Supporting Information for

Synthesis of chromeno[3,4-*b*]piperazines by an enol-Ugi/reduction/cyclization sequence

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CONTENT

Starting materials

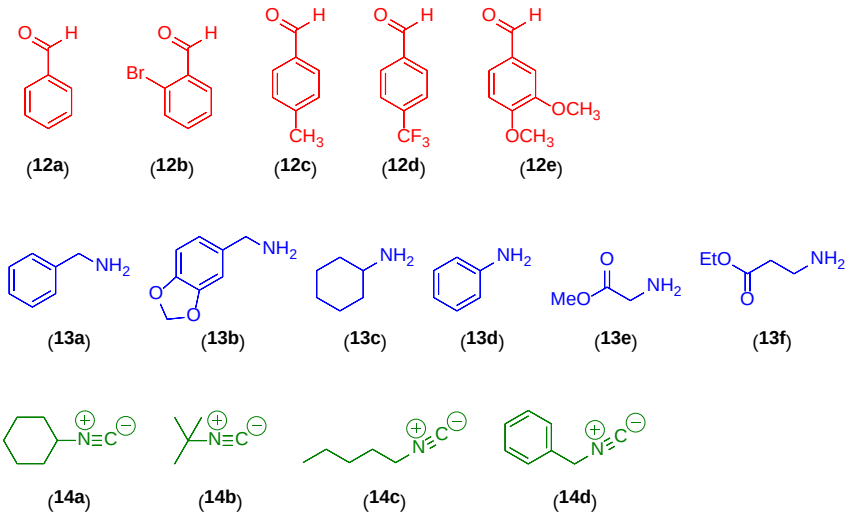
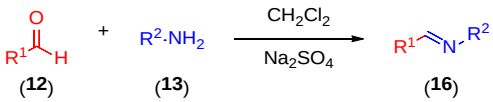


Figure S1. Aldehydes, amines, and isocyanides used as starting materials.

Synthesis and characterization of imines



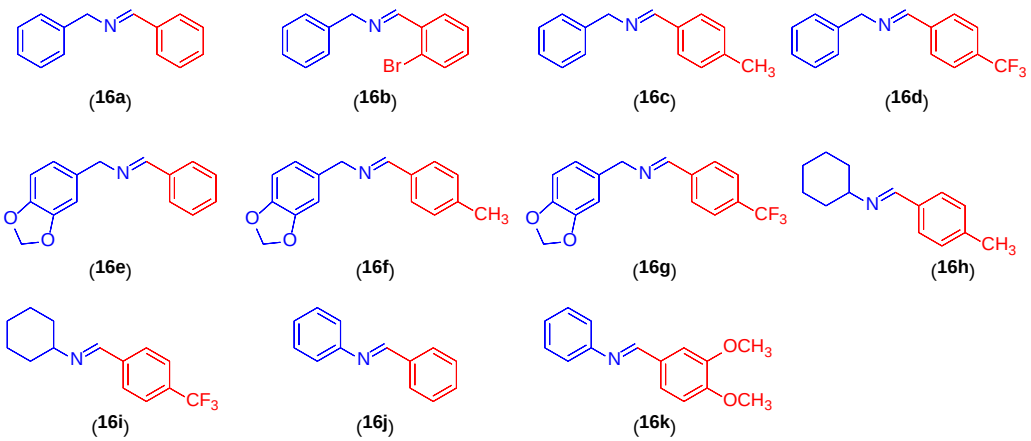


Figure S2. Imines used as starting materials.

General procedure: To a solution of 10 mmol of aldehyde **12** in 20 mL of dry CH_2Cl_2, 10 mmol of anhydrous Na_2SO_4 and 10 mmol of amine **13** were successively added. After 24 hours stirring at room temperature, the reaction went to completion, as judged by tlc. Then the Na_2SO_4

was filtered off and the solvent was eliminated to yield the imines **16** that were used without further purification in the Ugi reaction.

(*E*)-*N*-benzyl-1-phenylmethanimine (**16a**) [1], (*E*)-*N*-benzyl-1-(2-bromophenyl)methanimine (**16b**) [1], (*E*)-*N*-benzyl-1-(*p*-tolyl)methanimine (**16c**) [1], (*E*)-*N*-benzyl-1-(4-(trifluoromethyl)phenyl)methanimine (**16d**) [1], (*E*)-*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-1-phenylmethanimine (**16e**) [2], (*E*)-*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(*p*-tolyl)methanimine (**16f**) [3], (*E*)-*N*-cyclohexyl-1-(*p*-tolyl)methanimine (**16h**) [4], (*E*)-*N*-cyclohexyl-1-(4-(trifluoromethyl)phenyl)methanimine (**16i**) [5], (*E*)-*N*,1-diphenylmethanimine (**16j**) [6, 7] and (*E*)-1-(3,4-dimethoxyphenyl)-*N*-phenylmethanimine (**16k**) [8] showed physical and spectroscopic data consistent with the literature.

(*E*)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(4-(trifluoromethyl)phenyl)methanimine (16g). Obtained from aldehyde **12d** and amine **13b** as a light brown oil **(**93%); IR (cm^{-1}) 2915, 2857, 2820, 1649, 1493, 1442, 1337,1247, 1106, 1066, 1045, 953, 931, 838, 801, 598; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 6.83 (s, 1H), 6.79 (d, *J* = 0.9 Hz, 2H), 5.94 (s, 2H), 4.75 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.29 (CH), 148.02 (C), 146.90 (C), 139.40 (C), 132.76 (C), 128.60 (CH), 125.75 (CH), 125.72 (CH), 125.69 (CH), 125.66 (CH), 121.32 (CH), 108.81 (CH), 108.45 (CH), 101.12 (CH_2), 64.93 (CH_2); MS (qTOF) m/z (%) 308 (M^+ + 1, 100), 135 (9); HRMS (qTOF) Calcd for $C_{16}H_{13}F_3NO_2$: 308.0898. Found: 308.094.

References

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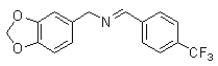
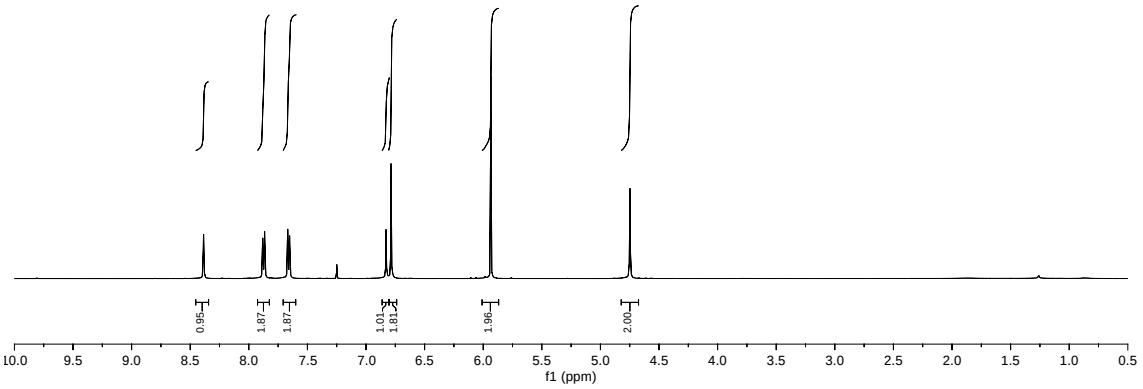
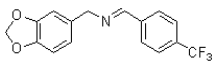
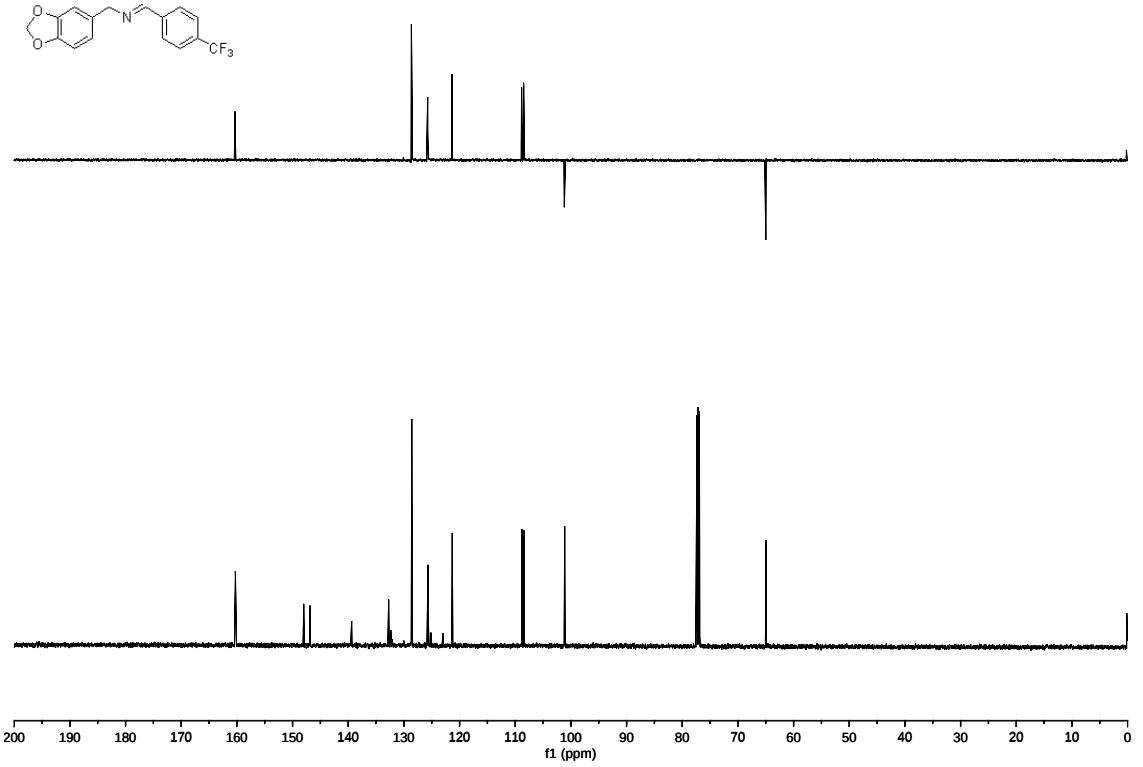
NMR Spectra

(*E*)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(4-(trifluoromethyl)phenyl)methanimine (16g).

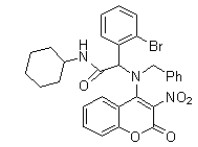


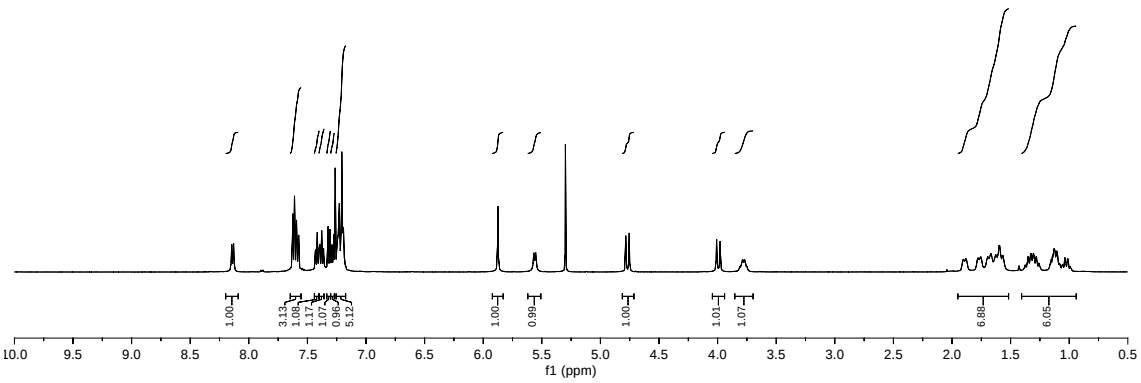


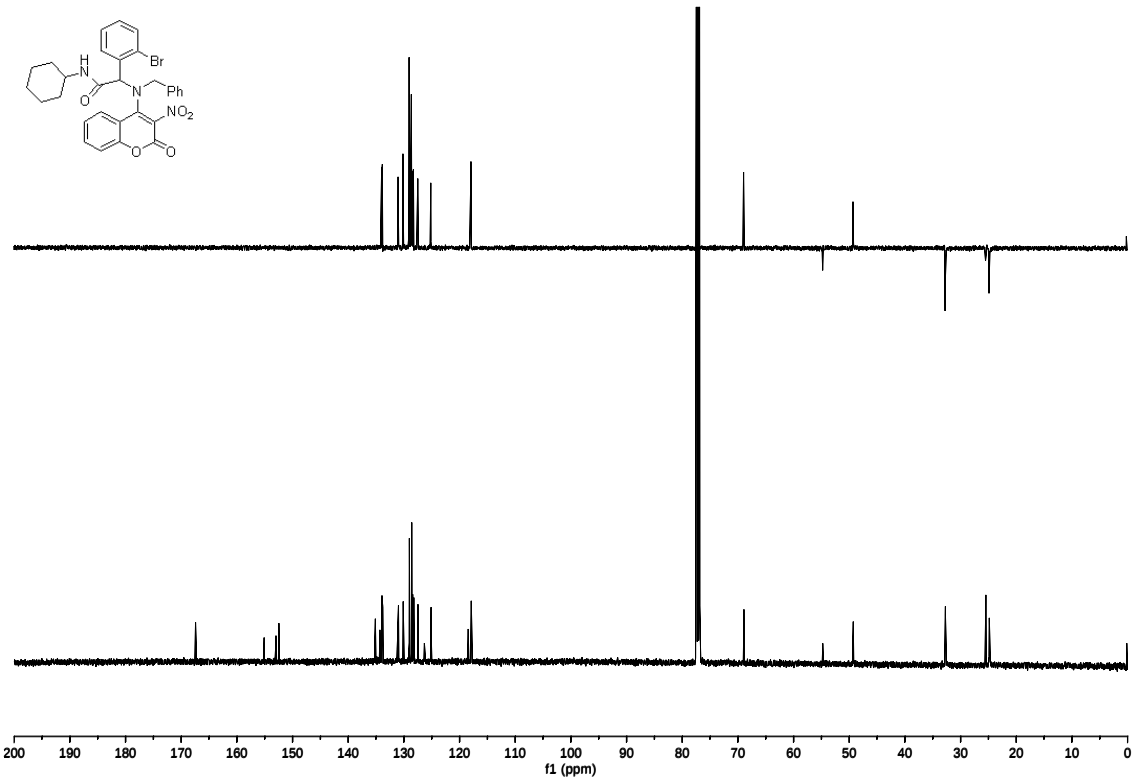




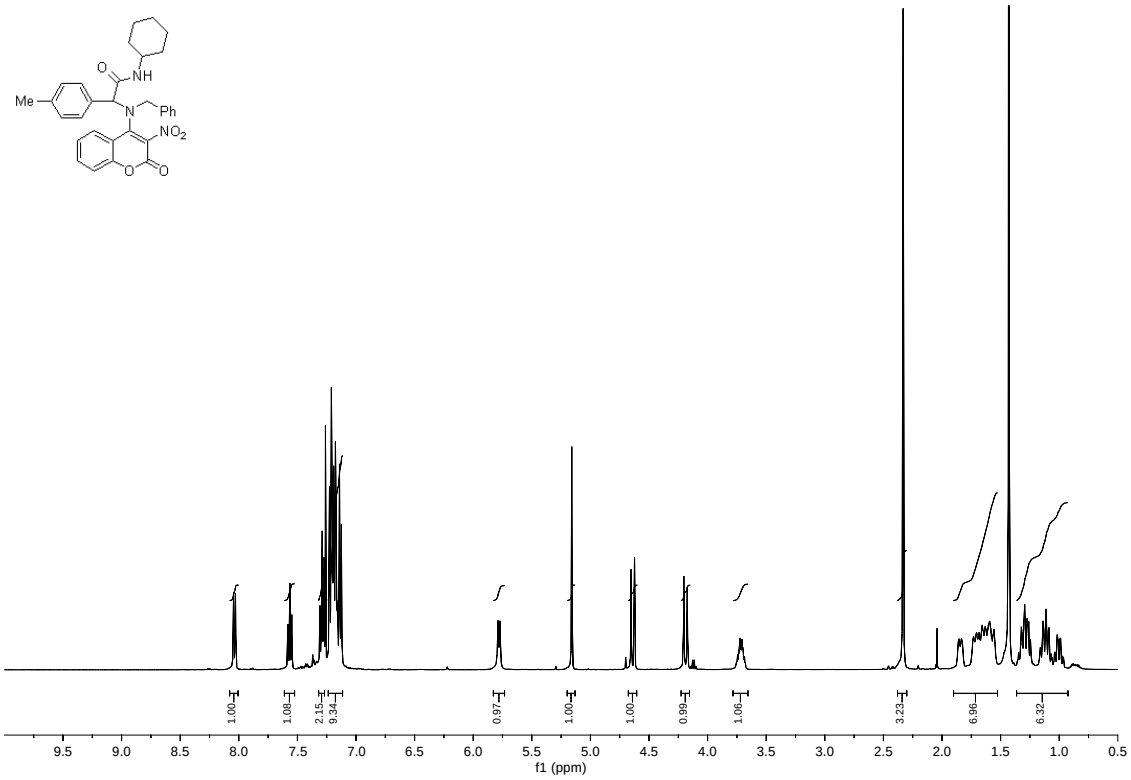
2-(Benzyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-2-(2-bromophenyl)-*N*-cyclohexyl acetamide (17b).

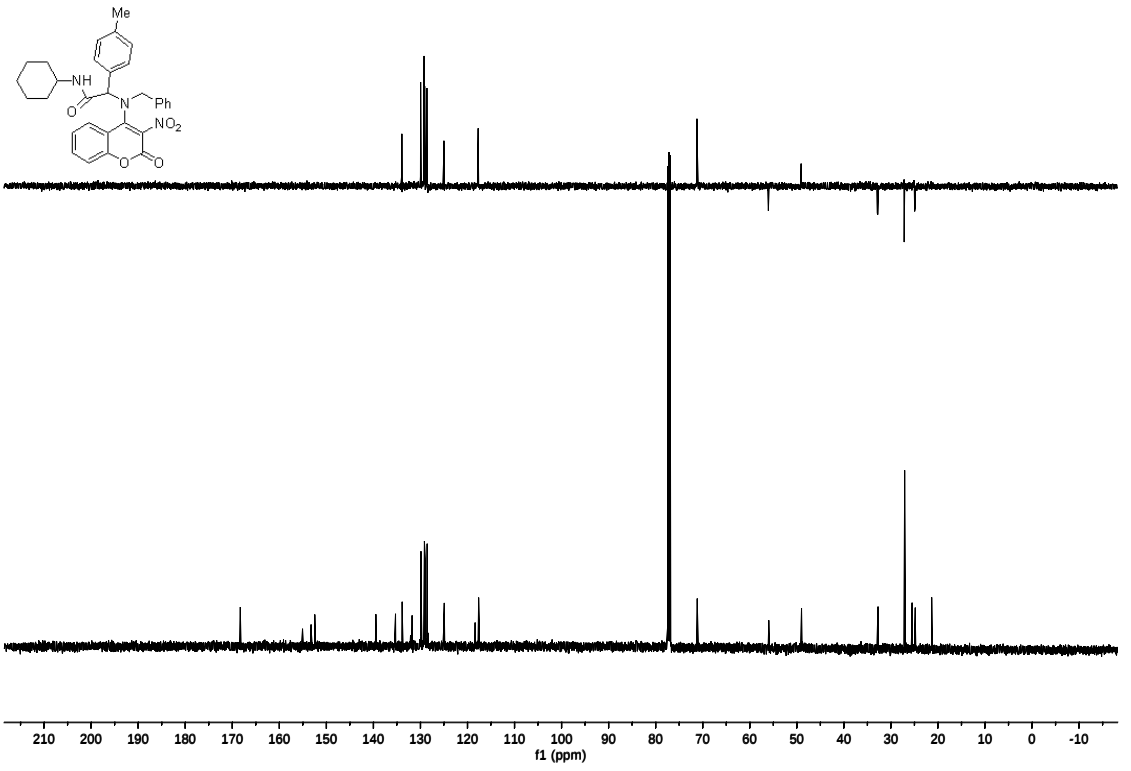




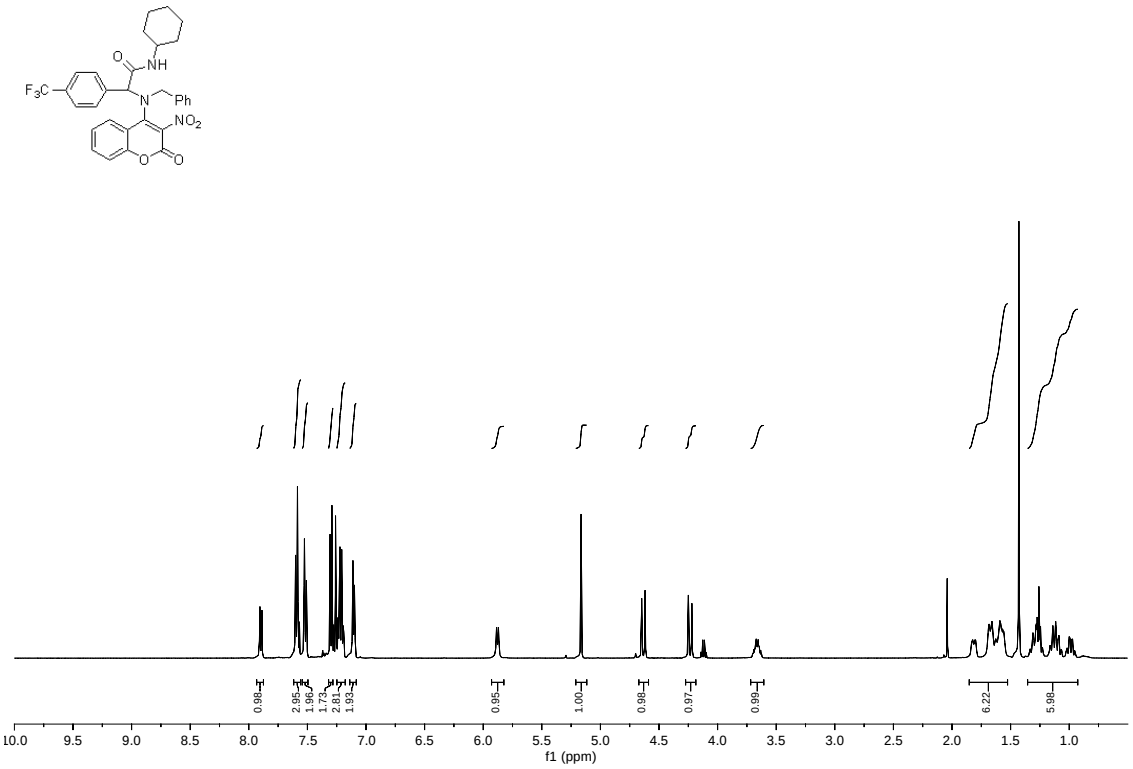


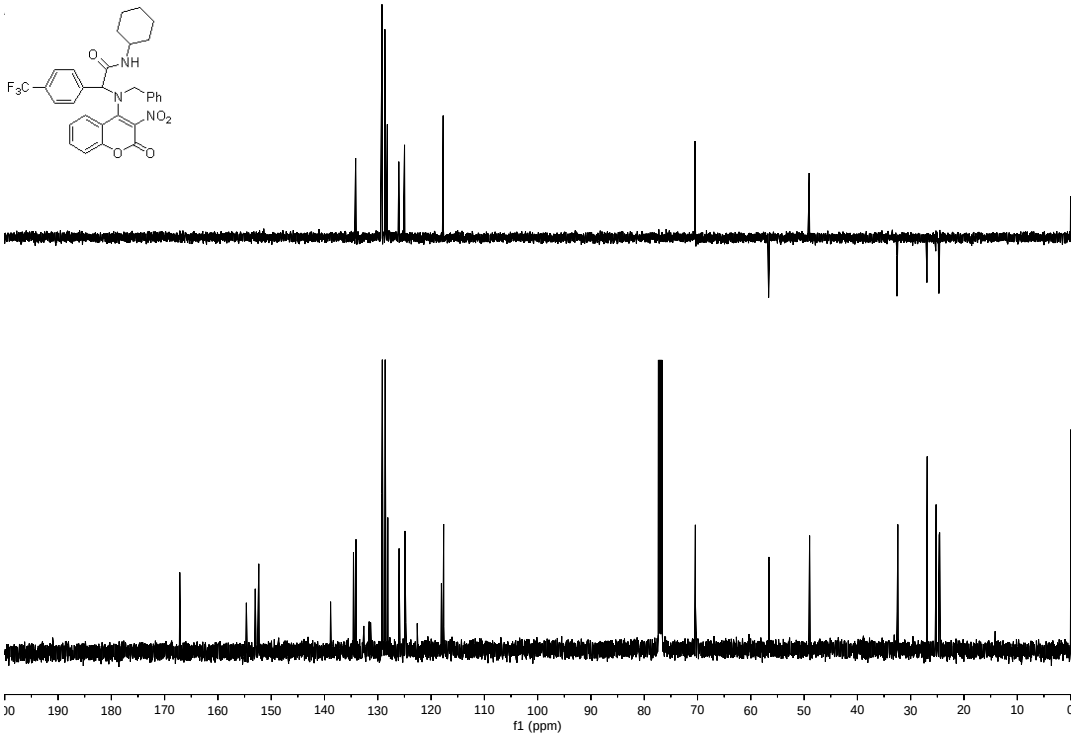
2-(Benzyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-2-(2-bromophenyl)-*N*-cyclohexyl acetamide (17c).



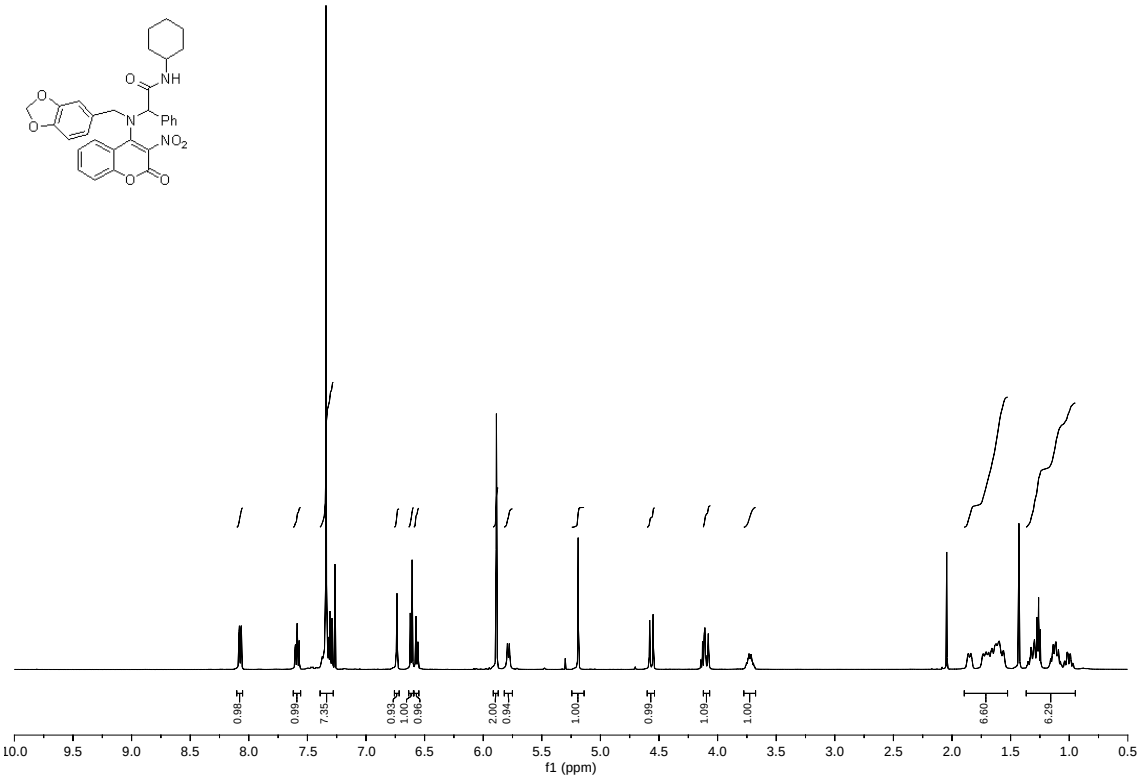


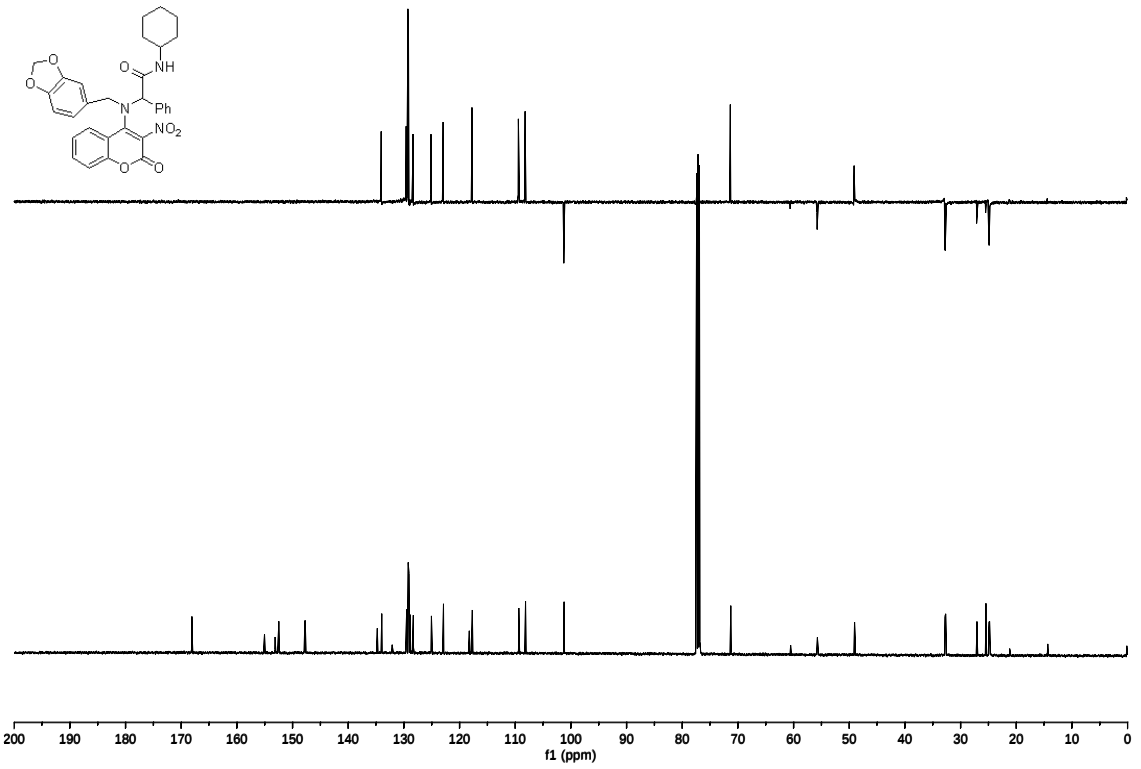
2-(Benzyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-*N*-cyclohexyl-2-(4-(trifluoromethyl) phenyl)acetamide (17d).



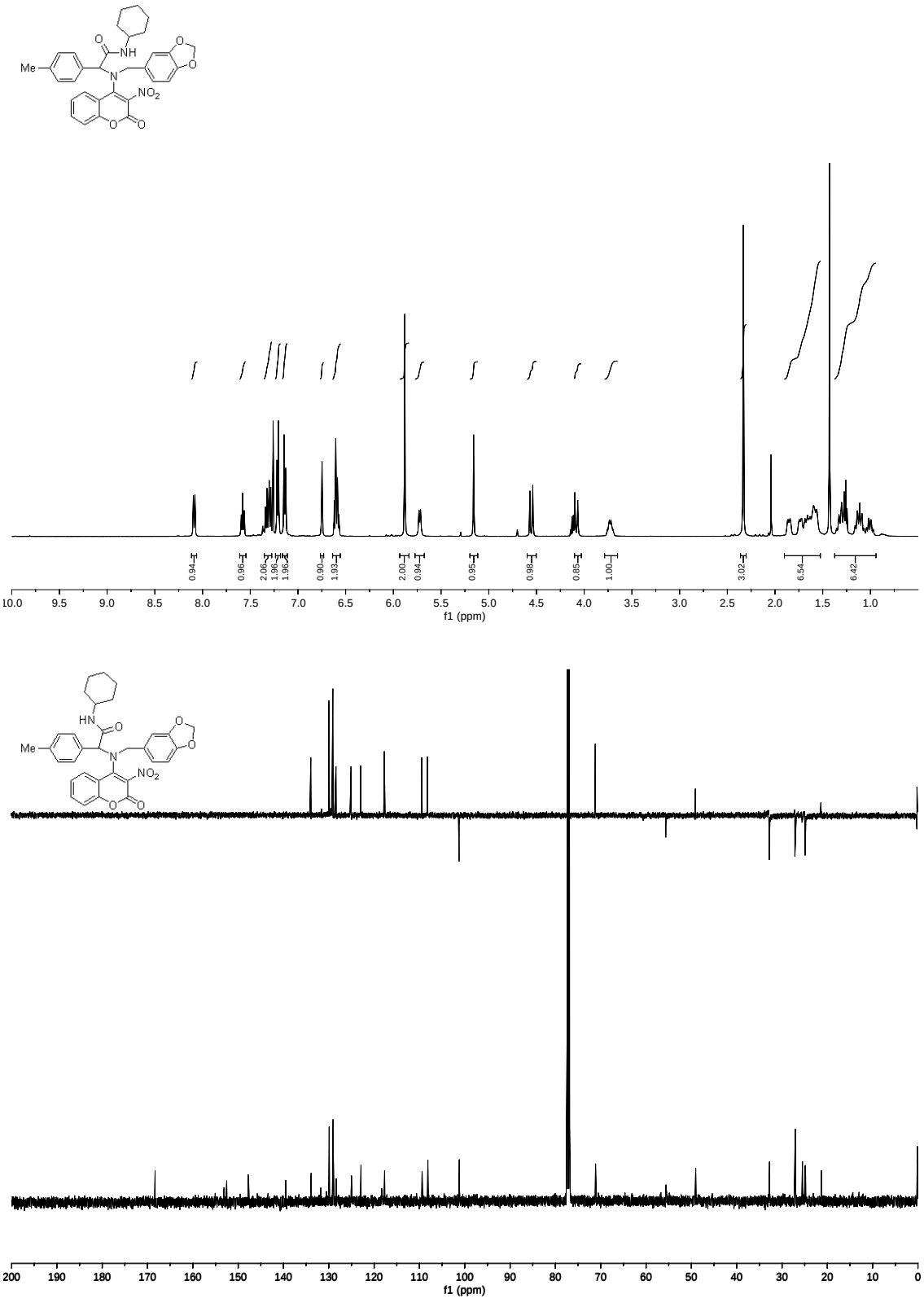


2-((Benzo[*d*][1,3]dioxol-5-ylmethyl)(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-*N*-cyclohexyl-2-phenylacetamide (17e).

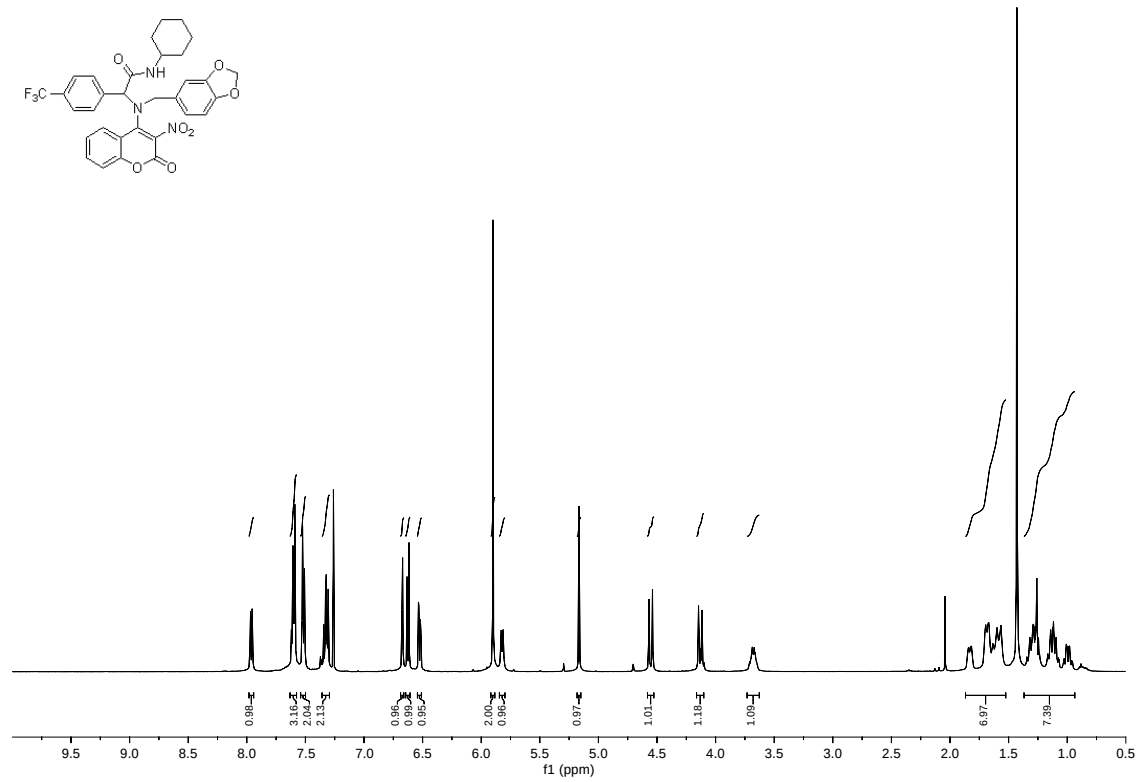


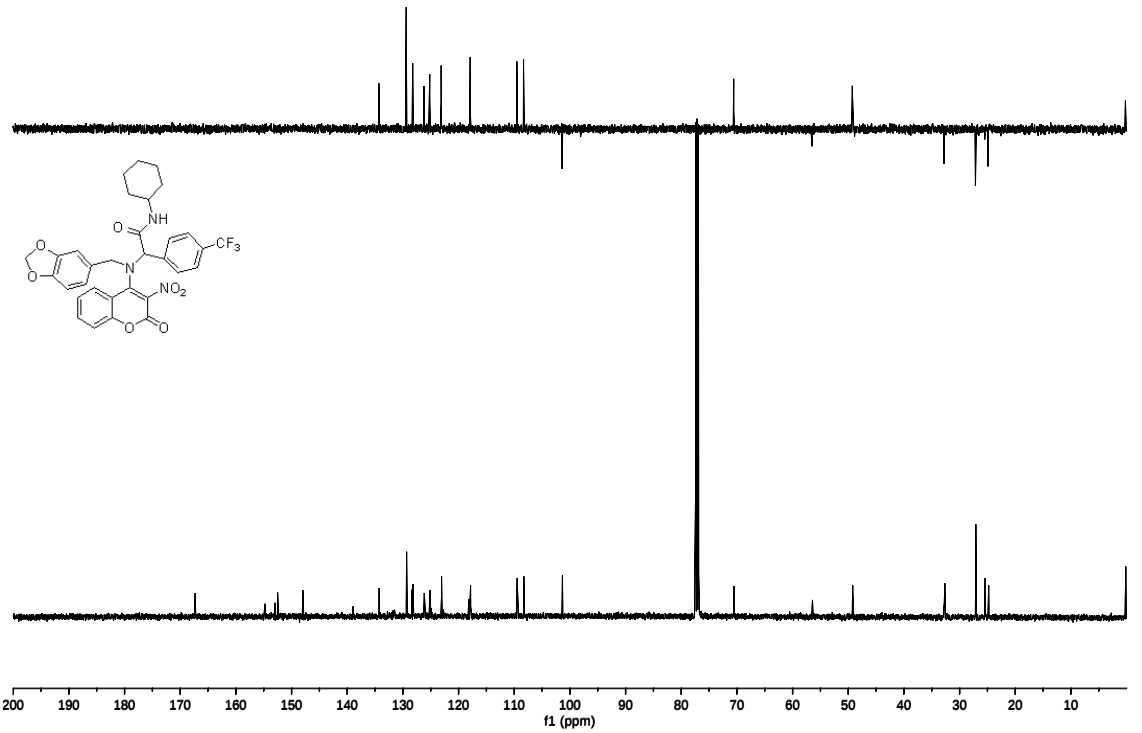


2-((Benzo[*d*][1,3]dioxol-5-ylmethyl)(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-*N*-cyclohexyl-2-(*p*-tolyl)acetamide (17f).

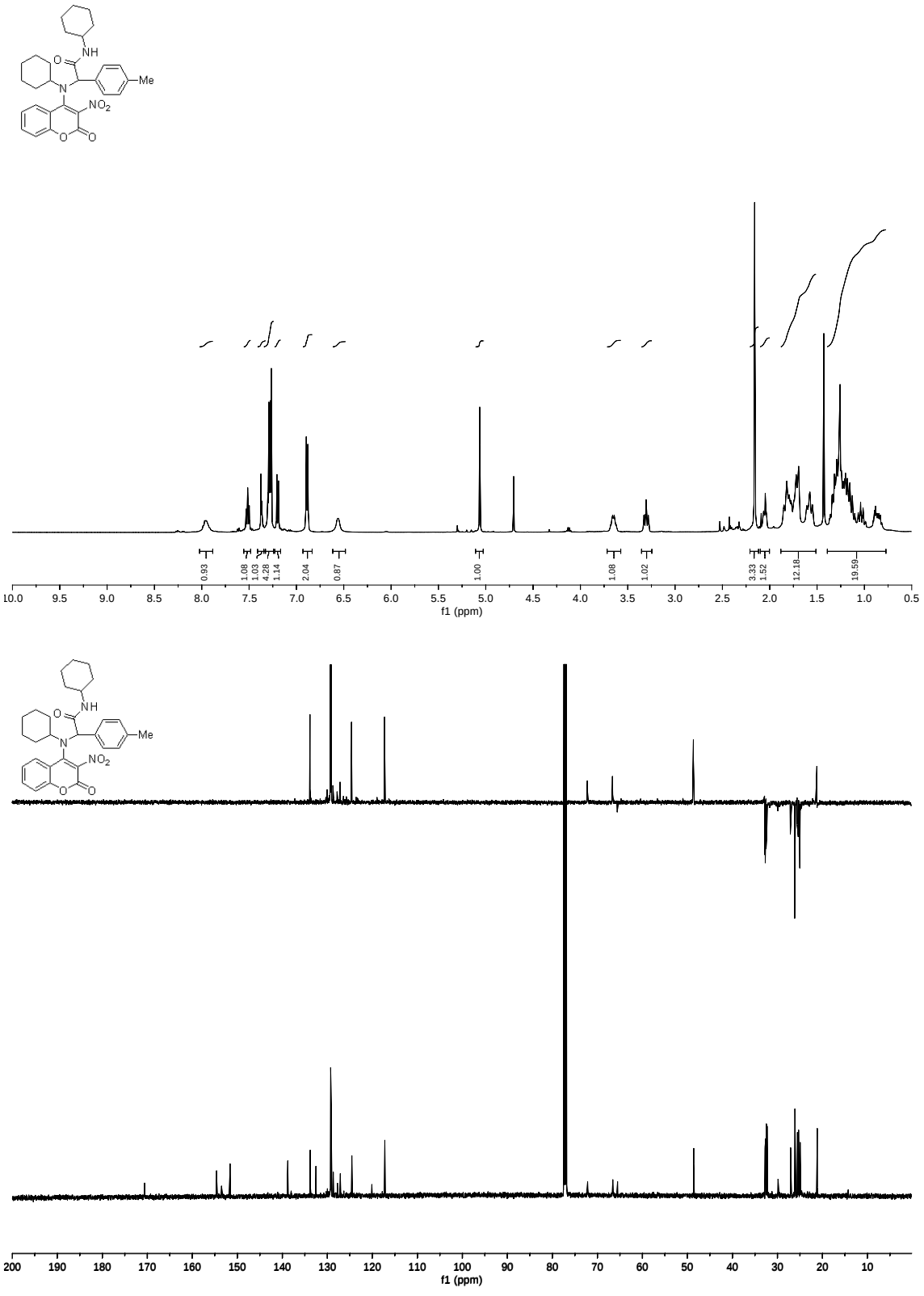


2-((Benzo[*d*][1,3]dioxol-5-ylmethyl)(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-*N*-cyclohexyl-2-(4-(trifluoromethyl)phenyl)acetamide (17g).

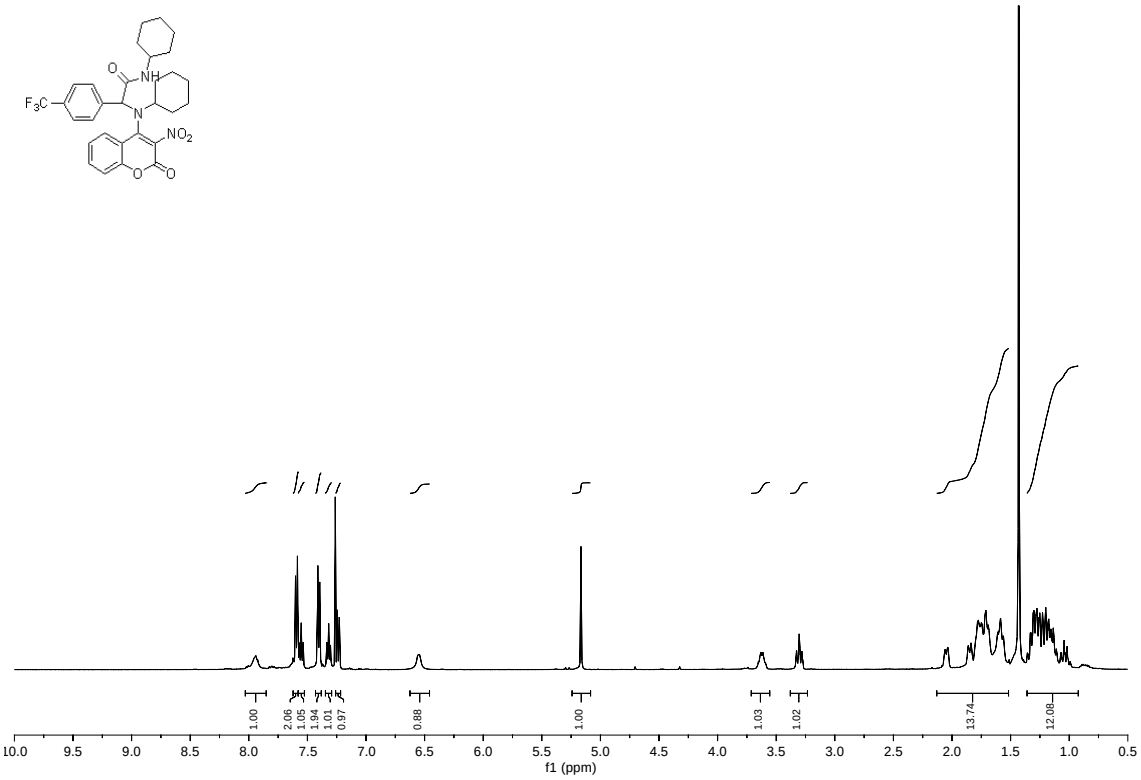


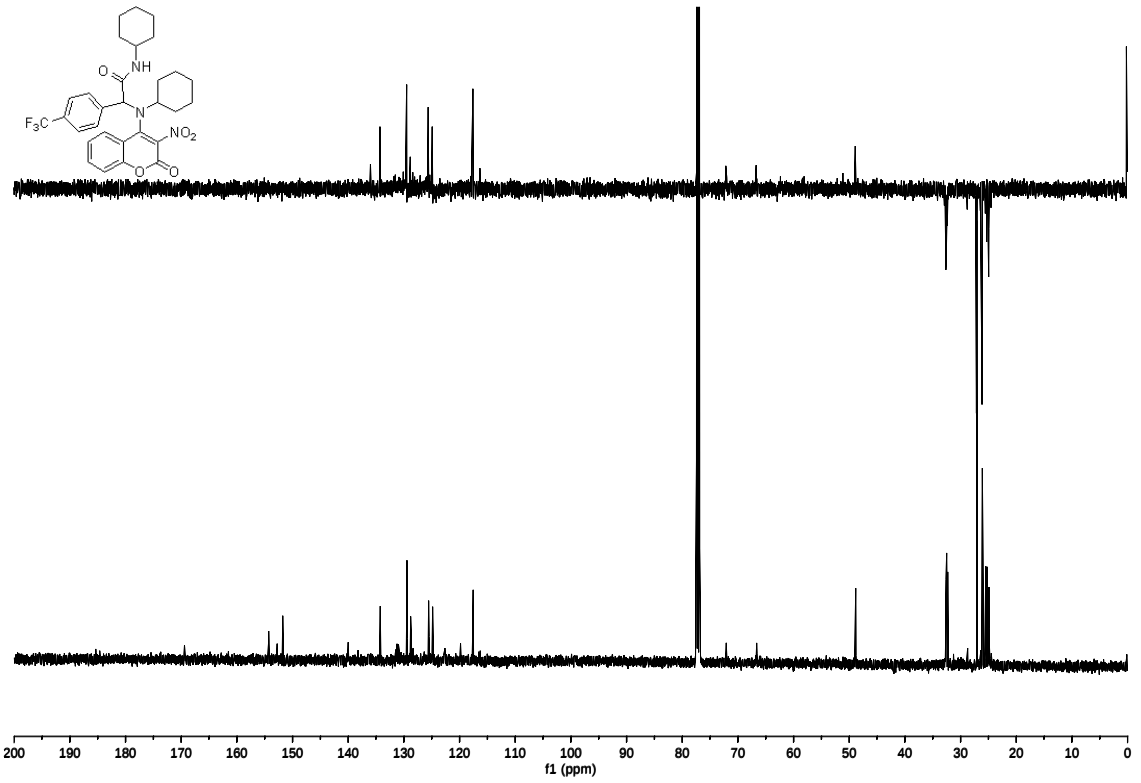


_N_-Cyclohexyl-2-(cyclohexyl(3-nitro-2-oxo-2_H_-chromen-4-yl)amino)-2-(_p_-tolyl)acetamide (17h).

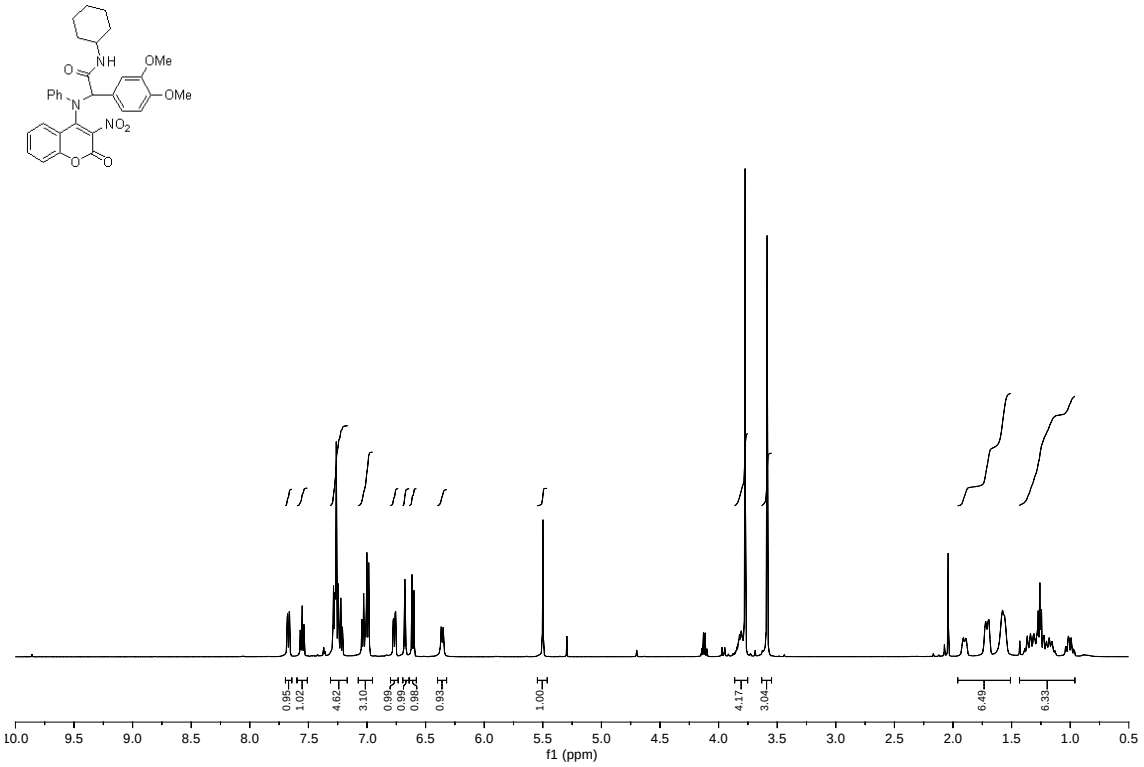


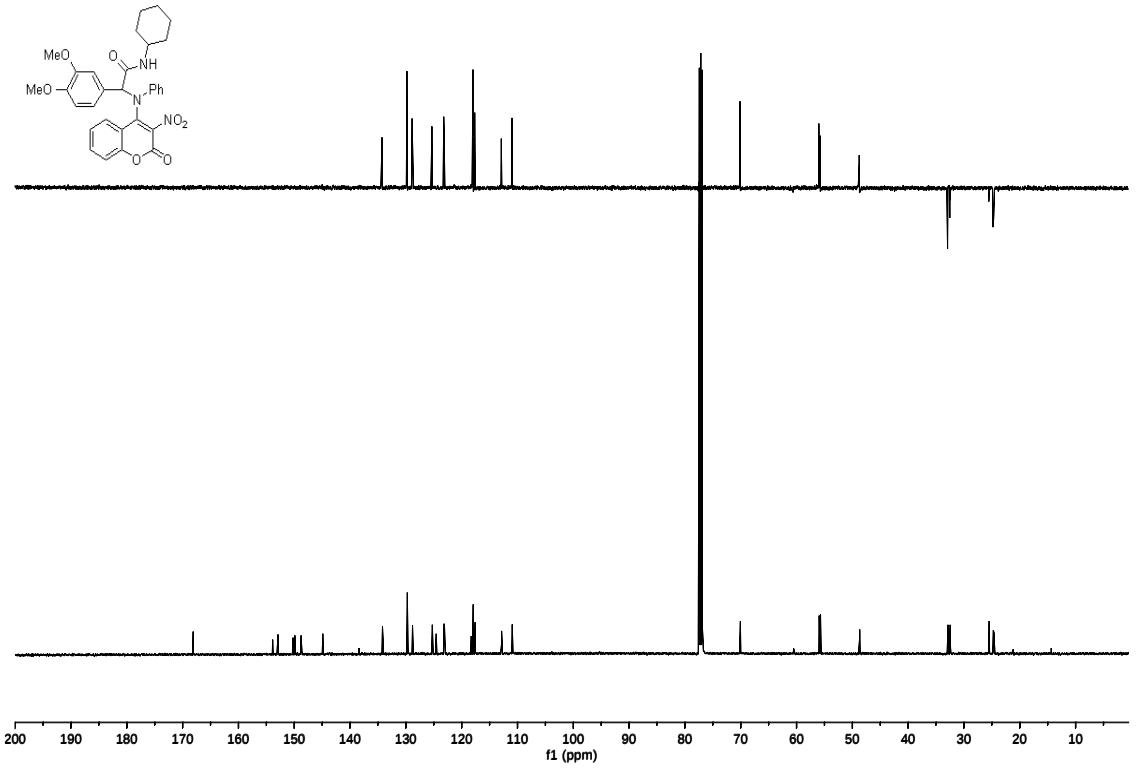
***N*-Cyclohexyl-2-(cyclohexyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)-2-(4-(trifluoromethyl) phenyl)acetamide (17i).**



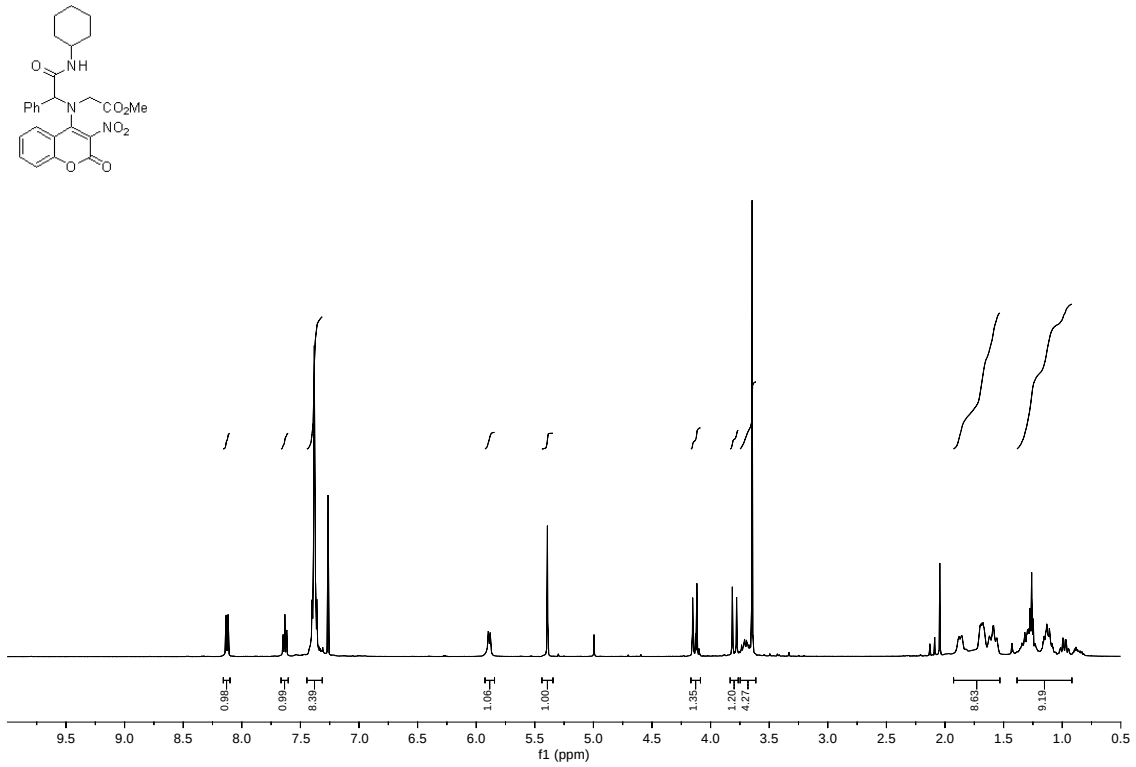


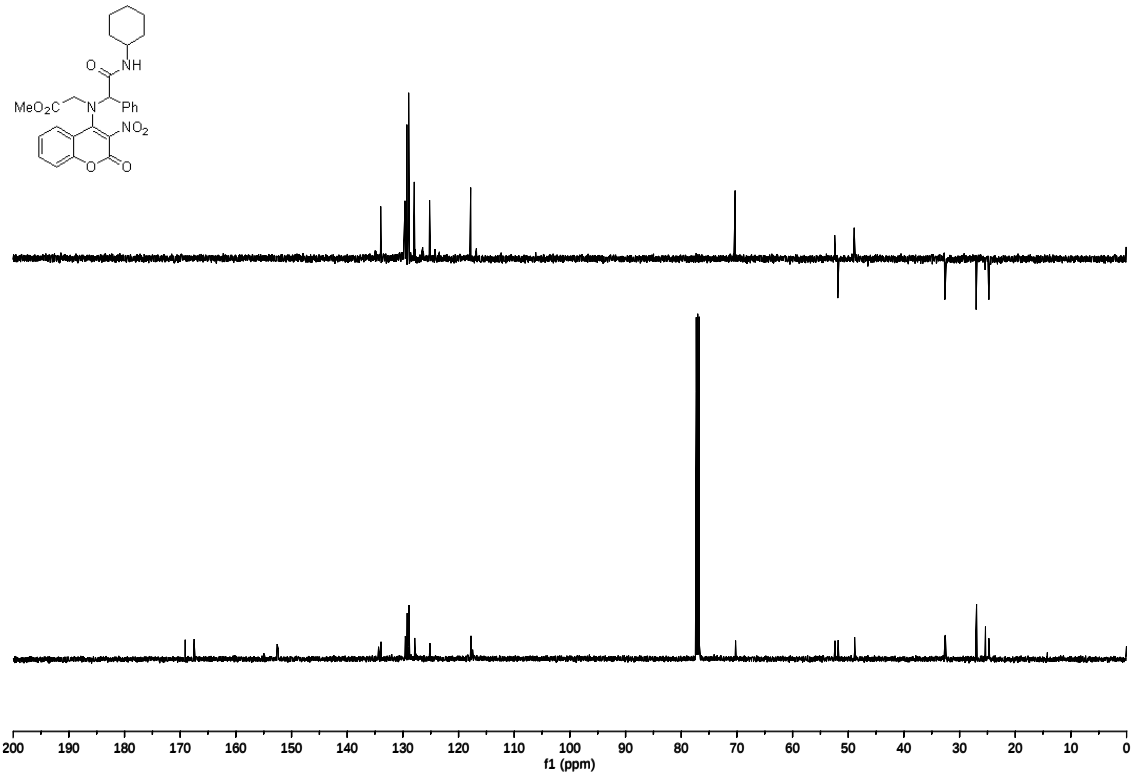
***N*-Cyclohexyl-2-(3,4-dimethoxyphenyl)-2-((3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino) acetamide (17k).**





Methyl *N*-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(3-nitro-2-oxo-2*H*-chromen-4-yl)glycinate (17l).





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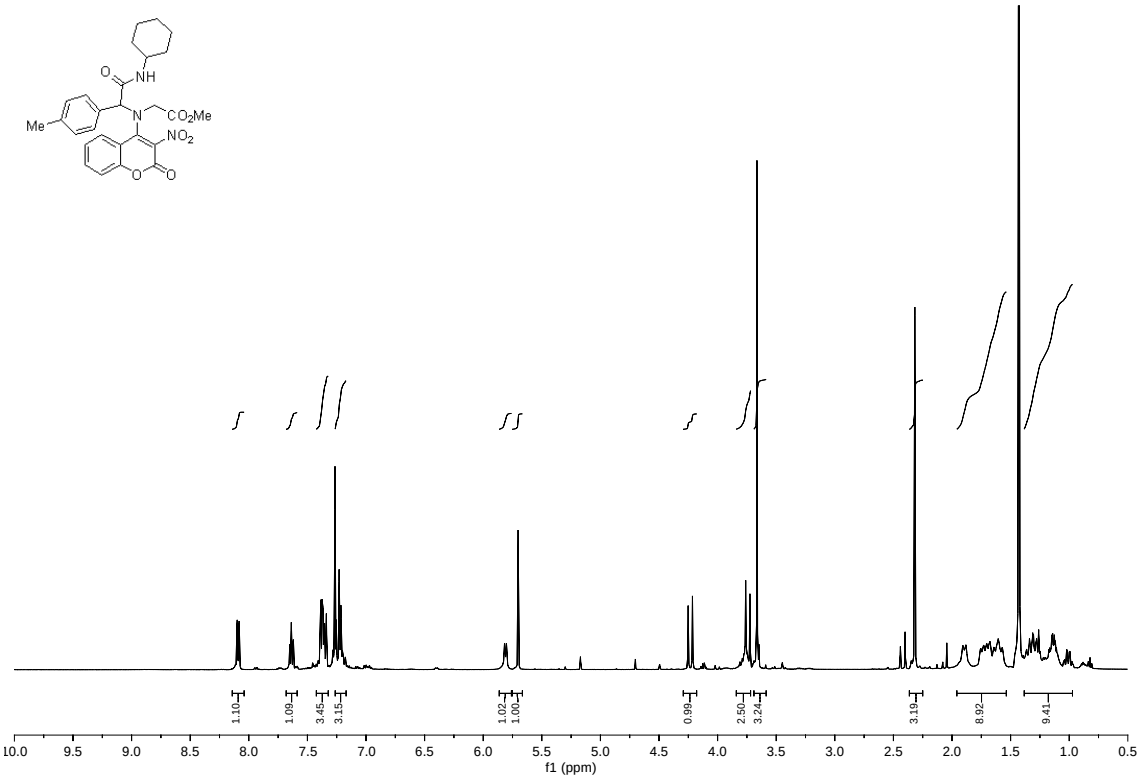
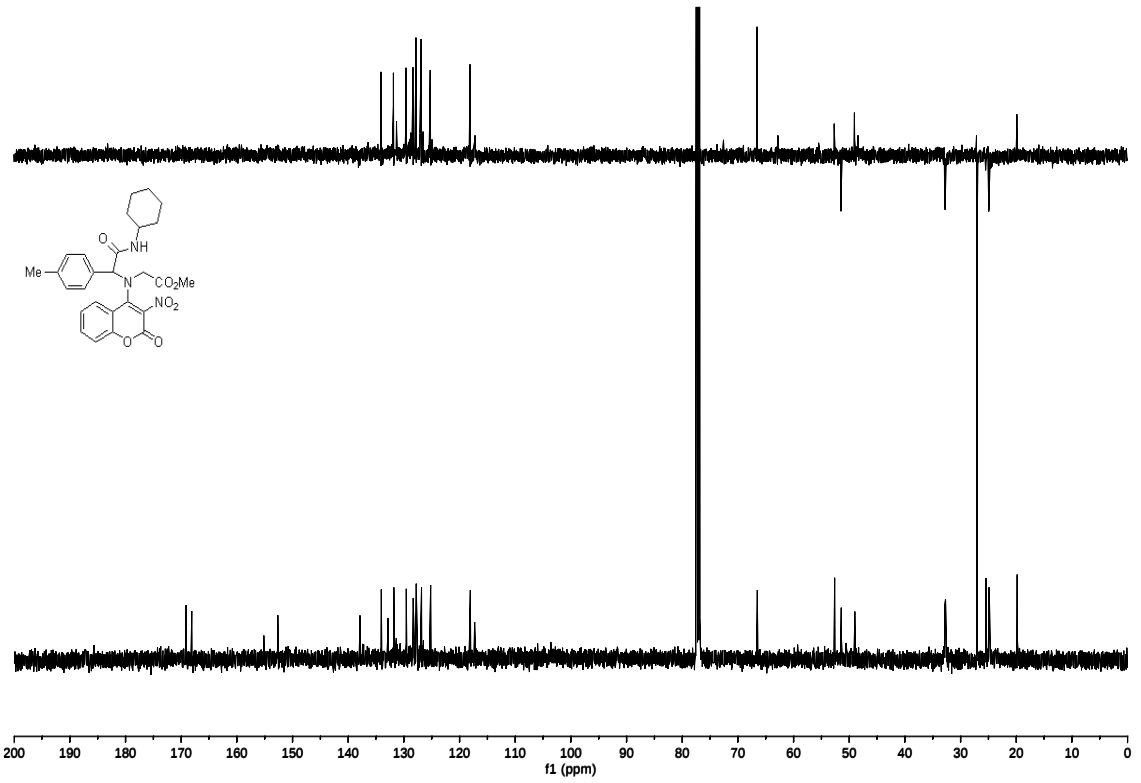
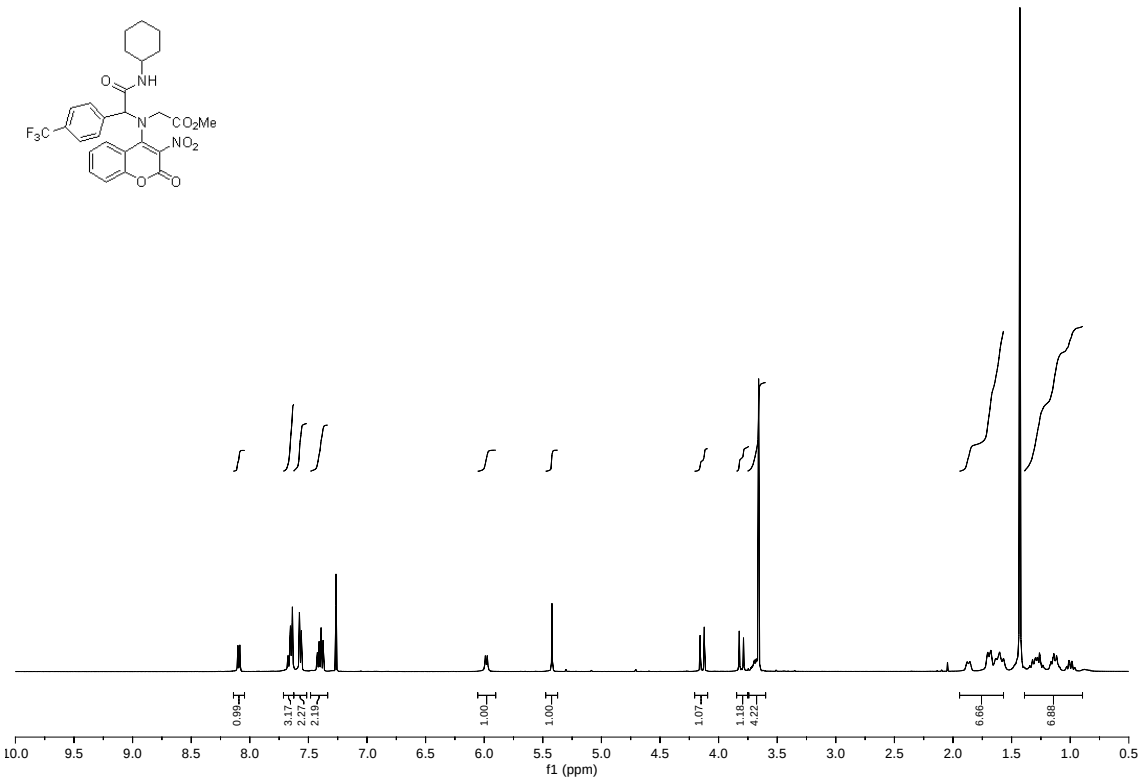
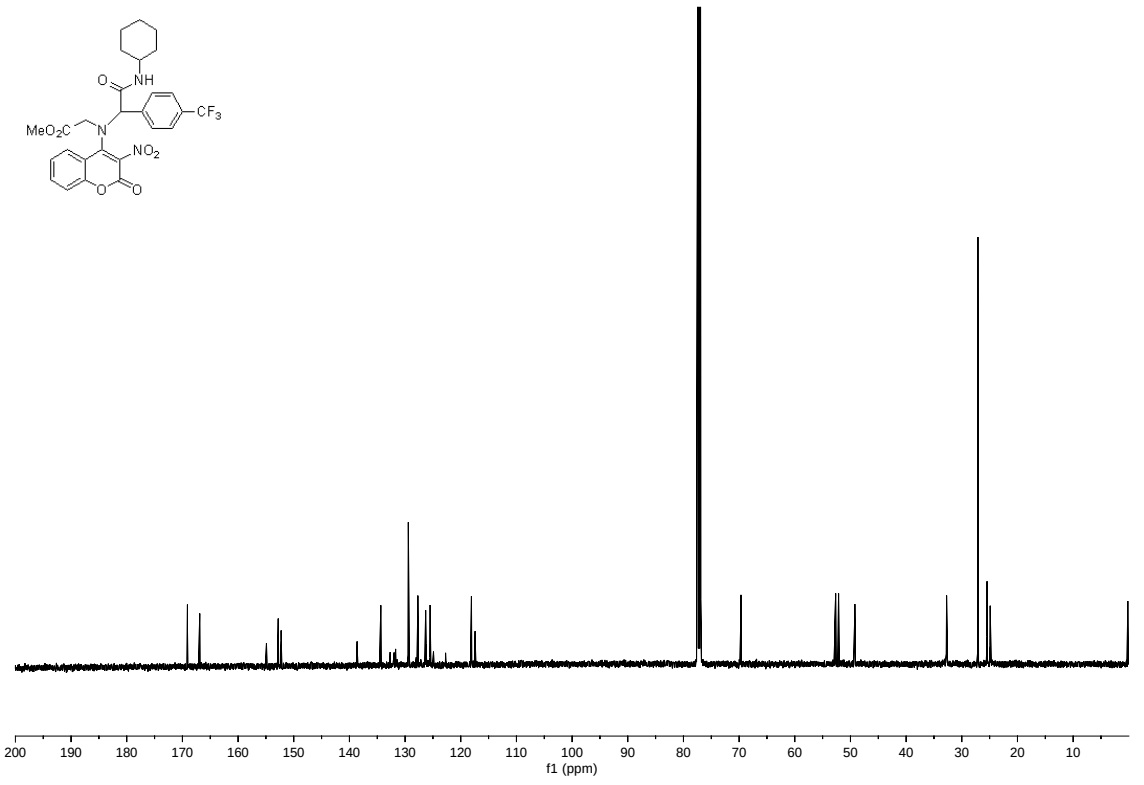




Methyl *N*-(2-(cyclohexylamino)-2-oxo-1-(4-(trifluoromethyl)phenyl)ethyl)-*N*-(3-nitro-2-oxo-2*H*-chromen-4-yl)glycinate (17n).





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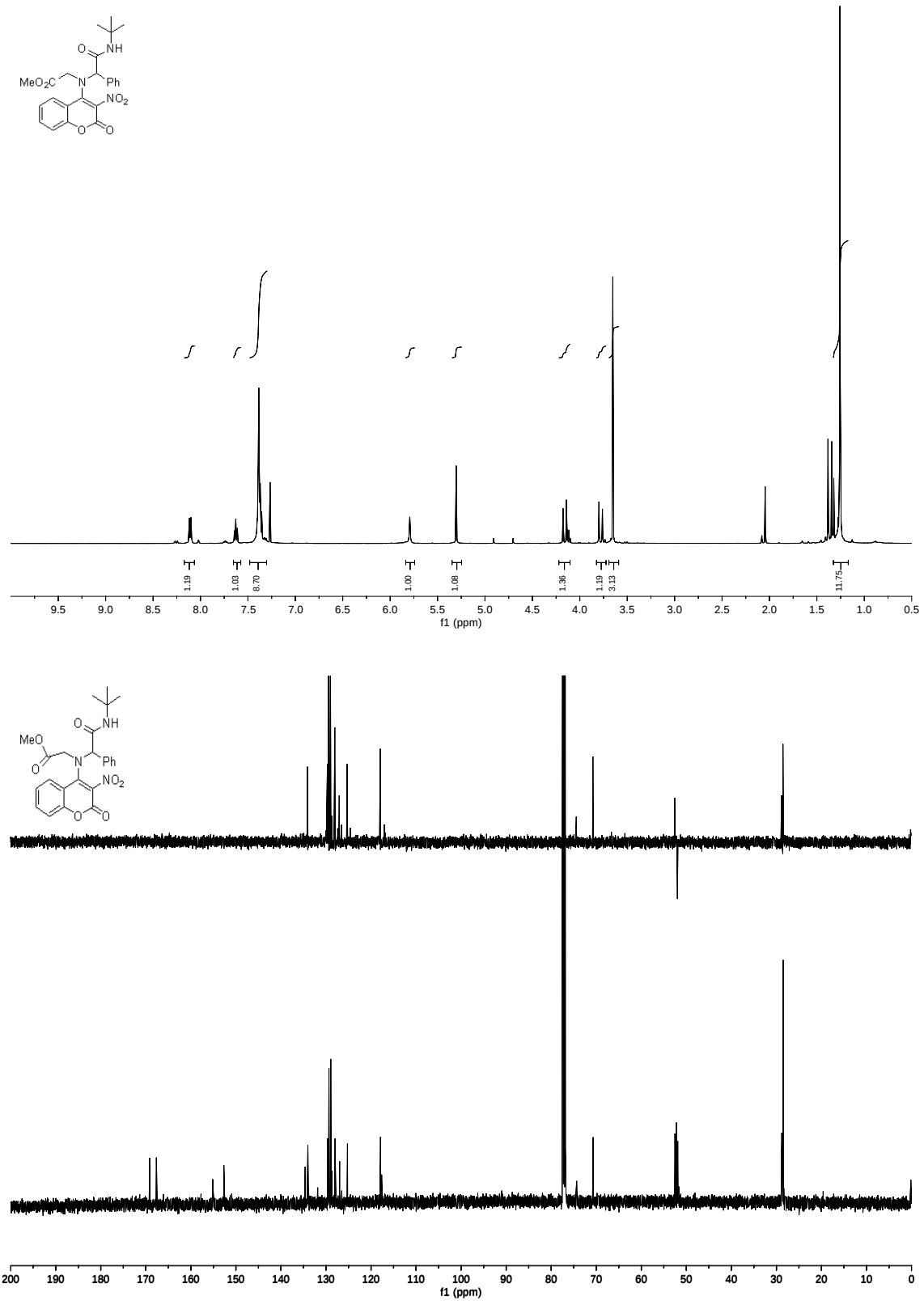
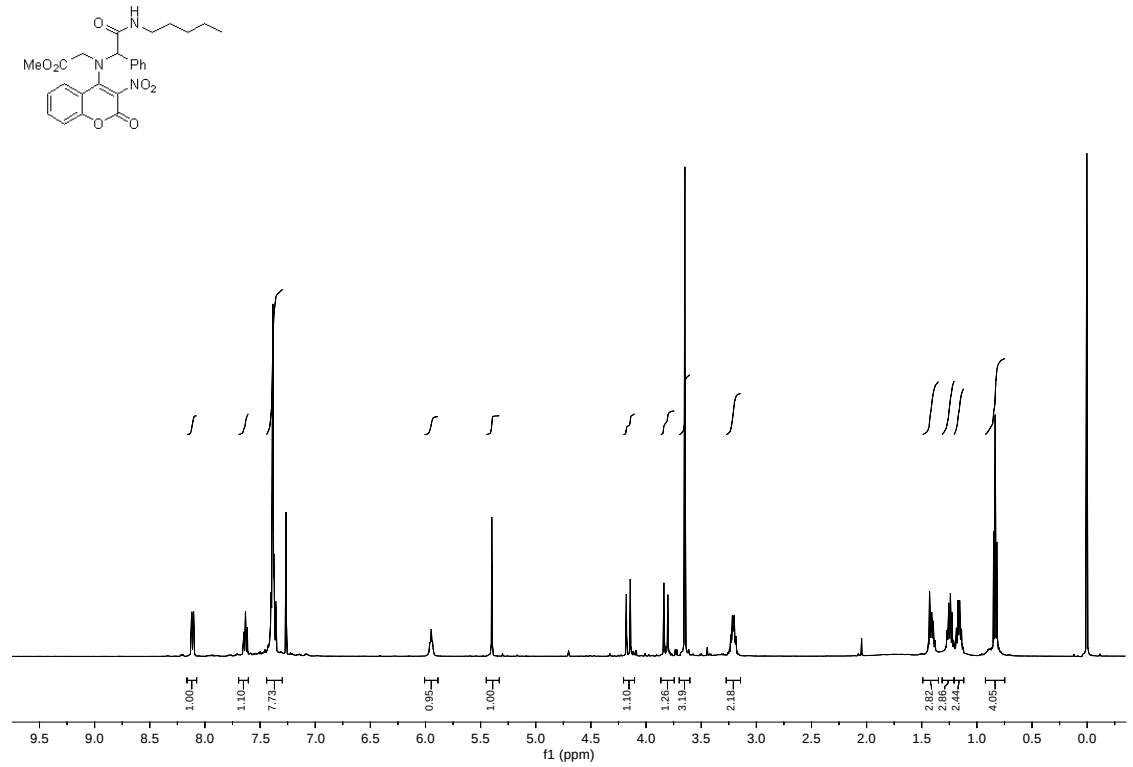
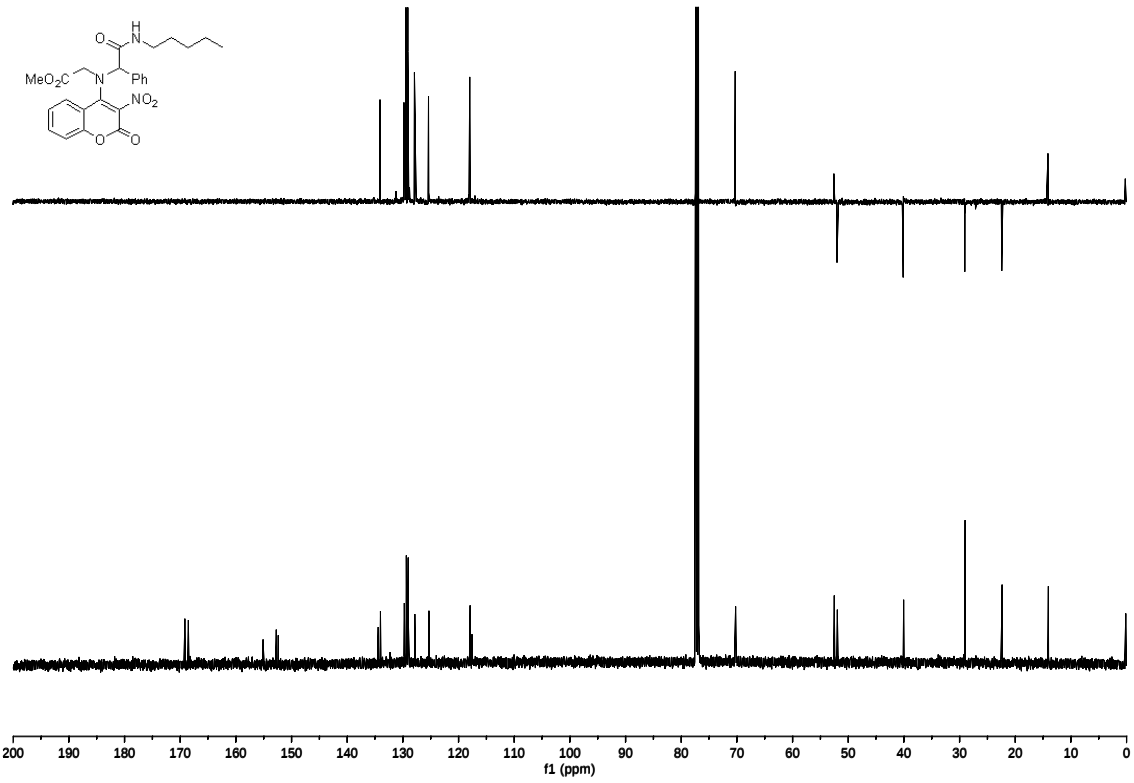
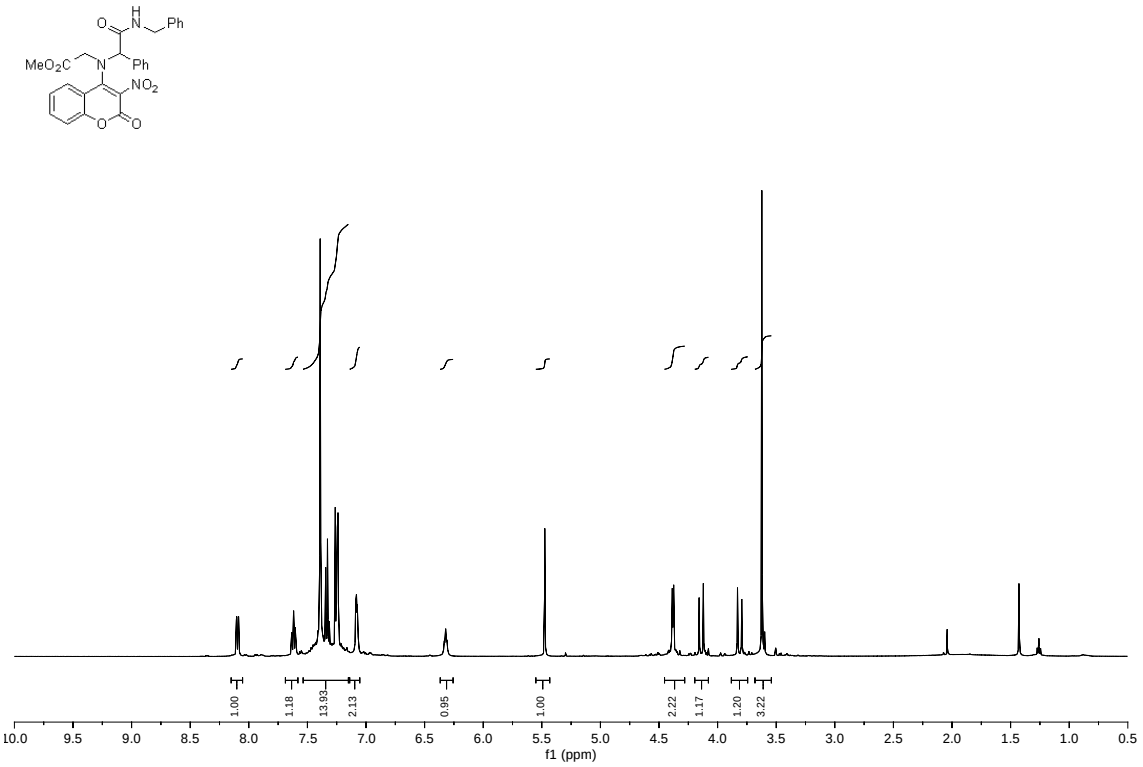


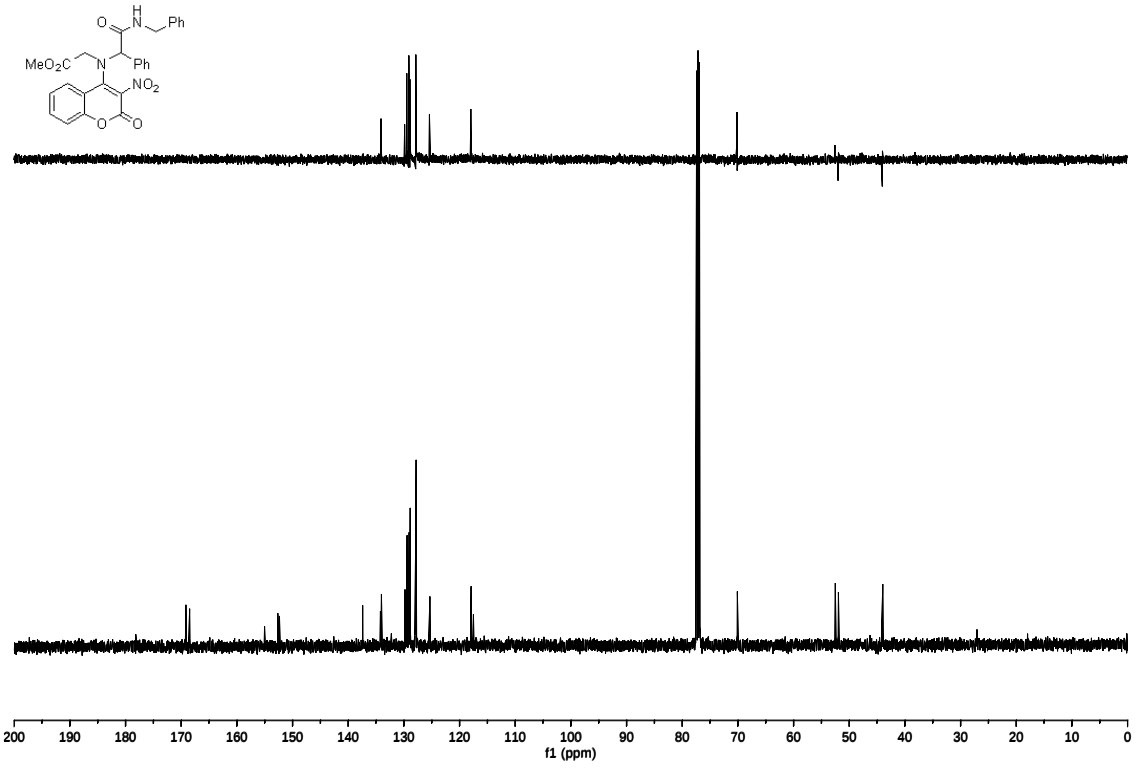
Methyl *N*-(3-nitro-2-oxo-2*H*-chromen-4-yl)-*N*-(2-oxo-2-(pentylamino)-1-phenylethyl) glycinate (17g).





Methyl *N*-(2-(benzylamino)-2-oxo-1-phenylethyl)-*N*-(3-nitro-2-oxo-2*H*-chromen-4-yl)glycinate (17q)





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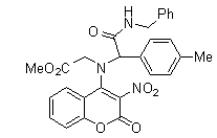
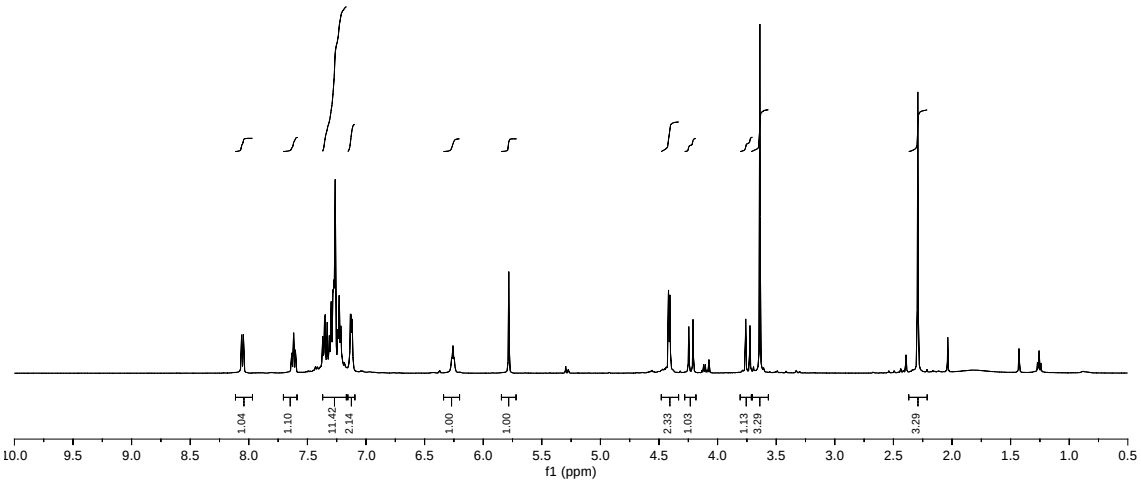
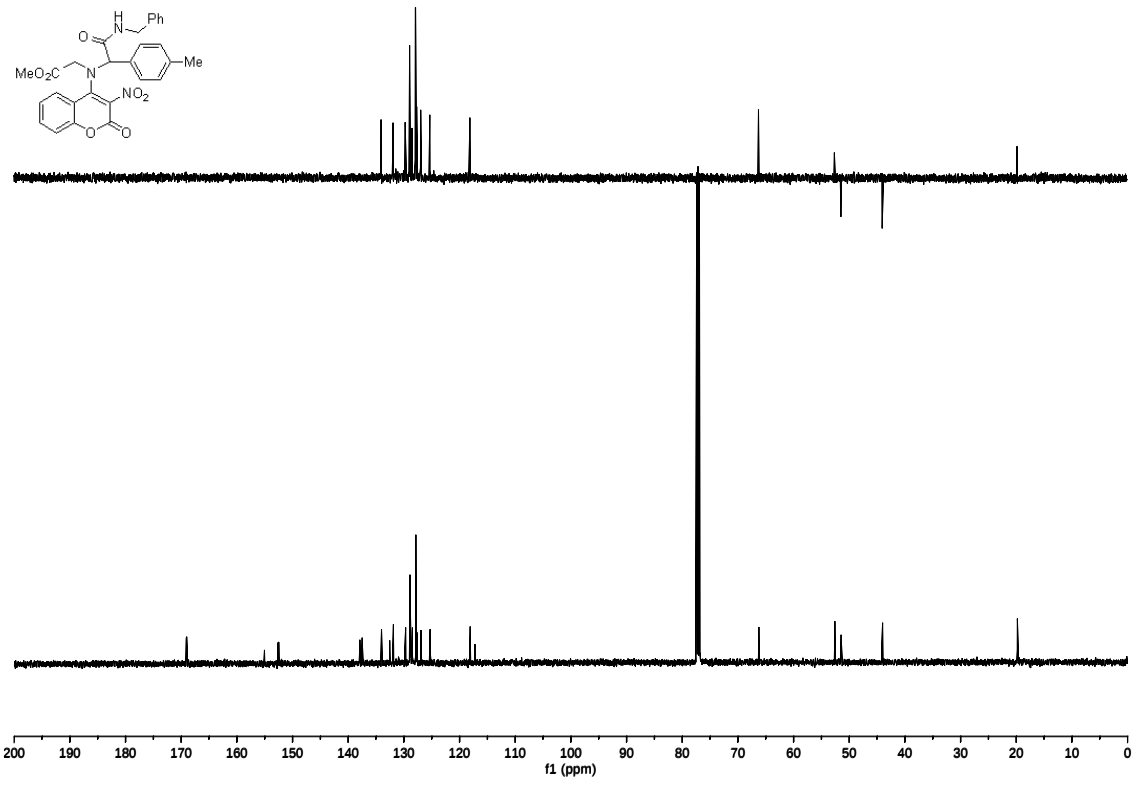
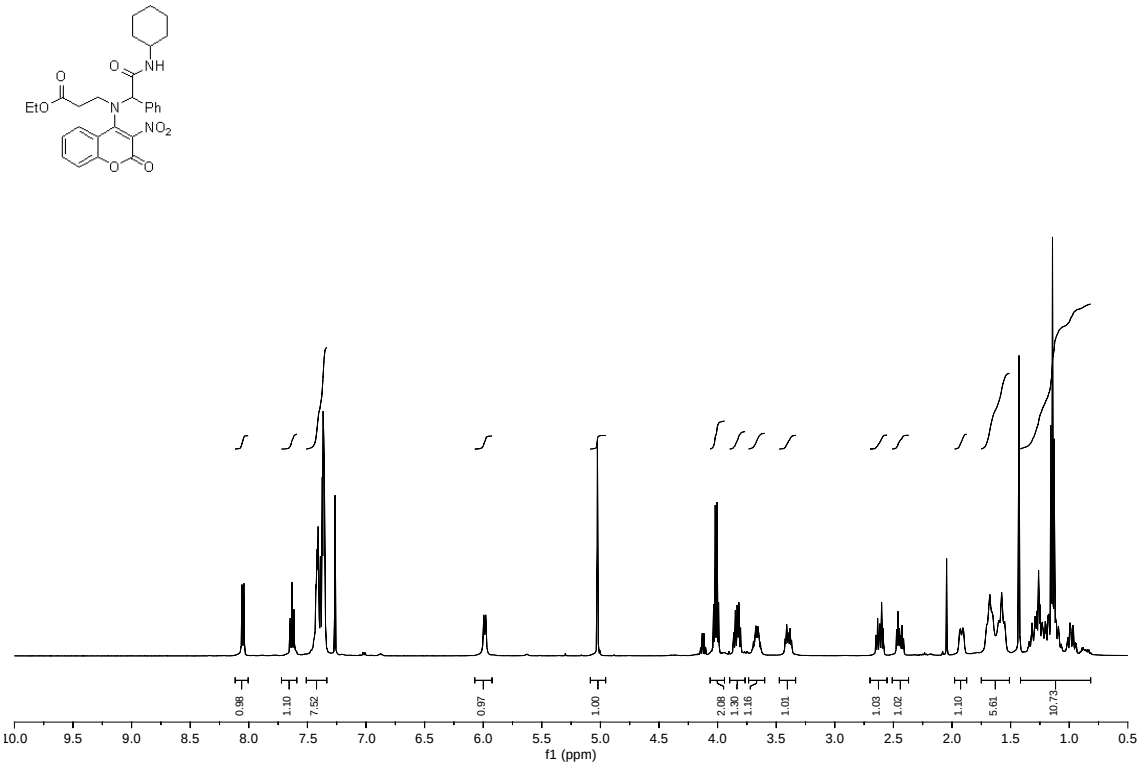
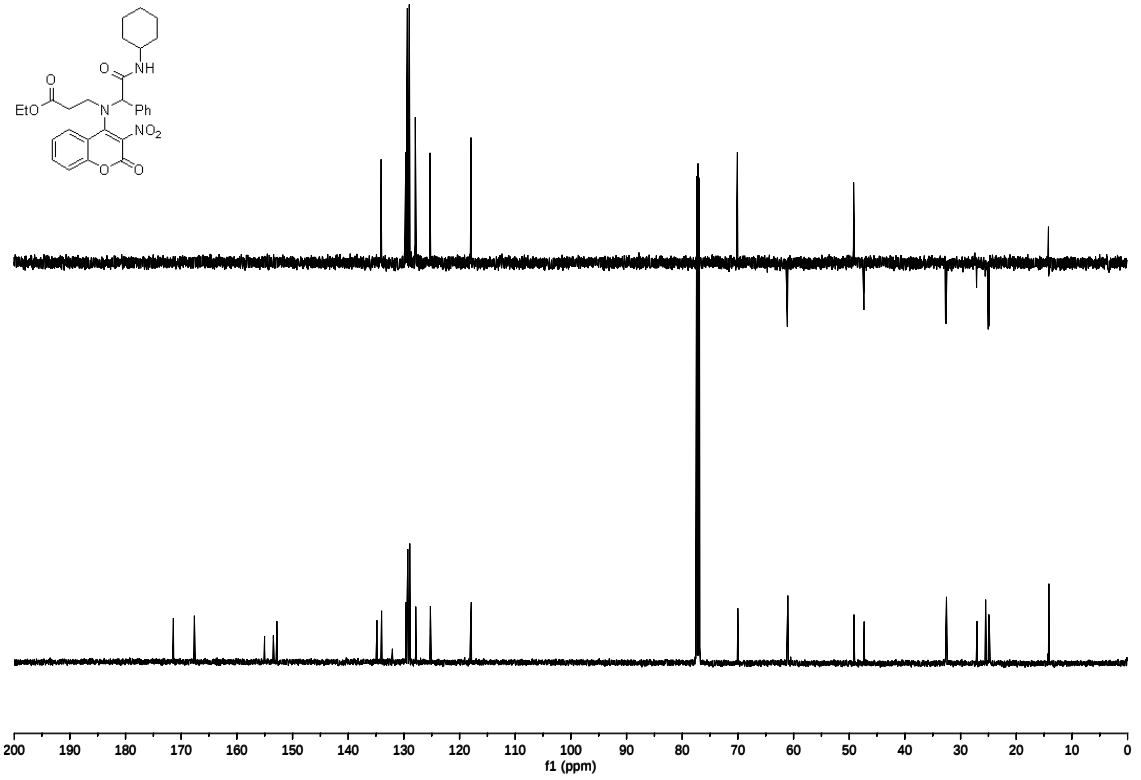




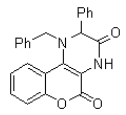


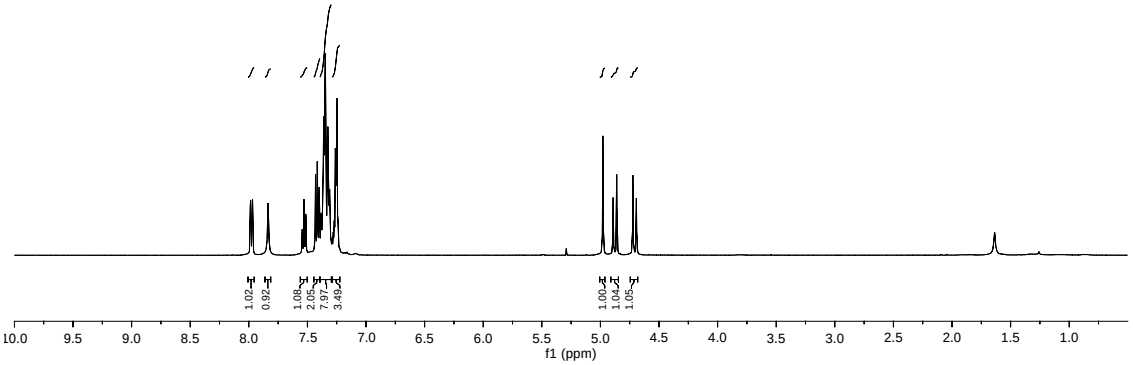
Ethyl 3-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)(3-nitro-2-oxo-2*H*-chromen-4-yl)amino)propanoate (17s).

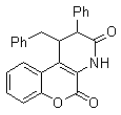


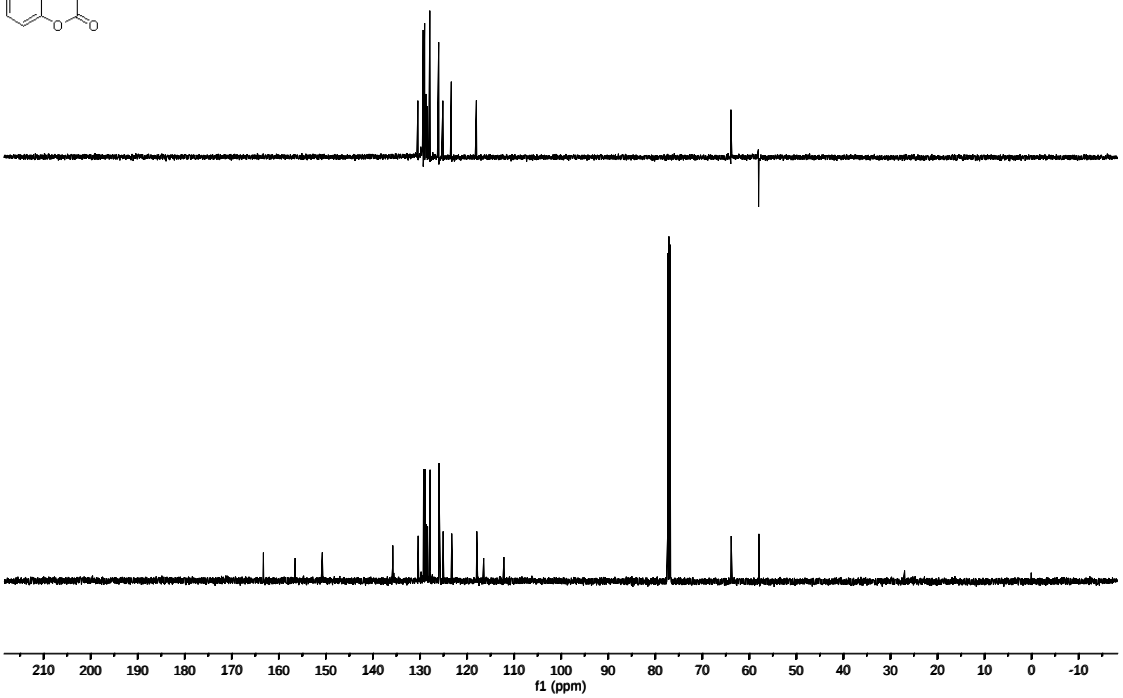


1-Benzyl-2-phenyl-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19a).

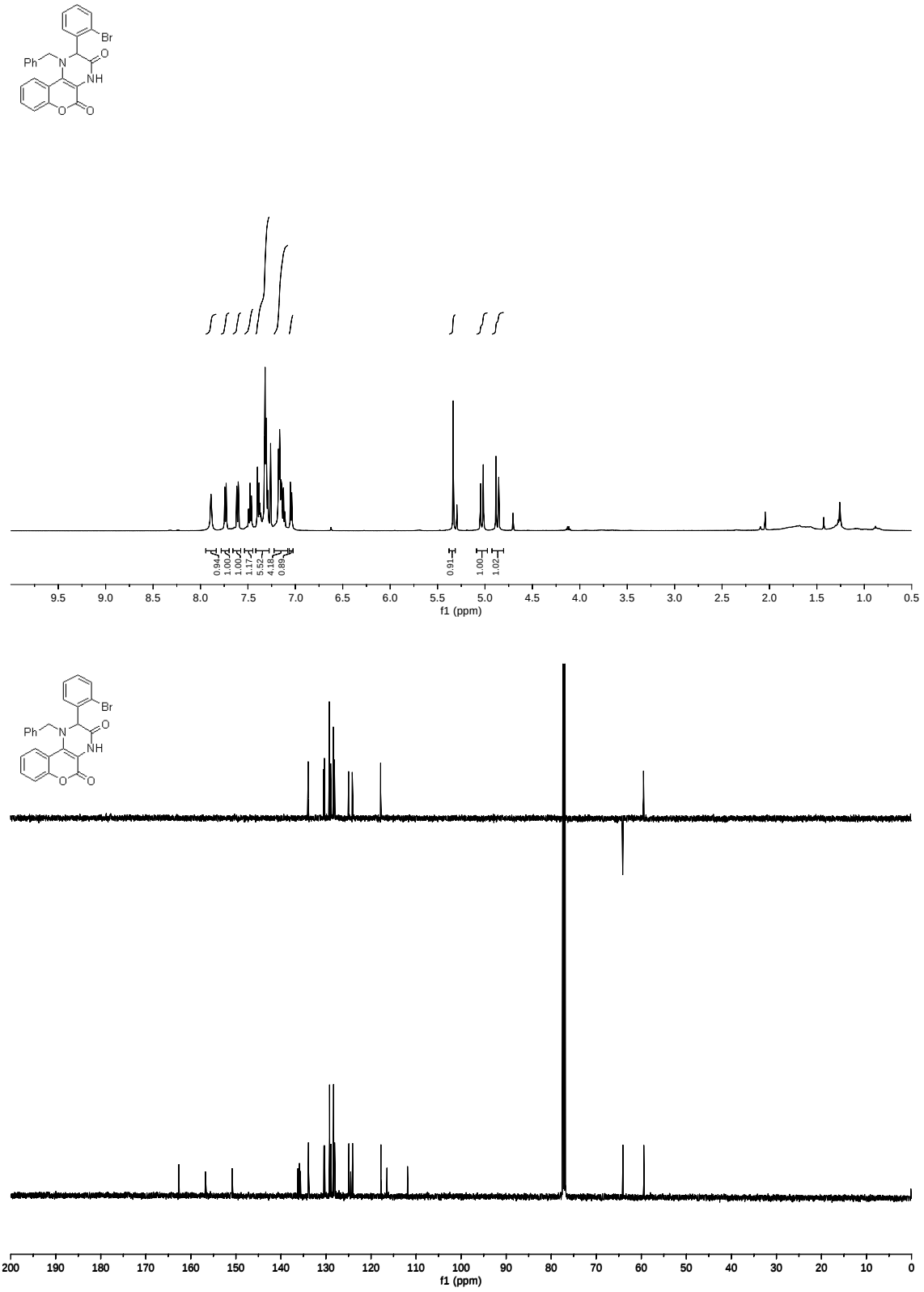




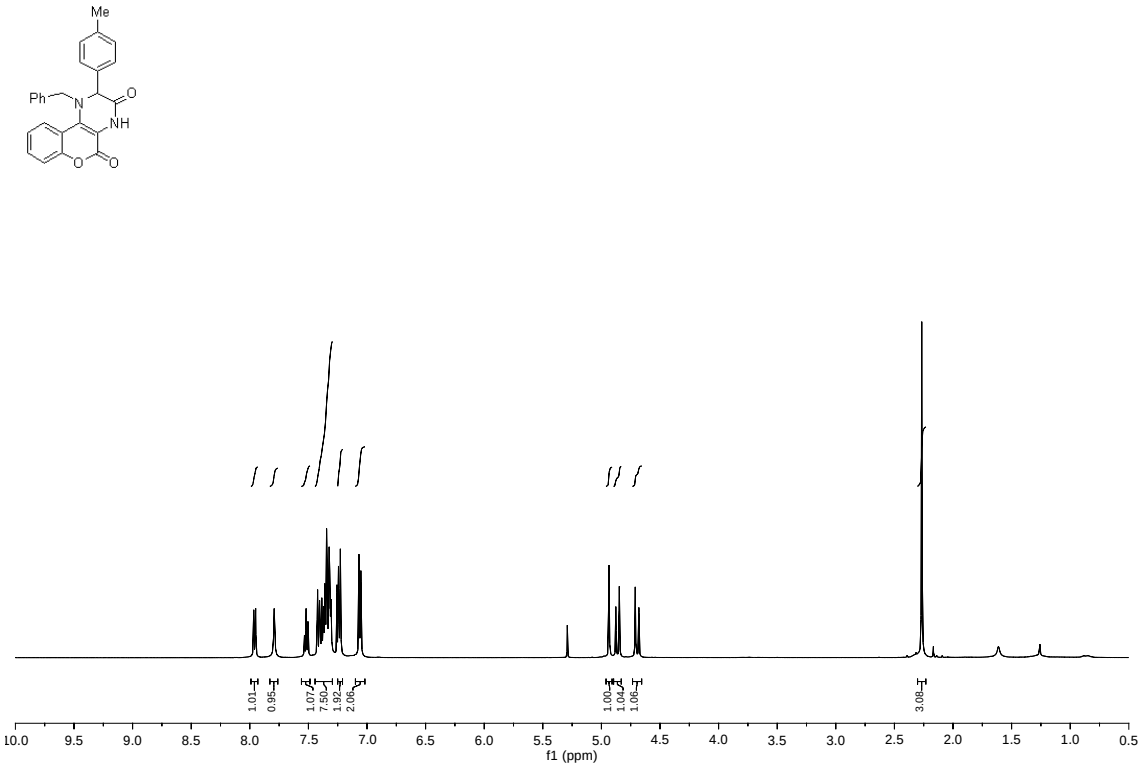


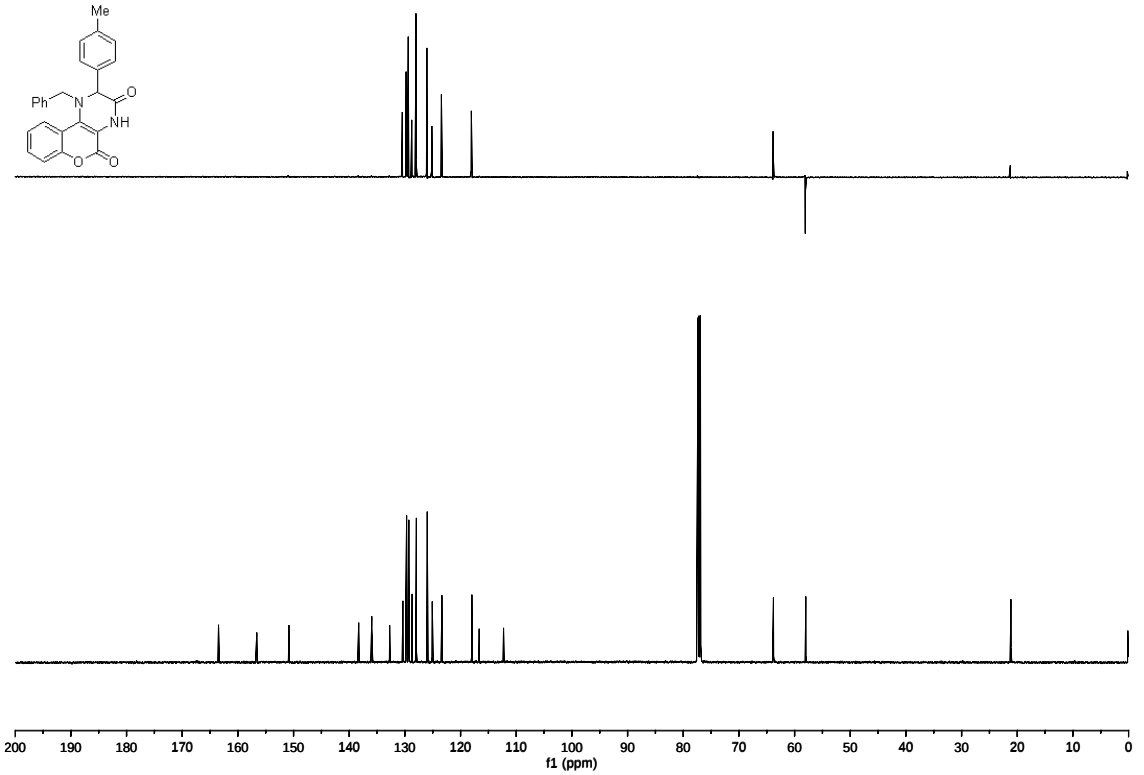


1-Benzyl-2-(2-bromophenyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19b)

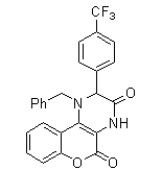


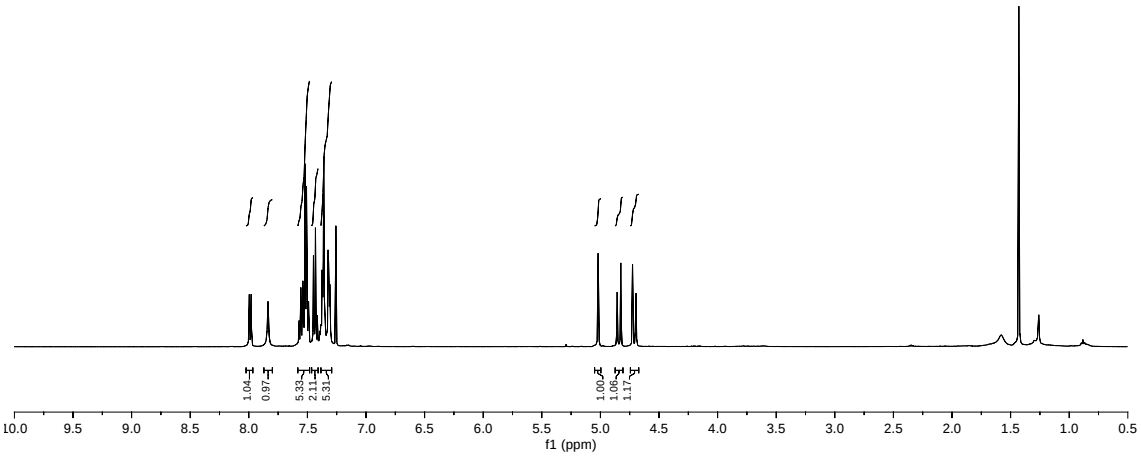
1-Benzyl-2-(*p*-tolyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19c).

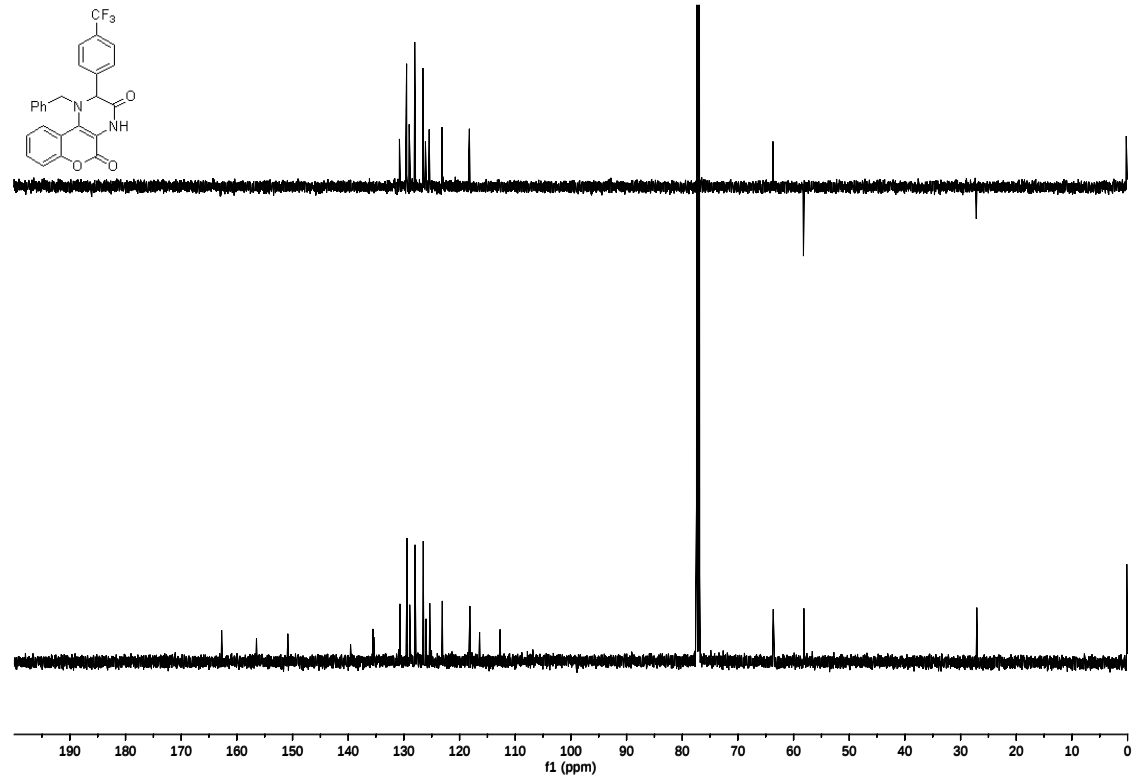




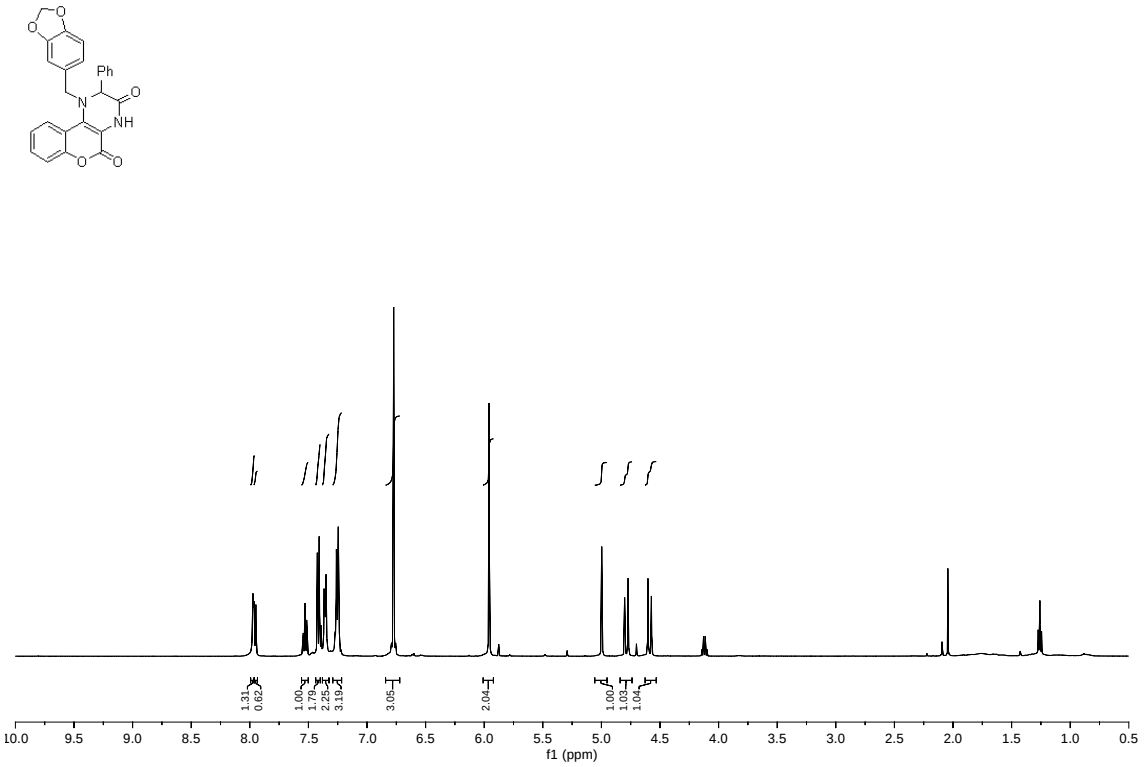
1-Benzyl-2-(4-(trifluoromethyl)phenyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19d).

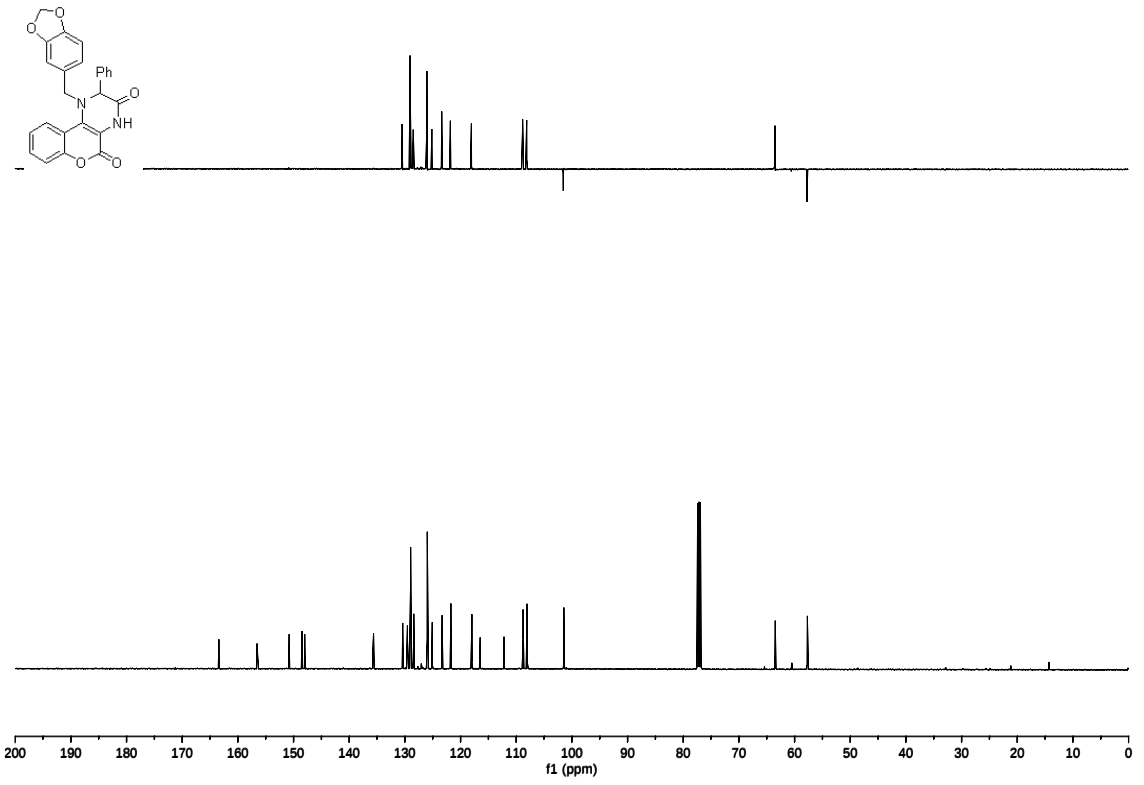




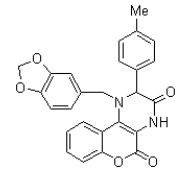


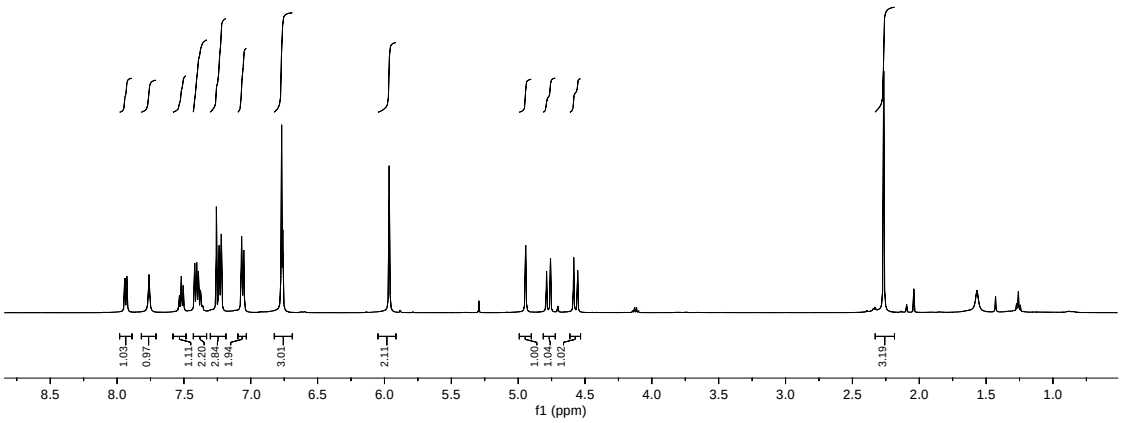
1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-phenyl-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19e).

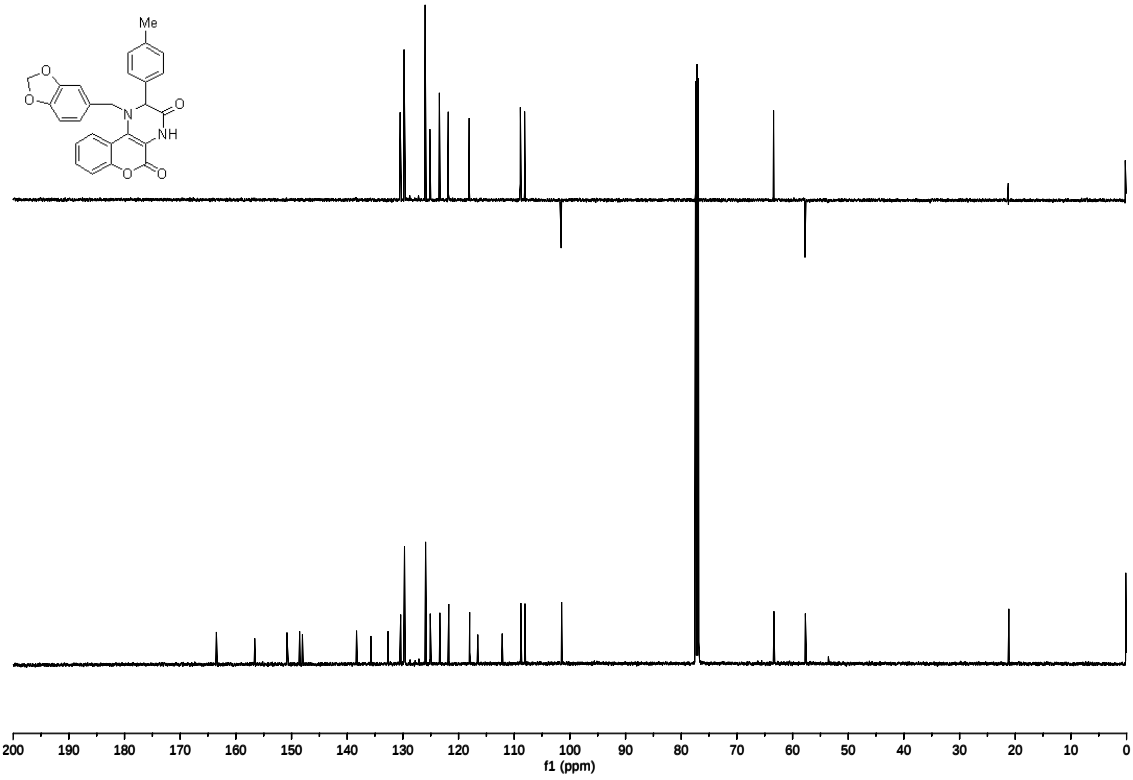




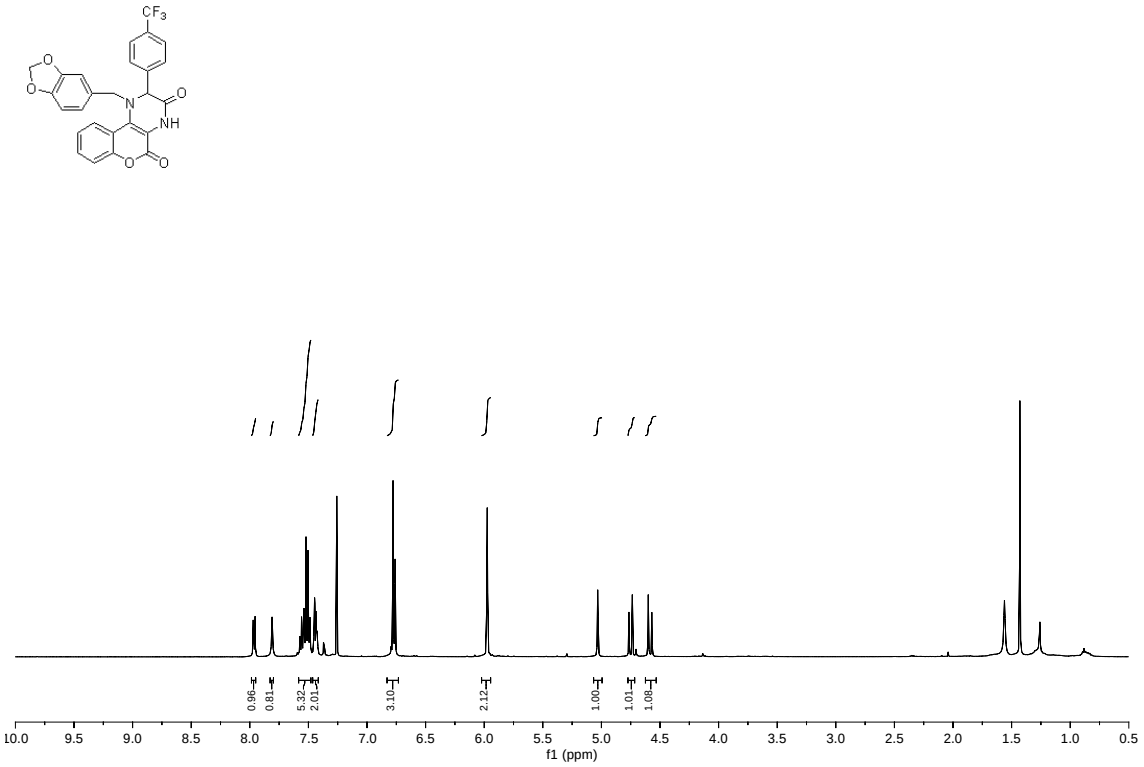
1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(*p*-tolyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19f).

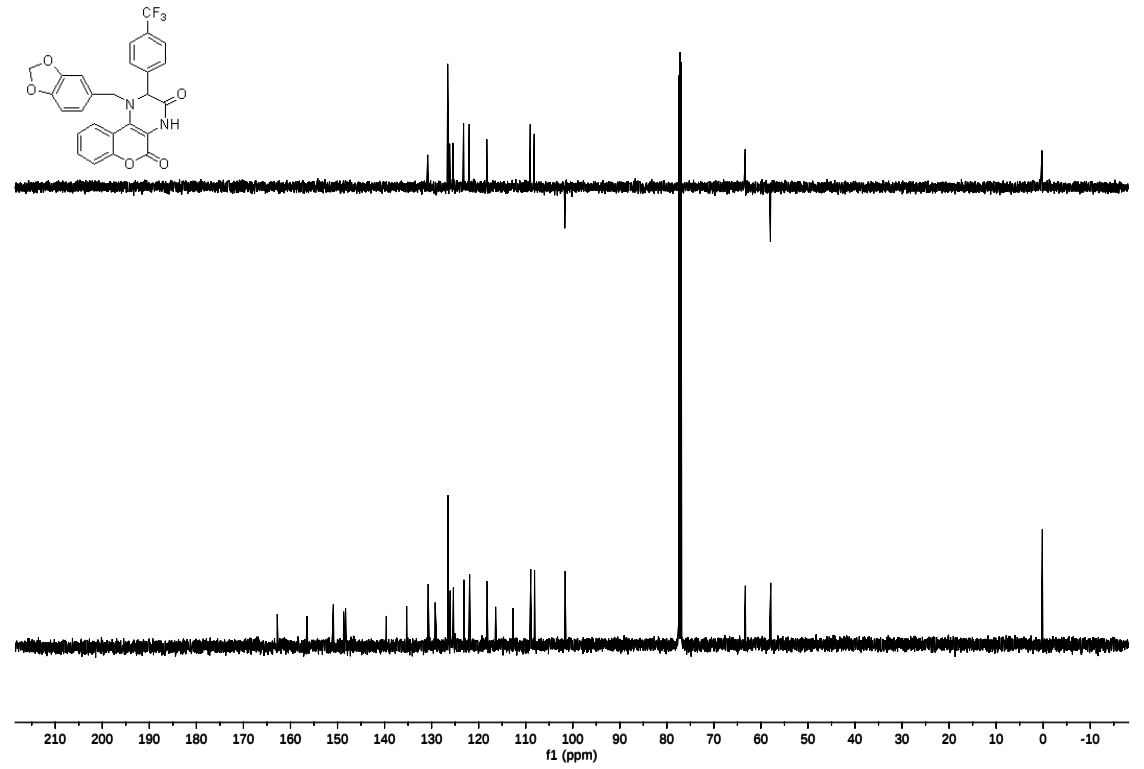




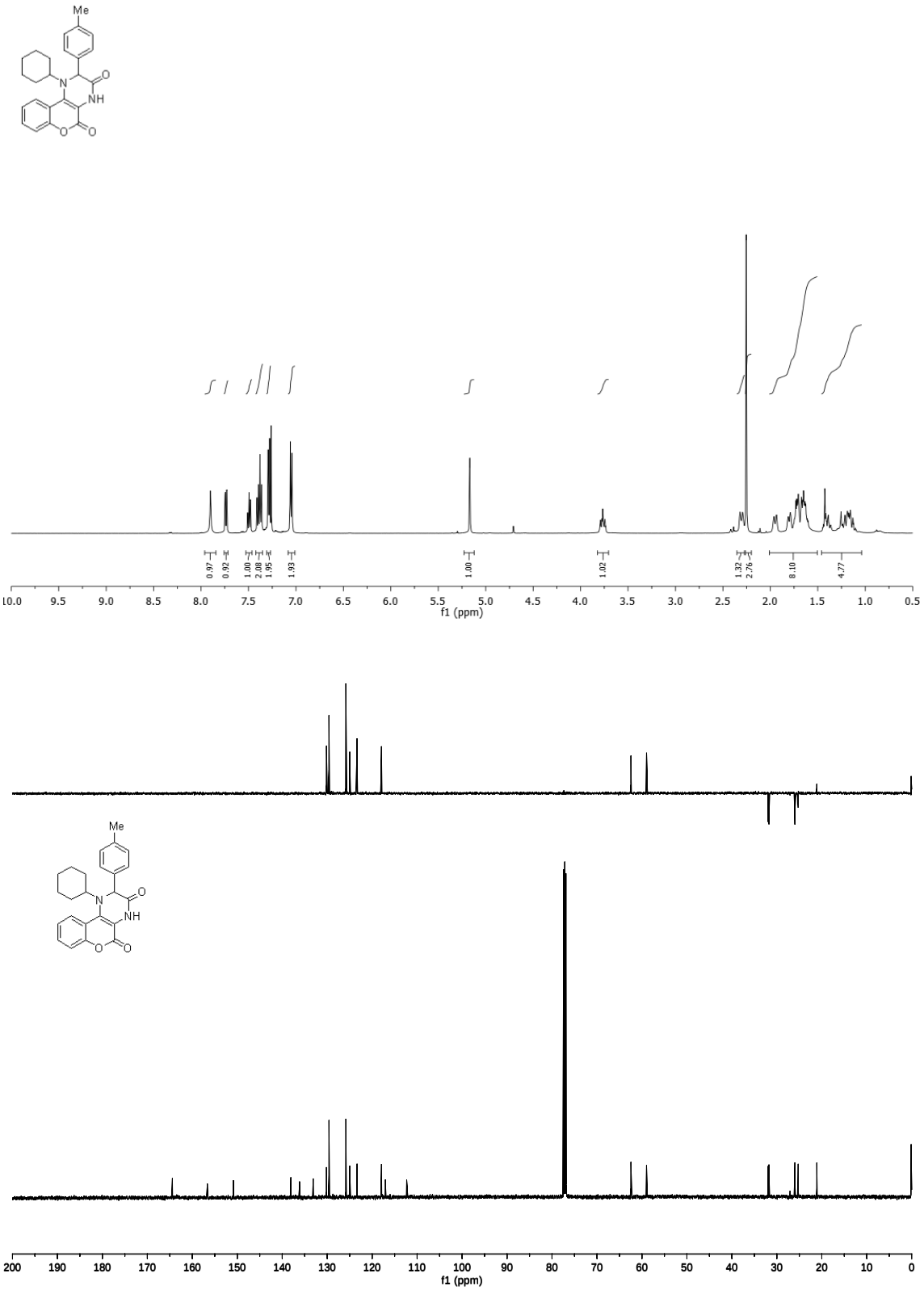


1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-(trifluoromethyl)phenyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19g).

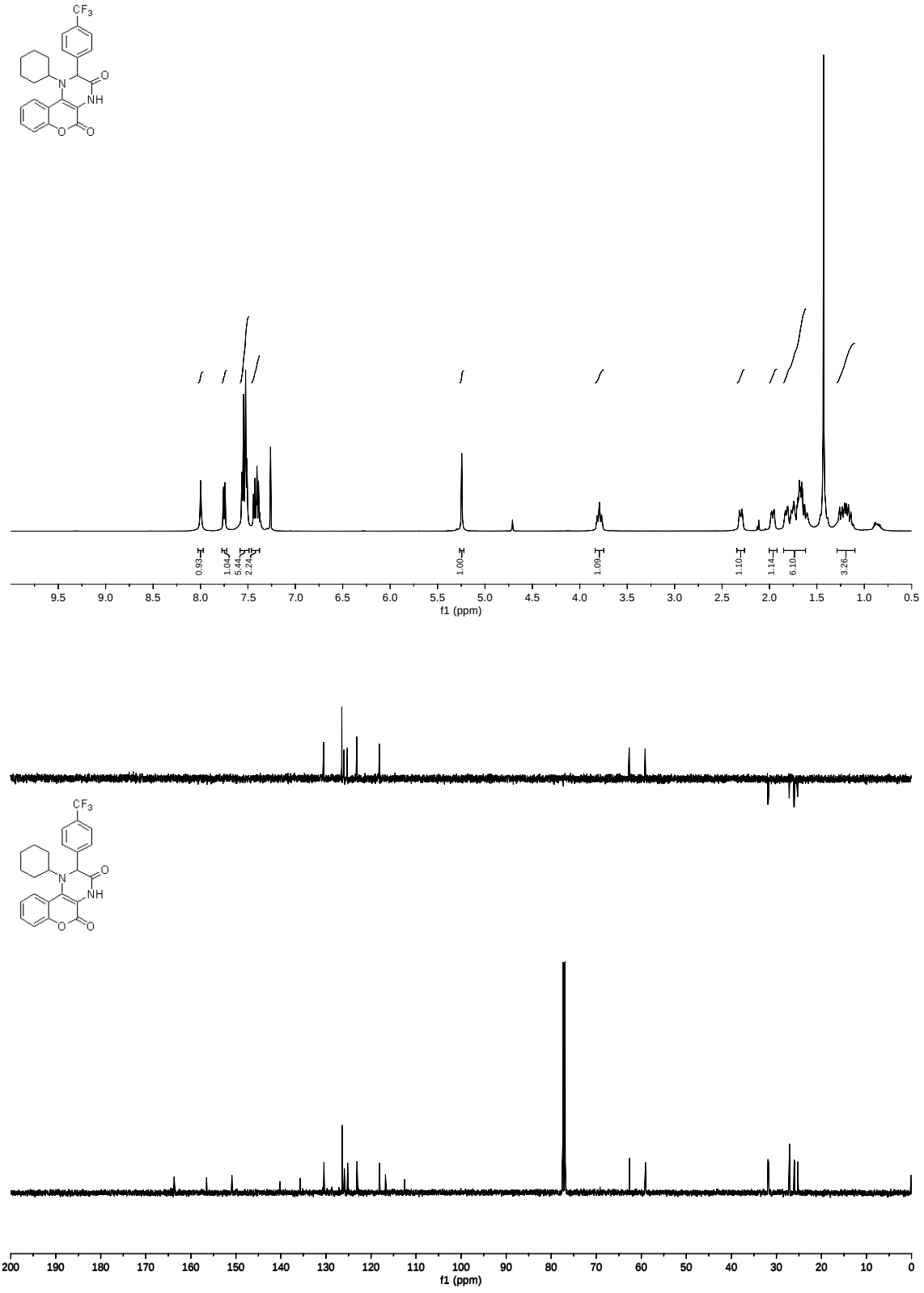




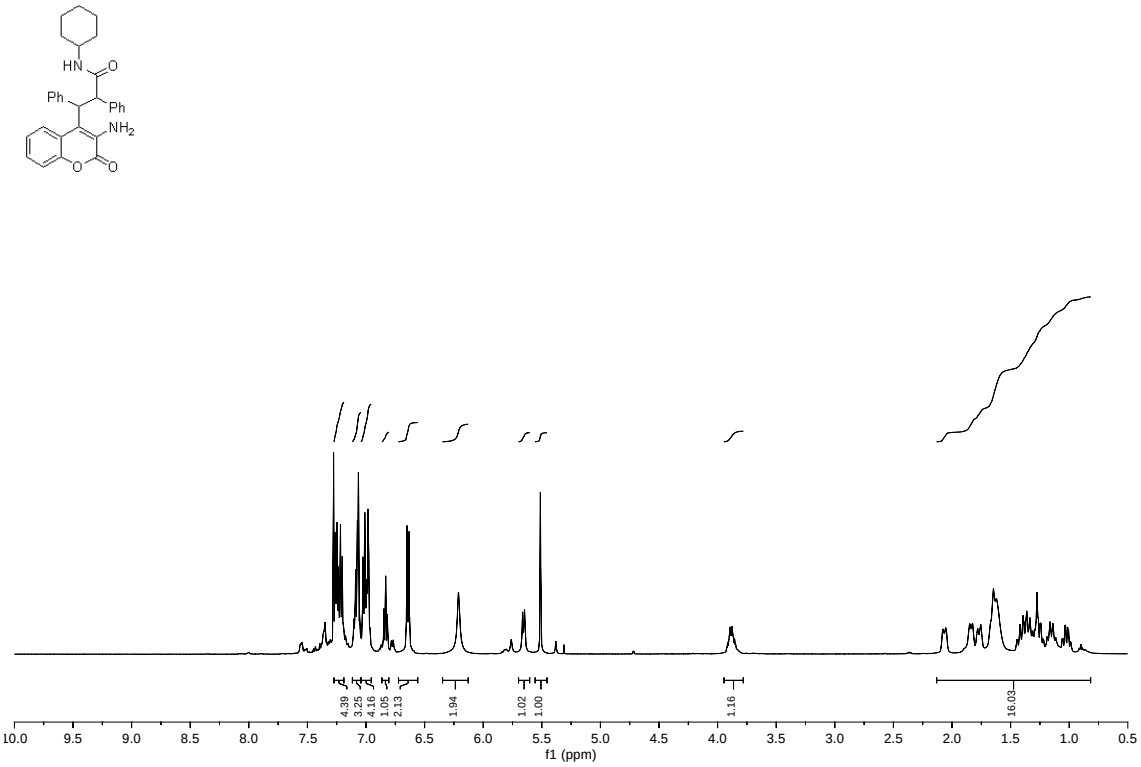
1-Cyclohexyl-2-(*p*-tolyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19h).

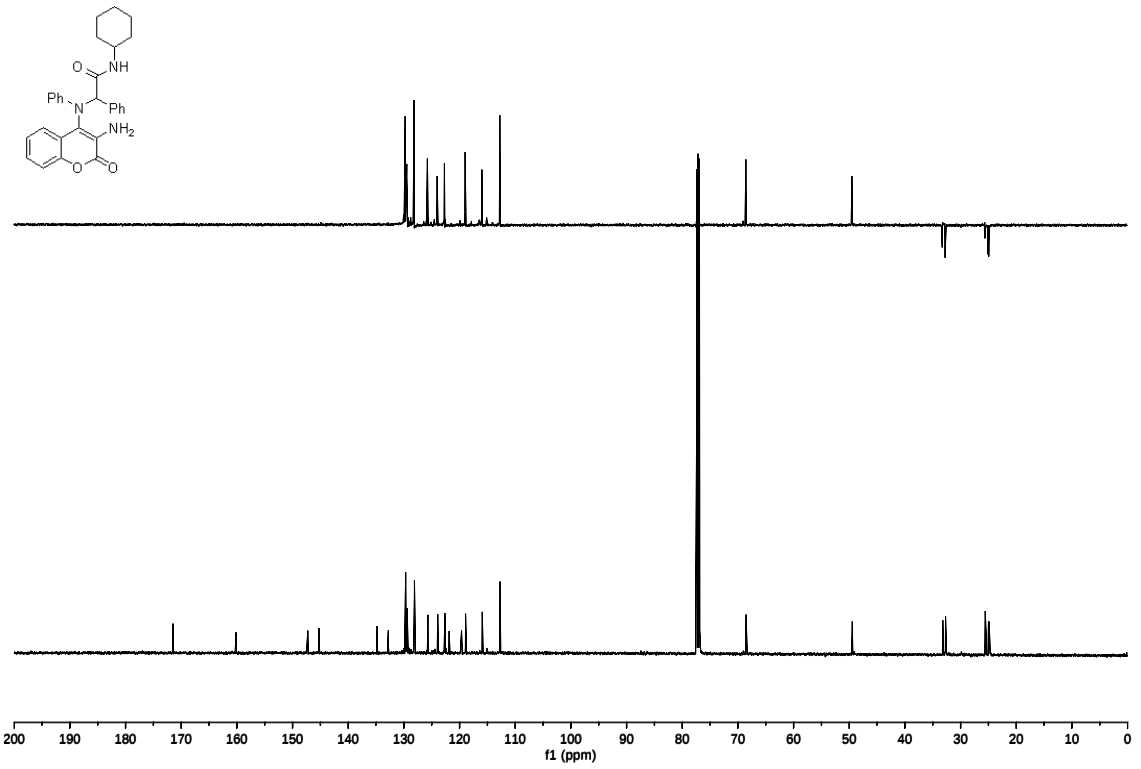


1-Cyclohexyl-2-(4-(trifluoromethyl)phenyl)-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19i)

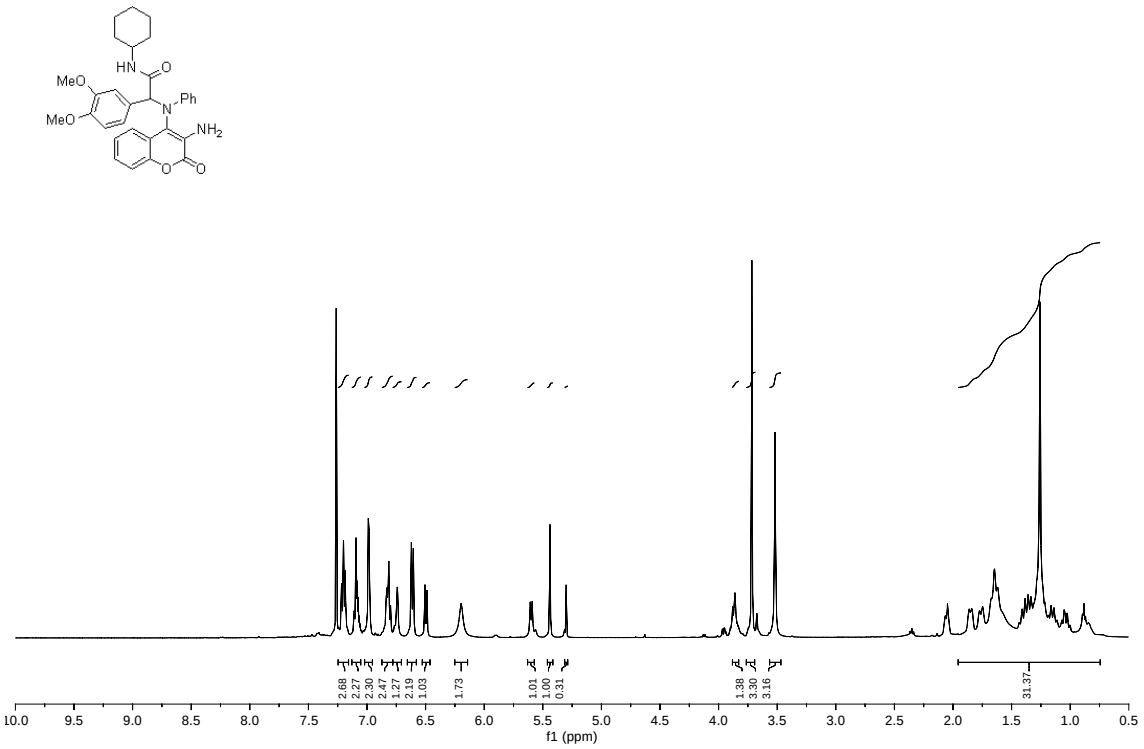


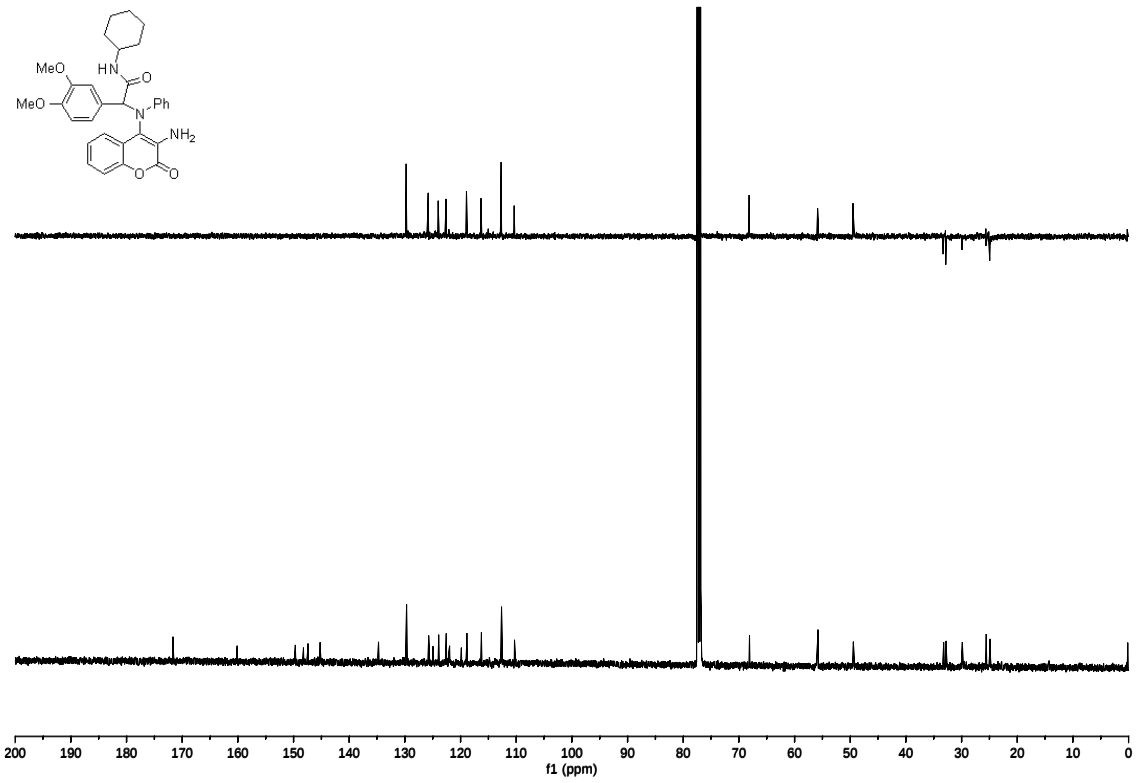
2-((3-Amino-2-oxo-2*H*-chromen-4-yl)(phenyl)amino)-*N*-cyclohexyl-2-phenylacetamide (18j).



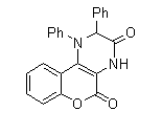


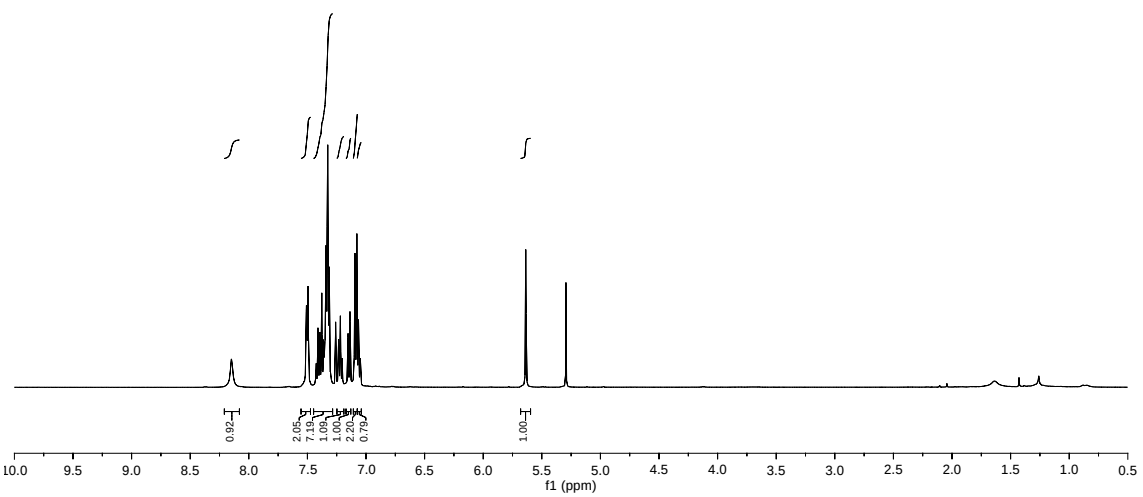
2-((3-Amino-2-oxo-2*H*-chromen-4-yl)(phenyl)amino)-*N*-cyclohexyl-2-(3,4-dimethoxyphenyl)acetamide (18k).

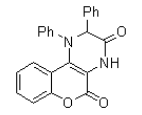


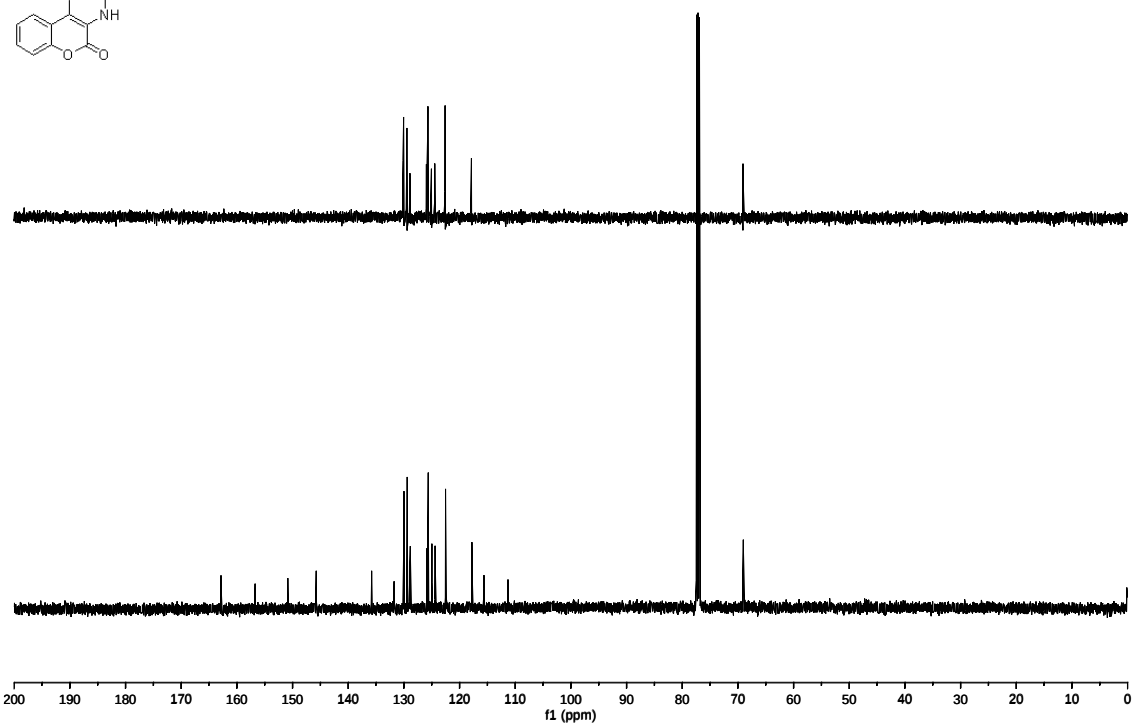


1,2-Diphenyl-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19j).

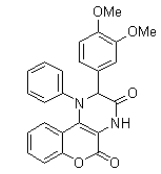


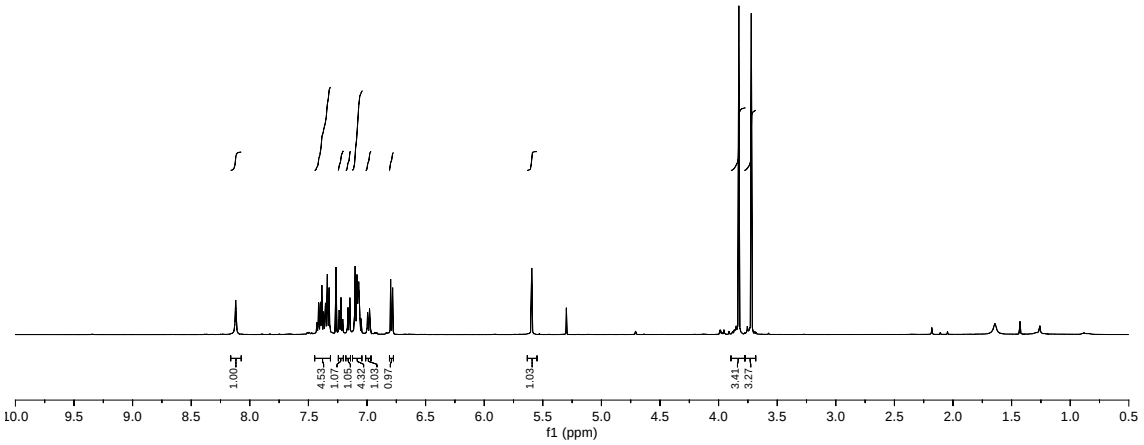


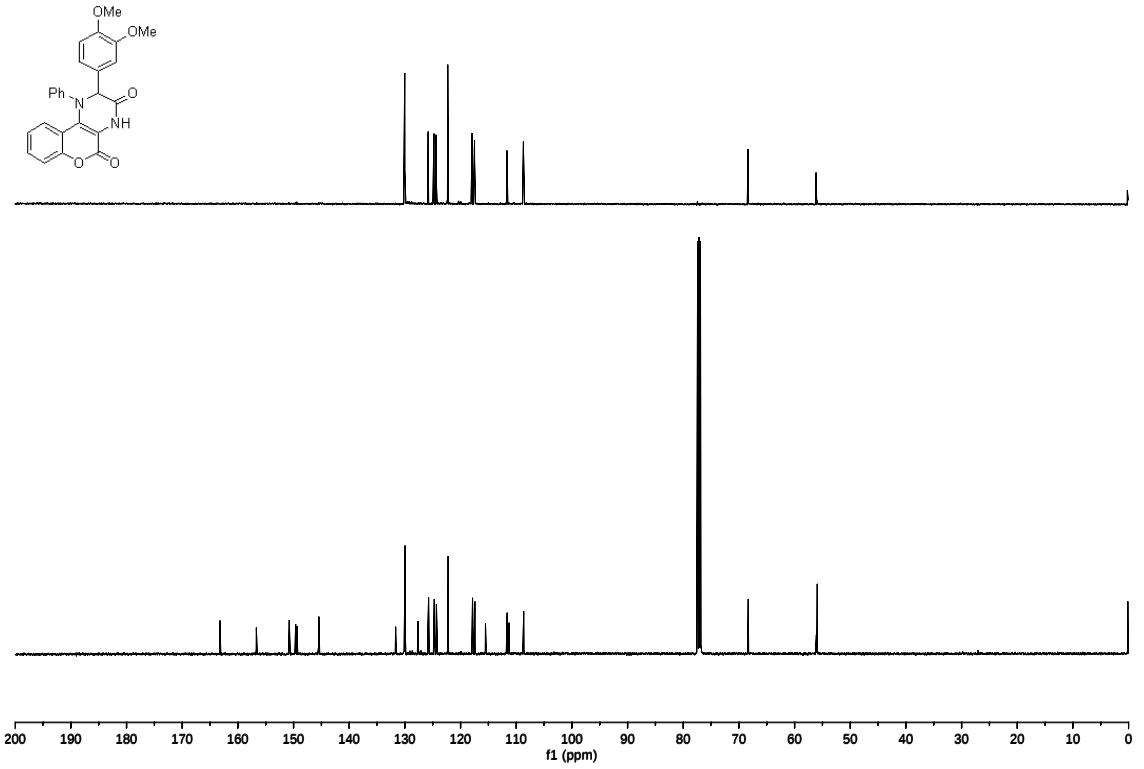




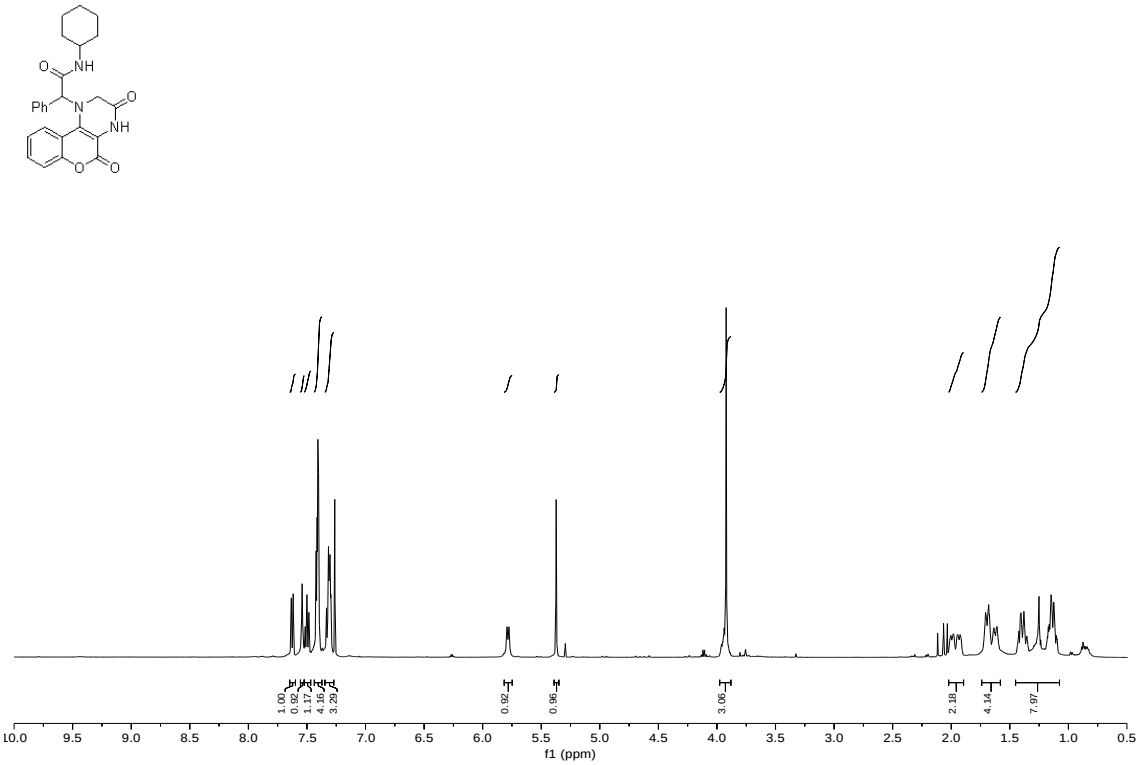
2-(3,4-Dimethoxyphenyl)-1-phenyl-1,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazine-3,5-dione (19k).

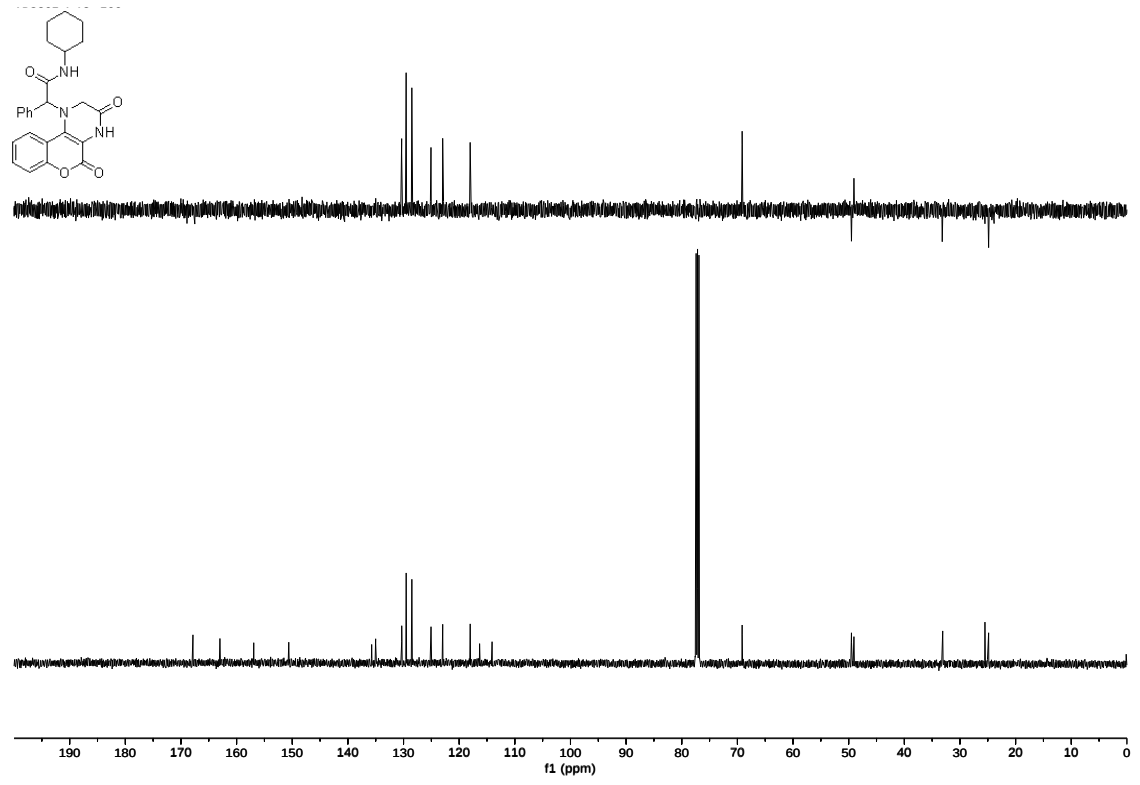




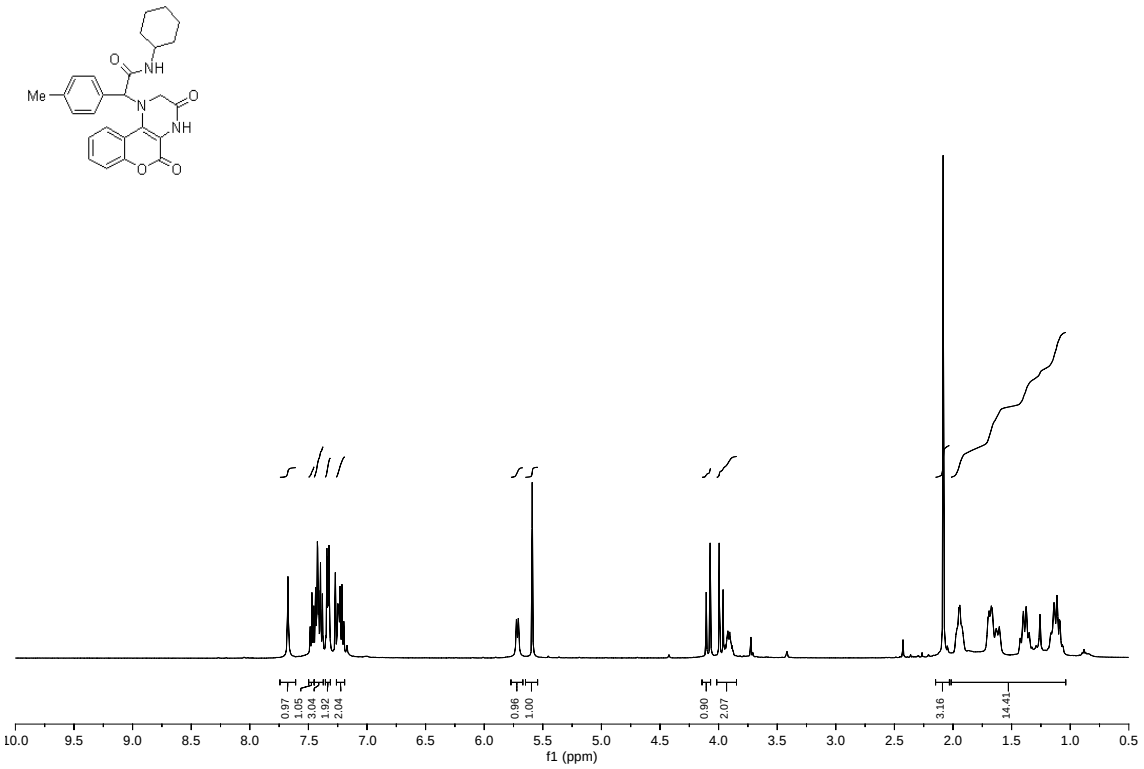


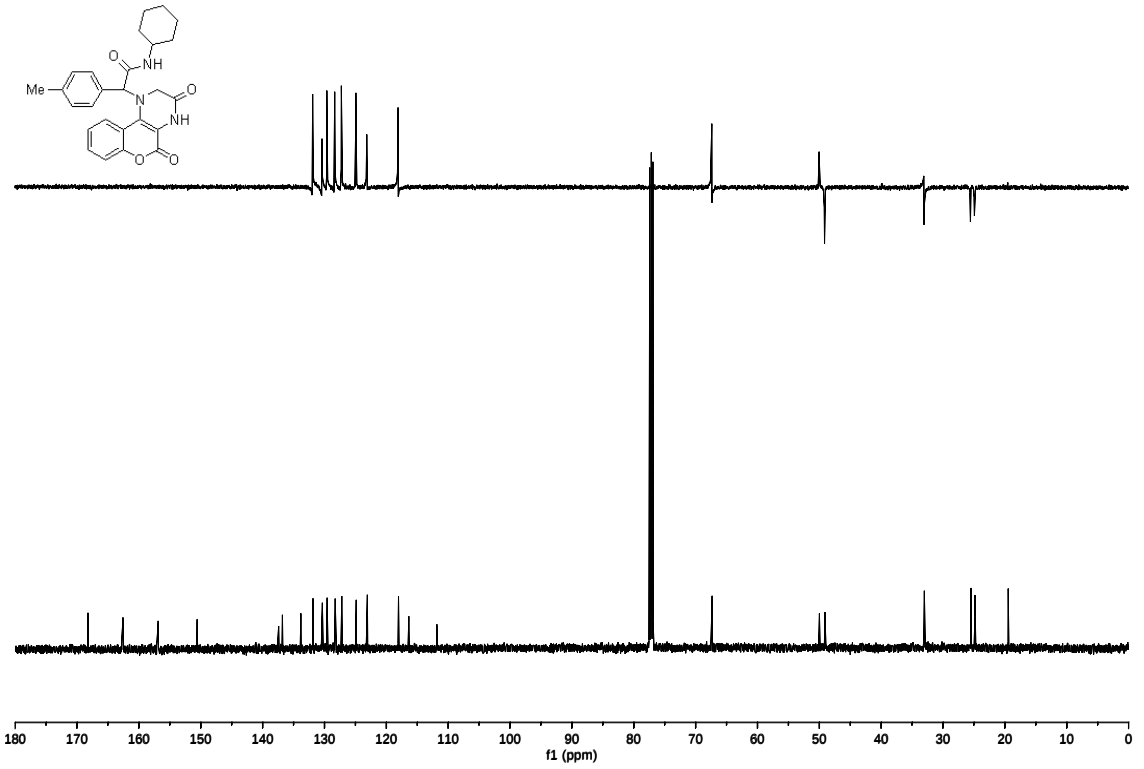
_N_-cyclohexyl-2-(3,5-dioxo-3,4-dihydro-2_H_-chromeno[3,4-_b_]pyrazin-1(5_H_)-yl)-2-phenyl acetamide (20l)



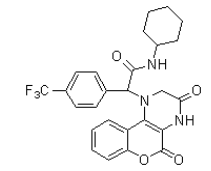


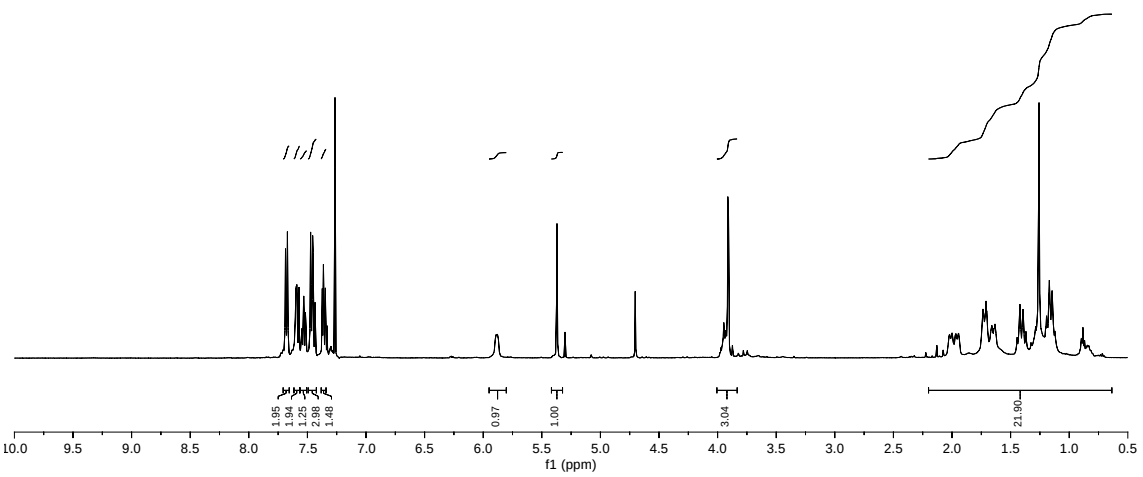
***N*-cyclohexyl-2-(3,5-dioxo-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)-2-(*p*-tolyl)acetamide (20m).**

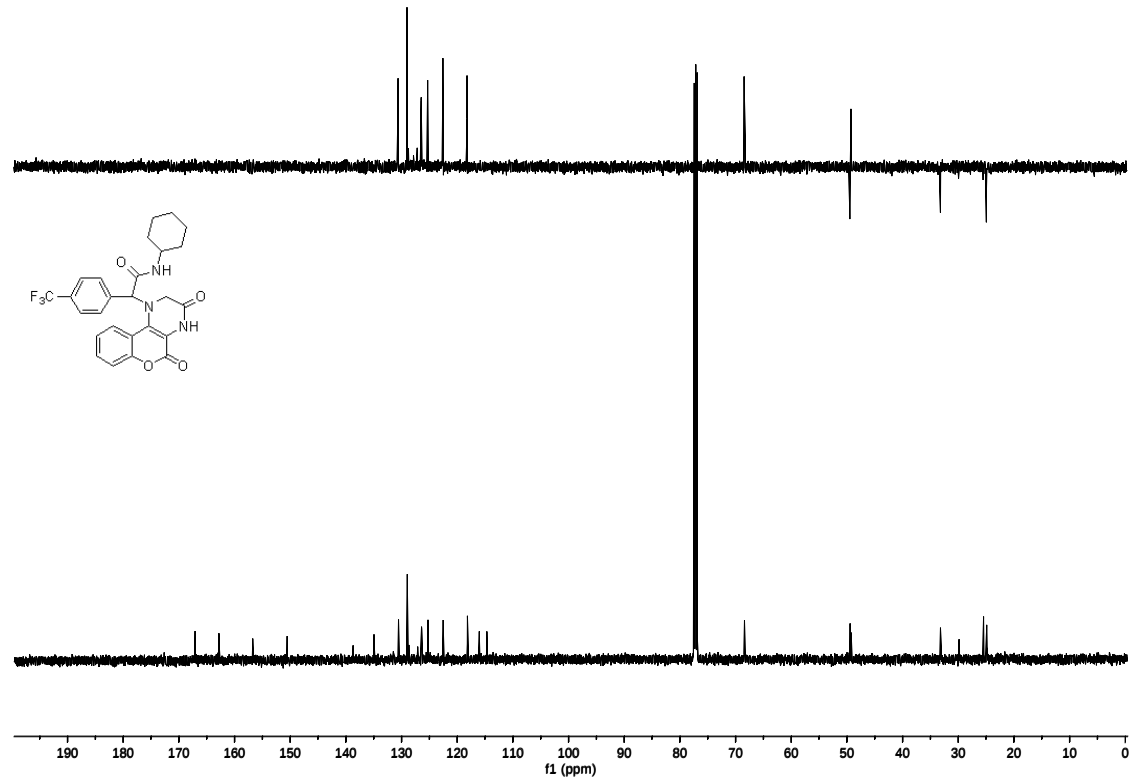




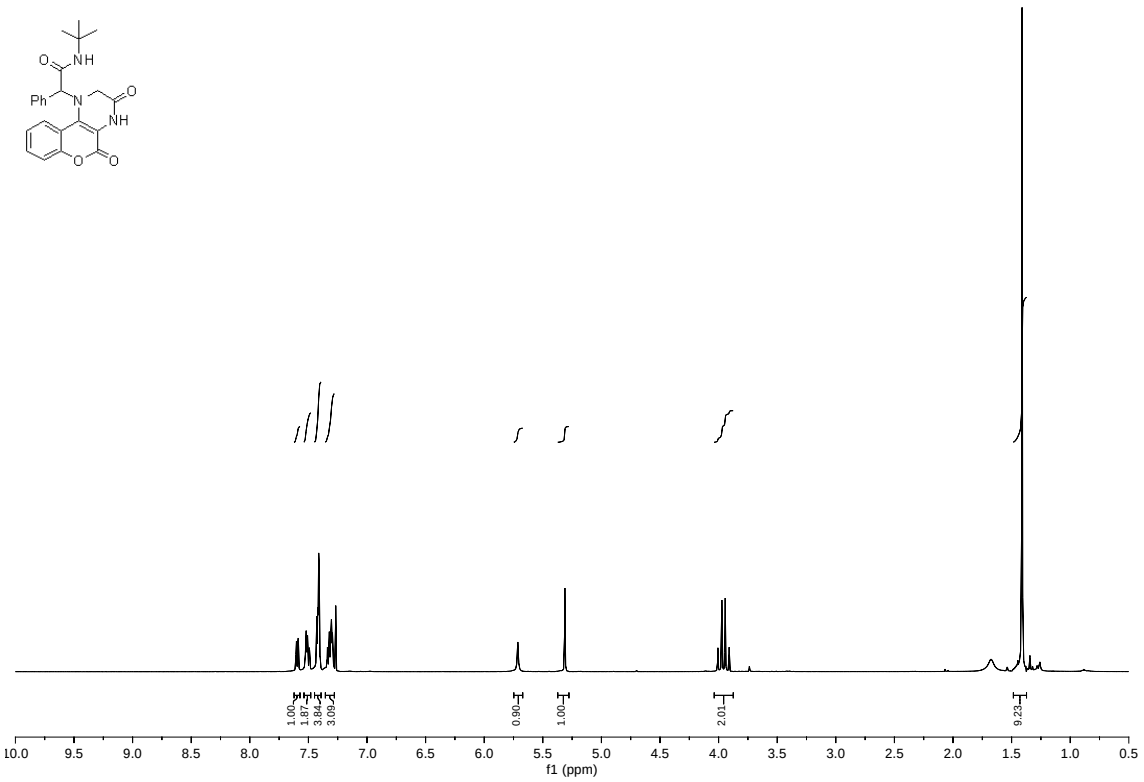
***N*-cyclohexyl-2-(3,5-dioxo-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (20n).**

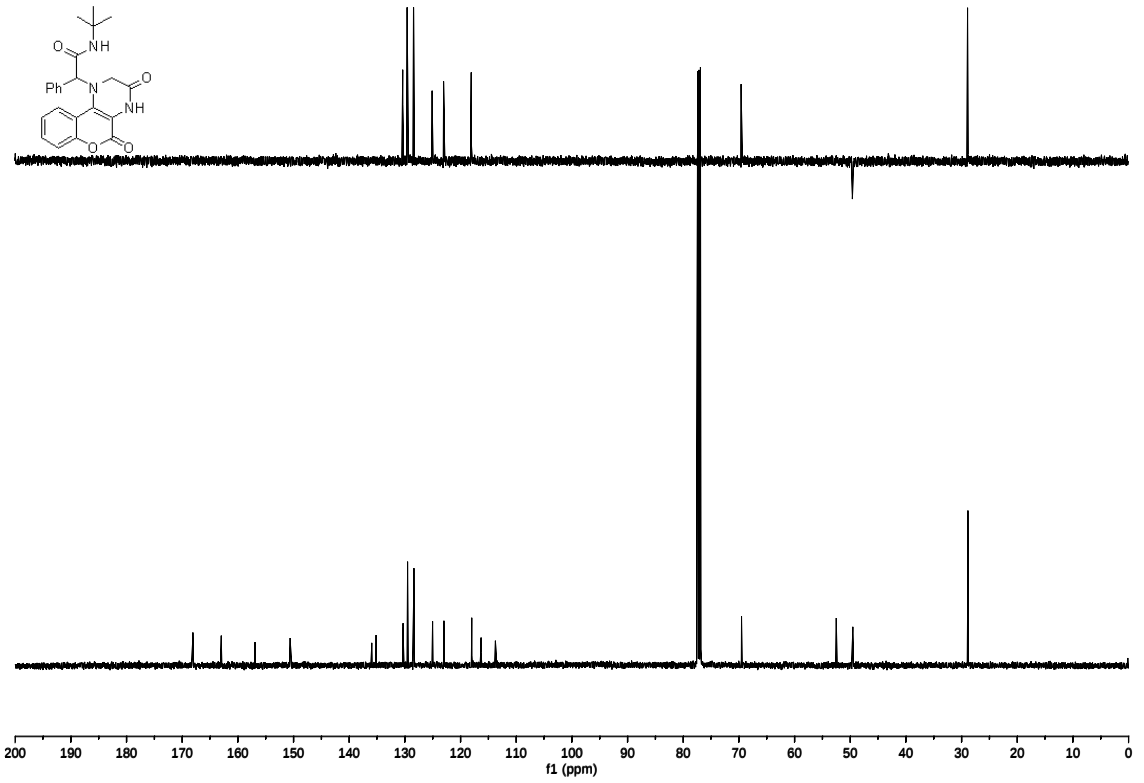




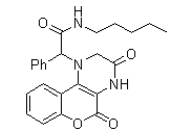


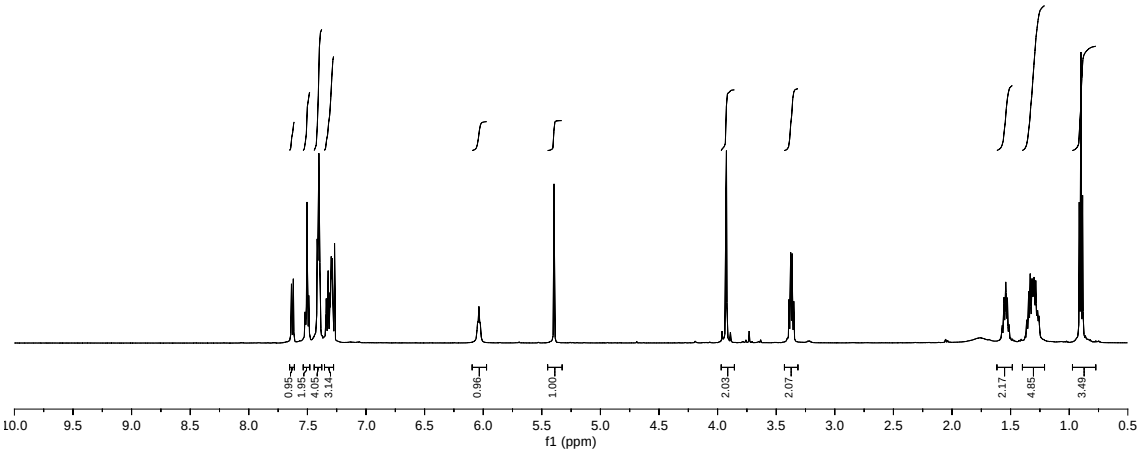
***N*-(*tert*-butyl)-2-(3,5-dioxo-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)-2-phenylacetamide (20o).**

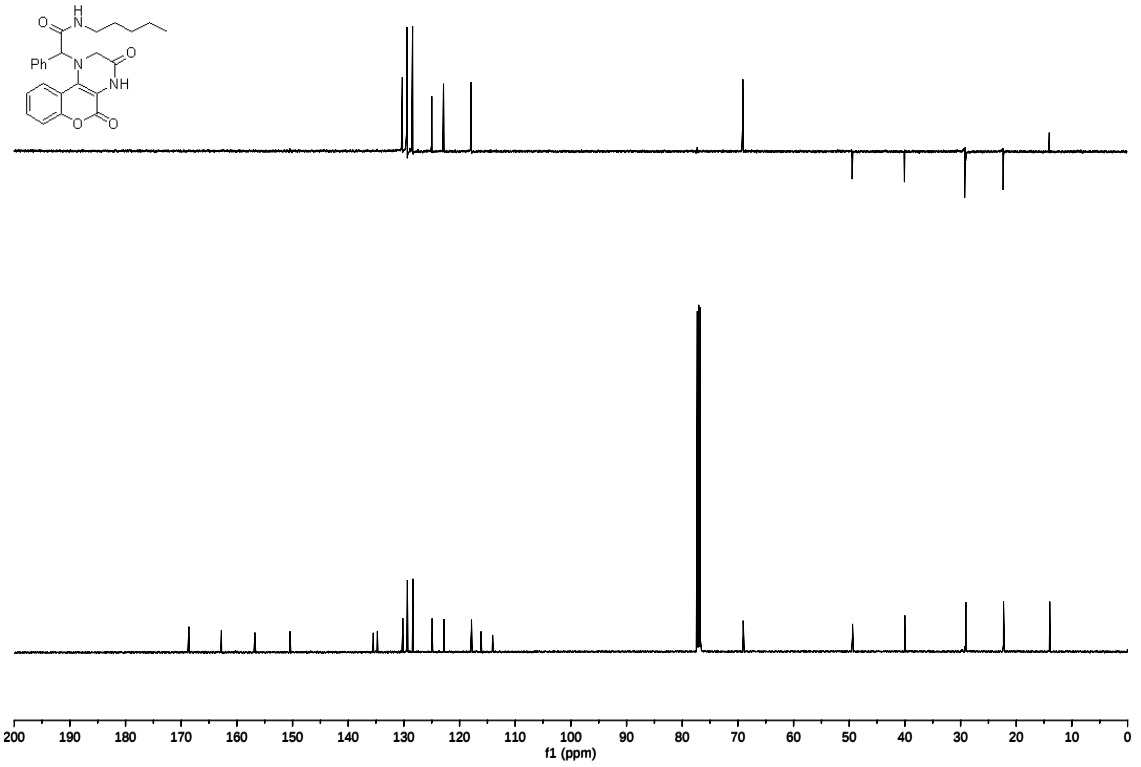




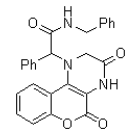
2-(3,5-Dioxo-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)-*N*-pentyl-2-phenylacetamide (20p).

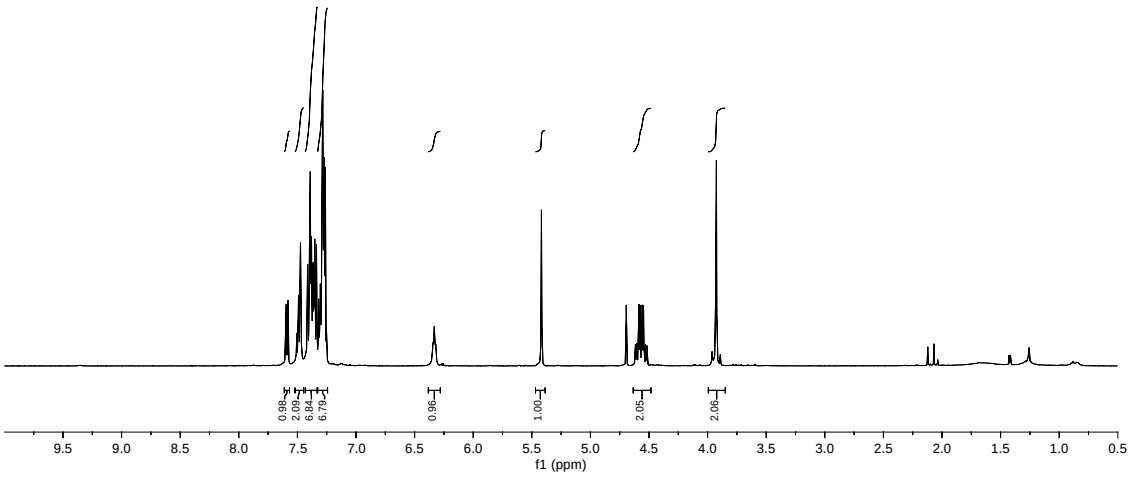


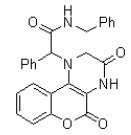


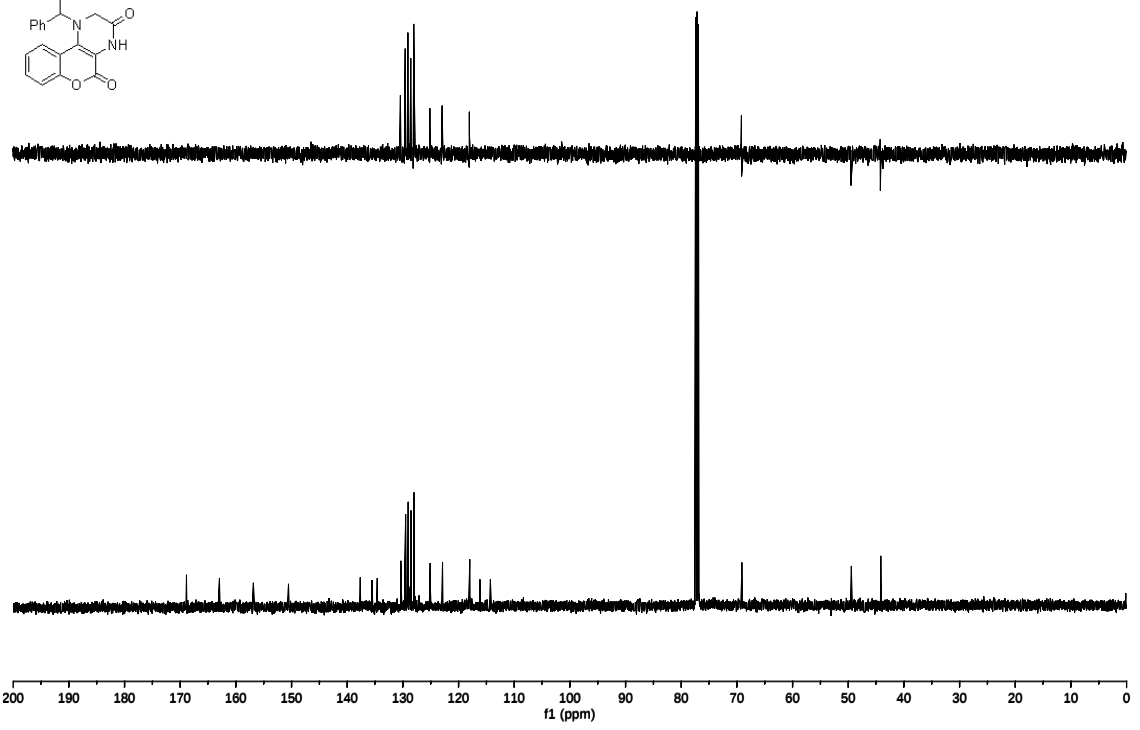


_N_-benzyl-2-(3,5-dioxo-3,4-dihydro-2_H_-chromeno[3,4-_b_]pyrazin-1(5_H_)-yl)-2-phenylacetamide (20q).

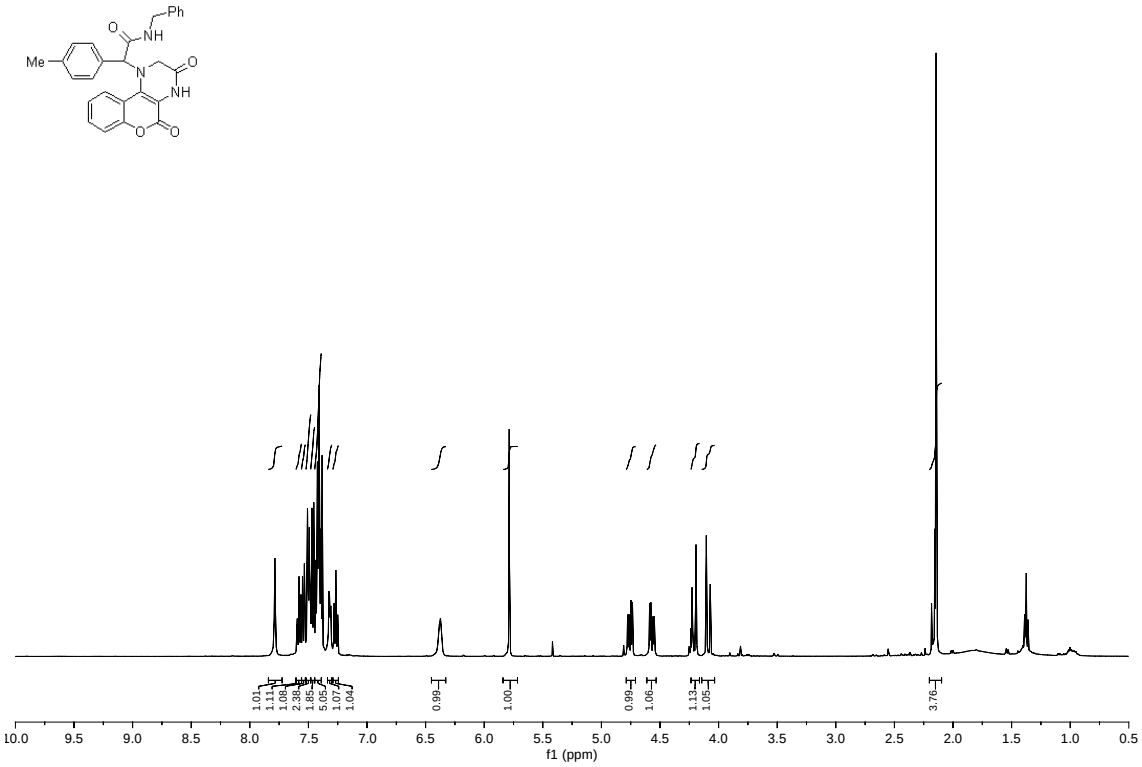


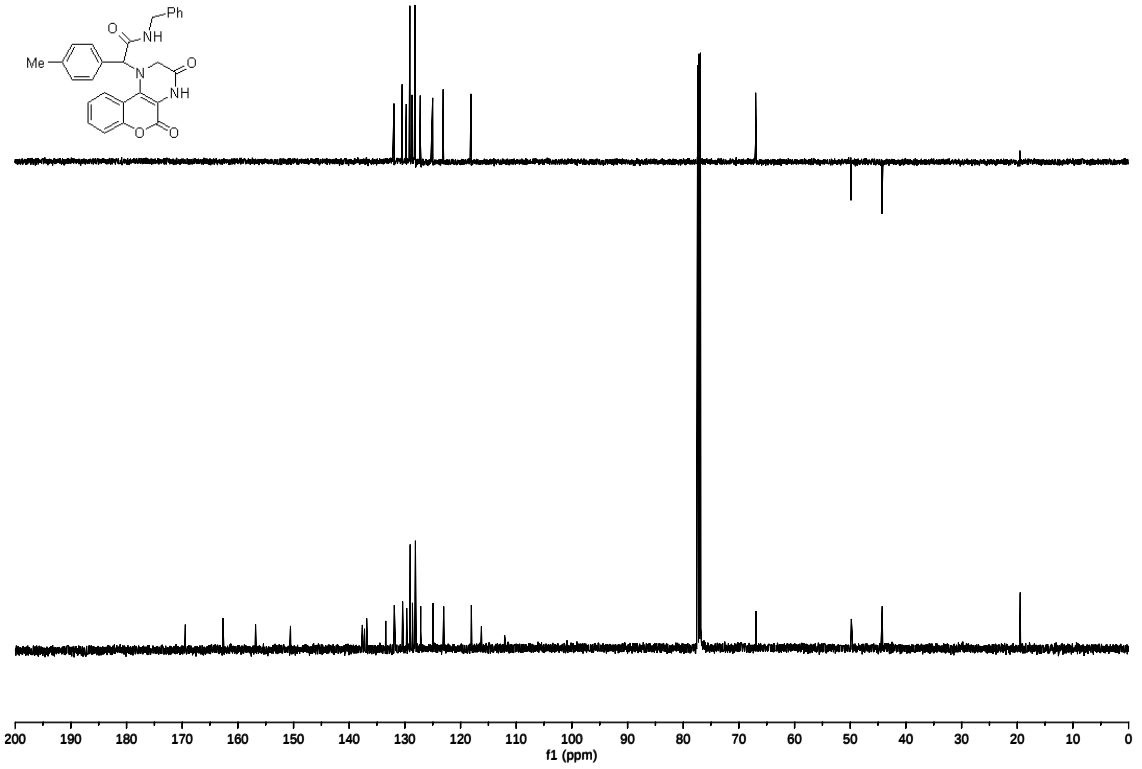






***N*-benzyl-2-(3,5-dioxo-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)-2-(*p*-tolyl)acetamide (20r).**





Ethyl 3-(3,5-dioxo-2-phenyl-3,4-dihydro-2*H*-chromeno[3,4-*b*]pyrazin-1(5*H*)-yl)propanoate (19s).