High Content Screening of diverse compound libraries identifies potent modulators of tubulin dynamics

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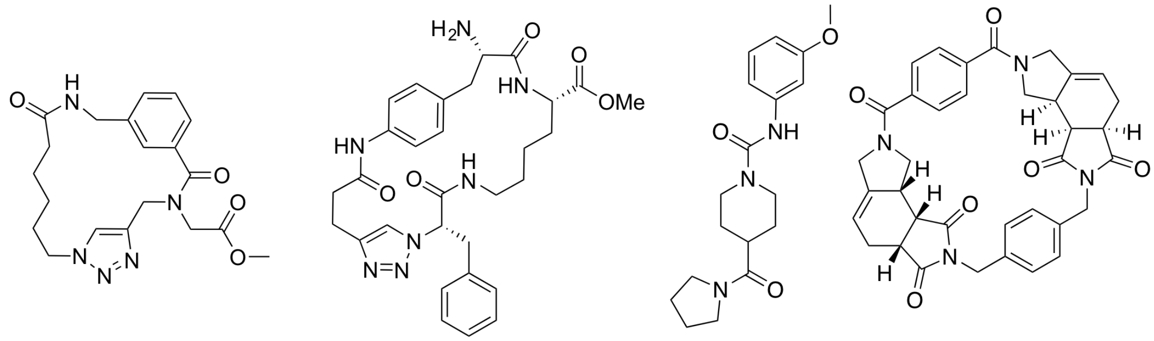
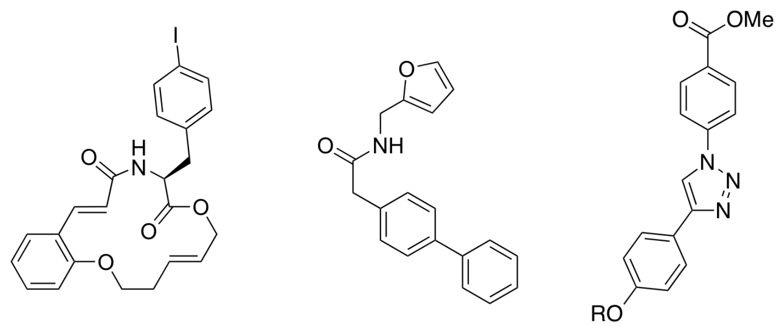
1 Supplementary Figures and Tables

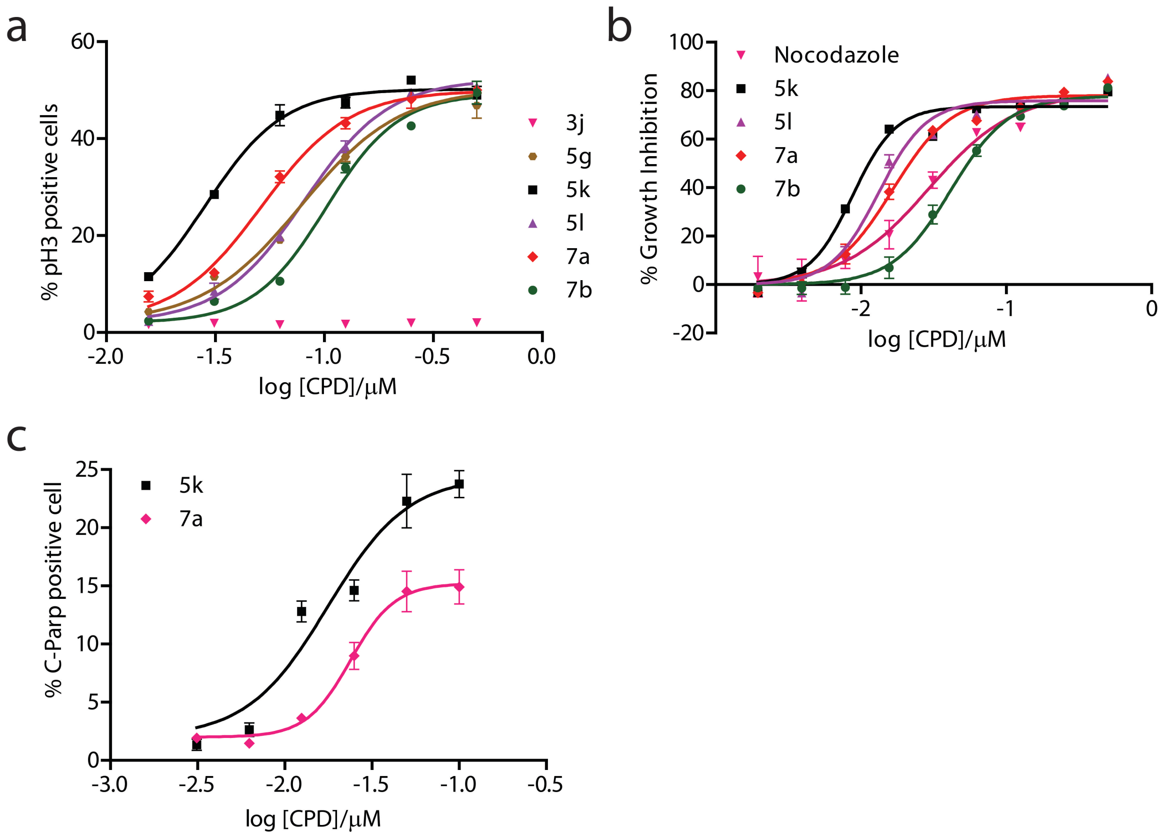


HB Non-peptidic Macrocycle Library (59) **AIL Peptidic Macrocycle Library (180)** **LL Urea Library (54)** **KO Macrocycle Library (14)**



MM Macrocycle Library (45) **JES Amide Library (15)** **COC Click Library (40)**

Supplementary Figure S1. Representative compounds for each library used in the phenotypic screen for mitotic arrest; number of compounds for each subset of the total library is indicated in parentheses.



Supplementary Figure S2. Representative data for anti-mitotic compounds: (a) mitotic arrest as caused by biphenylacetamides. U2oS cells were treated with test compounds for 20 h, fixed and stained with Hoechst and a phospho-Histone H3 specific antibody, and imaged using a Cellomics Arrayscan. Data shown is mean ± s.e.m. for an experiment conducted in triplicate; (b) growth inhibitory data for biphenylacetamides. U2oS cells were treated with compounds for 72 h, before being fixed and stained with Sulforhodamine B. Data shown is mean ± s.e.m. for an experiment conducted in triplicate; (c) induction of apoptosis data for biphenylacetamides. U2oS cells were treated with compounds for 72 h, stained with Hoechst and a cleaved PARP antibody and imaged using a Cellomics Arrayscan. Both compounds induced significant apoptosis. Data shown is mean ± s.e.m. for an experiment conducted in triplicate;

Compound Code	Molecular Weight	clogP	clogS	cell perm. (nm/s)	PSA (Å^2)
2f	277.32	4.22	-5.02	3217.43	44.88
3a	301.39	4.70	-5.03	2585.48	36.30
3b	315.41	4.75	-4.70	2253.57	34.52
3d	315.41	4.97	-5.44	3895.37	27.12
3e	331.41	4.80	-5.26	2595.95	44.57
3f	380.28	5.28	-5.89	2617.51	36.31
3g	302.38	3.77	-4.36	1526.91	48.52
3h	302.38	4.05	-4.77	1936.92	49.25
3i	287.36	4.95	-5.66	4181.50	35.76
3j	267.37	3.91	-3.86	1845.77	36.59
5a	333.39	3.47	-3.95	945.74	72.29
5b	348.40	3.33	-4.65	658.11	84.01
5c	323.37	4.53	-5.16	2377.80	45.40
5d	381.43	4.39	-4.99	2376.68	64.78
5e	349.43	4.63	-5.24	2399.49	52.48
5f	375.35	5.16	-5.79	2379.67	53.13
5g	333.39	3.51	-4.54	755.92	74.39
5h	349.39	3.73	-4.91	507.03	81.31
5i	316.36	3.27	-5.27	493.59	71.20
5j	335.36	3.55	-3.83	2379.58	64.14
5k	343.42	4.19	-5.28	825.14	65.29
5l	359.42	4.43	-5.79	735.48	72.43
6	335.36	3.20	-3.89	60.73	94.80
7a	348.40	3.39	-4.78	679.26	84.19
7b	390.48	4.55	-5.85	1051.14	80.54

Supplementary Table S1. Calculated physiochemical properties for several tubulin inhibitors. Data generated using Schrodinger Qikprop. Ligands were prepared using ligprep and the output used directly in Qikprop; clogP refers to the calculated partition coefficient between octanol and water; clogS refers to the calculated solubitlity in mol/dm^3; cell perm. refers to the calculated cell permeability using the Caco-2 model for the human gut.

Code	Polymerisation rate (OD/min)	% inhibition of polymerisation
DMSO	0.081	-
1	0.046	33.7
3f	0.081	-1.4
5i	0.060	26.9
7a	0.027	35.7
Nocodazole	0.005	53.6

Supplementary Table S2. Extrapolated data for inhibition of tubulin polymerization. Polymerisation rate was calculated by taking the gradient of the linear growth phase of the tubulin polymer. % inhibition of polymerization was calculated from the difference in final OD between tubulin treated with test compounds and the DMSO control.

2 General Methods: Biology

2.1 General Reagents

All compounds assayed were synthesized in our labs according to the procedures specified in the supporting information. Hoechst was purchased from Invitrogen (H3570) and used at 1:2500. Anti phospho-histone H3 (S10) was purchased from Abcam (ab5176) and used at 1:2000. AlexaFluor 488 goat anti-rabbit IgG was purchased from Invitrogen (A11034) and used at 1:500. Sulforhodamine B was purchased from Sigma Aldrich. Tubulin was purchased from Cytoskeleton Inc. (Denver, USA). Colchicine was purchased from Sigma Aldrich, and Vinblastine sulfate was purchased from Alfa Aesar. BODIPY-Vinblastine was purchased from Invitrogen.

2.2 Cell culture

U2OS cells were obtained from the American Type Culture Collection (ATCC) and grown in DMEM containing L-glutamine (2 mM) supplemented with 10% fetal bovine serum (FBS; Invitrogen) at 37 °C in a 5% CO_2 atmosphere.

2.3 High Content Screen for mitotic arrest

HCA was performed using an Arrayscan II HCS reader and integrated software from Cellomics as previously described[1]. U2OS osteosarcoma cells were seeded in a NUNC clear flat-bottomed 96-well plate at 10,000/well in a total of 100 µL. They were incubated at 37 ºC overnight. Cells were then treated with compounds (25 µL) to give the desired final concentration. Cells were then incubated at 37 ºC for 72 h. The medium was gently removed from all the wells and 50 µL 12.5 % formaldehyde was added to each well. This was incubated at RT for 10 min, before the formaldehyde was removed. To the wells was then added 100 µL/well permeabilization buffer (PB, contains PBS + 0.1% Triton X-100), incubating for 10 min. PB was removed and wells washed with 100 µL/well blocking buffer (BB, contains PBS + 1% BSA). BB was removed and 50 µL/well of primary antibody solution (anti-PH3 (S10), 1:800) was added. Plates were incubated for 1 h at room temperature. The antibody was removed and wells washed with 2 x 100 µL/well BB. BB was removed and 50 µL/well of secondary antibody solution containing Hoechst (1:2500) and AlexaFluor 546 Goat anti-mouse IgG (1:500) was added. Plates were incubated at RT for 1 h in the dark. Secondary antibody solution was removed and plates washed with 2 x 100 µL BB. The BB was then removed and 100 µL PBS/well were added. The plates were sealed with opaque film and images taken on a 20x 0.4 NA objective. Data was analysed on Cellomics Arrayscan software using the Target Activation v4 protocol. Critical output features are: ValidObjectCount and %Responder_AvgIntenCh2. EC_{50} data was calculated using Prism (Graphpad) and is an average of three independent experiments conducted in triplicate.

2.4 Sulforhodamine B colorimetric assay for cytotoxicity screening

This assay was conducted according to literarure procedure [2]. U2OS cells were seeded at 4000 cells/well in 180 µL. Compounds were added after 24 h at a final top concentration of 200 µM from a dilution plate. After incubation for 72 h at 37 °C the medium was removed by aspiration, and 100 µL of 1% TCA solution was added. This was incubated for 1 h and then removed. The plates were washed 4 x with tap water and the plates were allowed to air dry at rt. 100 µL of a 0.057 % wt/vol solution of Sulforhodamine B (Sigma) were added to each well, incubating for 30 min. The plates were then washed quickly with 4 x 100 µL of 1% acetic acid solution and then airdried. 200 µL of 10 mM TRIS pH 8.0 was added to each well to resolubilize the dye. The plates were then read at 510 nm on a TECAN UV spectrophotometer. IC_{50} data was calculated using Prism (Graphpad) and is an average of three independent experiments conducted in triplicate.

2.5 Confocal Microscopy

Confocal microscopy was performed as previously described[3]. 200,000 U2OS cells were seeded on coverslips in 2 mL medium in a six-well plate and incubated at 37 °C overnight. Compounds were added in DMSO to the appropriate concentration and the cells were incubated for 20 h. The medium was then aspirated and the cells were then fixed in 1 mL PBS containing 4% *para*-formaldehyde for 10 min. Cells were permeabilised in PBS containg 0.1% Triton-X (PBS-T) for 10 min and then washed with 1 mL PBS containg 1% BSA (PBS-BSA). Tubulin was visualized using a-tubulin antibody (1:1000) in 500 µL for 2 hrs. The primary antibody was then removed and the cells were washed with 1 mL PBS-BSA three times. Alexafluor-488 conjugated goat anti-rabbit secondary antibody was then added in 500 µL PBS-BSA for 1 h. The secondary antibody was removed and cells were washed twice with PBS-BSA and once with PBS. The coverslips were mounted on slides with mounting medium containing DAPI and imaged on a Zeiss LSM-510 confocal microscope with a 100X objective.

2.6 Tubulin *in vitro* polymerisation assay

The tubulin polymerisation assay was performed as previously described[4]. Compounds were dissolved up to 10 µL at 10x the desired final concentration in 1X General Tubulin buffer (PEM) containing 80 mM Na-PIPES pH 7.0, 1 mM $MgCl_2$ and 1 mM EGTA from their DMSO stocks and added to wells in a clear flat-bottomed 96-well plate. The tubulin solution was prepared by dissolving porcine α/β-tubulin (> 99% pure, Cytoskeleton, USA) to 3 mg/mL in 1X General Tubulin Buffer containing 10% glycerol, and 1 mM GTP. 90 µL of this tubulin solution was added to the compound solutions or the controls in the pre-warmed 96-well plate at 37 °C. Tubulin polymerisation was monitored over 60 min by reading the increase in absorbance at 340 nm in a Infinite® M200 plate reader (Tecan, Austria).

2.7 Vinblastine competition assay

The vinblastine competition assay was performed as described in Ibbeson *et al*[3]*.* Tubulin (2 µM) and BODIPY-FL-vinblastine (2 µM, Invitrogen) were incubated in PEM buffer with different concentrations of test compounds, or vinblastine for 20 min at rt in a total volume of 45 µL/well. Fluorescence polarization readings (ex/em 485/520 nm) were performed in black 384 well plates using a PHERASTAR plate reader. Values were normalized to the DMSO control.

2.8 Colchicine competition assay

The colchicine competition assay was performed as described in Ibbeson *et al*[3]. Tubulin (3 µM) was incubated with colchicine (3 µM) and different concentrations of test compounds or nocodazole in PEM buffer for 1 h at 37 °C for a total volume of 45 µL/well. Fluorescence intensity readings (ex/em 365/435 nm) were performed in black 384 well plates using Infinite® M200 plate reader (Tecan, Austria). Values were normalized to the DMSO control.

2.9 Calculating physiochemical properties using Schrodinger

Ligands were initially prepared using Ligprep[5]. Structures were saved as sdf files and imported directly into Ligprep. Ionisation states were calculated for pH 7 ± 2. The resulting output from Ligprep was directly used to calculate physiochemical properties using Qikprop[6]. Results displayed include the ionisation state at pH 7 only.

3 General Methods: Chemistry

3.1 General Directions

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at ambient probe temperature, unless otherwise stated, on a Bruker Avance 500 BB ATM or Bruker Avance 500 Dual Cryo fourier transform spectrometer. Chemical shifts (δ) are quoted in ppm relative to the residual non-deuterated solvent signal. Data are reported as follows: chemical shift, integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; app, apparent; or a combination of these, e.g. br s or dd), coupling constants (*J* in Hz), and assignment. For ^{13}C NMR, Cq refers to a quaternary carbon. The numbering system used in the assignments does not follow the IUPAC convention. Assignment of the proton and carbon spectra is supported by DEPT-135, COSY, HMQC or HMBC spectra where necessary.

Infra-red (IR) spectra were recorded as neat oils or solids on a Perkin Elmer Spectrum One FT-IR spectrophotometer fitted with an attenuated total reflectance (ATR) sampling accessory. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) with the following abbreviations: w, weak; m, medium; s, strong; br, broad. Melting points were measured using a Büchi B545 melting point apparatus and are uncorrected. High-resolution mass spectrometry (HRMS) was carried out using a Waters LCT Premier Time of Flight (ToF) mass spectrometer or Micromass Quadrupole-Time of Flight (Q-ToF) mass spectrometer. Reported mass values are within the error limits of ± 5 ppm.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. All compounds were purified to >95% as assessed by HPLC at 250 nm. Analytical thin layer chromatography was carried out on glass Merck Kieselgel 60 F254 plates, visualised by the quenching of UV fluorescence or potassium permanganate stain, prepared by standard procedures. Flash column chromatography was performed using silica gel 60 (230-400 mesh), distilled solvents and a positive pressure of air or nitrogen.

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Solvents were distilled before use. Dichloromethane, ethyl acetate, methanol and toluene were distilled from calcium hydride. Tetrahydrofuran was dried over Na wire and distilled from a mixture of lithium aluminium hydride and calcium hydride. Diethyl ether was distilled from a mixture of lithium aluminium hydride and calcium hydride. Petroleum ether (pet. ether) refers to the fraction of petroleum with the boiling range 40-60 °C. Glassware was oven-dried before use. Room temperature (rt) refers to ambient temperature. Temperatures of 0 °C were maintained using an ice-water bath.

3.2 General Procedures

3.2.1 General Procedure I: Amide Coupling using T3P

The amine (1.0 eq) and the acid (1.0 eq) were dissolved in EtOAc and the resultant solution was cooled to 0 °C. DIPEA (2.0 eq) and T3P (50% solution in EtOAc, 1.3 eq) were added to the solution, which was then stirred at 0 °C for 30 min and rt between 3 and 24 h. The reaction was quenched with H_2O, the aqueous and organic layers separated and the aqueous layer extracted three times with EtOAc. The organic layers were combined, dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure leaving the crude product which was purified by flash column chromatography (SiO_2; CH_2Cl_2-MeOH gradient) to give the desired amides.

3.2.2 General Procedure II: variation of amide coupling using T3P

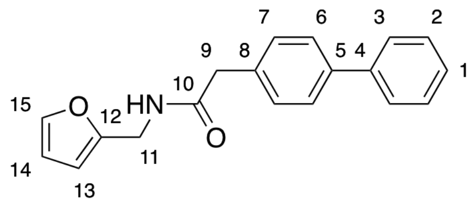
To an oven-dried round-bottomed flask were added the acid (1 eq) and the amine (1.1 eq) in dry EtOAc (0.1 M). The mixture was cooled to 0 °C and T3P (1.2 eq, 50% solution in EtOAc) was added. The mixture was warmed to rt and stirred overnight. The mixture was worked-up by diluting in EtOAc, and washing with 1M HCl, followed by sat. Na_2CO_3. The organic was then dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield the desired amide.

3.2.3 General Procedure III – Suzuki Coupling

To a 10 mL microwave vial were added the aryl bromide (1 eq.), the boronic acid (1.5 eq.), 1,4-dioxane (0.05 M) and $Pd(PPh_3)_4$ (5 mol %). To this was added a 2M solution of Na_2CO_3 (0.1 M). The mixture was heated in a CEM Discover SP microwave at 120 °C for 1-2 hrs. The mixture was then filtered through celite, washing with EtOAc. The organic was washed with brine, dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (FC) eluting with a gradient of EtOAc:Petrol (40-60).

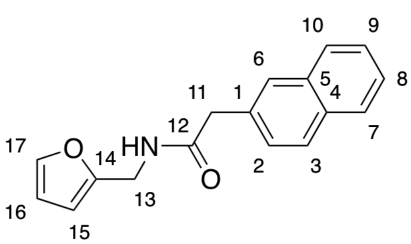
4 Compound Characterisation

2-([1,1'-biphenyl]-4-yl)-*N*-(furan-2-ylmethyl)acetamide (1)



4-biphenylacetic acid (100 mg, 0.47 mmol, 1.0 eq) and furfurylamine (42.0 μl, 0.47 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **1** as a white solid (90.0 mg, 0.31 mmol, 66%). **mp** 179-184 °C (CH_2Cl_2-MeOH, 79:1); **IR** ν_{max} (solid) 3233 m (-NH), 1629 s ($C{=}O_{amide}$) cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.59-7.57 (4H, m, CH^{Ar}), 7.46-7.43 (2H, m, CH^{Ar}), 7.37-7.32 (4H, m, C15-H and 3 x CH^{Ar}), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C14-H), 6.17 (1H, dd, *J* = 3.0, 1.0 Hz, C13-H), 5.75 (1H, br s, -NH), 4.43 (2H, app d, *J* 5.5 Hz, C11-H_2), 3.65 (2H, s, C9-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 170.6 (C10), 151.1 (C14), 142.2 (C15), 140.5 (C^{Ar}), 140.3 (C^{Ar}), 133.5 (C^{Ar}), 129.8 (C^{Ar}), 128.8 (C^{Ar}), 127.7 (C^{Ar}), 127.4 (C^{Ar}), 127.0 (C^{Ar}), 110.4 (C13), 107.3 (C12), 43.3 (C9), 36.6 (C11); **HRMS** (ESI+) *m/z* found $[M+H]^+$ 292.1322, $C_{19}H_{18}NO_2^+$ required 292.1338.

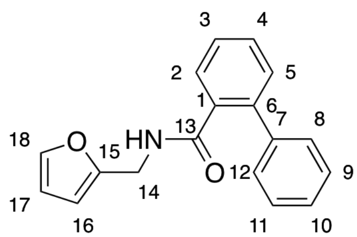
***N*-(furan-2-ylmethyl)-2-(naphthalen-2-yl)acetamide (2a)**



Naphthyleneacetic acid (100 mg, 0.54 mmol, 1.0 eq) and furfurylamine (47.0 μl, 0.54 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **2a** as a white solid (64.4 mg, 0.24 mmol, 45%). **mp** 134-136 °C (CH_2Cl_2-MeOH, 79:1); **IR** ν_{max} (solid) 3222 m (-NH), 1630 s ($C{=}O_{amide}$) cm^{-1} ; **^{1}H**

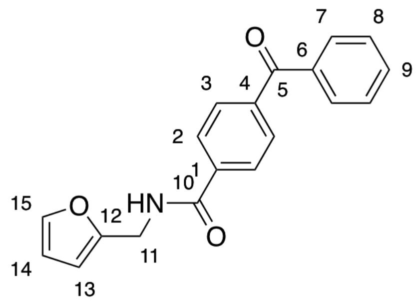
NMR (500 MHz; $CDCl_3$) δ 7.84-7.79 (3H, m, CH^{Ar}), 7.70 (1H, s, CH^{Ar}), 7.52-7.49 (2H, m, CH^{Ar}), 7.37 (1H, dd, *J* = 8.5, 1.5 Hz, C17-H), 7.30 (1H, app t, *J* = 1.0 Hz, CH^{Ar}), 6.27 (1H, dd, *J* = 3.0 Hz, 2.5 Hz, C16-H), 6.14 (1H, d, *J* = 3.0 Hz, C15-H), 5.87 (1H, br s, -NH), 4.40 (2H, app d, *J* = 5.5 Hz, C13-H_2), 3.75 (2H, s, C11-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 170.7 (C12), 151.1 (C14), 142.1 (C17), 133.5 (C^{Ar}), 132.5 (C^{Ar}), 132.1 (C^{Ar}), 128.8 (C^{Ar}), 128.3 (C^{Ar}), 127.7 (C^{Ar}), 127.6 (C^{Ar}), 127.3 (C^{Ar}), 126.4 (C^{Ar}), 126.0 (C^{Ar}), 110.2 (C16), 107.3 (C15), 43.8 (C13), 36.6 (C11); **HRMS** (ESI+) *m/z* found $[M+H]^+$ 266.1172, $C_{17}H_{16}NO_2^+$ required 266.1181.

***N*-(furan-2-ylmethyl)-[1,1'-biphenyl]-2-carboxamide (2b)**



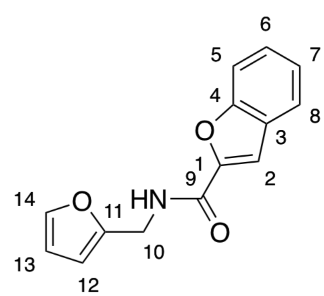
Biphenyl-2-carboxylic acid (100 mg, 0.58 mmol, 1.0 eq) and furfurylamine (53.0 μl, 0.58 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **2b** as a white crystalline solid (82.7 mg, 0.33 mmol, 56%). **mp** 81-84 °C (CH_2Cl_2-MeOH, 39:1); **IR** ν_{max} (solid) 3273 m (-NH), 1631 s ($C{=}O_{amide}$) cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.74-7.72 (1H, m, CH^{Ar}), 7.48 (1H, app td, *J* = 7.5 Hz and 1.5 Hz, CH^{Ar}), 7.41 (1H, app td, *J* = 7.5 Hz and 1.5 Hz, CH^{Ar}), 7.38-7.32 (6H, m, 6 x CH^{Ar}), 7.22 (1H, dd, *J* = 2.0 Hz and 1.0 Hz, C18-H), 6.24-6.23 (1H, m, C17-H), 5.97-5.96 (1H, m, C16-H), 5.52 (1H, br s, -NH), 4.34 (2H, app d, *J* = 5.5 Hz, C14-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 169.0 (C13), 150.5 (C15), 142.0 (C18), 139.8 (Cq^{Ar}), 139.6 (Cq^{Ar}), 135.1 (Cq^{Ar}), 130.2 (C^{Ar}), 130.2 (C^{Ar}), 128.9 (C^{Ar}), 128.6 (C^{Ar}), 128.5 (C^{Ar}), 127.7 (C^{Ar}), 127.5 (C^{Ar}), 110.2 (C17), 107.3 (C16), 36.7 (C14); **HRMS** (ESI+) *m/z* found $[M+H]^+$ 278.1181, $C_{18}H_{16}NO_2^+$ required 278.1181.

4-benzoyl-*N*-(furan-2-ylmethyl)benzamide (2c)



4-benzoylbenzoic acid (100 mg, 0.44 mmol, 1.0 eq) and furfurylamine (39.0 μl, 0.44 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **2c** as an orange solid (93.2 mg, 0.31 mmol, 69%). **mp** 119-123 °C (CH_2Cl_2-MeOH, 79:1); **IR** ν_{max} (solid) 3256 m (-NH), 1638 s (C=O_{amide}) cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.89 (2H, br d, *J* = 7.0 Hz, 2 x CH^{Ar}), 7.78-7.74 (4H, br m, 4 x CH^{Ar}), 7.59 (1H, br t, *J* = 7.0 Hz, CH^{Ar}), 7.48-7.45 (2H, br m, 2 x CH^{Ar}), 7.34 (1H, br s, C15-H), 6.96 (1H, br s, -NH), 6.30 (2H, app d, *J* = 13.0 Hz, C13-H and C14-H), 4.64 (2H, s, C11-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 196.0 (C5), 166.5 (C10), 150.9 (C12), 142.3 (C15), 140.0 (Cq^{Ar}), 137.4 (Cq^{Ar}), 136.9 (Cq^{Ar}), 132.9 (C^{Ar}), 130.0 (C^{Ar}), 130.0 (C^{Ar}), 128.4 (C^{Ar}), 127.1 (C^{Ar}), 110.5 (C14), 107.9 (C13), 37.1 (C11); **HRMS** (ESI+) *m/z* found $[M+H]^+$ 306.1130, $C_{19}H_{16}NO_3^+$ required 306.1151.

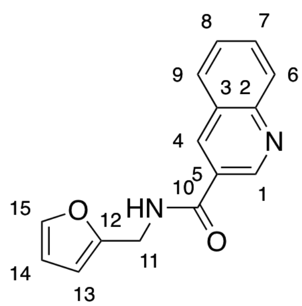
***N*-(furan-2-ylmethyl)benzofuran-2-carboxamide (2d)**



Benzofuran-2-carboxylic acid (100 mg, 0.62 mmol, 1.0 eq) and furfurylamine (55.0 μl, 0.62 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **2d** as a light orange solid (83.2 mg, 0.35 mmol, 59%). **mp** 85-88 °C (CH_2Cl_2-MeOH, 39:1); **IR** ν_{max} (solid) 3257 m (-NH), 1644 s (C=O_{amide}) cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.67-7.66 (1H, m, CH^{Ar}), 7.50-7.47

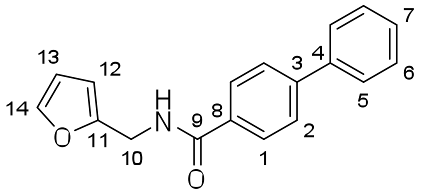
(2H, m, 2 x CH^{Ar}), 7.42-7.39 (2H, m, C14-H and and CH^{Ar}), 7.29 (1H, app td, J = 7.5 Hz and 1.0 Hz, CH^{Ar}), 6.94 (1H, br s, -NH), 6.36-6.37 (2H, m, C12-H and C13-H), 4.67 (2H, app d, J = 5.5 Hz, C10-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 158.6 (C9), 154.7 (C4), 150.7 (C11), 148.4 (Cq^{Ar}), 142.4 (C14), 127.5 (C3), 126.9 (C^{Ar}), 123.7 (C^{Ar}), 122.7 (C^{Ar}), 111.7 (C^{Ar}), 110.7 (C^{Ar}), 110.5 (C13), 107.9 (C12), 36.2 (C10); **HRMS** (ESI+) *m/z* found $[M+Na]^+$ 263.9870, $C_{14}H_{11}NO_3Na^+$ required 264.0637.

***N*-(furan-2-ylmethyl)quinoline-3-carboxamide (2e)**



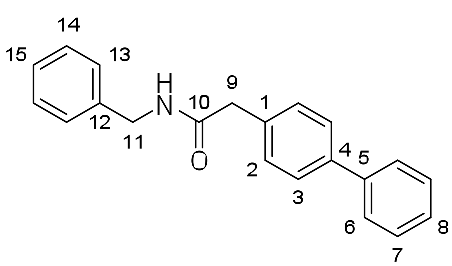
3-quinolinecarboxylic acid (100 mg, 0.58 mmol, 1.0 eq) and furfurylamine (53.0 μl, 0.58 mmol, 1.0 eq) were combined according to general procedure I to give the title compound **2e** as a white crystalline solid (82.7 mg, 0.33 mmol, 56%). **mp** 117-122 °C (CH_2Cl_2-MeOH, 39:1); **IR** ν_{max} (solid) 3238 m (-NH), 1660 s ($C{=}O_{amide}$) cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 9.24 (1H, d, J = 2.0 Hz, quinoline -NH), 8.55 (1H, d, J = 2.0 Hz, CH^{Ar}), 8.01 (1H, d, J = 8.5 Hz, CH^{Ar}), 7.73-7.68 (2H, m, CH^{Ar}), 7.54 (1H, br t, J = 5.5 Hz, amide -NH), 7.51-7.48 (1H, m, CH^{Ar}), 7.29 (1H, dd, J = 1.5 Hz and 1.0 Hz, C15-H), 6.27-6.25 (2H, m, C13-H and C14-H), 4.64 (2H, d, J = 5.5 Hz, C11-H_2); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 165.6 (C10), 150.9 (C12), 149.0 (C^{Ar}), 148.2 (C^{Ar}), 142.3 (C15), 135.8 (C^{Ar}), 131.2 (C^{Ar}), 129.0 (C^{Ar}), 128.7 (C^{Ar}), 127.4 (C^{Ar}), 126.8 (Cq^{Ar}), 126.7 (Cq^{Ar}), 110.5 (C14), 107.9 (C13), 37.0 (C11); **HRMS** (ESI+) *m/z* found $[M+H]^+$ 253.0934, $C_{15}H_{13}N_2O_2^+$ required 253.0926.

N-(furan-2-ylmethyl)-[1,1'-biphenyl]-4-carboxamide (2f)



Using the general procedure II, biphenyl carboxylic acid (50 mg, 0.25 mmol), and furfurylamine (26 μL, 0.26 mmol) were combined according to general procedure I to yield the desired amide **2f** as a yellow amorphous solid (40 mg, 56 %). **IR** (solid) ν_{max} 3272 (N-H stretch, br), 1641 (C=C stretch, br), 1597 (C=C stretch, sharp), 1519 (C=C stretch, br) 1474 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.77 (1H, m, C14-H), 7.48 – 7.52 (1H, m, CH^{Ar}), 7.41 – 7.45 (2H, m, CH^{Ar}), 7.37 (5H, m, CH^{Ar}), 7.25 (1H, dd, *J* = 1.8, 0.8 Hz, CH^{Ar}), 6.25 (1H, dd, *J* = 3.2, 1.9 Hz, C13-H), 5.99 (1H, dd, *J* = 3.2, 0.7 Hz, C12-H), 5.54 (1H, s, -NH), 4.36 (2H, d, *J* = 5.6 Hz, C10-H_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.1 (C9), 150.5 (Cq^{Ar}), 142.0 (C14), 139.8 (Cq^{Ar}), 139.6 (Cq^{Ar}), 135.1 (Cq^{Ar}), 130.3 (C^{Ar}), 129.0 (C^{Ar}), 128.6 (C^{Ar}), 127.7 (C^{Ar}), 127.6 (C^{Ar}), 110.3 (C13), 107.3 (C12), 36.8 (C10); **HRMS** (ESI^+, *m/z*) $C_{18}H_{16}NO_2$ calculated 278.1181 (MH^+), found 278.1184 (Δ = 1.1 ppm).

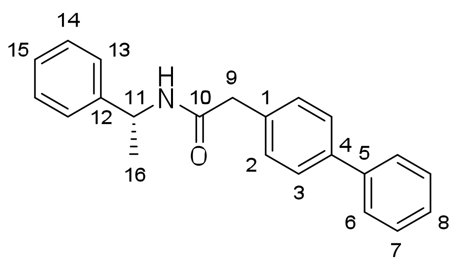
2-([1,1'-biphenyl]-4-yl)-N-benzylacetamide (3a)



Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and benzylamine (27 μL, 0.25 mmol) were combined according to general procedure I to yield the amide **3a** as a white solid (58 mg, 80 %). **m.p.** 177-180 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3283 (N-H stretch, s), 1738 (C=O stretch, s), 1634 (C=C stretch, w), 1551 (C=C stretch, br) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.59 (1H, t, *J* = 5.8 Hz, N-H), 7.65 (2H, app d, *J* = 8.5 Hz,

CH^{Ar}), 7.60 (2H, app d, J = 8.5 Hz, CH^{Ar}), 7.43 - 7.50 (2H, m, CH^{Ar}), 7.29 - 7.40 (5H, m, CH^{Ar}), 7.21 - 7.28 (3H, m, CH^{Ar}), 4.29 (2H, d, J = 5.8 Hz, C11-H), 3.53 (2H, s, C9-H); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.5 (C10), 140.5 (Cq^{Ar}), 139.9 (Cq^{Ar}), 138.8 (Cq^{Ar}), 136.1 (Cq^{Ar}), 130.1 (C^{Ar}), 129.4 (C^{Ar}), 128.7 (C^{Ar}), 127.7 (C^{Ar}), 127.7 (C^{Ar}), 127.2 (C^{Ar}), 127.0 (C^{Ar}), 127.0 (C^{Ar}), 42.7 (C9), 42.4 (C11); **HRMS** (ESI$^+$, *m/z*) $C_{21}H_{20}NO$ calculated 302.1545 (MH^+), found 302.1552 (Δ = 2.3 ppm)

(R)-2-([1,1'-biphenyl]-4-yl)-N-(1-phenylethyl)acetamide (3b)

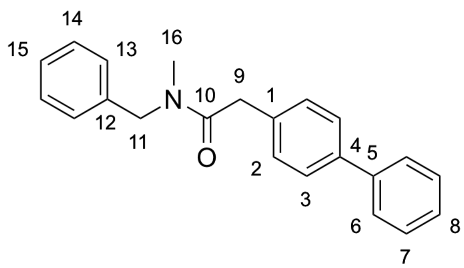


Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and *R*-phenylethylamine (30 µL, 0.25 mmol) were combined according to general procedure I to yield the amide **3b** as a white solid (70 mg, 86 %). **m.p.** 152 – 154 °C (EtOAc); α_D^{28} = +62° (c 0.2, MeOH); **IR** (solid) ν_{max} 3303 (N-H stretch, br), 1639 (C=O stretch, s), 1544 (C=C stretch, br) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO) δ ppm 8.56 (1H, d, J = 8.0 Hz, -NH), 7.64 (2H, app dd, J = 8.3, 1.1 Hz, CH^{Ar}), 7.58 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.45 (2H, app t, J = 7.6 Hz, CH^{Ar}), 7.32 - 7.38 (3H, m, CH^{Ar}), 7.28 - 7.31 (4H, m, CH^{Ar}), 7.18 - 7.25 (1H, m, CH^{Ar}), 4.90 (1H, m, C11-H), 3.49 (2H, s, C9-H_2), 1.36 (3H, d, J = 7.0 Hz, C16-H_3); **^{13}C NMR** (101 MHz, DMSO) δ ppm 169.2 (C10), 144.7 (Cq^{Ar}), 140.1 (Cq^{Ar}), 138.3 (Cq^{Ar}), 135.9 (Cq^{Ar}), 129.6 (C^{Ar}), 129.0 (C^{Ar}), 128.3 (C^{Ar}), 127.4 (C^{Ar}), 126.7 (C^{Ar}), 126.6 (C^{Ar}), 126.6 (C^{Ar}), 126.0 (C^{Ar}), 48.0 (C11), 42.0 (C9), 22.7 (C16); **HRMS** (ESI$^+$, *m/z*) $C_{22}H_{21}NONa$ calculated 338.1521 (MH^+), found 338.1534 (Δ = 3.8 ppm)

(S)-2-([1,1'-biphenyl]-4-yl)-N-(1-phenylethyl)acetamide (3c)

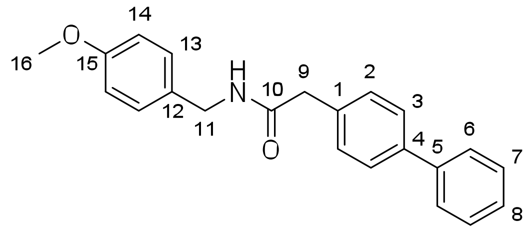
Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and *S*-phenylethylamine (30 µL, 0.25 mmol) were combined to yield the amide **3c** as a white solid (74 mg, 92 %). All spectroscopic data was equivalent to the R-enantiomer, with the exception of optical rotation: α_D^{28} = -62° (c 0.2, MeOH).

2-([1,1'-biphenyl]-4-yl)-N-benzyl-N-methylacetamide (3d)



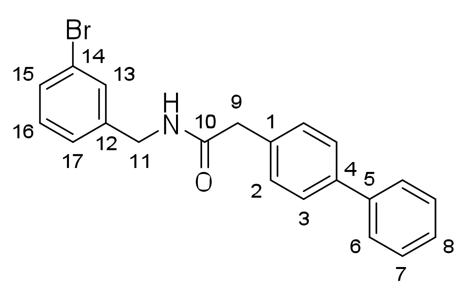
Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and N-methylbenzylamine (30 µL, 0.25 mmol) were combined to yield the amide **3d** as an amorphous solid (71 mg, 94 %). **IR** (solid) ν_{max} 1737 (C=O stretch, br), 1638 (C=C stretch, s), 1486 (strong), 1450 (strong) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6, 120 °C) δ ppm 7.60 - 7.66 (2H, m, CH^{Ar}), 7.54 - 7.60 (2H, m, CH^{Ar}), 7.41 - 7.49 (2H, m, CH^{Ar}), 7.30 - 7.38 (5H, m, CH^{Ar}), 7.20 - 7.29 (3H, m, CH^{Ar}), 4.60 (2H, s, C11-H_2), 3.81 (2H, s, C9-H_2), 2.84 (3H, s, C16-H_3); **^{13}C NMR** (126 MHz, DMSO-d_6, 120 °C) δ ppm 169.8 (C10), 139.7 (Cq^{Ar}), 138.0 (Cq^{Ar}), 137.2 (Cq^{Ar}), 134.5 (Cq^{Ar}), 128.9 (C^{Ar}), 128.1 (C^{Ar}), 127.8 (C^{Ar}), 126.7 (C^{Ar}), 126.5 (C^{Ar}), 126.4 (C^{Ar}), 125.9 (C^{Ar}), 125.9 (Cq^{Ar}), 53.2 (C16), 50.5 (C9), 35.6 (C11); **HRMS** (ESI$^+$, *m/z*) $C_{22}H_{21}NO$ calculated 316.1701 (MH$^+$), found 316.1695 (Δ = -1.9 ppm).

2-([1,1'-biphenyl]-4-yl)-N-(4-methoxybenzyl)acetamide (3e)



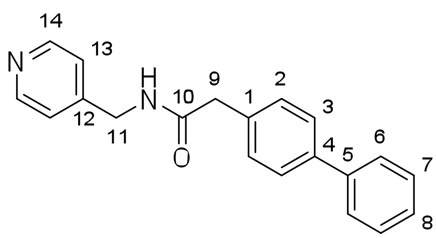
Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and *p*-methoxybenzylamine (34 μL, 0.25 mmol) were combined to yield the amide **3e** as a white solid (60 mg, 80 %). **m.p.** >260 °C (EtOAc); **IR** (solid) ν_{max} 3285 (N-H stretch, s), 1737 (C=O stretch, br), 1634 (C=C stretch, s), 1551 (C=C stretch, br) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 8.50 (1H, t, *J* = 5.8 Hz, -NH), 7.65 (2H, app dd, *J* = 8.5, 1.2 Hz, CH^{Ar}), 7.59 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.45 (2H, app t, *J* = 7.0 Hz, CH^{Ar}), 7.36 (2H, app d, *J* = 7.9 Hz, CH^{Ar}), 7.17 (2H, app d, *J* = 8.5 Hz, C13-H), 6.88 (2H, app d, *J* = 8.5 Hz, C14-H), 4.21 (2H, d, *J* = 5.8 Hz, C11-H_2), 3.72 (3H, s, C16-H_3), 3.50 (2H, s, C9-H_2); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.3 (C10), 158.7 (C15), 140.5 (C^{Ar}), 138.7 (C^{Ar}), 136.2 (C^{Ar}), 131.8 (C^{Ar}), 130.0 (C^{Ar}), 129.4 (C^{Ar}), 129.1 (C^{Ar}), 127.7 (C^{Ar}), 127.0 (C^{Ar}), 127.0 (C^{Ar}), 114.2 (C^{Ar}), 55.5 (C16), 42.4 (C11), 42.2 (C9); **HRMS** (ESI^+, *m/z*) $C_{22}H_{21}NO_2$ calculated 332.1651 (MH^+), found 332.1657 (Δ = 1.8 ppm).

2-([1,1'-biphenyl]-4-yl)-N-(3-bromobenzyl)acetamide (3f)



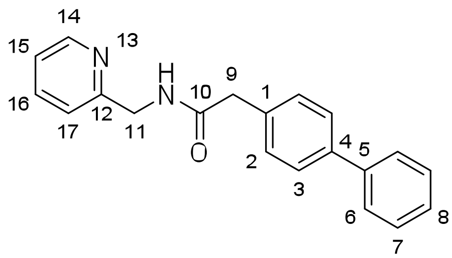
Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and 3-bromobenzylamine (47 mg, 0.25 mmol) were combined to yield the amide **3f** as an off-white solid (90 mg, 98 %). **m.p.** 175-178 °C (EtOAc); **IR** (solid) ν_{max} 3229 (N-H stretch, sharp), 1741 (C=O stretch, br), 1647 (C=C stretch, s), 1625 (C=C stretch, sharp), 1556 (C=C stretch, br) 1459 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.64 (1H, t, *J* = 5.8 Hz, -NH), 7.65 (2H, app dd, *J* = 8.4, 1.4 Hz, CH^{Ar}), 7.61 (2H, app d, *J* = 8.2 Hz, CH^{Ar}), 7.35 - 7.49 (8H, m, CH^{Ar}), 7.23 - 7.30 (2H, m, CH^{Ar}), 4.28 (2H, d, *J* = 5.8 Hz, C11-H_2), 3.53 (2H, s, C9-H_2); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.7 (C10), 142.9 (Cq^{Ar}), 140.5 (Cq^{Ar}), 138.8 (Cq^{Ar}), 136.0 (Cq^{Ar}), 133.6 (C^{Ar}), 130.9 (C^{Ar}), 130.3 (C^{Ar}), 130.1 (C^{Ar}), 130.0 (C^{Ar}), 129.4 (C^{Ar}), 127.7 (C^{Ar}), 127.0 (C^{Ar}), 127.0 (C^{Ar}), 126.7 (C^{Ar}), 42.5 (C9), 42.0 (C11); **HRMS** (ESI^+, *m/z*) $C_{21}H_{18}NOBr$ calculated 380.0650 (MH^+), found 380.0646 (Δ = -1.1 ppm)

2-([1,1'-biphenyl]-4-yl)-N-(pyridin-4-ylmethyl)acetamide (3g)



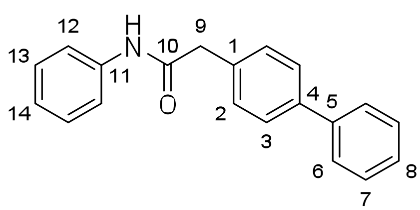
Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and 4-picolylamine (27 mg, 0.25 mmol) were combined to yield the amide **3g** as a white solid (36 mg, 50 %). **m.p.** 175-179 °C (EtOAc); **IR** (solid) ν_{max} 3284 (N-H stretch, sharp), 1740 (C=O stretch, br), 1635 (C=C stretch, s), 1595 (C=C stretch, sharp), 1547 (C=C stretch, br) 1486 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.69 (1H, t, *J* = 6.0 Hz, -NH), 8.47 - 8.51 (2H, dd, *J* = 4.5, 1.6 Hz, C14-H), 7.64 - 7.68 (2H, m, CH^{Ar}), 7.62 (2H, app d, *J* = 8.2 Hz, CH^{Ar}), 7.46 (2H, app t, *J* = 7.6 Hz, CH^{Ar}), 7.34 - 7.40 (3H, m, CH^{Ar}), 7.22 - 7.25 (2H, app d, *J* = 4.5 Hz, C13-H), 4.31 (2H, d, *J* = 6.0 Hz, C11-H_2), 3.57 (2H, s, C9-H_2); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.9 (C10), 150.0 (C14), 148.9 (C12), 140.4 (Cq^{Ar}), 138.8 (Cq^{Ar}), 135.9 (Cq^{Ar}), 130.1 (C^{Ar}), 129.4 (C^{Ar}), 127.8 (C^{Ar}), 127.0 (C^{Ar}), 126.9 (C^{Ar}), 122.5 (C^{Ar}), 42.4 (C9), 41.7 (C11); **HRMS** (ESI^+, *m/z*) $C_{20}H_{19}N_2O$ calculated 303.1497 (MH^+), found 303.1501 (Δ = 1.3 ppm).

2-([1,1'-biphenyl]-4-yl)-N-(pyridin-2-ylmethyl)acetamide (3h)



Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and 2-picolylamine (27 mg, 0.25 mmol) were combined to yield the amide **3h** as a white solid (58 mg, 32 %). **m.p.** 115-120 °C (EtOAc); **IR** (solid) ν_{max} 3283 (N-H stretch, sharp), 1738 (C=O stretch, br), 1637 (C=C stretch, s), 1590 (C=C stretch, sharp), 1548 (C=C stretch, br) 1486 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.72 (1H, t, *J* = 5.8 Hz, -NH), 8.55 (1H, dd, *J* = 5.5, 2.0 Hz, C14-H), 7.82 - 7.89 (1H, m, CH^{Ar}), 7.65 (1H, dd, *J* = 8.5, 1.5 Hz, CH^{Ar}), 7.61 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.46 (2H, app t, *J* = 7.5 Hz, CH^{Ar}), 7.30 - 7.42 (4H, m, CH^{Ar}), 4.41 (2H, d, *J* = 5.8 Hz, C11-H_2), 3.58 (2H, s, C9-H_2); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.9 (C10), 158.4 (C12), 140.5 (Cq^{Ar}), 138.8 (Cq^{Ar}), 136.0 (Cq^{Ar}), 130.4 (C^{Ar}), 130.1 (C^{Ar}), 129.4 (C^{Ar}), 127.8 (C^{Ar}), 127.8 (C^{Ar}), 127.0 (C^{Ar}), 127.0 (C^{Ar}), 123.0 (C^{Ar}), 122.0 (C^{Ar}), 44.3 (C9), 42.3 (C11); **HRMS** (ESI^+, *m/z*) $C_{20}H_{18}N_2O$ calculated 303.1497 (MH^+), found 303.1508 (Δ = 3.6 ppm).

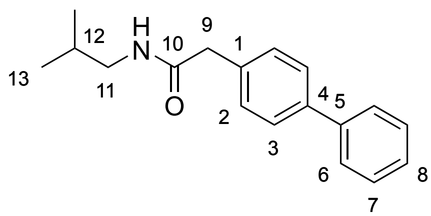
2-([1,1'-biphenyl]-4-yl)-N-phenylacetamide (3i)



Using the general procedure II, biphenylacetic acid (50 mg, 0.24 mmol) and aniline (24 µL, 0.25 mmol) were combined to yield the amide **3i** as a white solid (60 mg, 90 %). **m.p.** 174 – 176 °C (EtOAc); **IR** (solid) ν_{max} 3242 (N-H stretch, br), 1651 (C=O stretch, br), 1594 (C=C stretch, s), 1545 (C=C stretch, sharp), 1498 (C=C stretch, sharp) 1484 (sharp) cm^{-1}; **^{1}HNMR** (400 MHz, DMSO) d ppm 10.19

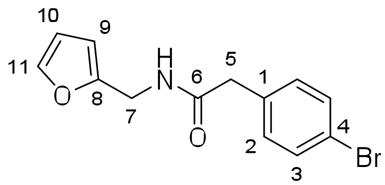
(1H, s, -NH), 7.59 - 7.67 (6H, m, CH^{Ar}), 7.41 - 7.49 (4H, m, CH^{Ar}), 7.33 - 7.38 (1H, m, CH^{Ar}), 7.27 - 7.33 (2H, m, CH^{Ar}), 7.01 - 7.07 (1H, m, CH^{Ar}), 3.69 (2H, s, C9-H_2); **^{13}CNMR** (100 MHz, $CDCl_3$) d ppm 169.5 (C10), 140.4 (Cq^{Ar}), 139.7 (Cq^{Ar}), 139.0 (Cq^{Ar}), 135.7 (Cq^{Ar}), 130.1 (Cq^{Ar}), 129.4 (C^{Ar}), 129.2 (C^{Ar}), 127.8 (C^{Ar}), 127.1 (C^{Ar}), 127.0 (C^{Ar}), 123.7 (C^{Ar}), 119.6 (C^{Ar}), 43.4 (C9); **HRMS** (ESI^+, *m/z*) $C_{20}H_{18}NO$ calculated 288.1388 (MH^+), found 288.1395 (Δ = 2.4 ppm)

2-([1,1'-biphenyl]-4-yl)-*N*-isobutylacetamide (3j)



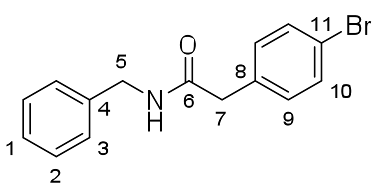
Using the general procedure **II**, biphenylacetic acid (50 mg, 0.24 mmol) and aniline (25 µL, 0.25 mmol) were combined to yield the amide **3j** as a white solid (40 mg, 60 %). **m.p.** 169 – 170 °C (EtOAc); **IR** (solid) ν_{max} 3246 (N-H stretch, br), 1651 (C=0 stretch, sharp), 1624 (C=C stretch, sharp), 1557 (C=C stretch, br) 1467 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ 8.04 (1H, t, *J* = 5.5 Hz, -NH), 7.61 – 7.66 (2H, m, CH^{Ar}), 7.57 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.44 (2H, app t, *J* = 8.5 Hz, CH^{Ar}), 7.37 – 7.31 (3H, m, CH^{Ar}), 3.44 (2H, s, C9-H_2), 2.84 – 2.91 (2H, dd, *J* = 6.0, 5.5 Hz, C11-H_2), 1.60 – 1.73 (1H, m, C12-H), 0.82 (6H, d, *J* = 6.7 Hz, 2 x C13-H_3). **^{13}C NMR** (126 MHz, DMSO) δ 170.0 (C10), 140.1 (Cq^{Ar}), 138.3 (Cq^{Ar}), 136.1 (Cq^{Ar}), 129.6 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 126.6 (C^{Ar}), 46.2 (C11), 42.1 (C9), 28.2 (C12), 20.2 (C13); **HRMS** (ESI^+, *m/z*) $C_{18}H_{22}NO$ calculated 268.1701 (MH^+), found 268.1709 (Δ = 3.0 ppm).

2-(4-bromophenyl)-N-(furan-2-ylmethyl)acetamide (4a)



Using the general procedure II, biphenylacetic acid (200 mg, 0.94 mmol) and furfurylamine (94 µL, 0.96 mmol) were combined to yield the amide **4a** as an off-white solid (260 mg, 92 %). **m.p.** 159-160 °C (EtOAc); **IR** (solid) ν_{max} 3294 (N-H stretch, sharp), 1738 (C=O stretch, br), 1640 (C=C stretch, s), 1591 (C=C stretch, weak), 1542 (C=C stretch, br), 1488 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.47 - 7.52 (2H, app d, *J* = 8.4 Hz, CH^{Ar}), 7.33 - 7.37 (1H, m, C11-H), 7.13 - 7.19 (2H, app d, *J* = 8.4 Hz, CH^{Ar}), 6.32 (1H, dd, *J* = 3.0, 2.5 Hz, C10-H), 6.19 (1H, d, *J* = 2.5 Hz, C9-H), 5.70 (1H, br. s, -NH), 4.43 (2H, d, *J* = 5.5 Hz, C7-H_2), 3.56 (2H, s, C5-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 170.3 (C6), 142.7 (C11), 134.0 (Cq^{Ar}), 132.5 (Cq^{Ar}), 131.5 (C^{Ar}), 121.8 (C^{Ar}), 110.8 (C10), 107.9 (C9), 43.4 (C5), 37.1 (C7); **HRMS** (ESI$^+$, *m/z*) $C_{13}H_{13}NO_2Br$ calculated 294.0130 (MH$^+$), found 294.0129 (Δ = -0.3 ppm)

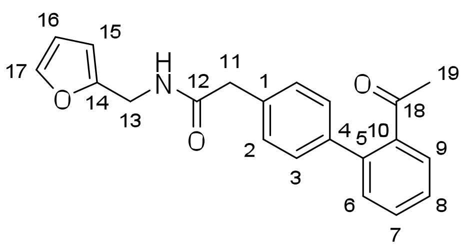
N-benzyl-2-(4-bromophenyl)acetamide (4b)



4-bromophenylacetic acid (400 mg, 1.88 mmol) and benzylamine (214 µL, 2.0 mmol) were dissolved in EtOAc (10 mL). DIPEA (500 µL, 3.80 mmol) was added and the mixture was cooled to 0 °C before T3P (1.4 mL, 50%, 2.20 mmols) was added. The mixture was stirred for 30 min at 0 °C before warming to rt and stirring overnight. The reaction was worked-up by diluting in EtOAc (20 mL) and washing with 1M HCl (2 x 5 mL), followed by sat. Na_2CO_3 (2 x 5 mL). The organics were then dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield the desired amide **4b** as a pale off-white solid

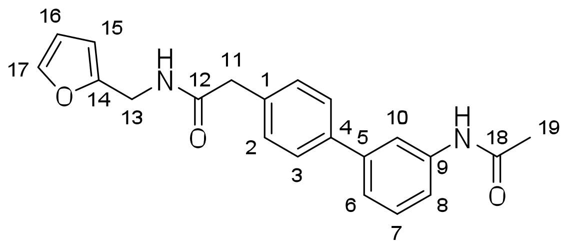
(530 mg, 93 %). **m.p.** 166 – 167 °C (EtOAc); **IR** (solid) ν_{max} 3279 (N-H stretch, br), 1643 (C=O stretch, sharp), 1589 (C=C stretch, sharp), 1538 (C=C stretch, br) 1486 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 8.54 (1H, t, J = 5.4 Hz, -NH), 7.47 (2H, app d, J = 8.5 Hz, CH^{Ar}), 7.26 - 7.32 (2H, m, CH^{Ar}), 7.17 - 7.25 (5H, m, CH^{Ar}), 4.24 (2H, d, J = 5.8 Hz, C5-H$_2$), 3.45 (2H, s, C7-H$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 169.6 (C6), 139.3 (Cq^{Ar}), 135.8 (Cq^{Ar}), 131.3 (C^{Ar}), 131.0 (C^{Ar}), 128.3 (C^{Ar}), 127.2 (C^{Ar}), 126.8 (C^{Ar}), 119.5 (Cq^{Ar}), 42.2 (C5), 41.5 (C7); **HRMS** (ESI$^+$, m/z) $C_{15}H_{15}NOBr$ calculated 304.0337 (MH$^+$), found 304.0335 (Δ = -0.7 ppm)

2-(2'-acetyl-[1,1'-biphenyl]-4-yl)-N-(furan-2-ylmethyl)acetamide (5a)



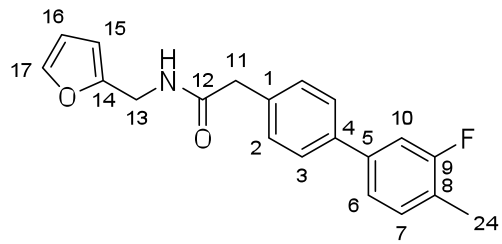
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 2-acetylboronic acid (33 mg, 0.21 mmol) were combined to yield **5a** as a white solid (37 mg, 82 %). **m.p.** 89 – 93 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3300 (N-H stretch, sharp), 1737 (C=O stretch, br), 1671 (C=C stretch, s), 1633 (C=C stretch, sharp), 1536 (C=C stretch, br), 1441 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.57 (1H, t, J = 5.5 Hz, -NH), 7.60 – 7.55 (3H, m, 2 x CH^{Ar} + C17-H), 7.47 (1H, m, CH^{Ar}), 7.43 – 7.39 (1H, m, CH^{Ar}), 7.33 (2H, app d, J = 8.2 Hz, C2/3-H), 7.23 (2H, app d, J = 8.2 Hz, C2/3-H), 6.39 (1H, dd, J = 3.2, 1.9 Hz, C16-H), 6.21 (1H, dd, J = 3.2, 0.8 Hz, C15-H), 4.28 (2H, d, J = 5.6 Hz, C13-H$_2$), 3.50 (2H, s, C11-H$_2$), 2.13 (3H, s, C19-H$_3$); **^{13}C NMR** (126 MHz, DMSO) δ ppm 203.9 (C18), 170.3 (C12), 152.6 (C10), 142.6 (C17), 140.8 (Cq^{Ar}), 140.1 (Cq^{Ar}), 138.9 (Cq^{Ar}), 136.2 (Cq^{Ar}), 131.3 (C^{Ar}), 130.7 (C^{Ar}), 129.7 (C^{Ar}), 128.9 (C^{Ar}), 128.1 (C^{Ar}), 127.8 (C^{Ar}), 110.9 (C16), 107.3 (C15), 42.2 (C11), 36.1 (C13), 30.8 (C19); **HRMS** (ESI$^+$, m/z) $C_{21}H_{19}NO_3$ calculated 334.1443 (MH$^+$), found 334.1443 (Δ = 0.0 ppm)

2-(3'-acetamido-[1,1'-biphenyl]-4-yl)-N-(furan-2-ylmethyl)acetamide (5b)



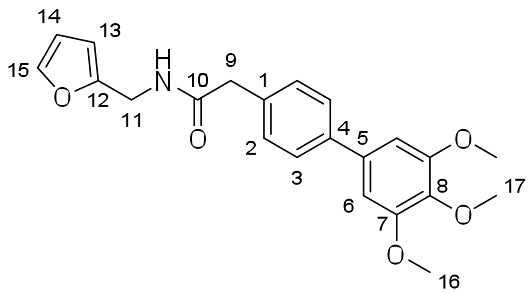
Using the general procedure **III**, compound **4a** (40 mg, 0.14 mmol) and 3-N-acetylboronic acid (38 mg, 0.21 mmol) were combined to yield **5b** as a white solid (35 mg, 74 %). **m.p.** 166 – 170 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3286 (N-H stretch, br), 1737 (C=O stretch, br), 1648 (C=C stretch, s), 1606 (C=C stretch, sharp), 1539 (C=C stretch, br) 1487 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 10.02 (1H, s, -NH), 8.55 (1H, t, *J* = 5.5 Hz, -NH), 7.86 (1H, m, C17-H), 7.59 – 7.51 (4H, m, CH^{Ar}), 7.39 – 7.33 (3H, m, CH^{Ar}), 7.30 (1H, dd, *J* = 6.6, 1.4 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.2, 1.9 Hz, C16-H), 6.22 (1H, dd, *J* = 3.2, 0.8 Hz, C15-H), 4.27 (2H, d, *J* = 5.5 Hz, C13-H_2), 3.49 (2H, s, C11-H_2), 2.07 (3H, s, C19-H_3). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.3 (C12), 168.9 (C18), 142.6 (C17), 141.0 (Cq^{Ar}), 140.3 (Cq^{Ar}), 138.8 (Cq^{Ar}), 136.1 (Cq^{Ar}), 132.0 (C^{Ar}), 130.1 (C^{Ar}), 129.7 (C^{Ar}), 126.9 (C^{Ar}), 121.7 (C^{Ar}), 118.4 (C^{Ar}), 117.5 (C^{Ar}), 110.9 (C16), 107.3 (C15), 42.2 (C11), 36.1 (C13), 24.5 (C19); **HRMS** (ESI$^+$, *m/z*) $C_{21}H_{20}N_2O$ calculated 349.1552 (MH^+), found 349.1548 (Δ = -1.1 ppm)

2-(3'-fluoro-4'-methyl-[1,1'-biphenyl]-4-yl)-N-(furan-2-ylmethyl)acetamide (5c)



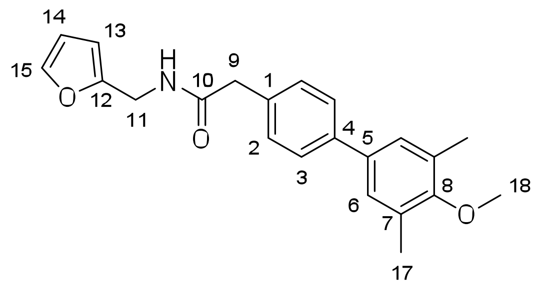
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 3-fluoro-4-methyl-phenylboronic acid (35 mg, 0.21 mmol) were combined to yield **5c** as a white solid (37 mg, 85 %). **m.p.** 169 – 172 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3241 (N-H stretch, sharp), 1741 (C=O stretch, br), 1657 (C=C stretch, s), 1626 (C=C stretch, sharp), 1554 (C=C stretch, br), 1491 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.55 (1H, t, *J* = 5.5 Hz, 1-NH), 7.61 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.58 (1H, dd, *J* = 1.9, 0.8 Hz, C17-H), 7.46 – 7.39 (2H, m, CH^{Ar}), 7.38 – 7.31 (3H, m, CH^{Ar}), 6.39 (1H, dd, *J* = 3.2, 1.9 Hz, C16-H), 6.22 (1H, dd, *J* = 3.2, 0.8 Hz, C15-H), 4.27 (2H, d, *J* = 5.6 Hz, C13-H_2), 3.49 (2H, s, C11-H_2), 2.26 (3H, s, C24-H_3); **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.3 (C12), 161.5 (d, *J* = 241.3 Hz, C9) 152.7 (Cq^{Ar}), 142.6 (C17), 140.2 (Cq^{Ar}), 140.2 (Cq^{Ar}), 137.3 (Cq^{Ar}), 136.4 (Cq^{Ar}), 132.1 (C^{Ar}), 132.1 (C^{Ar}), 129.7 (C^{Ar}), 126.4 (C^{Ar}), 123.0 (d, *J* = 15.9 Hz, C8), 122.2 (d, *J* = 2.2 Hz, C7), 112.8 (d, *J* = 22.6 Hz, C10), 110.5 (C16), 106.9 (C15), 41.8 (C11), 35.7 (C13), 13.9 (d, *J* = 2.4 Hz, C24); **^{19}F NMR** (376 MHz, DMSO) δ ppm -117.6 (C9-F); **HRMS** (ESI$^+$, *m/z*) $C_{20}H_{18}NO_2F$ calculated 324.1400 (MH^+), found 324.1406 (Δ = 1.9 ppm)

N-(furan-2-ylmethyl)-2-(3',4',5'-trimethoxy-[1,1'-biphenyl]-4-yl)acetamide (5d)



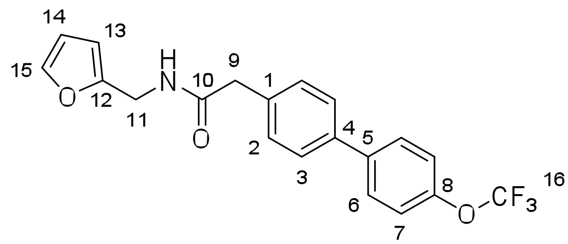
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 4-3,4,5-trimethoxy-phenylboronic acid (43 mg, 0.21 mmol) were combined to yield the product **5d** as a white solid (39 mg, 71 %). **m.p.** 145 – 147 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3290 (N-H stretch, br), 1641 (C=C stretch, s), 1586 (C=C stretch, sharp), 1562 (C=C stretch, br) 1501 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.54 (1H, t, *J* = 5.5 Hz, -NH), 7.62 – 7.59 (2H, app d, *J* = 8.3 Hz, C2/3-H), 7.58 (1H, dd, *J* = 1.9, 0.8 Hz, C15-H), 7.33 (2H, app d, *J* = 8.3 Hz, C2/3-H), 6.89 (2H, s, C6-H), 6.39 (1H, dd, *J* = 3.2, 1.9 Hz, C14-H), 6.22 (1H, dd, *J* = 3.2, 0.8 Hz, C13-H), 4.27 (2H, d, *J* = 5.5 Hz, C11-H_2), 3.85 (6H, s, 2 x C16-H_3), 3.69 (3H, s, C17-H_3), 3.48 (2H, s, C9-H). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.4 (C10), 153.6 (C7), 152.7 (Cq^{Ar}), 142.6 (C15), 139.0 (Cq^{Ar}), 137.5 (Cq^{Ar}), 136.3 (Cq^{Ar}), 135.8 (Cq^{Ar}), 129.8 (C2/3), 127.1 (C2/3), 110.9 (C14), 107.3 (C13), 104.5 (C6), 60.5 (C17), 56.4 (C16), 42.3 (C9), 36.1 (C11); **HRMS** (ESI^+, *m/z*) $C_{22}H_{24}NO_5$ calculated 382.1654 (MH^+), found 382.1657 (Δ = 0.8 ppm)

N-(furan-2-ylmethyl)-2-(4'-methoxy-3',5'-dimethyl-[1,1'-biphenyl]-4-yl)acetamide (5e)



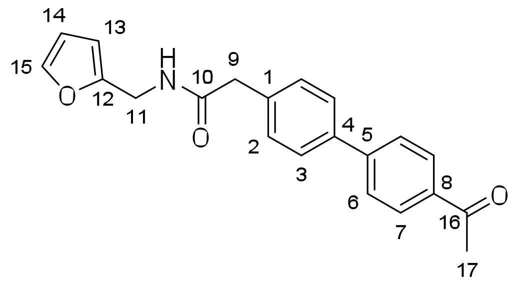
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 4-(3,4,5-trimethoxy)-phenylboronic acid (37 mg, 0.21 mmol) were combined to yield the product **5e** as a white solid (42 mg, 86 %). **m.p.** 120 – 123 °C (EtOAc:Pet Ether (40-60) 1:1); **IR** (solid) ν_{max} 3236 (N-H stretch, br), 1656 (C=O stretch, br), 1631 (C=C stretch, s), 1555 (C=C stretch, br), 1478 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.52 (1H, t, *J* = 5.6 Hz, -NH), 7.56 (1H, dd, *J* = 1.8, 0.9 Hz, C15-H), 7.53 – 7.48 (2H, app d, *J* = 8.4 Hz, CH^{Ar}), 7.28 – 7.30 (4H, m, CH^{Ar}), 6.37 (1H, dd, *J* = 3.2, 1.9 Hz, C14-H), 6.20 (1H, dd, *J* = 3.2, 0.8 Hz, C13-H), 4.25 (2H, d, *J* = 5.6 Hz, C11-H), 3.65 (3H, s, C18-H_3), 3.45 (2H, s, C9-H_2), 2.26 (6H, s, 2 x C17-H_3). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.0 (C10), 156.3 (Cq^{Ar}), 152.3 (Cq^{Ar}), 142.2 (C15), 138.1 (Cq^{Ar}), 135.4 (Cq^{Ar}), 135.1 (Cq^{Ar}), 130.7 (Cq^{Ar}), 129.5 (C^{Ar}), 126.9 (C^{Ar}), 126.3 (C^{Ar}), 110.5 (C14), 106.9 (C13), 59.8 (C6), 59.4 (C18), 41.8 (C9), 35.7 (C11), 16.1 (C17); **HRMS** (ESI$^+$, *m/z*) $C_{22}H_{24}NO_3$ calculated 350.1756 (MH^+), found 350.1758 (Δ = 0.6 ppm)

N-(furan-2-ylmethyl)-2-(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)acetamide (5f)



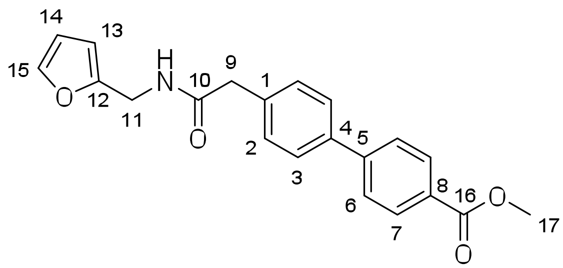
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 4-trifluoromethoxy-phenylboronic acid (42 mg, 0.21 mmol) were combined to yield the product **5f** as a white solid (47 mg, 89 %). **m.p.** 201 – 203 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3230 (N-H stretch, br), 1655 (C=O stretch, br), 1627 (C=C stretch, s), 1608 (C=C stretch, sharp), 1556 (C=C stretch, br), 1493 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.56 (1H, t, *J* = 5.5 Hz, -NH), 7.80 – 7.75 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.61 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.58 (1H, dd, *J* = 1.8, 0.9 Hz, C15-H), 7.44 (2H, app d, *J* = 8.3, CH^{Ar}), 7.37 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.2, 1.8 Hz, C14-H), 6.22 (1H, dd, *J* = 3.2, 0.9 Hz, C13-H), 4.27 (2H, d, *J* = 5.5 Hz, C11-H_2), 3.50 (2H, s, C9-H_2). **^{13}C NMR** (126 MHz, DMSO) δ ppm 169.9 (C10), 152.3 (Cq^{Ar}), 147.8 (Cq^{Ar}), 142.2 (C15), 139.4 (Cq^{Ar}), 136.9 (Cq^{Ar}), 136.2 (C^{Ar}), 129.8 (C^{Ar}), 128.5 (C^{Ar}), 126.7 (C^{Ar}), 121.5 (C^{Ar}), 110.5 (C14), 106.9 (C13), 41.8 (C9), 35.6 (C11); **^{19}F NMR** (376 MHz, DMSO) δ ppm -57.0 (CF_3); **HRMS** (ESI^+, *m/z*) $C_{20}H_{17}NO_3F_3$ calculated 376.1161 (MH^+), found 376.1165 (Δ = 1.1 ppm)

2-(4'-acetyl-[1,1'-biphenyl]-4-yl)-N-(furan-2-ylmethyl)acetamide (5g)



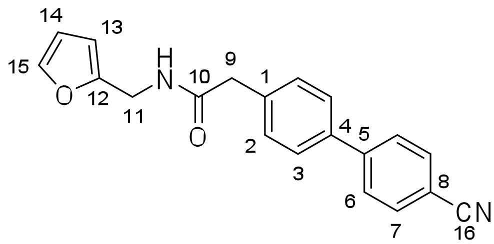
Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 4-acetylboronic acid (33 mg, 0.21 mmol) were combined to yield the product **5g** as a white solid (22 mg, 49 %). **m.p.** 209 – 211 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3238 (N-H stretch, sharp), 1739 (C=O stretch, br), 1673 (C=C stretch, s), 1655 (C=C stretch, sharp), 1627 (C=C stretch, sharp), 1550 (C=C stretch, br) 1426 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.57 (1H, t, *J* = 5.5 Hz, -NH), 8.04 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.82 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.69 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.50 - 7.66 (1H, m, C13-H), 7.39 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.4, 1.8 Hz, C14-H), 6.17 - 6.27 (1H, m, C13-H), 4.28 (2H, d, *J* = 5.5 Hz, C11-H_2), 3.51 (2H, s, C9-H_2), 2.61 (3H, s, C17-H_3); **^{13}C NMR** (126 MHz, DMSO) δ ppm 197.6 (C16), 169.9 (C10), 152.3 (Cq^{Ar}), 144.4 (Cq^{Ar}), 142.2 (C15), 137.1 (Cq^{Ar}), 136.7 (Cq^{Ar}), 135.6 (Cq^{Ar}), 131.6 (C^{Ar}), 131.5 (C^{Ar}), 129.8 (s), 129.0 (C^{Ar}), 129.0 (C^{Ar}), 128.8 (C^{Ar}), 126.9 (C^{Ar}), 126.8 (C^{Ar}), 110.5 (C14), 106.9 (C13), 41.9 (C9), 35.7 (C11), 26.8 (C17); **HRMS** (ESI^+, *m/z*) $C_{21}H_{19}NO_3$ calculated 334.1443 (MH^+), found 334.1448 (Δ = 1.5 ppm).

methyl 4'-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-[1,1'-biphenyl]-4-carboxylate (5h)



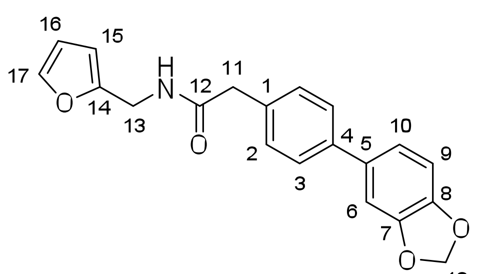
Using the general procedure **III**, compound **4a** (40 mg, 0.14 mmol) and 4-methoxycarbonyl-phenylboronic acid (37 mg, 0.21 mmol) were combined to yield the product **5h** as a white solid (20 mg, 41 %). **m.p.** 214 – 215 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3239 (N-H stretch, br), 1716 (C=O stretch, br), 1657 (C=C stretch, s), 1629 (br), 1608 (C=C stretch, sharp), 1551 (C=C stretch, br), 1494 (s) cm^{-1}; ^{1}**H NMR** (500 MHz, DMSO) δ ppm 8.57 (1H, t, *J* = 5.5 Hz, -NH), 8.03 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.82 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.68 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.58 (1H, dd, *J* = 1.8, 0.8 Hz, C15-H), 7.39 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.2, 1.8 Hz, C14-H), 6.23 (1H, dd, *J* = 3.2, 0.8 Hz, C13-H), 4.27 (2H, d, *J* = 5.5 Hz, C11-H$_2$), 3.88 (3H, s, C17-H$_3$), 3.51 (2H, s, C9-H$_2$). ^{13}**C NMR** (126 MHz, DMSO) δ ppm 170.2 (C10), 166.5 (C16), 152.6 (Cq^{Ar}), 145.0 (Cq^{Ar}), 142.6 (C15), 137.4 (Cq^{Ar}), 137.1 (Cq^{Ar}), 130.3 (Cq^{Ar}), 130.2 (C^{Ar}), 128.7 (C^{Ar}), 127.3 (C^{Ar}), 127.2 (C^{Ar}), 110.9 (C14), 107.3 (C13), 52.6 (C17), 42.2 (C9), 36.1 (C11); **HRMS** (ESI^{+}, *m/z*) $C_{21}H_{20}NO_4$ calculated 350.1392 (MH^{+}), found 350.1390 (Δ = -0.6 ppm).

2-(4'-cyano-[1,1'-biphenyl]-4-yl)-N-(furan-2-ylmethyl)acetamide (5i)



Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 4-4-cyano-phenylboronic acid (30 mg, 0.21 mmol) were combined to yield the product **5i** as a white solid (43 mg, 99 %). **m.p.** 163 – 165 °C (EtOAc:Pet Ether (40-60) 1:1); **IR** (solid) ν_{max} 3285 (N-H stretch, br), 1640 (C=O stretch, br), 1602 (C=C stretch, sharp), 1546 (C=C stretch, sharp), 1493 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.57 (1H, t, *J* = 5.5 Hz, -NH), 7.95 – 7.84 (4H, m, CH^{Ar}), 7.72 – 7.66 (2H, app d, *J* = 6.5 Hz, CH^{Ar}), 7.58 (1H, dd, *J* = 1.8, 0.8 Hz, C15-H), 7.40 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.2, 1.8 Hz, C14-H), 6.23 (1H, dd, *J* = 3.2, 0.8 Hz, C13-H), 4.27 (2H, d, *J* = 5.5 Hz, C11-H_2), 3.52 (2H, s, C9-H_2). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.2 (C10), 152.6 (Cq^{Ar}), 144.9 (Cq^{Ar}), 142.6 (C15), 137.5 (Cq^{Ar}), 136.8 (Cq^{Ar}), 133.3 (C^{Ar}), 130.3 (C^{Ar}), 127.8 (C^{Ar}), 127.4 (C^{Ar}), 119.4 (Cq^{Ar}), 110.9 (C16), 110.3 (C14), 107.3 (C13), 42.2 (C9), 36.1 (C11); **HRMS** (ESI$^+$, *m/z*) $C_{20}H_{17}N_2O_2$ calculated 317.1290 (MH$^+$), found 317.1304 (Δ = 4.4 ppm)

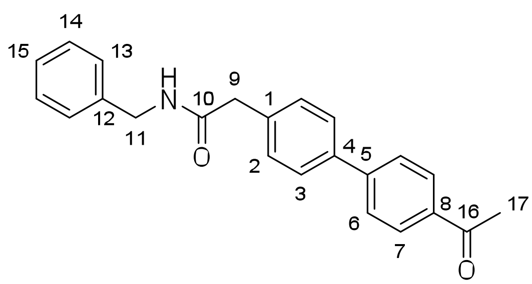
2-(4-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(furan-2-ylmethyl)acetamide (5j)



Using the general procedure III, compound **4a** (40 mg, 0.14 mmol) and 3,4-(methylenedioxy)phenylboronic acid (34 mg, 0.21 mmol) were combined to yield the product **5j** as a white solid (41 mg, 87 %). **m.p.** 169 – 170 °C (EtOAc:Petrol

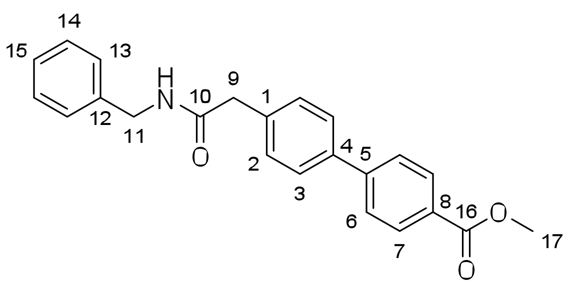
(40-60), 1:1); **IR** (solid) ν_{max} 3243 (N-H stretch, br), 1656 (C=O stretch, sharp), 1626 (C=C stretch, s), 1555 (C=C stretch, br), 1505 (C=C stretch, sharp) 1482 (s) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.53 (1H, t, *J* = 5.5 Hz, -NH), 7.58 (1H, dd, *J* = 1.9, 0.8 Hz, C17-H), 7.54 – 7.49 (2H, app d, *J* = 8.3 Hz, C2/3-H), 7.30 (2H, app d, *J* = 8.3 Hz, C2/3-H), 7.22 (1H, d, *J* = 1.8 Hz, C6-H), 7.12 (1H, dd, *J* = 8.1, 1.8 Hz, C10-H), 6.99 (1H, d, *J* = 8.1 Hz, C9-H), 6.39 (1H, dd, *J* = 3.2, 1.9 Hz, C16-H), 6.22 (1H, dd, *J* = 3.2, 0.8 Hz, C15-H), 6.05 (2H, s, C18-H_2), 4.27 (2H, d, *J* = 5.5 Hz, C13-H_2), 3.47 (2H, s, C11-H_2). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.4 (C12), 152.7 (Cq^{Ar}), 148.4 (Cq^{Ar}), 147.2 (Cq^{Ar}), 142.6 (C17), 138.5 (Cq^{Ar}), 135.5 (Cq^{Ar}), 134.8 (Cq^{Ar}), 129.9 (C^{Ar}), 126.7 (C^{Ar}), 120.5 (C^{Ar}), 110.9 (C16), 109.0 (C^{Ar}), 107.5 (C^{Ar}), 107.3 (C15), 101.5 (C18), 42.2 (C11), 36.1 (C13); **HRMS** (ESI^+, *m/z*) $C_{20}H_{18}NO_4$ calculated 336.1236 (MH^+), found 336.1237 (Δ = 0.3 ppm)

2-(4'-acetyl-[1,1'-biphenyl]-4-yl)-N-benzylacetamide (5k)



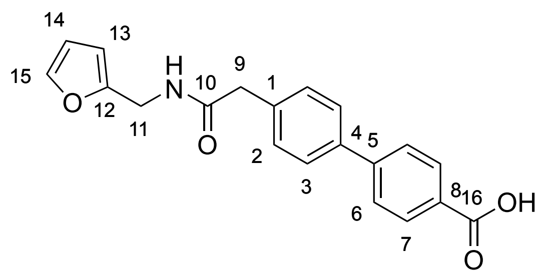
Using the general procedure **III**, but purifying by FC eluting with EtOAc:Pet Ether (40-60) gradient (50 – 100 %), **4b** (100 mg, 0.33 mmol) and 4-acetylboronic acid (75 mg, 0.49 mmol) were combined to yield the product **5k** as a white solid (12 mg, 10 %). **m.p.** 210 – 215 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3285 (N-H stretch, br), 1678 (C=O stretch, sharp), 1634 (C=C stretch, sharp), 1601 (C=C stretch, sharp), 1556 (C=C stretch, br), 1494 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.60 (1H, t, *J* = 5.8 Hz, -NH), 8.03 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.83 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.70 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 7.41 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.34 – 7.29 (2H, m, CH^{Ar}), 7.24 (3H, m, CH^{Ar}), 4.29 (2H, d, J = 5.8 Hz, C11-H_2), 3.55 (2H, s, C9-H_2), 2.61 (3H, s, C17-H_3). **^{13}C NMR** (126 MHz, DMSO) δ ppm 197.9 (C16), 170.6 (C10), 145.1 (Cq^{Ar}), 139.9 (Cq^{Ar}), 137.5 (Cq^{Ar}), 137.2 (Cq^{Ar}), 136.0 (Cq^{Ar}), 130.2 (C^{Ar}), 129.4 (C^{Ar}), 128.7 (C^{Ar}), 127.7 (C^{Ar}), 127.3 (2 x C^{Ar}), 127.1 (C^{Ar}), 42.7 (C9/11), 42.4 (C9/11), 27.2 (C17); **HRMS** (ESI$^+$, *m/z*) $C_{23}H_{22}NO_2$ calculated 344.1651 (MH^+), found 344.1650 (Δ = -0.3 ppm)

methyl 4'-(2-(benzylamino)-2-oxoethyl)-[1,1'-biphenyl]-4-carboxylate (5l)



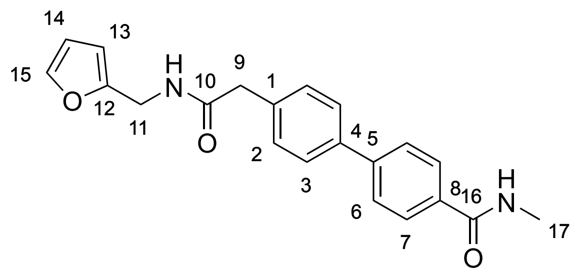
Using the general procedure III, but purifying by FC eluting with EtOAc:Pet Ether (40-60) gradient (50 – 100 %), **4b** (100 mg, 0.33 mmol) and 4-methoxycarbonyl-phenylboronic acid (88 mg, 0.49 mmol) were combined to yield the product **5l** as a white solid (70 mg, 59 %). **m.p.** 206 – 208 °C (EtOAc:Petrol (40-60), 1:1); **IR** (solid) ν_{max} 3277 (N-H stretch, br), 1720 (C=O ester stretch, br), 1635 (C=O stretch, s), 1558 (C=C stretch, br), 1493 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.60 (1H, t, J = 5.8 Hz, -NH), 8.03 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.83 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.69 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.41 (2H, app d, J = 8.3 Hz, CH^{Ar}), 7.31 (2H, m, CH^{Ar}), 7.27 – 7.21 (3H, m, CH^{Ar}), 4.29 (2H, d, J = 5.8 Hz, C11-H_2), 3.88 (3H, s, C17-H_3), 3.55 (2H, s, C9-H_2). **^{13}C NMR** (126 MHz, DMSO) δ ppm 170.4 (C10), 166.5 (C16), 145.0 (Cq^{Ar}), 139.9 (Cq^{Ar}), 137.4 (Cq^{Ar}), 137.3 (Cq^{Ar}), 132.5 (C^{Ar}), 132.0 (C^{Ar}), 131.9 (C^{Ar}), 130.2 (C^{Ar}), 129.3 (C^{Ar}), 129.2 (C^{Ar}), 128.7 (C^{Ar}), 127.7 (C^{Ar}), 127.3 (C^{Ar}), 127.2 (C^{Ar}), 52.6 (C17), 42.7 (C9/11), 42.4 (C9/11); **HRMS** (ESI$^+$, *m/z*) $C_{23}H_{22}NO_3$ calculated 360.1600 (MH^+), found 360.1597 (Δ = -0.8 ppm)

4'-(2-[(furan-2-ylmethyl)amino]-2-oxoethyl)-[1,1'-biphenyl]-4-carboxylic acid (6)



Using the general procedure III, but purifying by FC eluting MeOH:EtOAc:AcOH gradient (99:0:1 – 95:4:1), compound **4a** (100 mg, 0.33 mmol) and 4-carboxy-phenylboronic acid (84 mg, 0.49 mmol) were combined to yield the product **6** as a white solid (70 mg, 59 %). **m.p.** >260 °C (EtOAc); **IR** (solid) ν_{max} 3289 (N-H stretch, br), 1681 (C=O stretch, br), 1633 (C=C stretch, s), 1607 (C=C stretch, br), 1542 (C=C stretch, br) 1493 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.57 (1H, t, *J* = 5.6 Hz, -NH), 8.00 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.75 (2H, app d, *J* = 8.2 Hz, CH^{Ar}), 7.66 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.52 - 7.57 (1H, m, C15-H), 7.38 (2H, app d, *J* = 8.2 Hz, CH^{Ar}), 6.39 (1H, dd, *J* = 3.1, 1.8 Hz, C14-H), 6.22 (1H, dd, *J* = 3.1, 0.9 Hz, C13-H), 4.27 (2 H, d, *J* = 5.6 Hz, C11-H_2), 3.51 (2H, s, C9-H_2); **^{13}C NMR** (126 MHz, DMSO) δ ppm 169.8 (C10), 169.3 (C16), 152.2 (Cq^{Ar}), 143.4 (Cq^{Ar}), 142.1 (C15), 137.3 (Cq^{Ar}), 136.3 (Cq^{Ar}), 129.9 (C^{Ar}), 129.7 (C^{Ar}), 129.4 (Cq^{Ar}), 126.7 (C^{Ar}), 126.4 (C^{Ar}), 110.4 (C14), 106.8 (C13), 41.8 (C9), 35.6 (C11); **HRMS** (ESI^+, *m/z*) $C_{20}H_{17}NO_4$ calculated 336.1236 (MH^+), found 336.1251 (Δ = 4.5 ppm)

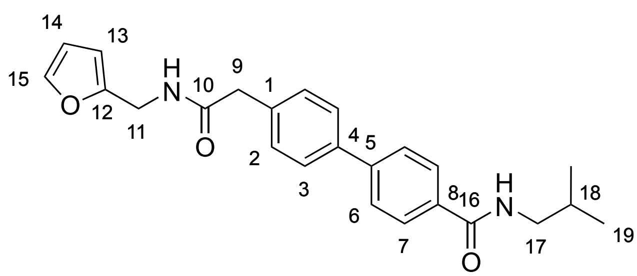
4'-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-*N*-methyl-[1,1'-biphenyl]-4-carboxamide (7a)



6 (20 mg, 0.059 mmol) and methylamine (9 µL, 40%, 0.10 mmol) were dissolved in EtOAc (1.5 mL). DIPEA (30 µL, 0.20 mmol) was added and the mixture cooled to 0 °C before T3P (120 µL, 50%, 0.20 mmol) was added. The mixture was stirred for 30 min before warming to rt and stirring overnight. Six additional equivalents of T3P (360 µL, 50%, 0.60 mmol) and the amine (54 µL, 40%, 0.60 mmol) and stirring at rt for a further 48 h were required to push the reaction to completion. The reaction was worked-up by diluting in EtOAc (20 mL) and washing with 1M HCl (2 x 5 mL), followed by sat. Na_2CO_3 (2 x 5 mL). The organic was then dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield the desired amide **7a** as a pale off-white solid (7 mg, 34 %). **m.p.** 240 – 242 °C; **IR** (solid) ν_{max} 3325 (N-H stretch, br), 3238 (N-H stretch, br), 1653 (C=O ester stretch, br), 1635 (C=O stretch, sharp), 1630 (C=C stretch, br), 1547 (C=C stretch, sharp), 1494 (sharp) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.54 (1H, t, *J* = 5.5 Hz, -NH(C11)), 8.46 (1H, q, *J* = 4.3 Hz, -NH(Me)), 7.90 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.73 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.64 (2H, *J* = 8.5 Hz, CH^{Ar}), 7.57 (1H, dd, *J* = 1.8, 0.9 Hz, C15-H), 7.36 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 6.38 (1H, dd, *J* = 3.2, 1.9 Hz, C14-H), 6.21 (1H, dd, *J* = 3.2, 0.8 Hz, C13-H), 4.26 (2H, d, *J* = 5.6 Hz, C11-H_2), 3.49 (2H, s, C9-H_2), 2.79 (3H, d, *J* = 4.5 Hz, C17-H_3). **^{13}C NMR** (126 MHz, DMSO) δ ppm 169.9 (C10), 166.3 (C16), 152.3 (Cq^{Ar}), 142.2 (C15), 142.1 (Cq^{Ar}), 137.3 (Cq^{Ar}), 136.2 (Cq^{Ar}), 133.0 (Cq^{Ar}), 129.7 (C^{Ar}), 127.8 (C^{Ar}), 126.7 (C^{Ar}), 126.4 (C^{Ar}), 110.5 (C14), 106.9 (C13), 41.9 (C9), 35.7

(C11), 26.3 (C17); **HRMS** (ESI^+, *m/z*) $C_{21}H_{21}N_2O_3$ calculated 349.1552 (MH^+), found 349.1568 (Δ = 4.6 ppm)

4'-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-*N*-isobutyl-[1,1'-biphenyl]-4-carboxamide (7b)

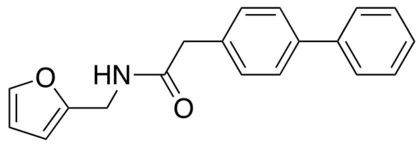


6 (20 mg, 0.059 mmol) and *sec*-isobutylamine (10 μL, 0.1 mmol) were dissolved in EtOAc (1.5 mL). DIPEA (30 μL, 0.2 mmol) was added and the mixture cooled to 0 °C before T3P (120 μL, 50%, 0.2 mmol) was added. The mixture was stirred for 30 min before warming to rt and stirring overnight. One additional equivalent of T3P and the amine followed by stirring at rt for a further 24 h were required to push the reaction to completion. The reaction was worked-up by diluting in EtOAc (20 mL) and washing with 1M HCl (2 x 5 mL), followed by sat. Na_2CO_3 (2 x 5 mL). The organic was then dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield the desired amide **7b** as a pale off-white solid (15 mg, 56 %). **m.p.** 237 – 239 °C (EtOAc); **IR** (solid) ν_{max} 3305 (N-H stretch, br), 3257 (N-H stretch, br) 1655 (C=O ester stretch, sharp), 1635 (C=O stretch, br), 1607 (C=C stretch, sharp), 1542 (C=C stretch, sharp), 1495 (sharp) cm^{-1} **^{1}H NMR** (500 MHz, DMSO) δ ppm 8.54 (1H, t, *J* = 5.6 Hz, -NH(C11)), 8.48 (1H, t, *J* = 5.8 Hz,-NH(C17)), 7.92 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.73 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.64 (2H, app d, *J* = 8.5 Hz, CH^{Ar}), 7.57 (1H, dd, *J* = 1.8, 0.9 Hz, C15-H), 7.36 (2H, app d, *J* = 8.3 Hz, CH^{Ar}), 4.26 (2H, d, *J* = 5.6 Hz, C11-H), 3.49 (2H, s, C9-H_2), 3.09 (2H, dd, *J* = 6.9, 6.0 Hz, C17-H_2), 1.92 – 1.77 (1H, m, C18-H), 0.89 (6H, d, *J* = 6.7 Hz, 2 x C19-H_3); **^{13}C NMR** (126 MHz, DMSO) δ ppm

169.9 (C10), 166.0 (C16), 152.2 (Cq^{Ar}), 142.4 (Cq^{Ar}), 142.2 (C15), 137.4 (Cq^{Ar}), 136.3 (Cq^{Ar}), 133.5 (Cq^{Ar}), 129.8 (C^{Ar}), 127.9 (C^{Ar}), 126.8 (C^{Ar}), 126.3 (C^{Ar}), 110.5 (C14), 106.9 (C13), 46.8 (C17), 41.9 (C9), 35.7 (C11), 28.2 (C18), 20.3 (C19); **HRMS** (ESI^+, *m/z*) $C_{24}H_{27}N_2O_3$ calculated 391.2022 (MH^+), found 391.2031 (Δ = 2.3 ppm)

5 NMR data for compounds

1



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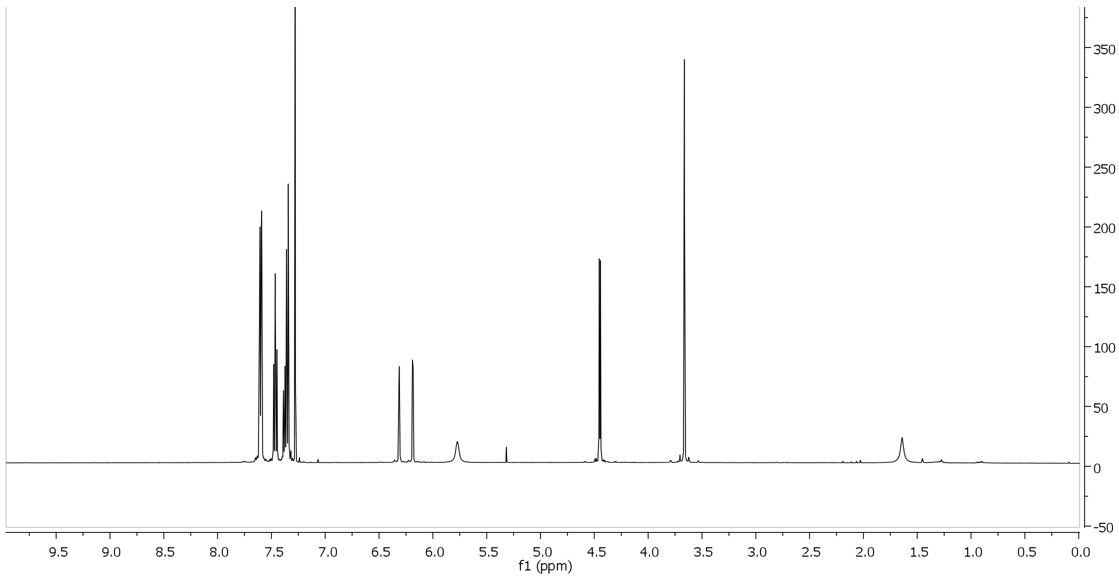

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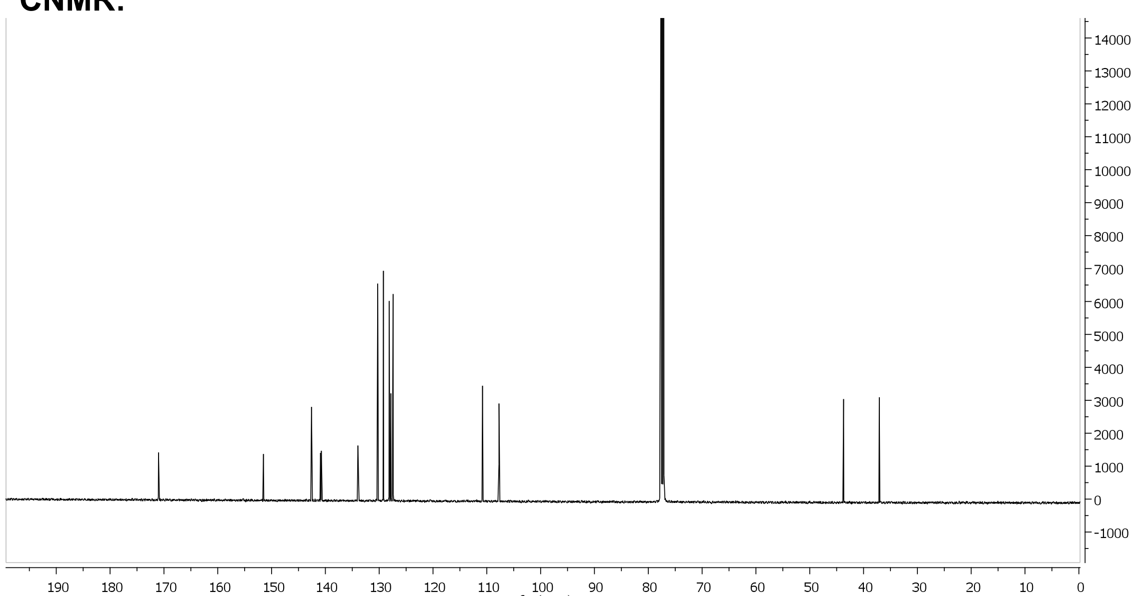

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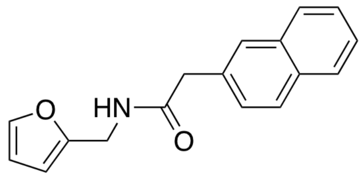

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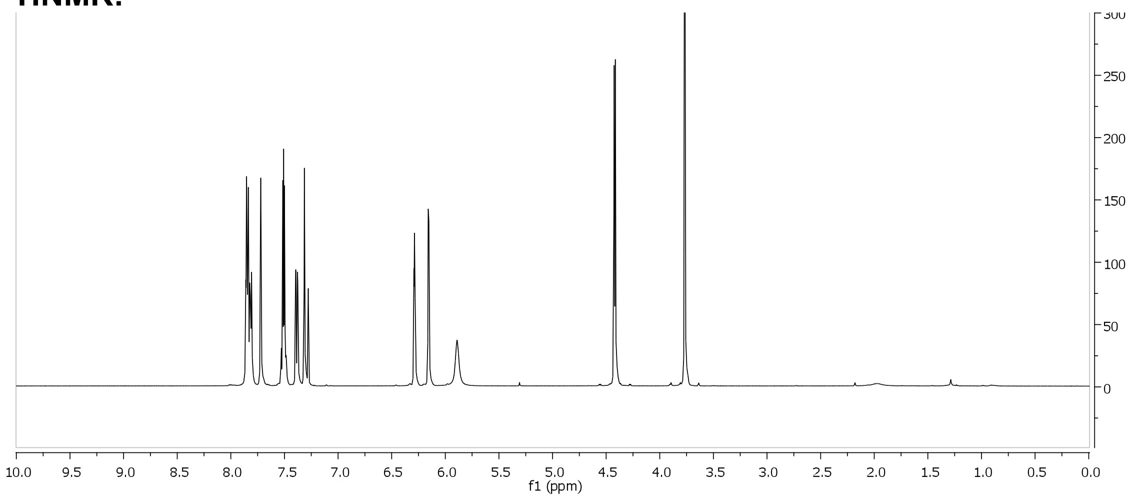

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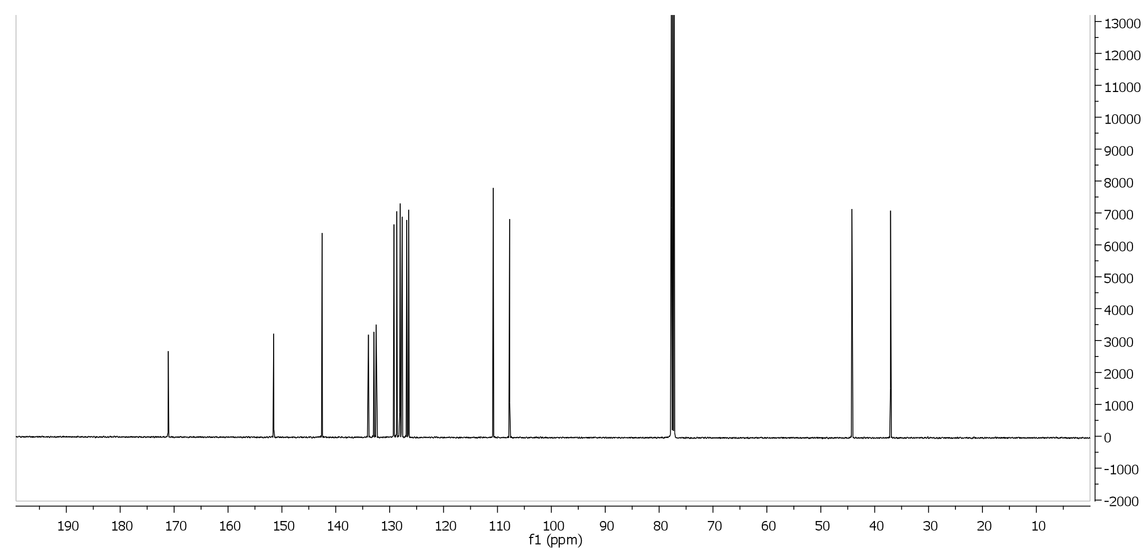

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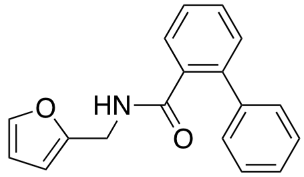

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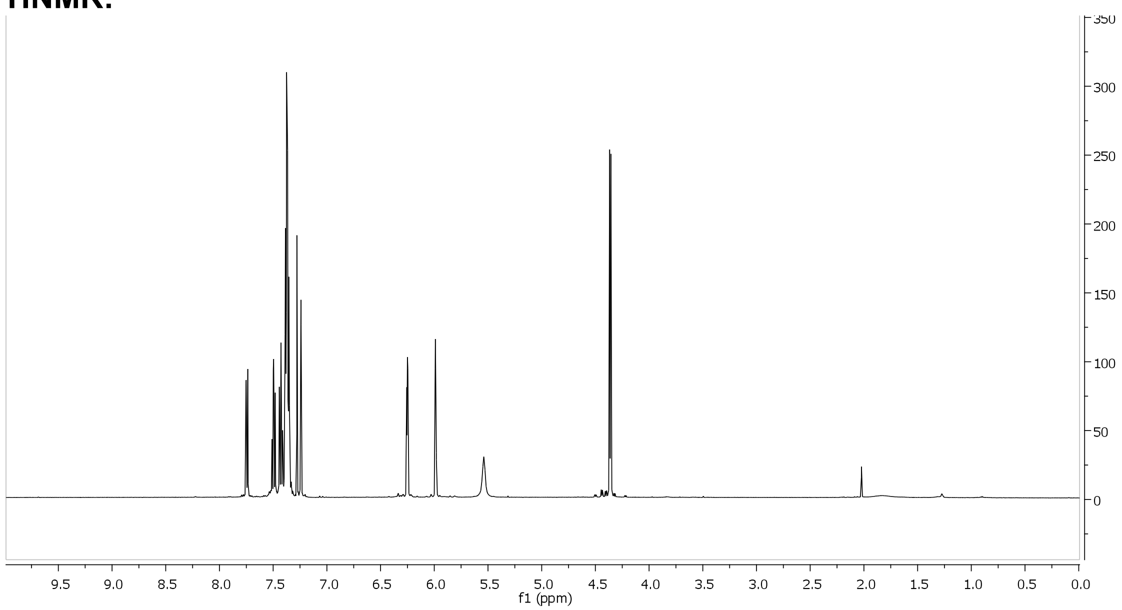

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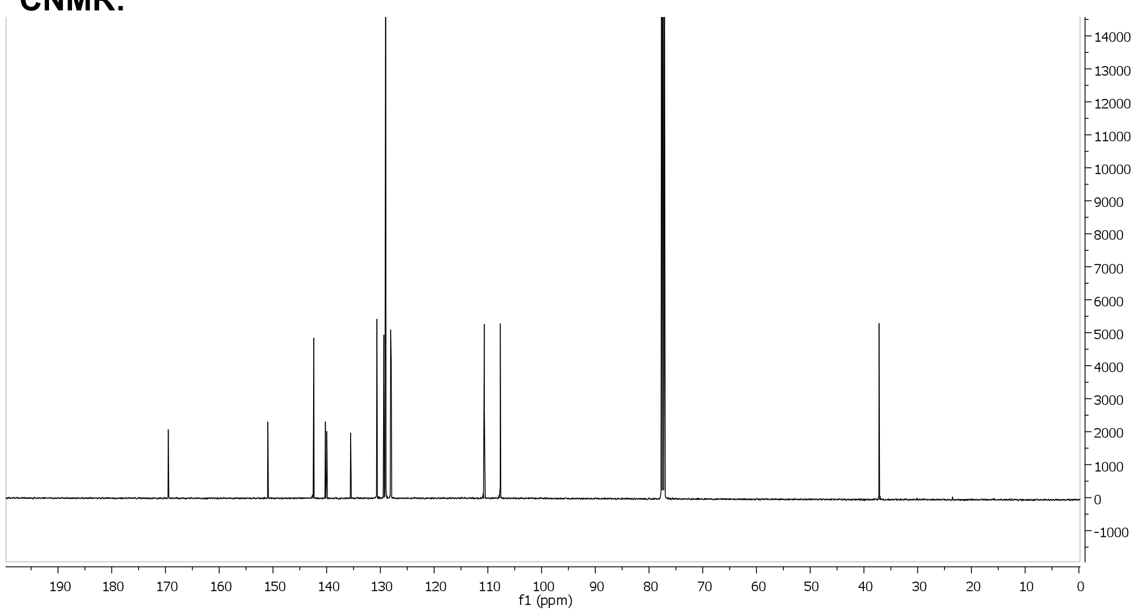

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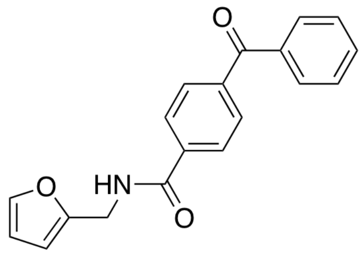

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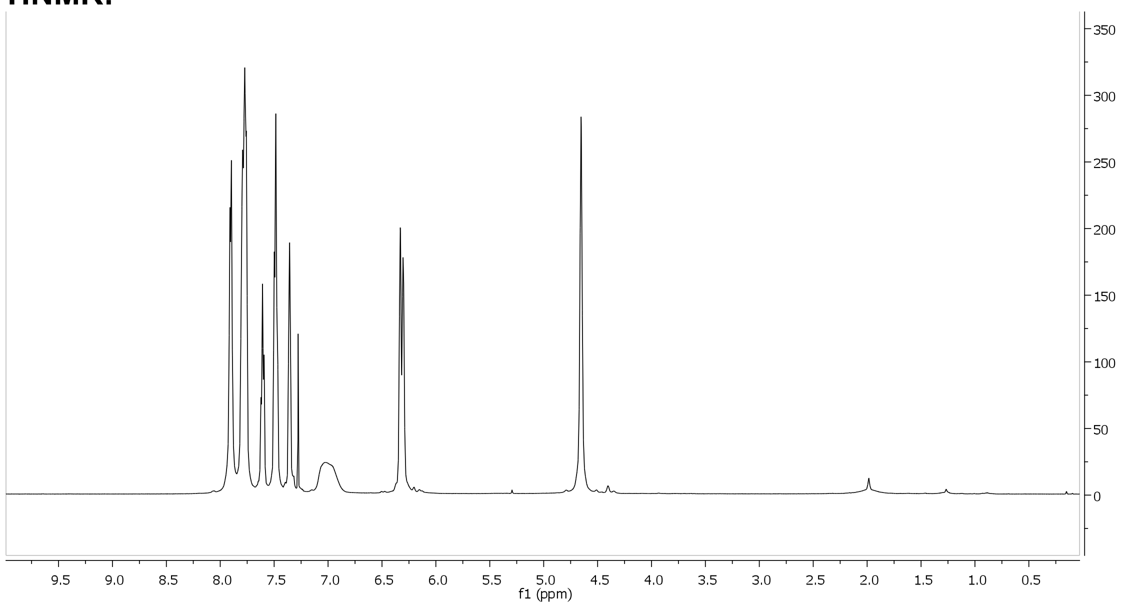

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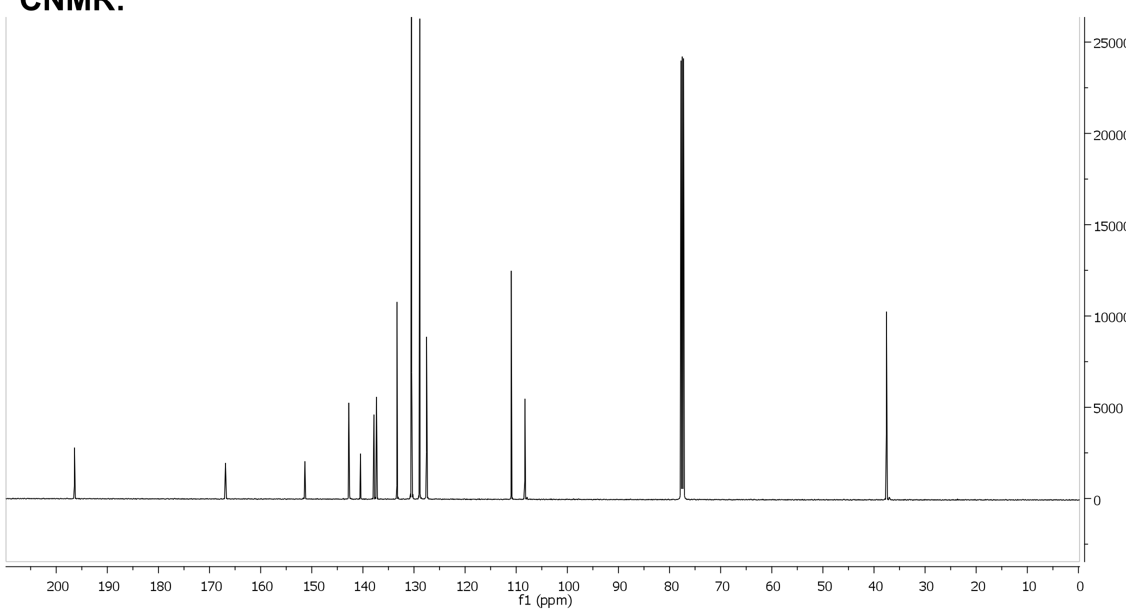

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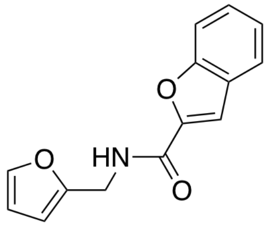

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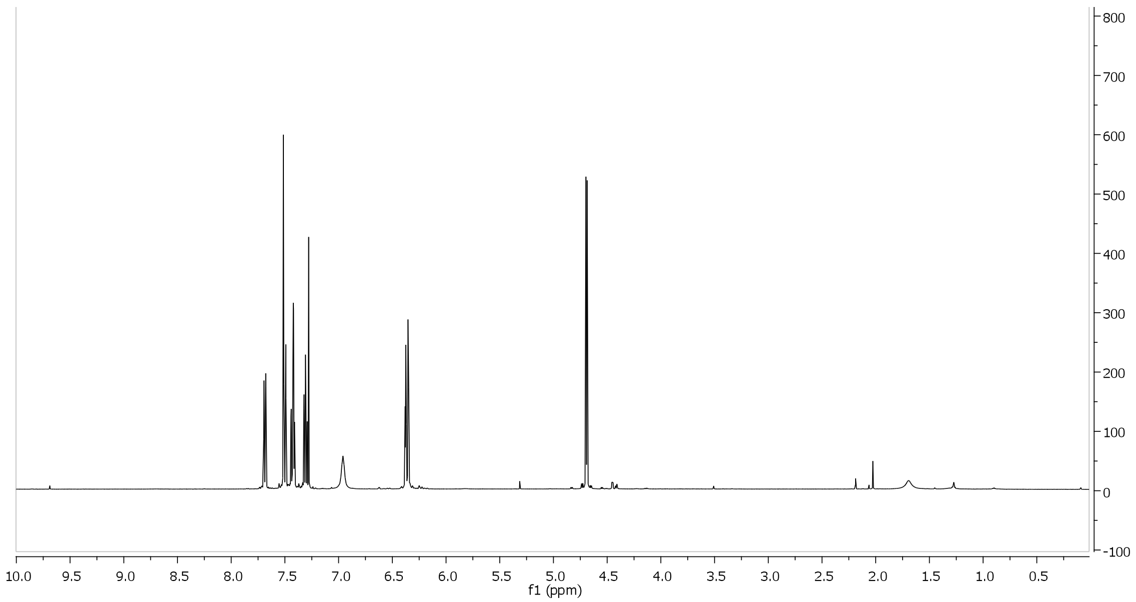

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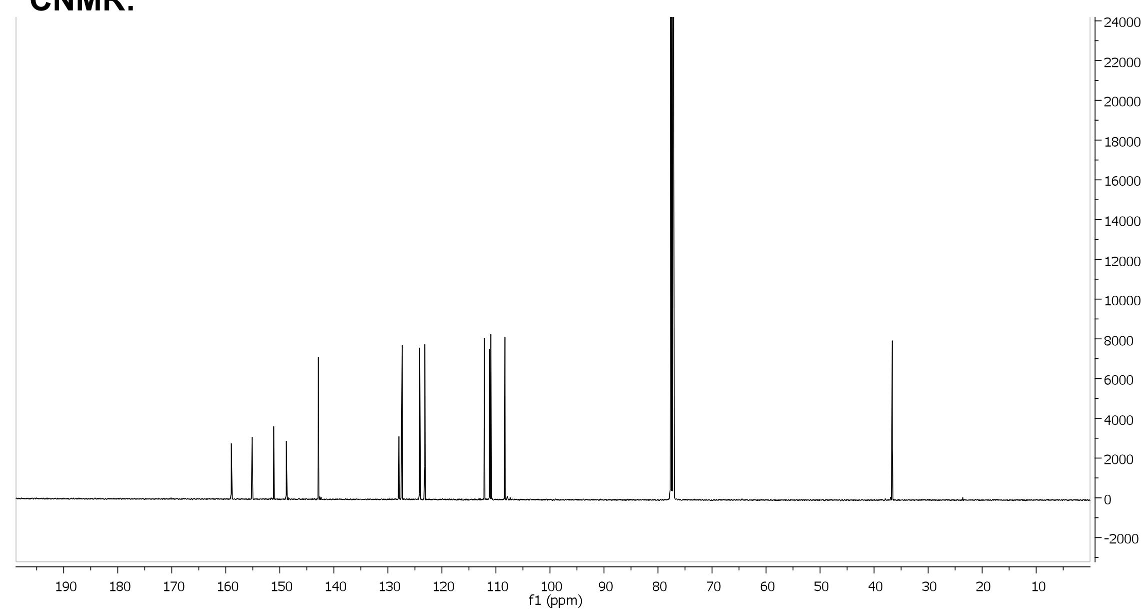

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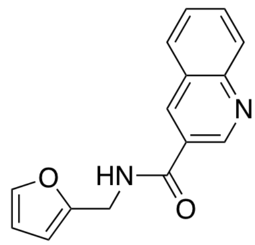

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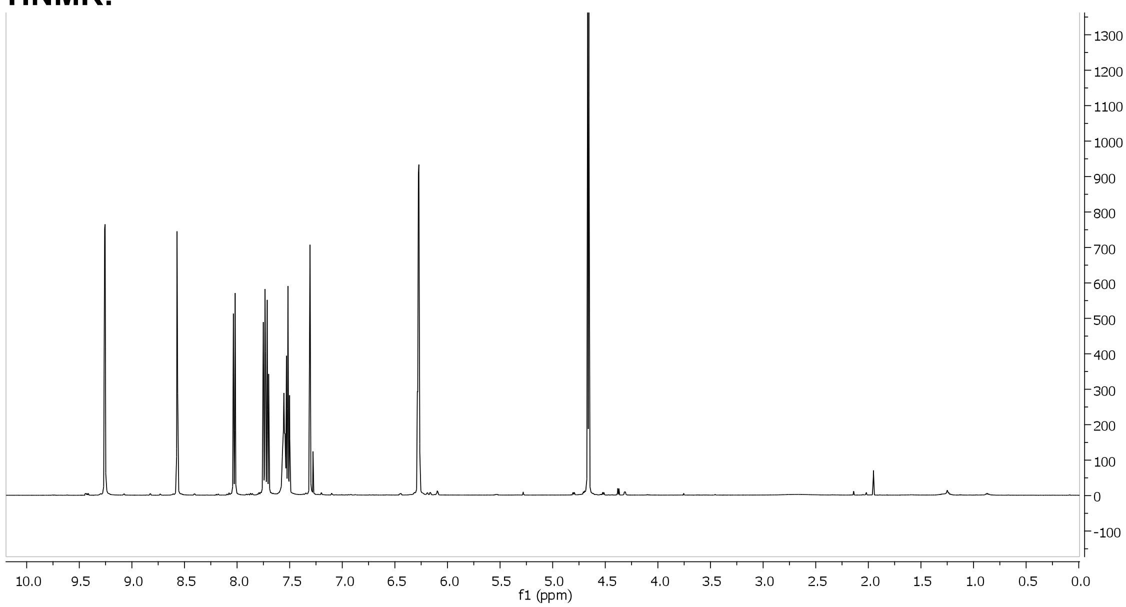

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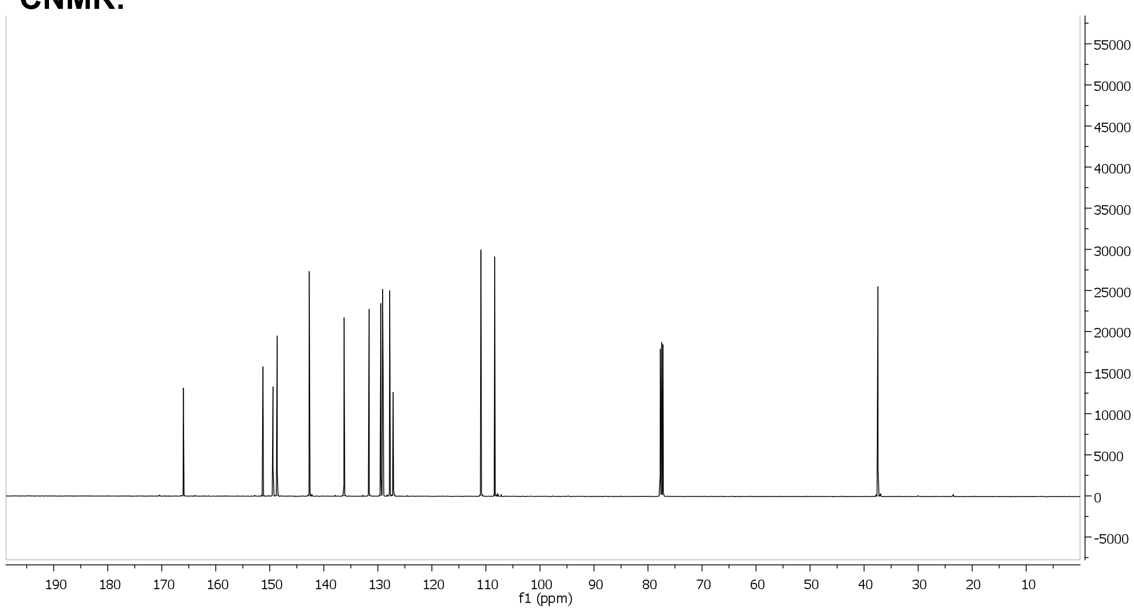

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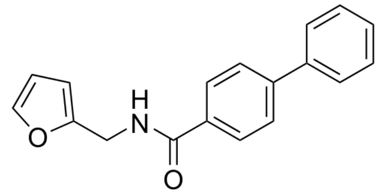

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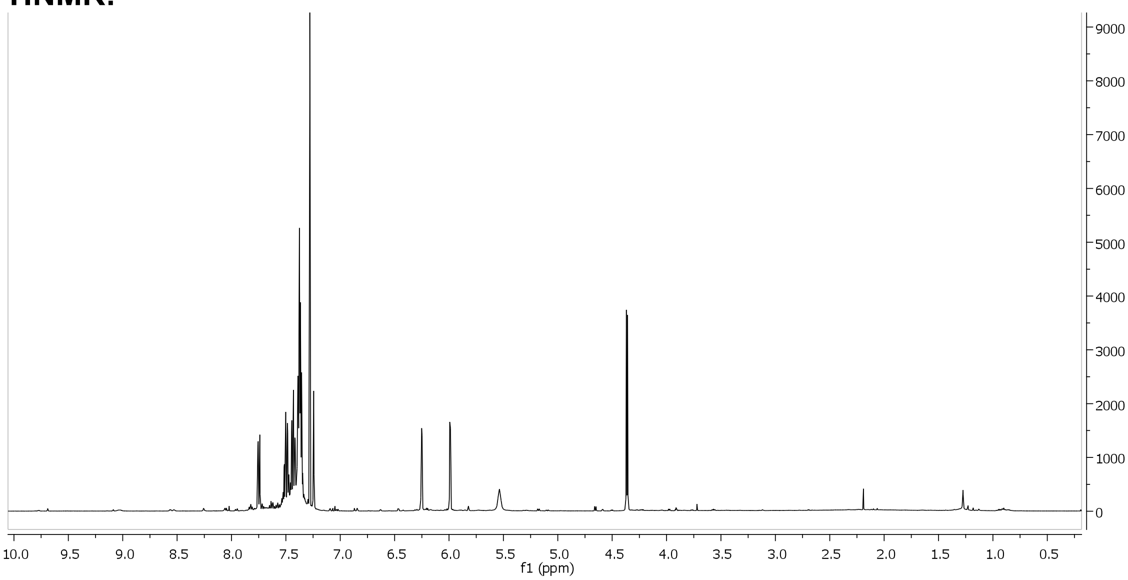

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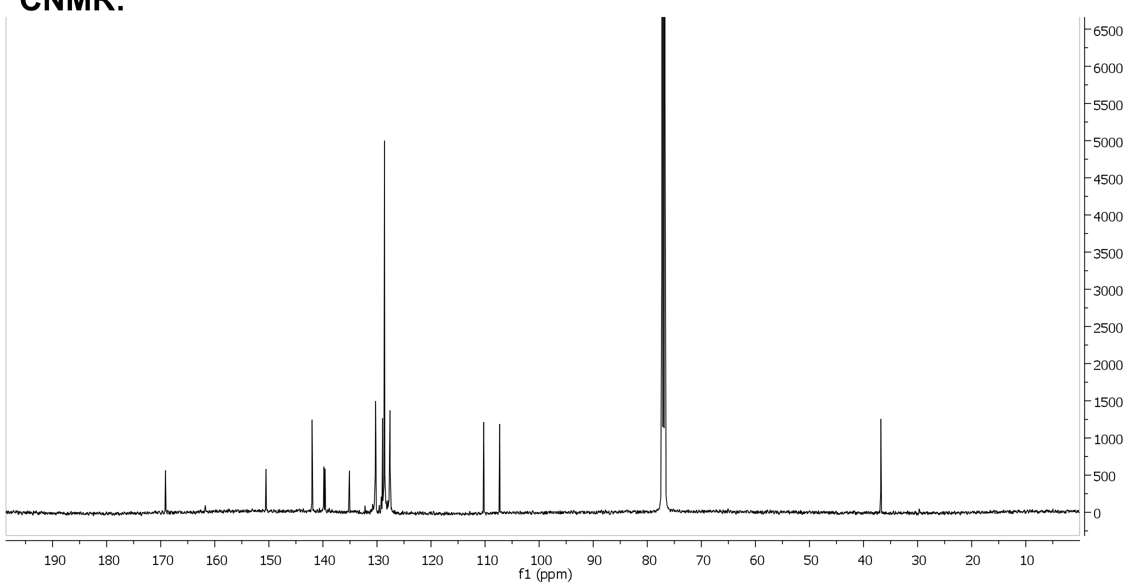

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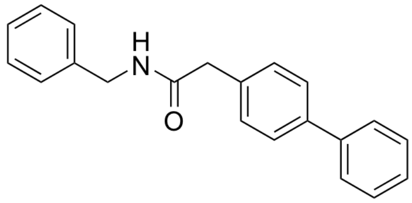

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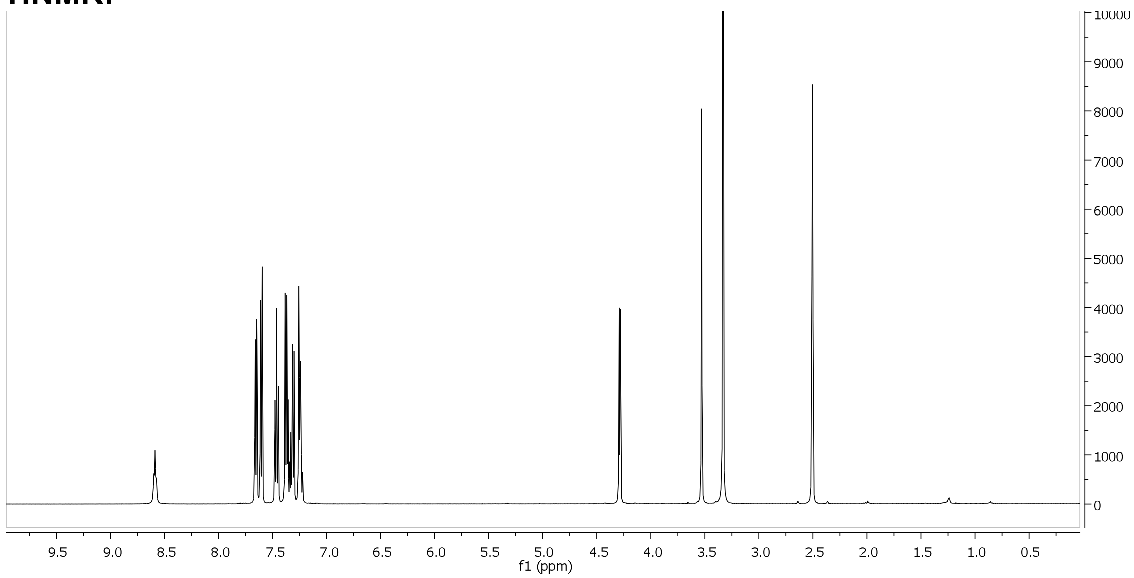

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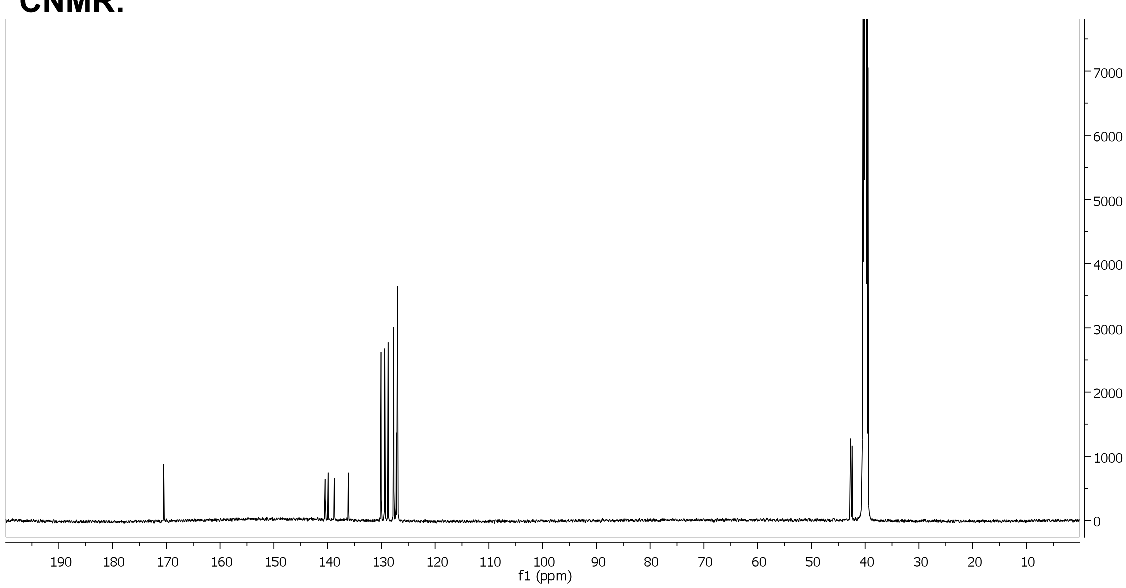

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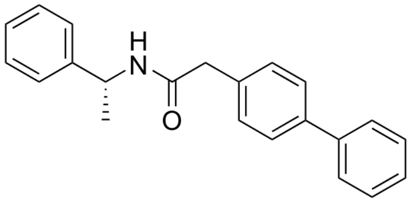

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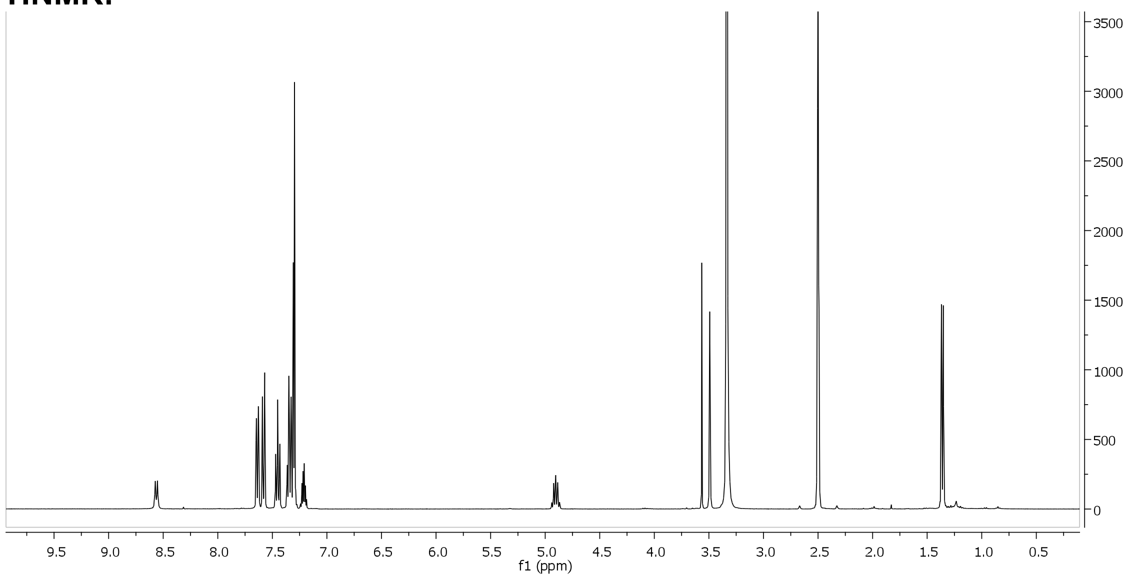

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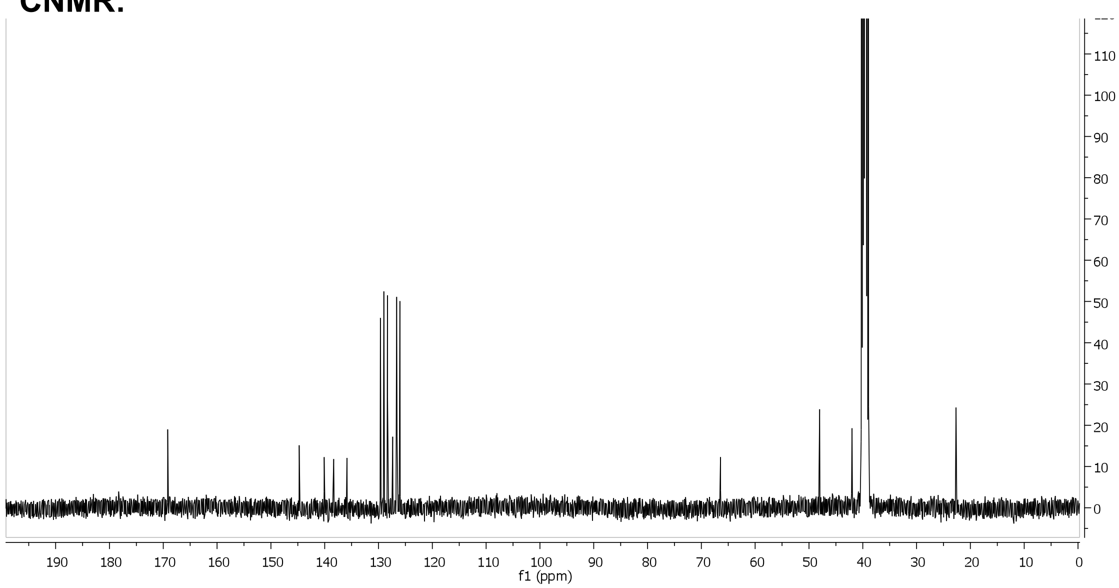

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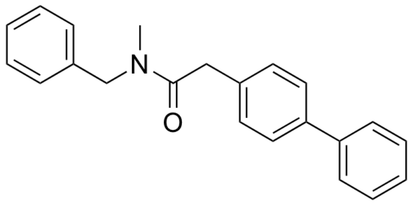

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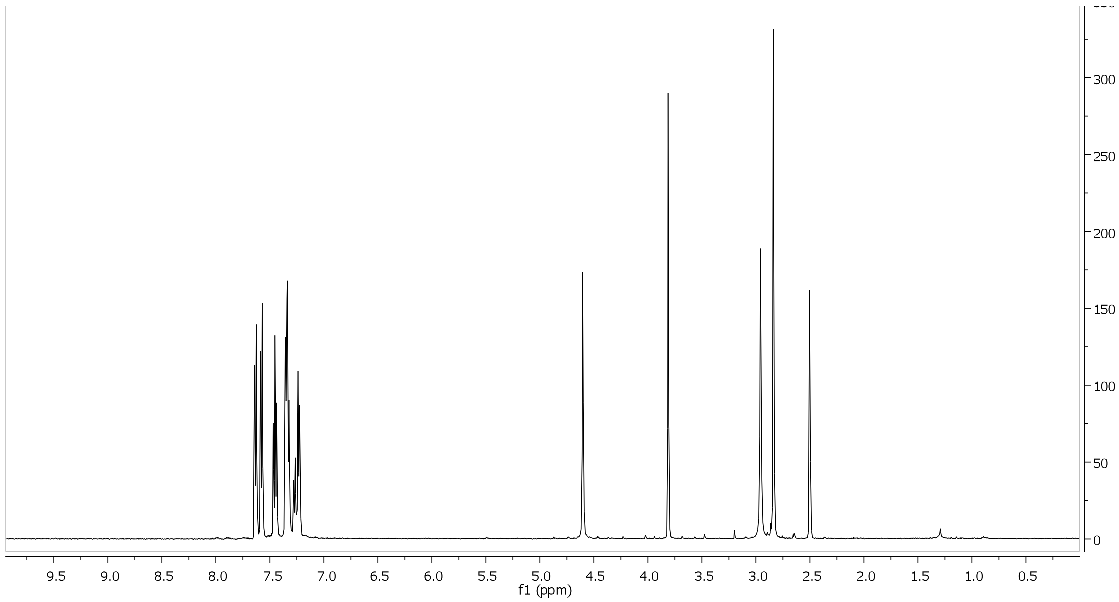

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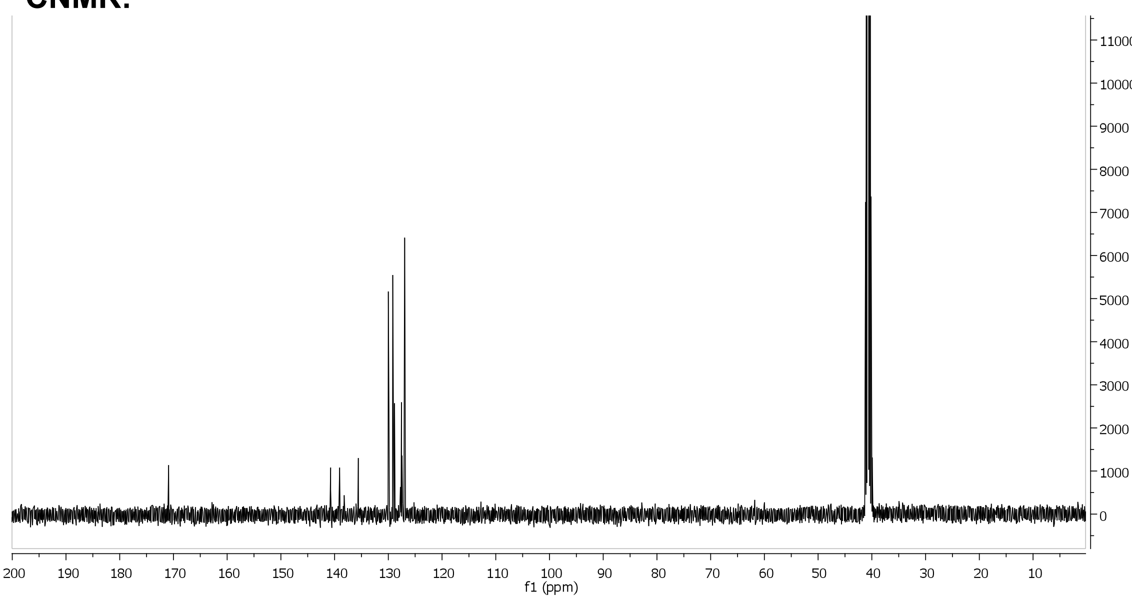

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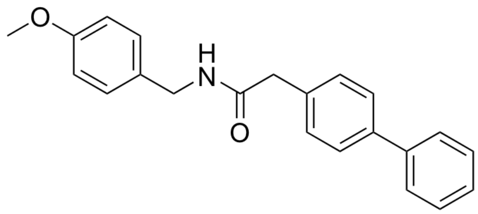

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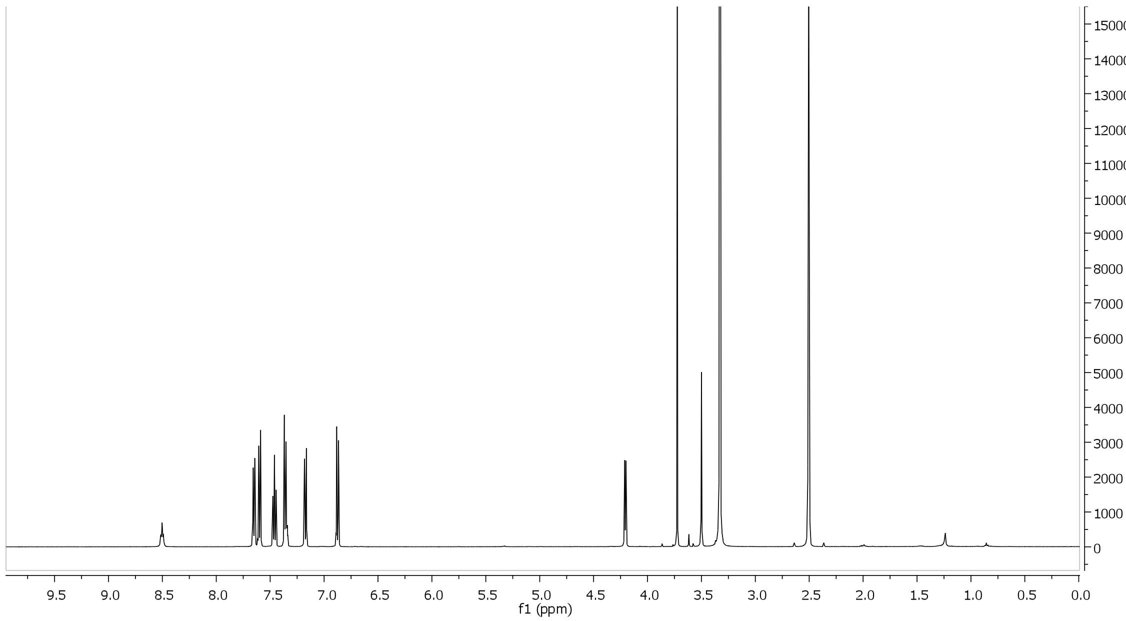

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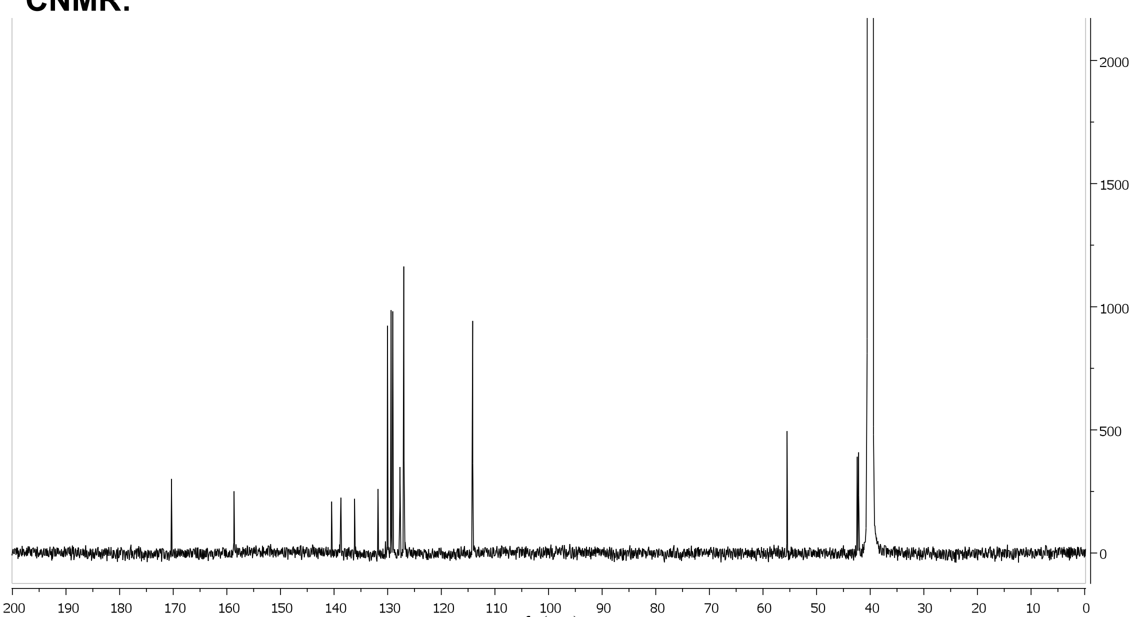

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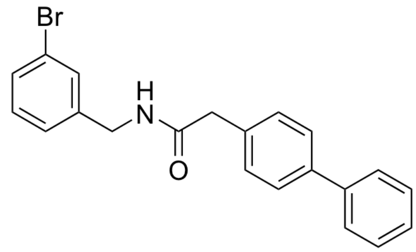

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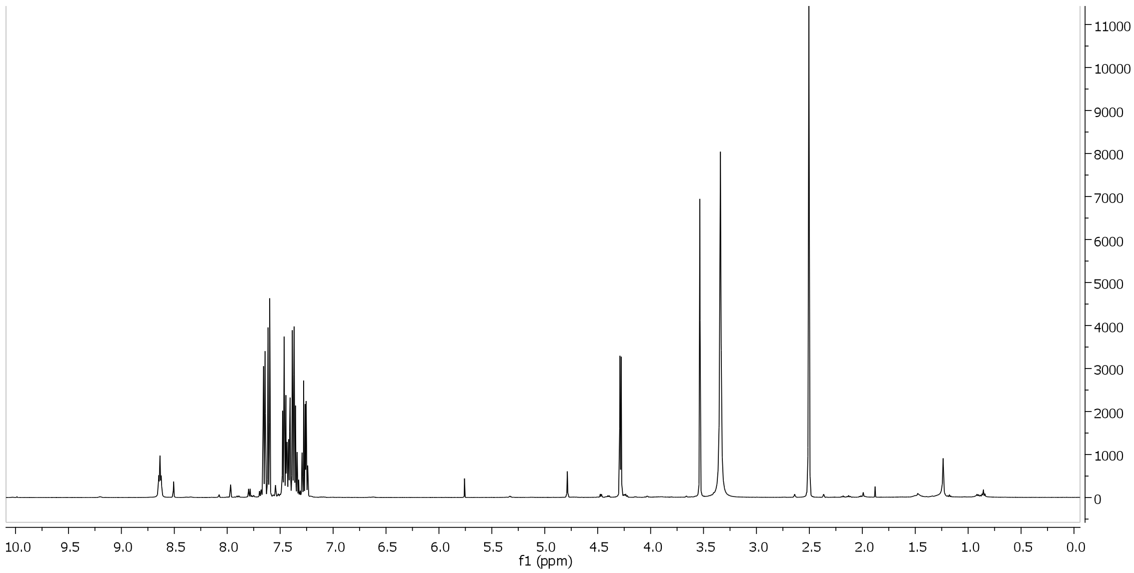

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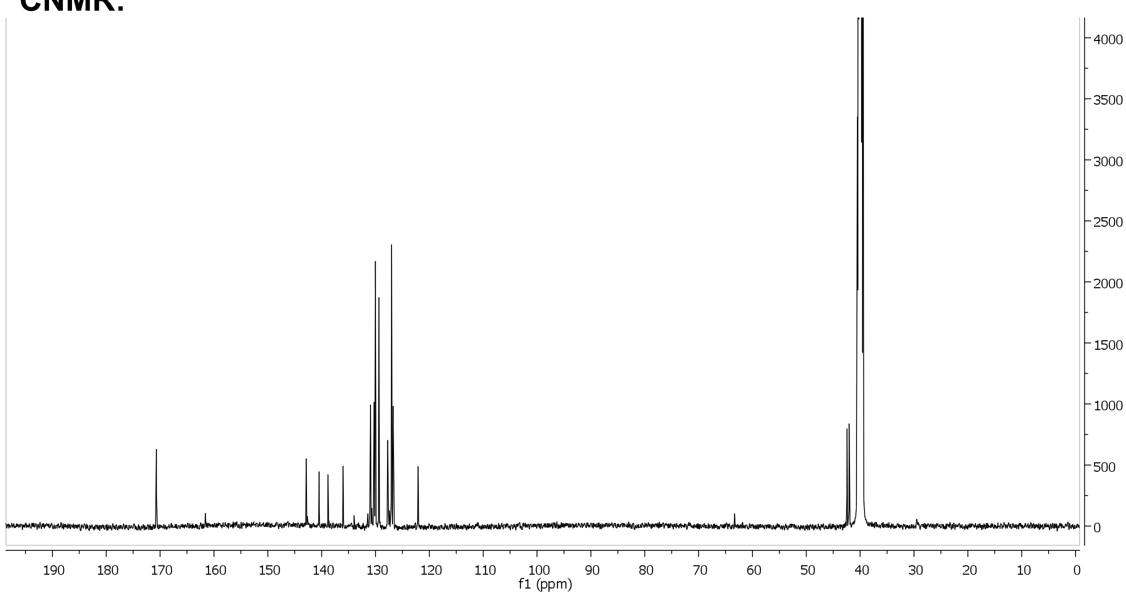

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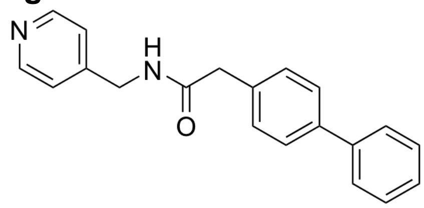

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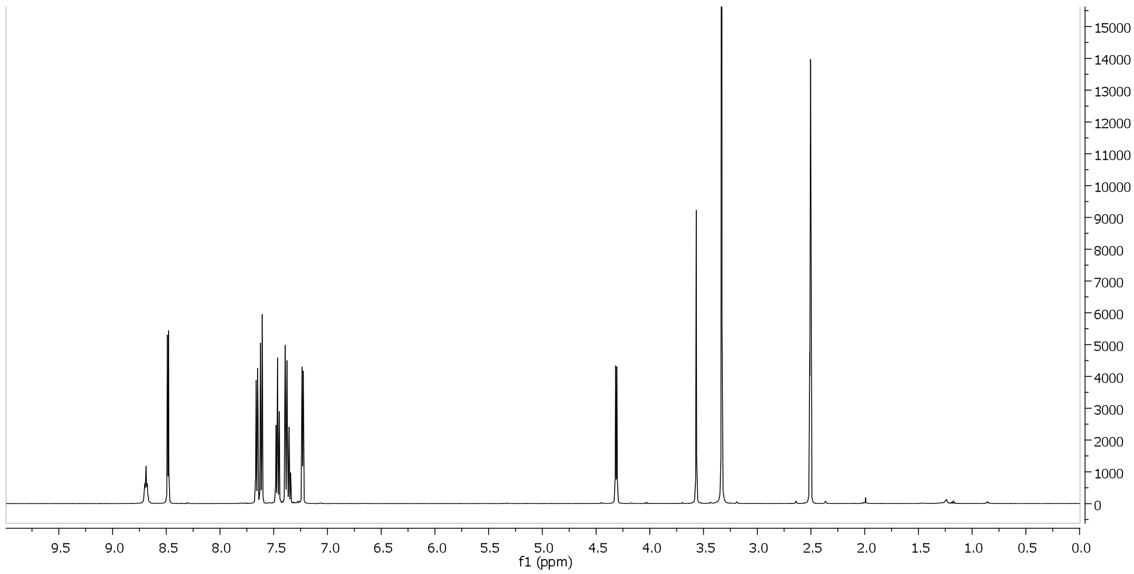

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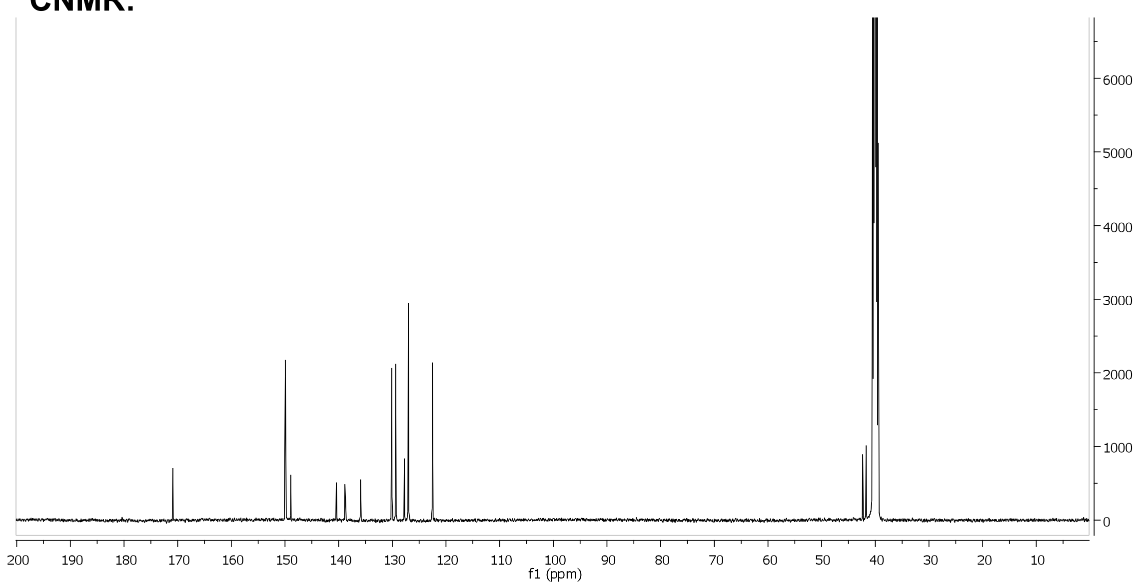

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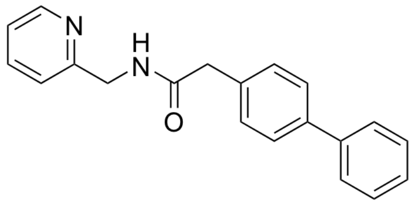

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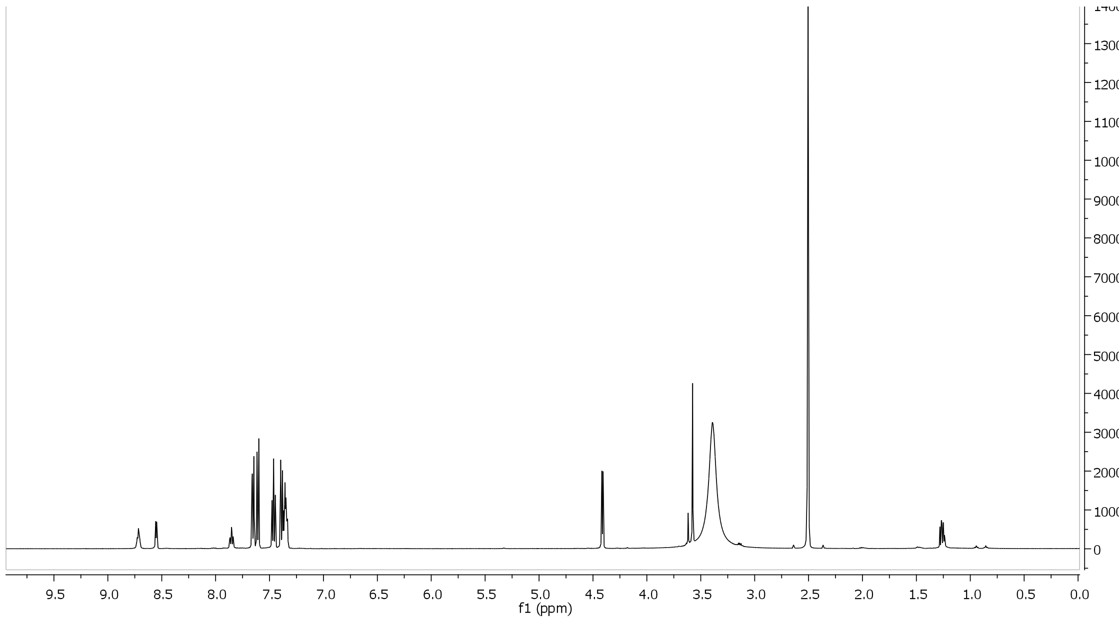

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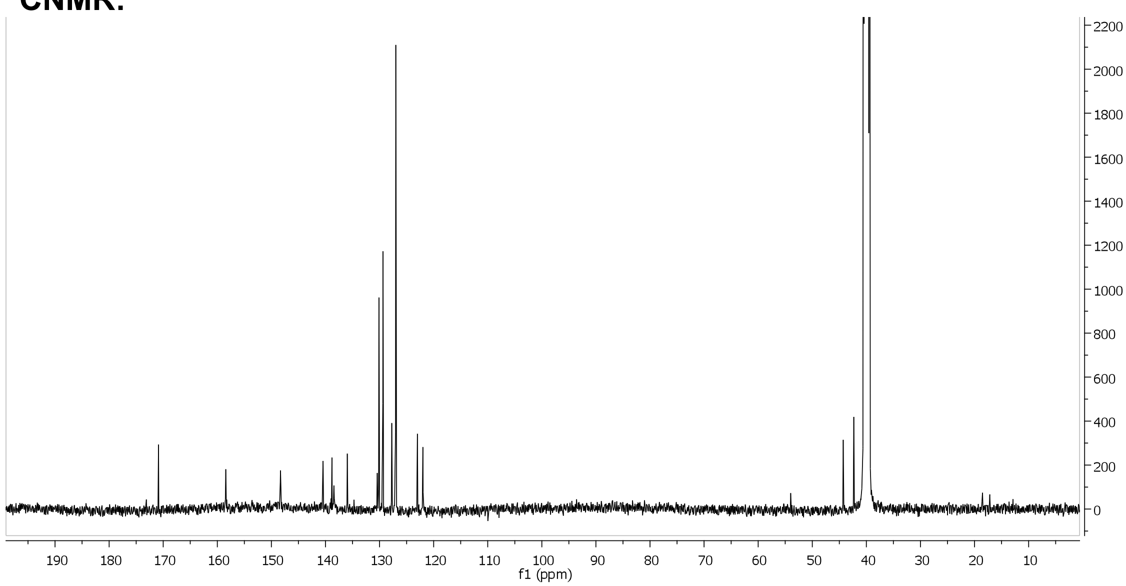

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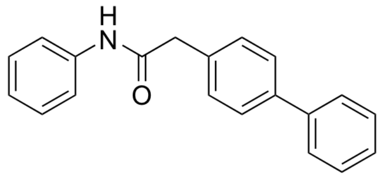

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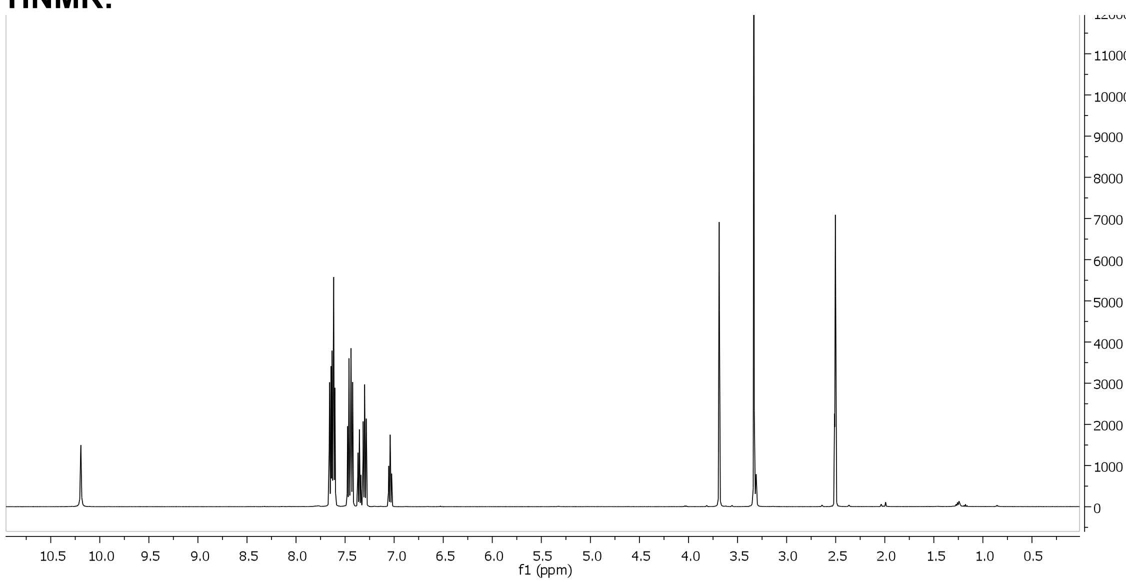

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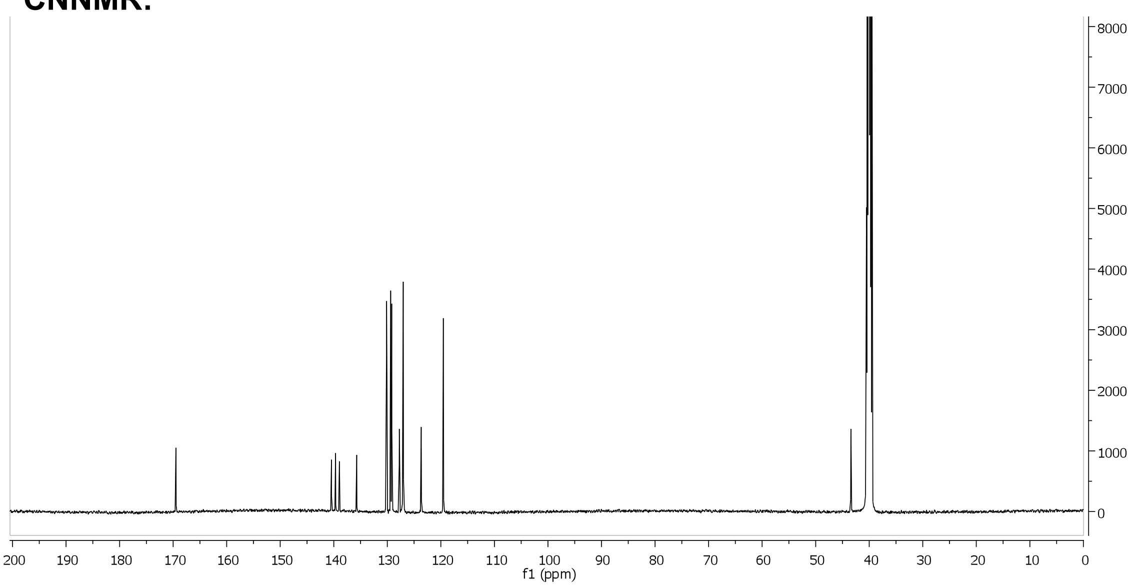

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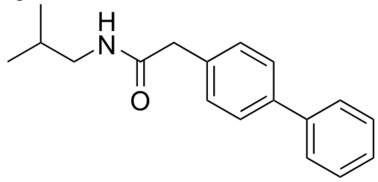

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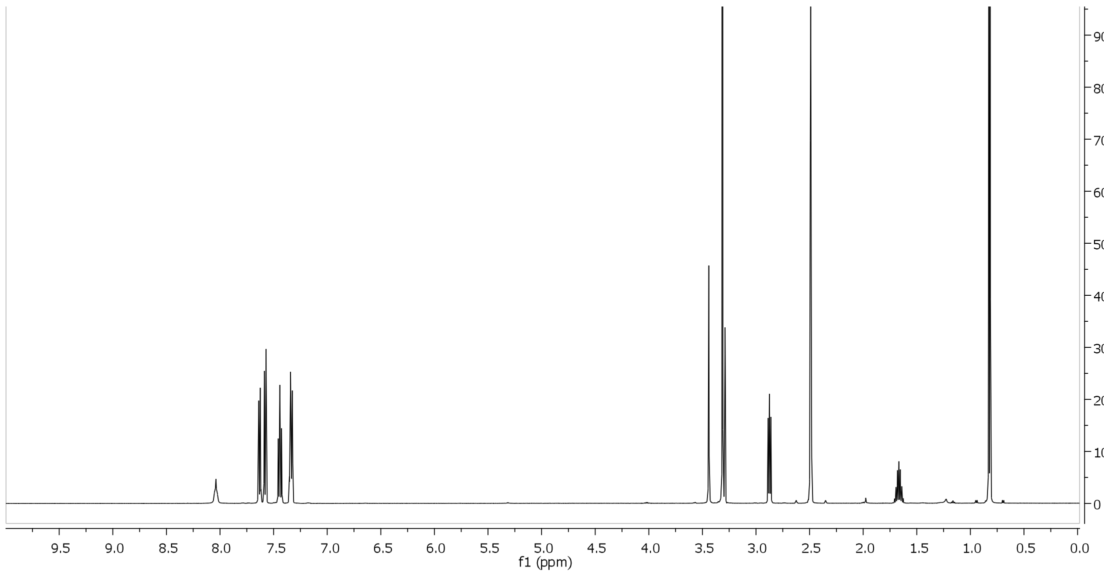

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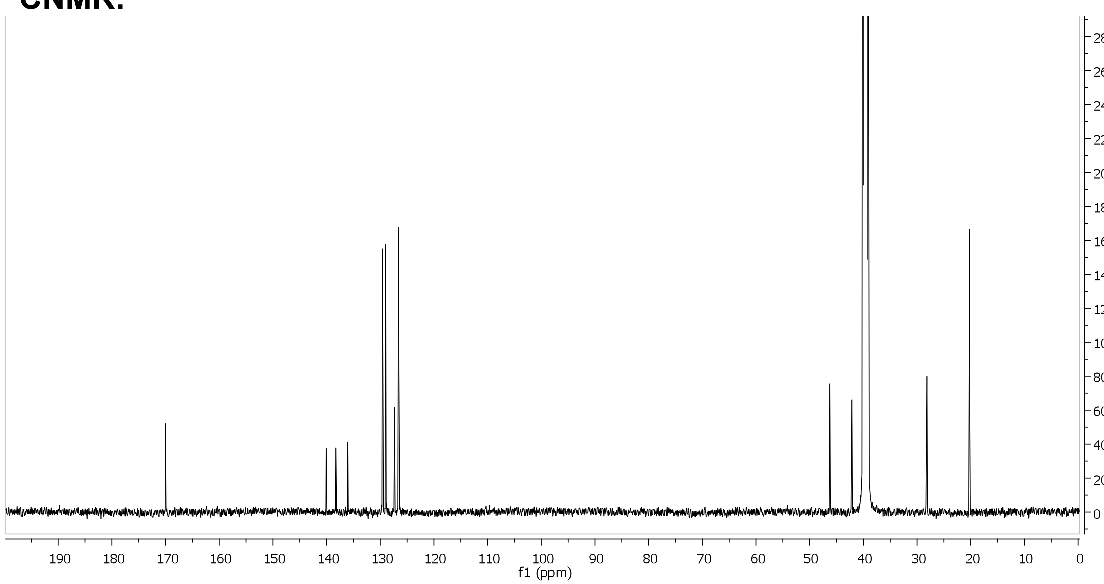

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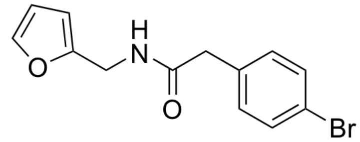

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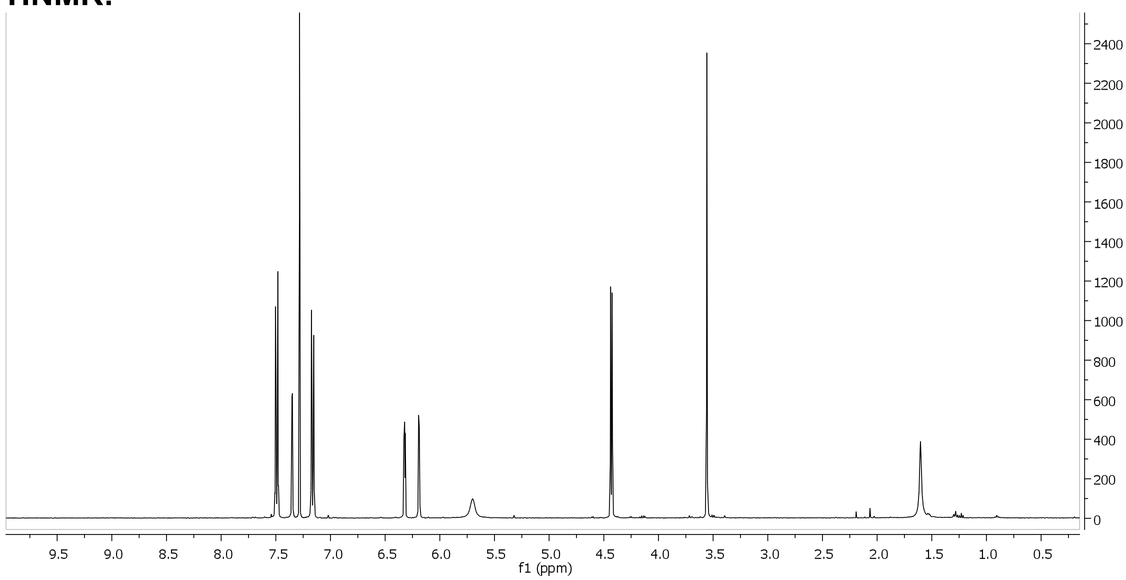

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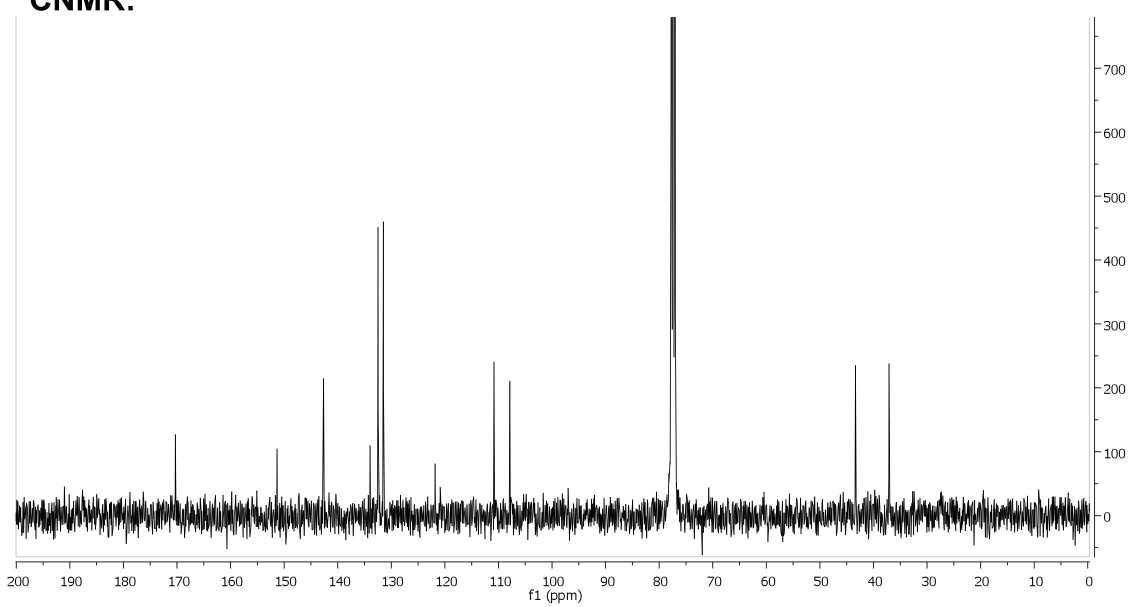

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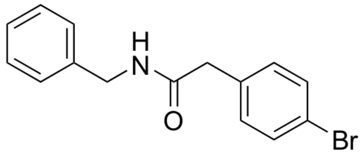

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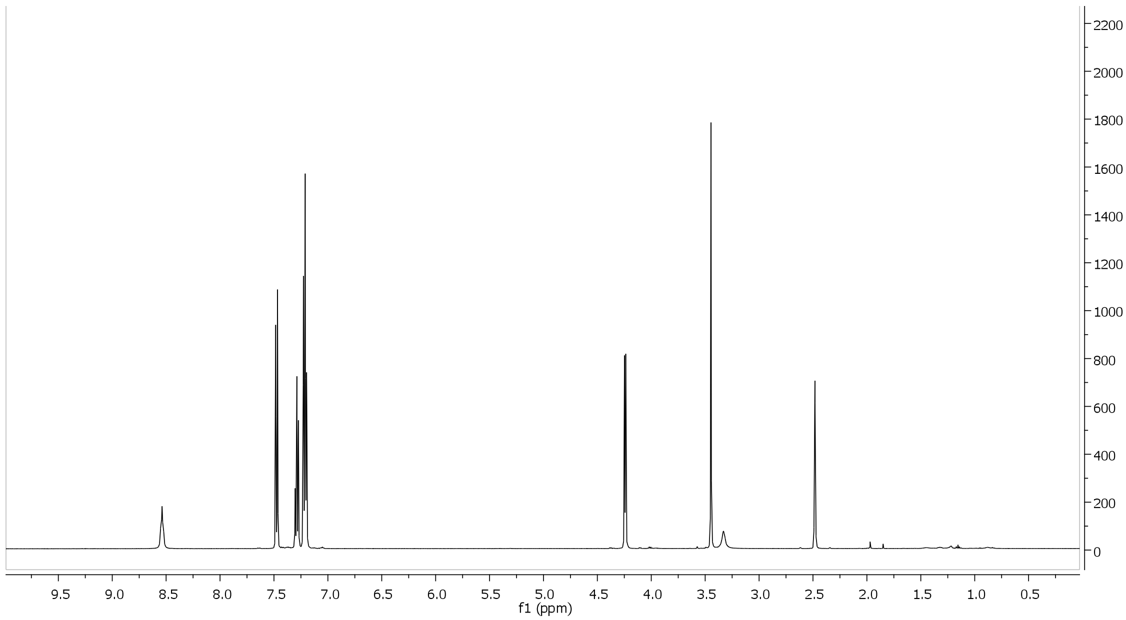

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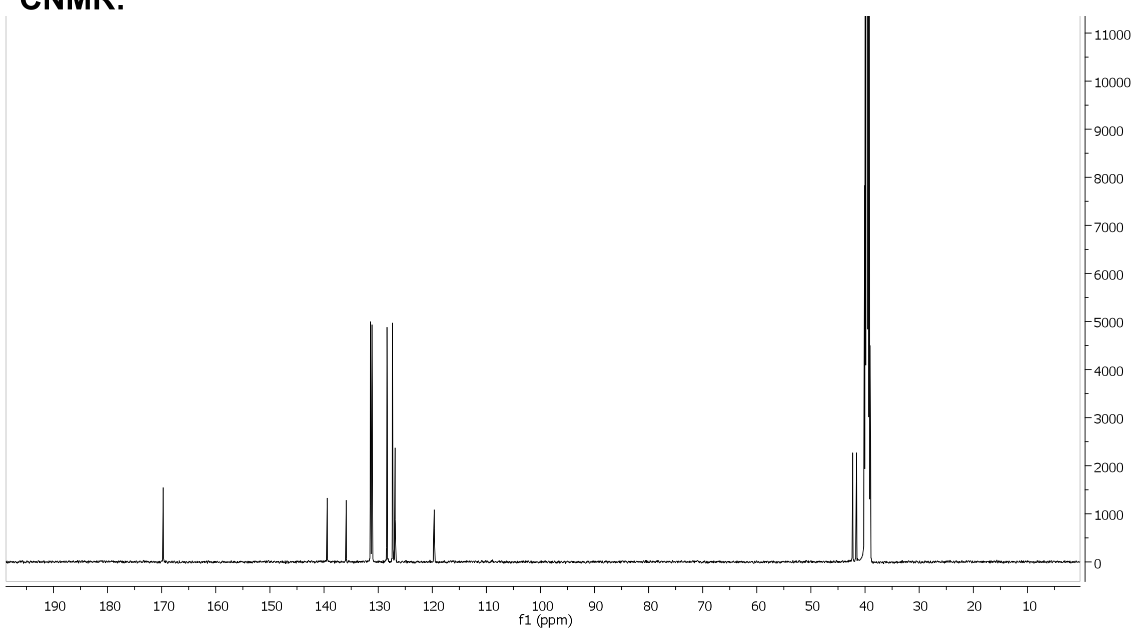

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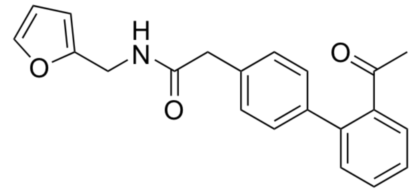

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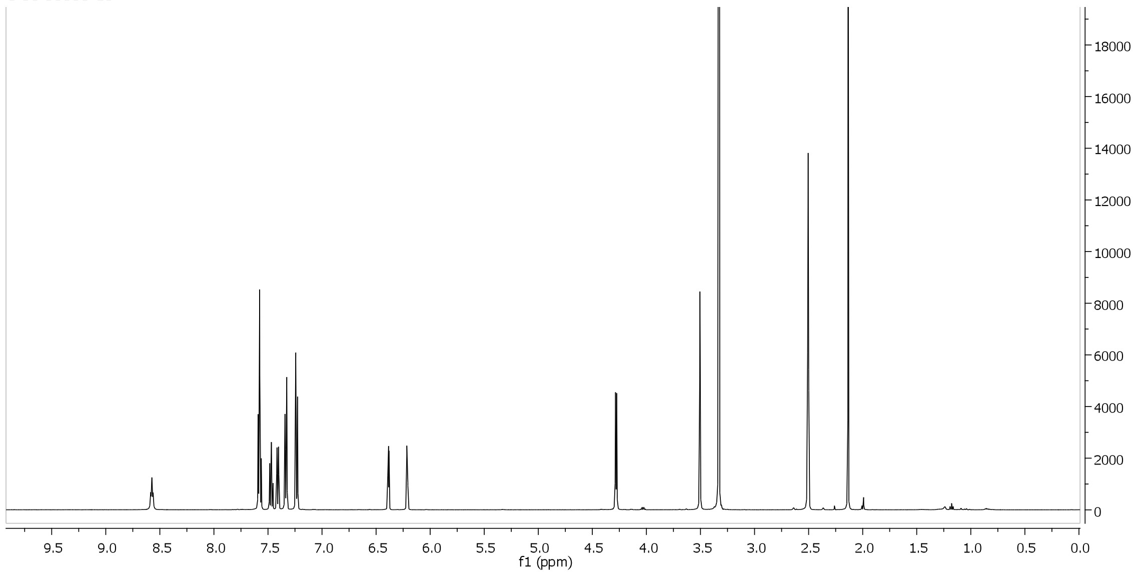

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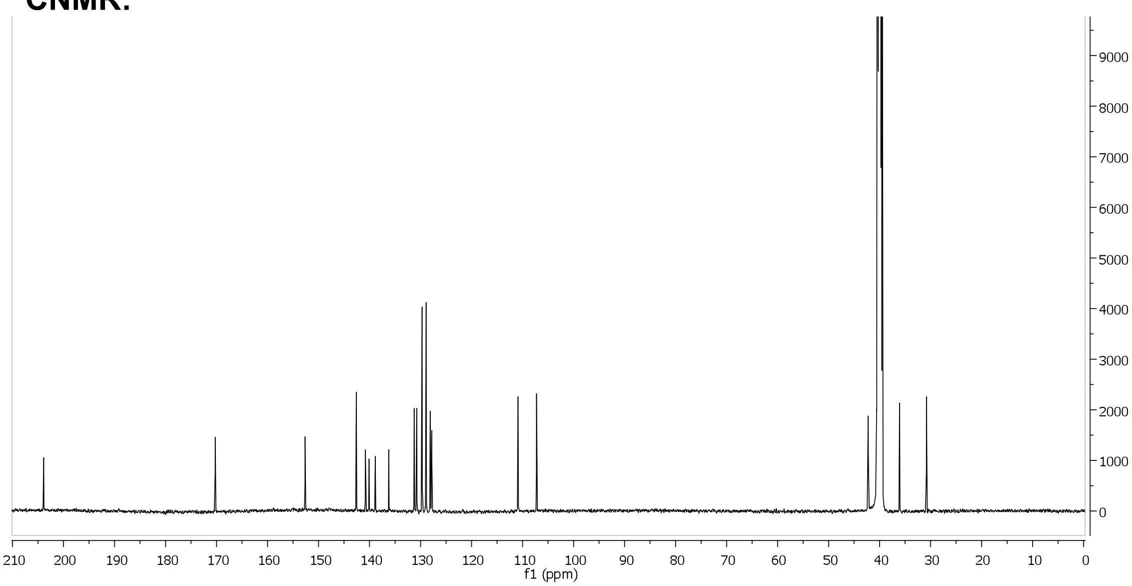

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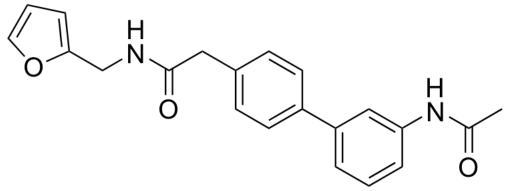

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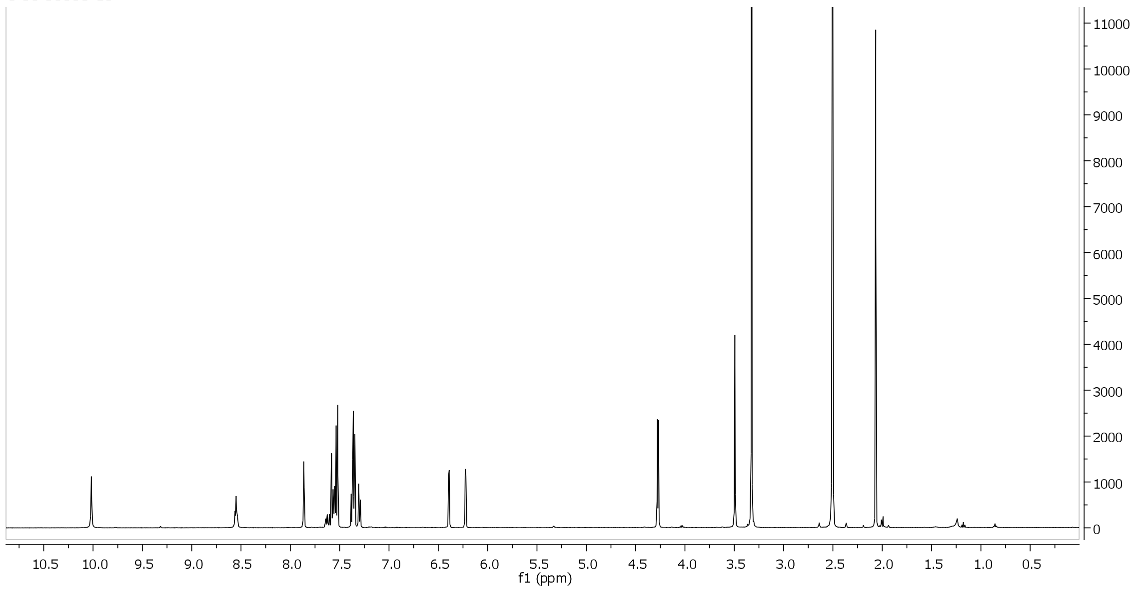

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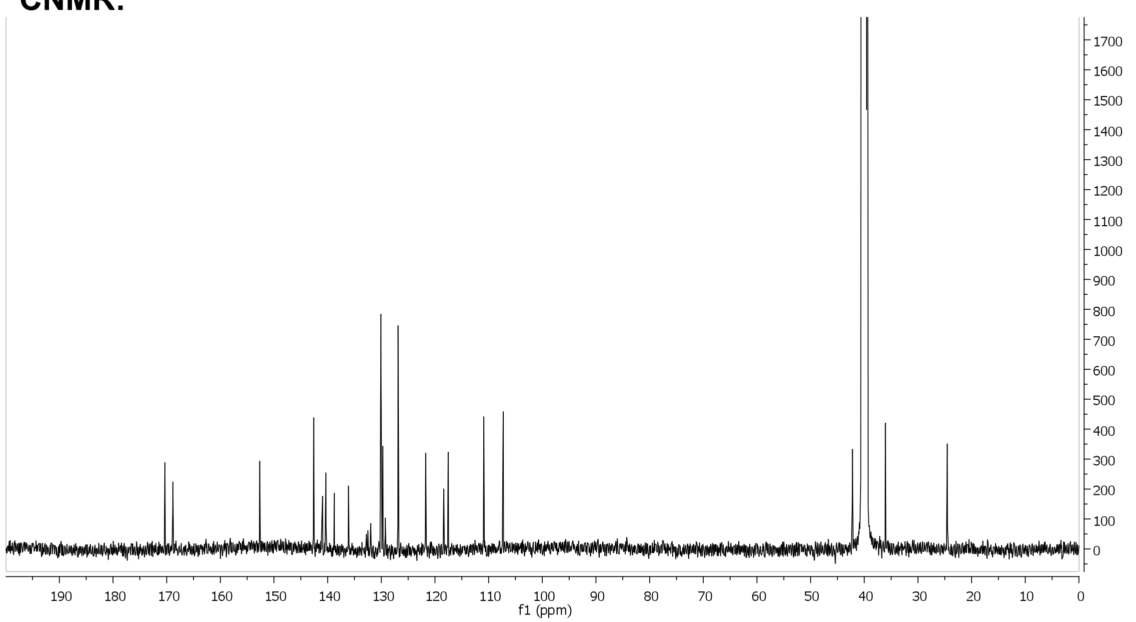

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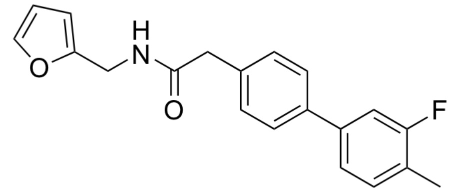

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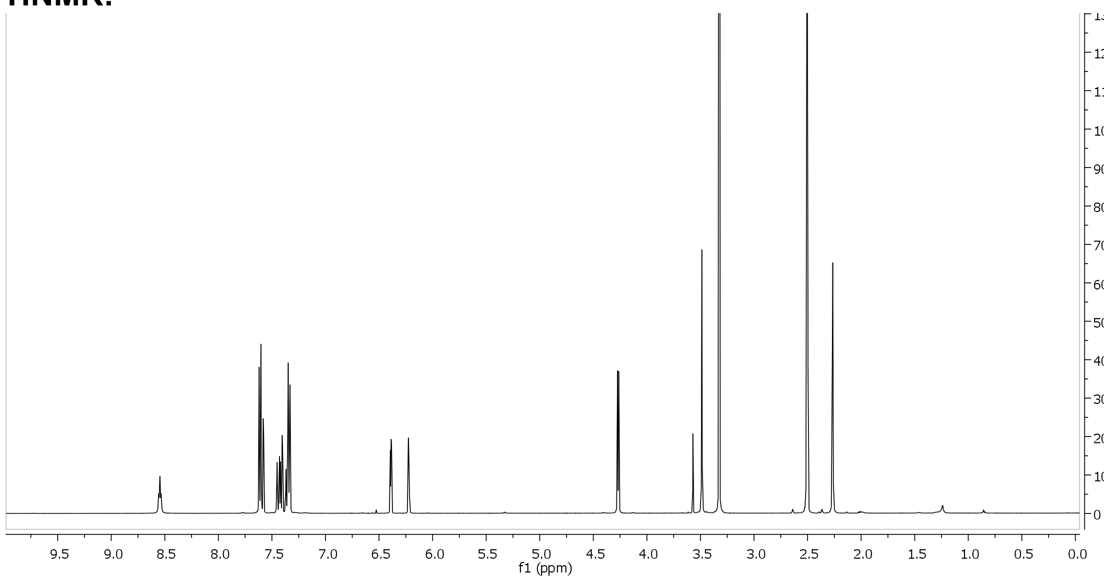

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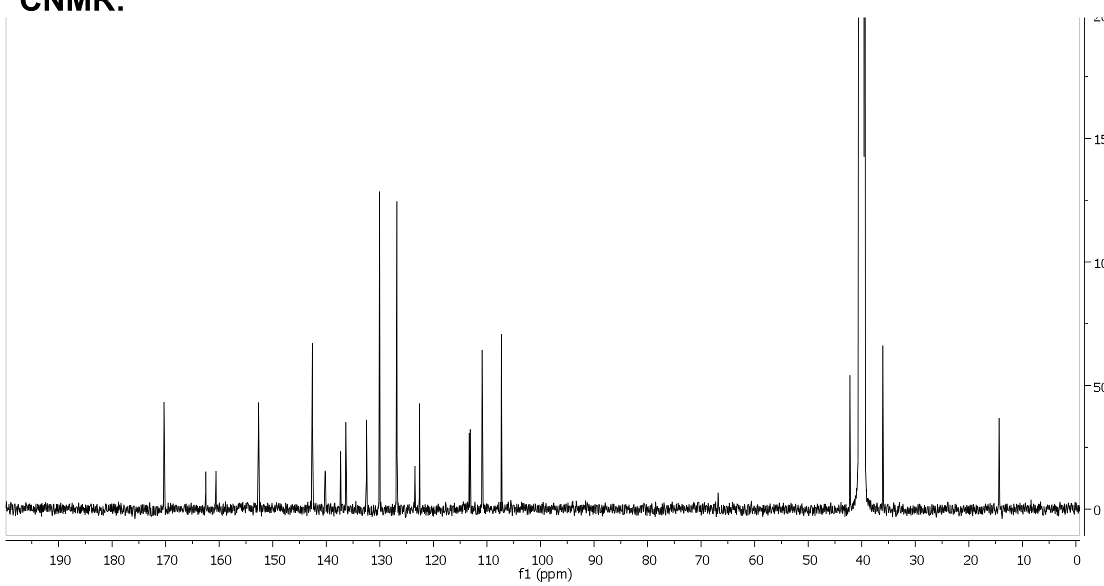

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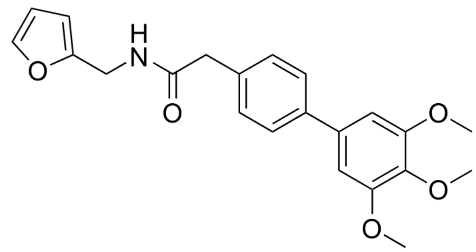

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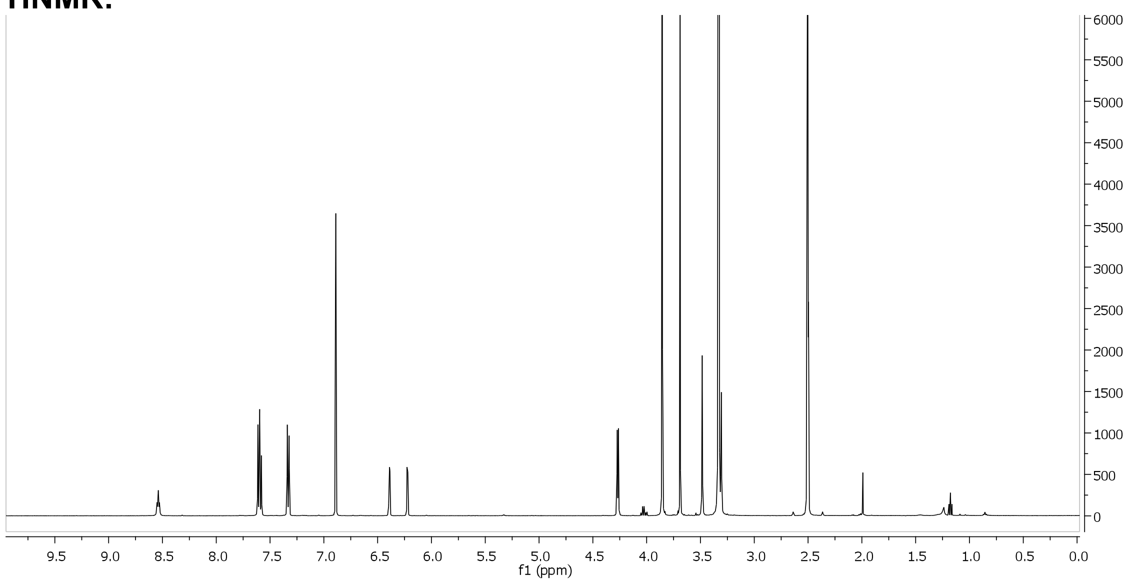

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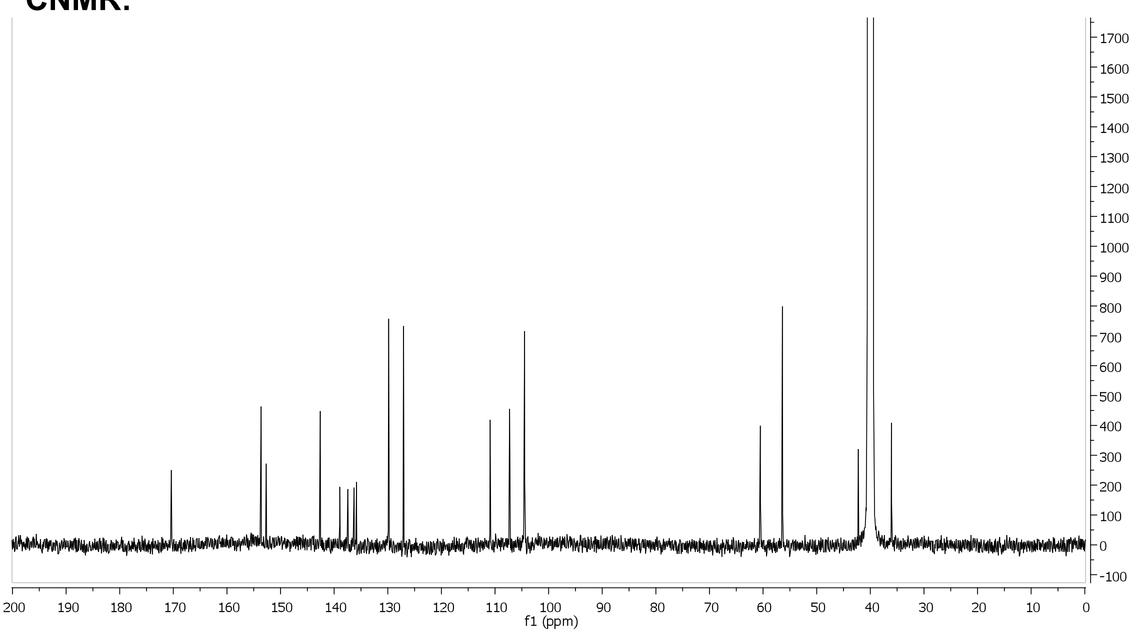

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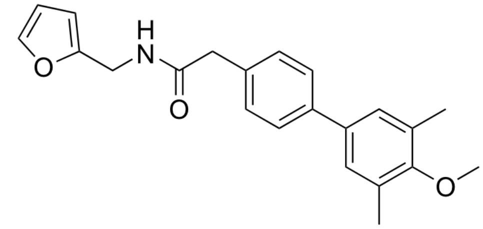

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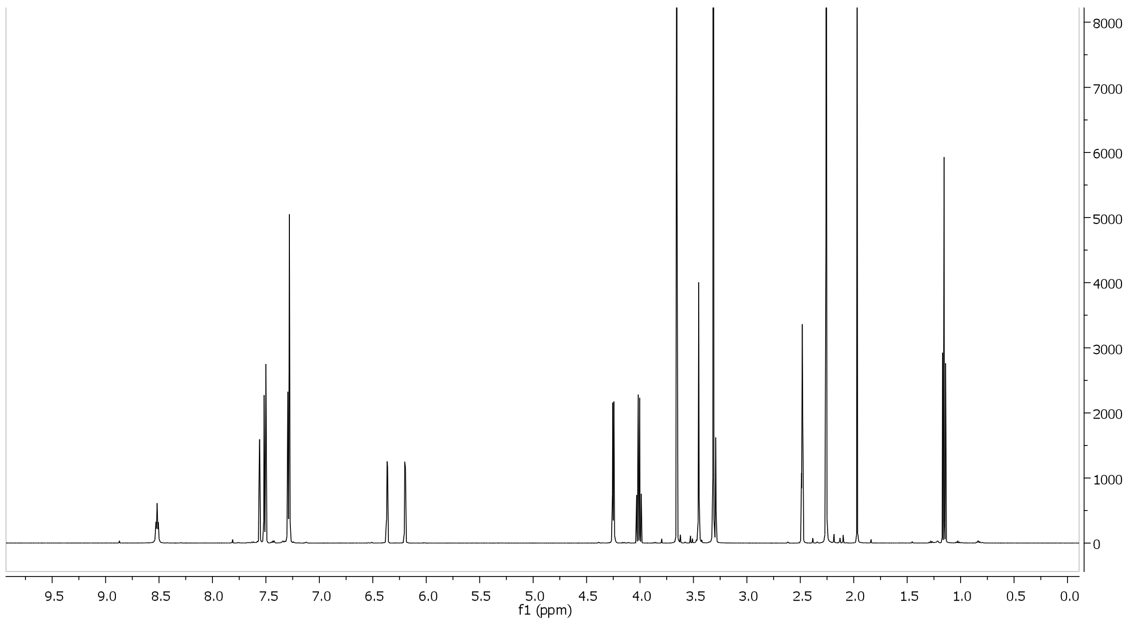

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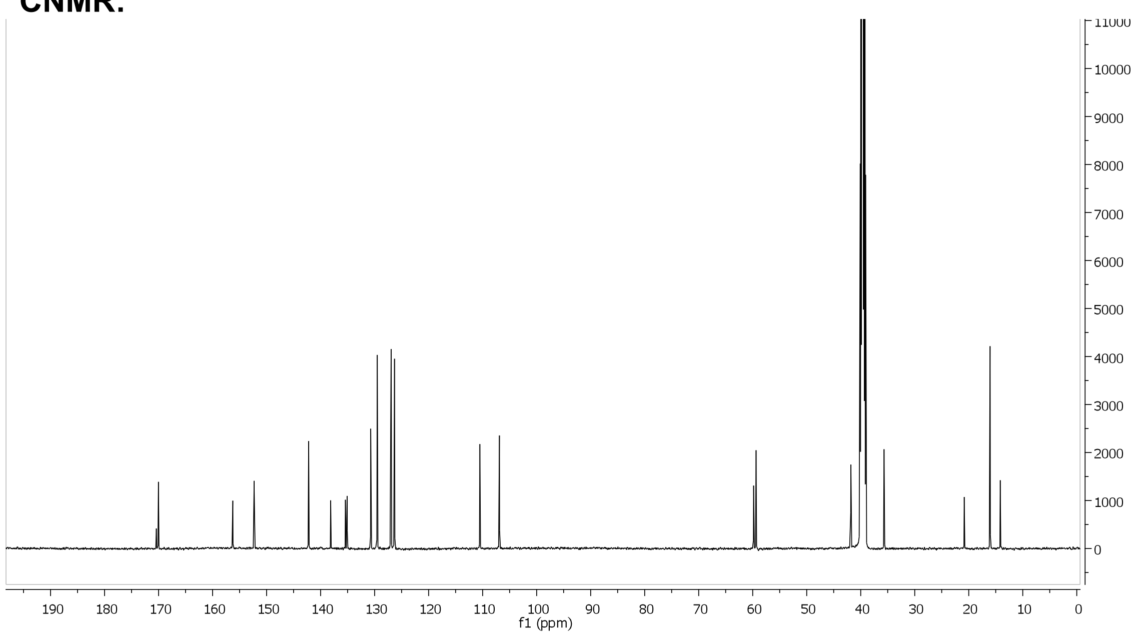

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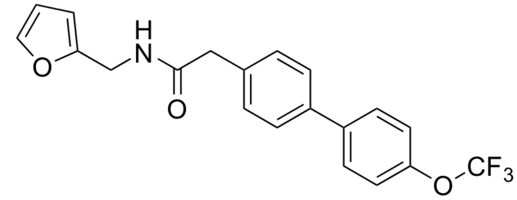

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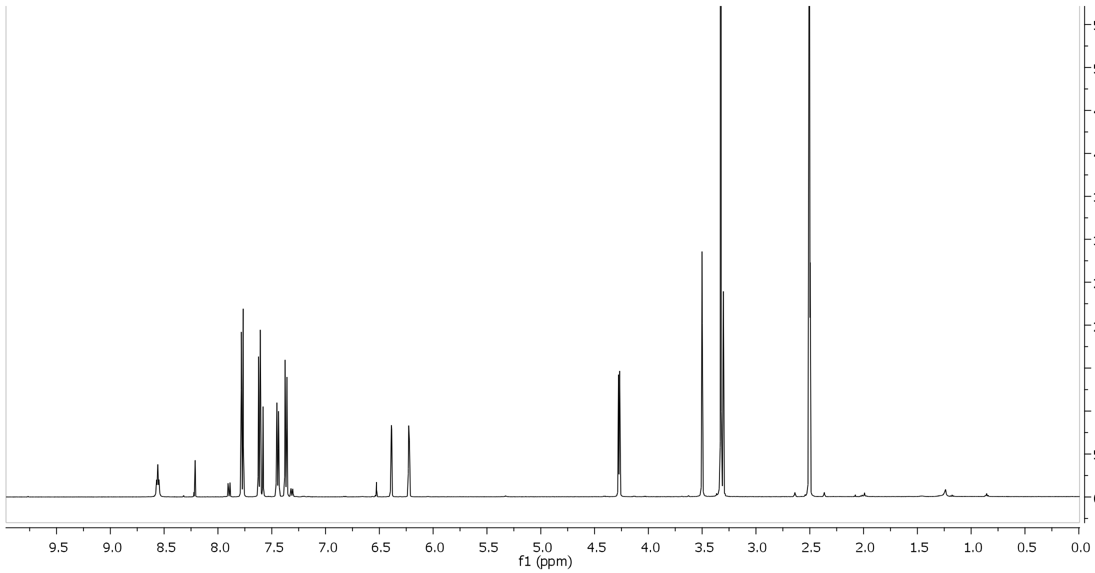

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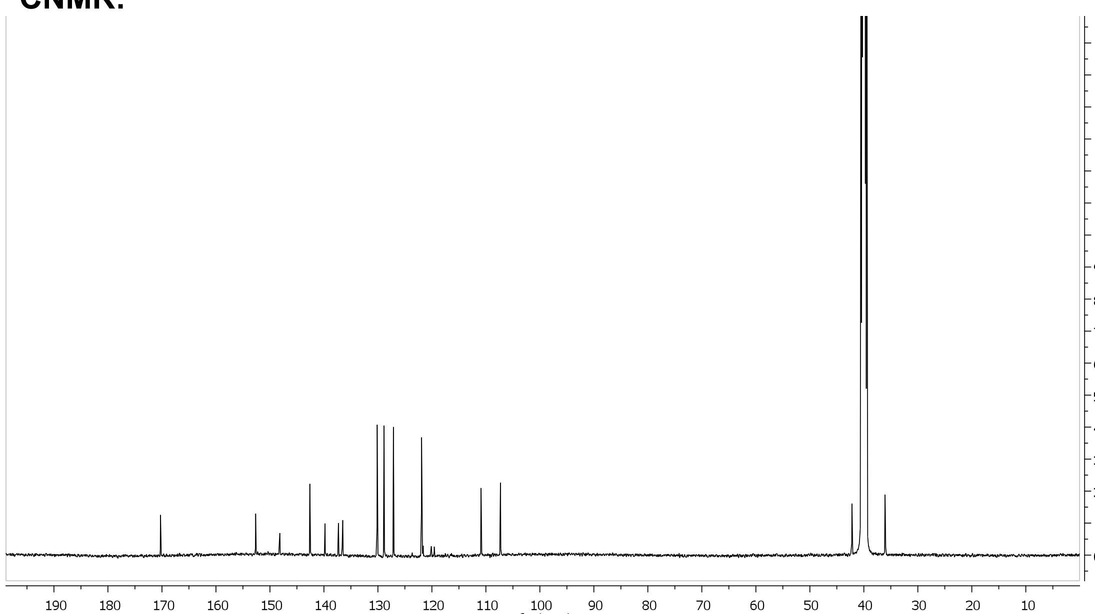

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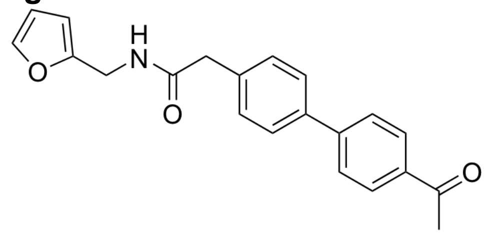

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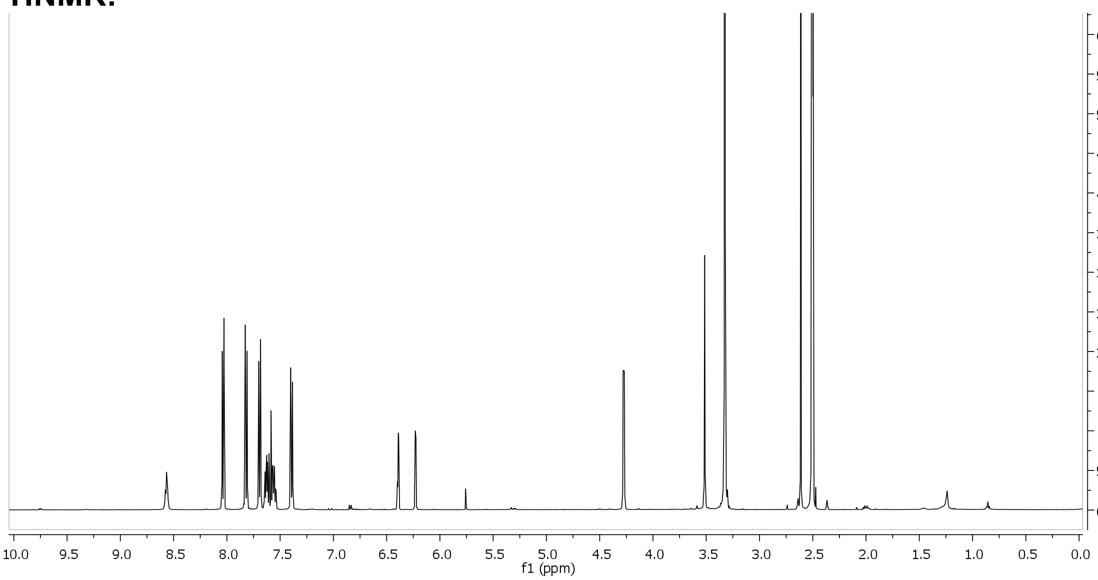

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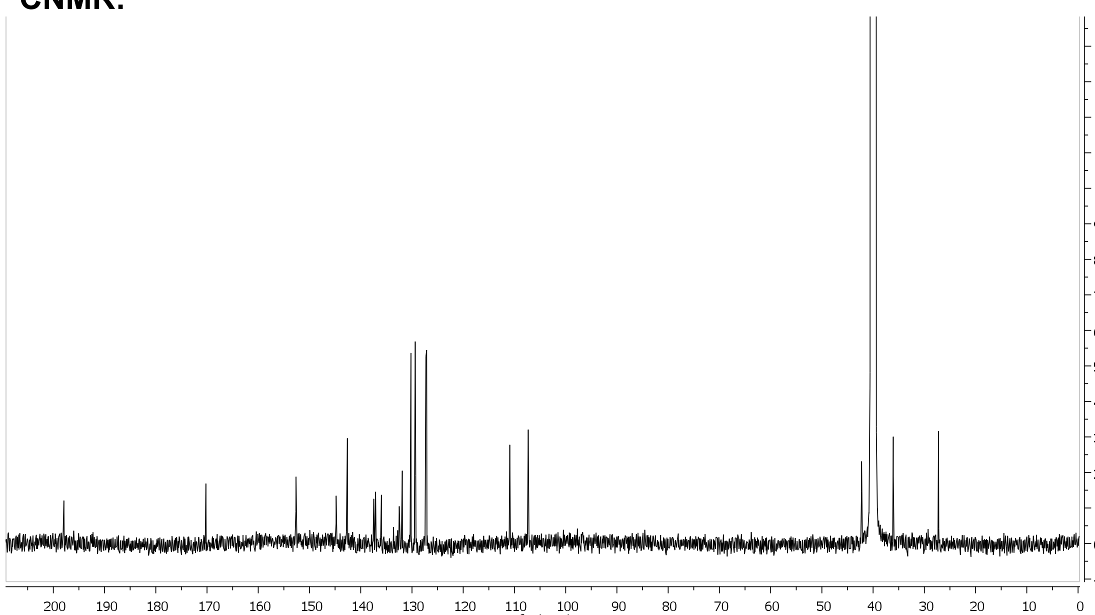

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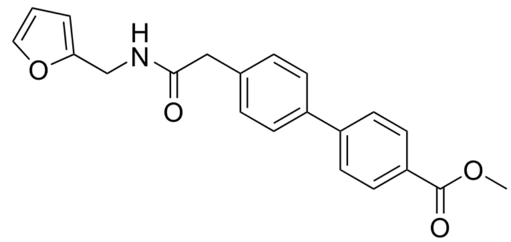

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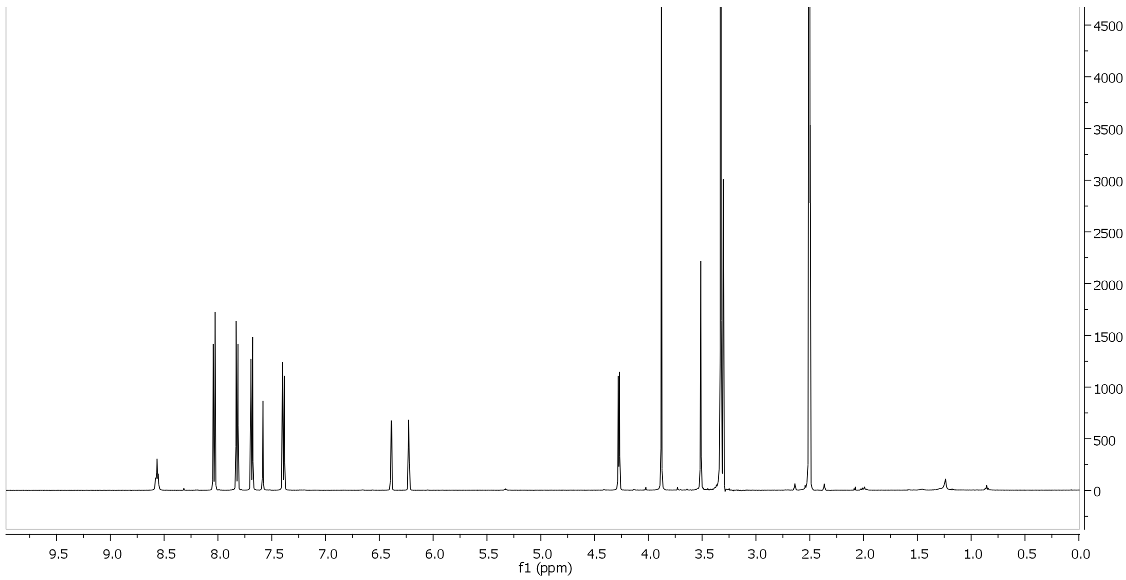

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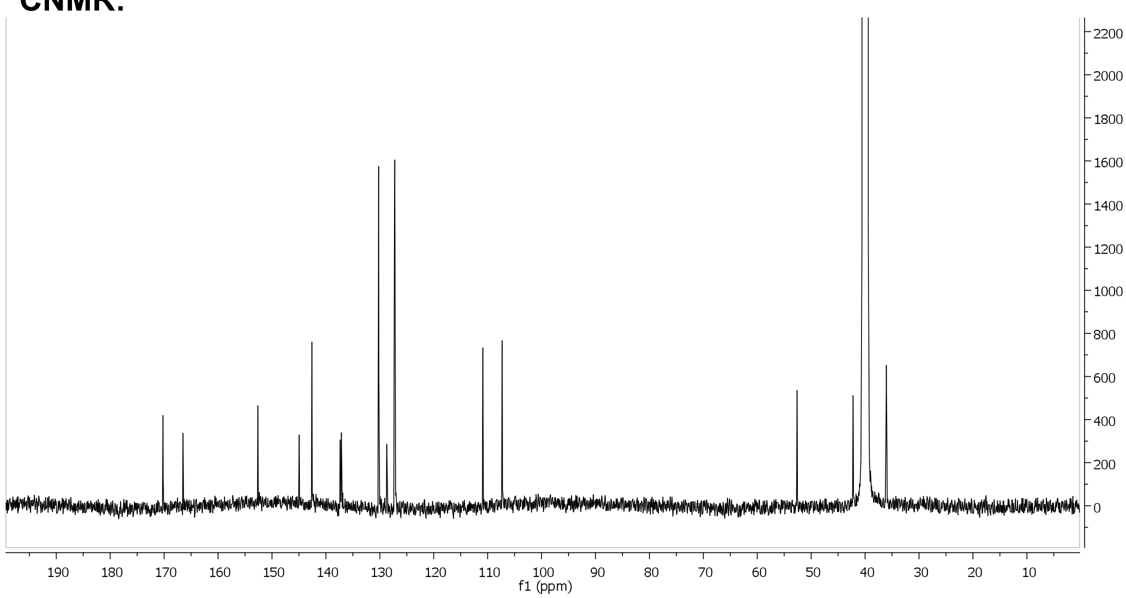

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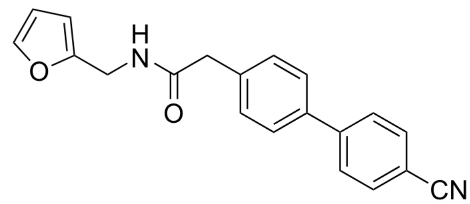

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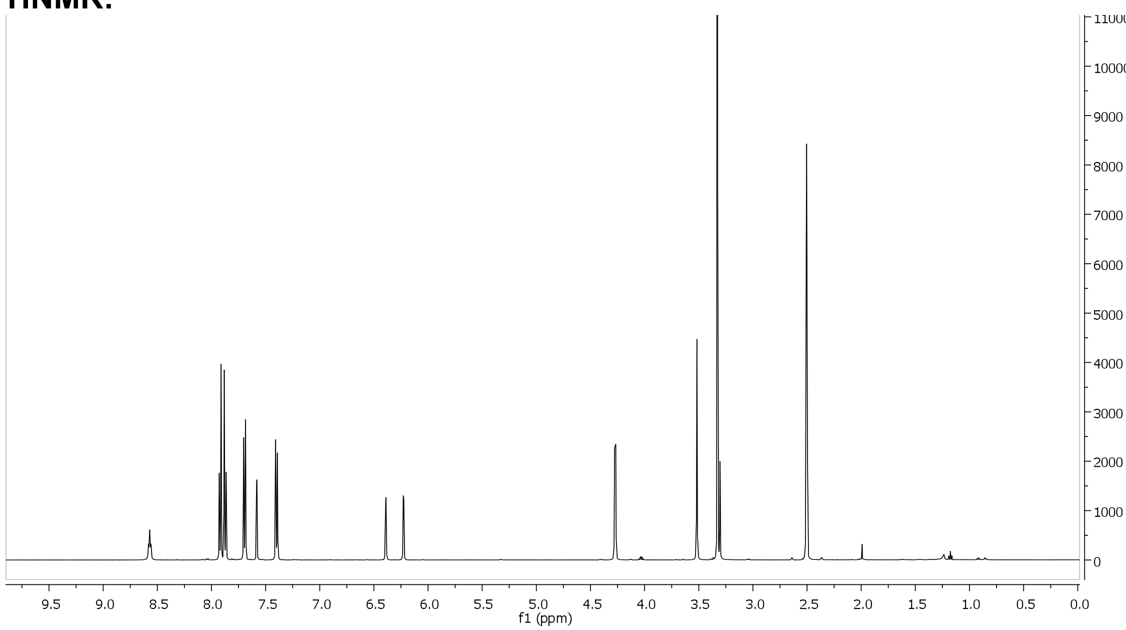

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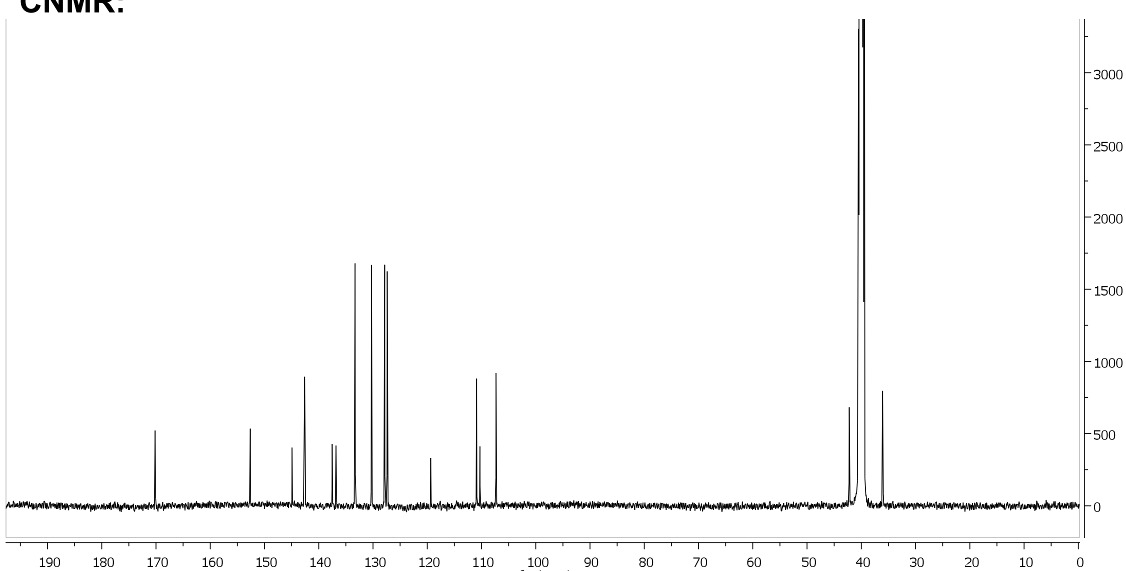

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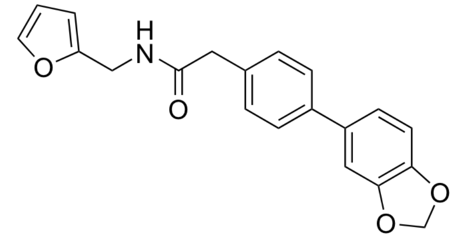

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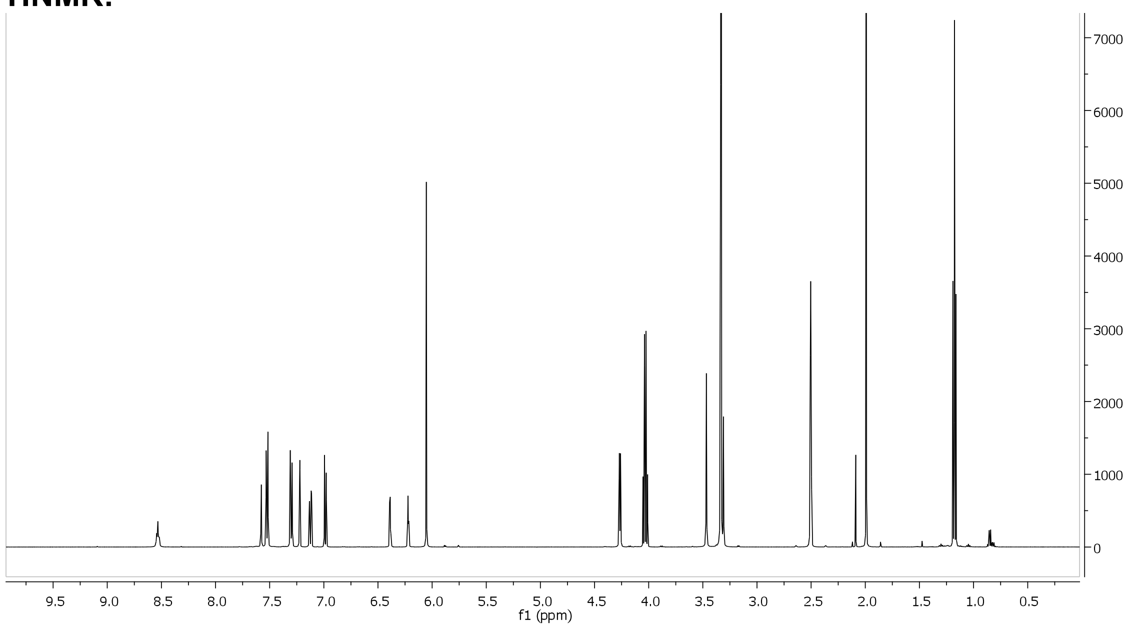

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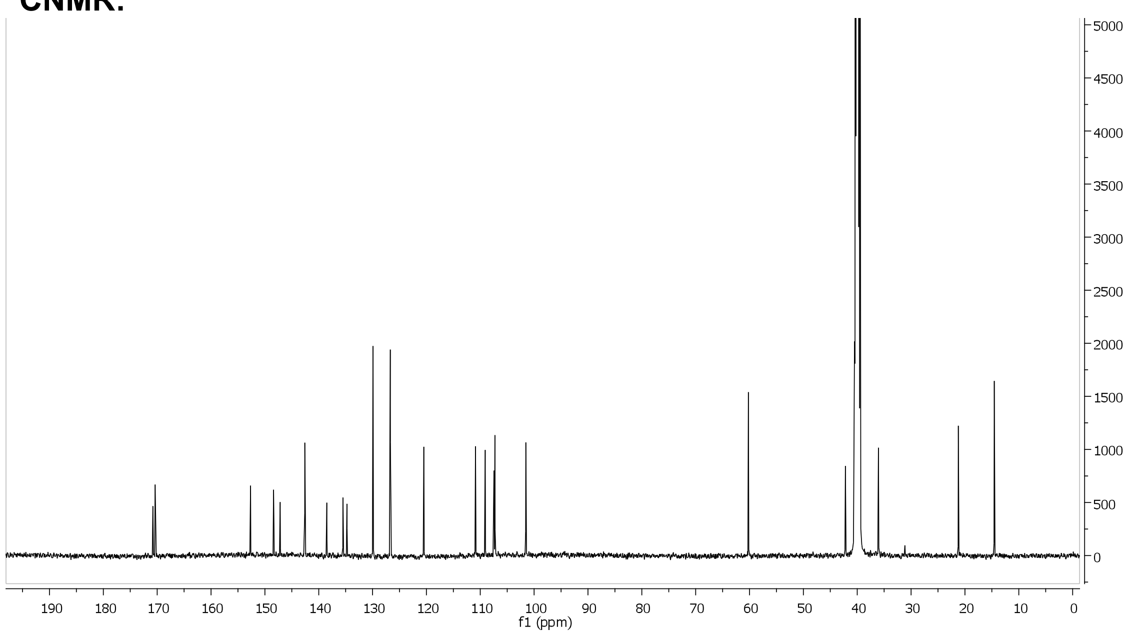

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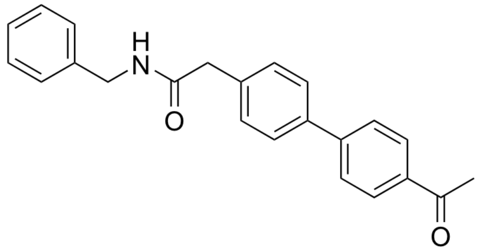

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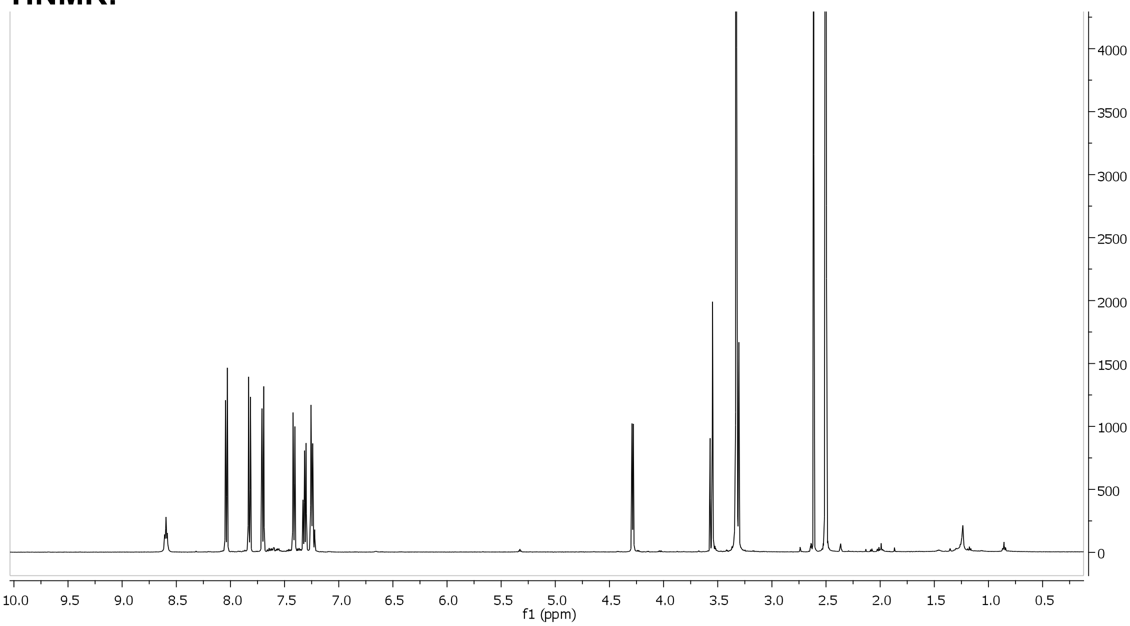

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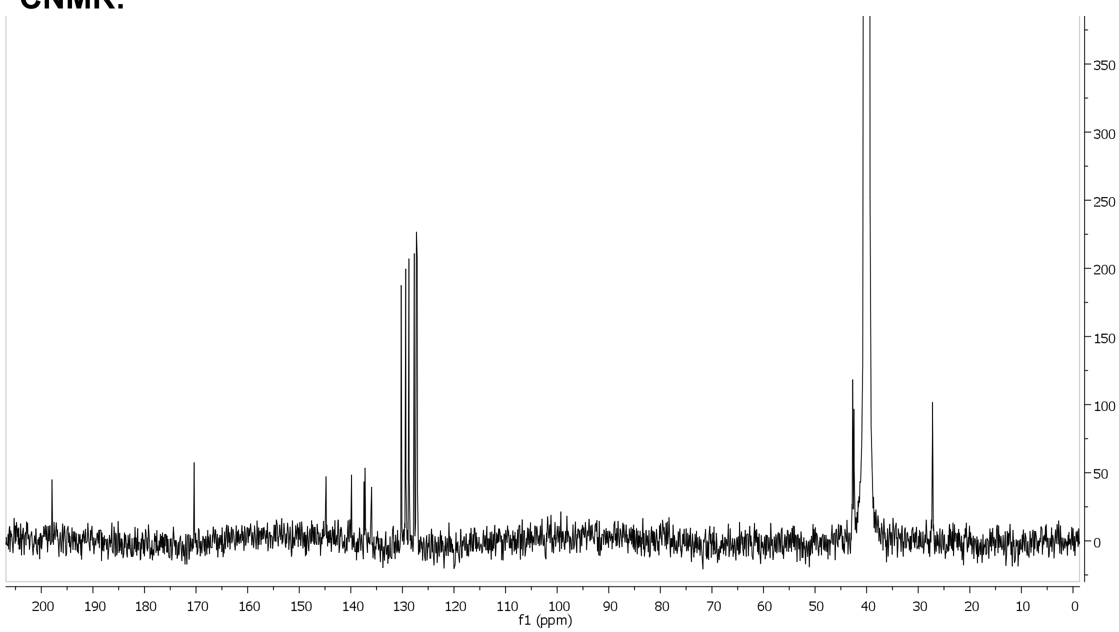

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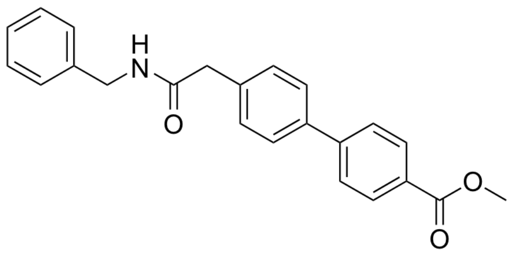

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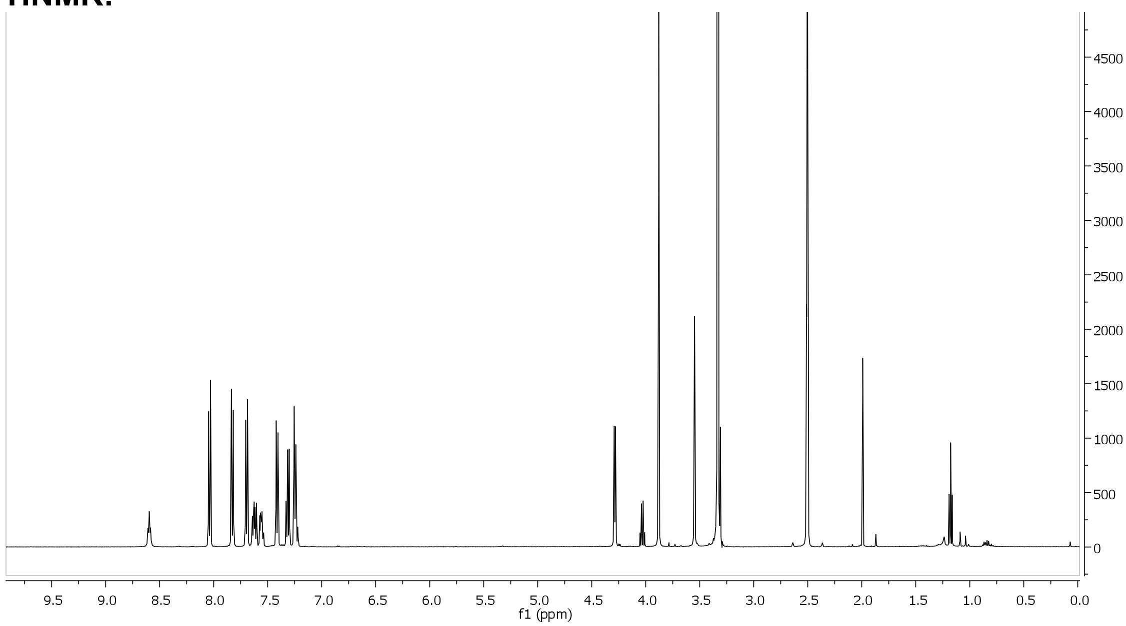

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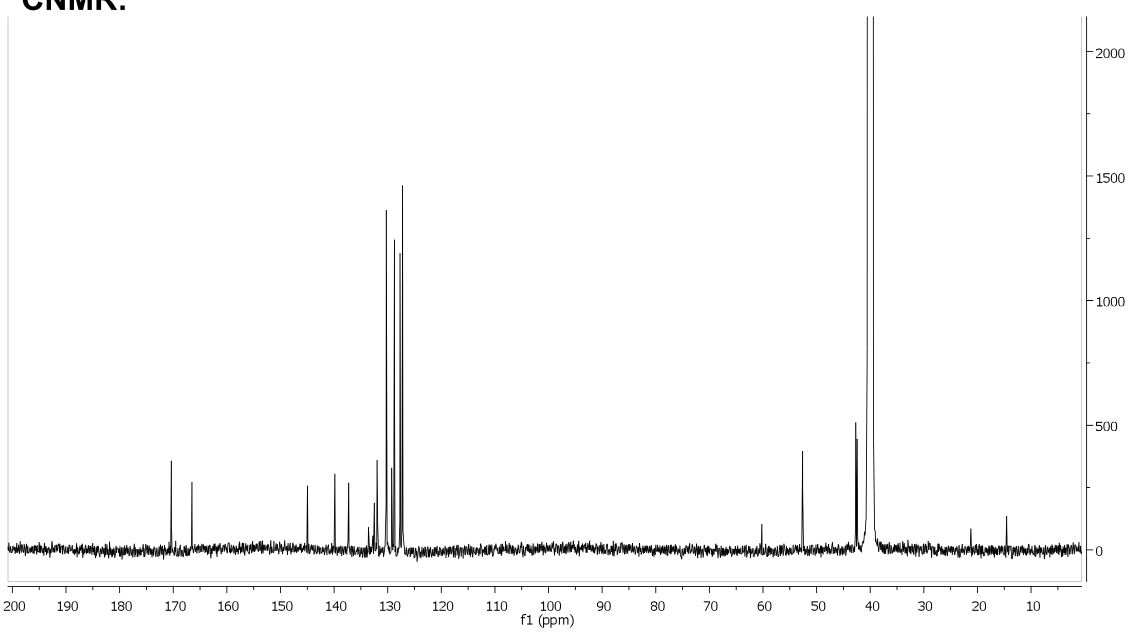

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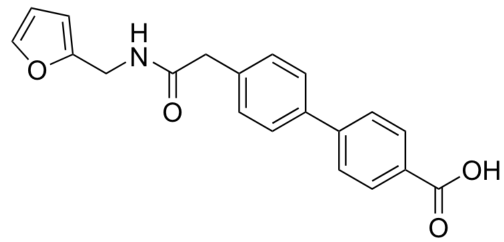

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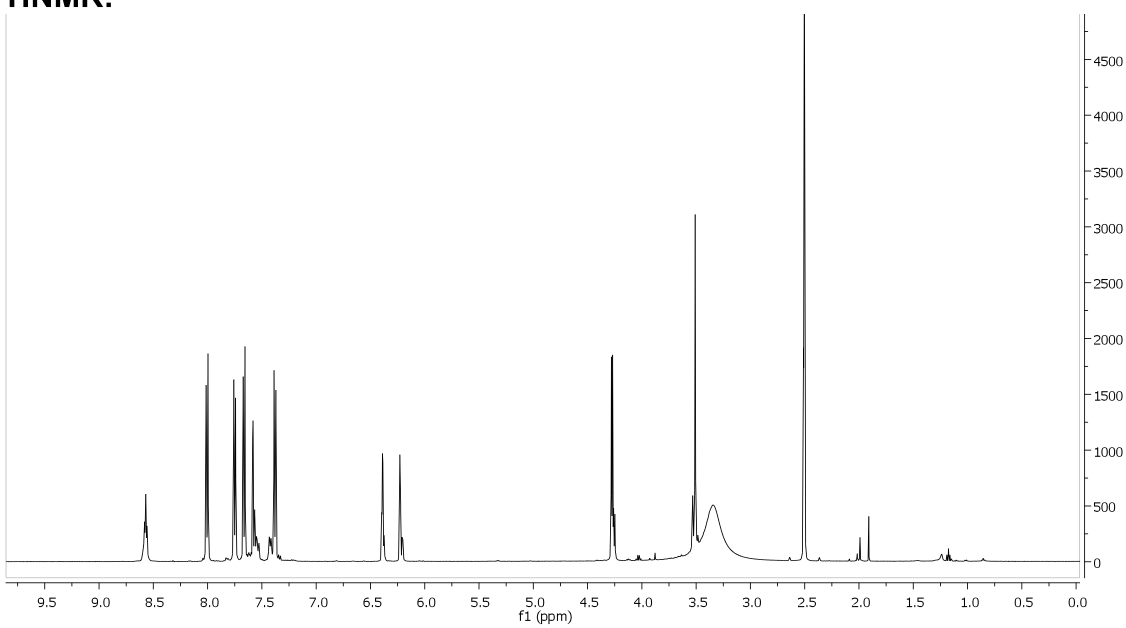

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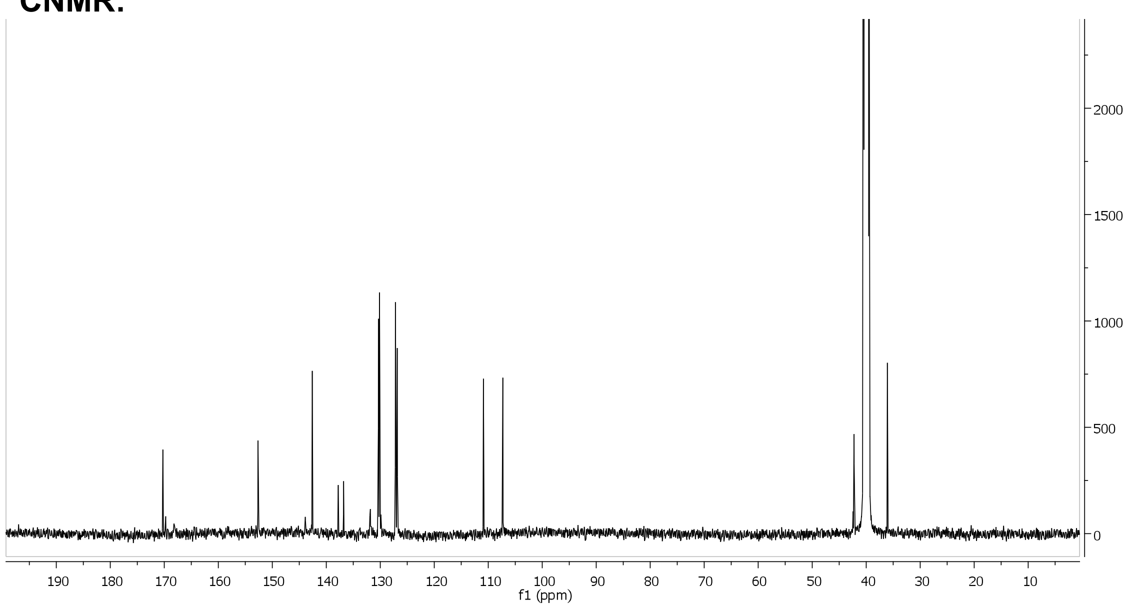

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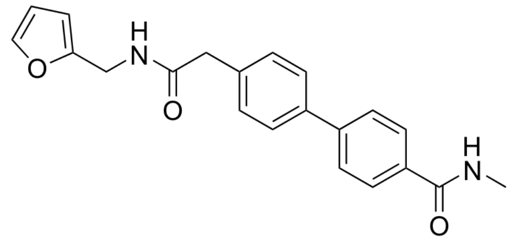

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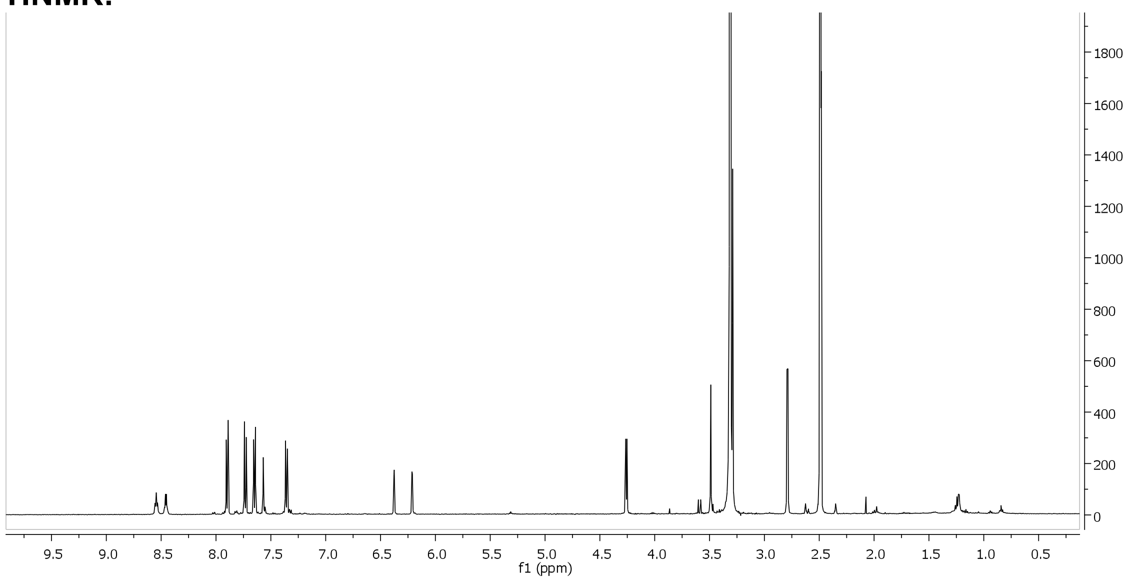

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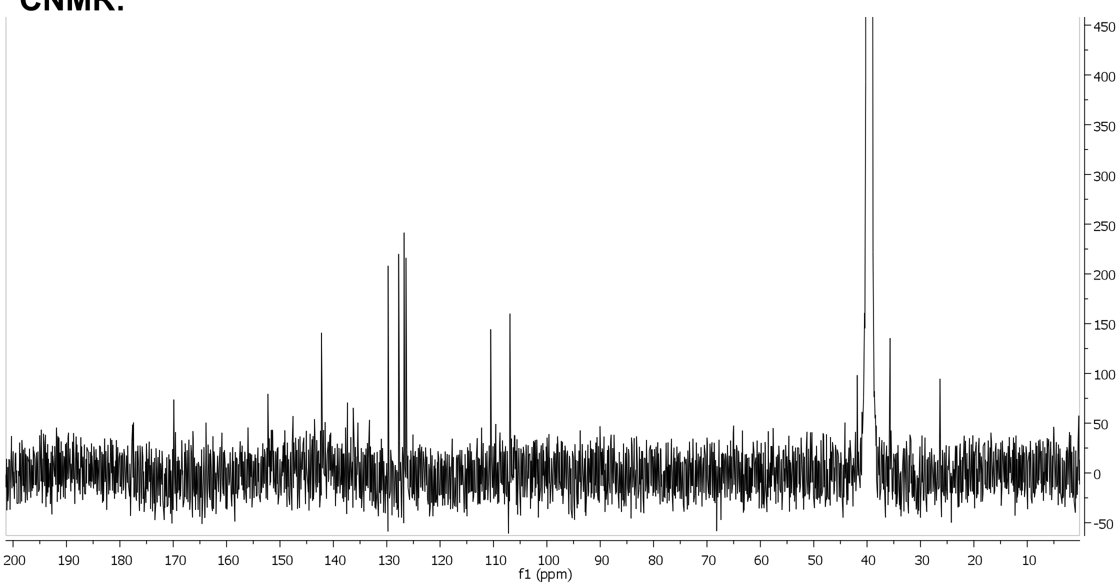

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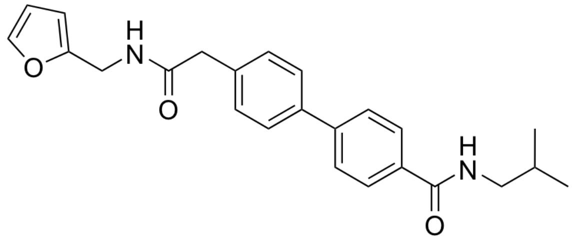

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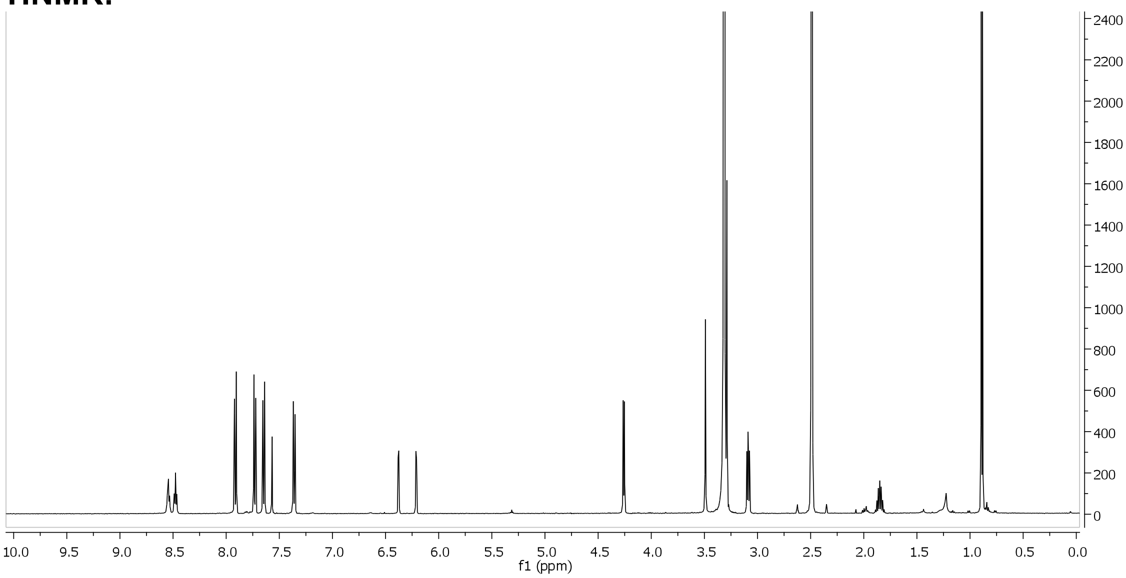

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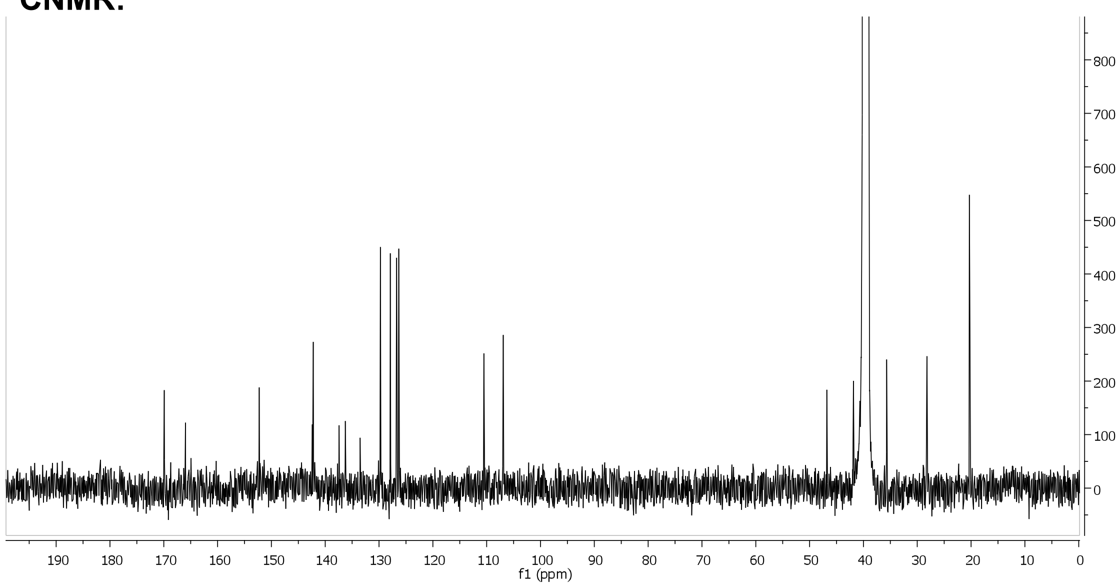
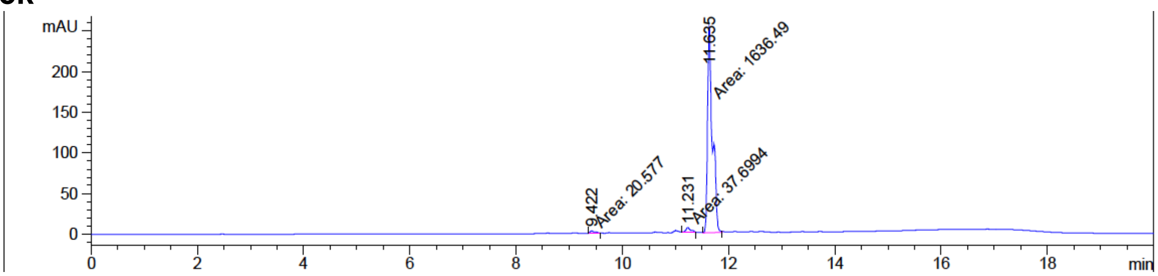


6 Purity Assessment by HPLC

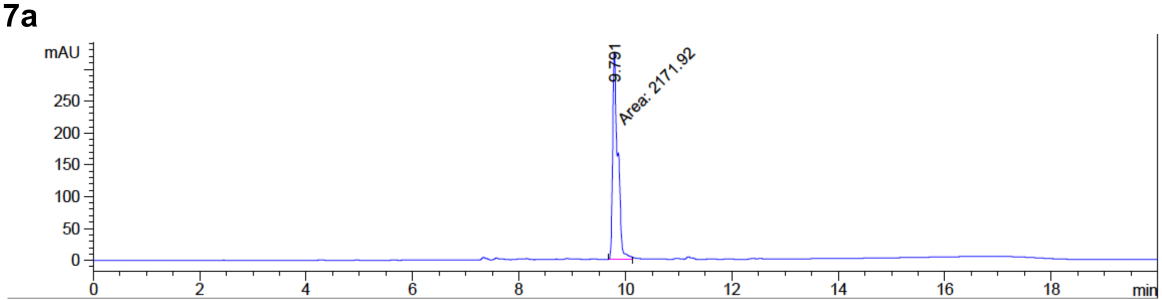
Compounds were analyzed by analytical HPLC on an Agilent 160 Infinity with a Supelcosil ABZ+ column (Supelco) eluting with an acetonitrile:water gradient of 5 – 100% over 15 min followed by 5 min at 100% acetonitrile. All compounds displayed a purity of >95%. Chromatograms of select key compounds are shown below.

5k



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.422	MM	0.1204	20.57705	2.84808	1.2141
2	11.231	MM	0.1050	37.69945	5.98439	2.2245
3	11.635	MM	0.1075	1636.49500	253.67931	96.5614

7a



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.791	MM	0.1112	2171.91650	325.55804	100.0000

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