

Mechanochemical IMCR and post-MCR transformation-based domino strategies: Towards the sustainable DOS of dipeptides-like and heterocyclic peptidomimetics.

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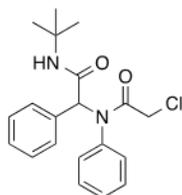
General information

All reactions were carried out in 10 mL stoppered glass tube. Reactions were monitored by silica gel TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light at 254 or 365 nm, using mixture of hexane and ethyl acetate (AcOEt) as eluents. Column chromatography was performed using silica gel (230-400 mesh) and mixtures of hexane with AcOEt in different proportions (v/v) as mobile phase. Melting points were determined on an Electrothermal apparatus and were uncorrected. ¹H NMR spectra were recorded on Bruker Advance III spectrometer (500 MHz) at 295 K in CDCl₃; chemical shifts (δ in ppm) and coupling constants (*J*/Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_{\text{H}} = 0$ ppm) or CHCl₃ ($\delta_{\text{H}} = 7.26$ ppm). ¹³C NMR spectra were recorded on Bruker Advance III spectrometer (126 MHz) at room temperature in CDCl₃; chemical shifts (δ in ppm) are reported relative to CHCl₃ ($\delta_{\text{C}} = 77.00$ ppm). In ¹H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, dd = doublet of doublet, m = multiplet and bs = broad singlet. The assignment of signals was confirmed by ¹H and ¹³C spectral data. NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. HRMS spectra were acquired on a Bruker Daltonics Maxis Impact ESI-qTOF MS spectrometer. HRMS samples were ionized by ESI⁺ mode and recorded via the TOF method. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

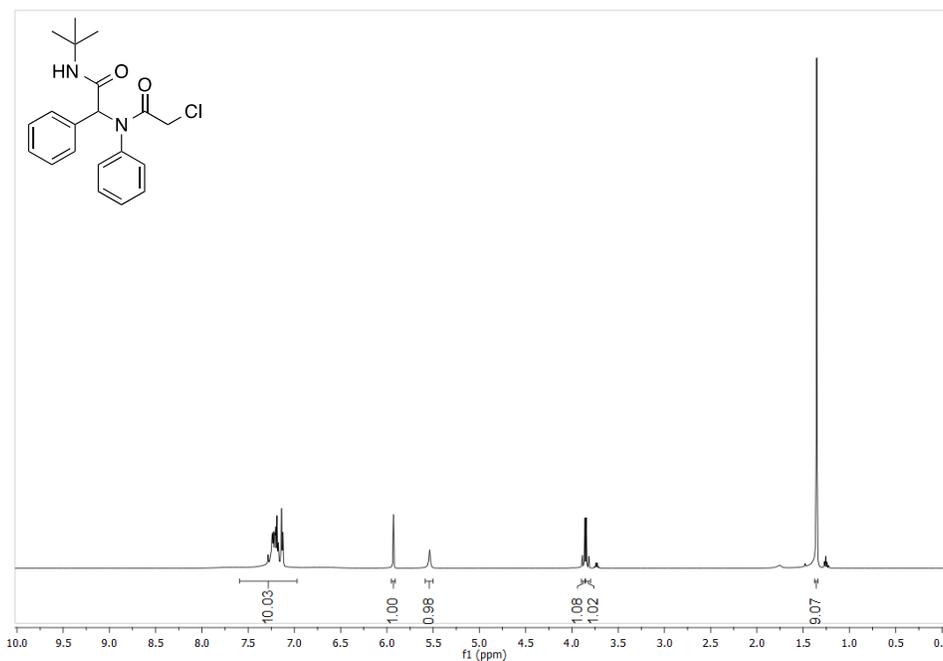
General procedure for Ugi-4CR (GP)

A mixture of aldehyde **1** (1.0 equiv.), amine **2** (1.0 equiv.), isocyanide **3** (1.0 equiv.) and carboxylic acid **4** (1.0 equiv.) was thoroughly mixed in an agate mortar and grinded with a pestle manually for 3 minutes (a mixture which was initially particulate liquefied and eventually solidified to generate the Ugi product (**5**). The resultant crude product was washed with hexane:EtOAc (9:1) mixture to remove the traces of isocyanide and imine and was recrystallized in hot EtOH to afford pure Ugi products (**5**).

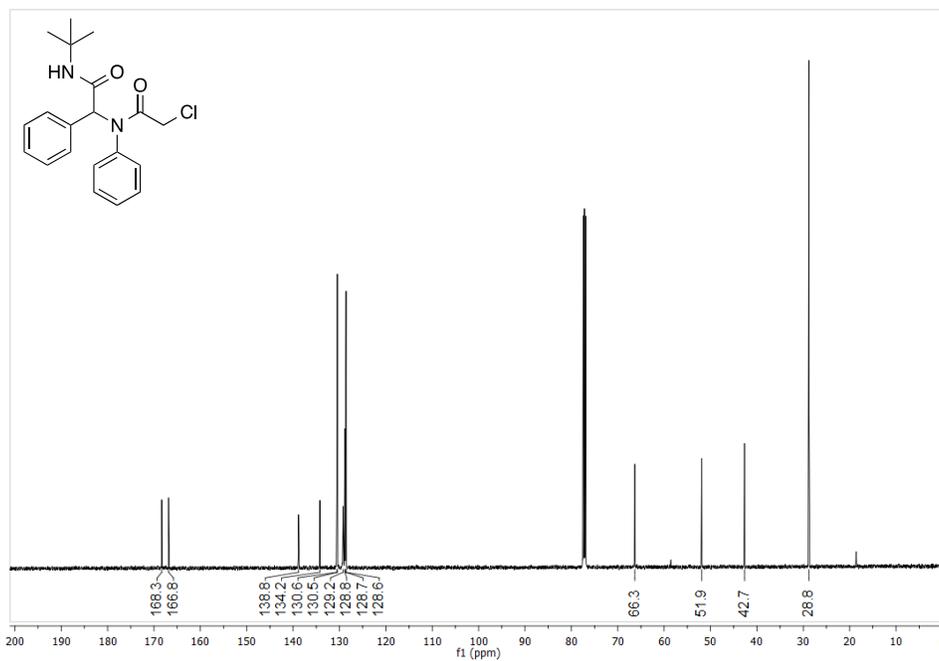
N-(*tert*-Butyl)-2-(2-chloro-*N*-phenylacetamido)-2-phenylacetamide (**5a**)



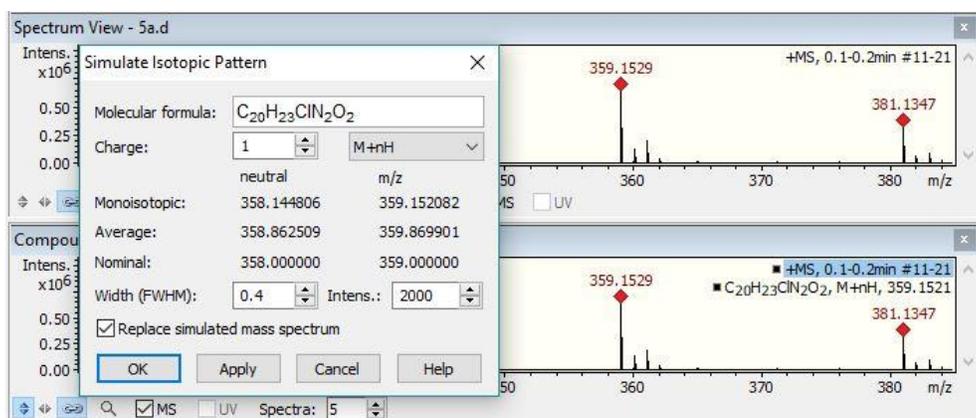
Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 0.053 mL *tert*-butyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 154.0 mg (91%) as a light brown needle shaped crystals; mp 110-112 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.58 – 6.95 (m, 10H), 5.93 (s, 1H), 5.54 (bs, 1H), 3.87 (d, J = 13.7 Hz, 2H), 3.83 (d, J = 13.7 Hz, 2H), 1.35 (s, 9H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 168.3, 166.8, 138.8, 134.2, 130.6, 130.5, 129.2, 128.8, 128.7, 128.6, 66.3, 51.9, 42.7, 28.8; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{20}\text{H}_{24}\text{ClN}_2\text{O}_2^+$ [$\text{M} + \text{H}$]⁺ 359.1521, found 359.1529.



$^1\text{H NMR}$ spectra of the compound **5a**

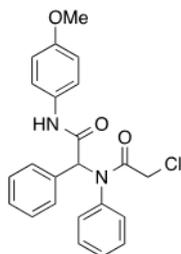


¹³C NMR spectra of the compound **5a**

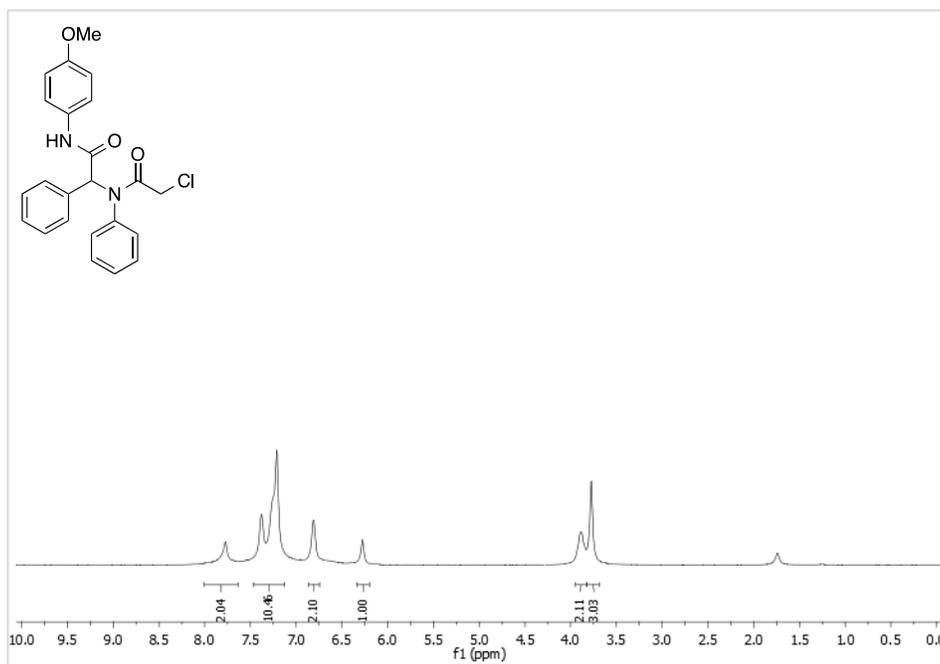


HRMS spectra of the compound **5a**

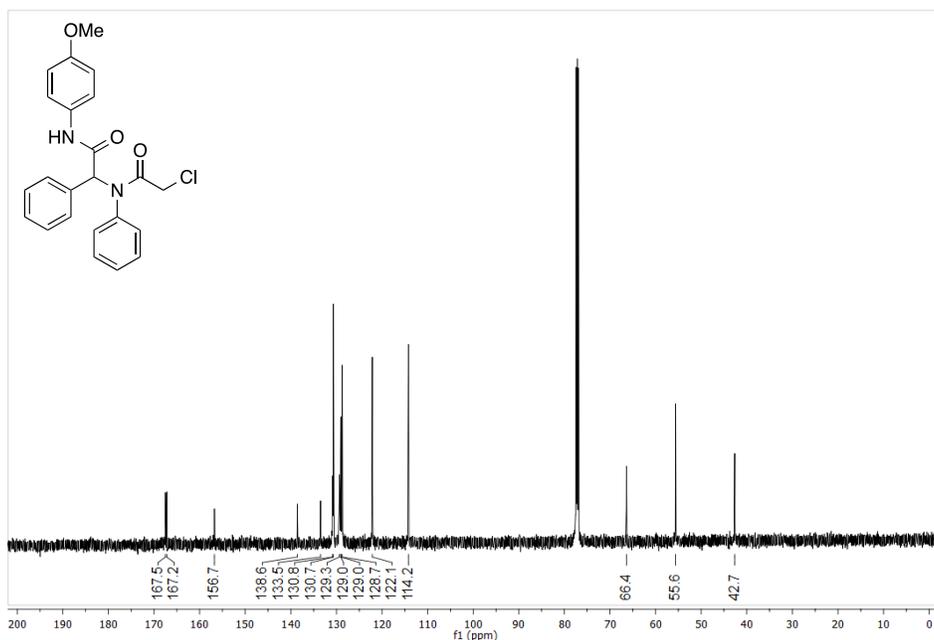
2-Chloro-N-(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)-N-phenylacetamide (5b)



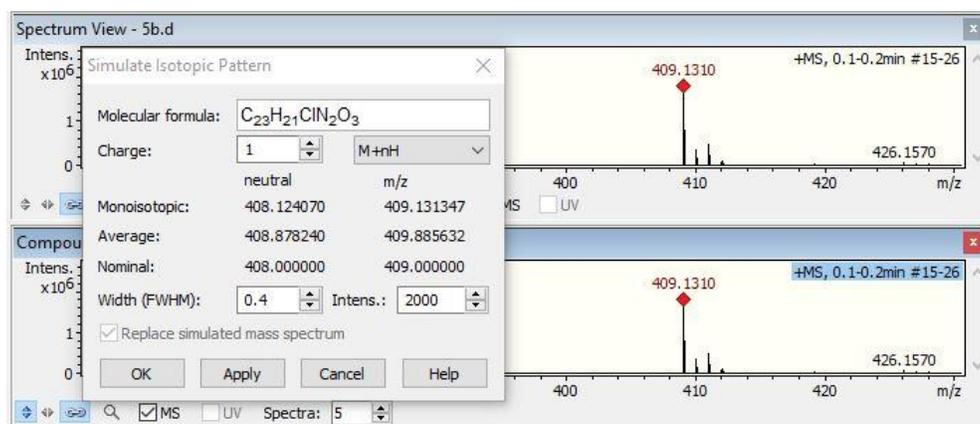
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 174.0 mg (90%) as a light yellow needle shaped crystals; mp 118-119 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.77 (s, 2H), 7.47 – 7.14 (m, 10H), 6.81 (s, 2H), 6.27 (s, 1H), 3.89 (d, J = 6.7 Hz, 2H), 3.77 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 167.5, 167.2, 156.7, 138.6, 133.5, 130.8, 130.7, 129.3, 129.0(2), 128.7, 122.1, 114.2, 66.4, 55.6, 42.7; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{23}\text{H}_{22}\text{ClN}_2\text{O}_3^+$ [$\text{M} + \text{H}$] $^+$ 409.1313, found 409.1310.



$^1\text{H NMR}$ spectra of the compound **5b**

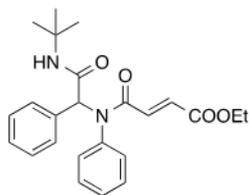


¹³C NMR spectra of the compound **5b**

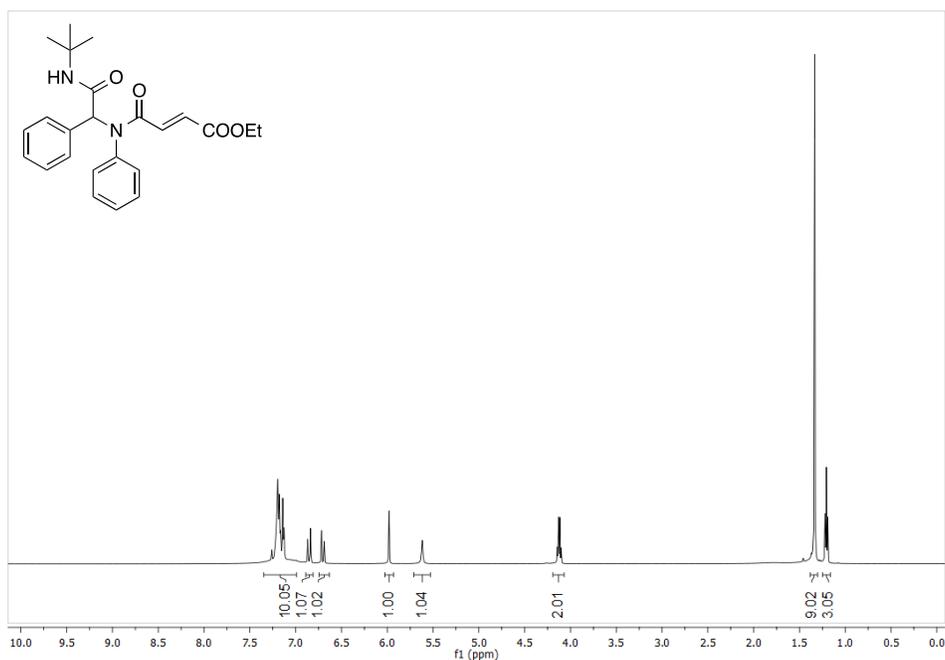


HRMS spectra of the compound **5b**

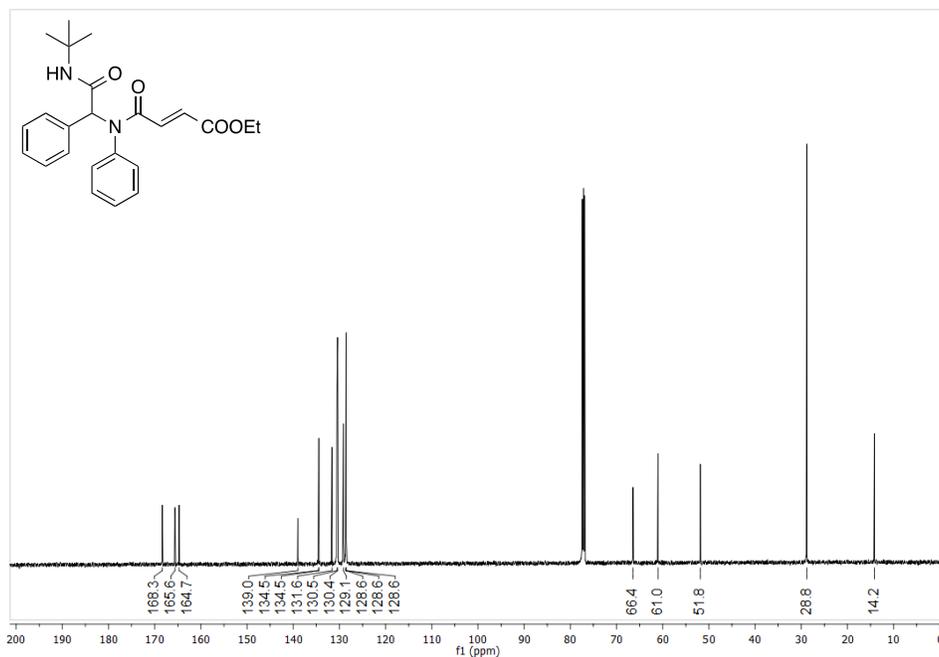
Ethyl (E)-4-((2-(*tert*-butylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-4-oxobut-2-enoate (5c)



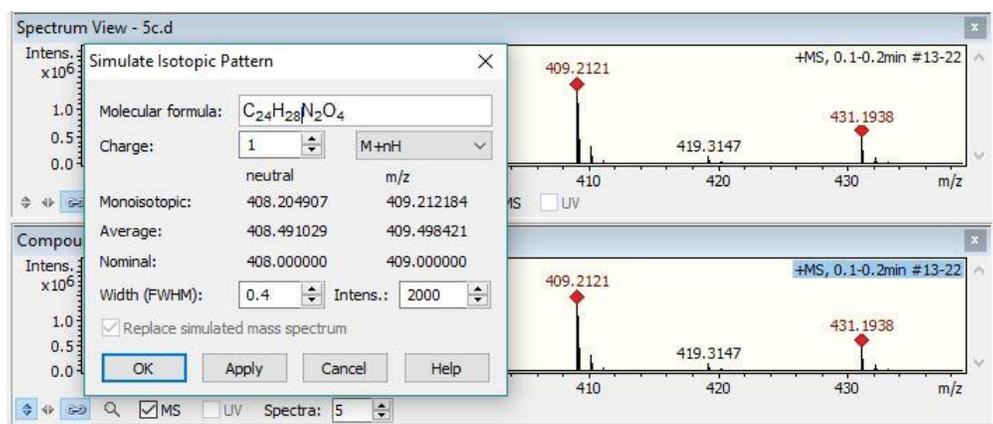
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 0.053 mL *tert*-butyl isocyanide (0.47 mmol) and 67.0 mg (E)-4-ethoxy-4-oxobut-2-enoic acid (0.47 mmol) were grinded together to afford 160.0 mg (83%) as a white needle shaped crystals; mp 148-150 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.35 – 6.99 (m, 10H), 6.85 (d, J = 15.3 Hz, 1H), 6.70 (d, J = 15.3 Hz, 1H), 5.98 (s, 1H), 5.62 (bs, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.35 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 168.3, 165.6, 164.7, 139.0, 134.5, 134.5, 131.6, 130.5, 130.4, 129.1, 128.6, 128.6, 128.6, 66.4, 61.0, 51.8, 28.8, 14.2; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4^+$ [$\text{M} + \text{H}$]⁺ 409.2122, found 409.2121.



$^1\text{H NMR}$ spectra of the compound **5c**

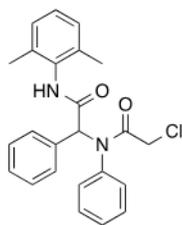


¹³C NMR spectra of the compound 5c

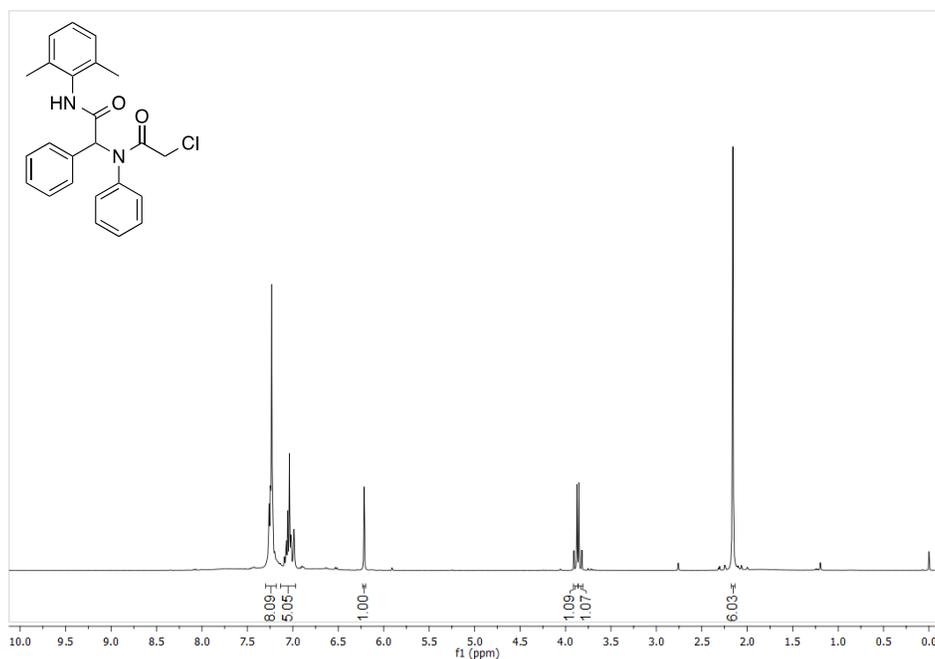


HRMS spectra of the compound 5c

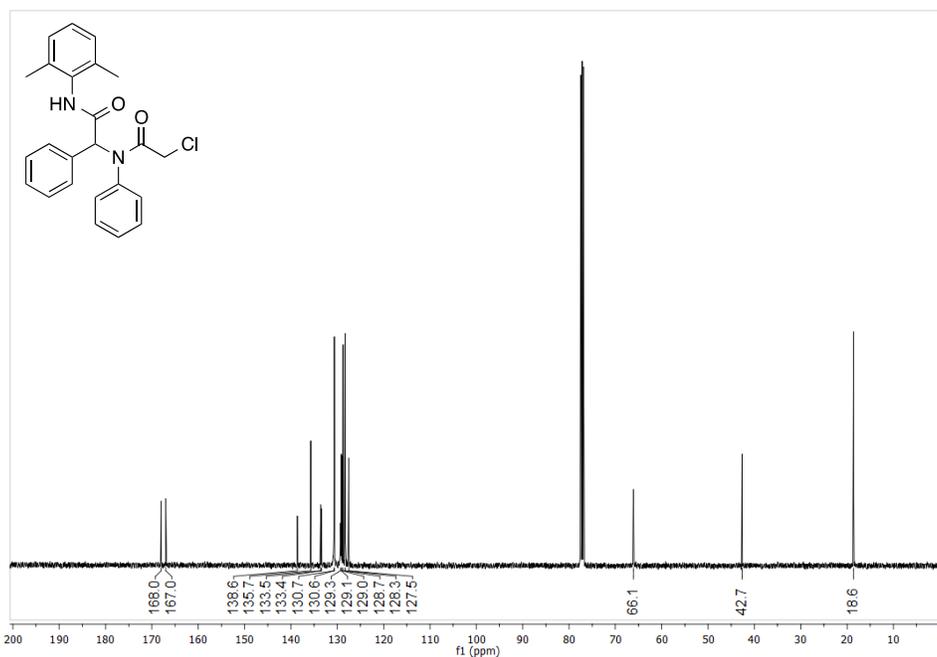
2-Chloro-*N*-(2-((2,6-dimethylphenyl)amino)-2-oxo-1-phenylethyl)-*N*-phenylacetamide (5d)



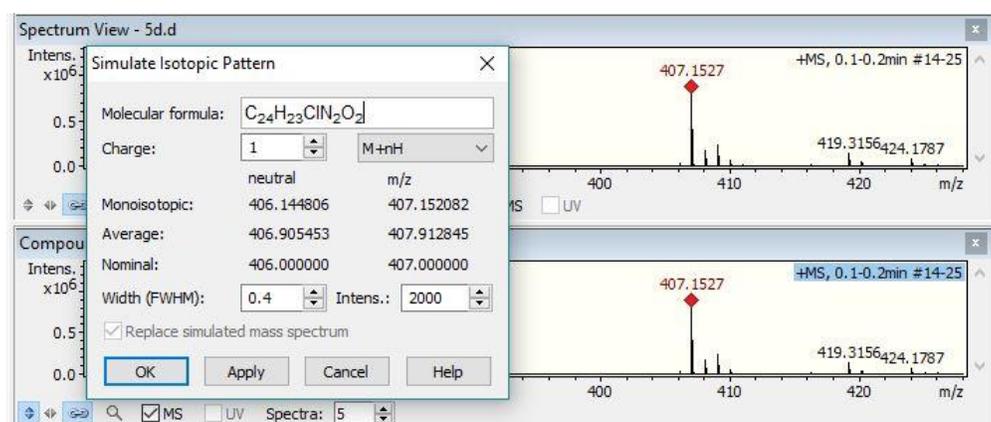
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 169.0 mg (88%) as a light yellow needle shaped crystals; mp 115-118 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.30 – 7.17 (m, 8H), 7.13 – 6.95 (m, 5H), 6.22 (s, 1H), 3.86 (d, J = 13.7 Hz, 1H), 3.84 (d, J = 13.7 Hz, 1H), 2.16 (s, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 168.0, 167.0, 138.6, 135.7, 133.5, 133.4, 130.7, 130.6, 129.3, 129.1, 129.0, 128.7, 128.3, 127.5, 66.1, 42.7, 18.6; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_2^+$ $[\text{M} + \text{H}]^+$ 407.1521, found 407.1527.



$^1\text{H NMR}$ spectra of the compound **5d**

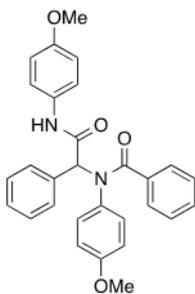


^{13}C NMR spectra of the compound **5d**

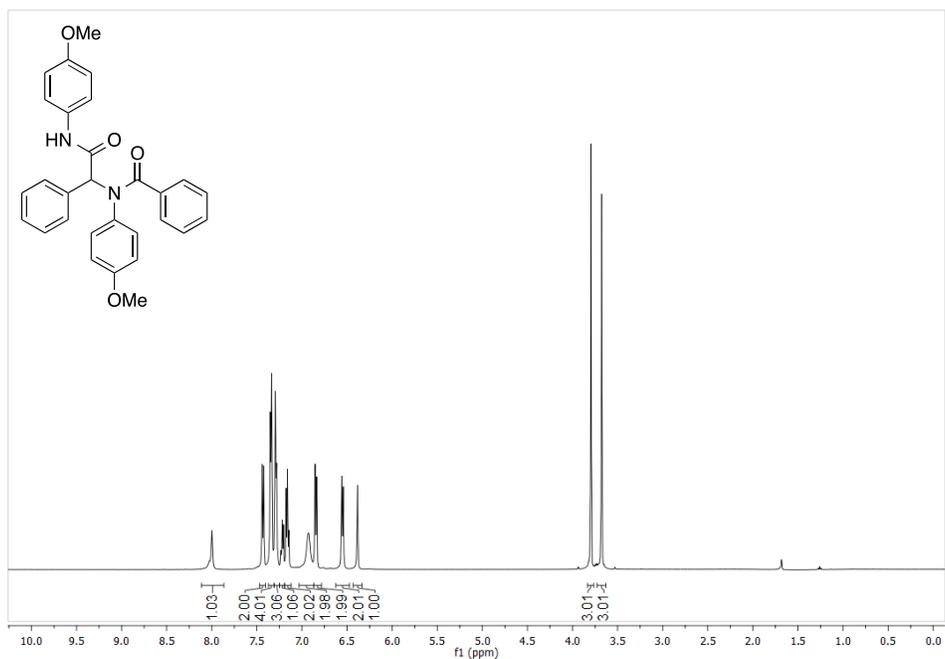


HRMS spectra of the compound **5d**

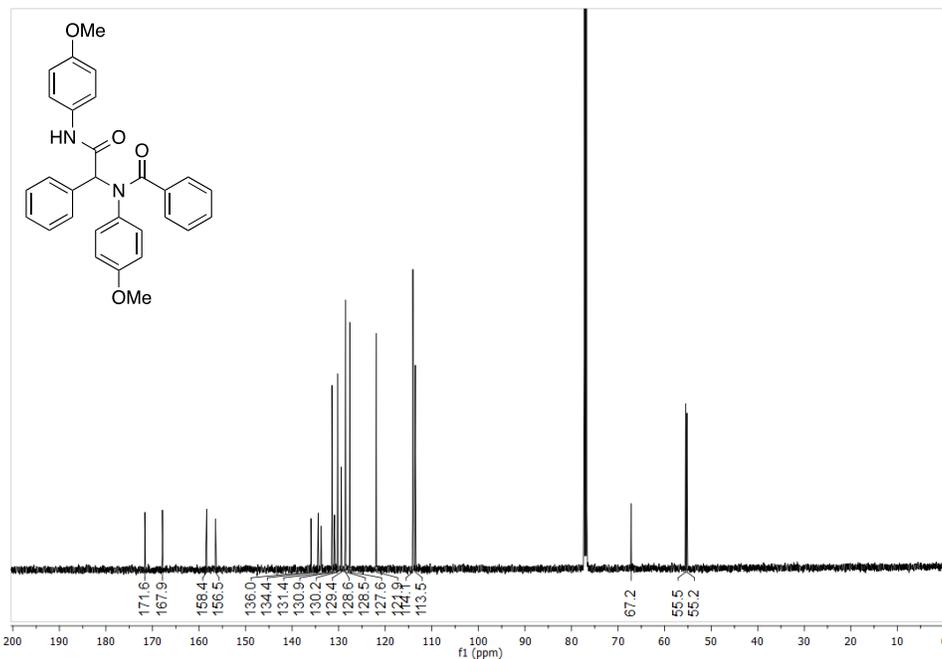
***N*-(4-Methoxyphenyl)-*N*-(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)benzamide (5e)**



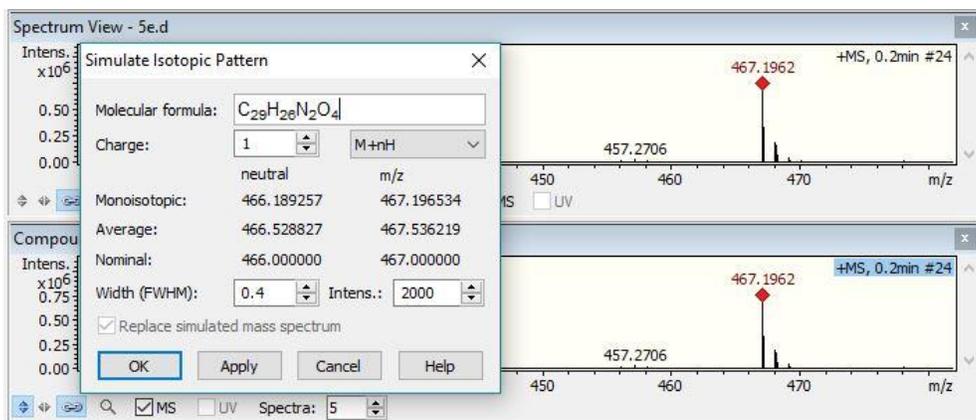
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 58.0 mg 4-methoxyaniline (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 57.0 mg benzoic acid (0.47 mmol) were grinded together to afford 176.0 mg (80%) as a light brown needle shaped crystals; mp 128-129 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.00 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 7.3 Hz, 4H), 7.29 (d, J = 5.8 Hz, 3H), 7.22 (t, J = 7.1 Hz, 1H), 7.16 (t, J = 7.4 Hz, 2H), 6.93 (bs, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 3.79 (s, 3H), 3.68 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 171.6, 167.9, 158.4, 156.5, 136.0, 134.4, 133.8, 131.4, 130.9, 130.2, 129.4, 128.6, 128.5, 127.6, 121.9, 114.1, 113.5, 67.4, 55.6, 55.3; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 467.1965, found 467.1962.



$^1\text{H NMR}$ spectra of the compound **5e**

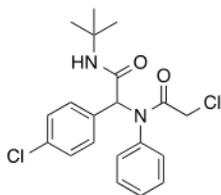


¹³C NMR spectra of the compound 5e

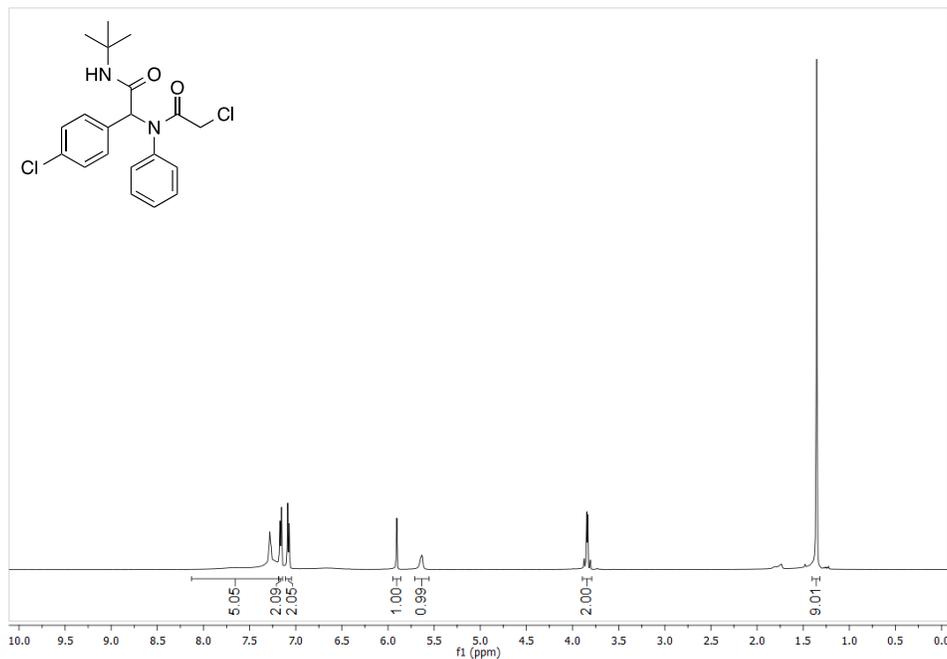


HRMS spectra of the compound 5e

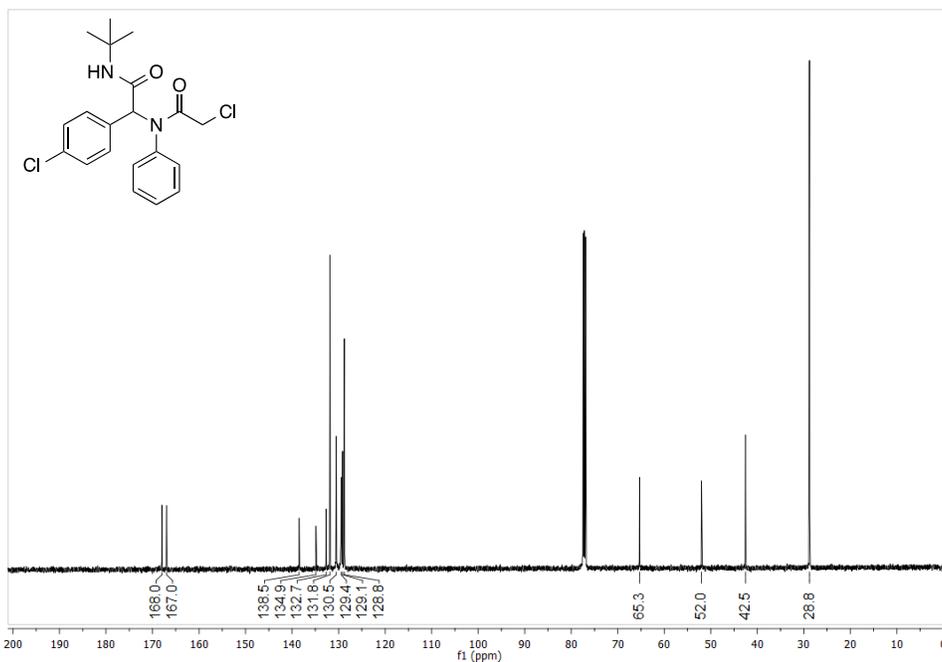
***N*-(*tert*-Butyl)-2-(2-chloro-*N*-phenylacetamido)-2-(4-chlorophenyl)acetamide (5f)**



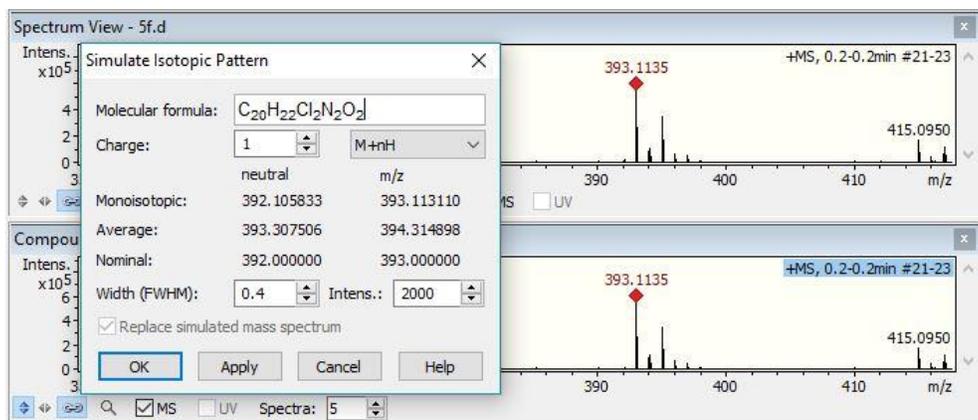
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 0.040 mL *tert*-butyl isocyanide (0.35 mmol) and 33.0 mg monochloroacetic acid (0.35 mmol) were grinded together to afford 110.0 mg (78%) as a brown needle shaped crystals; mp 108-111 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.13 – 7.19 (m, 5H), 7.16 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.90 (s, 1H), 5.63 (s, 1H), 3.90 – 3.79 (m, 2H), 1.35 (s, 9H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 168.0, 167.0, 138.5, 134.9, 132.7, 131.8, 130.5, 129.4, 129.1, 128.8, 65.3, 52.0, 42.5, 28.8; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{20}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_2^+$ [$\text{M} + \text{H}$]⁺ 393.1131, found 393.1135.



$^1\text{H NMR}$ spectra of the compound **5f**

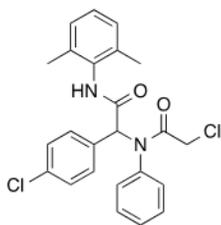


¹³C NMR spectra of the compound 5f

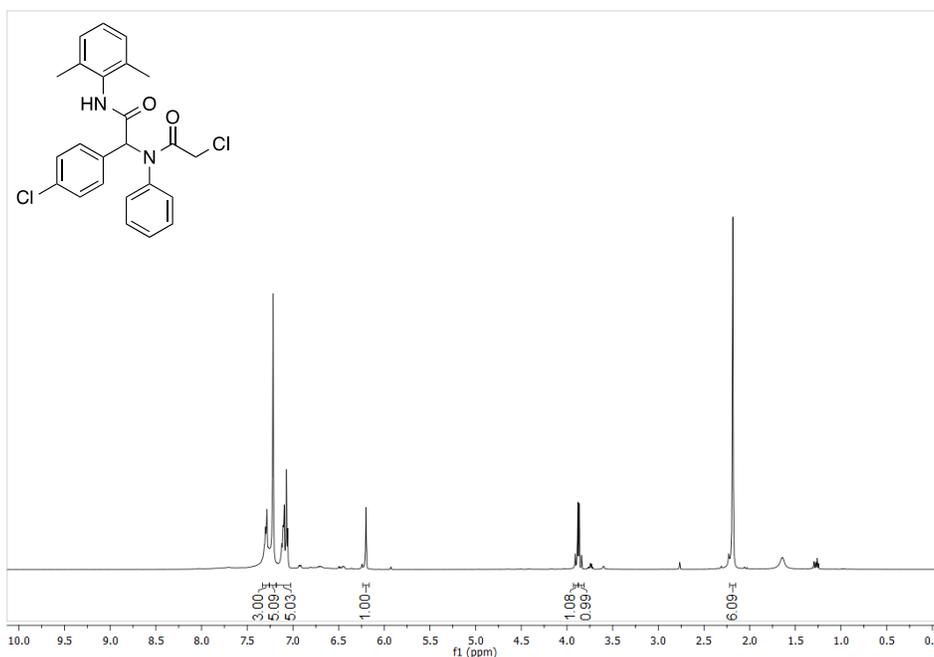


HRMS spectra of the compound 5f

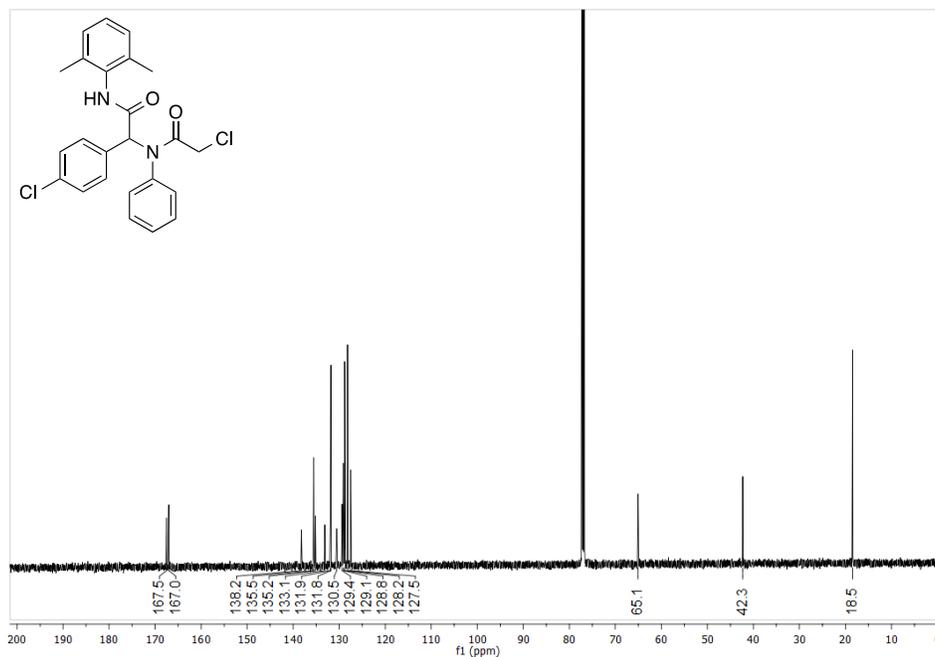
2-Chloro-N-(1-(4-chlorophenyl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-phenylacetamide (5g)



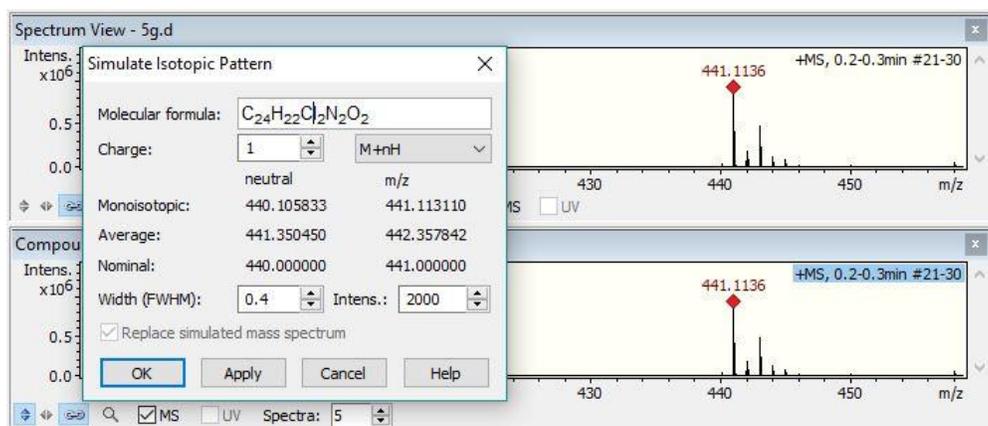
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 47.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 33.0 mg monochloroacetic acid (0.35 mmol) were grinded together to afford 141.0 mg (90%) as a light yellow needle shaped crystals; mp 123-125 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.32 – 7.28 (m, 3H), 7.25 – 7.19 (m, 5H), 7.18 – 7.02 (m, 5H), 6.20 (s, 1H), 3.89 (d, J = 13.7 Hz, 1H), 3.85 (d, J = 13.7 Hz, 1H), 2.18 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 167.5, 167.0, 138.2, 135.5, 135.2, 133.1, 131.9, 131.8, 130.5, 129.4, 129.1, 128.8, 128.2, 127.5, 65.1, 42.3, 18.5; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{24}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_2^+$ [$\text{M} + \text{H}$]⁺ 441.1131, found 441.1136.



$^1\text{H NMR}$ spectra of the compound **5g**

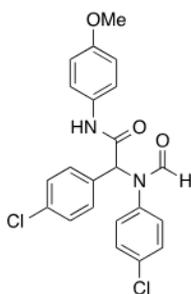


¹³C NMR spectra of the compound **5g**

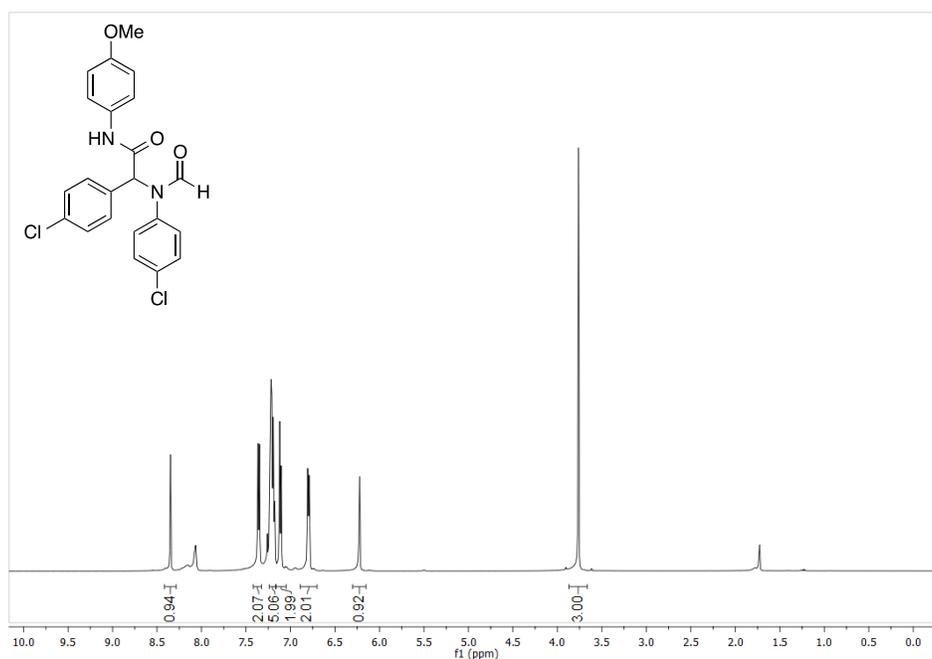


HRMS spectra of the compound **5g**

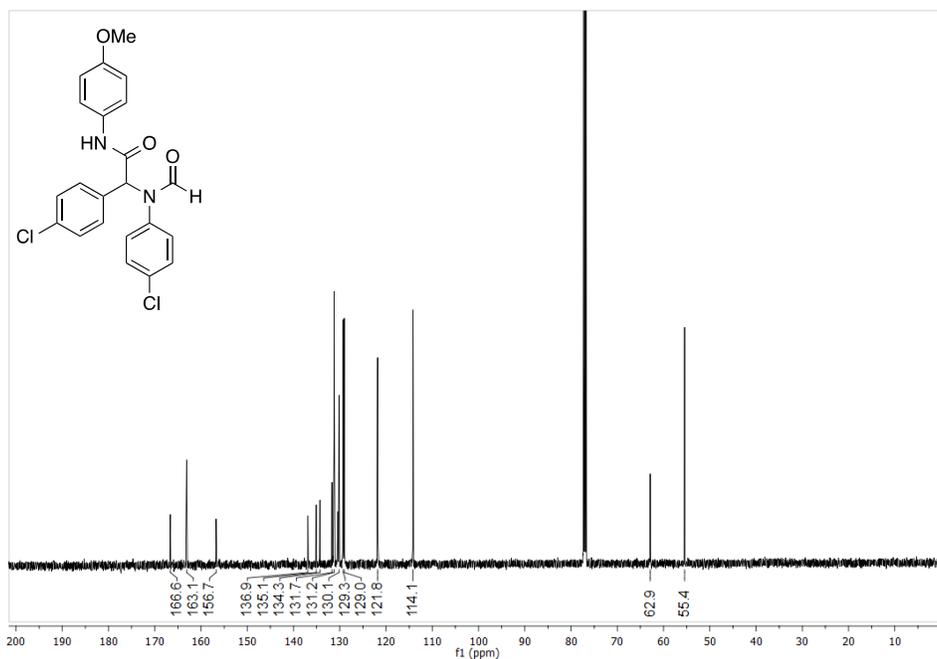
2-(4-Chlorophenyl)-2-(*N*-(4-chlorophenyl)formamido)-*N*-(4-methoxyphenyl)acetamide (5h)



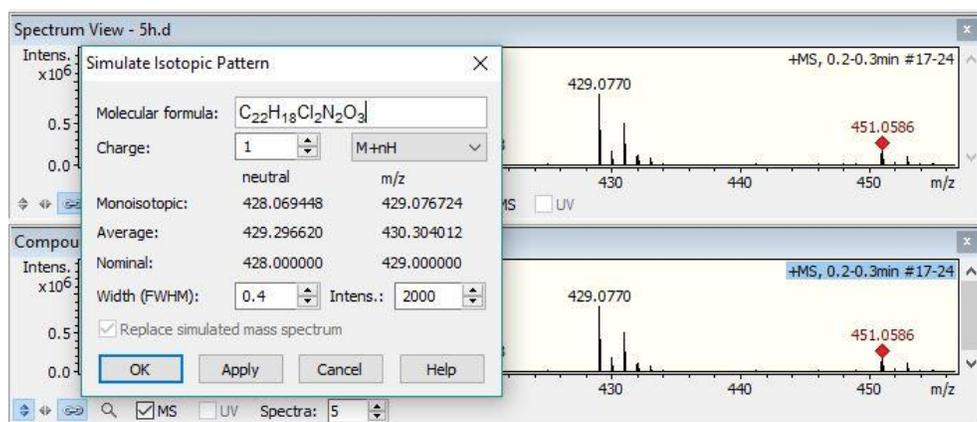
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 47.0 mg 4-methoxyphenyl isocyanide (0.35 mmol) and 0.013 mL formic acid (0.35 mmol) were grinded together to afford 125.0 mg (82%) as a white needle shaped crystals; mp 134-136 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.35 (s, 1H), 8.07 (bs, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.25 – 7.16 (m, 6H), 7.11 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.22 (s, 1H), 3.76 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 166.6, 163.1, 156.7, 136.9, 135.1, 134.3, 131.7, 131.2, 130.1, 129.3, 129.0, 121.8, 114.1, 62.9, 55.4; **HRMS (ESI)⁺**: m/z calcd. for $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_3^+$ [$\text{M} + \text{H}$]⁺ 429.0767, found 429.0770.



$^1\text{H NMR}$ spectra of the compound **5h**

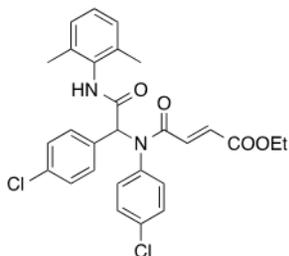


¹³C NMR spectra of the compound **5h**

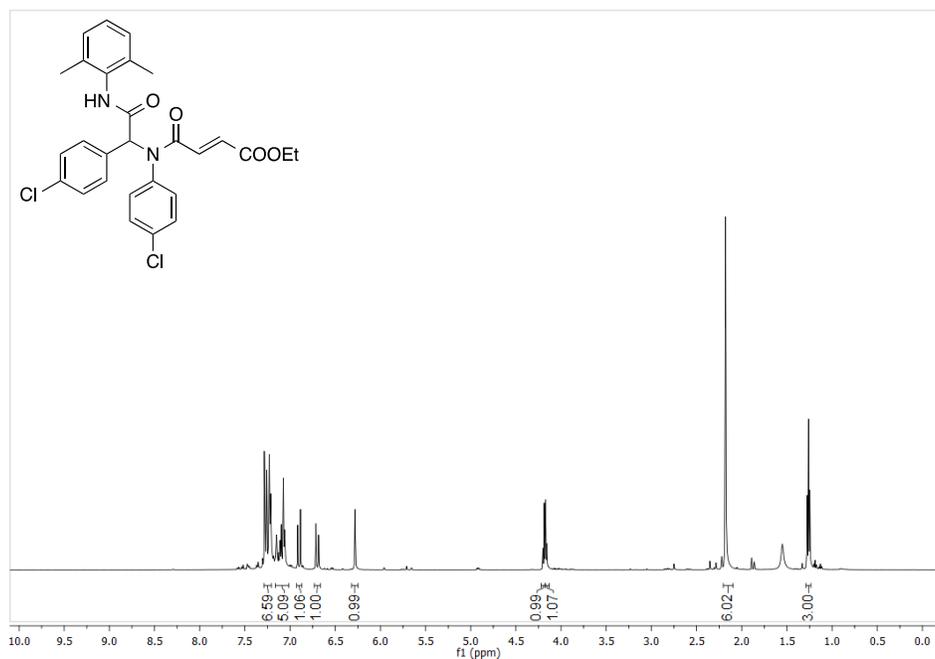


HRMS spectra of the compound **5h**

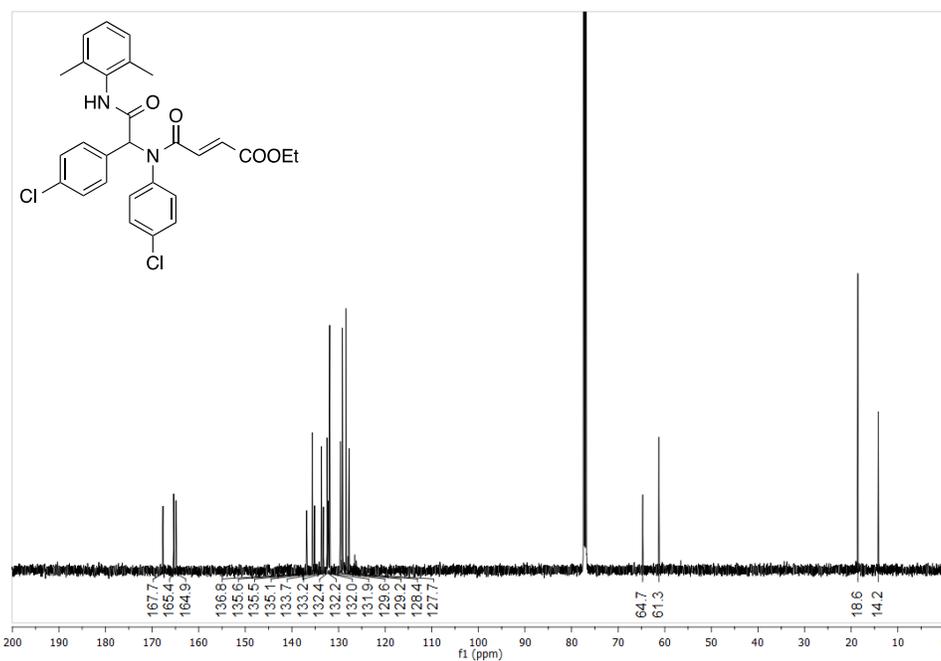
Ethyl (E)-4-((4-chlorophenyl)(1-(4-chlorophenyl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl)amino)-4-oxobut-2-enoate (5i)



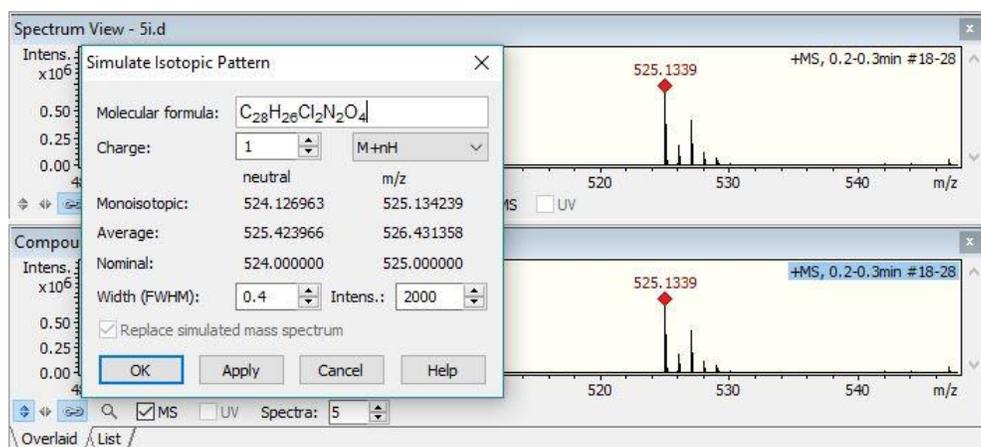
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 47.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 51.0 mg (E)-4-ethoxy-4-oxobut-2-enoic acid (0.35 mmol) were grinded together to afford 151.0 mg (80%) as a light yellow needle shaped crystals; mp 131-133 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.29 – 7.20 (m, 6H), 7.16 – 7.04 (m, 5H), 6.90 (d, J = 15.3 Hz, 1H), 6.70 (d, J = 15.3 Hz, 1H), 6.28 (s, 1H), 4.19 (d, J = 7.1 Hz, 2H), 4.17 (d, J = 7.1 Hz, 2H), 2.18 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 167.7, 165.4, 164.9, 136.8, 135.6, 135.5, 135.1, 133.7, 133.2, 132.4, 132.2, 132.0, 131.9, 129.6, 129.2, 128.4, 127.7, 64.7, 61.3, 18.6, 14.2; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 525.1342, found 525.1339.



$^1\text{H NMR}$ spectra of the compound **5i**

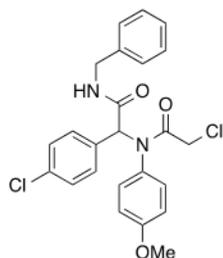


¹³C NMR spectra of the compound 5i

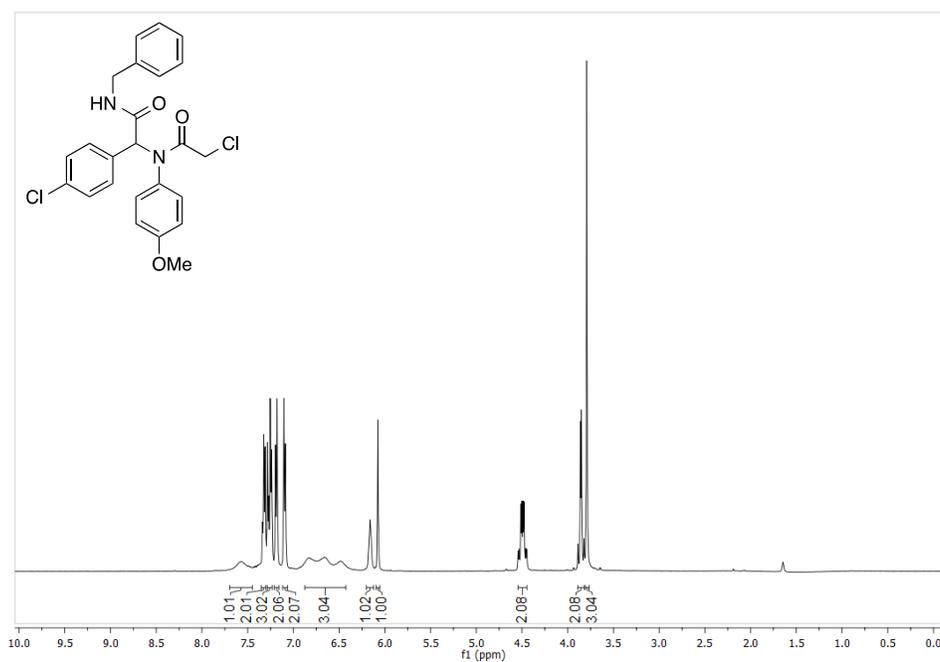


HRMS spectra of the compound 5i

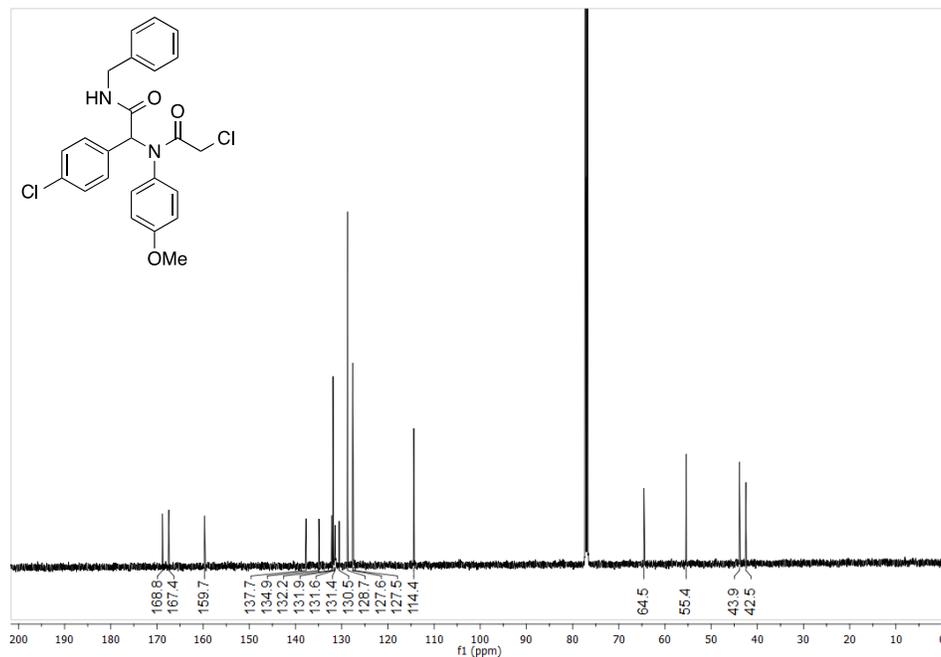
N-Benzyl-2-(2-chloro-N-(4-methoxyphenyl)acetamido)-2-(4-chlorophenyl)acetamide (5j)



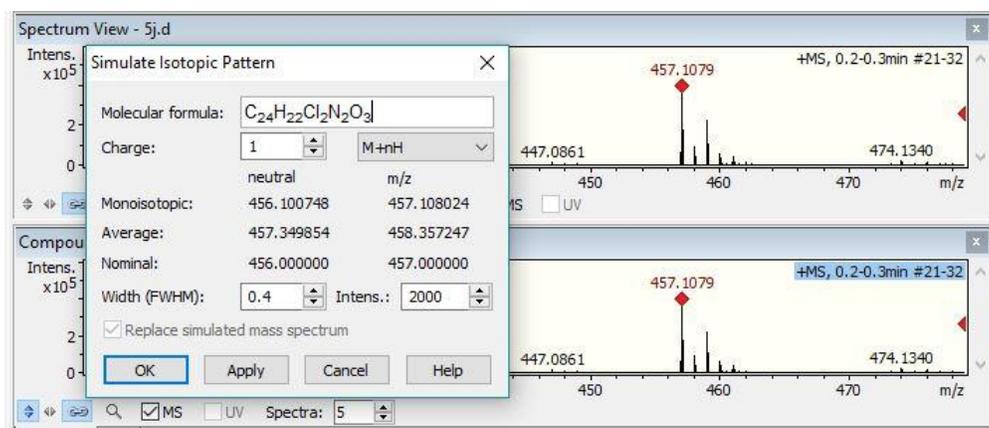
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 44.0 mg 4-methoxyaniline (0.35 mmol), 46.0 mg benzyl isocyanide (0.35 mmol) and 33.0 mg monochloro acetic acid (0.35 mmol) were grinded together to afford 140.0 mg (86%) as a light brown needle shaped crystals; mp 111-112 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.57 (bs, 1H), 7.35 – 7.30 (m, 2H), 7.29 – 7.23 (m, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.87 – 6.42 (m, 3H), 6.16 (sb, 1H), 6.08 (s, 1H), 4.50 (qd, J = 14.8, 5.7 Hz, 2H), 3.90 – 3.81 (m, 2H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 168.8, 167.4, 159.7, 137.7, 134.9, 132.2, 131.9, 131.6, 131.4, 130.5, 128.7, 127.6, 127.5, 114.4, 64.5, 55.4, 43.9, 42.5; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{24}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_3$ $^+$ [$\text{M} + \text{H}$] $^+$ 457.1080, found 457.1079.



$^1\text{H NMR}$ spectra of the compound **5j**

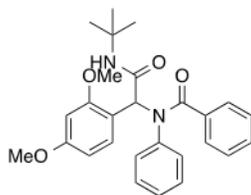


¹³C NMR spectra of the compound 5j

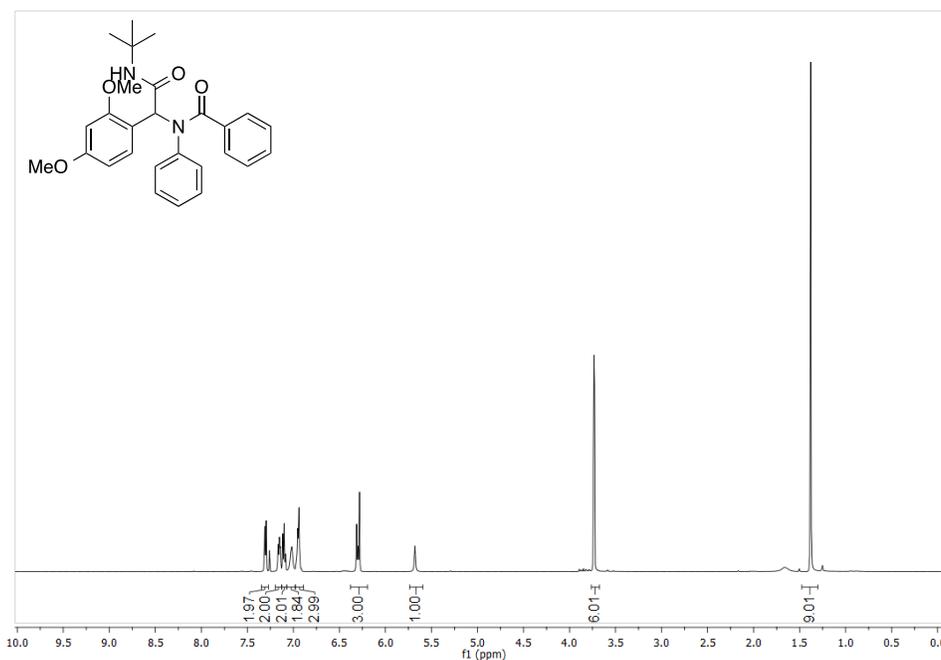


HRMS spectra of the compound 5j

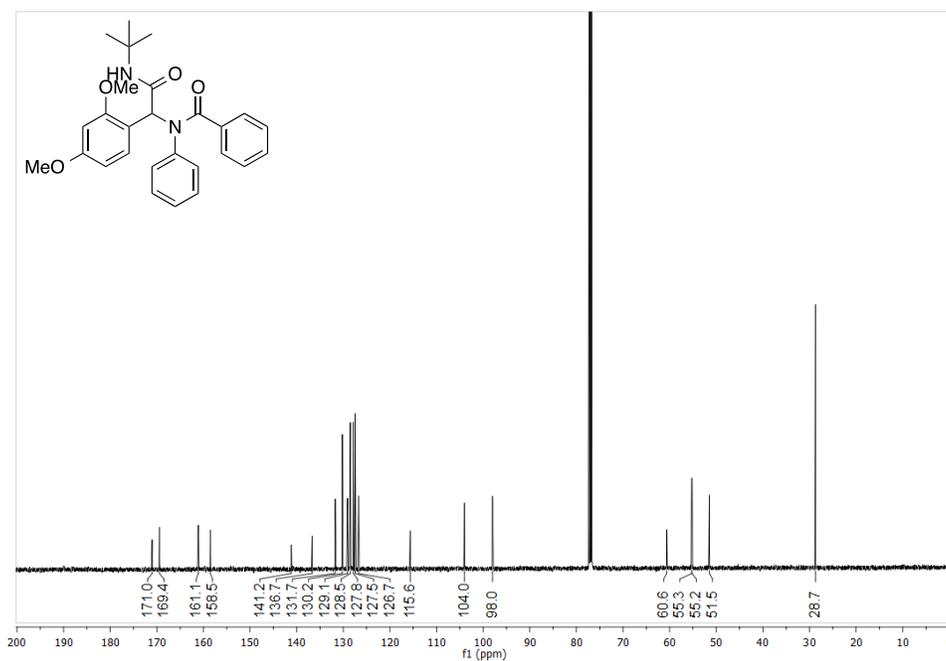
***N*-(2-(*tert*-Butylamino)-1-(2,4-dimethoxyphenyl)-2-oxoethyl)-*N*-phenylbenzamide (5k)**



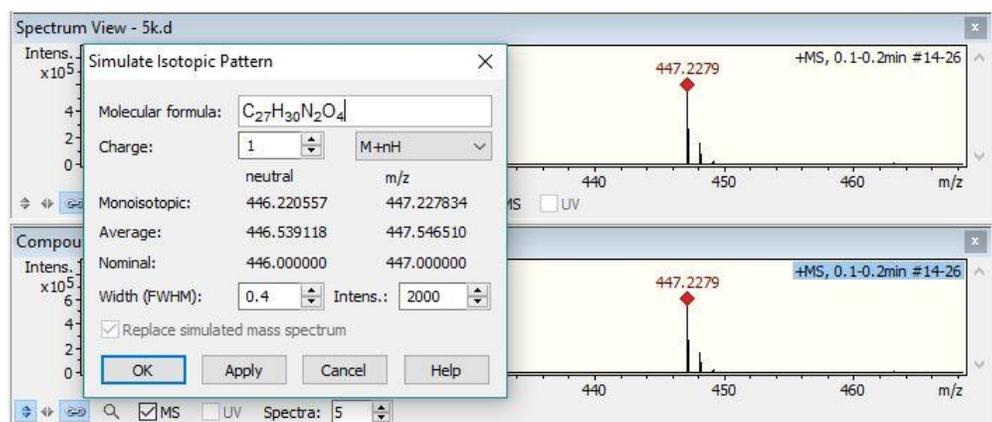
Based on *GP*, 50.0 mg 2,4-dimethoxybenzaldehyde (0.30 mmol), 0.028 mL aniline (0.30 mmol), 0.034 mL *tert*-butyl isocyanide (0.30 mmol) and 36.0 mg benzoic acid (0.30 mmol) were grinded together to afford 101.0 mg (75%) as a white solid; mp 142-143 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.30 (d, J = 7.6 Hz, 2H), 7.20 – 7.12 (m, 2H), 7.12 – 7.07 (m, 2H), 7.07 – 6.98 (m, 2H), 6.98 – 6.89 (m, 3H), 6.38 – 6.20 (m, 3H), 5.68 (s, 1H), 3.73 (s, 6H), 1.38 (s, 9H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 171.0, 169.4, 161.1, 158.5, 141.2, 136.7, 131.7, 130.2, 129.1, 128.5, 127.8, 127.5, 126.7, 115.6, 104.0, 98.0, 60.6, 55.3, 55.2, 51.5, 28.7; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 447.2278, found 447.2279.



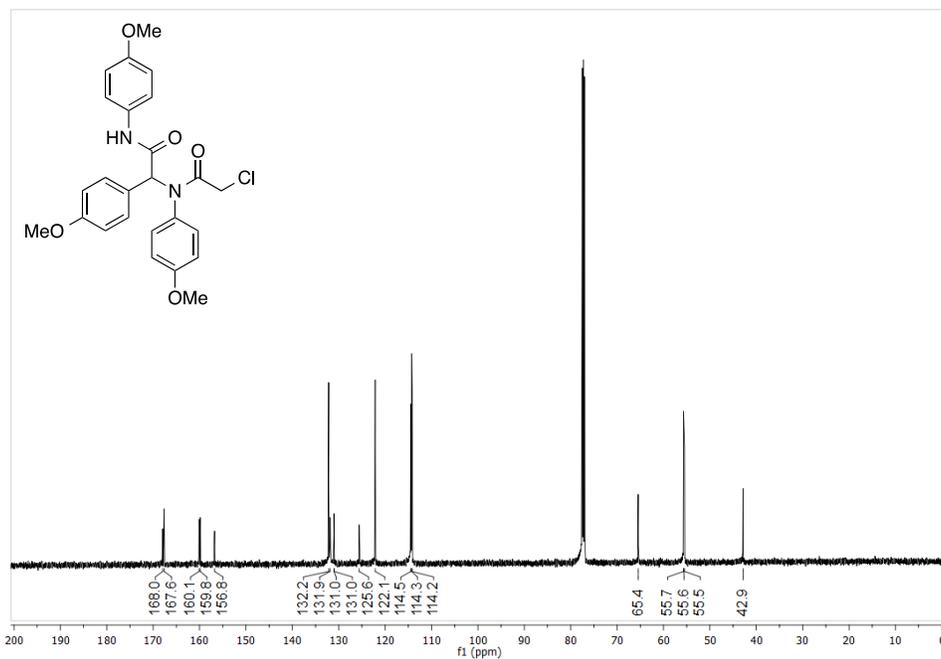
$^1\text{H NMR}$ spectra of the compound **5k**



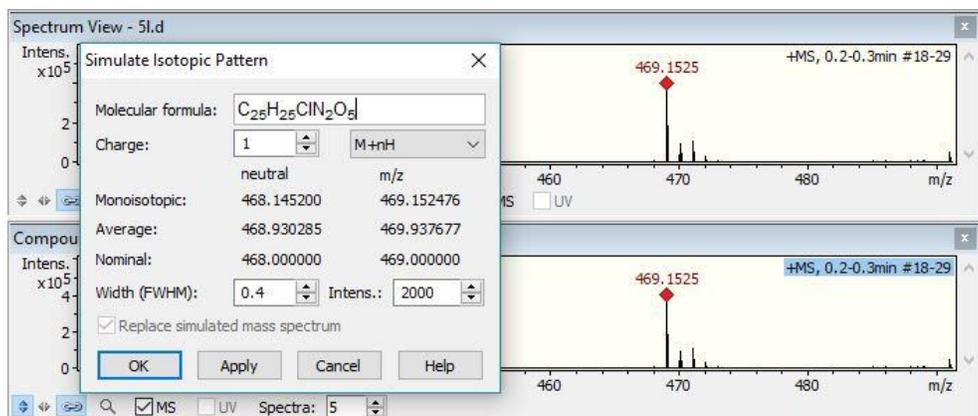
¹³C NMR spectra of the compound **5k**



HRMS spectra of the compound **5k**

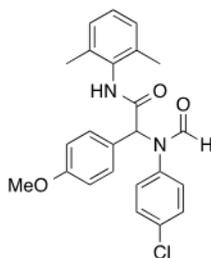


¹³C NMR spectra of the compound 5I

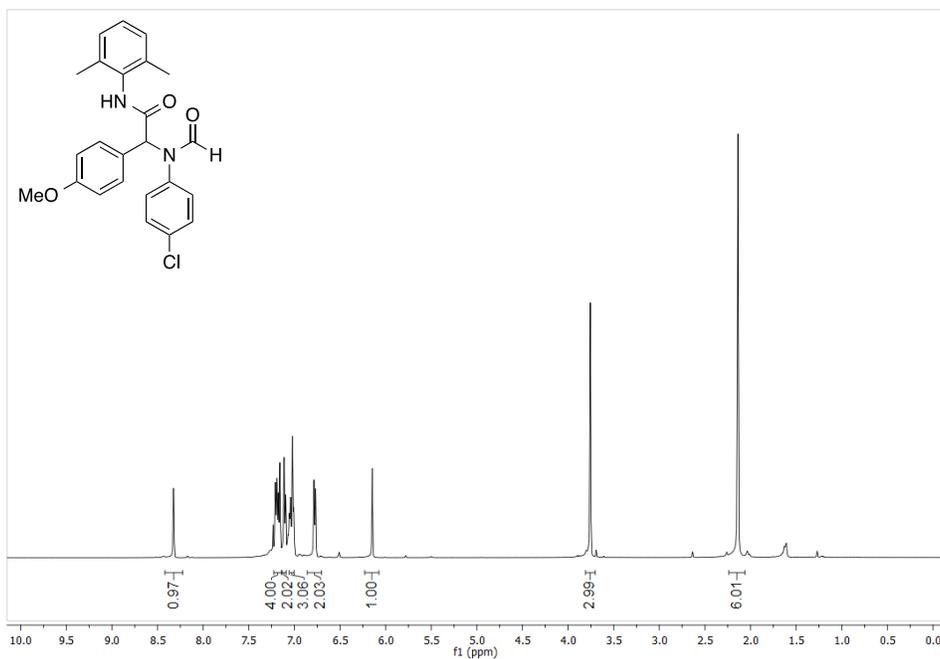


HRMS spectra of the compound 5I

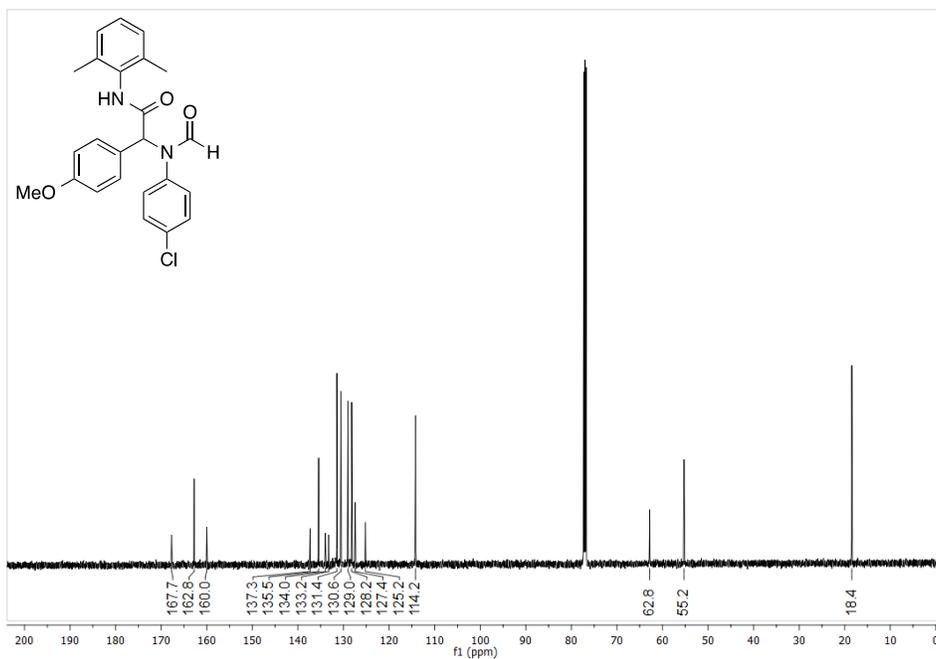
2-(*N*-(4-Chlorophenyl)formamido)-*N*-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetamide (5m)



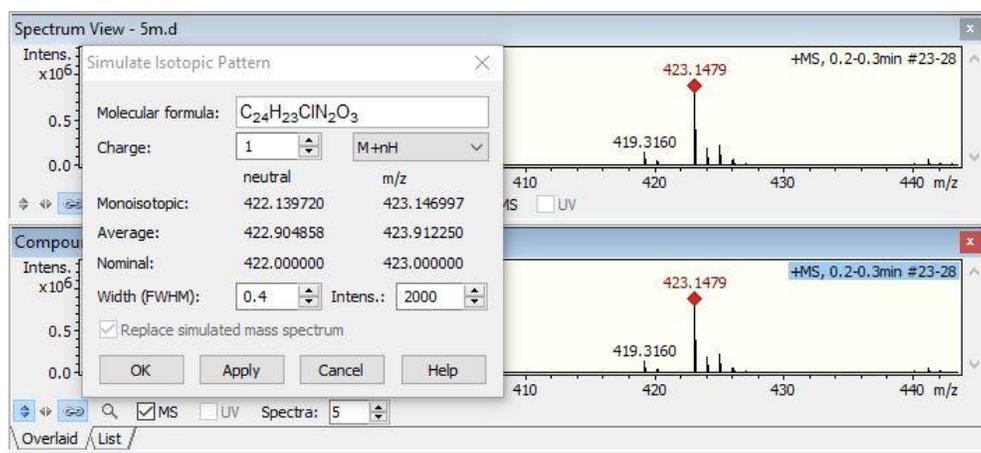
Based on *GP*, 0.044 mL 4-methoxybenzaldehyde (0.36 mmol), 46.0 mg 4-chloroaniline (0.36 mmol), 48.0 mg 2,6-dimethylphenyl isocyanide (0.36 mmol) and 0.014 mL formic acid (0.36 mmol) were grinded together to afford 130.0 mg (84%) as a light white crystals; mp 110-111 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.33 (s, 1H), 7.23 – 7.14 (m, 4H), 7.10 (d, J = 8.2 Hz, 2H), 7.06 – 7.00 (m, 3H), 6.78 (d, J = 8.2 Hz, 2H), 6.20 (s, 1H), 3.81 (s, 3H), 2.19 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 167.7, 162.8, 160.0, 137.3, 135.5, 134.0, 133.2, 131.4, 130.6, 129.0, 128.2, 127.4, 125.2, 114.2, 62.8, 55.2, 18.4; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_3$ [M + H]⁺ 423.1470, found 423.1479.



$^1\text{H NMR}$ spectra of the compound **5m**

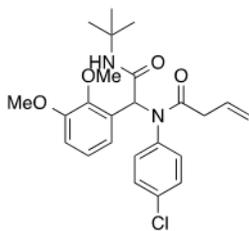


¹³C NMR spectra of the compound 5m

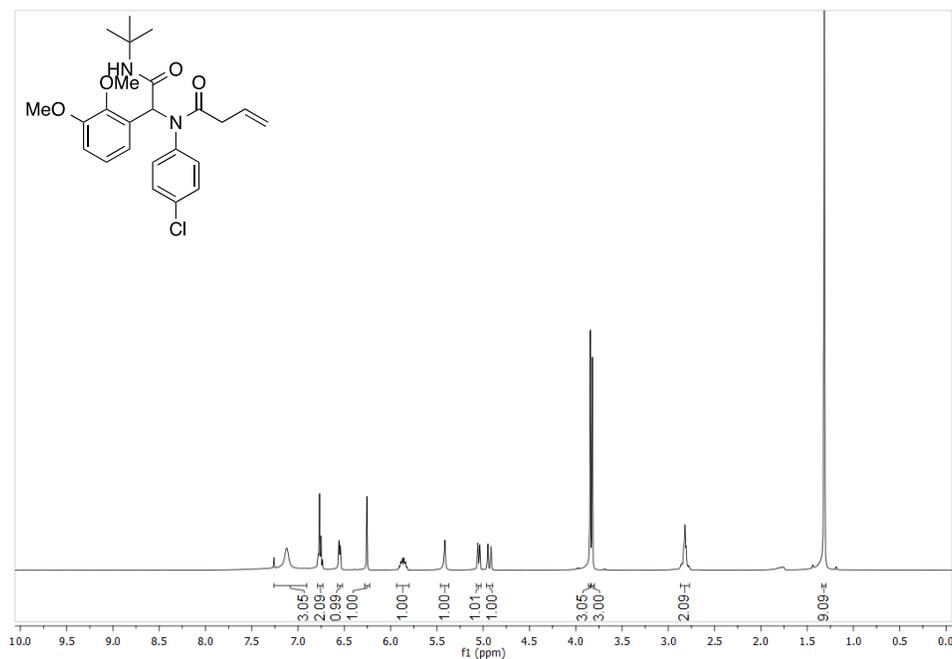


HRMS spectra of the compound 5m

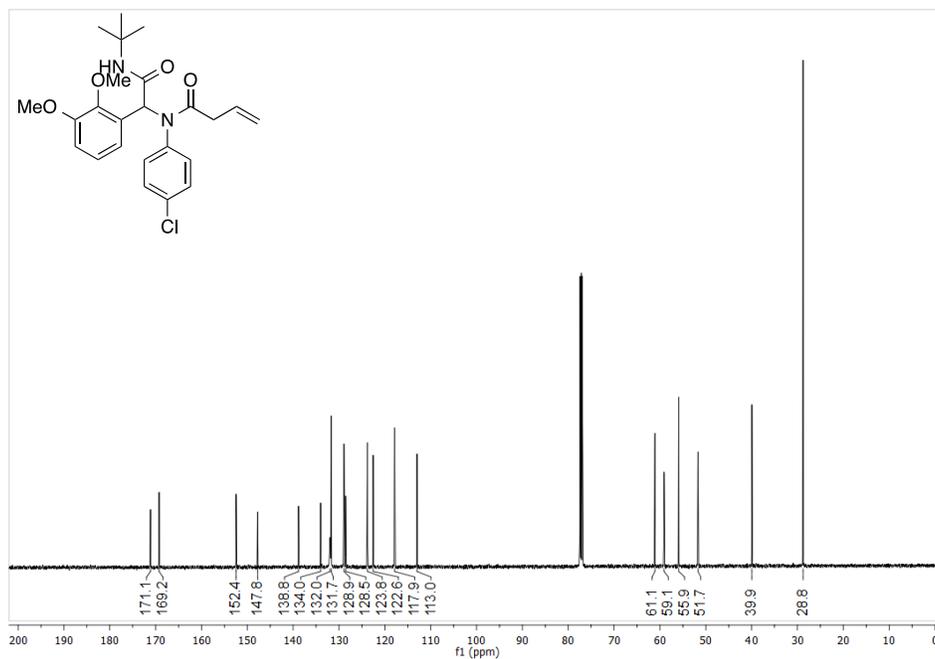
***N*-(2-(*tert*-Butylamino)-1-(2,3-dimethoxyphenyl)-2-oxoethyl)-*N*-(4-chlorophenyl)but-3-enamide (5n)**



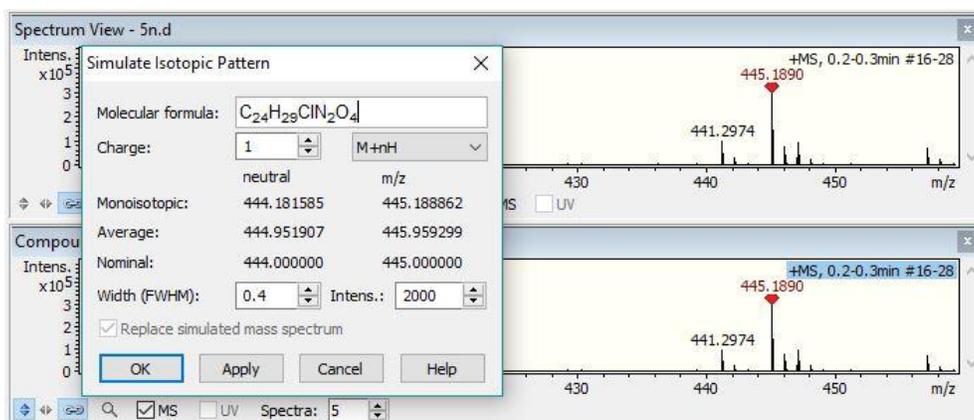
Based on *GP*, 50.0 mg 2,3-dimethoxybenzaldehyde (0.30 mmol), 38.0 mg 4-chloroaniline (0.30 mmol), 0.034 mL *tert*-butyl isocyanide (0.30 mmol) and 25.0 mg 3-butenic acid (0.30 mmol) were grinded together to afford 107.0 mg (80%) as a light white crystals; mp 105-107 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.25 – 6.91 (m, 3H), 6.79 – 6.71 (m, 2H), 6.55 (d, J = 7.0 Hz, 1H), 6.25 (s, 1H), 5.93 – 5.80 (m, 1H), 5.41 (s, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.93 (d, J = 17.2 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.88 – 2.76 (m, 2H), 1.31 (s, 9H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 171.1, 169.2, 152.4, 147.8, 138.8, 134.0, 132.0, 131.7, 128.9, 128.5, 123.8, 122.6, 117.9, 113.0, 61.1, 59.1, 55.9, 51.7, 39.9, 28.8; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{24}\text{H}_{30}\text{ClN}_2\text{O}_4$ [$\text{M} + \text{H}$]⁺ 445.1889, found 445.1890.



$^1\text{H NMR}$ spectra of the compound **5n**

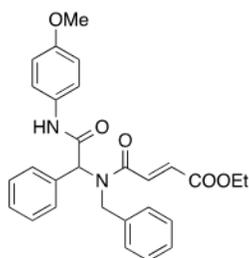


¹³C NMR spectra of the compound **5n**

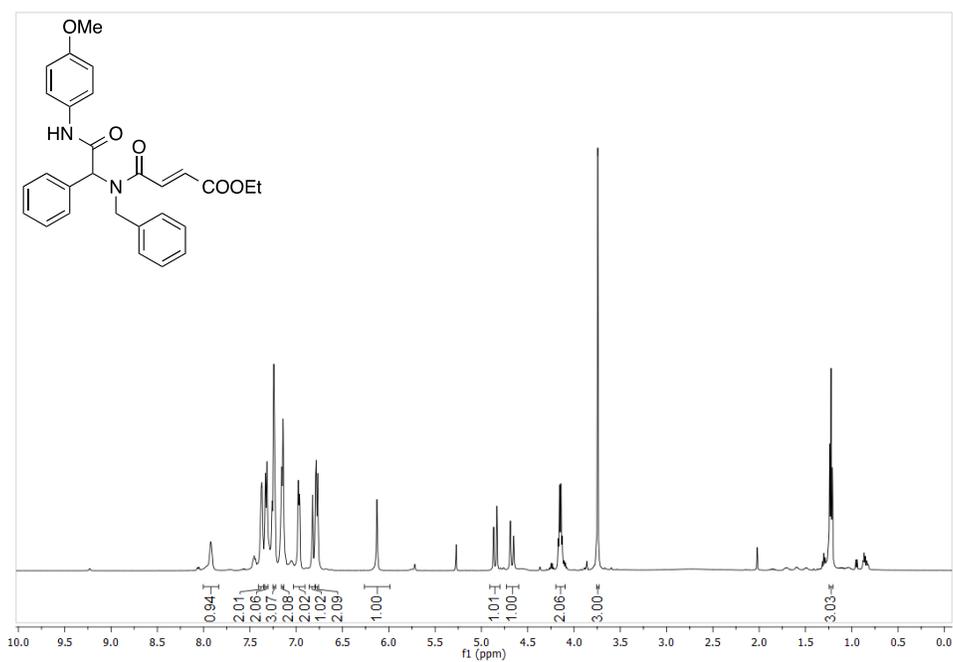


HRMS spectra of the compound **5n**

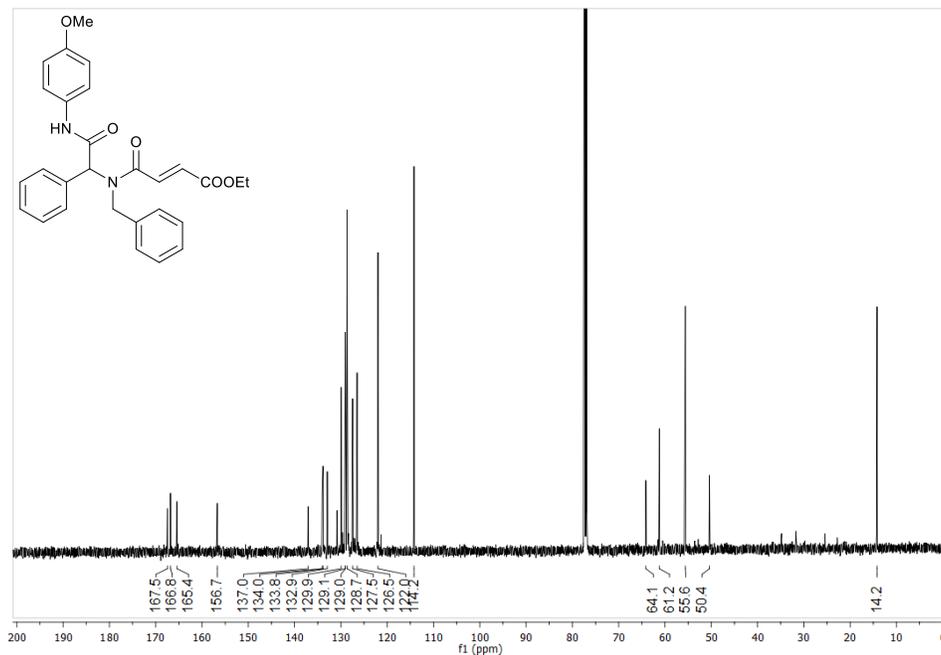
Ethyl (*E*)-4-(benzyl(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)amino)-4-oxobut-2-enoate (5o**)**



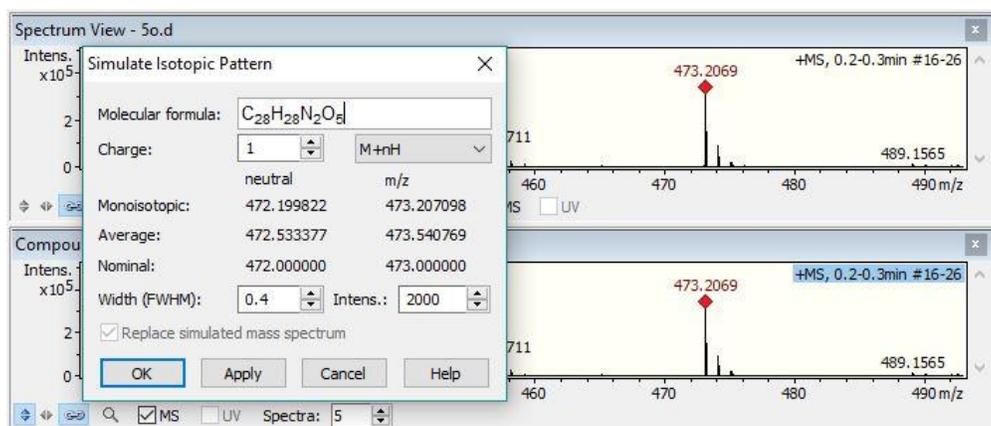
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 0.051 mL benzylamine (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 67.0 mg (*E*)-4-ethoxy-4-oxobut-2-enoic acid (0.47 mmol) were grinded together to afford 113.0 mg (51%) as a light yellow solid; mp 121-122 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.92 (bs, 1H), 7.45 – 7.35 (m, 3H), 7.32 (d, J = 8.1 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.15 (d, J = 6.9 Hz, 2H), 6.97 (d, J = 6.6 Hz, 2H), 6.83 – 6.75 (m, 3H), 6.13 (s, 1H), 4.85 (d, J = 17.5 Hz, 1H), 4.67 (d, J = 17.6 Hz, 1H), 4.15 (q, J = 6.9 Hz, 2H), 3.74 (s, 3H), 1.22 (t, J = 7.1 Hz, 4H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 167.5, 166.8, 165.4, 156.7, 137.0, 134.0, 133.8, 132.9, 130.8, 129.9, 129.1, 129.0, 128.7, 127.5, 126.5, 122.0, 114.2, 64.1, 61.2, 55.6, 50.4, 14.2; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 473.2071, found 473.2069.



$^1\text{H NMR}$ spectra of the compound **5o**

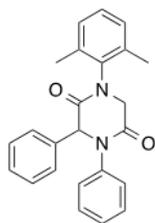


^{13}C NMR spectra of the compound **5o**

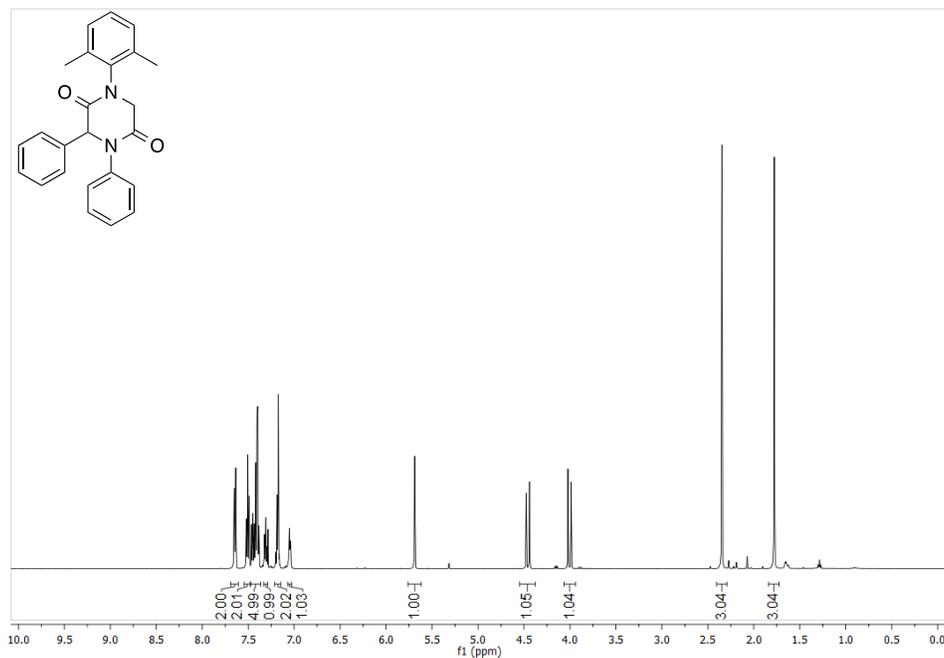


HRMS spectra of the compound **5o**

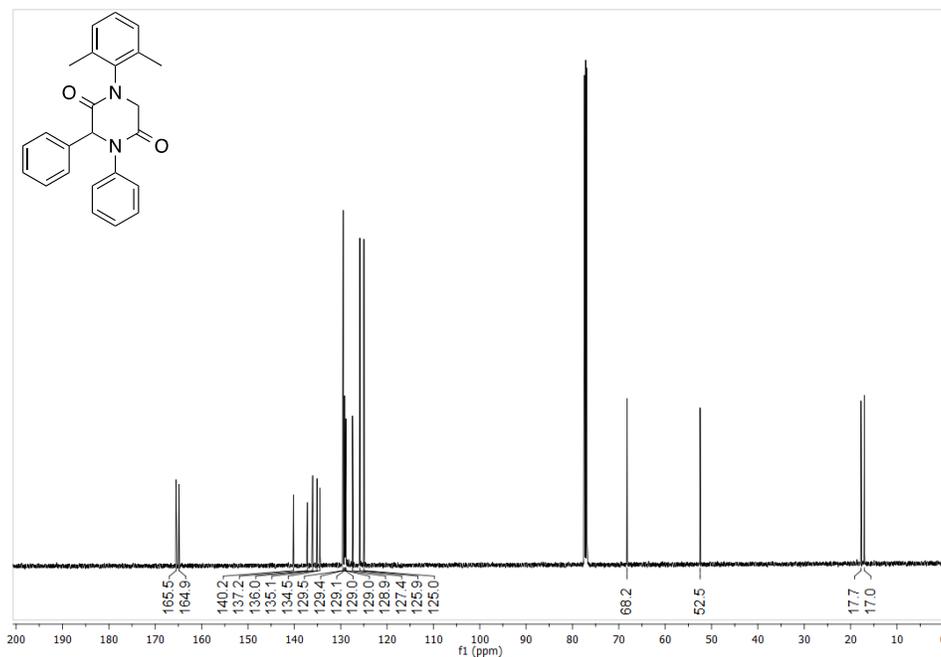
1-(2,6-Dimethylphenyl)-3,4-diphenylpiperazine-2,5-dione (6a)



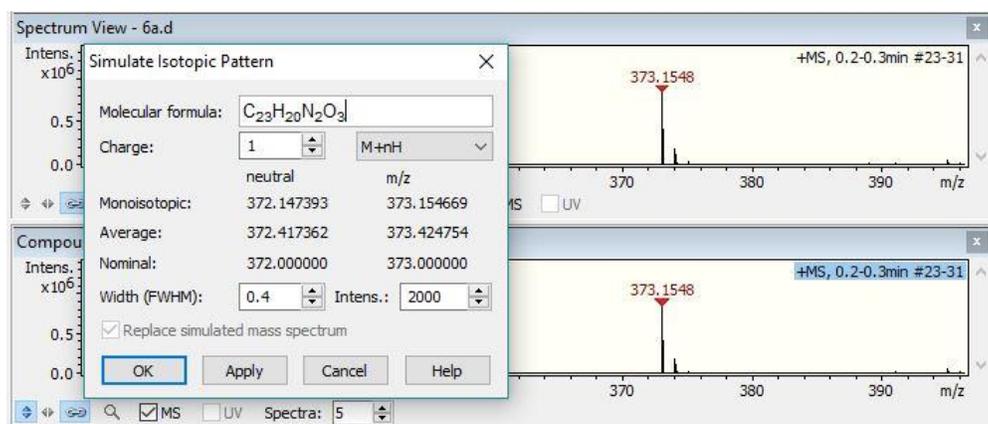
Based on *GP*, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 230.0 mg of Cs_2CO_3 (0.70 mmol) was added with 0.2 μL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na_2SO_4 . The obtained crude product was purified via column using EtOAc: hexane (30:70) mixture to afford 116.0 mg (66%) of pure product as white solid; mp 145-147 $^\circ\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.64 (d, J = 7.8 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.37 (m, 5H), 7.33 – 7.29 (m, 1H), 7.21 – 7.15 (m, 2H), 7.07 – 7.03 (m, 1H), 5.69 (s, 1H), 4.46 (d, J = 17.4 Hz, 1H), 4.00 (d, J = 17.4 Hz, 1H), 2.35 (s, 3H), 1.78 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 165.5, 164.9, 140.2, 137.2, 136.0, 135.1, 134.5, 129.5, 129.4, 129.1, 129.0(2), 128.9, 127.4, 125.9, 125.0, 68.2, 52.5, 17.7, 17.0; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_3$ $^+$ [M + H] $^+$ 373.1547, found 373.1548.



$^1\text{H NMR}$ spectra of the compound **6a**

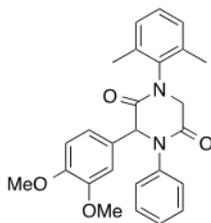


¹³C NMR spectra of the compound 6a

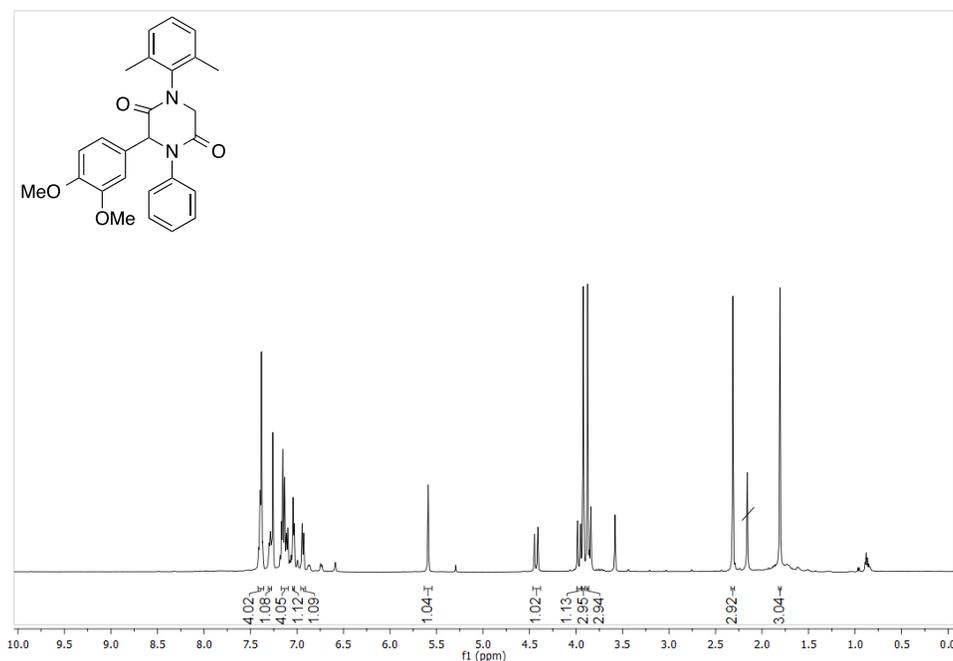


HRMS spectra of the compound 6a

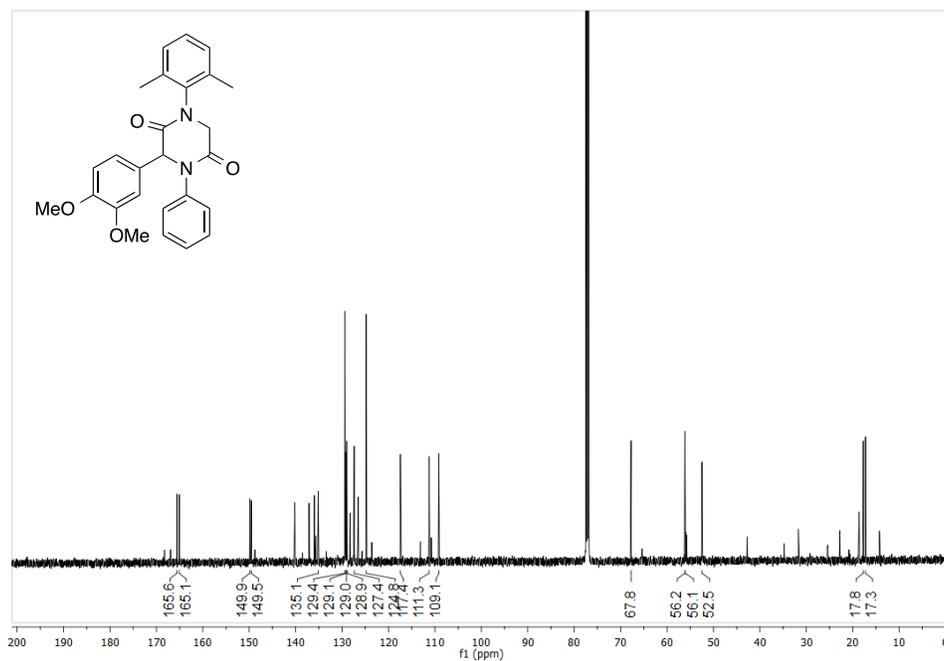
3-(3,4-Dimethoxyphenyl)-1-(2,6-dimethylphenyl)-4-phenylpiperazine-2,5-dione (6b)



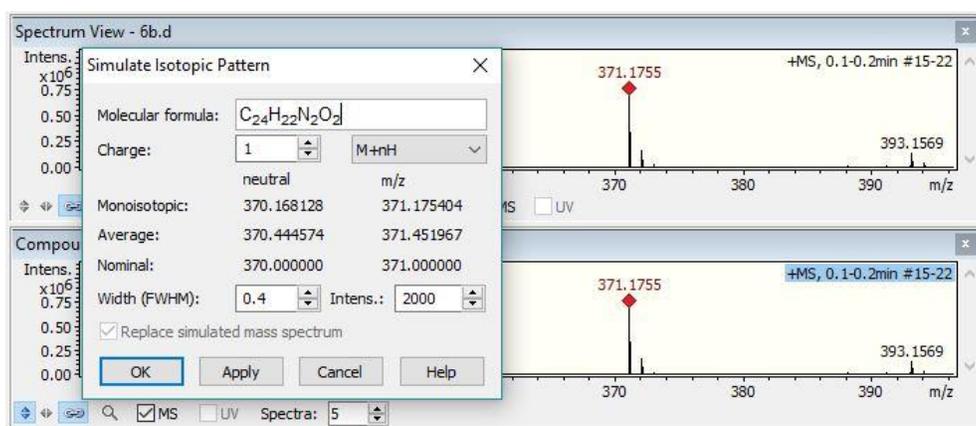
Based on *GP*, 0.048 mL 3,4-dimethoxybenzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg 4-chloro acetic acid (0.47 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 230.0 mg of Cs_2CO_3 (0.70) was added with 0.2 μL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na_2SO_4 . The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 116.0 mg (60%) of pure product as white solid; mp 139-140 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.42 – 7.36 (m, 4H), 7.31 – 7.27 (m, 1H), 7.18 – 7.09 (m, 4H), 7.04 (d, J = 6.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.59 (s, 1H), 4.43 (d, J = 17.4 Hz, 1H), 3.97 (d, J = 17.2 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 165.6, 165.1, 149.9, 149.5, 140.2, 137.1, 136.0, 135.1, 129.4, 129.1, 129.0, 128.9, 128.3, 127.4, 126.5, 124.8, 117.4, 111.3, 109.1, 67.8, 56.2, 56.1, 52.5, 17.8, 17.3; **HRMS (ESI⁺)**: m/z calcd. for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_2^+$ [$\text{M} + \text{H}$]⁺ 371.1754, found 371.1755.



$^1\text{H NMR}$ spectra of the compound **6b**

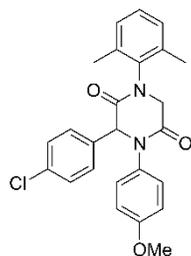


¹³C NMR spectra of the compound **6b**

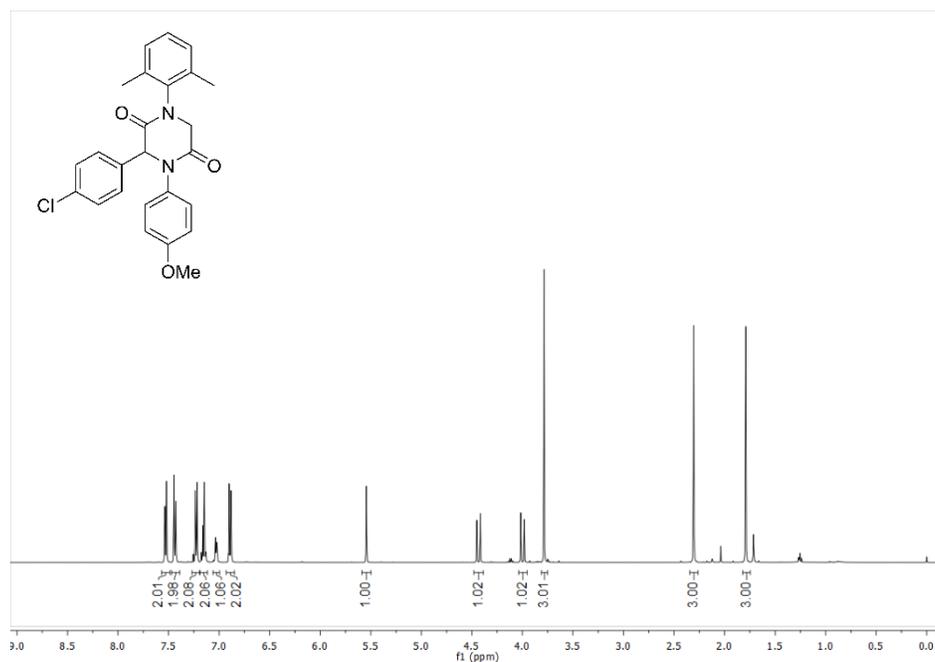


HRMS spectra of the compound **6b**

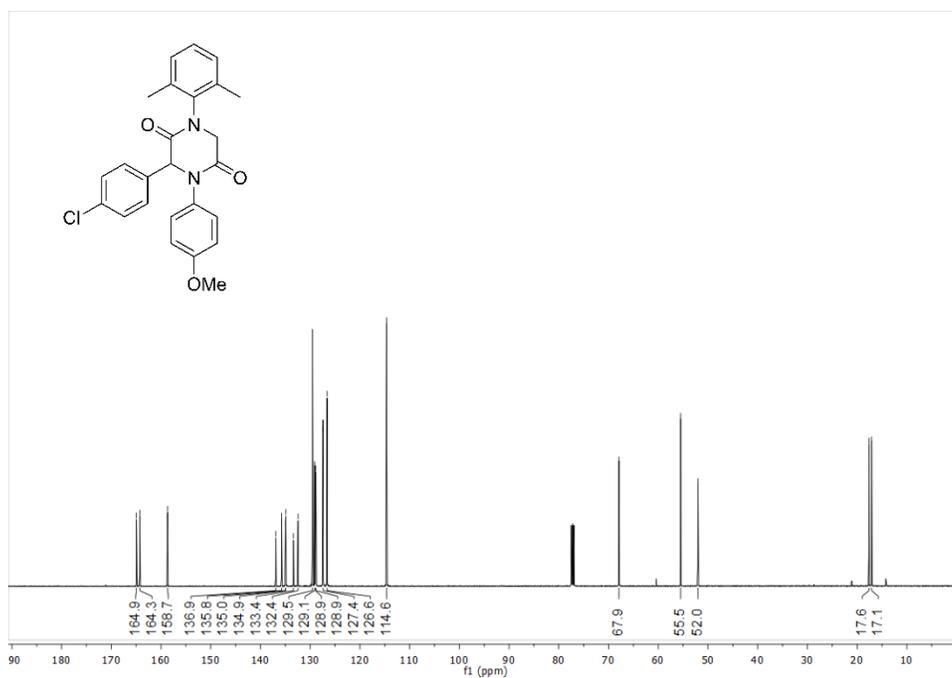
3-(4-chlorophenyl)-1-(2,6-dimethylphenyl)-4-(4-methoxyphenyl)piperazine-2,5-dione (6c)



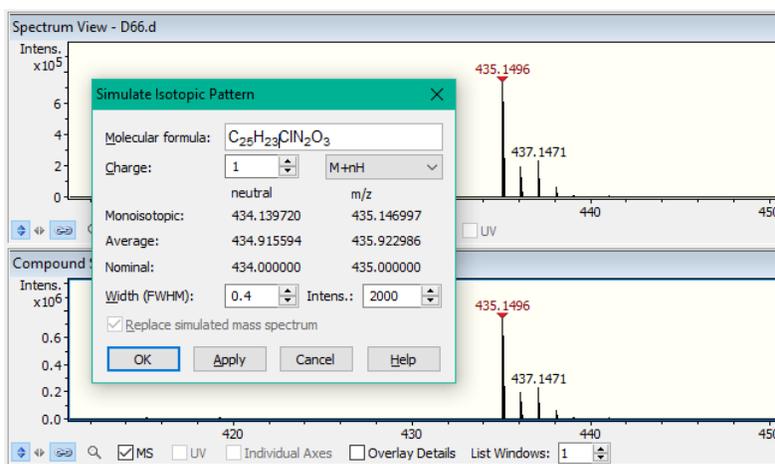
Based on GP, 57.0 mg 4-chlorobenzaldehyde (0.406 mmol), 50.0 mg 4-methoxyaniline (0.406 mmol), 53.0 mg 2,6-dimethylphenyl isocyanide (0.406 mmol) and 38.0 mg monochloroacetic acid (0.406 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 198.0 mg of Cs_2CO_3 (0.608) was added with 0.2 μL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na_2SO_4 . The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 103.0 mg (58%) of pure product as white solid; mp 144-145 $^\circ\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.53 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.18 – 7.10 (m, 2H), 7.05 – 6.99 (m, 1H), 6.88 (d, J = 8.9 Hz, 1H), 5.54 (s, 1H), 4.44 (d, J = 17.5 Hz, 1H), 3.99 (d, J = 17.5 Hz, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 1.79 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 164.9, 164.3, 158.7, 136.9, 135.8, 135.0, 134.9, 133.4, 132.4, 129.5, 129.1, 128.9, 128.9, 127.4, 126.6, 114.6, 67.9, 55.5, 52.0, 17.6, 17.1.; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 435.1470, found 435.1496.



$^1\text{H NMR}$ spectra of the compound 6c

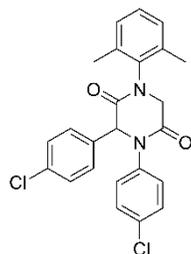


¹³C NMR spectra of the compound **6c**

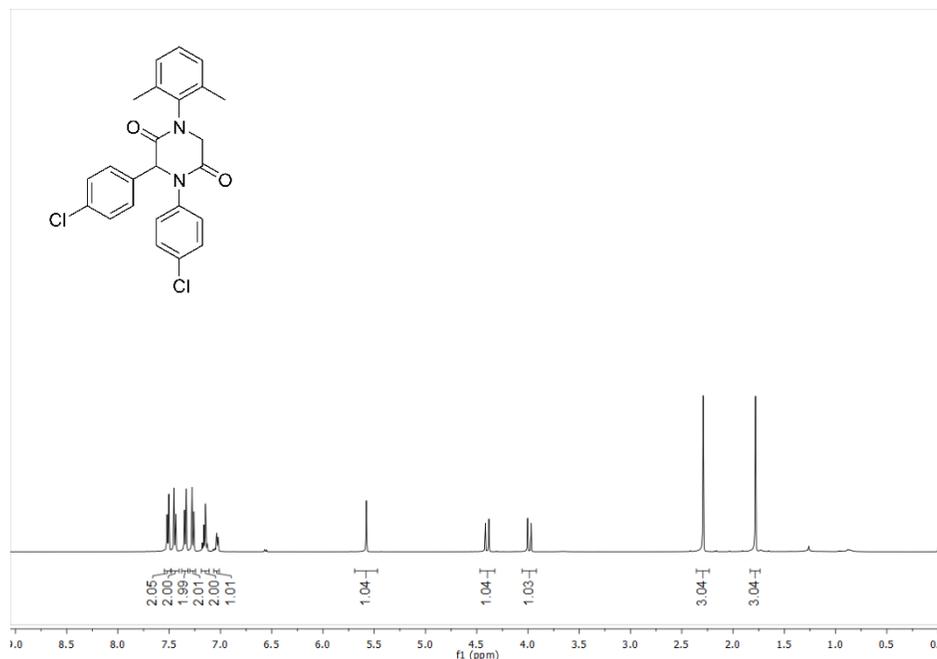


HRMS spectra of the compound **6c**

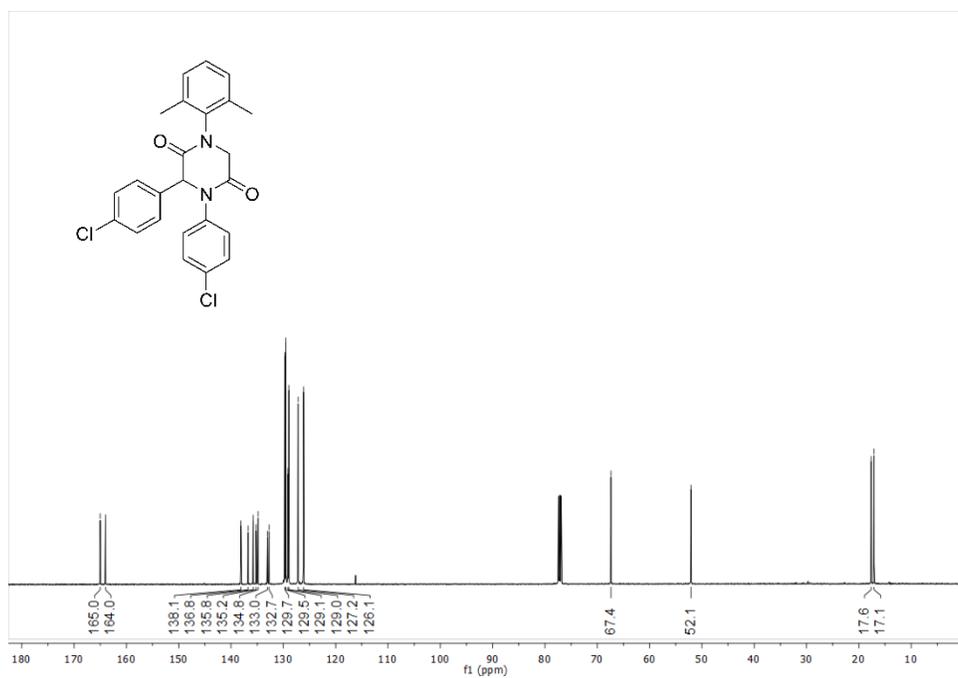
3,4-bis(4-chlorophenyl)-1-(2,6-dimethylphenyl)piperazine-2,5-dione (6d)



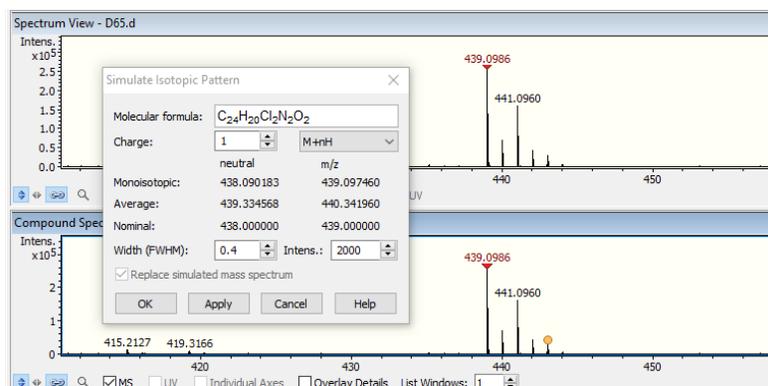
Based on *GP*, 50.0 mg 55.0 mg 4-chloroaniline (0.392 mmol), 4-chlorobenzaldehyde (0.392 mmol), 51.0 mg 2,6-dimethylphenyl isocyanide (0.392 mmol) and 37.0 mg monochloroacetic acid (0.392 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 191.0 mg of Cs_2CO_3 (0.388) was added with 0.2 μL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na_2SO_4 . The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 97.0 mg (56%) of pure product as white solid; mp 150-151 $^\circ\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.51 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 – 7.12 (m, 2H), 7.06 – 7.01 (m, 1H), 5.58 (s, 1H), 4.40 (d, J = 17.6 Hz, 1H), 3.99 (d, J = 17.6 Hz, 1H), 2.29 (s, 3H), 1.78 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 165.0, 164.0, 138.1, 136.8, 135.8, 135.2, 134.8, 133.0, 132.7, 129.7, 129.5, 129.1, 129.0, 127.2, 126.1, 67.4, 52.1, 17.65, 17.1; **HRMS (ESI $^+$)**: m/z calcd. for $\text{C}_{24}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_2$ $^+$ [M + H] $^+$ 439.0975, found 439.0986.



$^1\text{H NMR}$ spectra of the compound **6d**

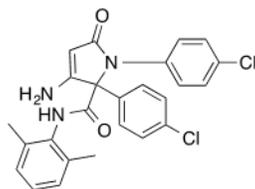


¹³C NMR spectra of the compound 6d

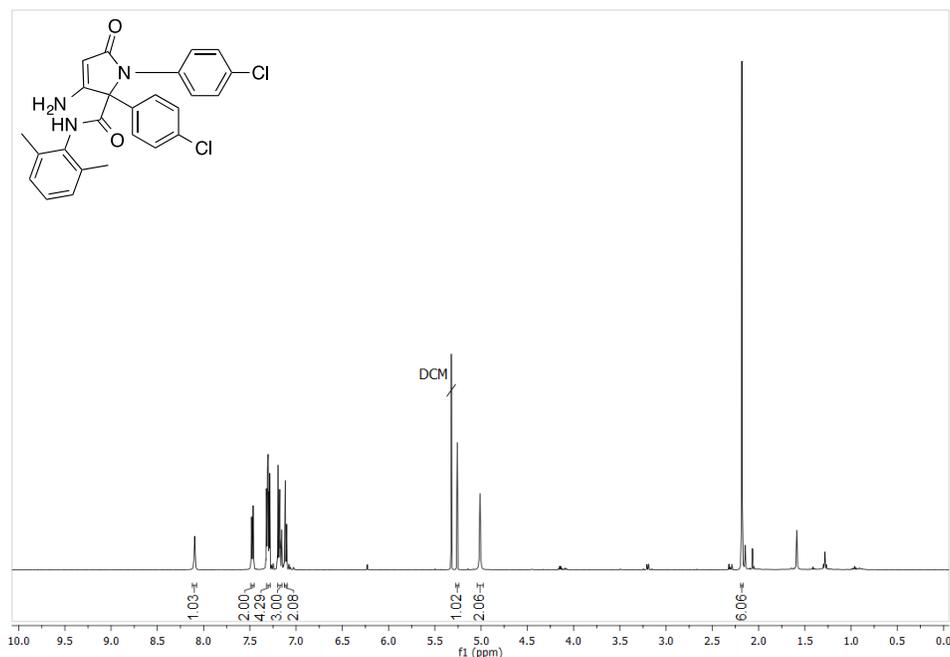


HRMS spectra of the compound 6d

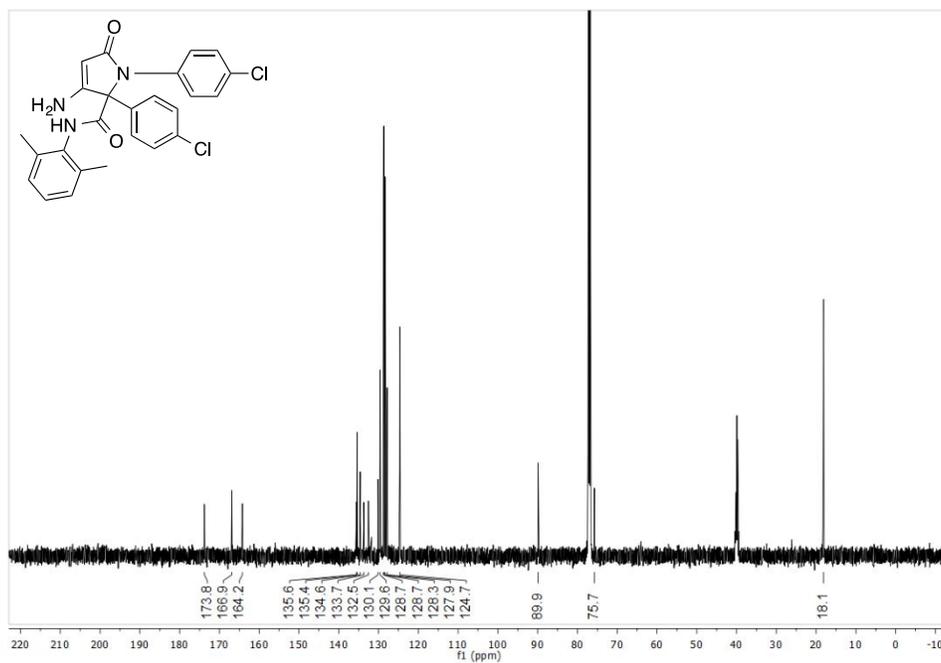
(S)-3-Amino-1,2-bis(4-chlorophenyl)-N-(2,6-dimethylphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7a)



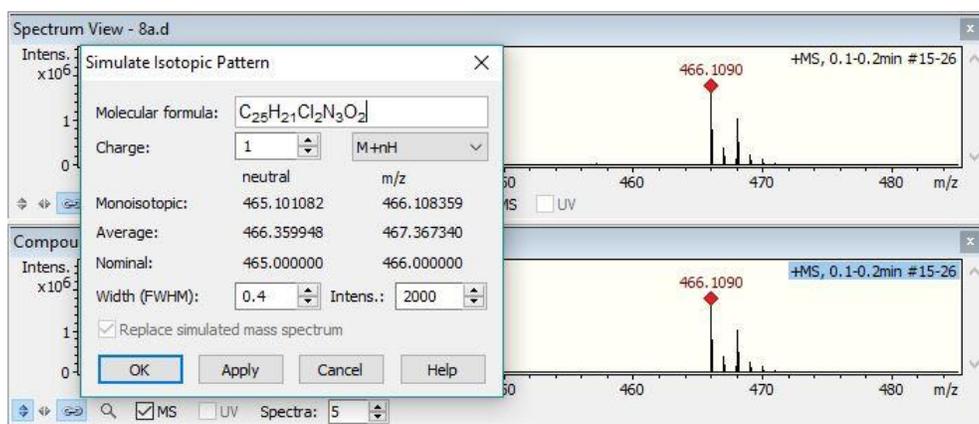
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 μ L EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 137.0 mg (64 %) of pure product as white solid; mp 159-160 °C; ¹H NMR (500 MHz, CDCl₃) δ = 8.10 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.32 – 7.28 (m, 4H), 7.20 – 7.16 (m, 3H), 7.11 (d, *J* = 7.5 Hz, 2H), 5.26 (s, 1H), 5.01 (s, 2H), 2.18 (s, 6H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ = 173.8, 166.9, 164.2, 135.6, 135.4, 134.6, 133.7, 132.5, 130.1, 129.6, 128.7(2), 128.3, 127.9, 124.7, 89.9, 75.7, 18.1; HRMS (ESI⁺): *m/z* calcd. for C₂₅H₂₂Cl₂N₃O₂⁺ [M + H]⁺ 466.1083, found 466.1090.



¹H NMR spectra of the compound 7a

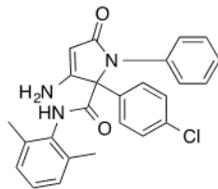


^{13}C NMR spectra of the compound 7a

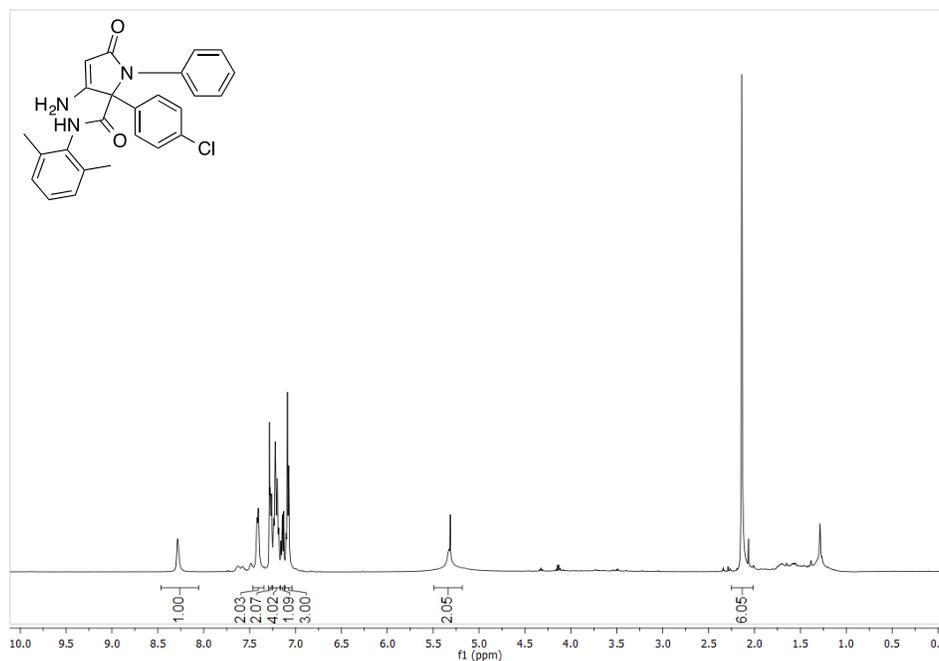


HRMS spectra of the compound 7a

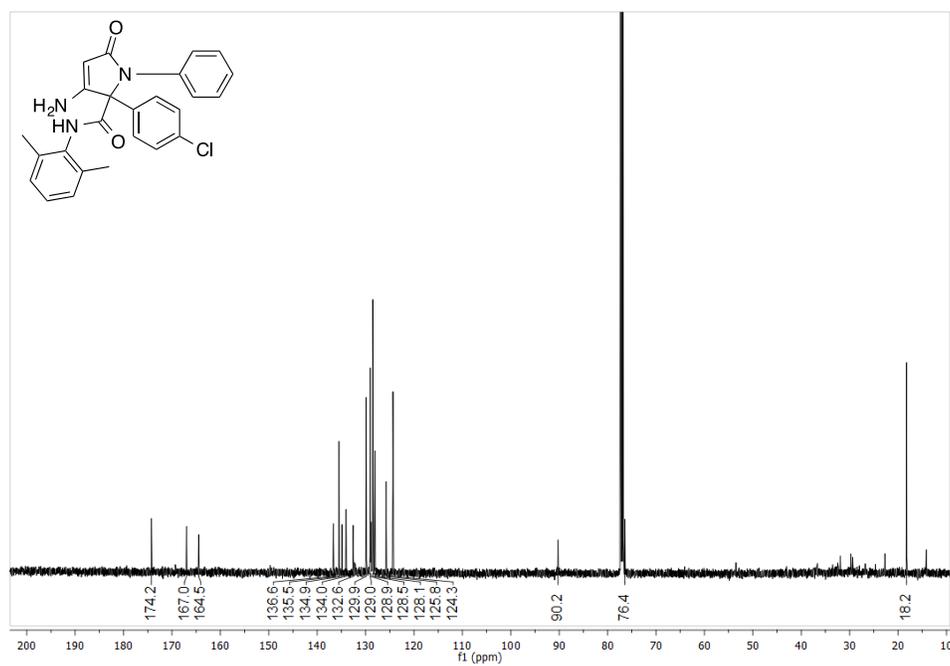
3-Amino-2-(4-chlorophenyl)-N-(2,6-dimethylphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7b)



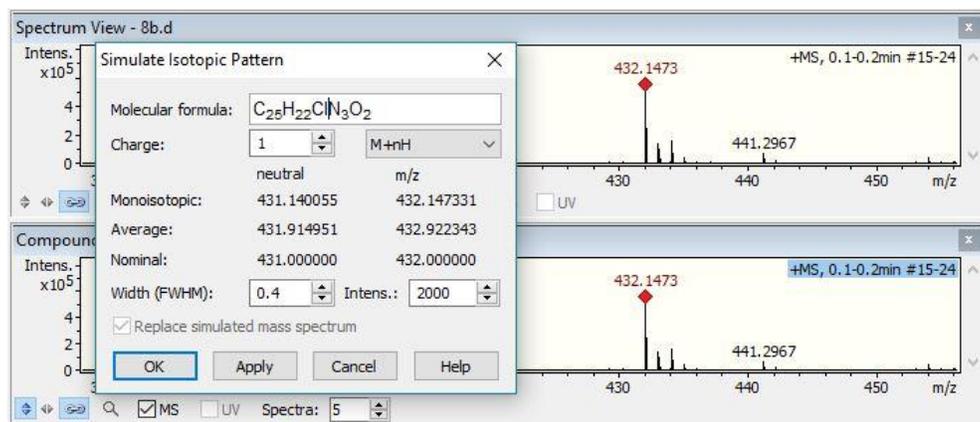
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 μ L EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 127.0 mg (51%) of pure product as white solid; mp 151-152 °C; **¹H NMR** (500 MHz, DMSO-*d*₆) δ = 8.29 (bs, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.25 – 7.17 (m, 4H), 7.17 – 7.12 (m, 1H), 7.11 – 7.04 (m, 3H), 5.23 (s, 1H), 2.54 (bs, 2H), 2.14 (s, 6H); **¹³C NMR** (126 MHz, CDCl₃ + DMSO-*d*₆) δ = 174.2, 167.0, 164.5, 136.6, 135.5, 134.9, 134.0, 132.6, 129.9(2), 128.9, 128.5, 128.1, 125.8, 124.3, 90.2, 76.4, 18.2; **HRMS (ESI⁺)**: *m/z* calcd. for C₂₅H₂₃ClN₃O₂⁺ [M + H]⁺ 432.1473, found 432.1473.



¹H NMR spectra of the compound 7b

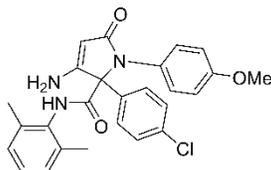


¹³C NMR spectra of the compound **7b**

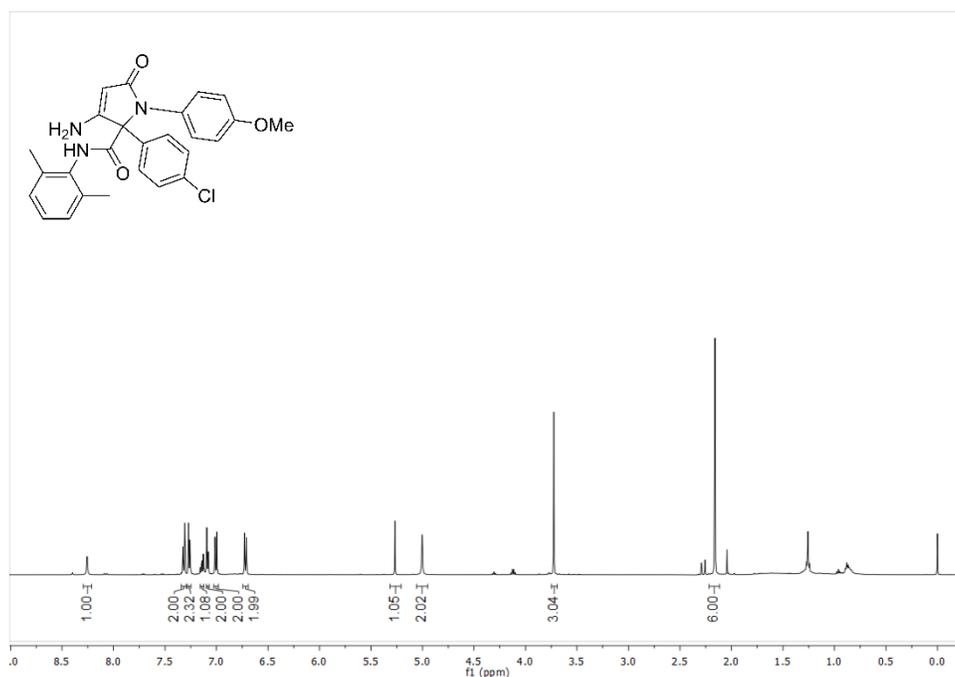


HRMS spectra of the compound **7b**

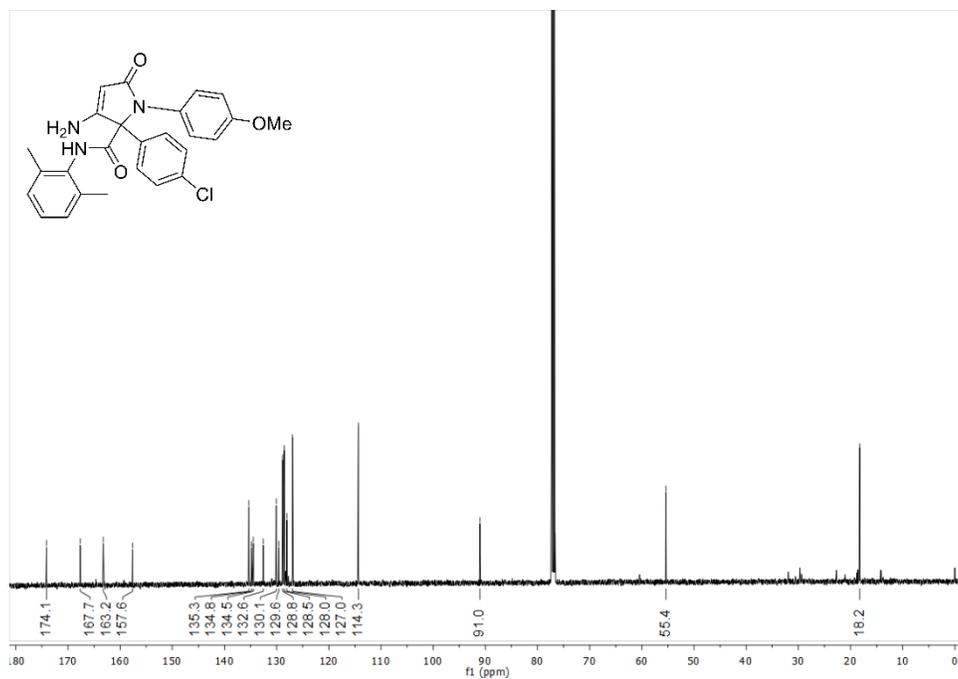
3-amino-2-(4-chlorophenyl)-N-(2,6-dimethylphenyl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7c)



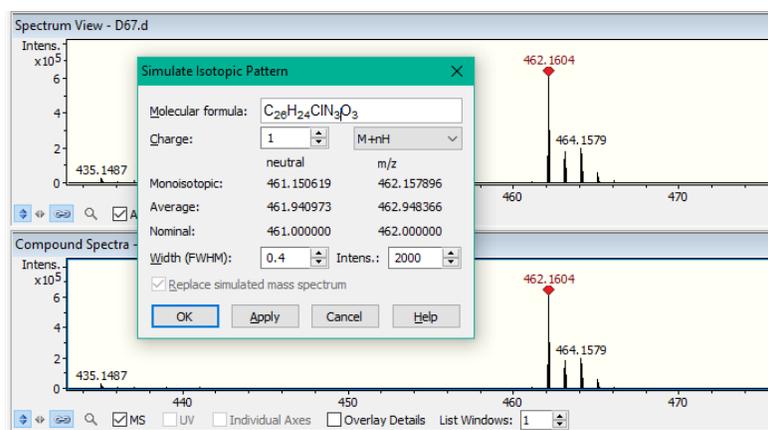
Based on *GP*, 50.0 mg 4-chlorobenzaldehyde (0.36 mmol), 43.0 mg aniline (0.36 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.36 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 μ L EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 91.0 mg (55%) of pure product as white solid; mp 160-161 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 8.26 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.16 – 7.12 (m, 1H), 7.10 – 7.07 (m, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 5.27 (s, 1H), 5.00 (s, 2H), 3.72 (s, 3H), 2.16 (s, 6H).; **¹³C NMR** (126 MHz, CDCl₃) δ = 174.1, 167.7, 163.2, 157.6, 135.3, 134.8, 134.5, 132.6, 130.1, 129.6, 128.8, 128.5, 128.0, 127.0, 114.3, 91.0, 55.4, 18.2; **HRMS (ESI⁺)**: *m/z* calcd. for C₂₆H₂₅ClN₃O₃⁺ [M + H]⁺ 462.1579, found 462.1607.



¹H NMR spectra of the compound 7c

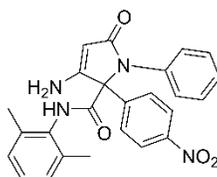


¹³C NMR spectra of the compound 7c

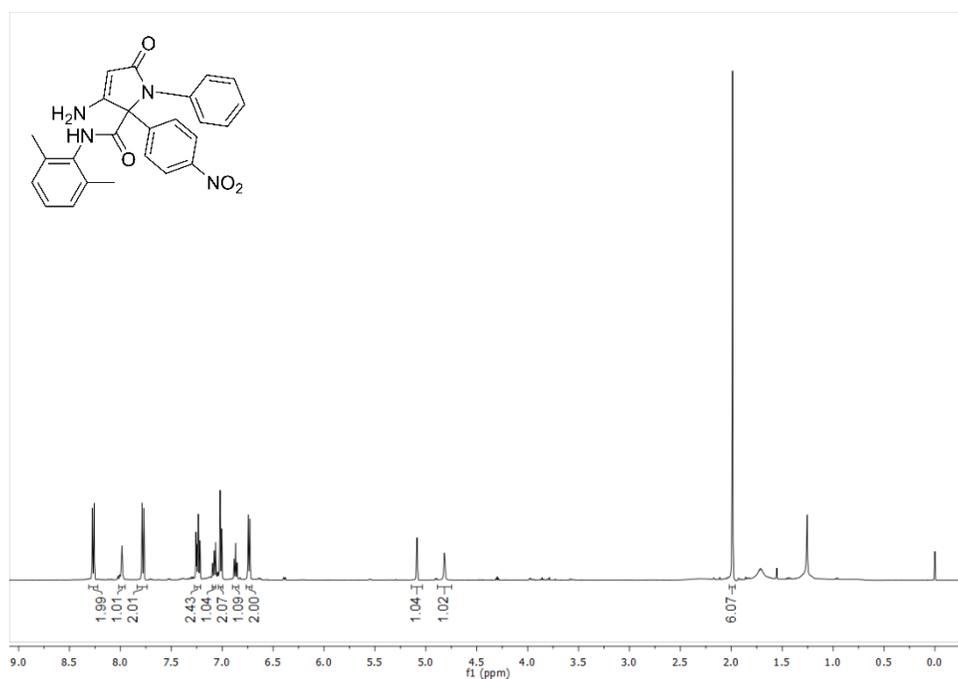


HRMS spectra of the compound 7c

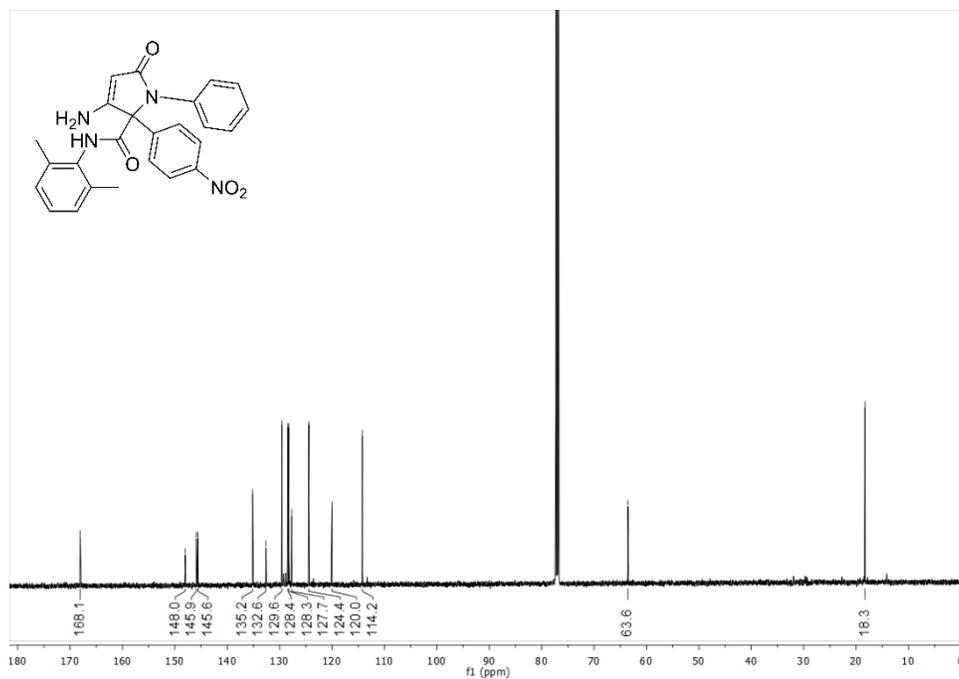
3-amino-N-(2,6-dimethylphenyl)-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7d)



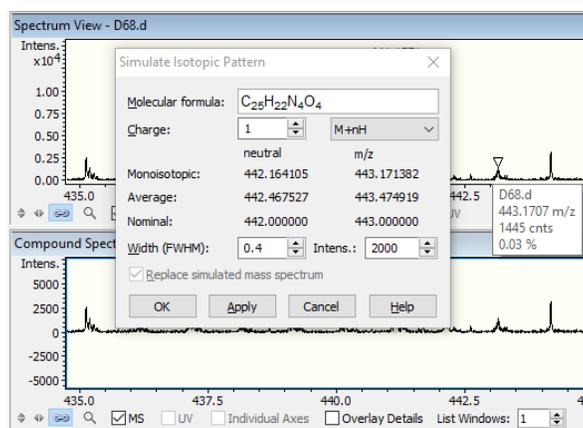
Based on GP, 50.0 mg 4-nitrobenzaldehyde (0.33 mmol), 0.031 mL aniline (0.33 mmol), 43.0 mg 2,6-dimethylphenyl isocyanide (0.33 mmol) and 28.0 mg cyanoacetic acid (0.33 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 26.0 mg of NaOH (0.66 mmol) was added with 0.2 μ L EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 78.0 mg (53%) of pure product as white solid; mp 166-167 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 8.27 (d, J = 8.7 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.10 – 7.06 (m, 1H), 7.04 – 6.99 (m, 2H), 6.90 – 6.84 (m, 1H), 6.76 – 6.71 (m, 1H), 5.09 (d, J = 2.7 Hz, 1H), 4.82 (d, J = 3.1 Hz, 1H), 1.99 (s, 6H); **¹³C NMR** (126 MHz, CDCl₃) δ = 13C NMR (126 MHz, CDCl₃) δ 168.1, 148.0, 145.9, 145.6, 135.2, 132.6, 129.6, 128.4, 128.3, 127.7, 124.4, 120.0, 114.2, 63.6, 18.3; **HRMS (ESI⁺)**: *m/z* calcd. for C₂₅H₂₃N₄O₄⁺ [M + H]⁺ 443.1714, found 443.1707.



¹H NMR spectra of the compound **7d**



¹³C NMR spectra of the compound **7d**



HRMS spectra of the compound **7d**