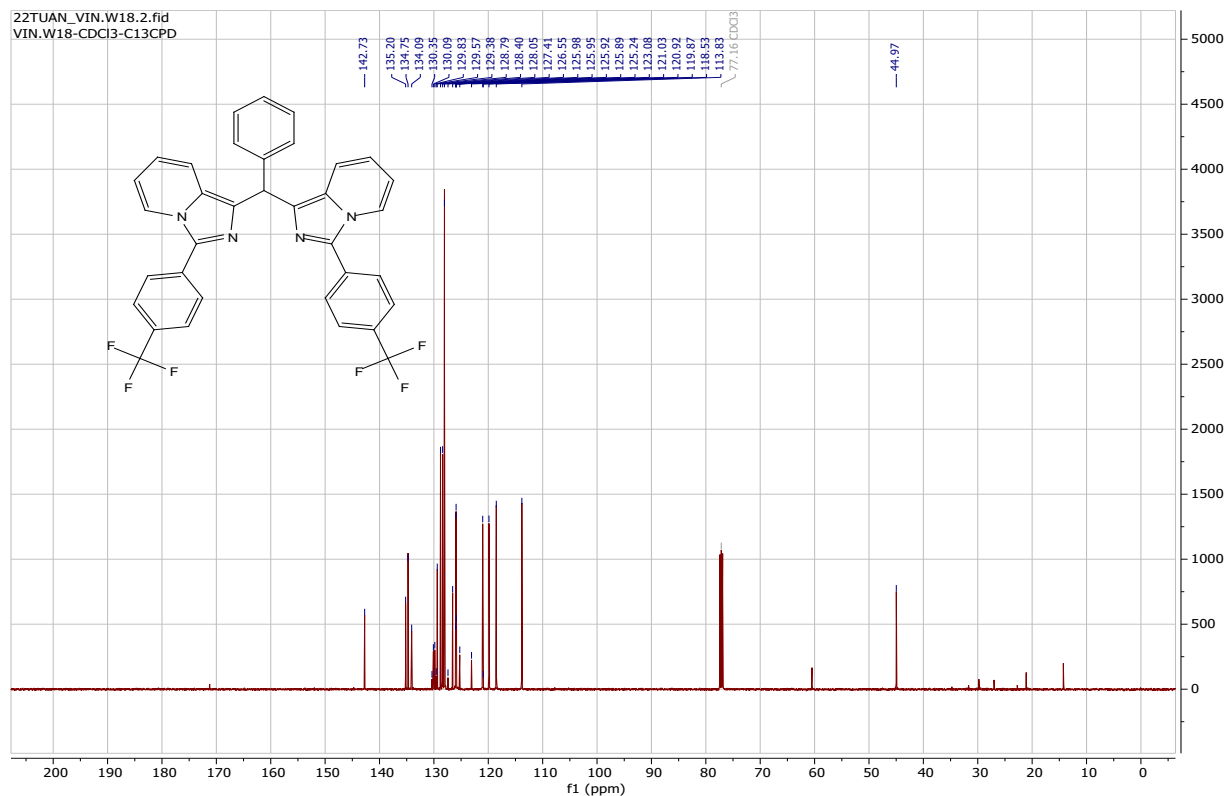
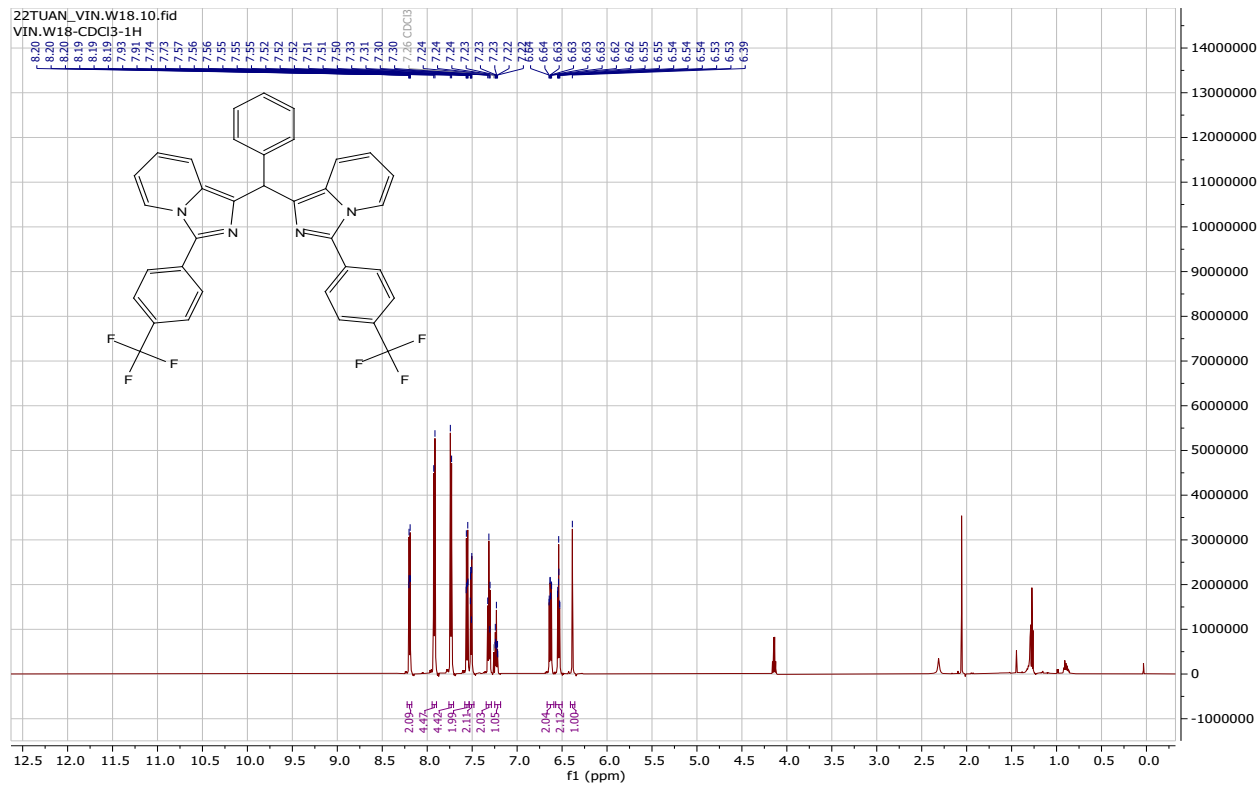
1,1'-(phenylmethylene)bis(3-(p-tolyl)imidazo[1,5-a]pyridine) 3p



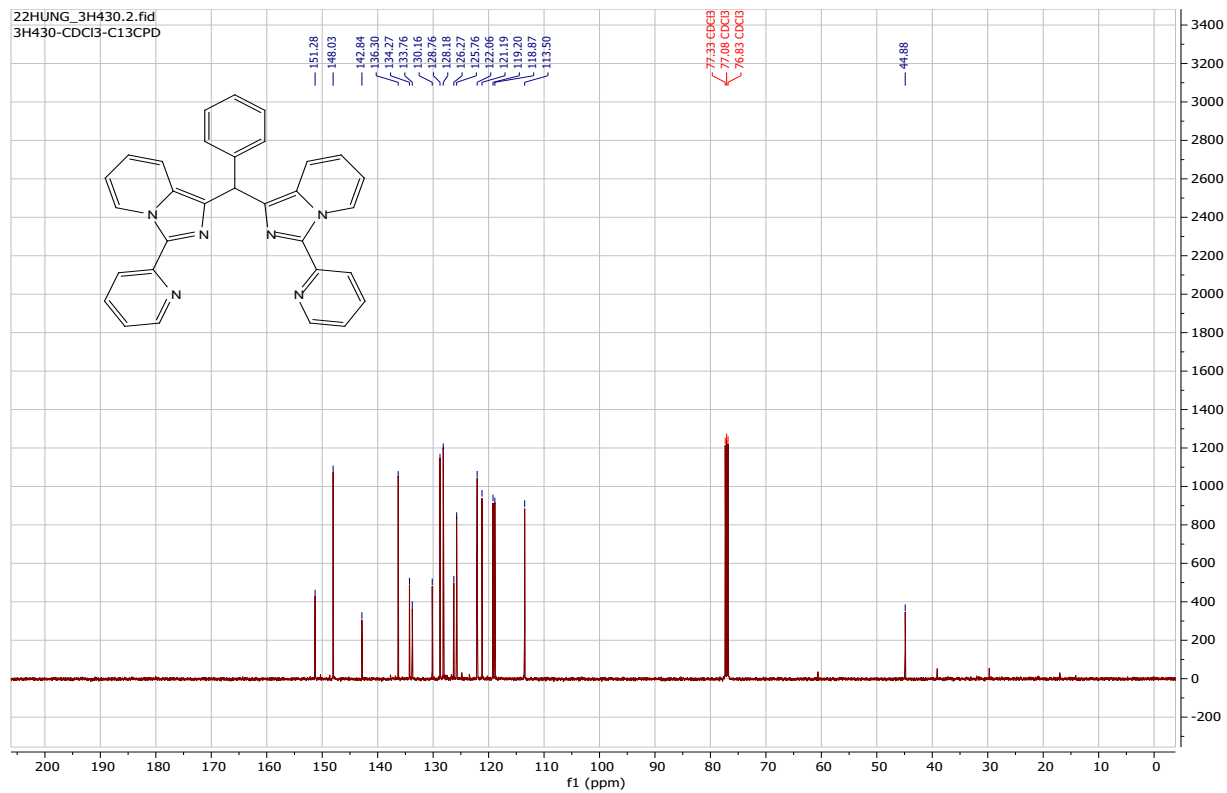
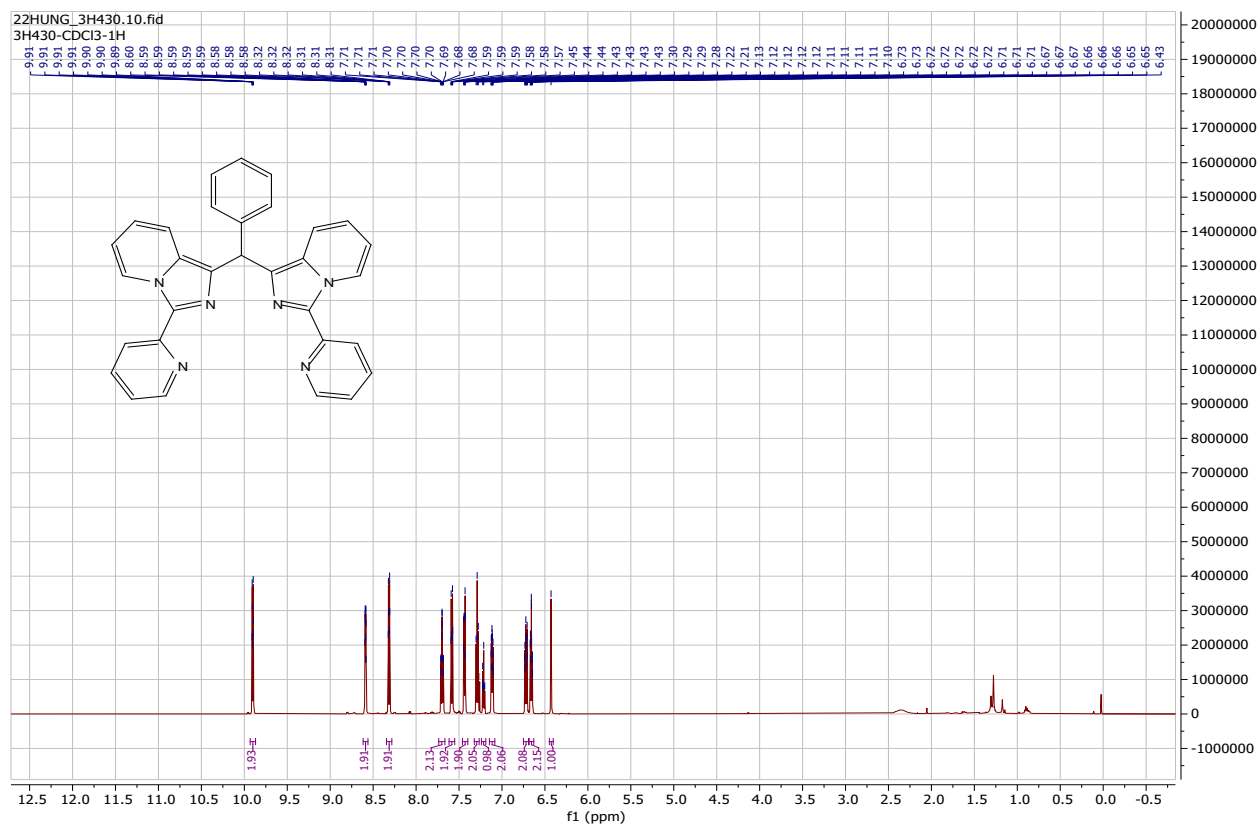
4,4'-((phenylmethylene)bis(imidazo[1,5-a]pyridine-1,3-diy))diphenol 3q



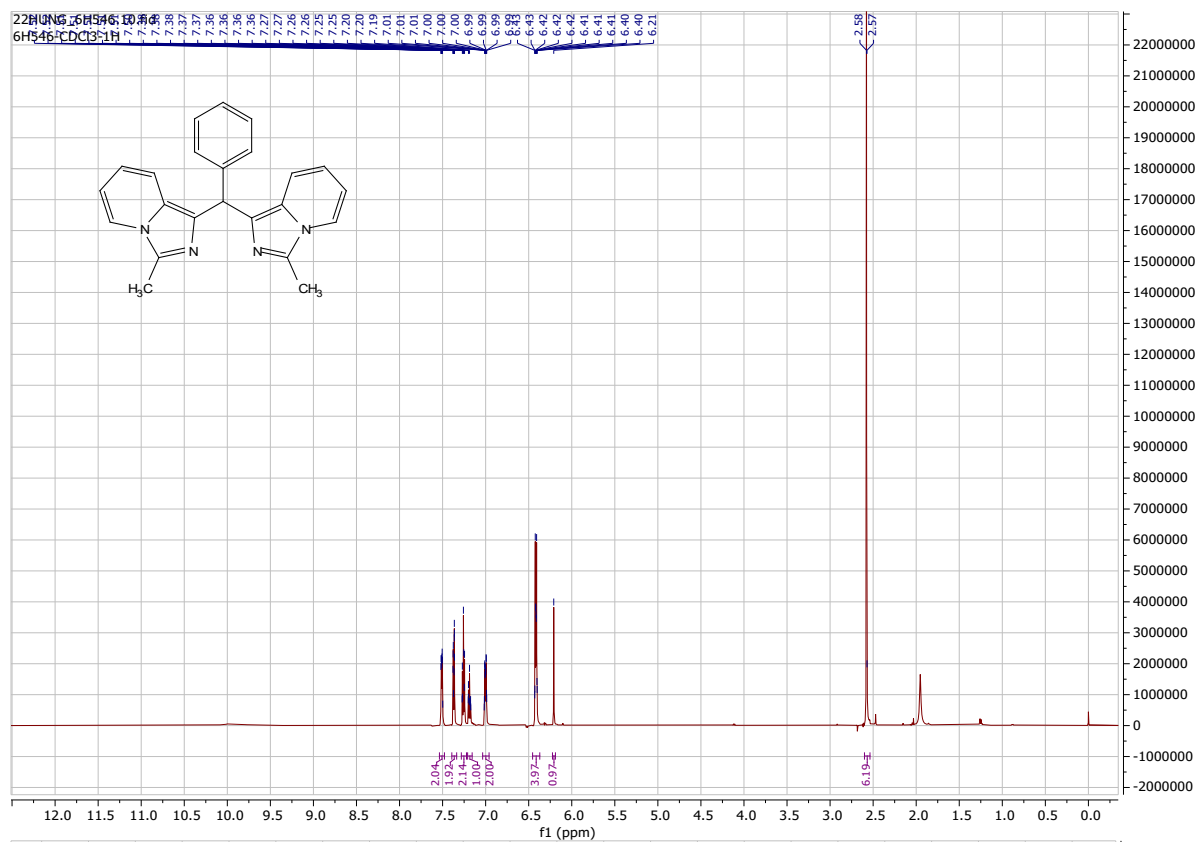
1,1'-(phenylmethylene)bis(3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine) 3s



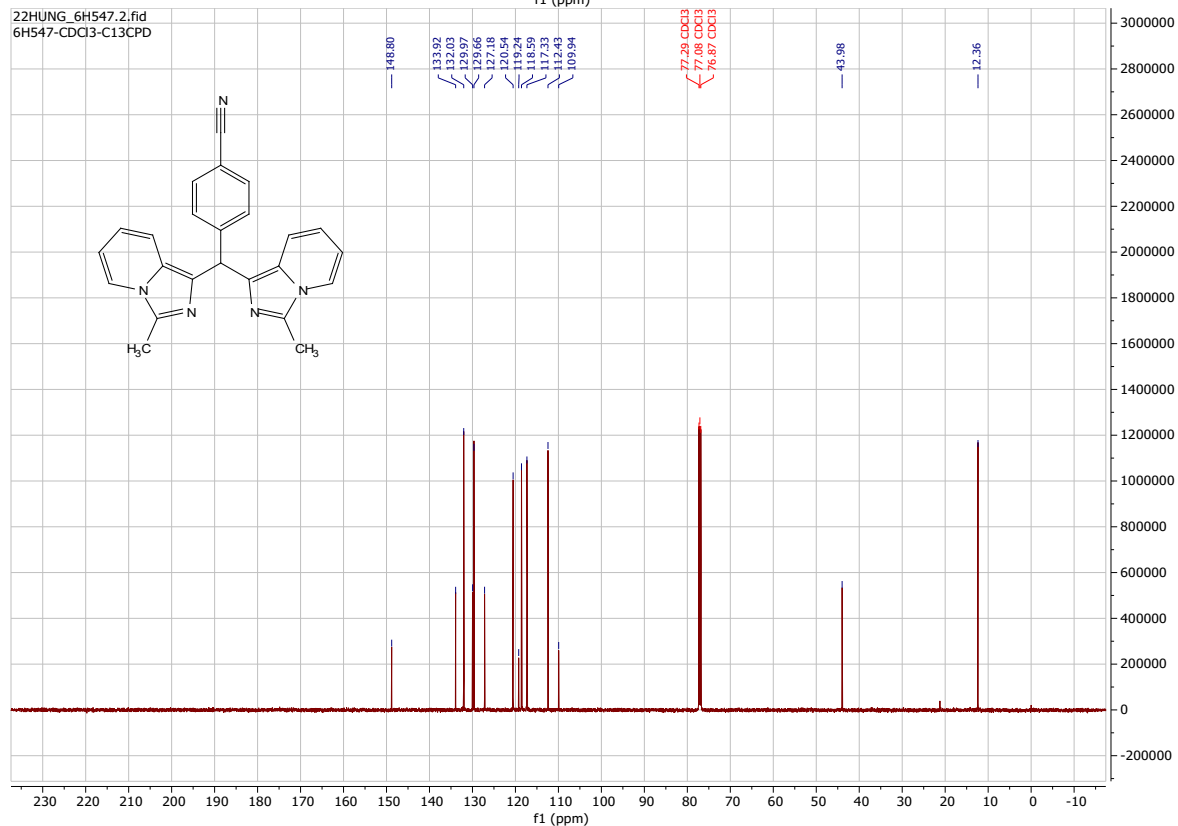
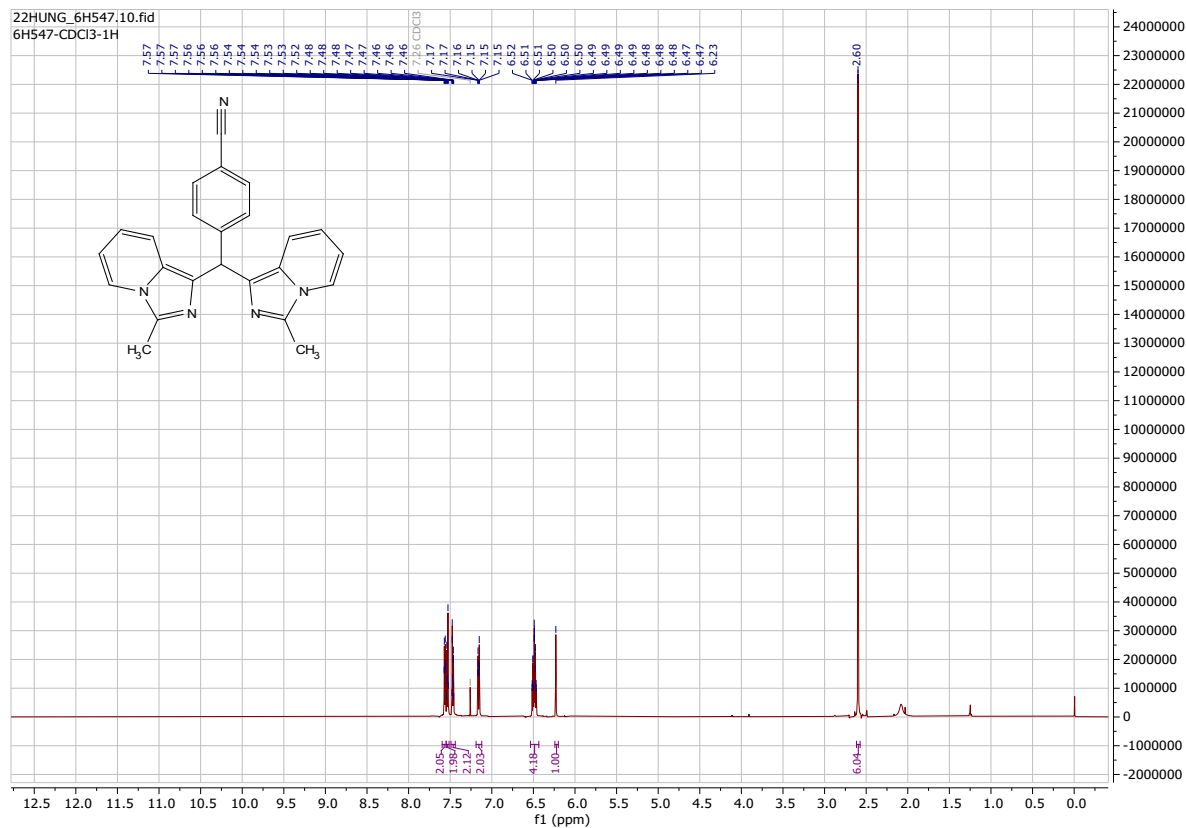
1,1'-(phenylmethylene)bis(3-(pyridin-2-yl)imidazo[1,5-a]pyridine) 3t



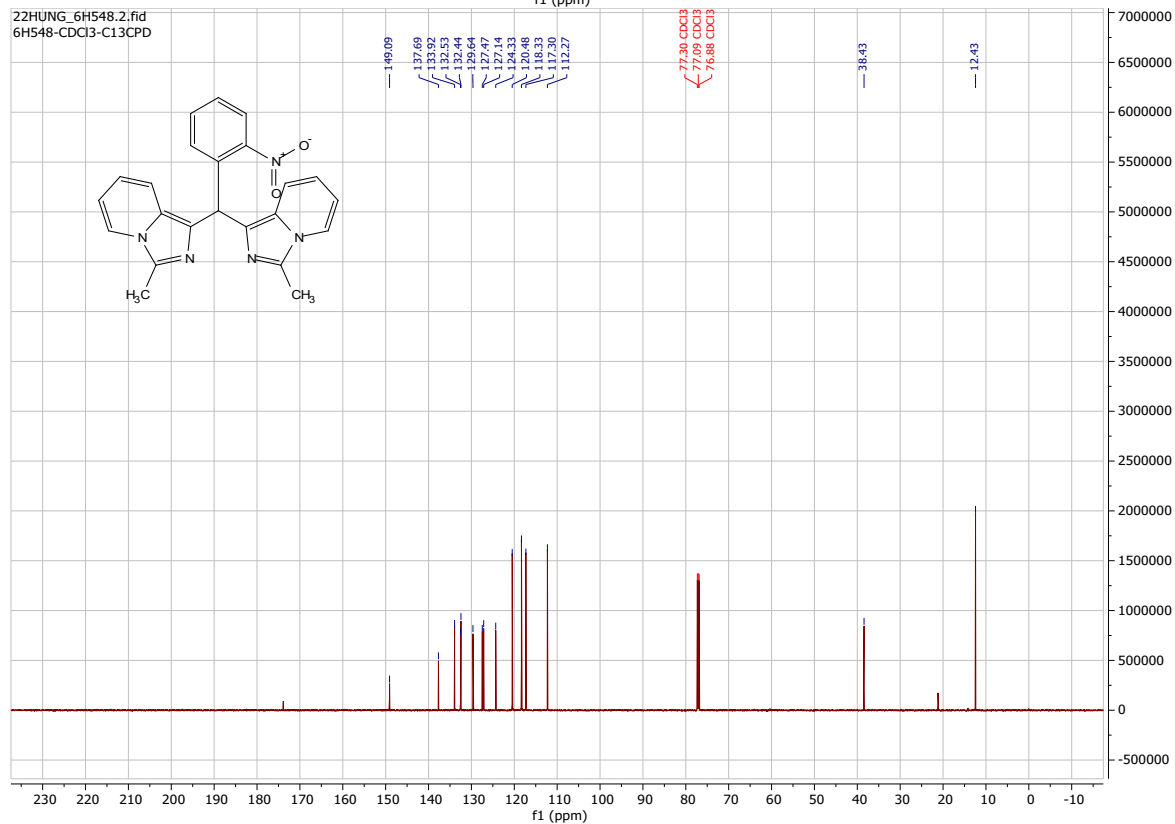
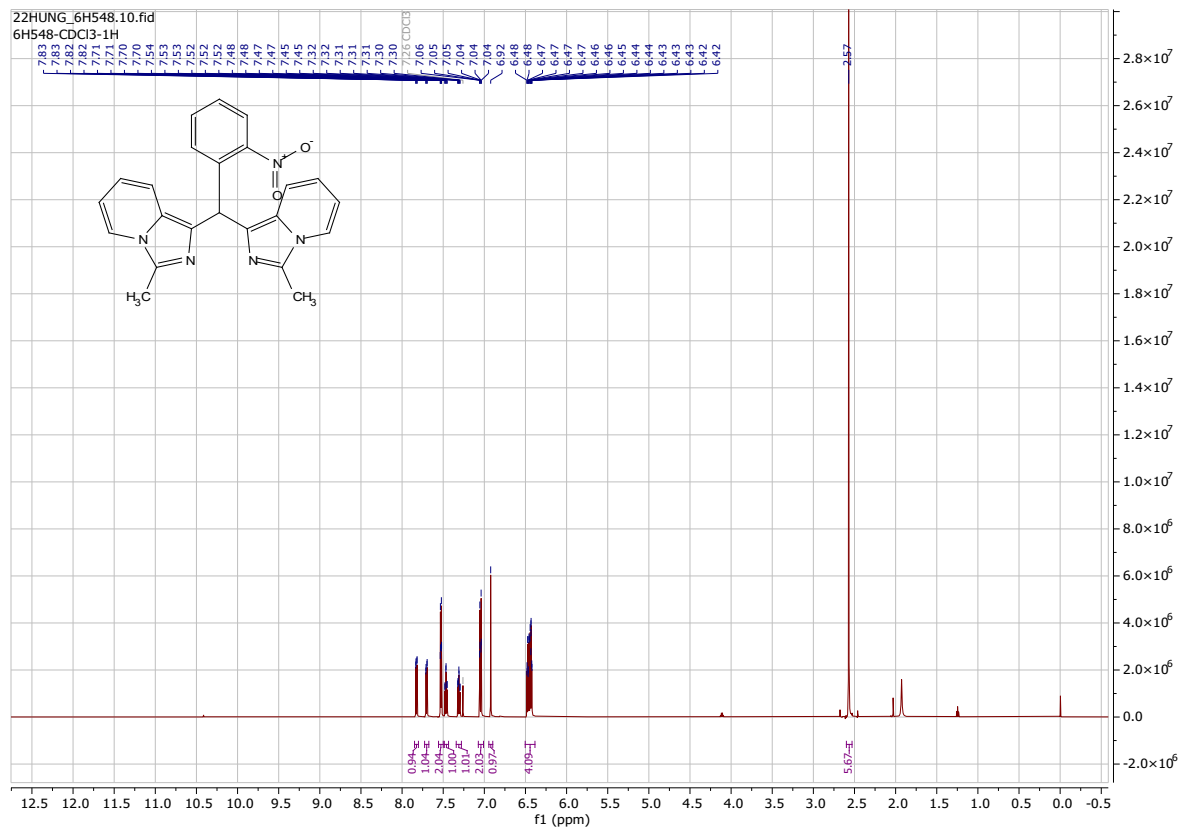
1,1'-(phenylmethylene)bis(3-methylimidazo[1,5-a]pyridine) 3u



4-(bis(3-methylimidazo[1,5-a]pyridin-1-yl)methyl)benzonitrile 3v



1,1'-((2-nitrophenyl)methylene)bis(3-methylimidazo[1,5-a]pyridine) 3x



4. References

1. Q. Wang, et al., *CBr₄ Mediated [4 + 1] Dehydrocyclization for the Synthesis of Functionalized Imidazo[1,5-a]heterocycles from Pyridin-2-ylmethanamines and Aldehydes*, *ACS Omega*, 2021, **6**, 20303-20308.
2. V.S. Arvapalli et al., *Microwave-assisted organic synthesis of 3-substituted-imidazo[1,5-a]pyridines*, *Tetrahedron Lett.*, 2010, **51**, 284-286.
3. M. Li et al., *Cu(I)-Catalyzed Transannulation of N-Heteroaryl Aldehydes or Ketones with Alkylamines via C(sp³)-H Amination*, *Org. Lett.*, 2014, **16**, 6232-6235.
4. B.V. Phuc et al., *Facile iodine-promoted synthesis of bis(1-imidazo[1,5-a]pyridyl)arylmethanes and exploration of applications*, *Chem. Commun.*, 2023, **59**, 1947-1950.
5. P. Skehan, et al., *New colorimetric cytotoxicity assay for anticancer-drug screening*. *JNCI: J. Nat. Cancer Inst.*, 1990, **82**, 1107-1112.
6. J.P. Hughes et al., *Principles of early drug discovery*. *British J. Pharm.*, 2011, **162**, 1239-1249.