# Structural systematics and conformational analyses of a 3×3 isomer grid of nine *N*-(tolyl)pyridinecarboxamides and three chlorinated relatives.

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## Electronic Supplementary Information

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## 1. Detailed description of synthetic procedures

As acyl chlorides are very reactive, the reactions were performed in anhydrous conditions in $CH_2Cl_2$ (under $N_2$), initially at 5°C and then at room temperature. A by-product is HCl, and triethylamine ($Et_3N$) was employed to drive the reaction equilibrium towards the **NxxM** product. The pyridinoyl chlorides technically were used in the form of hydrochlorides so an additional mole of $Et_3N$ was used to enhance their solubility in $CH_2Cl_2$ so that in total, two molar equivalents of triethylamine ($Et_3N$) were added per reaction.

Condensation reactions were performed with the 4-, 3- or 2-toluidines (1 ml, 10.41 mmol) added to a 250 ml flask placed on an ice bath and with subsequent stirring. Then, 30 ml of $CH_2Cl_2$ was added to the flask followed by addition of $Et_3N$ (1.5 ml, 10.76 mmol). Finally, the 4-, 3- or 2-pyridinoyl chlorides (2 g, 11.23 mmol) were added in portions directly into this solution mixture. Another 30 ml of $CH_2Cl_2$ and 1.5 ml of $NEt_3$ was added to accelerate the dissolution of any solids and the reaction mixture was allowed to warm to room temperature and stirred overnight.

Organic washing and work-up was as standard: the organic reaction phase was washed with 20 ml of $KHCO_3$ (0.1 M) solution *ca.* 3-7 times and during purification, glassware was warmed to *ca.* 35°C. Then, 1.5 g of anhydrous $MgSO_4$ was added to the organic solutions for 20 minutes. The flask contents were filtered through a Büchner funnel (under vacuum) to remove $MgSO_4$. The filtrate was evaporated under vacuum and the crystallization induced giving the desired product in modest to good yields.

Separation and purification of **NoxM** compounds
The **NoxM** compounds were successfully separated from **5-Cl-NoxM** compounds by column chromatography using silica gel as stationary phase and mixture of chloroform, ethyl acetate and cyclohexane (4:2:1).

**Fig. 1**. Schematic diagram of the **NxxM** synthesis.

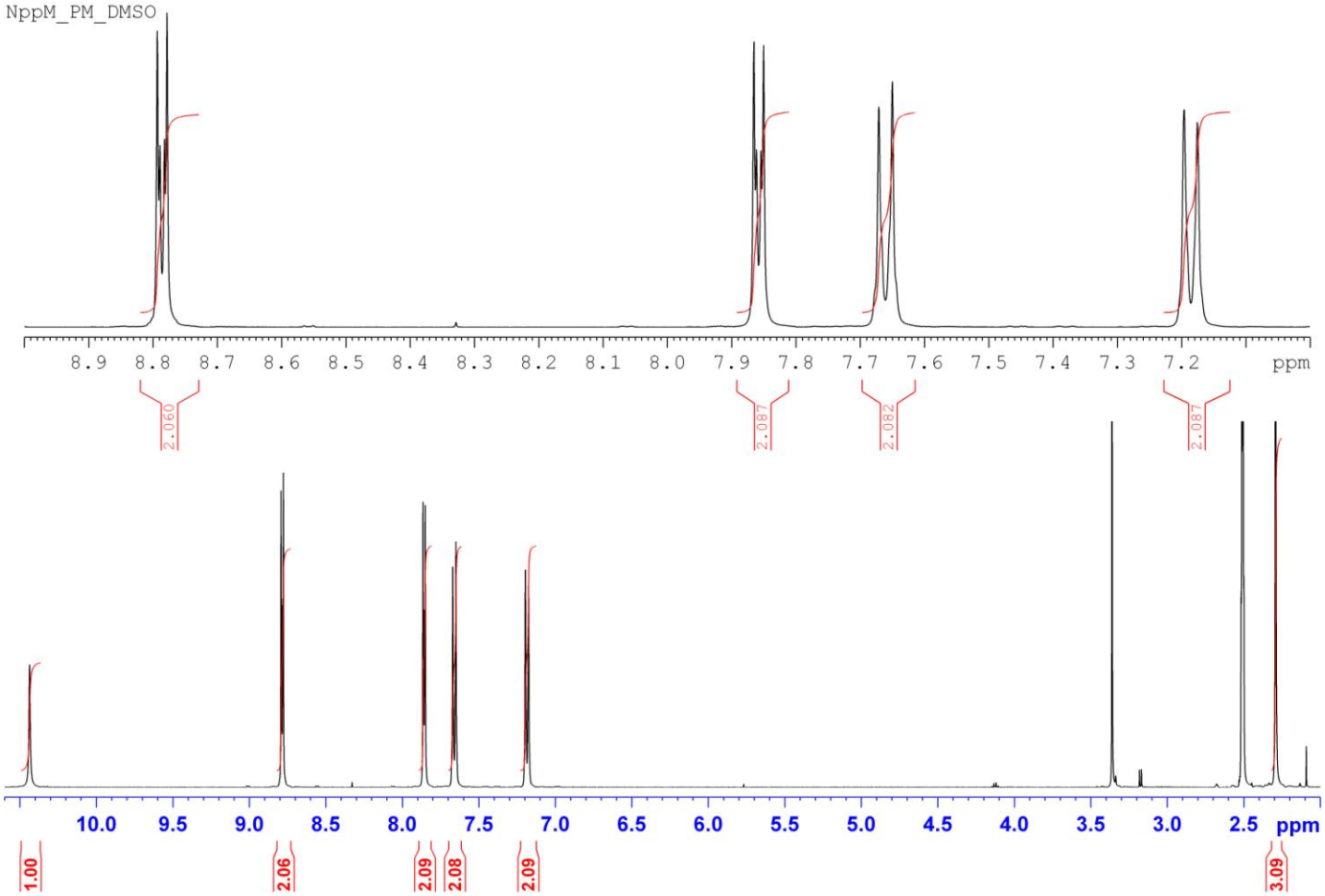
**Table 1** Obtained amounts, yields and melting point ranges of the **NxxM** isomers with 5-Cl-**NoxM**.

| NxxM | m/g | yield/% | m.p./ºC |
|---|---|---|---|
| **NppM** | 1.578 | 78.9 | 161.0-162.5 |
| **NmpM** | 1.847 | 92.3 | 140.2-142.9 |
| **NpoM** | 1.747 | 87.3 | 123.9-125.9 |
| **NmpM** | 1.863 | 93.1 | 147.6-148.3 |
| **NmmM** | 1.530 | 76.5 | 113.0-114.7 |
| **NmoM** | 1.390 | 69.5 | 106.1-107.0 |
| **NopM** | 1.340 | 67.0 | 104.7-105.2 |
| **NomM** | 0.876 | 43.8 | 49.2-50.5 |
| **NooM** | 1.134 | 56.7 | 64.1-64.9 |
| 5-Cl-**NopM** | 0.250 | 12.5 | 125.5-129.5 |
| 5-Cl-**NomM** | 0.224 | 11.2 | 70.2-73.9 |
| 5-Cl-**NooM** | 0.332 | 16.6 | 128.3-128.6 |

**2. $^{1}$H NMR data and spectra**

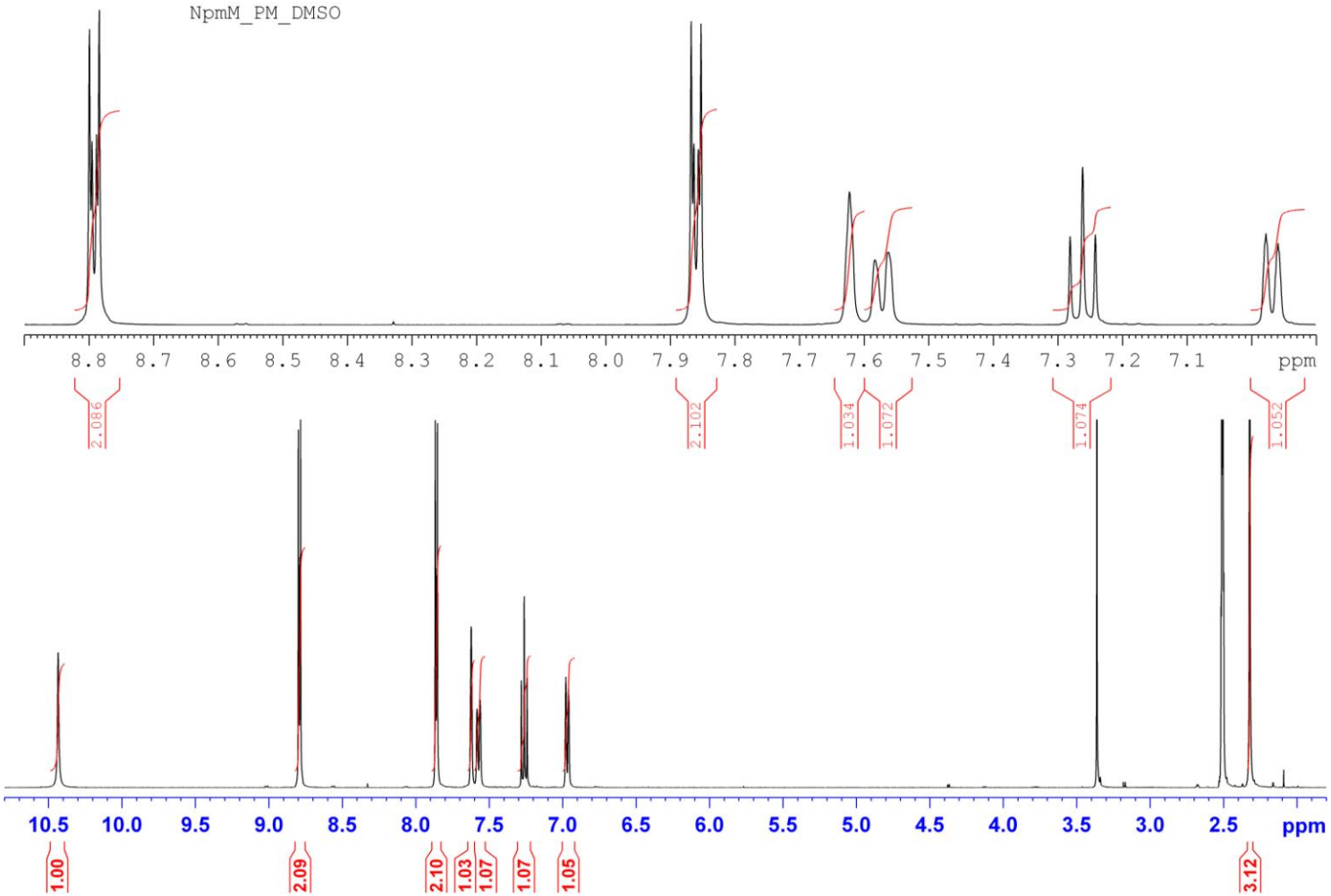
**2.1 NppM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.37 (3H, s), 7.21 (2H, d, $^{3}J$ = 8), 7.54 (2H, d, $^{3}J$ = 8), 7.73 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.5), 8.00 (1H, br s), 8.80 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.5); **$^{1}$H NMR (DMSO-$d^6$)** δ 2.29 (3H, s), 7.19 (2H, d, $^{3}J$ = 8), 7.66 (2H, d, $^{3}J$ = 8.4), 7.86 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.6), 8.79 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.6), 10.44 (1H, br s); **$^{13}$C NMR (DMSO-$d^6$)** δ 20.49, 120.43, 121.52, 129.09, 133.20, 136.03, 141.96, 150.21, 163.70.



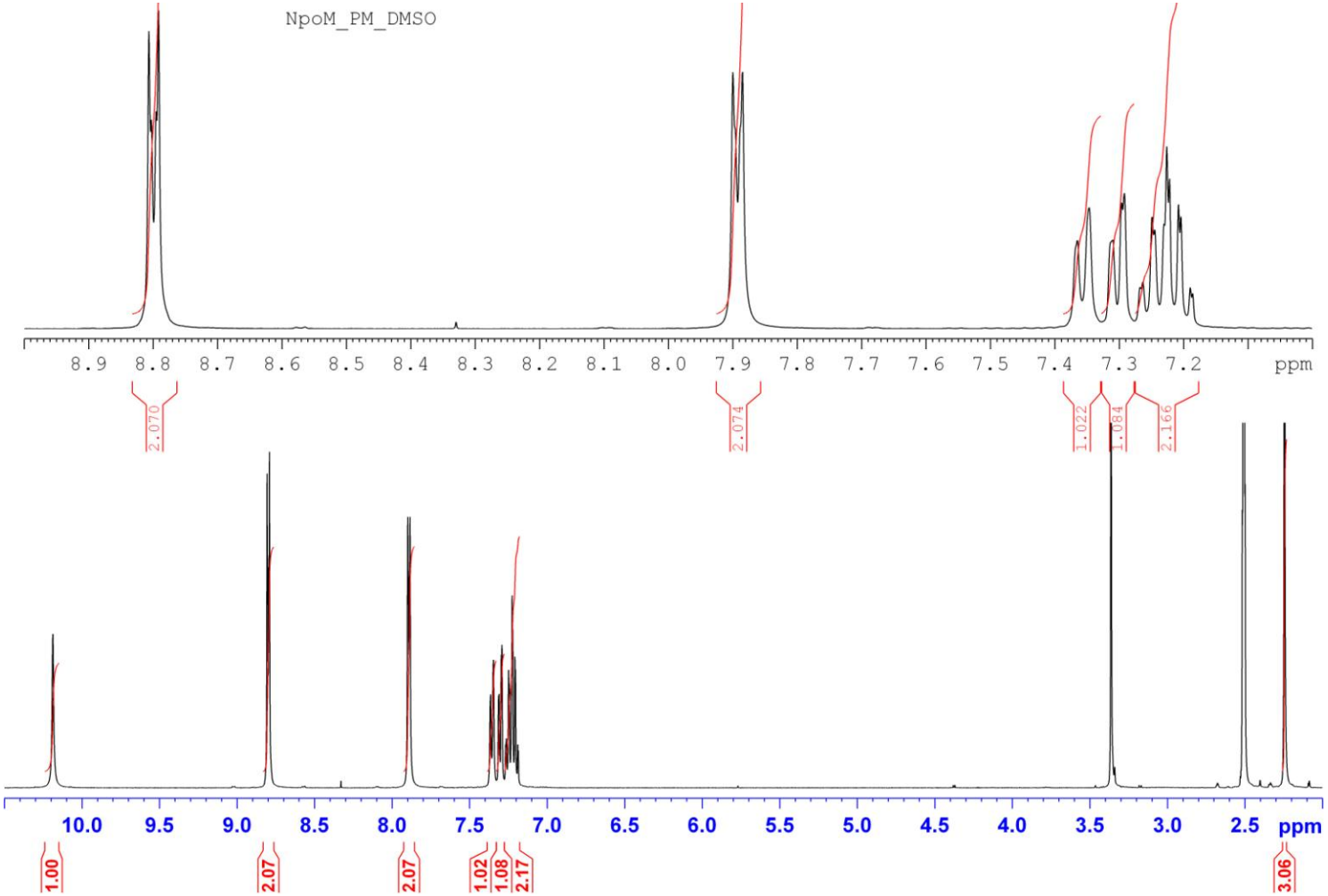
**2.2 NpmM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.31 (3H, s), 6.94 (1H, d, $^{3}J$ = 8), 7.20 (1H, t, $^{3}J$ = 8), 7.35 (1H, d, $^{3}J$ = 8), 7.44 (1H, s), 7.65 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.5), 7.96 (1H, br s), 8.72 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.5); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ 2.32 (3H, s), 6.97 (1H, d, $^{3}J$ = 7.6), 7.26 (1H, t, $^{3}J$ = 7.8), 7.57 (1H, d, $^{3}J$ = 8), 7.62 (1H, s), 7.86 (2H, dd, $^{3}J$ = 4.3, $^{4}J$ = 1.7), 8.79 (2H, dd, $^{3}J$ = 4.3, $^{4}J$ = 1.7), 10.43 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 21.62, 118.06, 121.40, 121.98, 125.32, 128.99, 138.34, 138.93, 142.39, 150.69, 164.32.



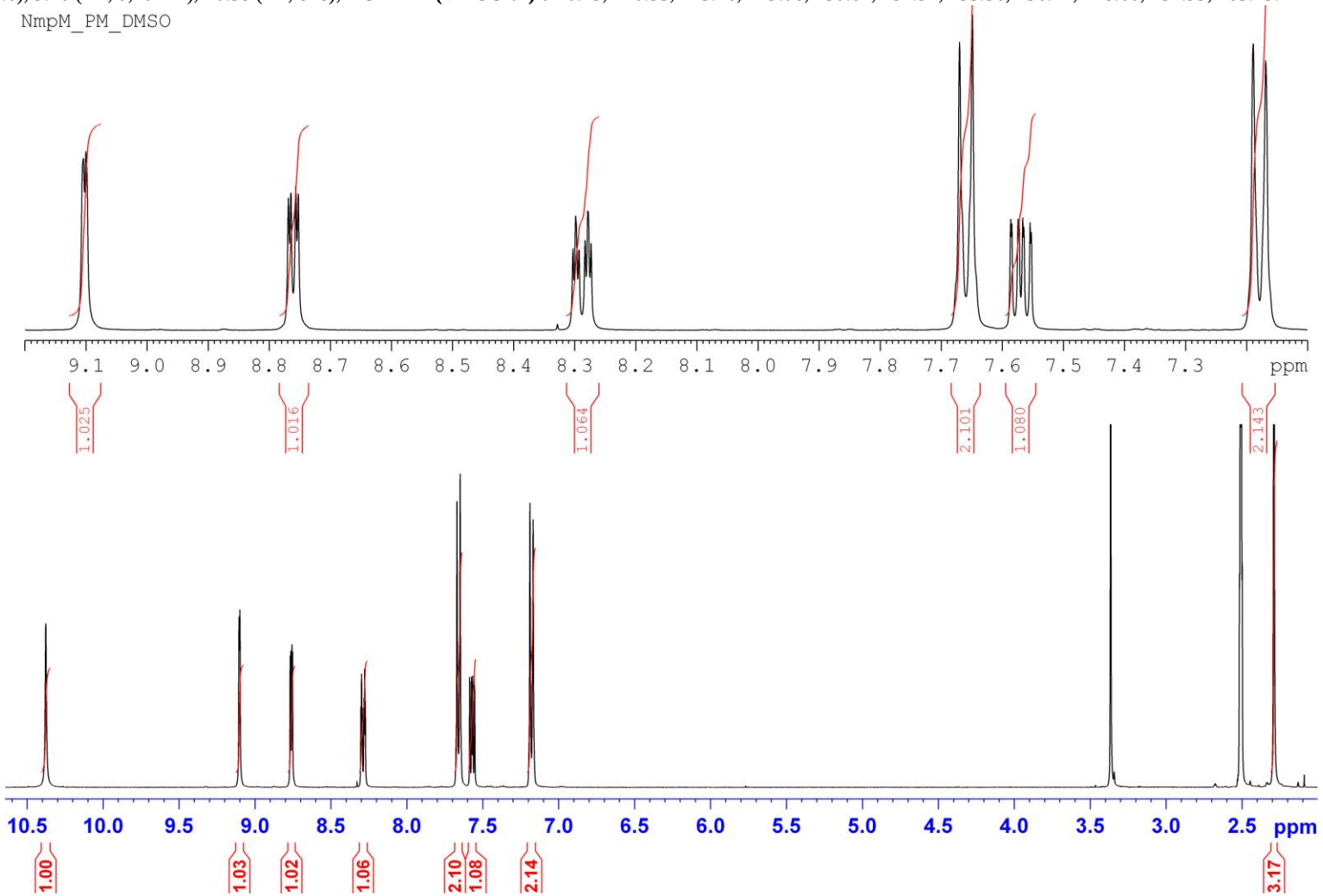
**2.3 NpoM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.35 (3H, s), 7.19 (1H, td, $^{3}J$ = 7.5, $^{4}J$ = 1), 7.28 (2H, m), 7.76 (2H, d, $^{3}J$ = 4.2), 7.87 (1H, d, $^{3}J$ = 8), 7.90 (1H, br s), 8.8 (2H, d, $^{3}J$ = 4.8); **$^{1}$H NMR (DMSO-$d^6$)** δ 2.25 (3H, s), 7.21 (1H, td, $^{3}J$ =7.3, $^{4}J$ = 1.5), 7.25 (1H, td, $^{3}J$ = 7.6, $^{4}J$ = 1.7) 7.30 (1H, dd, $^{3}J$ =7, $^{4}J$ = 1.5), 7.36 (1H, d, $^{3}J$ =7.5), 7.89 (2H, dd, $^{3}J$ = 4.6, $^{4}J$ = 1.4), 8.80 (2H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1.5), 10.19 (1H, br s); **$^{13}$C NMR (DMSO-$d^6$)** δ 17.82, 121.55, 126.10, 126.40, 126.57, 130.40, 133.76, 135.70, 141.46, 150.31, 163.76.



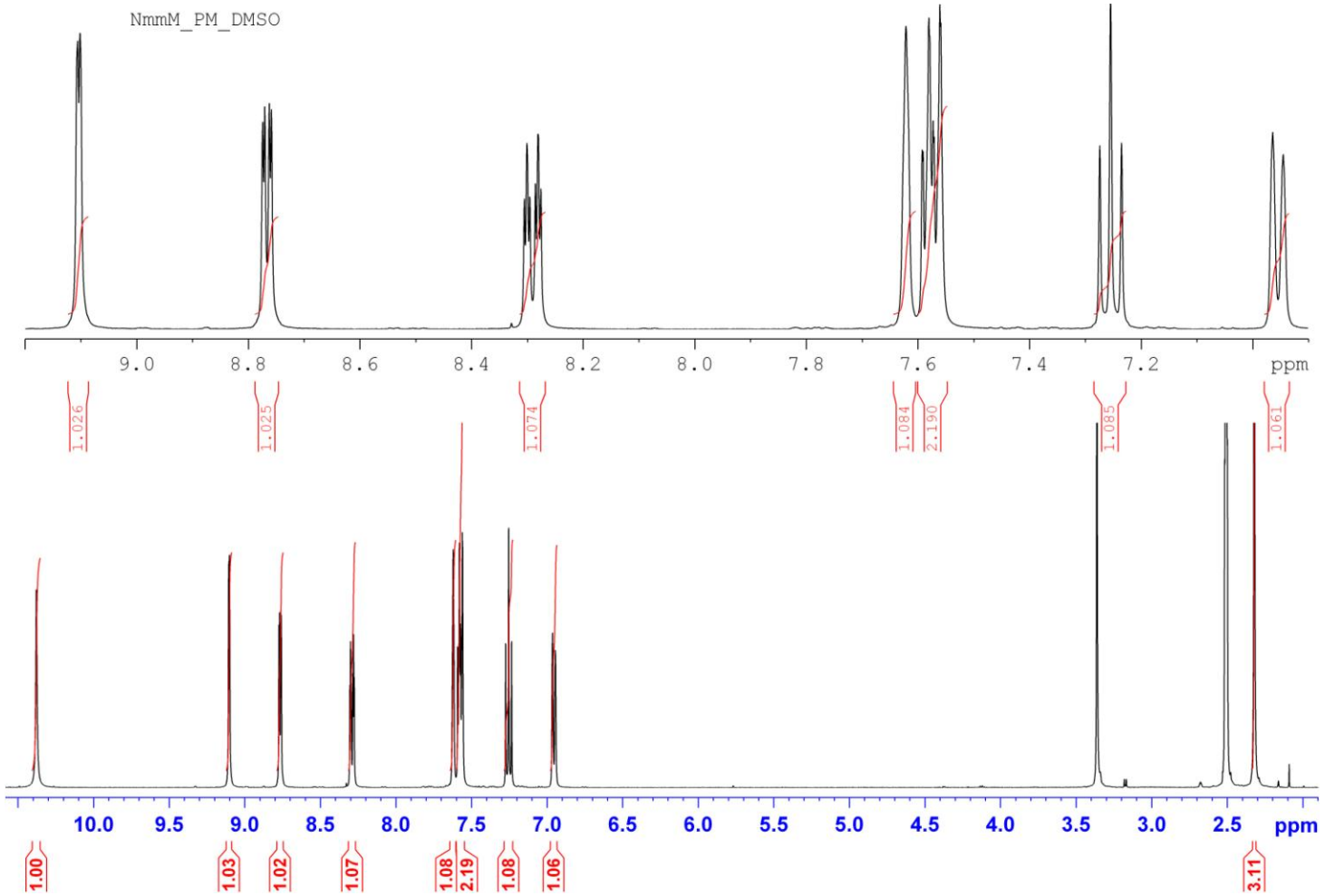
**2.4. NmpM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.36 (3H, s), 7.19 (2H, d, $^{3}J$ = 8), 7.44 (1H, dd, $^{3}J$ = 8, $^{4}J$ = 5), 7.55 (2H, d, $^{3}J$ = 8), 8.22 (1H, br s), 8.23 (1H, d, $^{3}J$ = 7.5), 8.75 (1H, dd, $^{3}J$ = 4.5, $^{4}J$ = 1), 9.12 (1H, s); **$^{1}$H NMR (DMSO-$d^6$)** δ 2.29 (3H, s), 7.18 (2H, d, $^{3}J$ = 8.3), 7.57 (1H, ddd, $^{3}J$ = 8, $^{4}J$ = 4.8, $^{5}J$ = 0.8), 7.66 (2H, d, $^{3}J$ = 8.4), 8.29 (1H, dt, $^{3}J$ = 8, $^{4}J$ = 2), 8.76 (1H, dd, $^{3}J$ = 4.8, $^{4}J$ = 1.6), 9.10 (1H, d, $^{3}J$ = 2), 10.38 (1H, br s); **$^{13}$C NMR (DMSO-$d^6$)** δ 20.49, 120.33, 123.46, 129.06, 130.61, 132.94, 135.36, 136.27, 148.60, 151.99, 163.79.



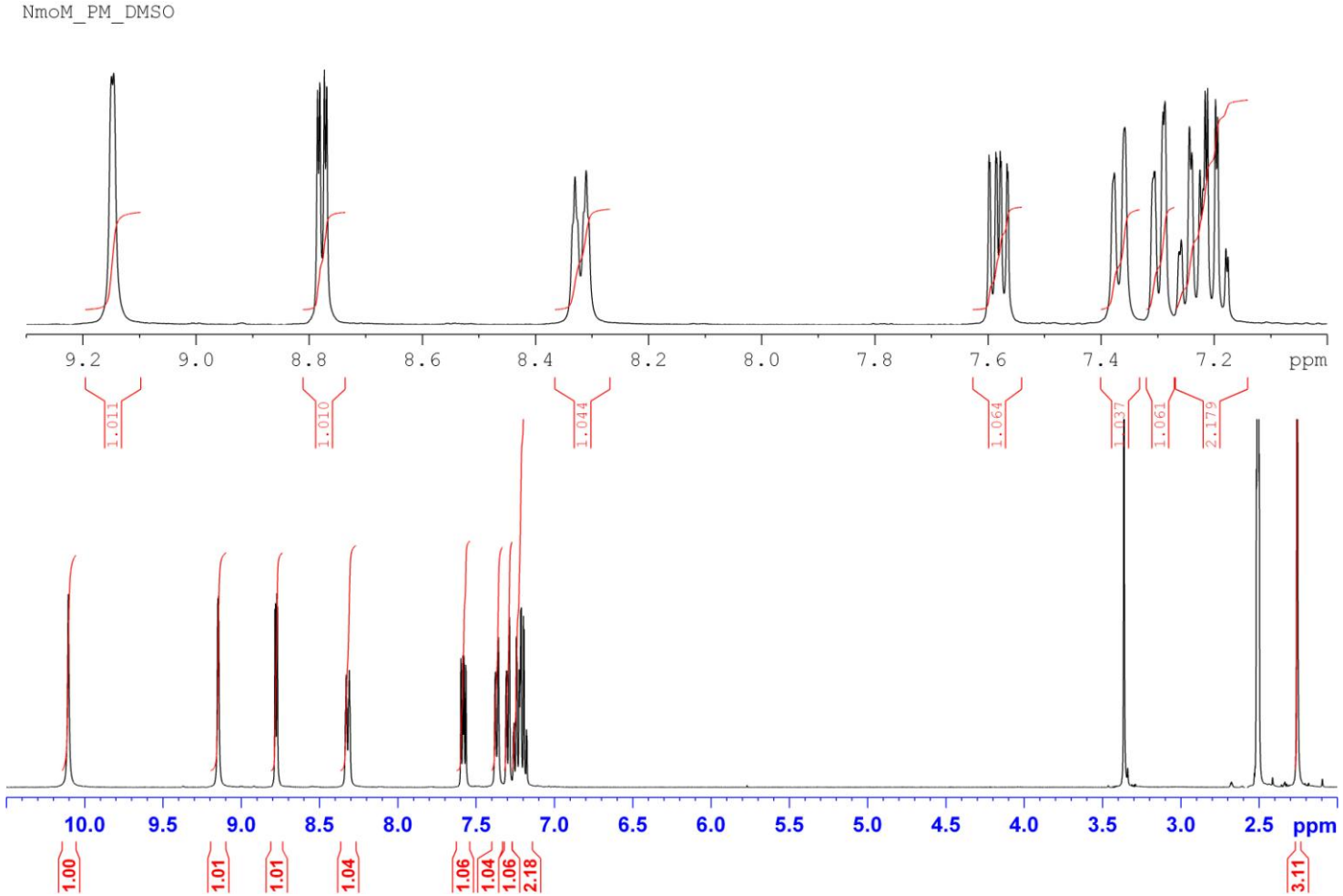
**2.5. NmmM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.38 (3H, s), 7.01 (1H, d, $^{3}J$ = 7.5), 7.27 (1H, t, $^{3}J$ = 7.7), 7.44 (2H, d, $^{3}J$ =7.2), 7.53 (1H, s), 8.23 (1H, d, $^{3}J$ =7.5), 8.26, (1H, br s), 8.75 (1H, d, $^{3}J$ = 4.2), 9.11 (1H, s); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ 2.32 (3H, s), 6.95 (1H, d, $^{3}J$ = 7.5), 7.25 (1H, t, $^{3}J$ = 7.8), 7.57 (1H, dd, $^{3}J$= 8, $^{4}J$ = 0.5), 7.57 (1H, ddd, $^{3}J$ = 8, $^{4}J$ = 4.8, $^{5}J$ = 0.5), 7.62 (1H, s), 8.29 (1H, dt, $^{3}J$ = 8, $^{4}J$ = 2), 8.76 (1H, dd, $^{3}J$ = 4.8, $^{4}J$ = 1.6), 9.10 (1H, d, $^{3}J$ = 2), 10.38 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 21.61, 117.93, 121.27, 123.90, 125.07, 128.94, 131.02, 135.82, 138.26, 139.14, 149.05, 152.47, 164.37.



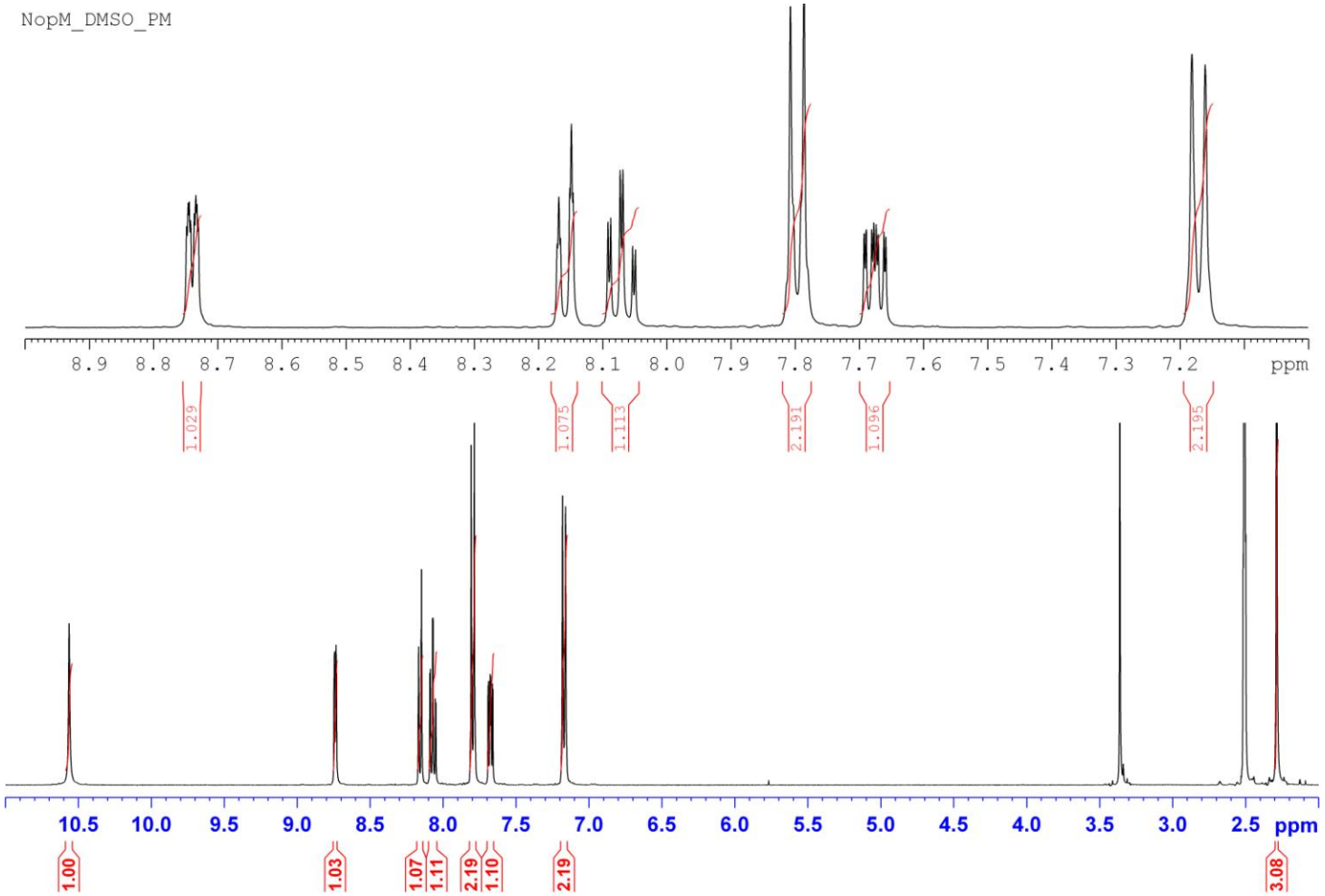
**2.6. NmoM**

**$^{1}$H NMR ($CDCl_3$)**: δ 2.27 (3H, s) 7.09 (1H, td, $^{3}J$ = 8, $^{4}J$ = 1), 7.19 (2H, m), 7.39 (1H, dd, $^{3}J$ = 8.5, $^{4}J$ = 4.8), 7.78 (1H, d, $^{3}J$ = 6.3), 7.81 (1H, br s), 8.18 (1H, d, $^{3}J$ = 6.8), 8.71 (1H, d, $^{3}J$ = 4.2), 9.07 (1H, s); **$^{1}$H NMR (DMSO-*d*$^{6}$)**: δ 2.26 (3H, s), 7.20 (1H, td, $^{3}J$ = 7.3, $^{4}J$ = 1.6), 7.24 (1H, td, $^{3}J$ = 7.6, $^{4}J$ = 1.5), 7.30 (1H, dd, $^{3}J$ =7, $^{4}J$ =1.3), 7.37 (1H, d, $^{3}J$ =7.8), 7.58 (1H, ddd, $^{3}J$ = 4, $^{4}J$ = 4.8, $^{5}J$ = 0.7), 8.32 (1H, dt, $^{3}J$ = 8, $^{4}J$ = 1.8), 8.78 (1H, dd, $^{3}J$ = 4.8, $^{4}J$ = 1.6), 9.15 (1H, d, $^{3}J$ = 1.6), 10.10 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)**: δ 17.88, 123.54, 126.05, 126.22, 126.54, 130.08, 130.37, 133.68, 135.40, 135.93, 148.67, 152.11, 163.84.



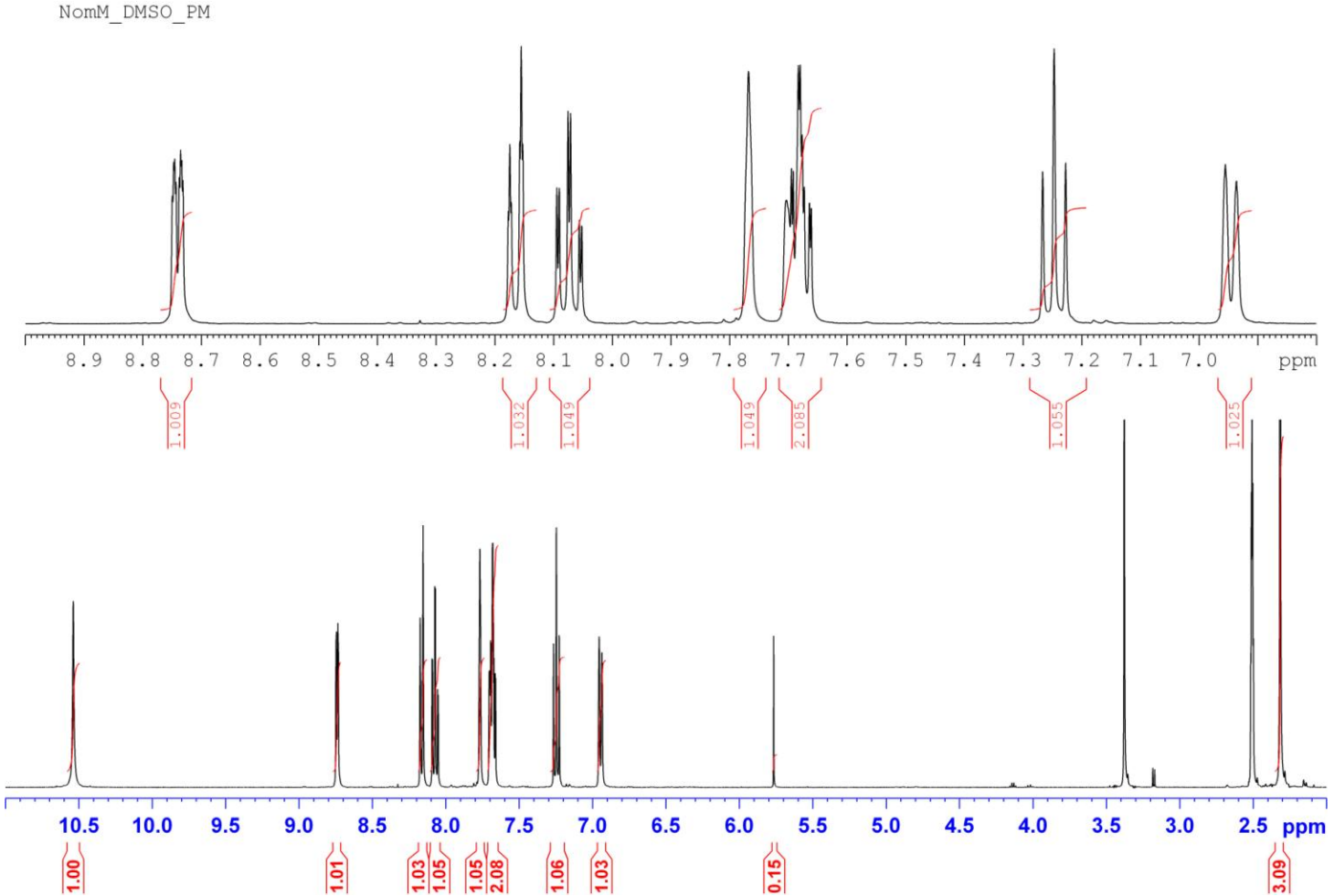
**2.7. NopM**

**$^{1}$H NMR ($CDCl_3$)**: δ 2.27 (3H, s), 7.12 (2H, d, $^{3}J$ = 8), 7.40 (1H, ddd, $^{3}J$ = 7.5, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.60 (2H, d, $^{3}J$ = 8.4), 7.83 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.23 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.54 (1H, dq, $^{3}J$ = 4.8, $^{4}J$ = 0.8), 9.90 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)**: δ 2.29 (3H, s), 7.17 (2H, d, $^{3}J$ = 8.4), 7.67 (1H, ddd, $^{3}J$ = 7.6, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.80 (2H, d, $^{3}J$ = 8.4), 8.07 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.16 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.74 (1H, dq, $^{3}J$ = 4.8, $^{4}J$ = 0.8), 10.56 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 20.49, 120.15, 122.27, 126.81, 129.05, 132.87, 135.80, 138.10, 148.38, 149.94, 162.21.



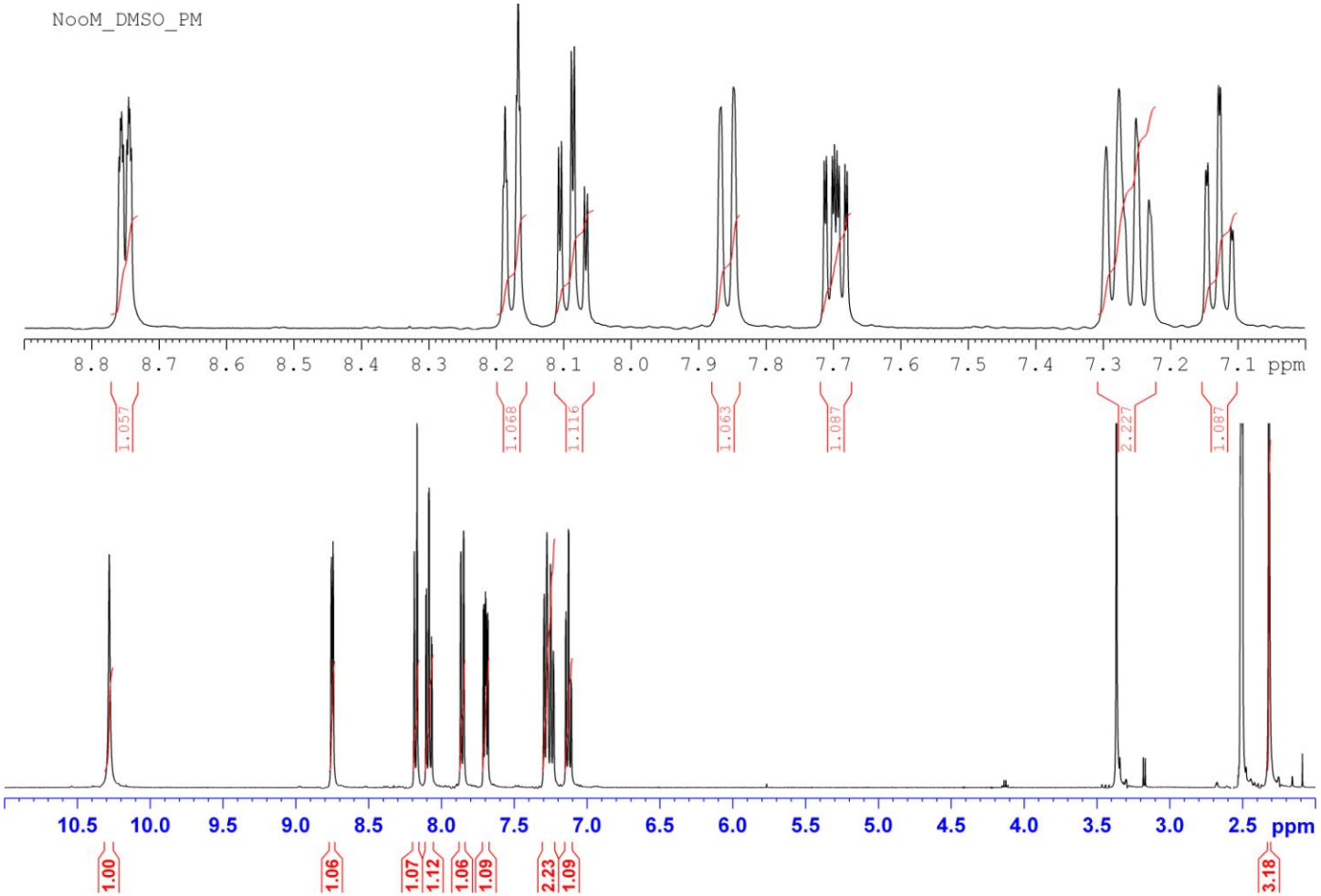
**2.8 NomM**

**$^{1}$H NMR ($CDCl_3$)**: δ 2.31 (3H, s), 6.90 (1H, d, $^{3}J$ = 7.5), 7.2 (1H, t, $^{3}J$ = 7.8), 7.41 (1H, ddd, $^{3}J$ = 7.6, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.50 (1H, d, $^{3}J$ = 8), 7.58 (1H, s), 7.84 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.23 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.54 (1H, dq, $^{3}J$ = 4.7, $^{4}J$ = 0.8), 9.94 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ: 2.32 (3H, s), 6.95 (1H, d, $^{3}J$ = 7.5), 7.25 (1H, t, $^{3}J$ = 7.7), 7.68 (1H, ddd, $^{3}J$ = 7.6, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.69 (1H, d, $^{3}J$ = 8), 7.77 (1H, s), 8.07 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.16 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.74 (1H, dq, $^{3}J$ = 4.7, $^{4}J$ = 0.8), 10.54 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)**: δ 21.19, 117.34, 120.66, 122.28, 124.60, 126.88, 128.51, 137.86, 138.13, 138.18, 148.39, 149.86, 162.30.



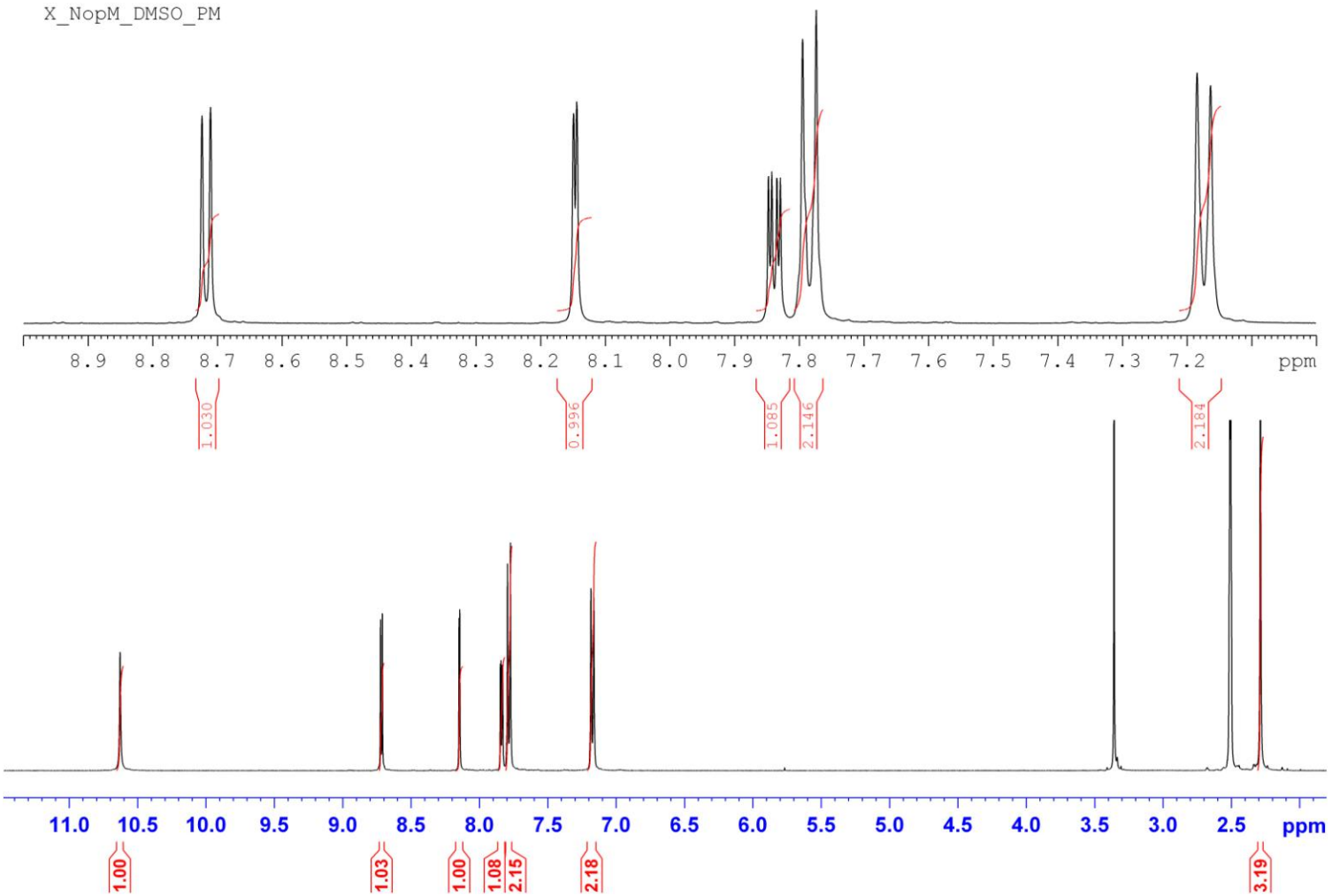
**2.9 NooM**

**$^{1}$H NMR ($CDCl_3$) δ**: 2.35 (3H, s), 7.02 (1H, td, $^{3}J$ = 7.4, $^{4}J$ = 1), 7.16 (1H, d, $^{3}J$ = 7.4), 7.21 (1H, t, $^{3}J$ = 7.8), 7.41 (1H, ddd, $^{3}J$ = 7.7, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.84 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.21 (1H, d, $^{3}J$ = 8), 8.24 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.56 (1H, dq, $^{3}J$ = 4.8, $^{4}J$ = 0.8), 10.03 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)**: δ 2.32 (3H, s), 7.13 (1H, td, $^{3}J$ = 7.4, $^{4}J$ = 1.2), 7.25 (1H, dt, $^{3}J$ =7.7, $^{4}J$ =1.1), 7.29 (1H, d, $^{3}J$ = 7.6), 7.70 (1H, ddd, $^{3}J$ = 7.6, $^{4}J$ = 4.8, $^{5}J$ = 1.2), 7.86 (1H, d, $^{3}J$ = 8), 8.09 (1H, td, $^{3}J$ = 7.7, $^{4}J$ = 1.7), 8.18 (1H, dt, $^{3}J$ = 7.8, $^{4}J$ = 1), 8.75 (1H, dq, $^{3}J$ = 4.8, $^{4}J$ = 0.8), 10.28 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 17.49, 122.15, 123.02, 124.97, 126.26, 127.05, 130.23, 130.32, 135.91, 138.23, 148.55, 149.59, 161.89.



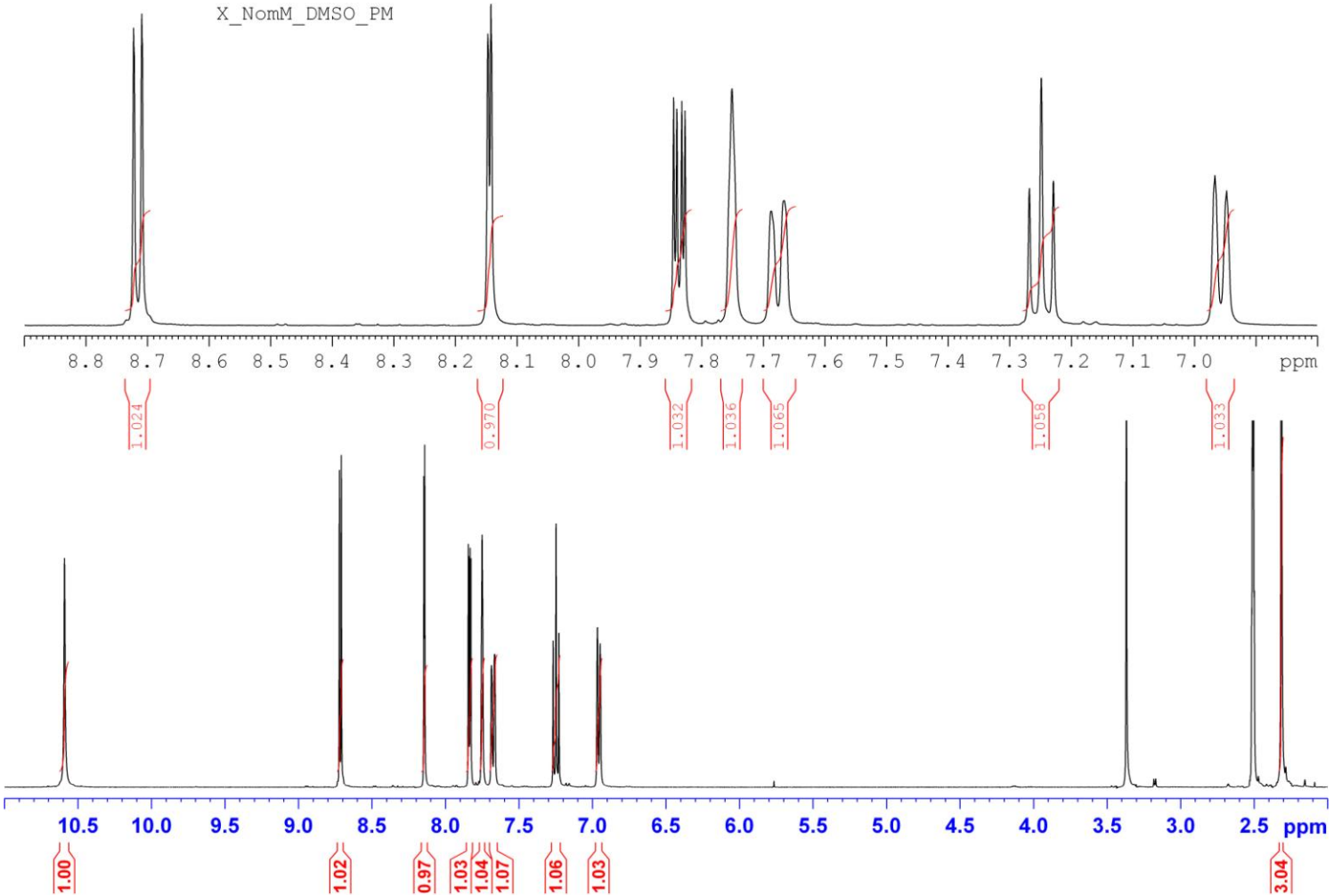
**2.10. 5-Cl-NopM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.27 (3H, s), 7.12 (2H, d, $^{3}J$ = 8.3), 7.40 (1H, dd, $^{3}J$ = 5.2, $^{4}J$ = 2), 7.57 (2H, d, $^{3}J$ = 8.5), 8.22 (1H, dd, $^{3}J$ = 2, $^{4}J$ = 0.5), 8.43 (1H, d, $^{3}J$ = 5.3), 9.79 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ 2.29 (3H, s), 7.17 (2H, d, $^{3}J$ = 8.3), 7.78 (2H, d, $^{3}J$ = 8.4), 7.84 (1H, dd, $^{3}J$ = 5.3, $^{4}J$ = 2), 8.15 (1H, d, $^{3}J$ = 2), 8.72 (1H, d, $^{3}J$ = 5.3), 10.63 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$):** δ 20.49, 120.32, 122.37, 126.70, 129.06, 133.16, 135.60, 144.79, 149.96, 151.79, 161.10.



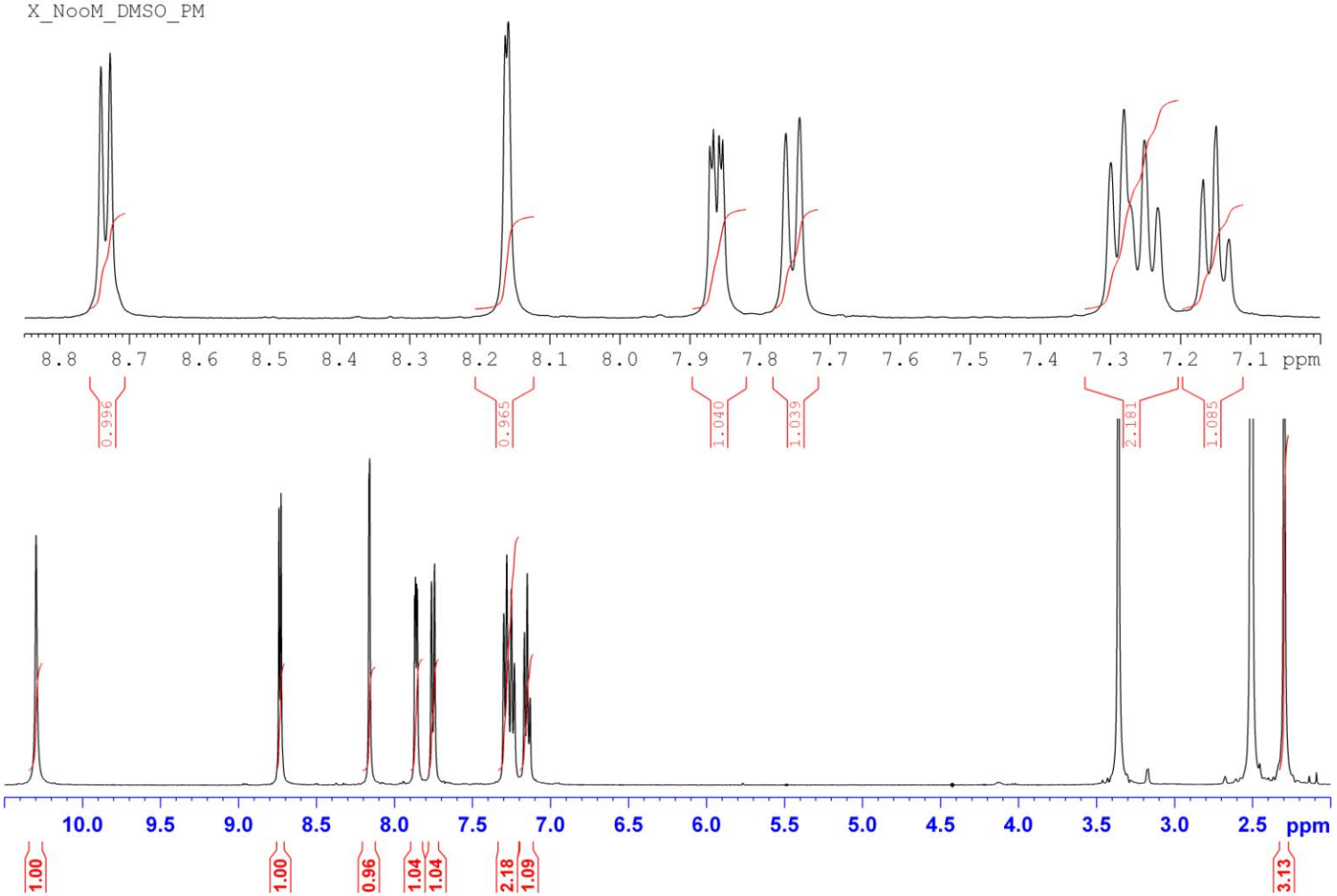
**2.11. 5-Cl-NomM**

**$^{1}$H NMR ($CDCl_3$)** δ 2.31 (3H, s), 6.91 (1H, d, $^{3}J$ = 7.6), 7.20 (1H, t, $^{3}J$ = 7.8), 7.41 (1H, dd, $^{3}J$ = 5.3, $^{3}J$ = 2), 7.48 (1H, d, $^{3}J$ = 8), 7.54 (1H, s), 8.22 (1H, d, $^{3}J$ = 2), 8.43 (1H, dd, $^{3}J$ = 5, $^{4}J$ = 0.5), 9.80 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ 2.31(3H, s), 6.96 (1H, d, $^{3}J$ = 7.6), 7.25 (1H, t, $^{3}J$ = 7.9), 7.68 (1H, d, $^{3}J$ = 8), 7.75 (1H, s), 7.84 (1H, dd, $^{3}J$ = 5.3, $^{4}J$ = 2), 8.14 (1H, d, $^{3}J$ = 2), 8.71 (1H, d, $^{3}J$ = 5.2), 10.59 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 21.18, 117.53, 120.84, 122.38, 124.85, 126.76, 128.51, 137.88, 137.97, 144.81, 149.97, 151.71, 161.19.



**2.12. 5-Cl-NooM**

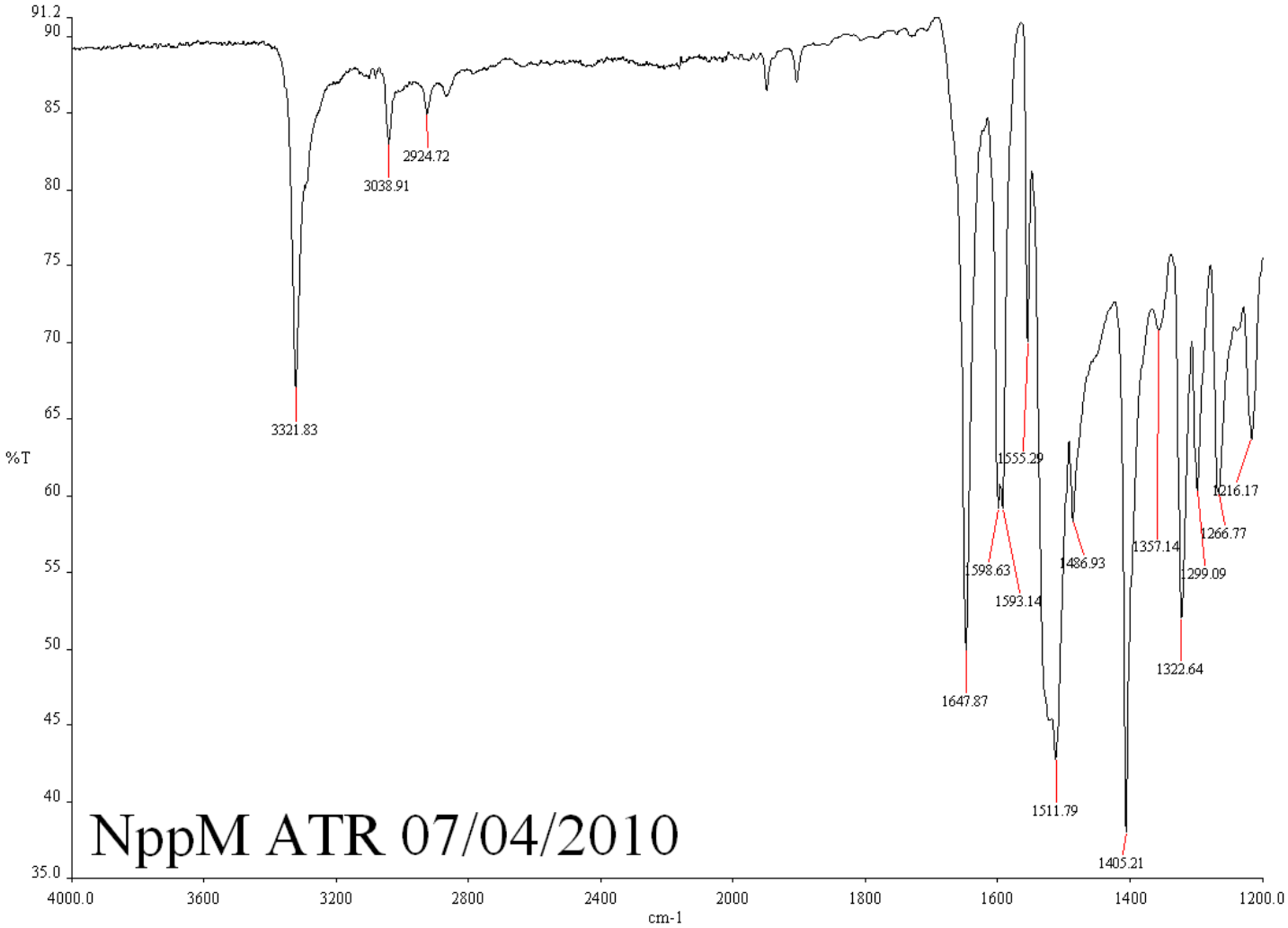
**$^{1}$H NMR ($CDCl_3$)** δ 2.34 (3H, s), 7.03 (1H , td, $^{3}J$ = 7.4, $^{4}J$ = 1.2), 7.16 (1H, d, $^{3}J$ = 7.5), 7.21 (1H, t, $^{3}J$ = 7.7), 7.42 (1H, dd, $^{3}J$ =5.2, $^{4}J$ = 2.0), 8.17 (1H, dd, $^{3}J$ = 8, $^{3}J$ = 0.9), 8.24 (1H, dd, $^{3}J$ = 2, $^{3}J$ = 0.4), 8.45 (1H, d, $^{3}J$ = 5.2), 9.90 (1H, br s); **$^{1}$H NMR (DMSO-*d*$^{6}$)** δ 2.30 (3H, s), 7.15 (1H, t, $^{3}J$ = 7.4), 7.25 (1H, t, $^{3}J$ = 7.7), 7.29 (1H, d, $^{3}J$ = 7.5), 7.75 (1H, d, $^{3}J$ = 7.7), 7.86 (1H, dd, $^{3}J$ = 5.3, $^{3}J$ = 2), 8.16 (1H, d, $^{3}J$ = 1.6), 8.73 (1H, d, $^{3}J$ = 5.3), 10.30 (1H, br s); **$^{13}$C NMR (DMSO-*d*$^{6}$)** δ 17.50, 122.26, 123.65, 125.38, 126.24, 126.87, 130.34, 130.90, 135.66, 144.92, 150.13, 151.44, 160.89.



**3. IR (ATR)**

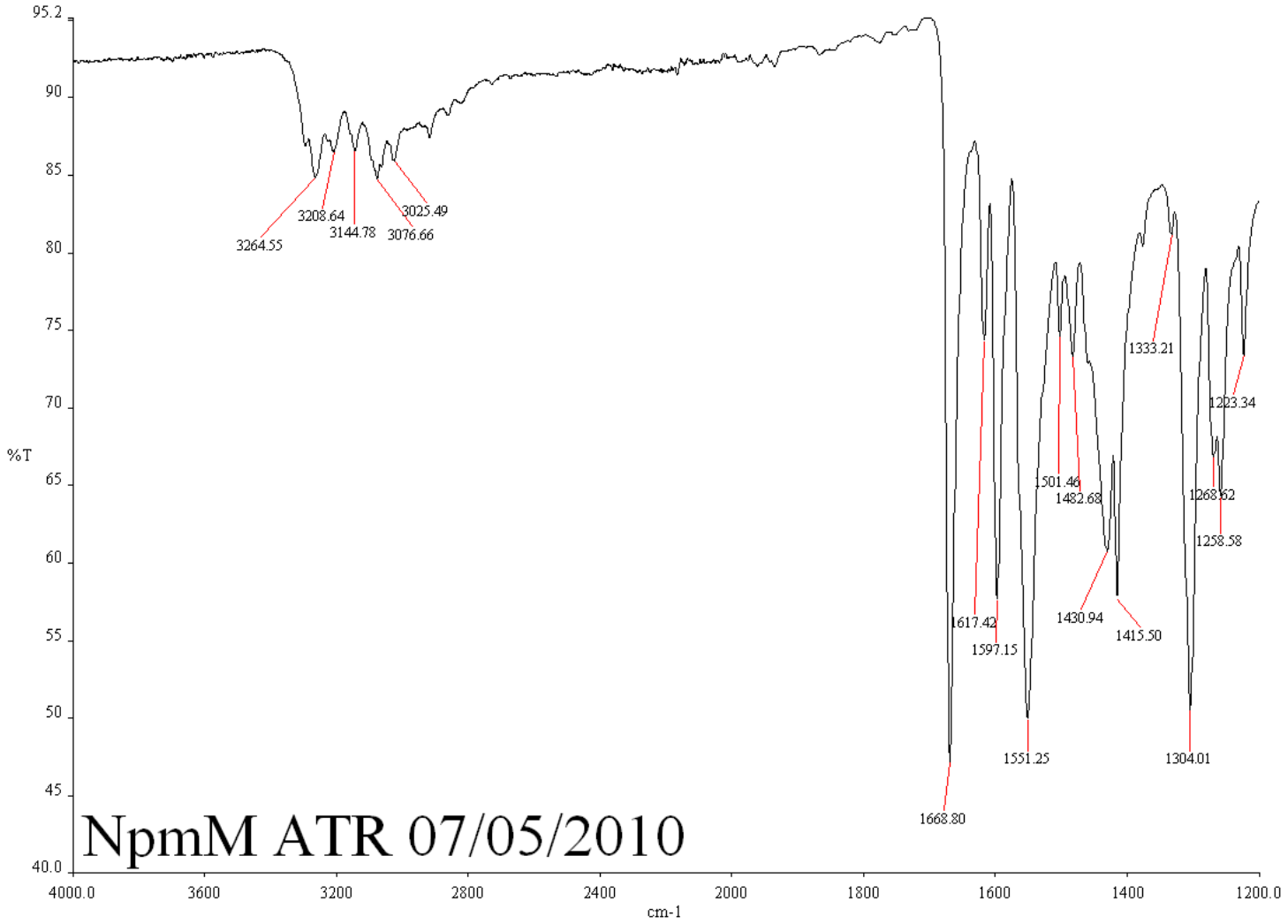
**3.1. NppM**

IR (ATR): 3321 (m), 1647 (s), 1598 (s), 1555 (m), 1512 (s), 1405 (s).



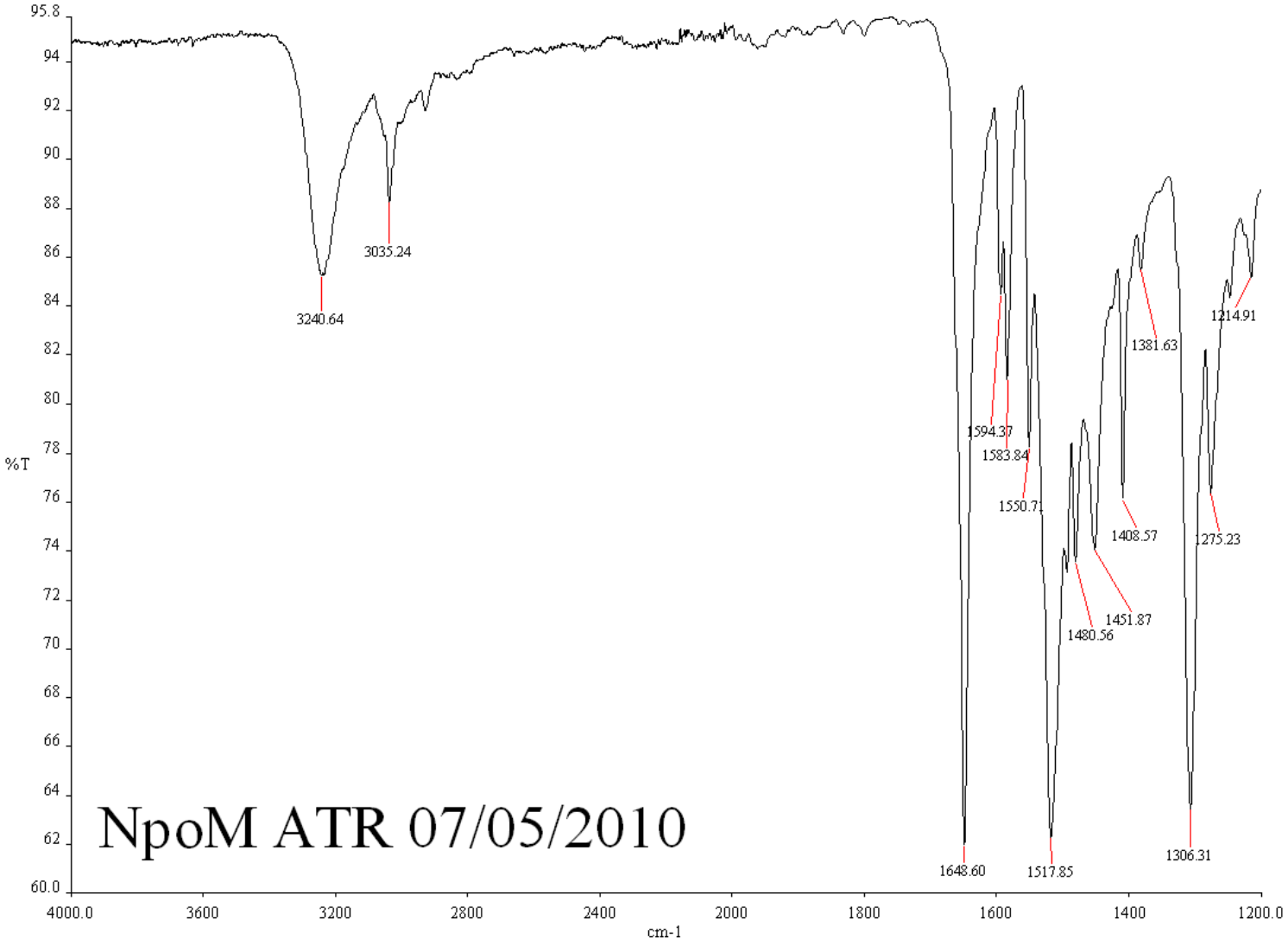
**3.2. NpmM**

IR (ATR): 3264 (w), 1669 (s), 1597 (m), 1551(s), 1431 (m), 1415(m);



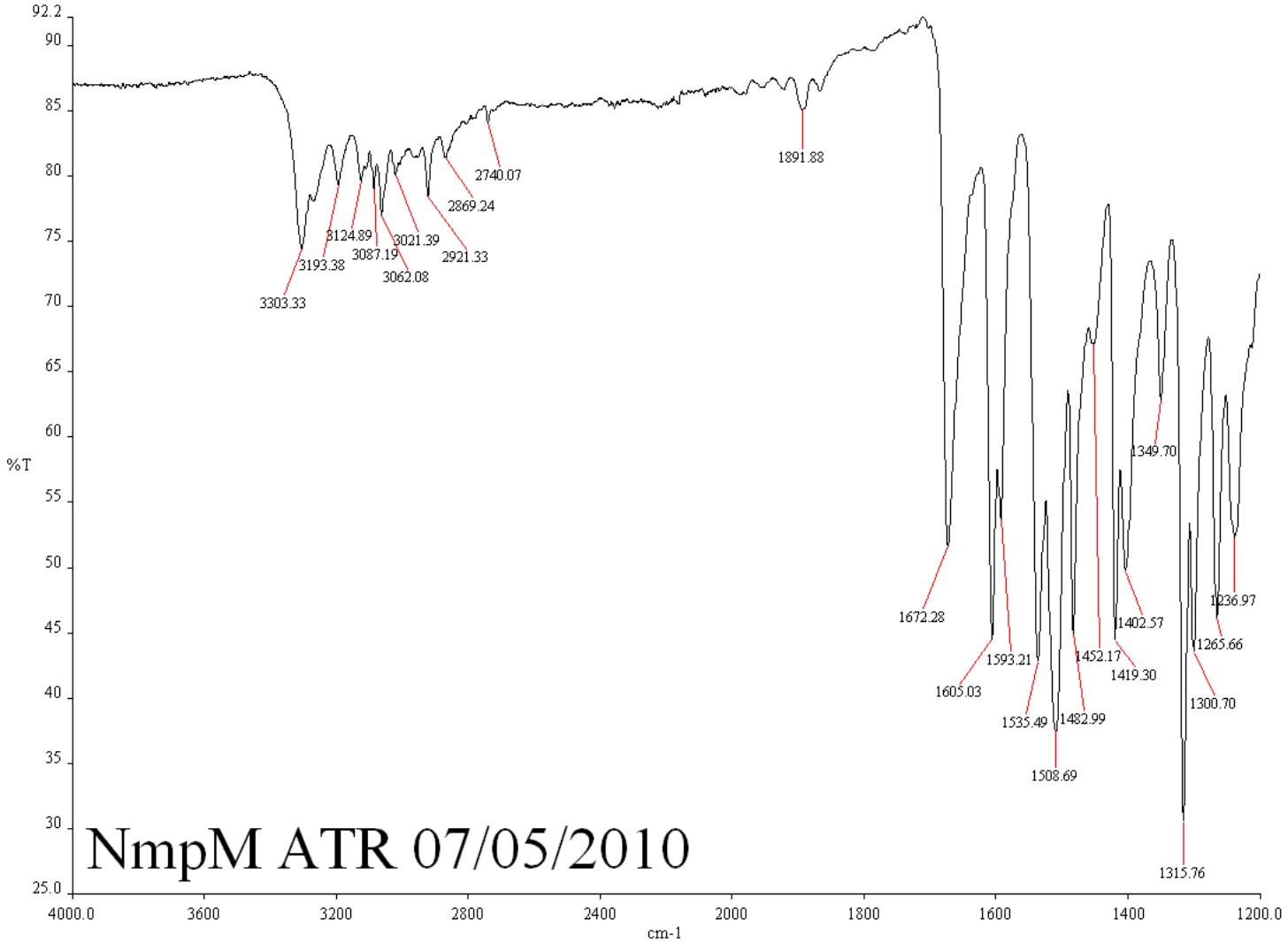
**3.3. NpoM**

IR (ATR): 3241 (m), 3035 (w), 1649 (s), 1584(m), 1551 (m), 1518 (s), 1451 (m), 1408 (m);



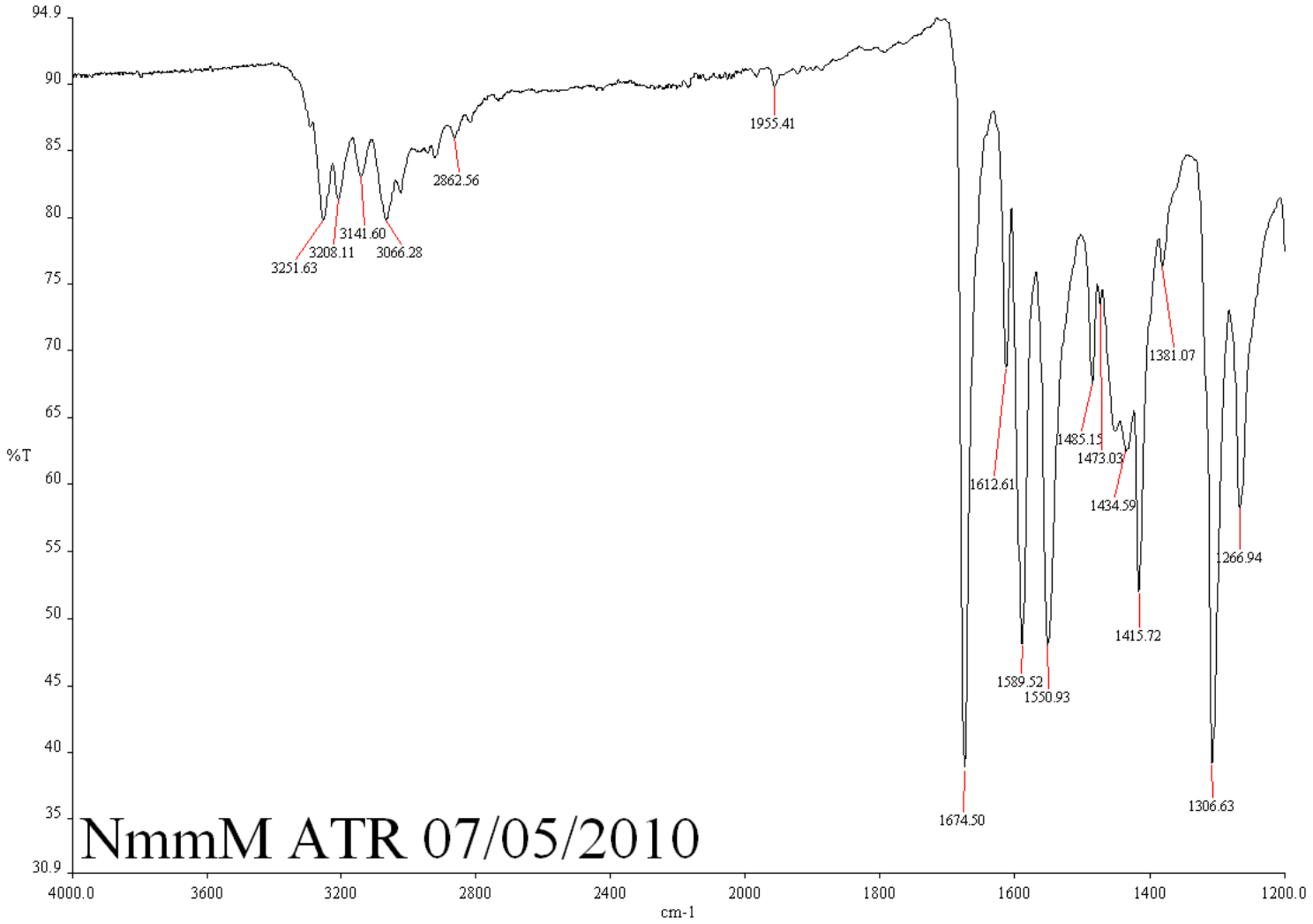
**3.4. NmpM**

IR (ATR): 3303 (m), 1672 (s), 1605 (s), 1535 (s), 1509 (s), 1483 (s), 1419 (s)



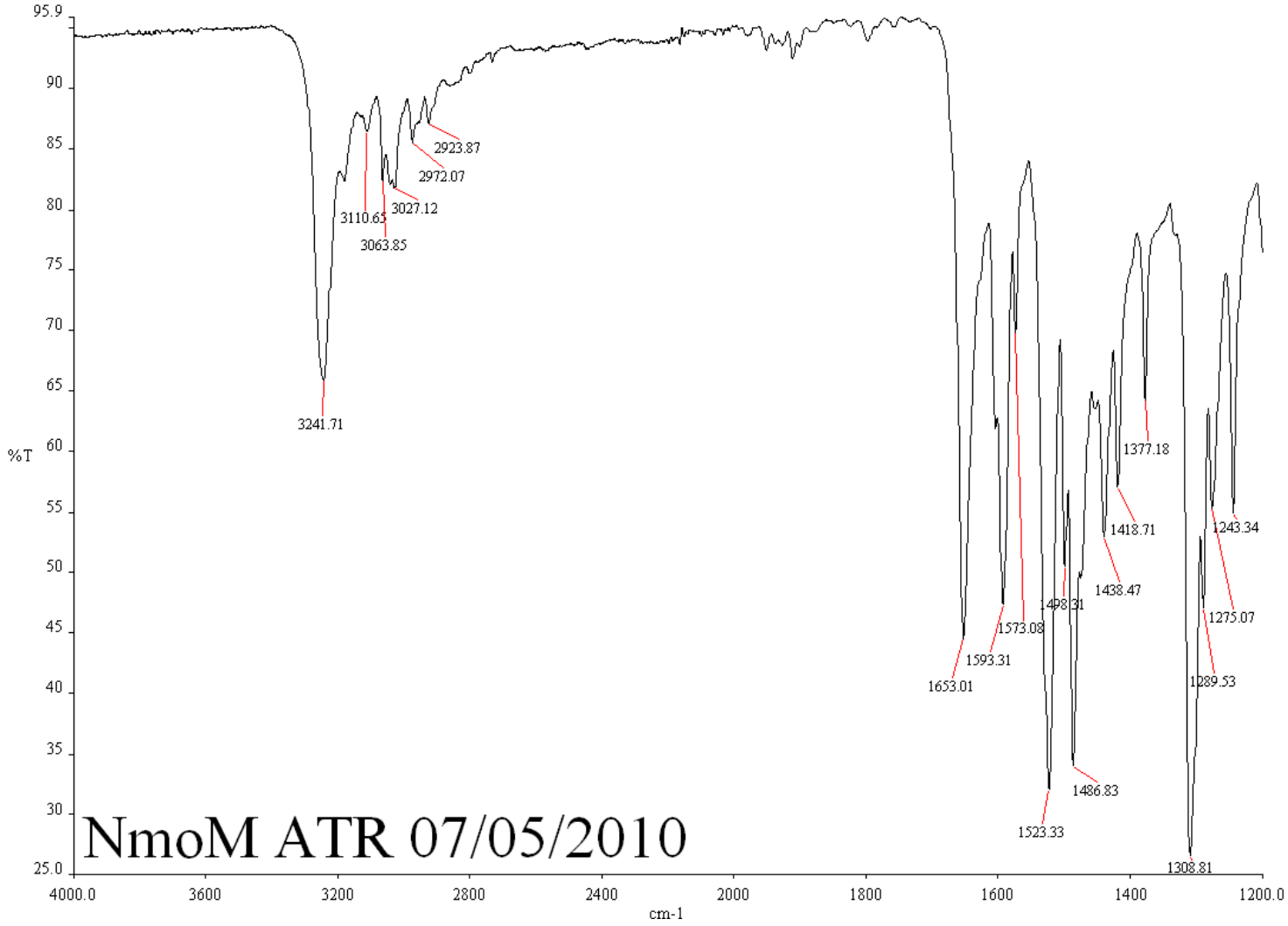
**3.5. NmmM**

IR (ATR): 3252 (w), 3066 (w), 1674 (s), 1589 (s), 1551 (s), 1485 (m), 1416 (s)



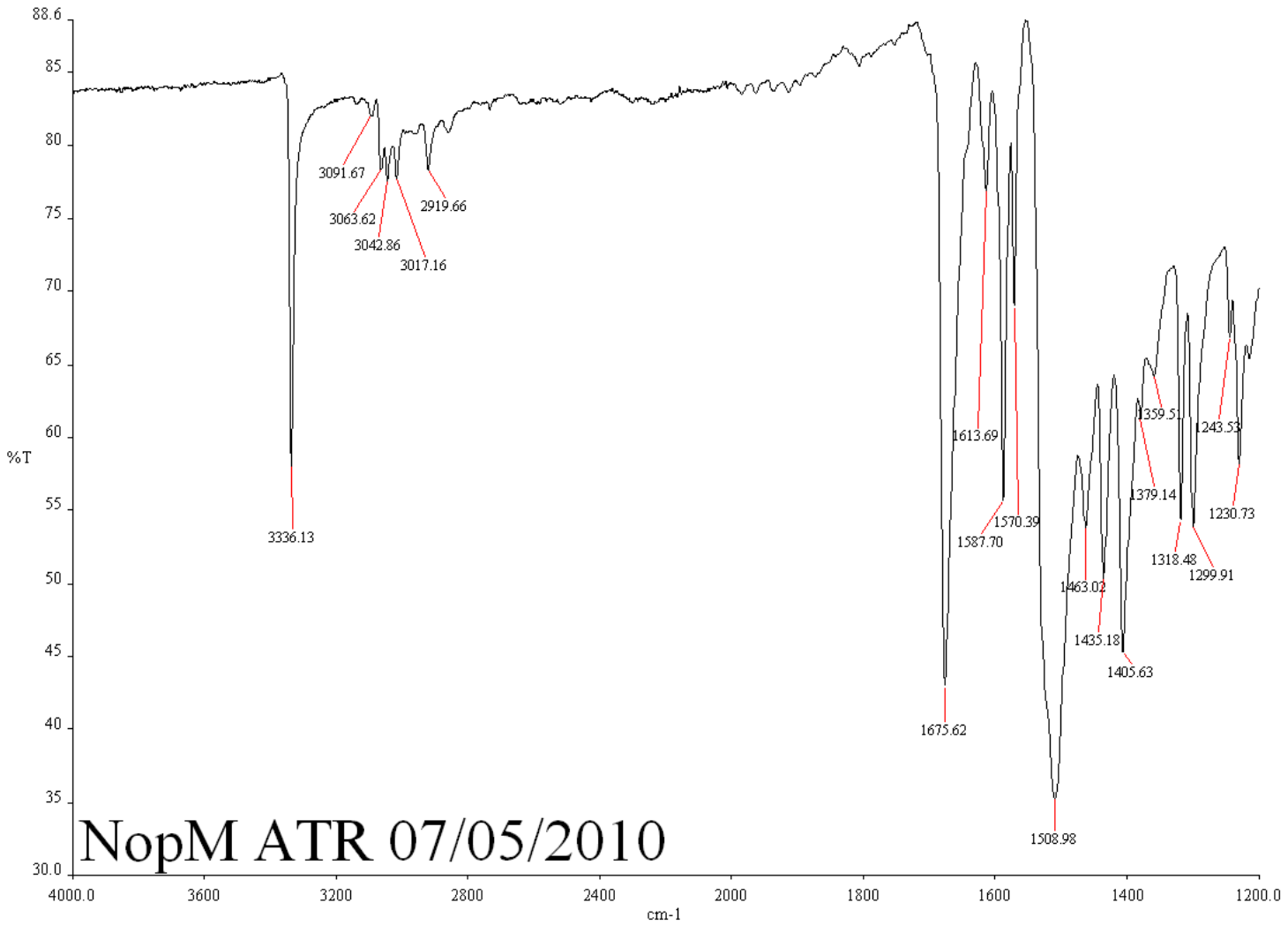
**3.6. NmoM**

IR (ATR): 3241 (m), 1653 (s), 1593 (s), 1523 (s), 1487(s), 1438 (m), 1418 (m);



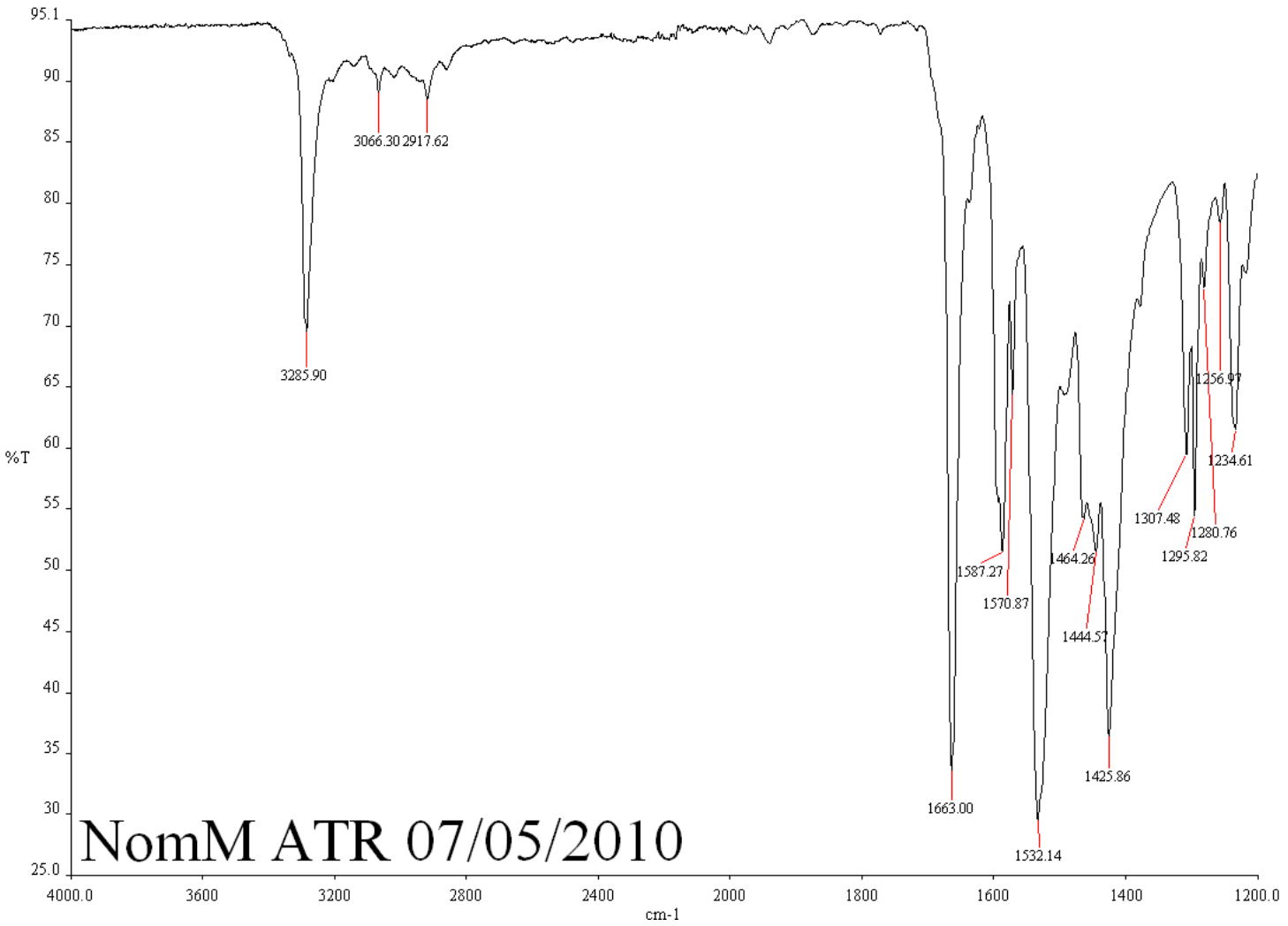
**3.7. NopM**

IR (ATR): 3336 (m), 1676 (s), 1588 (s), 1509 (s), 1463 (m), 1435 (m), 1406 (s);



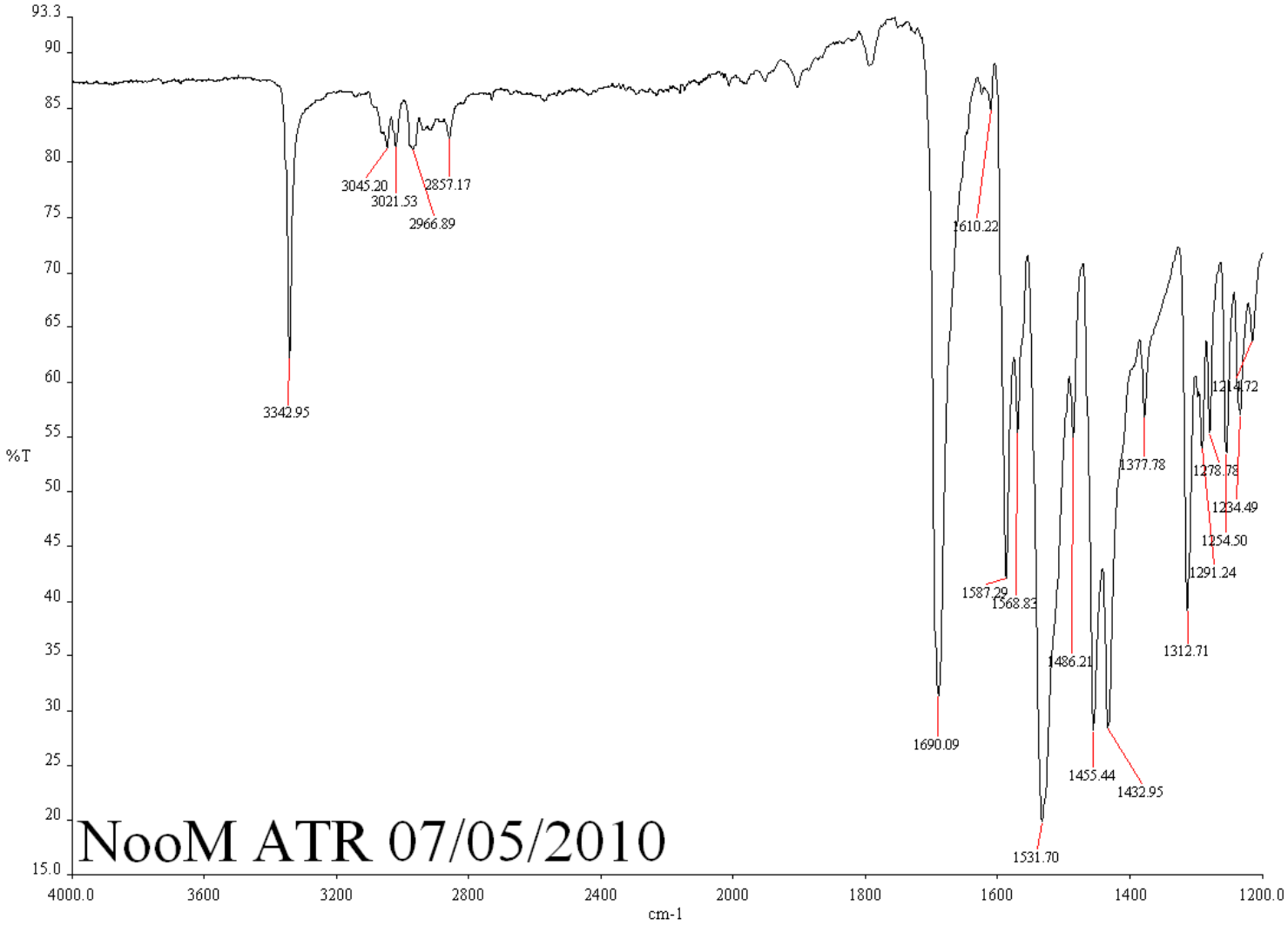
**3.8. NomM**

IR (ATR): 3286 (m), 1663 (s), 1587 (m), 1532 (s), 1444 (m), 1426 (s);



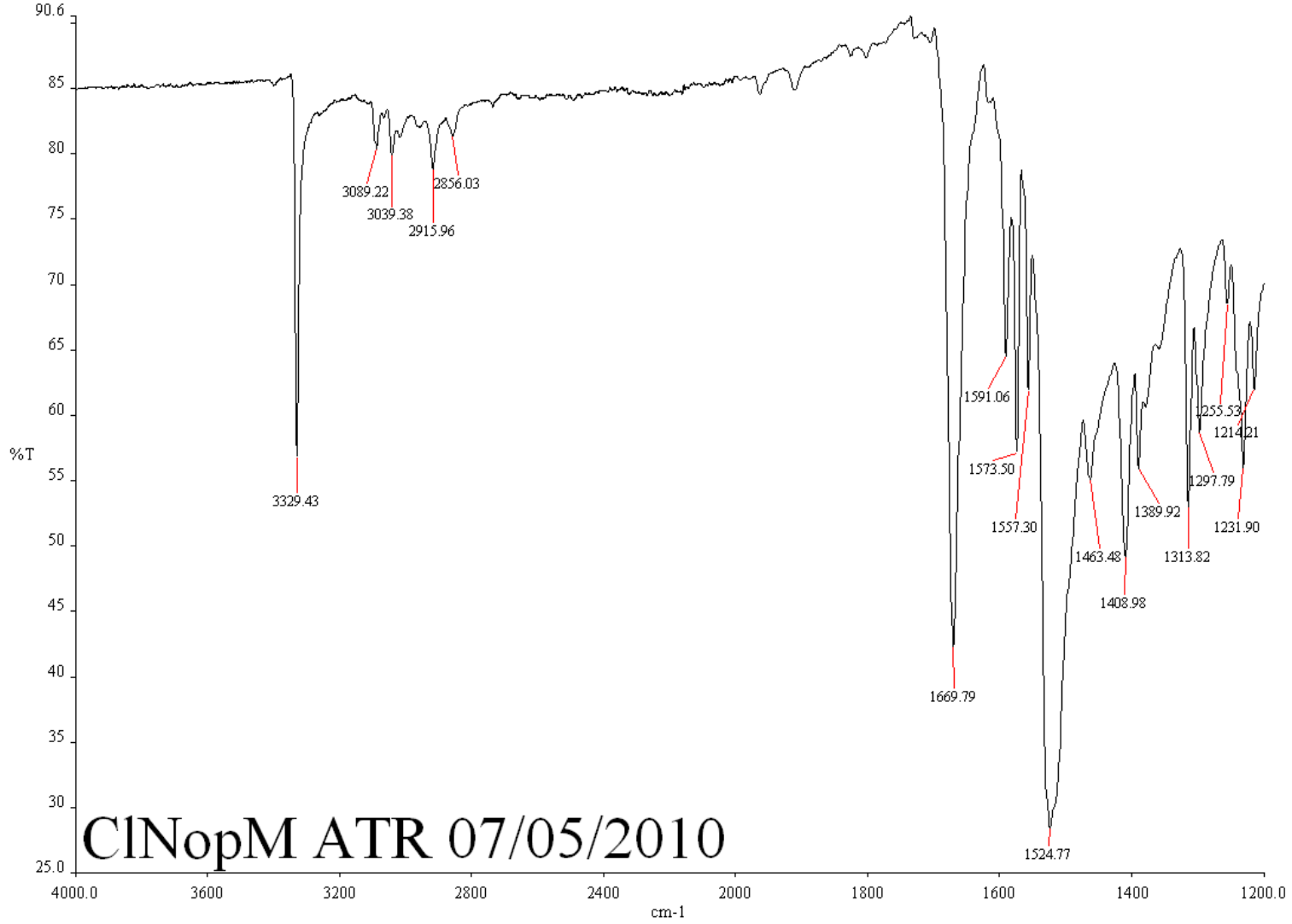
**3.9. NooM**

IR (ATR): 3343 (m), 1690 (s), 1587 (s), 1569 (m), 1532 (s), 1486 (m), 1455 (s), 1433 (s);



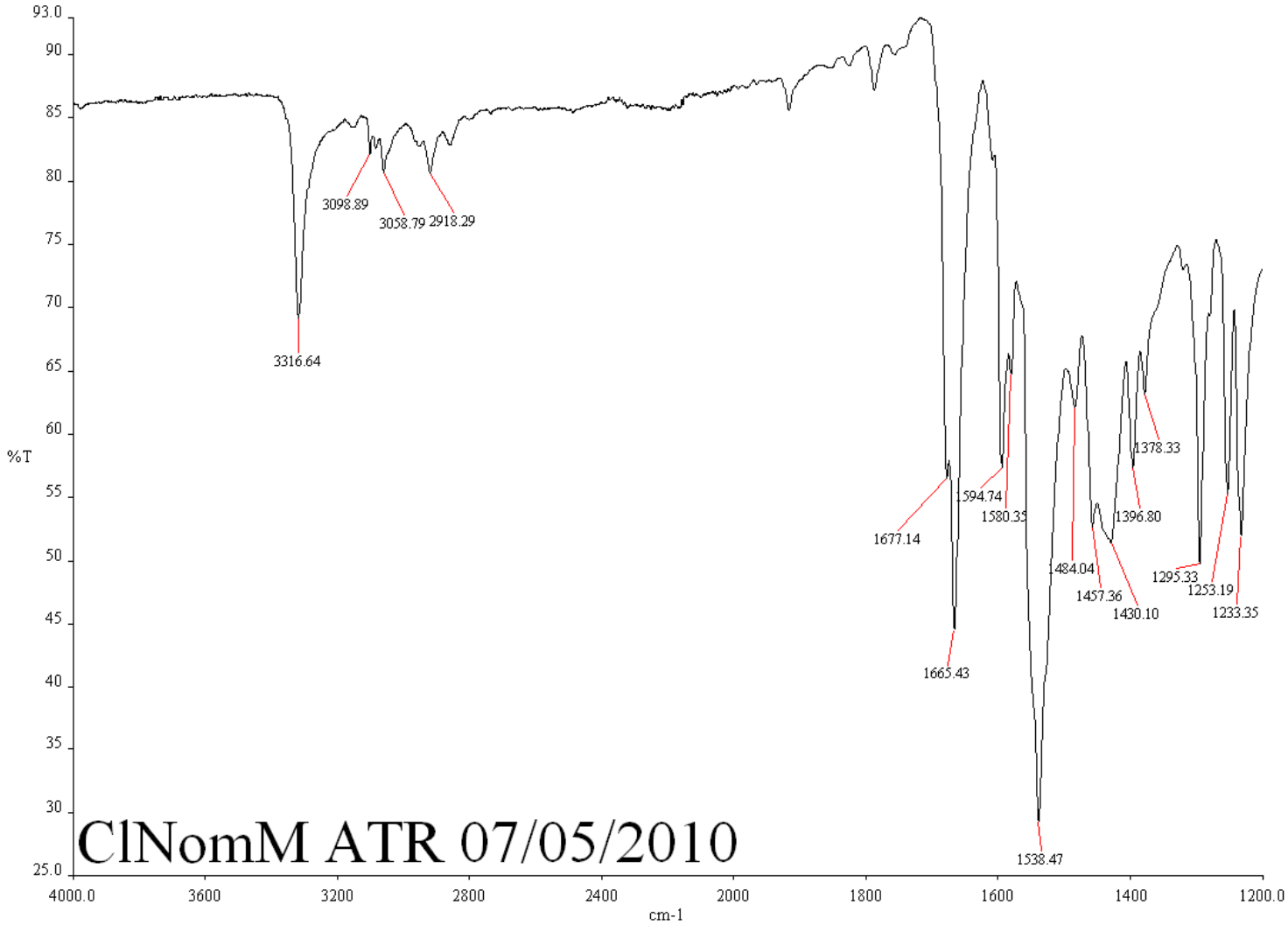
**3.10. 5-Cl-NopM**

IR (ATR): 3329 (s), 1670 (s), 1591 (m), 1573 (m), 1557 (m), 1525 (s), 1463 (m), 1409 (s);



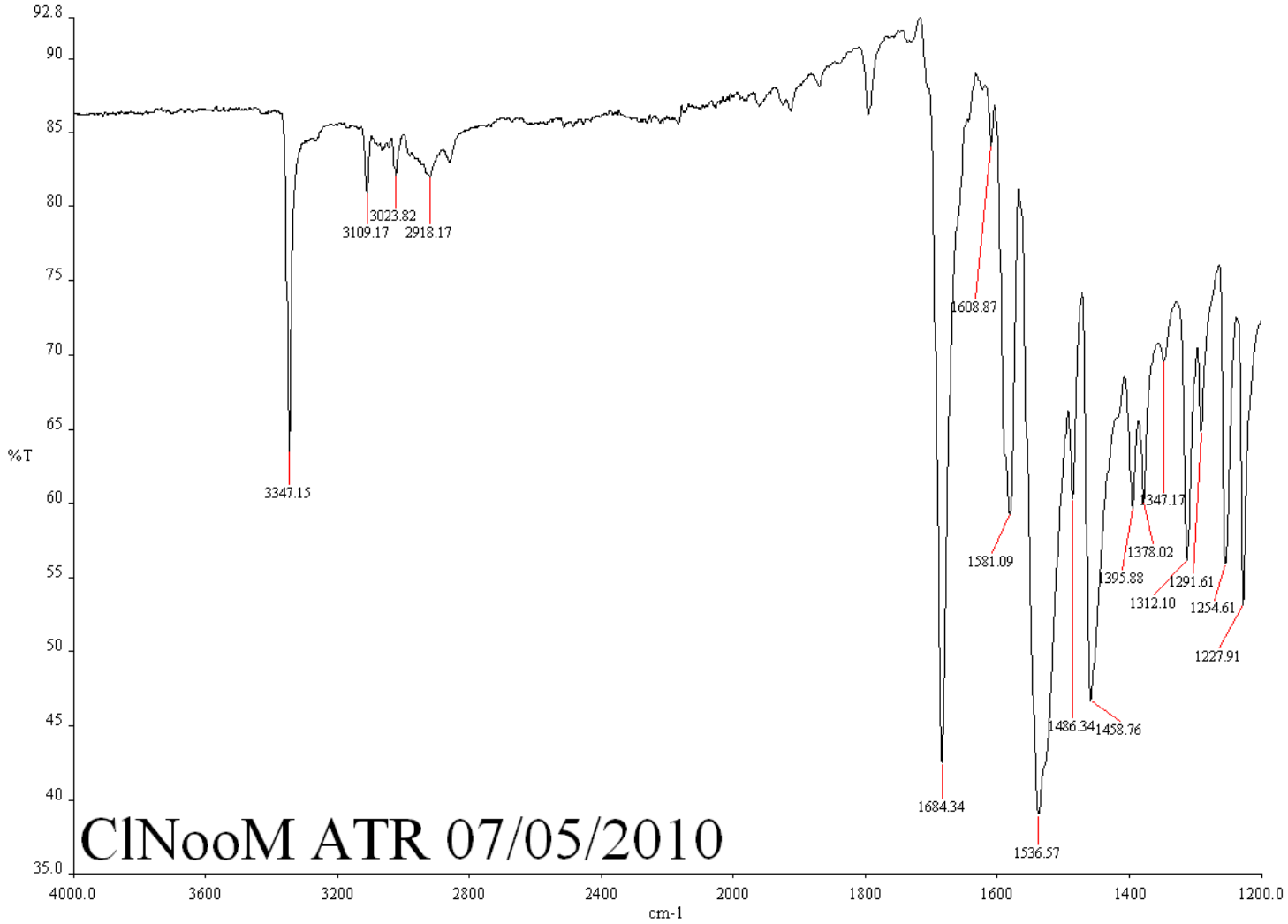
**3.11. 5-Cl-NomM**

IR (ATR): 3317 (m), 1677(m), 1665 (s), 1595 (m), 1580 (m), 1538 (s), 1484 (m), 1457 (m), 1430 (m);



**3.12. 5-Cl-NooM**

IR (ATR): 3347 (s), 1684 (s), 1581 (s), 1536 (s), 1486 (s), 1458 (s), 1396 (m);



**4. Crystallographic details for nine NxxM isomers.**

**4.1. Table 2. Experimental details for the nine NxxM isomers**

For all **NxxM** structures: $C_{13}H_{12}N_2O$, $M_r$ = 212.25. Experiments were undertaken at 294(1) K with Mo $K\alpha$ radiation using an Xcalibur, Sapphire3, Gemini Ultra diffractometer. H atoms were treated by a mixture of independent (N-H) and constrained refinement (C-H).

| | **NppM** | **NpmM** | **NpoM** | **NmpM** | **NmmM** |
|---|---|---|---|---|---|
| **Crystal data** | | | | | |
| Crystal system, space group | Monoclinic, *P*2/*c* | Monoclinic, $P2_1/n$ | Monoclinic, *Cc* | Monoclinic, $P2_1/c$ | Triclinic, $P\bar{1}$ |
| *a*, *b*, *c* (Å) | 7.7391(4), 5.2338(2), 26.9102(13) | 8.2919(3), 10.2600(3), 13.5713(4) | 13.0101(6), 10.4826(3), 9.7957(4) | 10.5017(5), 4.8807(2), 21.3459(9) | 9.3767(4), 9.9187(3), 12.3386(4) |
| α, β, γ (°) | 90, 90.321(5), 90 | 90, 100.919(3), 90 | 90, 122.729(6), 90 | 90, 100.868(4), 90 | 86.958(3), 86.980(3), 71.410(3) |
| $V$ (Å$^3$) | 1089.98(9) | 1133.67(6) | 1123.84(11) | 1074.47(8) | 1085.36(7) |
| $Z$ | 4 | 4 | 4 | 4 | 4 |
| μ (mm$^{-1}$) | 0.08 | 0.08 | 0.08 | 0.09 | 0.08 |
| Crystal size (mm) | 0.53×0.33×0.14 | 0.38×0.24×0.06 | 0.47×0.43×0.25 | 0.67×0.06×0.06 | 0.44×0.34×0.18 |
| **Data collection** | | | | | |
| Absorption correction | Analytical (ABSFAC. Clark & Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) |
| $T_{min}$, $T_{max}$ | 0.966, 0.988 | 0.970, 0.995 | 0.963, 0.980 | 0.945, 0.995 | 0.964, 0.985 |
| No. of measured, independent and observed reflections | 8356, 8356, 5194 {$I > 2\sigma(I)$} | 5751, 1836, 1170 {$I > 2\sigma(I)$} | 8432, 1285, 1109 {$I > 2\sigma(I)$} | 11243, 2070, 1001 {$I > 2\sigma(I)$} | 26207, 6987, 4966 {$I > 2\sigma(I)$} |
| $R_{int}$ | 0.00 | 0.024 | 0.031 | 0.055 | 0.026 |
| **Refinement** | | | | | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.051,0.141,0.97 | 0.034,0.083,0.90 | 0.030,0.081,0.99 | 0.036,0.073,0.77 | 0.057,0.179,1.09 |
| No. of reflections | 8356 | 1836 | 1285 | 2070 | 6987 |
| No. of parameters | 152 | 151 | 150 | 151 | 299 |
| No. of restraints | 0 | 0 | 2 | 0 | 0 |
| $\Delta\rangle_{max}$,$\Delta\rangle_{min}$ (eÅ$^{-3}$) | 0.30, -0.25 | 0.11, -0.09 | 0.14, -0.11 | 0.12, -0.10 | 0.28, -0.24 |

| | **NmoM** | **NopM** | **NomM** | **NooM** |
|---|---|---|---|---|
| **Crystal data** | | | | |
| Crystal system, space group | Orthorhombic, *Pbca* | Monoclinic, $P2_1/c$ | Monoclinic, $P2_1$ | Monoclinic, $P2_1/c$ |
| *a*, *b*, *c* (Å) | 8.0664(2), 9.4009(2), 29.5324(8) | 6.0828(2), 27.0507(8), 7.1963(3) | 9.2326(4), 14.0836(4), 9.4162(4) | 7.7696(2), 17.6232(3), 8.8462(3) |
| α, β, γ (°) | 90, 90, 90 | 90, 111.673(4), 90 | 90, 105.661(4), 90 | 90, 114.817(4), 90 |
| *V* (Å$^3$) | 2239.48(10) | 1100.40(7) | 1178.92(8) | 1099.41(5) |
| *Z* | 8 | 4 | 4 | 4 |
| μ (mm$^{-1}$) | 0.08 | 0.08 | 0.08 | 0.08 |
| Crystal size (mm) | 0.42×0.34×0.06 | 0.25×0.22×0.06 | 0.22×0.16×0.05 | 0.44×0.13×0.11 |
| **Data collection** | | | | |
| Absorption correction | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) |
| $T_{min}$, $T_{max}$ | 0.967, 0.995 | 0.980, 0.995 | 0.983, 0.996 | 0.964, 0.991 |
| No. of measured, independent and observed reflections | 13292, 2421, 1591 {$I > 2\sigma(I)$} | 6058, 1970, 1176 {$I > 2\ \sigma(I)$} | 16614, 2780, 1026 {$I > 2\sigma(I)$} | 7586, 2389, 1541 {$I > 2\sigma(I)$} |
| $R_{int}$ | 0.036 | 0.038 | 0.096 | 0.021 |
| **Refinement** | | | | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S* | 0.040, 0.107, 0.98 | 0.035, 0.083, 0.84 | 0.029, 0.045, 0.67 | 0.037, 0.093, 0.93 |
| No. of reflections | 2421 | 1970 | 2780 | 2389 |
| No. of parameters | 150 | 150 | 298 | 151 |
| No. of restraints | 0 | 0 | 1 | 0 |
| $\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å$^{-3}$) | 0.15, -0.13 | 0.14, -0.11 | 0.08, -0.08 | 0.14, -0.11 |

Computer programs: CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.55 (release 05-01-2010 CrysAlis171 .NET) (compiled Jan 5 2010,16:28:46), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008) and SORTX (McArdle, 1995), *PLATON* (Spek, 2009), *SHELXL97*.

This crystallographic experimental table was compiled using the IUCr facilities in Chester, U.K.

**4.2 Table 3. Experimental details for the three Cl-5-NxxM isomers and mixed system NmpFM**

Experiments were carried out at 294 (1) K with Mo *K*□ radiation using an Xcalibur, Sapphire3, Gemini Ultra diffractometer. H atoms were treated by a mixture of independent (N-H) and constrained refinement (C-H).

| | 5-Cl_**NopM** | 5-Cl_**NomM** | 5-Cl_**NooM** | **NmpFM** |
|---|---|---|---|---|
| **Crystal data** | | | | |
| Chemical formula | $C_{13}H_{11}ClN_2O$ | $C_{13}H_{11}ClN_2O$ | $C_{13}H_{11}ClN_2O$ | $C_{13}H_{12}N_2O$:$C_{12}H_9FN_2O$ (1/1) |
| $M_r$ | 246.69 | 246.69 | 246.69 | 428.46 |
| Crystal system, space group | Orthorhombic, $Pca2_1$ | Monoclinic, $P2_1/c$ | Monoclinic, $P2_1/n$ | Orthorhombic, $Pna2_1$ |
| *a*, *b*, *c* (Å) | 7.36124 (11), 14.41068 (19), 11.21075 (16) | 7.417 (2), 21.006 (4), 8.546 (2) | 7.3288 (6), 7.4392 (5), 21.5025 (14) | 19.870 (2), 10.8608 (9), 4.9241 (5) |
| α, β, γ (°) | 90, 90, 90 | 90, 115.28 (3), 90 | 90, 91.481 (7), 90 | 90, 90, 90 |
| $V$ (Å$^3$) | 1189.24 (3) | 1204.0 (5) | 1171.93 (15) | 1062.66 (18) |
| Z | 4 | 4 | 4 | 2 |
| μ (mm$^{-1}$) | 0.31 | 0.30 | 0.31 | 0.09 |
| Crystal size (mm) | 0.26 × 0.23 × 0.16 | 0.53 × 0.19 × 0.11 | 0.39 × 0.31 × 0.10 | 0.51 × 0.23 × 0.13 |
| **Data collection** | | | | |
| Absorption correction | Analytical (ABSFAC. Clark & Reid, 1998) | Analytical (ABSFAC. Clark & Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) | Analytical (ABSFAC, Clark and Reid, 1998) |
| $T_{min}$, $T_{max}$ | 0.925, 0.953 | 0.857, 0.987 | 0.889, 0.970 | 0.954, 0.988 |
| No. of measured, independent and observed reflections | 8794, 8794, 7810 {$I > 2\sigma(I)$} | 8582, 2583, 1324 {$I > 2\sigma(I)$} | 9725, 3040, 2199 {$I > 2\sigma(I)$} | 6723, 1286, 1045 |
| $R_{int}$ | 0.00 | 0.048 | 0.017 | 0.021 |
| **Refinement** | | | | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.026, 0.065, 0.98 | 0.066, 0.233, 1.00 | 0.038, 0.103, 1.07 | 0.035, 0.093, 1.05 |
| No. of reflections | 8794 | 2583 | 3040 | 1286 |
| No. of parameters | 160 | 160 | 160 | 159 |
| No. of restraints | 1 | 0 | 0 | 1 |
| $\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å$^{-3}$) | 0.10, -0.16 | 0.32, -0.20 | 0.19, -0.22 | 0.11, -0.10 |

Computer programs: CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.55 (release 05-01-2010 CrysAlis171 .NET) (compiled Jan 5 2010,16:28:46), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008) and SORTX (McArdle, 1995), *PLATON* (Spek, 2009), *SHELXL97*. **The Flack parameter for 5-Cl_NopM is 0.00(4) [data were not merged].**

This crystallographic experimental table was compiled using the IUCr facilities in Chester, U.K.

**4.3 Table 4. Selected hydrogen-bond *and contact* parameters for the nine NxxM isomers.**[‡]

| *D*—H···*A* | *D*—H (Å) | H···*A* (Å) | *D*···*A* (Å) | *D*—H···*A* (°) |
|---|---|---|---|---|
| **NppM**_[10-002] | | | | |
| **N1—H1···O1**[i] | **0.832 (13)** | **2.270 (13)** | **3.0529 (14)** | **157.0 (11)** |
| *C12—H12···O1* | *0.93* | *2.47* | *2.9126 (17)* | *109* |
| C12—H12···Cg1[ii] | 0.93 | 2.89 | 3.5835 (16) | 133 |
| **NpmM**_[10-003] | | | | |
| **N1—H1···N24**[iii] | **0.911 (15)** | **2.240 (16)** | **3.1265(18)** | **164.1 (14)** |
| C22—H22···N24[iii] | 0.93 | 2.57 | 3.353 (2) | 142 |
| *C12—H12···O1* | *0.93* | *2.28* | *2.8615 (19)* | *120* |
| C23—H23···O1[iv] | 0.93 | 2.41 | 3.2538 (19) | 152 |
| **NpoM**_[10-004] | | | | |
| **N1—H1···O1**[v] | **0.80 (3)** | **2.06 (3)** | **2.825 (2)** | **159 (2)** |
| *C17—H17E···N1* | *0.96* | *2.47* | *2.914 (3)* | *108* |
| C23—H23···Cg1[vi] | 0.93 | 2.90 | 3.713 (3) | 147 |
| **NmpM**_[10-005] | | | | |
| **N1—H1···N23**[vii] | **0.879 (14)** | **2.367 (14)** | **3.223 (2)** | **164.7 (12)** |
| C12—H12···O1 | 0.93 | 2.24 | 2.841 (2) | 122 |
| *C22—H22···N1* | *0.93* | *2.58* | *2.901 (2)* | *101* |
| C22—H22···N23[vii] | 0.93 | 2.39 | 3.318 (2) | 176 |
| *C26—H26···O1*[viii] | *0.93* | *2.57* | *3.210 (2)* | *126* |
| **NmmM**_[10-006] | | | | |
| **N1A—H1A···N23B**[ix] | **0.91 (2)** | **2.23 (2)** | **3.090 (2)** | **157 (2)** |
| **N1B—H1B···N23A**[x] | **0.89 (2)** | **2.22 (2)** | **3.078 (2)** | **160.7 (19)** |
| *C12A—H12A···O1A* | *0.93* | *2.38* | *2.929 (2)* | *117* |
| *C12B—H12B···O1B* | *0.93* | *2.49* | *2.952 (2)* | *111* |
| C14A—H14A···O1B[ii] | 0.93 | 2.50 | 3.343 (2) | 151 |
| C14B—H14B···O1A[xi] | 0.93 | 2.50 | 3.328 (2) | 148 |
| C22A—H22A···Cg1[xii] | 0.93 | 2.82 | 3.555 (2) | 137 |
| C22B—H22B···Cg2[xiii] | 0.93 | 2.76 | 3.512 (2) | 138 |
| **NmoM**_[10-007] | | | | |
| **N1—H1···O1**[xiv] | **0.855 (17)** | **2.055 (18)** | **2.8978 (15)** | **168.6 (15)** |
| *C17—H17B···O1* | *0.96* | *2.57* | *3.072 (2)* | *113* |
| C26—H26···Cg1[xv] | 0.93 | 2.72 | 3.5751 (16) | 152 |
| **NopM**_[10-008] | | | | |
| **N1—H1···N22** | **0.903 (15)** | **2.160 (15)** | **2.6548 (18)** | **113.6 (11)** |
| *C12—H12···O1* | *0.93* | *2.46* | *2.9436 (18)* | *113* |

| | | | | |
|---|---|---|---|---|
| C16—H16···O1[xvi] | 0.93 | 2.40 | 3.3111 (18) | 168 |
| **NomM**_[10-009] | | | | |
| **N1A—H1A···O1B[xvii]** | **0.93 (2)** | **2.41 (2)** | **3.241 (3)** | **148 (2)** |
| **N1B—H1B···O1A** | **0.87 (2)** | **2.32 (2)** | **3.132 (3)** | **155 (2)** |
| **N1A—H1A···N22A** | **0.93 (2)** | **2.18 (2)** | **2.683 (4)** | **112.9 (18)** |
| **N1B—H1B···N22B** | **0.87 (2)** | **2.28 (2)** | **2.703 (4)** | **109.5 (19)** |
| *C12A—H12A···O1A* | *0.93* | *2.29* | *2.862 (4)* | *120* |
| C14B—H14B···Cg1[xviii] | 0.93 | 2.66 | 3.543 (4) | 160 |
| **NooM**_[10-075] | | | | |
| **N1—H1···N22** | **0.896 (14)** | **2.079 (13)** | **2.6209 (15)** | **118.0 (11)** |
| C16—H16···O1 | 0.93 | 2.35 | 2.9524 (16) | 122 |

Symmetry code(s): (i) *x*, *y*+1, *z*; (ii) -*x*+1, -*y*, -*z*+1; (iii) -*x*+1/2, *y*+1/2, -*z*+3/2; (iv) *x*+1/2, -*y*+1/2, *z*+1/2; (v) *x*, -*y*, *z*-1/2; (vi) *x*+1/2, *y*-1/2, *z*; (vii) -*x*, *y*-1/2, -*z*+1/2; (viii) -*x*, -*y*, -*z*+1; (ix) -*x*+1, -*y*, -*z*; (x) -*x*, -*y*+1, -*z*; (xi) -*x*, -*y*+1, -*z*+1; (xii) -*x*, -*y*, -*z*; (xiii) -*x*+1, -*y*+1, -*z*+1; (xiv) -*x*+1/2, *y*-1/2, *z*; (xv) *x*, -*y*-3/2, *z*-1/2; (xvi) *x*+1, *y*, *z*; (xvii) -*x*, *y*+1/2, -*z*; (xviii) -*x*+1, *y*-1/2, -*z*.

‡ **Additional Information for Tables 4 and 5 (pages 31-33 of the ESI)**:
For the purposes of distinguishing the primary and secondary hydrogen bonding interactions in the nine **NxxM** isomer series described in **Table 4** above, the **primary hydrogen bonding interactions** are labelled in **bold** for the two groups of (**NpxM**, **NmxM**) and (**NoxM** , 5-Cl_**NoxM**) with the primary interactions coloured (**orange**/**green**) as used in **Table 2** of the main paper. The contacts are labeled in *italics* and these are predominantly intramolecular contacts.

Please also refer to the paper from the CSD group 'Hydrogen-bond directionality at the donor H atom – analysis of interaction energies and database statistics' by Peter A. Wood, Frank H. Allen and Elna Pidcock, *CrystEngComm*, 2009, **11**, 1563 for further details on hydrogen bonding and interaction energies.

**4.4 Table 5. Selected hydrogen-bond *and contact* parameters for three 5-Cl-NxxM isomers and NmpFM[#].**

| *D*—H···*A* | *D*—H (Å) | H···*A* (Å) | *D*···*A* (Å) | *D*—H···*A* (°) |
|---|---|---|---|---|
| **Cl_NopM**_[10-024] | | | | |
| **N1—H1···N22** | **0.915 (9)** | **2.176 (9)** | **2.6514 (9)** | **111.5 (7)** |
| *C12—H12···O1* | *0.93* | *2.41* | *2.9453 (11)* | *116* |
| C23—H23···O1$^{i}$ | 0.93 | 2.53 | 3.4223 (11) | 161 |
| C17—H17A···Cg1$^{ii}$ | 0.96 | 2.82 | 3.6699 (12) | 147 |
| **Cl_NomM**_[10-096] | | | | |
| **N1—H1···N22** | **0.86 (5)** | **2.27 (4)** | **2.683 (4)** | **109 (4)** |
| N1—H1···O1$^{iii}$ | 0.86 (5) | 2.37 (5) | 3.035 (4) | 134 (4) |
| *C12—H12···O1* | *0.93* | *2.37* | *2.964 (5)* | *121.2* |
| **Cl_NooM**_[10-012] | | | | |
| **N1—H1···N22** | **0.860 (15)** | **2.175 (15)** | **2.6690 (15)** | **116.3 (12)** |
| *C16—H16···O1* | *0.93* | *2.30* | *2.9128 (19)* | *123* |
| C26—H26···Cl1$^{iv}$ | 0.93 | 2.83 | 3.7371 (14) | 165 |
| **NmpFM**_[10-086][#] | | | | |
| **N1—H1···N23$^{v}$** | **0.92 (3)** | **2.34 (2)** | **3.207 (2)** | **157 (3)** |
| C16—H16···N23$^{v}$ | 0.93 | 2.62 | 3.438 (3) | 147 |
| C22—H22···N23$^{v}$ | 0.93 | 2.41 | 3.337 (3) | 178 |
| *C12—H12···O1* | *0.93* | *2.24* | *2.835 (4)* | *122* |
| C26—H26···O1$^{i}$ | 0.93 | 2.58 | 3.194 (2) | 124 |
| C24—H24···F14$^{vi}$ | 0.93 | 2.93 | 3.677 (11) | 139 |

Symmetry code(s): (i) -*x*, -*y*, *z*+1/2; (ii) *x*+1/2, -*y*+1, *z*; (iii) *x*, -*y*+3/2, *z*-1/2; (iv) -*x*+1/2, *y*+1/2, -*z*+1/2; (v) -*x*, -*y*+1, *z*-1/2; (vi) *x*-1/2, -*y*+1/2, *z*+2.

**NmpFM refinement[#]**

Refinement with F only (with free variable) gives R = 0.042, F14 occupancy of 0.77(1), WGHT = 0.075.

Refinement as $CH_3$ only (with free variable) gives R = 0.042, $CH_3$ occupancy of 1.20(1), WGHT = 0.071.

Both refinements give poorer results for the overall refinement process [$CH_3$ with AFIX 137].

The final refinement gives R = 0.035 with 50% F and 50% $CH_3$ occupancy.

## 5. *Ab initio* calculation results

### 5.1. Energy results

**5.1.1. Table 6**. Optimisations in *gas phase*

| | $E_{SCF}$ | $\delta E_{SCF}$ | $E_0$ | $\delta E_0$ | E | δE | G | δG |
|---|---|---|---|---|---|---|---|---|
| **NppM** | -683.2662 | -4.38 | -686.1620 | 0.00 | -686.1490 | -1.64 | -686.2031 | 0.00 |
| **NpmM** | -683.2670 | -6.63 | -686.1623 | -0.76 | -686.1484 | 0.00 | -686.2063 | -8.38 |
| **NpoM** | -683.2645 | 0.00 | -686.1623 | -0.68 | -686.1487 | -0.91 | -686.2039 | -2.09 |
| **NmpM** | -683.2683 | -10.03 | -686.1627 | -1.84 | -686.1488 | -1.16 | -686.2057 | -6.64 |
| **NmmM** | -683.2692 | -12.36 | -686.1630 | -2.54 | -686.1491 | -1.88 | -686.2061 | -7.78 |
| **NmoM** | -683.2667 | -5.78 | -686.1631 | -2.77 | -686.1495 | -2.98 | -686.2047 | -4.23 |
| **NopM** | -683.2774 | -33.97 | -686.1728 | -28.26 | -686.1600 | -30.34 | -686.2134 | -27.00 |
| **NomM** | -683.2783 | -36.31 | -686.1730 | -28.98 | -686.1603 | -31.17 | -686.2135 | -27.31 |
| **NooM** | -683.2761 | -30.37 | -686.1733 | -29.66 | -686.1599 | -30.27 | -686.2145 | -29.93 |

**5.1.2. Table 7**. Optimisations in $CH_2Cl_2$

| | $E_{SCF}$ | $\delta E_{SCF}$ | $E_0$ | $\delta E_0$ | E | δE | G | δG |
|---|---|---|---|---|---|---|---|---|
| **NppM** | -683.2936 | -5.63 | -686.18678 | 0.00 | -686.1731 | 0.00 | -686.2288 | -0.69 |
| **NpmM** | -683.2944 | -7.63 | -686.18692 | -0.38 | -686.1733 | -0.43 | -686.2289 | -0.94 |
| **NpoM** | -683.2915 | 0.00 | -686.18703 | -0.67 | -686.1736 | -1.26 | -686.2285 | 0.00 |
| **NmpM** | -683.2957 | -10.99 | -686.18704 | -0.70 | -686.1734 | -0.68 | -686.2291 | -1.57 |
| **NmmM** | -683.2965 | -13.16 | -686.18726 | -1.28 | -686.1736 | -1.28 | -686.2293 | -2.11 |
| **NmoM** | -683.2937 | -5.71 | -686.18736 | -1.53 | -686.1739 | -2.02 | -686.2292 | -1.69 |
| **NopM** | -683.3010 | -24.99 | -686.19443 | -20.09 | -686.1816 | -22.32 | -686.2350 | -16.98 |
| **NomM** | -683.3018 | -26.99 | -686.19439 | -19.99 | -686.1808 | -20.22 | -686.2362 | -20.21 |
| **NooM** | -683.2994 | -20.73 | -686.19450 | -20.28 | -686.1813 | -21.38 | -686.2351 | -17.29 |

**5.1.3. Table 8**. Optimisations in $H_2O$

| | $E_{SCF}$ | $\delta E_{SCF}$ | $E_0$ | $\delta E_0$ | E | δE | G | δG |
|---|---|---|---|---|---|---|---|---|
| **NppM** | -683.2873 | -1.54 | -686.17900 | -0.30 | -686.1653 | -0.33 | -686.2212 | -1.83 |
| **NpmM** | -683.2879 | -3.33 | -686.17889 | 0.00 | -686.1652 | 0.00 | -686.2212 | -1.85 |
| **NpoM** | -683.2867 | 0.00 | -686.17960 | -1.85 | -686.1663 | -2.77 | -686.2205 | 0.00 |
| **NmpM** | -683.2897 | -7.84 | -686.17927 | -1.00 | -686.1656 | -0.96 | -686.2216 | -2.81 |
| **NmmM** | -683.2904 | -9.69 | -686.17916 | -0.71 | -686.1655 | -0.80 | -686.2212 | -1.74 |
| **NmoM** | -683.2892 | -6.60 | -686.17994 | -2.75 | -686.1666 | -3.56 | -686.2210 | -1.16 |
| **NopM** | -683.2922 | -14.44 | -686.18423 | -14.02 | -686.1722 | -18.27 | -686.2237 | -8.28 |
| **NomM** | -683.2930 | -16.64 | -686.18404 | -13.51 | -686.1704 | -13.66 | -686.2263 | -15.08 |
| **NooM** | -683.2904 | -9.81 | -686.18415 | -13.82 | -686.1717 | -16.96 | -686.2237 | -8.31 |

The tables present absolute values of electronic ($E_{SCF}$), zero point ($E_0$), energy (E) and Gibbs free energy (G) for the nine **NxxM** isomers expressed in Hartrees ($E_h$). The relative energies (**NppM, NpmM** or **NpoM** is taken as basis point) are shown in columns with suffix δ, and are expressed in $kJ.mol^{-1}$.

**5.1.4. Table 9**. Comparison of energies in different media

| | *gas phase*→$CH_2CH_2$ | | | | *gas phase*→$H_2O$ | | | | $CH_2Cl_2$→$H_2O$ | | | | $logK_{D/W}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\Delta E_{SCF}$ | $\Delta E_0$ | $\Delta E$ | $\Delta G_{solv}$ | $\Delta E_{SCF}$ | $\Delta E_0$ | $\Delta E$ | $\Delta G_{solv}$ | $\Delta\Delta E_{SCF}$ | $\Delta\Delta E_0$ | $\Delta\Delta E$ | $\Delta\Delta G_{solv}$ | |
| **NppM** | -72.09 | -65.04 | -63.25 | -67.33 | -55.38 | -44.63 | -42.82 | -47.53 | -16.71 | -20.41 | -20.42 | -19.80 | 3.47 |
| **NpmM** | -71.84 | -64.65 | -65.32 | -59.21 | -54.93 | -43.58 | -44.13 | -39.17 | -16.92 | -21.08 | -21.19 | -20.04 | 3.51 |
| **NpoM** | -70.84 | -65.03 | -65.24 | -64.55 | -58.22 | -45.51 | -45.99 | -43.61 | -12.62 | -19.52 | -19.24 | -20.94 | 3.67 |
| **NmpM** | -71.81 | -63.90 | -64.40 | -61.58 | -56.03 | -43.50 | -43.94 | -41.87 | -15.77 | -20.40 | -20.47 | -19.70 | 3.45 |
| **NmmM** | -71.64 | -63.78 | -64.28 | -60.98 | -55.55 | -42.51 | -43.05 | -39.66 | -16.09 | -21.27 | -21.24 | -21.32 | 3.73 |
| **NmoM** | -70.78 | -63.80 | -63.93 | -64.10 | -59.04 | -44.32 | -44.72 | -42.64 | -11.73 | -19.48 | -19.21 | -21.47 | 3.76 |
| **NopM** | -61.86 | -56.86 | -56.87 | -56.62 | -38.69 | -30.10 | -32.07 | -26.98 | -23.17 | -26.77 | -24.80 | -29.64 | 5.19 |
| **NomM** | -61.52 | -56.05 | -53.94 | -59.54 | -38.55 | -28.87 | -26.63 | -33.48 | -22.97 | -27.18 | -27.32 | -26.06 | 4.56 |
| **NooM** | -61.21 | -55.66 | -55.99 | -54.00 | -37.67 | -28.49 | -30.82 | -24.08 | -23.54 | -27.17 | -25.17 | -29.92 | 5.24 |

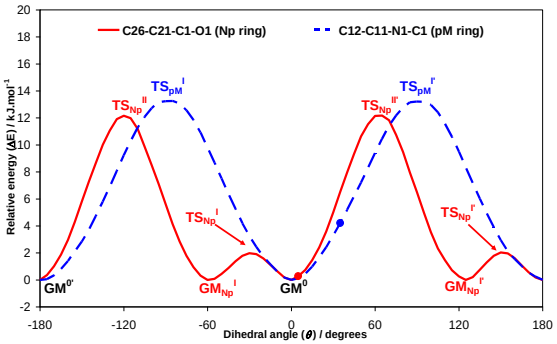
**Comment on energy calculations:**

The least stable molecules are **NppM** and **NpoM**, while the most stable, regardless of media is **NomM**. The **NoxM** molecules due to their inherent stabilisation through intramolecular N-H...$N_{pyr}$ hydrogen bonding are the most stable, with significant differences as compared to the other six **NpxM**/**NmxM** isomers. Another stabilisation factor is the methyl group located in a *meta* position, although this effect is less pronounced. In total, the effects of the pyridine **N** atom and $CH_3$ group positions on stability is summarised as: **No**>**Nm**>**Np** with **mM**>**pM**>**oM**. The estimated $\Delta G_{solv}$ in $CH_2Cl_2$ and $H_2O$, along with theoretical $logK_{D/W}$ are consistent with our experimental observations and with no unexpected results. All compounds should be $10^3$-$10^4$ times more soluble in $CH_2Cl_2$ than in $H_2O$; the **NoxM** series are expected to be the least soluble in water.

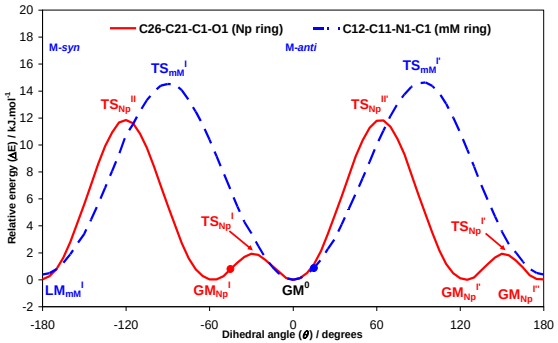
The **Table 9** above shows differences ($\Delta$) of the energies ($E_{SCF}$, $E_0$, E and G) for the nine **NxxM** isomers in different media expressed in kJ.mol$^{-1}$. The $\Delta G_{solv}$ represents the calculated energy of solvation, while $\Delta\Delta G_{solv}$ represents the difference of energies of solvation in two different solvents ($CH_2Cl_2$ and $H_2O$). The final variable, $logK_{D/W}$ presents the tentative (theoretical) values of the partition coefficient of the **NxxM** molecules between dichloromethane ($CH_2Cl_2$, DCM) and water ($H_2O$), calculated as $logK_{D/W} = -\Delta\Delta G_{solv}/2.303RT$. This model has not been validated using the exact experimental values of $logK_{D/W}$, therefore, it has exclusively relative (qualitative) not absolute (quantitative) significance and the tentative values of $logK_{D/W}$ should not be taken as final.

**5.2.** Potential energy surface (PES) scans of the nine **NxxM** conformers (rotamers), optimised in *gas phase*

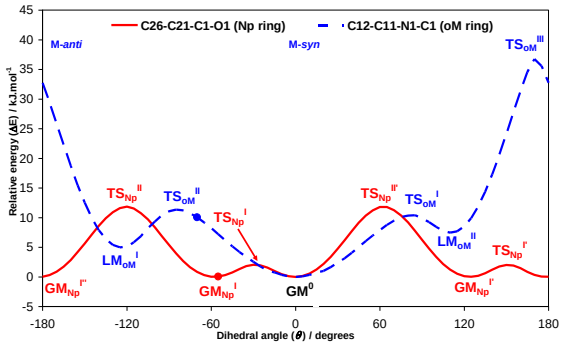
**NppM**



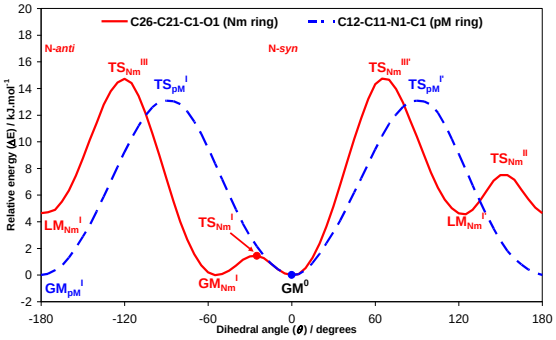

**NpmM**



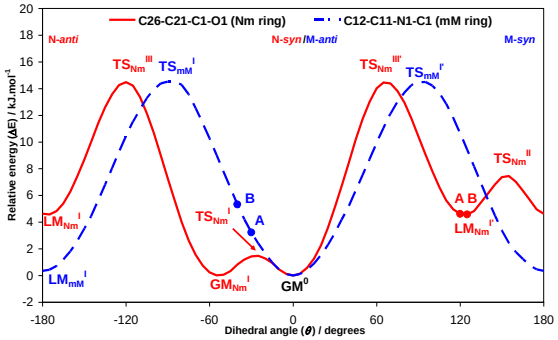

**NpoM**



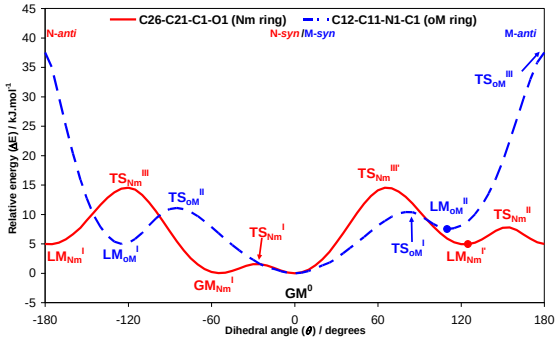

**NmpM**



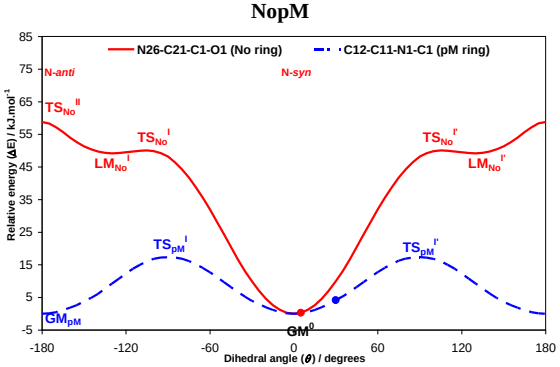

**NmmM**



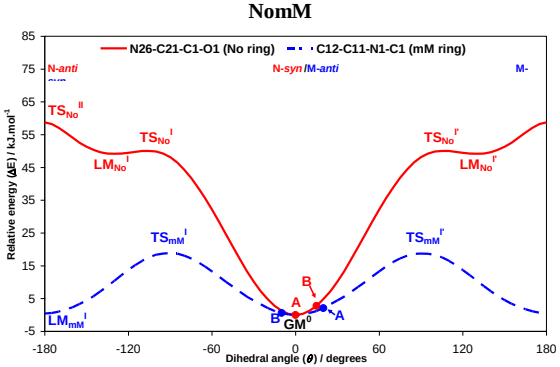

**NmoM**



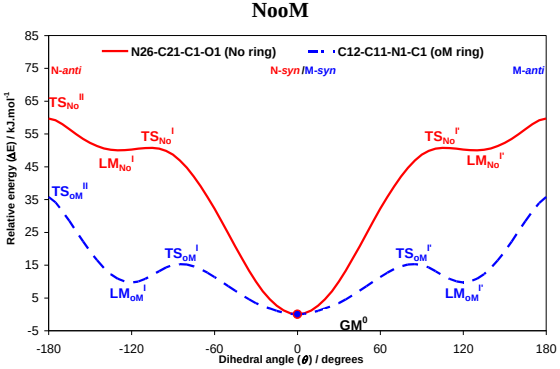

**NopM**




**NomM**




**NooM**



**Detailed description:**

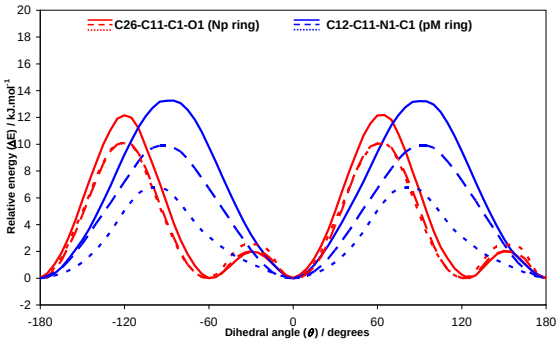
The *para*-pyridine (Np) ring has a PES curve with two global maxima at *ca*. 65º and -120º ($TS_{Np}^{II}$ = 11.94±0.18 kJ.mol$^{-1}$), two local maxima at around -30º and 150º ($TS_{Np}^{I}$ = 1.98±0.05 kJ.mol$^{-1}$) and four global minima at *ca*. 0, -55, 125 and ±180º.
The *meta*-pyridine (Nm) ring has two global maxima at *ca*. -120º and 65º, ($TS_{Nm}^{III}$ = 14.57±0.12 kJ.mol$^{-1}$), two local maxima at *ca*. -25º ($TS_{Nm}^{I}$ = 1.48±0.05 kJ.mol$^{-1}$) and 150º ($TS_{Nm}^{II}$ = 7.57±0.17 kJ.mol$^{-1}$), two local minima at *ca*. 125º and ±180º ($LM_{Nm}^{I}$ = 4.70±0.17 kJ.mol$^{-1}$) and two global minima at 0º and -55º.

The *ortho*-pyridine (No) ring shows a symmetric PES curve with one global maximum at ±180º ($TS_{No}^{II}$ = 59.07±0.53 kJ.mol$^{-1}$), two local maxima at ±105º ($TS_{No}^{I}$ = 50.28±0.34 kJ.mol$^{-1}$), two local minima at *ca*. ±130º ($LM_{No}^{I}$ = 49.44±0.41 kJ.mol$^{-1}$) and one global minimum at 0º. The *para*-tolyl (**pM**) gives a symmetric PES curve with two global maxima at *ca*. ±90º ($TS_{pM}^{I}$ = 13.15±0.09 kJ.mol$^{-1}$, while $TS_{pM}^{I}$[NopM] = 17.33 kJ.mol$^{-1}$), and two global minima at 0º and ±180º.

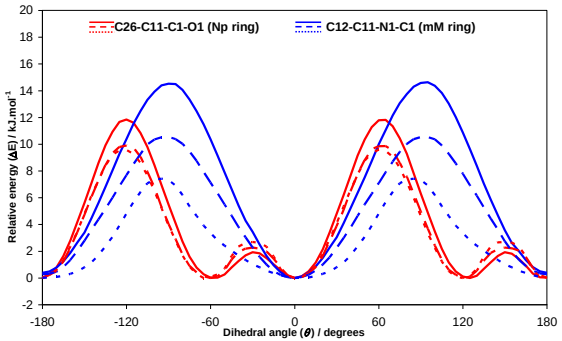
The *meta*-tolyl (mM) has a symmetric PES curve with two global maxima at *ca*. ± 90º ($TS_{mM}^{I}$ = 14.54 ± 0.06 kJ.mol$^{-1}$, while $TS_{mM}^{I}$[NomM] = 18.79±0.11 kJ.mol$^{-1}$), one local minima at *ca*. ±180º ($LM_{mM}^{I}$ = 0.37±0.02 kJ.mol$^{-1}$, while $LM_{mM}^{I}$[NomM] = 0.46 kJ.mol$^{-1}$) and one global minima at 0º.
The *ortho*-tolyl (oM) ring: The PES in **NpoM** has one global maximum at 170º, while in **NmoM** it is at ±180º ($TS_{oM}^{III}$ = 37.13±0.53 kJ.mol$^{-1}$). The PES curve has two local maxima at *ca*. 85º ($TS_{oM}^{I}$ = 10.39±0.01 kJ.mol$^{-1}$) and -85º ($TS_{oM}^{II}$ = 11.21±0.19 kJ.mol$^{-1}$), two local minima at *ca*. -125º ($LM_{oM}^{I}$ = 4.97 kJ.mol$^{-1}$) and 110º ($LM_{oM}^{II}$ = 7.47±0.03 kJ.mol$^{-1}$), and one global minimum (0º). The symmetric PES curve of the oM ring in **NooM** has one global maximum at ±180º ($TS_{oM}^{II}$[**NooM**] = 35.73 kJ.mol$^{-1}$), two local maxima at ±85º ($TS_{oM}^{I}$[**NooM**] = 15.31 kJ.mol$^{-1}$), two local minima at ±120º ($LM_{oM}^{I}$[**NooM**] = 9.73 kJ.mol$^{-1}$) and the global minimum at 0º.

**5.3.** PES scans of the nine **NxxM** conformers (rotamers), optimised in *gas phase* (full line), $CH_2Cl_2$ (dashed line) and in $H_2O$ (dotted line).

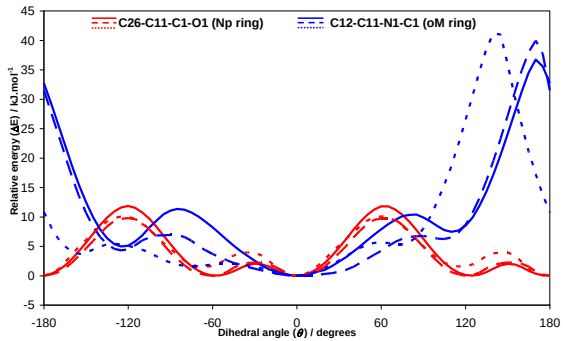
**NppM**



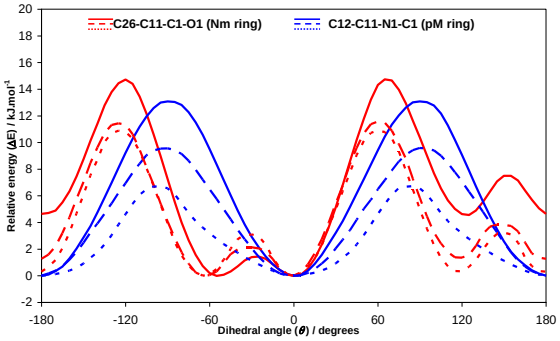

**NpmM**



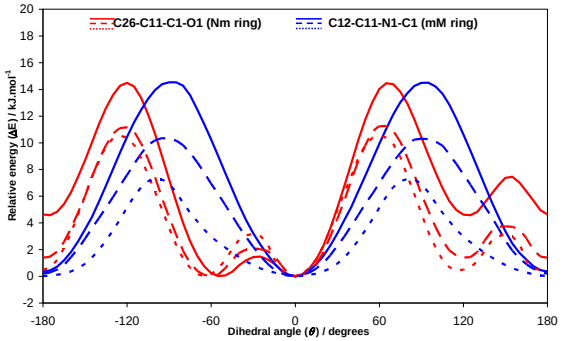

**NpoM**



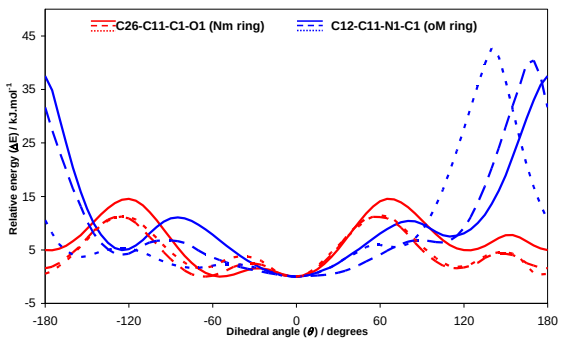

**NmpM**



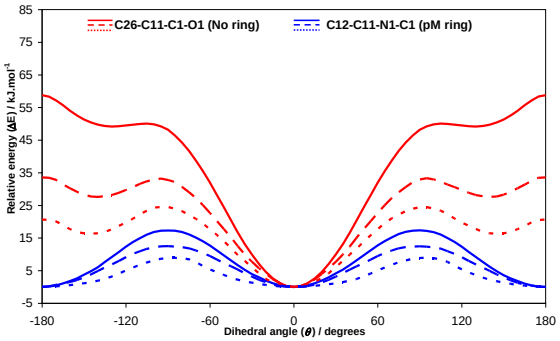

**NmmM**



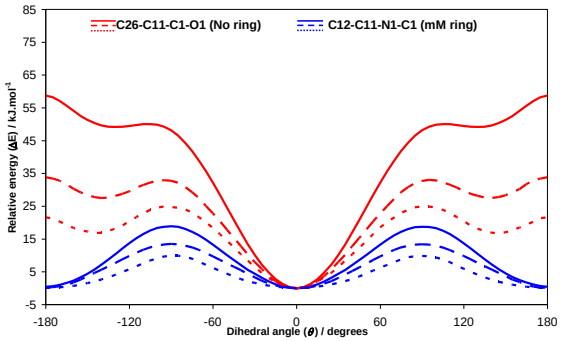

**NmoM**



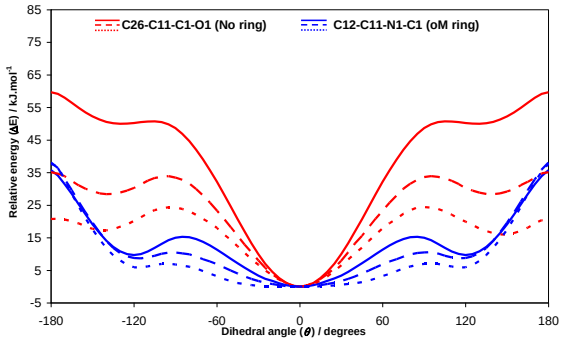

**NopM**




**NomM**




**NooM**



**Detailed description:**

When the *para*-pyridine (**Np**) ring rotates towards orthogonality (around $TS_{Np}^{II}$) the rotational barriers decrease by ~16.5% in $CH_2Cl_2$ (~17.2% in $H_2O$), whereas, in the areas of planarity (around $TS_{Np}^{I}$) the rotational barriers increase in $CH_2Cl_2$ by ~15% (~50% in $H_2O$). The decrease in when orthogonal is almost the same in both solvents, while when planar the more polar solvent has the higher impact on the barrier increase. The reason for the increase is augumentation of repulsion due to the higher dielectric field.

The *meta*-pyridine (**Nm**) ring has a specific rotational barrier change pattern. In the **N-*syn*** conformation (from $\theta$ = -120º→60º) the **Nm** ring is similar to the **Np** ring with the decrease with orthogonal rings of ~22.4% in $CH_2Cl_2$ (~25% in $H_2O$) and an increase when the rings are co-planar is ~54.1% in $CH_2Cl_2$ (~133.6% in $H_2O$). In the **N-*anti*** conformation a linear decrease by ~3.35 kJ.mol$^{-1}$ in $CH_2Cl_2$ (~3.87 kJ.mol$^{-1}$ in $H_2O$) is observed. A noticeable shift of barriers ($\Delta\theta$ ~5-10º) occurs due to the deviation of dihedral angles in solvents.

The rotational barrier for the *ortho*-pyridine (**No**) ring symmetrically decreases by ~41.7% ($CH_2Cl_2$) and ~63.2% ($H_2O$). Therefore, the solvent effect on the rotational barrier of the **No** ring is the most distinct, albeit as expected: the PCM-SMD model predicts the interaction of a strong solvent electric field with the intramolecular N-H...N hydrogen bond in the three **NoxM** and weakening the interaction.

The *para*-tolyl (**pM**) ring shows a regular decrease by ~27% in $CH_2Cl_2$ (~49% in $H_2O$). In **NopM** all of the barrier peaks are symmetrical, but in **NppM** and **NmpM** the peaks are shifted by ~5º in $CH_2Cl_2$ (~10º in $H_2O$). In the *meta*-tolyl (**mM**) ring the pattern is similar to the **pM** ring with decreases of ~28.5% in $CH_2Cl_2$ (~49% in $H_2O$), similar barrier shifts are noted as for the **pM** ring. The energy difference between **M-*anti*** and **M-*syn*** in $CH_2Cl_2$ decreases by ~43%, while in $H_2O$ the difference is almost cancelled (93%), making both conformations energetically equal. Theoretically, this observation implies that the **mM** ring in polar solvents can adopt both **M-*anti*** and **M-*syn*** conformations equivalently. The *ortho*-tolyl (**oM**) ring behaviour is more complex with the **NpoM**/**NmoM** isomers showing differences to **NooM**. The rotational barriers in the **M-*syn*** conformation decrease by ~37% ($CH_2Cl_2$) and in the **M-*anti*** conformation increase by ~8% in $CH_2Cl_2$, (~13% in $H_2O$). However, due to a strong additional rotation of the **oM** rings optimised in $H_2O$ the PES curve shape exhibits significant deviations. An extra local maximum is positioned at -45º *only* and $TS_{oM}^{III}$ is displaced (by $\Delta\theta$ = 40º). For the symmetrical **NooM** the pattern is much simpler: as **M-*syn*** the conformation barrier decrease is ~31% in $CH_2Cl_2$ (~54% in $H_2O$) and in **M-*anti*** the increase is 6.7% in $CH_2Cl_2$ (5.6% in $H_2O$) because solvent induced high dielectric field can amplify repulsion of methyl group and carbonyle oxygene.