Electronic Supplementary Material (ESI) for ChemComm.

Design and synthesis of tailored human caseinolytic protease P inhibitors

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Content

1. Supplementary Figures S1-S8

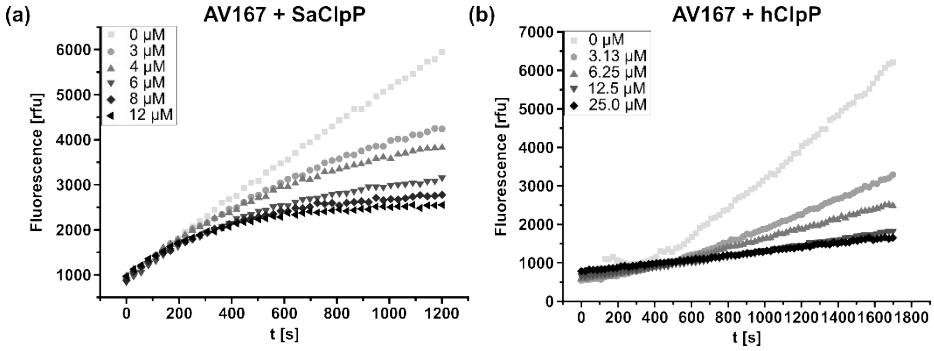


Figure S1. Representative raw data of k_{obs}/[I]-determination of AV167 against **a**. SaClpP[1] and **b**. hClpP. k_{obs} values describe the flattening of the recorded fluorescence signals of the ClpP substrate turn-over. In the case of SaClpP the curves flatten off during the measurement time, so that the binding event can be followed. However, for hClpP and AV167 no flattening-off can be observed, indicating that the binding event is too rapid to be resolved by the experimental set-up.

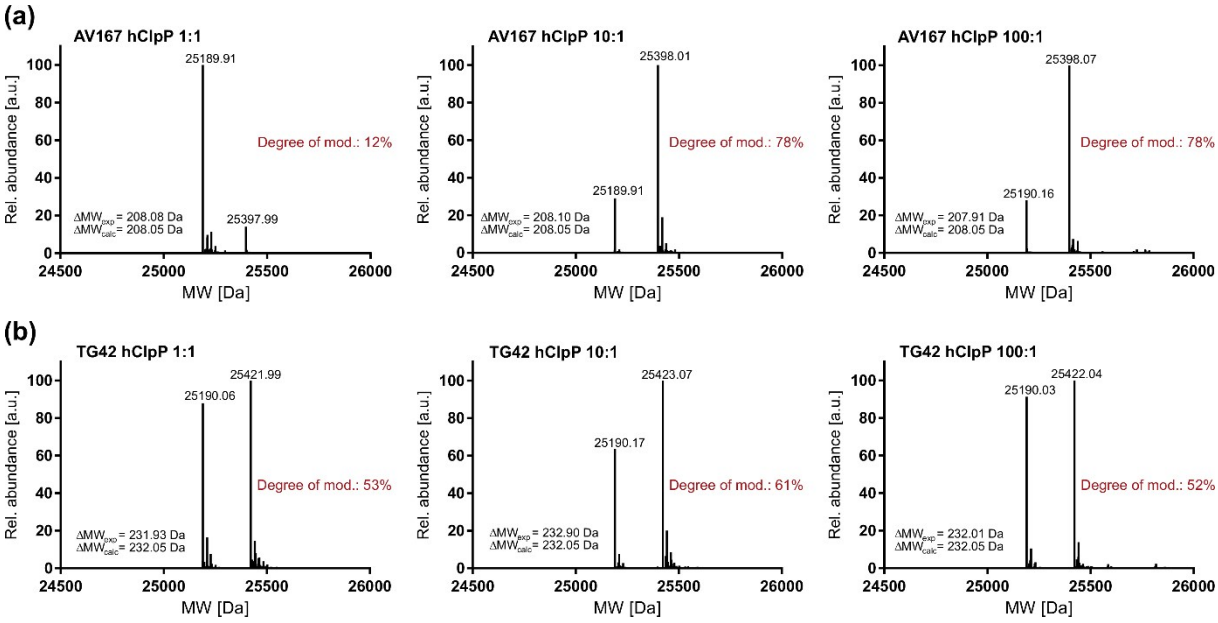


Figure S2. Intact protein mass spectrometry of human wild-type ClpP by phenyl esters **a. AV167** and **b. TG42**. Modifying compounds were introduced to up to 100-fold molar excess compared to the hClpP monomer and incubated for 1 h at room temperature, following MS-measurement on a *Thermo LTQ-FT Ultra*.

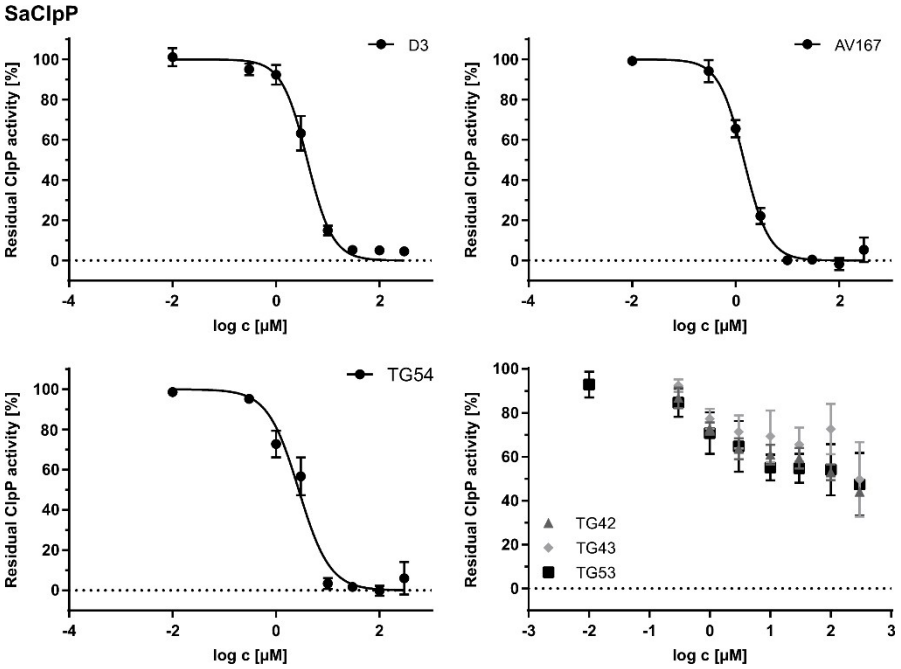


Figure S3. Raw data for the determination of apparent IC_{50} values for phenyl esters with SaClpP. Inhibitors were incubated with 1 µM SaClpP at 32 °C for 15 min prior to addition of fluorogenic substrate Suc-L-Y-AMC (200 µM). Apparent IC_{50} curves were generated by fitting a nonlinear regression curve to the data points representing results from at least six replicates (mean ± standard deviation).

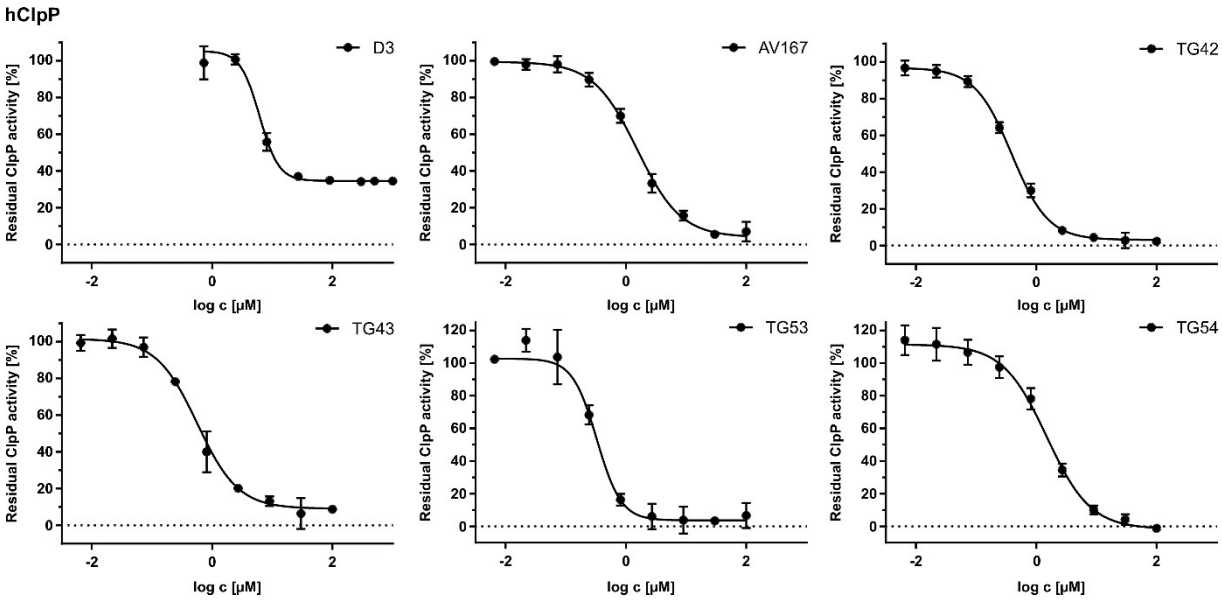


Figure S4. Raw data for the determination of apparent IC_{50} values for phenyl esters with hClpP. Inhibitors were incubated with 1 µM hClpP at 37 °C and peptidase activity was measured by the ability to cleave fluorogenic substrate Suc-L-Y-AMC (200 µM). Apparent IC_{50} curves were generated by fitting a nonlinear regression curve to data points representing results from at least six replicated (mean ± standard deviation).

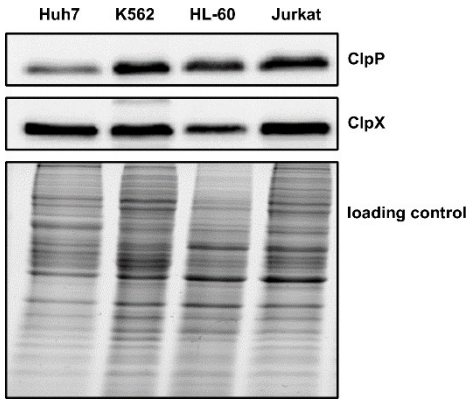


Figure S5. Comparison of ClpX and ClpP expression in different cancer cell lines (Huh7, K562, HL-60 and Jurkat) by Western blotting. Whole protein bands serve as loading control.

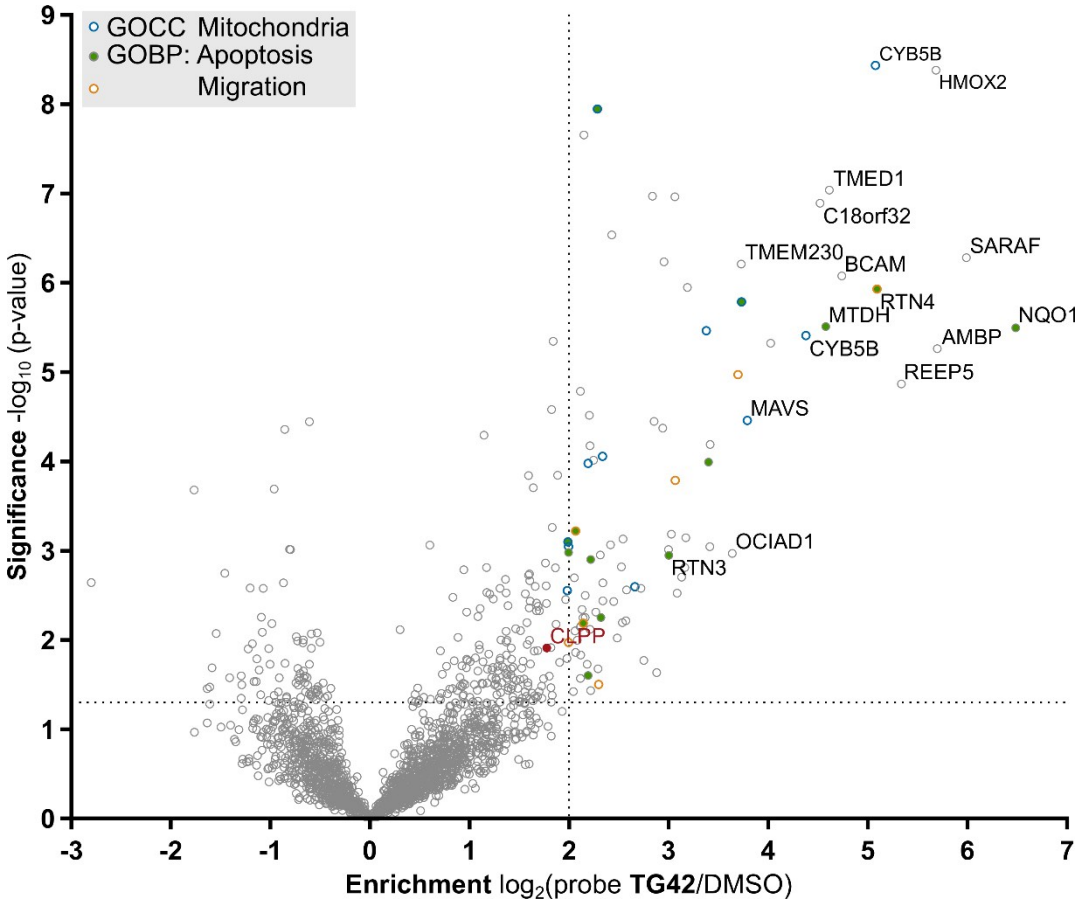


Figure S6. Supporting data for gel-free quantitative ABPP experiment with **TG42** in Huh7 cell line (20 µM **TG42**, 1 h labeling). Volcano Plot depicts enrichment and significance of enrichment from eight technical replicates. Color codes show connection to certain cell compartment (GOCC) and biological processes (GOBP) by gene ontology analysis. Two sample student's t-test was performed by comparison of labeled group against DMSO as single control group with Benjamini-Hochberg FDR correction set to 0.05. Cut-off lines were set at a minimum $\log_2$ fold change of 2 and a minimum p-value of 0.05.

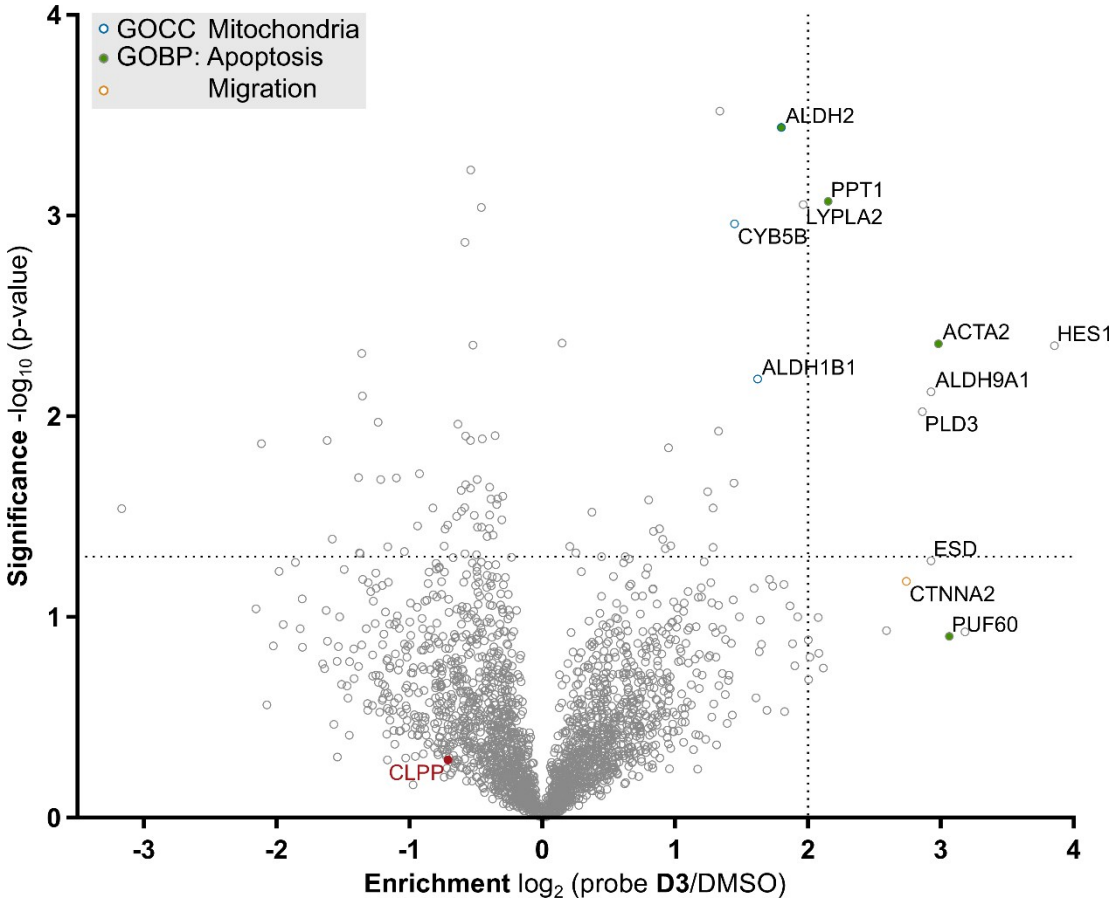


Figure S7. Supporting data for gel-free quantitative ABPP experiment with **D3** in Huh7 cells (20 µM **D3**, 1 h labeling). Volcano plot depicts enrichment and significance of enrichment from four technical replicates. Color codes show connection to certain cell compartment (GOCC) and biological processes (GOBP) by gene ontology analysis. Two sample student's t-test was performed by comparison of labeled group against DMSO as single control group with Benjamini-Hochberg FDR correction set to 0.05. Cut-off lines were set at a minimum $\log_2$ fold change of 2 and a minimum p-value of 0.05.

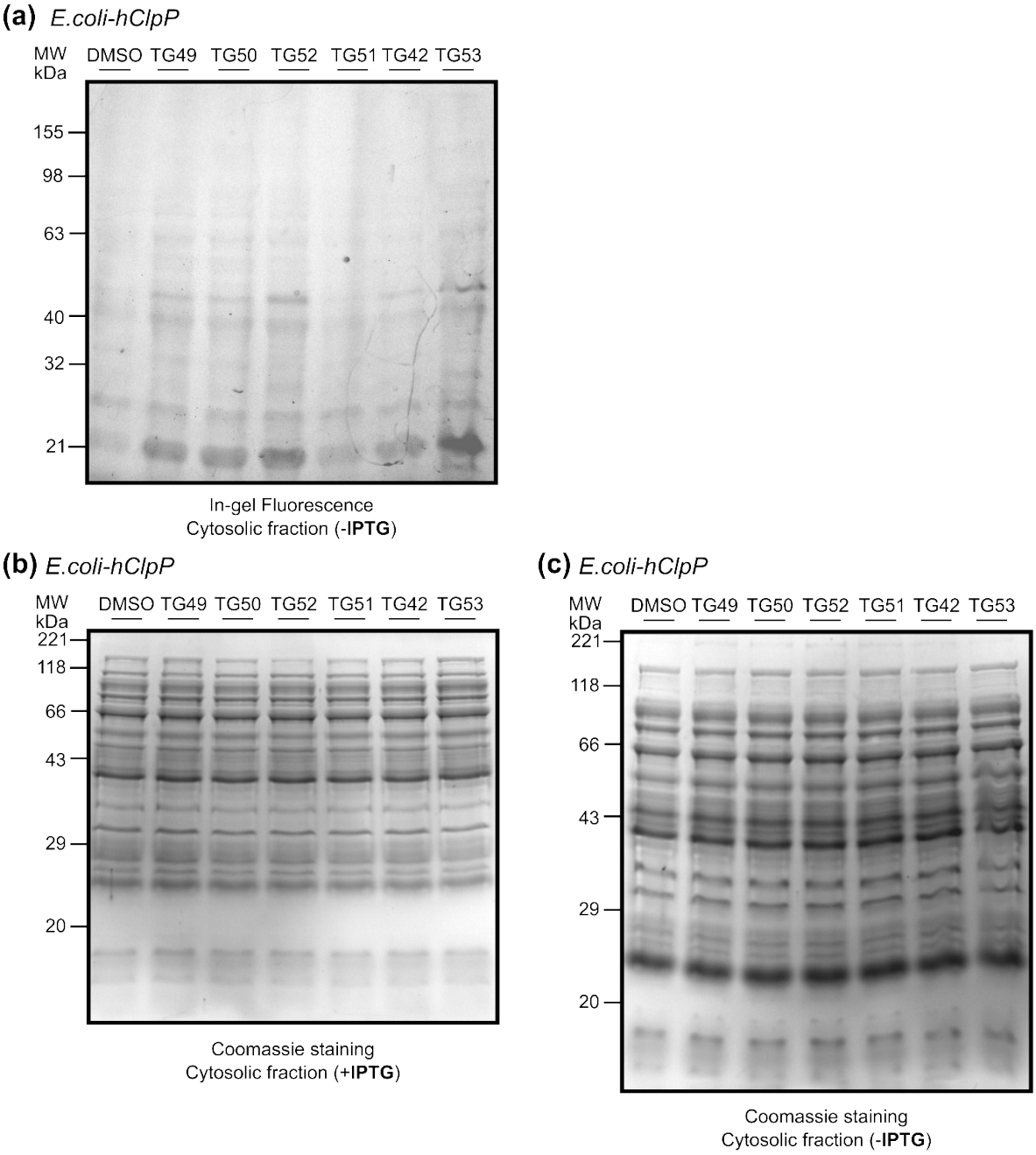


Figure S8. a. Fluorescence scan of *in situ* labeled samples without addition of IPTG. Coomassie staining of SDS-PAGE gels with in situ labeled proteins **b.** with induction of ClpP expression and **c.** without induction. *E. coli* expression strains were incubated for 1 h with ClpP inhibitors 3 h after induction of ClpP-expression.

2. Biochemical Procedures

2.1 Protein purification

Protein overexpression and purification were performed according to the general procedure in known literature.[1]

Expression of hClpP

For hClpP C-terminal STREP-II affinity tagged *H. sapiens* ClpP constructs were cloned in pET301 expression vectors via Gateway® cloning system (*Life Technologies*). hClpP was expressed overnight (20 h) in *E. coli* Rosetta2 (DE3) cells at 25 °C after induction at OD_{600} = 0.6 with 0.5 mM isopropyl β-D-thiogalactopyranoside (IPTG). Cells were harvested, centrifuged (6000 g, 10 min, 4 °C), washed by resuspending in PBS-buffer (140 mM NaCl, 10 mM Na_2HPO_4, 2.7 mM KCl, 1.8 mM KH_2PO_4, pH 7.3) and centrifugation (6000 g, 30 min, 4 °C) and stored at – 20 °C. Cell lysis was performed in Strep binding buffer (100 mM Tris/HCl, 150 mM NaCl, 1 mM EDTA, pH 8.0) by sonication under constant ice cooling. The lysate was cleared by centrifugation at 38,700 g (30 min, 4 °C) and the soluble fraction was loaded on a pre-equilibrated 5 mL StrepTrap™HP column (*GE Healthcare*) using an Äkta purifier 10 system (*GE Healthcare*). The column was washed with 5 column volumes binding buffer. Elution was performed with 4 column volumes elution buffer (Strep-binding buffer + 2.5 mM desthiobiotin). The fractions containing hClpP were collected, concentrated and subjected to preparative size exclusion chromatography (HiLoad 16/60Superdex 200 pg, *GE Healthcare*) using hClpP storage buffer (20 mM HEPES, 100 mM NaCl, pH 7.0). Fractions containing hClpP were pooled, concentrated and stored at – 80 °C.

Expression of SaClpP

S. aureus ClpP (SaClpP) expression was conducted in the same manner as hClpP, with *E. coli* BL21 (DE3) carrying a ClpP construct with a C-terminal Strep-II tag in a pET301 vector. Expression was again induced at OD_{600} = 0.6 with 0.5 mM IPTG, following incubation for 4 h at 37 °C. Strep-affinity chromatography and size exclusion chromatography was conducted in the same way as with hClpP using the same buffer systems.

Expression of EcClpX

EcClpX was overexpressed as previously described in *E. coli* (DE3) Rosetta 2 with a N-terminal His_6-TEV construct.[1] LB medium was inoculated with overnight cultures, incubated at 37 °C with constant shaking and overexpression was started at OD_{600} = 0.5 by addition of 0.5 mM IPTG. After incubation for 20 h at 25 °C bacteria were harvested, pelletized (15,000 g, 10 min, 4 °C) washed with PBS buffer (140 mM NaCl, 10 mM Na_2HPO_4, 2.7 mM KCl, 1.8 mM KH_2PO_4, pH 7.6) and lysed in lysis buffer I (50 mM HEPES, 300 mM KCl, 1 mM, DTT, 10 mM imidazol, 5 mM $MgCl_2$, 15% (v/v) glycerol, pH 7.6) by sonication. Cell debris was removed by centrifugation and clear lysate was applied to a pre-equilibrated HisTrap™HP affinity column. After washing with lysis buffer II (50 mM HEPES, 300 mM KCl, 1 mM, DTT, 40 mM imidazol, 15% (v/v) glycerol, pH 7.6) His-tagged protein was eluted with elution buffer (50 mM HEPES, 300 mM KCl, 1 mM, DTT, 300 mM imidazol, 15% (v/v) glycerol, pH 7.6). Fractions containing protein were pooled, 1 mM EDTA and 2 mg/mL TEV-protease were added and incubated overnight at

10 °C with constant shaking. Proteolysis was continued until intact protein mass spectrometry showed complete conversion. Crude protein was purified by size exclusion chromatography in lysis buffer I (without imidazol). Fractions containing EcClpX were pooled and concentrated using centrifugal filter tubes with a cut-off of 30 kDa.

SsrA-tagged GFP

eGFP with a N-terminally Strep-II-tag and a C-terminal SsrA tag (AANDENYALAA) was overexpressed in *E. coli* KY2266 (ΔclpXP, Δlon, ΔhslVU) using pDEST007 expression vector. Purification was performed by affinity chromatography (StrepTrap™HP 5 mL column (*GE Healthcare*)) and gel filtration with a HiLoad 16/60 Superdex 200 pg gel filtration column (*GE Healthcare*) in GF buffer (100 mM NaCl, 20 mM Tris, 10% (v/v) glycerol, pH 7.0). as described previously.[2]

2.2 High resolution intact protein mass spectrometry

The degree of modification of human wild-type ClpP by phenyl esters was determined by incubation of hClpP with inhibitors **AV167** and **TG42**. For this, 1 µM hClpP (monomer), in peptidase assay buffer (50 mM HEPES, 300 mM KCl, 1 mM DTT, 15% (v/v) glycerol, pH 7.5), was incubated with 1 µM, 10 µM or 100 µM of **AV167** or **TG42** for 1 h at room temperature. Intact protein masses were then measured on a *Dionex Ultimate 3000 HPLC* system coupled to *Thermo LTQ-FT Ultra* mass spectrometer with electrospray ionization source (capillary temp 275 °C, spray voltage 4.2 kV, tube lens 110 V, capillary voltage 48 V, sheath gas flow 60 arb, aux gas flow 10 arb, sweep gas flow 0.2 arb). 2 µL of protein-inhibitor mix were on-line desalted by a Massprep desalting cartridge (*Waters*). The mass spectrometer was operated in positive mode at a resolution of R = 200,000 from 600 - 2000 m/z. Data analysis and deconvolution was performed using *Thermo Xcalibur Xtract* software and respective theoretical monoisotopic masses were plotted.

2.3 Peptidase and protease activity assays

Peptidase activity assay

The potency of small molecule inhibitors on hClpP peptidase activity was analysed by measuring the residual activity upon treatment with inhibitors. Therefore, protein activity was measured by monitoring the cleavage of fluorogenic substrate Suc-L-Y-AMC (*Bachem*) as described previously.[1] In a black 96-well plate 1 µL inhibitor or DMSO as control was aliquoted in triplicates in three different concentrations (100 mM stock in DMSO, final concentration in assay: 1 µM, 10 µM, 100 µM). 98 µL enzyme buffer mix (final concentration of *H. sapiens* ClpP: 1.0 µM; assay buffer: 50 mM HEPES, 300 mM KCl, 1 mM DTT, 15% (v/v) glycerol, pH 7.5) was added to the wells and incubated at 37 °C for 15 min. Kinetic measurement was started after adding 1 µL of peptide Suc-L-Y-AMC (20 mM stock in DMSO, final concentration 200 µM). Fluorescence of the cleaved dye was detected for 90 min on a *Tecan Infinite M200 pro* (excitation: 380 nm; emission: 440 nm, gain: 150). The slope of the fluorescence over time signal was calculated in the time interval t = 500 – 2000 s via linear regression with Microsoft Office Excel. The residual activity of inhibitor treated protein was determined in comparison to DMSO treated control samples which were normalized to 100% activity.

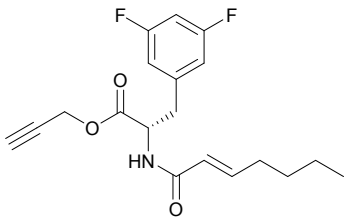
Apparent IC_{50} of ClpP inhibitors

Apparent IC_{50} values for the inhibition of ClpP peptidase activity were determined by peptidase activity assays as described above. For this, ClpP activity was measured after incubation with various concentrations of inhibitors. Fluorescence signals resulting from the cleavage of the fluorogenic substrate Suc-L-Y-AMC were measured on a *Tecan Infinte M200 pro* (excitation: 380 nm; emission: 440 nm). Nonlinear regression curves were generated from at least 6 replicates using *Microcal Origin 8.5* and *Prism 6.05*.

FITC-casein degradation assay

To assess the inhibitory potency on the proteolytic activity of hClpP, FITC-Casein assays were performed. ClpP alone is only capable to degrade small peptides, however for degradation of oligopeptides or proteins a chaperone of the AAA+ family (ATPases associated with diverse cellular activities) is needed which opens the pore to the proteolytic chamber and unfolds and directs the peptides to the peptidolytic core. The opening of the axial pore may also be triggered by small ADEP-fragments which leads to an indiscriminative degradation of substrate peptides.[3]

For FITC-casein assays ClpP was initially incubated with inhibitors then with ADEP fragment. Proteolytic activity was measured by the degradation of FITC-casein substrate which leads to the release of fluorogenic FITC (fluorescein isothiocyanate). In a black 96-well plate 1 µL inhibitor was aliquoted in triplicates in three different concentrations (from 100 mM DMSO stock: 100 µM, 10 µM, 1 µM final concentration). As control nine wells were filled with 1 µL DMSO. ClpP buffer mix (final concentration of hClpP in assay 1.0 µM; assay buffer: 50 mM HEPES, 300 mM KCl, 1 mM DTT, 15 % (v/v) glycerol, pH 7.5) was pre-warmed at 37 °C and then 80 µL were aliquoted and incubated together with inhibitors for 15 min at 37 °C. Afterwards 1 µL ADEP fragment was added (1:100 from 10 µM DMSO stock, final assay concentration 10 µM) and incubated again for 15 min at 37 °C. Kinetic measurement was started after the addition of 20 µL casein mix (10 µM final concentration Casein, 2 µM final concentration, FITC-casein). Fluorescence of the cleaved FITC was quantified over 120 min on a *Tecan Infinite M200 pro* (excitation: 485 nm, emission: 535 nm, gain 70). The slope of the fluorescence over time signal was calculated in the time interval t = 420 – 900 s via linear regression with Microsoft Office Excel. The residual activity of inhibitor treated protein was determined in comparison to DMSO treated control samples which were normalized to 100% activity.



Structure of ADEP-fragment.[3]

GFP-degradation assay

GFP degradation assays were performed with *H. sapiens* ClpP and *E. coli* ClpX which are able to form a functional complex. The assay was performed with white flat-bottom 96-well plates in PZ-buffer (25 mM HEPES, 200 mM KCl, 5 mM $MgCl_2$, 1 mM DTT, 10% (v/v) glycerol, pH 7.6) at 37 °C. 0.6 µL inhibitor was

aliquoted in triplicates and 59 µL enzyme-buffer mix (0.2 µM $hClpP_{14}$, 0.4 µM $eClpX_6$; ATP-regeneration mix: 4 mM ATP, 16 mM creatine phosphate, 20 U/mL creatine phosphokinase) was added and incubated for 15 min at 37 °C. Fluorescence measurement was started after addition of 1 µL SsrA-GFP (final concentration: 0.4 µM) on a *Tecan Infinite M200 Pro* (excitation: 485 nm, emission: 535 nm, gain: 28). The slope of the decreasing fluorescence signal was calculated in the time interval t = 0 - 500 s via linear regression with Microsoft Office Excel. The residual activity of inhibitor treated protein was determined in comparison to DMSO treated control samples which were normalized to 100% activity.

2.4 Analytical probe labeling in hclpP-wt expressing E. coli

Labeling of recombinantly expressed hClpP in *E. coli* was performed using *E. coli* Rosetta2 cells with a pET301 vector carrying a C-terminal STREP-II affinity tagged *H. sapiens* ClpP construct. LB-medium was inoculated (1:100) with an overnight culture of *E. Coli* Rosetta2. At OD_{600} ≈ 0.6 expression of hClpP was induced by addition of 0.5 mM IPTG and cells were grown for 3 h at 37 °C. As negative control, expression cultures without addition of IPTG were grown. Bacteria suspensions were centrifuged (3500 g, 10 min, 4 °C) and pellets were resuspended in appropriate volumes of cold PBS buffer (140 mM NaCl, 10 mM Na_2HPO_4, 2.7 mM KCl, 1.8 mM KH_2PO_4, pH 7.6) to an OD_{600} = 40. Then, 198 µL bacteria suspension was incubated with 2 µL inhibitor (20 µM final concentration: **TG42**, **TG49**-**TG53**,) or DMSO with constant shaking at 25 °C for 1 h. Afterwards bacteria cells were washed once with 200 µL PBS buffer and resuspended again in 200 µL PBS buffer. Cells were lysed by sonication and cell debris was separated by centrifugation (21,100 g, 45 min, 4 °C).

For visualization of labeled proteins, alkyne containing compounds were clicked via Cu-catalyzed alkyne-azide cycloaddition (CuAAC) with Rhodamine-N_3 (Rh-N_3, tetramethylrhodamine 5-carboxamido-(6-azidohexanyl), 5-isomer (*Life Technologies*). Click reagents were premixed in the following order (per sample: 2 µL Rh-N_3 in DMSO (5 mM), 2 µL TCEP (Tris(2-carboxyethyl)phosphine, 52 mM in H_2O), 6 µL TBTA ligand (1.67 mM in 80% (v/v) *t*-BuOH, 20% (v/v) DMSO)) and 10 µL were added to 100 µL cytosolic fraction. Click reaction was started by addition of 2 µL $CuSO_4$ (50 mM in H_2O) per sample following incubation at room temperature in the dark for 1 h. Afterwards, the reaction was quenched by addition of 110 µL 2x Laemmli sample buffer (63 mM Tris-HCl, 2% (v/v) glycerol, 139 mM sodium dodecylsulfate (SDS), 0.0025% (v/v) Bromophenol blue, 5% (v/v) 2-mercaptoethanol) and separation of proteins was conducted via SDS-PAGE.

2.5 Western-Blot

Proteins separated by SDS-PAGE were transferred to a nitrocellulose membrane (*Hybond-ECL, Amersham Bioscience*) by tank blotting (tank buffer: 48 mM Tris base, 39 mM Glycine, 20% (v/v) MeOH, ddH_2O) at 4 °C, 100 V for 90 min. Membranes were blocked with 5% non-fat dry milk powder (*Carl Roth*) and incubated overnight at 4 °C or at r.t. for 2 h with the respective primary antibody. Afterwards, membranes were washed with PBS-T (PBS buffer with 0.5% Tween-20®, pH 7.6) and incubated with the corresponding horseradish peroxidase (HRP)-conjugated secondary antibody for 1 h at r.t. Protein bands were visualized using enhanced chemiluminescence solution (ECL, 100 mM Tris, 2.5 mM Luminol, 1 mM *p*-Coumaric acid, 17 µM H_2O_2, H_2O, pH 8.5) and *ChemiDoc Touch Imaging System*. As loading control, the stain-free technology (Bio Rad) was used. This technique enables a quantification of the whole lane protein, and therefore can be used for the normalization of protein bands.[4]

Table S1. Primary antibody used for Western blotting

Antigene	Source	Dilution	Supplier
ClpP	Mouse	1:1000	Abcam, Cambridge, UK
ClpX	Rabbit	1:500	Abcam, Cambridge, UK

Table S2. Secondary antibody used for visualization of respective primary antibodies

Antigene	Dilution	Supplier
HRP, goat anti-mouse IgG	1:1000	Santa Cruz Biotechnology, Dallas, Texas USA
HRP, goat anti-rabbit IgG	1:1000	DIANOVA GmbG, Hamburg, Germany

2.6 Human cell culture

For labeling experiments cells were thawed from cryo stocks, reconstituted in appropriate supplemented medium and passaged every 2-3 days.

Huh7

Hepato cellular carcinoma cells Huh7 were generously provided from Prof. Dr. Angelika Vollmar (Ludwig-Maximilians Universität München, Departement of Pharmacy – Center for Drug Research, originally purchased from the Japanese Collection of Research Bioresources (JCRB) (Osaka Japan)). Cells were seeded in chemically defined Dulbecco's modified medium (DMEM, *Sigma-Aldrich*) with 10% (v/v) heat-inactivated fetal bovine serum (FBS, *Sigma-Aldrich*) and 2 mM L-glutamine (1:100 from 200 mM stock, *Sigma-Aldrich*) and were cultured under constant humidity at 37 °C and 5% CO_2 atmosphere. For cell passage, adherent cells were washed once with PBS and then detached by incubation for 3 - 5 min with Trypsin EDTA (1x) (1:10 from Trypsin EDTA (10x) stock in PBS, *GE Healthcare*). Cells were split 1:3 - 1:5 by adding fresh medium, maintaining a sub-confluent culture of 3 - 5 · 10^5 cell/cm^2. Prior to use, all culture flasks were pre-coated with collagen A containing solution (0.1 mg/mL Collagen A in PBS, pH 3.5, *Merck*, L7220).

Jurkat

Jurkat suspension cells (acute T cell leukemia, generously provided by Prof. Dr. Angelika Vollmar) were thawed from a cryo stock and reconstituted in chemically defined RPMI medium (*Sigma-Aldrich*) supplemented with 10% (v/v) heat-inactivated fetal bovine serum and 2 mM L-glutamine (1:100 from 200 mM stock, *Sigma-Aldrich*) and cultivated under constant humidity at 37 °C in 5% CO_2 atmosphere. For cell passage, Jurkat cells were centrifuged at 600 g for 6 min and split 1:3 - 1:5 by adding fresh medium. Cell density was kept between 0.1 · 10^6 and 1 · 10^6 viable cells/mL.

2.7 Proteomics methods

Labeling in Jurkat cell line

Cells were grown in RPMI medium supplemented with 10% (v/v) heat-inactivated FBS and 2 mM L-glutamine in T175 culture flasks (*Sarstedt*). For preparative labeling experiments cells were washed with warm PBS-buffer, centrifuged (600 g, 6 min, r.t.), reconstituted in medium without FBS and counted

using a *Neubauer improved* counting chamber. $2.9 \cdot 10^6$ cells/mL were seeded in each well of a 6-well plate leading to ≈ $17 \cdot 10^6$ cells per replicate. Labeling was conducted in four technical replicates per state. For this purpose, 1 µL of **TG42** in DMSO (20 µM final concentration) or DMSO as control were added to each well and were incubated for 1 h at 37 °C and 5% CO_2. Afterwards cells were harvested by gently scraping the surface of each well and transferring the cell suspension into centrifuge tubes, following a centrifugation step (600 g, 6 min, 4 °C), washing with ice-cold PBS-buffer and incubation with lysis buffer.

Labeling in Huh7 cell line

Huh7 cells were grown on TC150 dishes (*Sarstedt*) in DMEM medium supplemented with 10% (v/v) heat-inactivated FBS and 2 mM L-glutamine to a confluency of ≈ 70 – 80%. Prior to seeding culture dishes were coated with collagen A (0.1 mg/mL in PBS pH 3.5, *Merck*, L7220) according to manufacturer's protocol. For labeling experiments cells were washed once with warm PBS-buffer, then 12 mL labeling medium (DMEM, with 2 mM L-glutamine, without FBS) with probe (20 µM final concentration of **TG42** or **D3** in DMSO, max. 0.1% DMSO) or DMSO was added and cells were incubated for 1 h at 37 °C with 5% CO_2. Afterwards, medium was removed, cells were washed with 10 mL ice-cold PBS-buffer, gently scraped off and resuspended in 1 mL lysis buffer.

Cell lysis

Cells were lysed by disruption of cell walls with anionic and non-ionic tensides (lysis buffer: 1% (v/v) 4-Nonylphenyl-polyethylene glycol (NP-40), 1% (w/v) sodium deoxycholate, ddH_2O, pH 7.4). Cell pellets were incubated with 1 mL lysis buffer for 30 min (1 h for Huh7) on ice. Cytosolic fraction was obtained by pelletizing membranes and nuclei (21,000 g, 45 min, 4 °C). Protein concentration of cytosolic fractions were determined via BCA-assay using the Roti®Quant kit (*Carl Roth*) and adjusted by addition of lysis buffer to a final concentration of 1 - 2 mg protein/mL.

CuAAC, protein precipitation, enrichment, reduction, alkylation and digestion

In the case of labeling with **TG42** in Jurkat and Huh7 cells Cu-catalyzed alkyne-azide cycloaddition reaction was performed with 900 µL cytosolic fraction and 60 µL click mastermix (20 µL biotin-N_3 10 mM in DMSO, 10 µL TCEP 52 mM in H_2O, 30 µL TBTA ligand (1.67 mM in 80% (v/v) *t*-BuOH, 20% (v/v) DMSO)) and 10 µL $CuSO_4$ (50 mM in ddH_2O) for 1 h at room temperature. For labeling with **D3** in Huh7 cells 900 µL cytosolic cell lysate per replicate were incubated for 1 h at room temperature with 43 µL click mastermix consisting of the following components: 3 µL biotin-N_3 10 mM in DMSO, 10 µL TCEP 52 mM in H_2O, 30 µL TBTA ligand (1.67 mM in 80% (v/v) *t*-BuOH, 20% (v/v) DMSO)). Click reaction was started by addition of 20 µL $CuSO_4$ (50 mM in ddH_2O).

Protein precipitation was achieved by addition of four volumes acetone (– 80 °C) and incubation over night at – 20 °C. Precipitated proteins were pelletized by centrifugation (21,000 g, 15 min, 4 °C) and resuspended in 200 µL methanol (– 80 °C, LC-MS grade) by sonication. The supernatant was discarded, the protein pellet was taken up in 500 µL PBS buffer containing 0.2% (w/v) SDS and dissolved by sonication. Remaining precipitate was discarded after centrifugation (10,000 g, 10 min, 4 °C) and supernatant was used for the enrichment step.

For protein enrichment 50 µL avidin-agarose beads suspension (*Sigma-Aldrich*, A9207) per sample was washed three times (1 mL PBS-buffer + 0.4% (w/v) SDS, centrifugation 400 g, 2 min, r.t.) and incubated with protein solution under continuous mixing for 1 h at room temperature in LoBind *Eppendorf* tubes. Afterwards beads were centrifuged (400 g, 3 min, r.t.) and subsequently washed three times with PBS-buffer containing 0.2% (w/v) SDS and five times with PBS-buffer to remove unspecifically bound proteins. 30 - 50 µL Protein-Avidin beads suspension in PBS-buffer were successively reduced, and digested by addition of 25 µL digestion buffer (5 ng/µL Trypsin (in 50 mM acetic acid), 50 mM Tris-HCl, 2 M urea, 1 mM dithiothreitol (DTT) from fresh 1 M stock in water, pH 8.0) and incubation for 30 min at room temperature. Alkylation and further digestion of proteins was performed by addition of 100 µL alkylation buffer (50 mM Tris-HCl, 2 M urea, 5.5 mM iodoacetamide (freshly prepared from 550 mM stock in water), pH 8.0) following incubation overnight at 25 °C with continuous shaking at 600 rpm. Digestion was stopped by adjusting the pH to 2 – 3 with 10% (v/v) formic acid (FA) to a final concentration of 1% FA. Beads were centrifuged (16,000 g, 3 min, r.t.) and supernatant was desalted using Sep-Pak® C18 columns (50 mg sorbent per cartridge, 55 - 105 µm particle size, *Waters*, WAT054955). In brief, columns were washed once with 1 mL acetonitrile (MeCN), once with 500 µL elution buffer (80% MeCN, 19.5% H_2O, 0.5% FA) and three times with 1 mL 0.1% FA in H_2O. Samples were loaded and eluted in LoBind *Eppendorf* tubes with 250 µL elution buffer after washing twice with 1 mL 0.1% FA and once with 250 µL 0.5% FA. Samples were dried by speedvac solvent removal and stored at – 80 °C until further analysis.

Sample preparation for LC-MS/MS measurement

For MS-analysis peptide samples were dissolved in 25 - 40 µL 1% FA in H_2O, sonicated twice for 10 min and filtered with 0.22 µm Ultrafree-MC® centrifugal filters (*Merck*, UFC30GVNB) equilibrated with 1% FA in H_2O. Filtrates were transferred into MS vials and analyzed by LC-MS/MS.

Data acquisition by LC-MS/MS

Measurement on Orbitrap Fusion

Samples from labeling in Huh7 cells with **TG42** or **D3** were analyzed with an UltiMate 3000 nano HPLC system (Dionex) using Acclaim C18 PepMap100 75 µm ID x 2 cm trap and Acclaim PepMap RSLC C18 (75 µm ID x 50 cm) separation columns in an EASY-spray setting coupled to an Orbitrap Fusion (*Thermo Fisher*). 5 µL peptide samples (8 µL for **TG42**) were loaded on the trap and washed with 0.1% TFA, then transferred to the analytical column (buffer A: H_2O with 0.1% FA, buffer B: MeCN with 0.1% FA, flow 0.3 µL/min, gradient: to 5% buffer B in 7 min, from 5% to 22% buffer B in 105 min, then to 32% buffer B in 10 min, to 90% buffer B in 10 min and hold at 90% buffer B for 10 min, then to 5% buffer B in 0.1 min and hold 5% buffer B for 9.9 min) and ionized by nanospray ionization (NSI) with spray voltage of 1.7 kV (2.1 kV for **TG42**) and capillary temperature of 275 °C. Orbitrap Fusion was operated in a TOP speed data dependent mode. Full scan acquisition was performed in the orbitrap at a resolution of R = 120,000 and an AGC target of 2e5 in a scan range of 300 – 1500 m/z with a maximum injection time of 50 ms. Monoisotopic precursor selection as well as dynamic exclusion (dynamic exclusion duration: 60 s, mass tolerance low/high 10 ppm) was enabled. Precursors with charge states 2 - 7 and intensities greater than 5e3 were selected for fragmentation. Isolation was performed in the quadrupole using a window of 1.6 m/z. Precursors were analyzed to an AGC target of 1e5 and a maximum injection time of

50 ms with “inject ions for all available parallelizable time” set to true. Peptide fragments were generated by higher-energy collisional dissociation (HCD) with a collision energy of 30% and detected in the orbitrap with ion trap scan rate set to rapid.

Measurement on Q Exactive Plus

Samples from labeling in Jurkat cells with **TG42** were analyzed with an UltiMate 3000 nano HPLC system (Dionex) using Acclaim C18 PepMap100 75 µm ID x 2 cm trap and Acclaim PepMap RSLC C18 (75 µm ID x 50 cm) separation columns in an EASY-spray setting coupled to a Q Exactive Plus (*Thermo Fisher*). 5 µL peptide samples were loaded on the trap and washed with 0.1% TFA, then transferred to the analytical column (buffer A: H_2O with 0.1% FA, buffer B: MeCN with 0.1% FA, flow 0.3 µL/min, gradient: to 5% buffer B in 7 min, from 5% to 22% buffer B in 105 min, then to 32% buffer B in 10 min, to 90% buffer B in 10 min and hold at 90% buffer B for 10 min, then to 5% buffer B in 0.1 min and hold 5% buffer B for 9.9 min) and ionized at spray voltage of 2.0 kV and a capillary temperature of 275 °C. Q Exactive Plus was operated in a TOP12 data dependent mode with full scan acquisition in the orbitrap at a resolution of R = 140,000 and an AGC target of 3e6 in a scan range of 300 – 1500 m/z with a maximum injection time of 80 ms. Monoisotopic precursor selection as well as dynamic exclusion (dynamic exclusion duration: 60 s) was enabled. Precursors with charge states >1 and intensities greater than 1e4 were selected for fragmentation. Isolation was performed in the quadrupole using a window of 1.6 m/z. Precursors were analyzed in a scan range of 200 – 2000 m/z to an AGC target of 1e5 and a maximum injection time of 100 ms. Peptide fragments were generated by higher-energy collisional dissociation (HCD) with a normalized collision energy of 27% and detected in the orbitrap.

Data processing: general comments

MS-data were analyzed using MaxQuant software (versions 1.5.5.0 and 1.6.0.1). Peptides were identified by comparison of MS/MS spectra against Uniprot human reference proteome (taxon identifier 9606, canonical version, without isoforms, for **D3** labeling: downloaded 2017/03/13, for **TG42** labeling: downloaded 2017/07/18) using Andromeda search engine. MaxQuant settings were largely set on default. Carbamidomethylation of cysteines was used as fixed modifications and methionine oxidation and N-terminal acetylation were included as modifications in protein quantification. Trypsin/P was set as digestion enzyme and min. peptide length was set to 7. False discovery rate for proteins, sites and PSM was set to 0.01. Match between runs was enabled with a matching window of 0.7 min and alignment time window of 20 min.

Statistical analysis of proteomics data

Resulting data was further statistically analyzed with Perseus software (version 1.6.0.1). ProteinGroups files were loaded to Perseus, following $\log_2$-transformation and filtering by categorical columns. Protein groups satisfying the criteria of ‘only identified by site’, ‘reverse’ and ‘potential contaminants’ were excluded. Matrices were further filtered based on valid values (min. valids 50%), excluding protein groups that appear in less than half of all replicates. Missing values were replaced by imputation from normal distribution (width 0.3, down shift 0.9, total matrix). GO annotation downloaded from Uniprot and categorical annotation of probe treated samples and DMSO control was performed. To analyze the data two-sided student’s *t*-tests with DMSO as single control group and Benjamini-Hochberg false discovery

rate correction (FDR 0.05) were applied. Volcano plots were generated by plotting student's *t*-test difference (probe/DMSO) against *t*-test p-value (probe/DMSO).
The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE[5] partner repository with the dataset identifier PXD010277.

2.8 Cell viability assay

Cell viability was investigated using CellTiter-Blue™ Luminescent Cell Viability Assay (*Promega*) and was carried out according to the manufacturer's protocol. In brief, cells were seeded in 96-well plates and incubated with phenyl esters or DMSO for different time periods. Finally, cell viability was determined by addition of CellTiterBlue™ reagent and incubation for two to four hours following fluorescence readout using *Tecan SpectraFluor Plus*.

2.9 Apoptotic cell determination (Nicoletti assay)

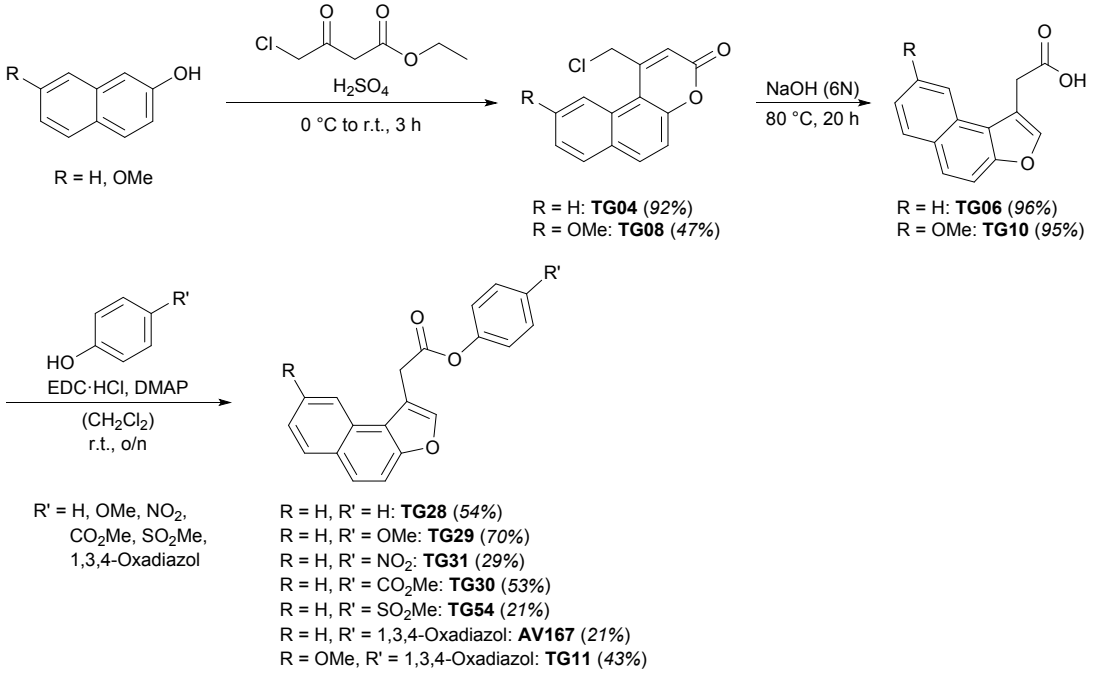
For the assessment of apoptotic cells upon treatment with phenyl esters cell death was measured as described by *Nicoletti et al.*[6] In brief, cells were treated with ClpP inhibitors for 48 h, then washed in cold PBS, pelleted (600 g, 5 min, 4 °C) and incubated with hypotonic fluorochrome solution containing propidium iodide (HFS-PI solution, 50 µg/mL, 4 °C, overnight). The amount of DNA within the cell depends on the stage of cell cycle and can be quantified by measuring the amount of DNA intercalating dye. The occurrence of a broad subG_1 phase peak indicates apoptotic cells and was measured by flow cytometry (FACSCantoII, *BD Biosciences*). Analysis was conducted using FlowJo 7.6 analysis software and percentage of specific apoptosis was calculated with the formula

$$100 \times \frac{\text{apoptosis}_{\text{experimental}}(\%) - \text{apoptosis}_{\text{spontaneous}}(\%)}{100\% - \text{apoptosis}_{\text{spontaneous}}(\%)}.$$

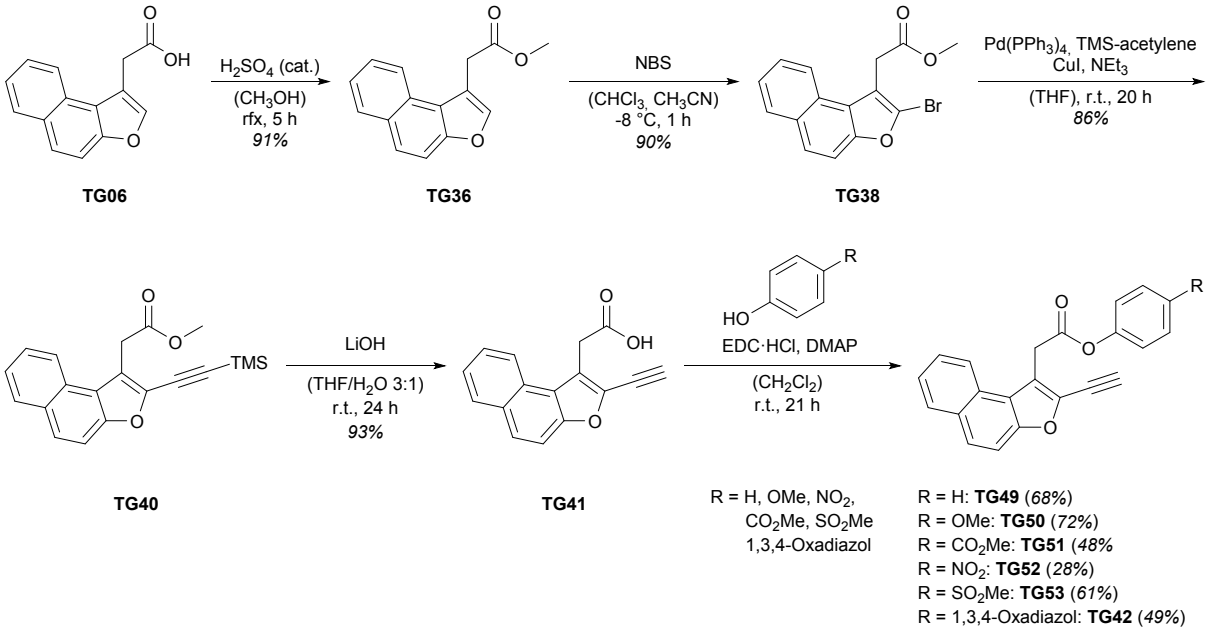
2.10 Migration assay

Migration assays were performed using boyden chambers with Transwell® permeable inserts (*Corning Inc.*, 6.5 mm polycarbonate membrane, 8.0 µm pore size). Compounds **TG42** or **TG53** were added to medium in the lower and upper compartment of the boyden chamber, while medium containing FBS was only added to the lower compartment. Cells were resuspended in medium without FBS (100,000 per insert) and added to the upper compartment. Cells migrated for 16 h and were stained afterwards with crystal violet. Four pictures per insert were taken and cells were counted and normalized to DMSO treated positive control. One chamber without FBS-gradient served as negative control.

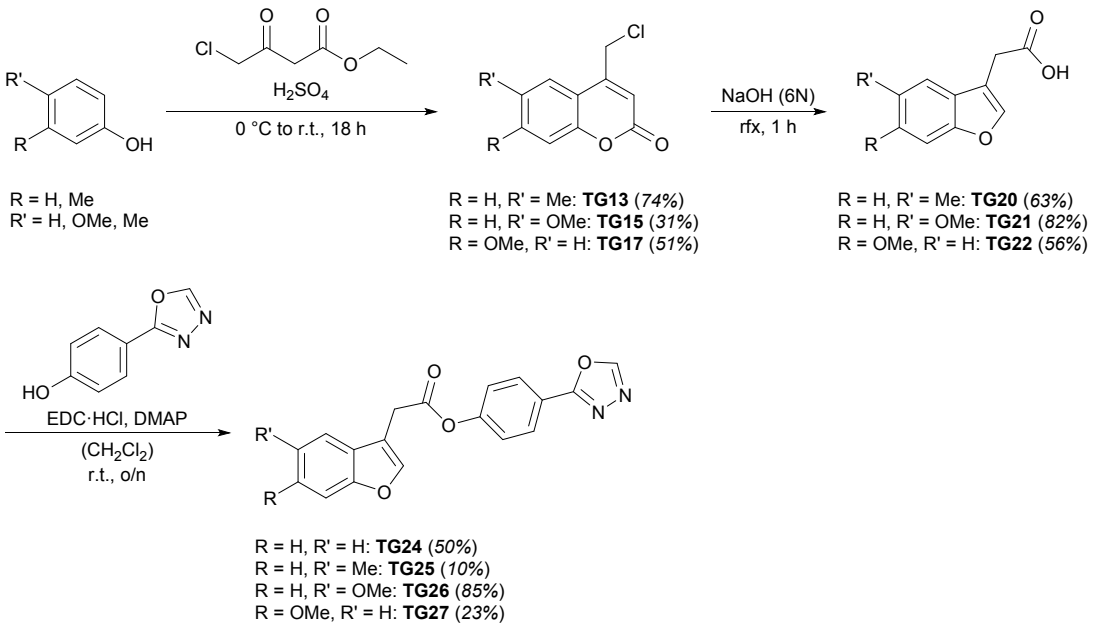
3. Supplementary Schemes



Scheme S1. Synthesis of phenol derivatives **AV167**, **TG11**, **TG28**, **TG29**, **TG30**, **TG31** and **TG54**.



Scheme S2. Synthesis of alkyne-containing phenol derivatives **TG42**, **TG49**-**TG53**.



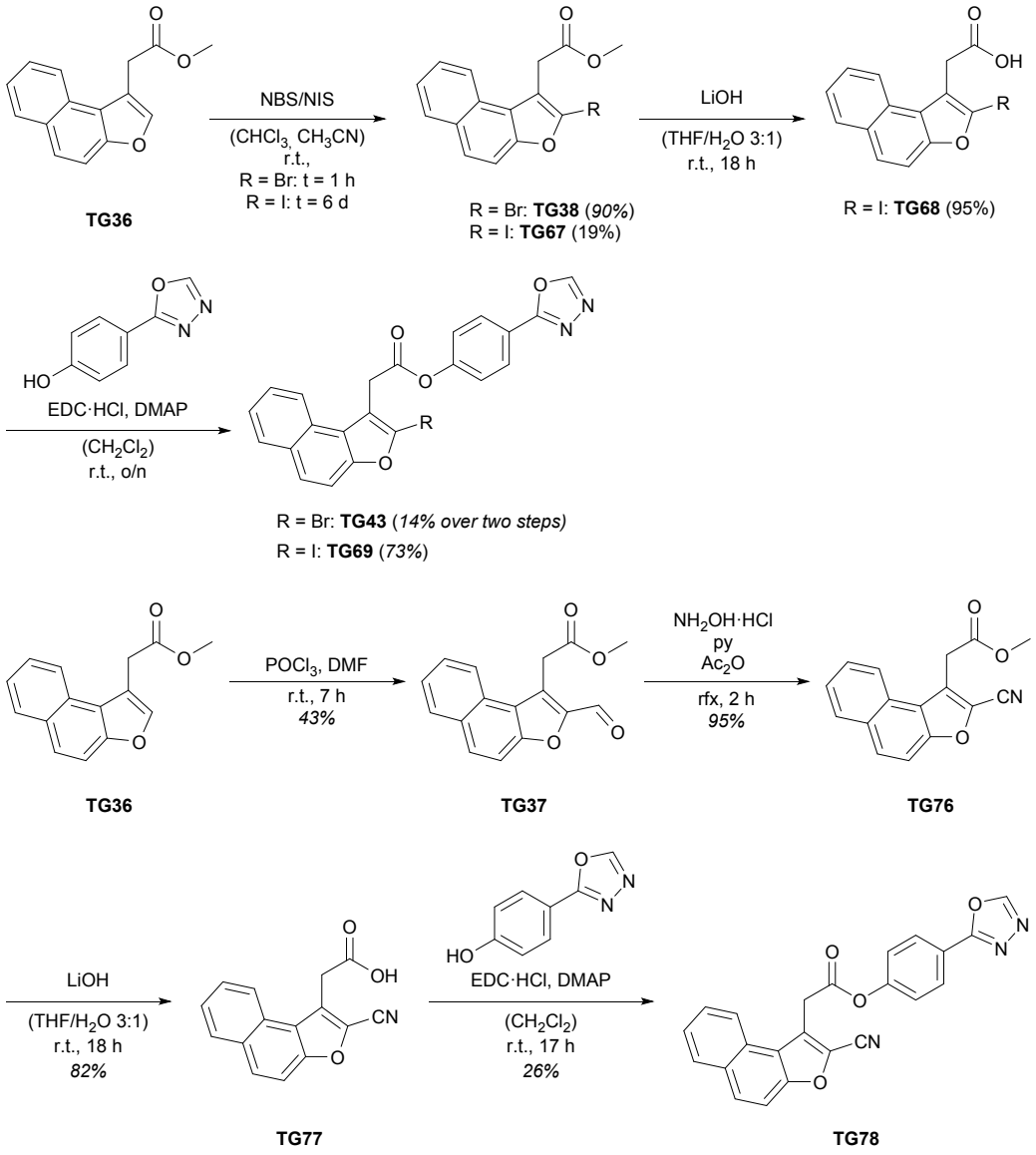
R = H, Me
R' = H, OMe, Me

R = H, R' = Me: **TG13** (*74%*)
R = H, R' = OMe: **TG15** (*31%*)
R = OMe, R' = H: **TG17** (*51%*)

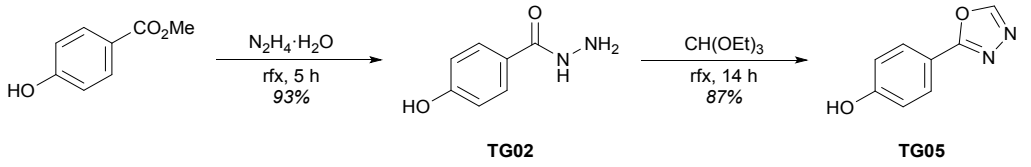
R = H, R' = Me: **TG20** (*63%*)
R = H, R' = OMe: **TG21** (*82%*)
R = OMe, R' = H: **TG22** (*56%*)

R = H, R' = H: **TG24** (*50%*)
R = H, R' = Me: **TG25** (*10%*)
R = H, R' = OMe: **TG26** (*85%*)
R = OMe, R' = H: **TG27** (*23%*)

Scheme S3. Synthesis of acid derivatives **TG24**, **TG25**, **TG26**, **TG27**.



Scheme S4. Synthesis of 2-furanyl substituted phenyl esters **TG43**, **TG69**, **TG78**.



Scheme S5. Synthesis of phenol **TG05**.

4. Chemical Synthesis

4.1 General Methods

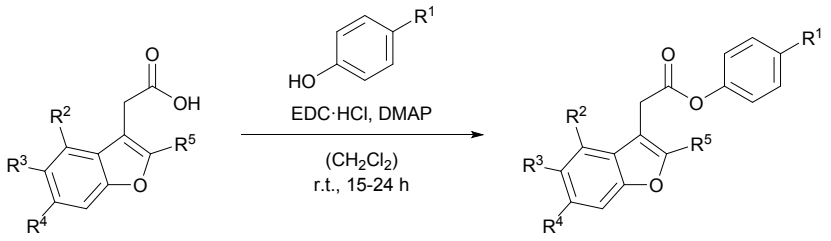
All reagents and solvents were purchased from commercial sources (*Acros Chemicals, Roth, Sigma-Aldrich Co., Merck KGaA, VWR International, Alfa Aesar, Fluka*), were of reagent grade or higher and were used without further purification. Solvents of technical grade were distilled once prior to use. All reactions were conducted using oven dried glassware and are unoptimized. Reactions containing moist or air sensitive reagents were carried out in thoroughly dried glassware under argon atmosphere. Dry solvents were handled using argon purged disposable syringes and solids were added under argon counter flow. For reaction monitoring pre-coated TLC Silica gel 60 F_{254} plates from *Merck KGaA* were used and visual detection was conducted under UV light (λ = 254 and 366 nm) or applying $KMnO_4$-stain (1.50 g $KMnO_4$, 10.0 g K_2CO_3, 1.25 mL $NaOH_{aq}$ (10 wt-%), 200 mL ddH_2O). Preparative silica gel column chromatography was performed using Silica gel 60 (particle size = 40 – 63 µM) from *VWR* with compressed air. Respective volumes of silica gel, column size and eluents are specified separately in each synthesis in the following order (silica gel, volume, column diameter, eluent ratio).

^{1}H-NMR experiments were recorded on *Avance-III* (AV-HD300, AV-HD400 or AV-HD500) NMR systems (*Bruker Co.*) at room temperature with $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are specified in parts per million (ppm) and are referenced to the residual proton signal of the corresponding deuterated solvent ($CDCl_3$: δ = 7.26 ppm, DMSO-d_6: δ = 2.50 ppm). Coupling constants (*J*) are reported in hertz (Hz) and for the assignment of multiplicity to the signals the following abbreviations were used: *br* s – broad singlet, s – singlet, d – doublet, dd – double doublet, ddd – double double doublet, t – triplet, td – triple doublet, q – quadruplet and m – multiplet. ^{13}C-NMR spectra were collected on *Avance-III* NMR systems (*Bruker Co.*) at 75, 101 or 126 MHz with $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts were referenced to the residual solvent peak as an internal standard ($CDCl_3$: δ = 77.16 ppm, DMSO-d_6: δ = 39.52 ppm).

High resolution mass spectra were recorded using a *LTQ-FT Ultra* (*Thermo Fisher Scientific Inc.*) coupled with a Dionex UltiMate 3000 HPLC system and ESI or APCI ion sources.

4.2 General Procedures

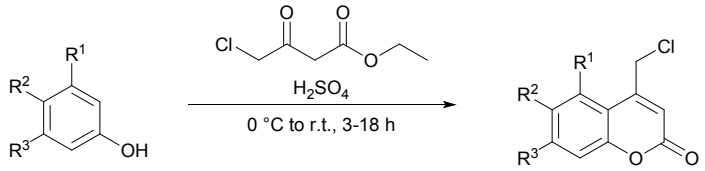
General procedure (I) for the synthesis of esters **AV167**, **TG11**, **TG24**-**31**, **TG42**, **TG43**, **TG49**-**54**, **TG69**, and **TG78**



R^1 = H, OMe, CO_2Me, NO_2, SO_2Me, 1,3,4-Oxadiazol
R^2 = H, -CH=CH-CH=CH-
R^3 = H, -CH=CH-CH=CH-, Me, OMe,
R^4 = H, OMe
R^5 = H, Br, I, -CN, -C≡CH

To a suspension of benzofuranyl/naphthofuranyl acetic acid (1.00 eq.) in CH_2Cl_2 (≈ 0.1 M) was added EDC · HCl (1.50 eq.), DMAP (0.50 eq.) and then the appropriate phenol (1.20 eq.). The resulting mixture was stirred at room temperature for 15 – 24 h under argon atmosphere. Afterwards, the reaction mixture was diluted with CH_2Cl_2 and the clear solution was washed with saturated $NaHCO_3$ solution, water and brine. The organic extracts were dried over Na_2SO_4, filtered and evaporated under vacuum. Purification of the crude product was carried out by silica gel column chromatography.

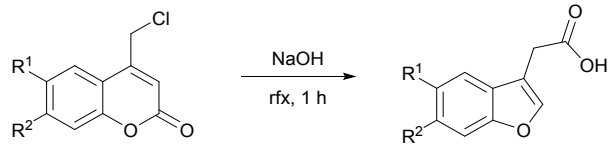
General procedure (II) for the synthesis of substituted coumarins **TG13**, **TG15**, **TG17**, and substituted benzo[*f*]coumarins **TG04**, **TG08**



R^1 = H, -CH=CH-CH=CH-
R^2 = H, -CH=CH-CH=CH-, Me, OMe
R^3 = H, OMe,

Substituted phenol or naphthol derivatives (1.00 eq.) and ethyl 4-chloroacetoacetate (1.00 eq.,1.14 eq. for naphthol derivatives) were mixed in a round bottom flask. Under ice cooling H_2SO_4 (70%, ≈ 1 mL/mmol substrate) was added dropwise over a period of 15 minutes. For naphthol derivatives, concentrated H_2SO_4 (98%, ≈ 0.5 mL/mmol substrate) was used. Following that, the reaction mixture was stirred at room temperature for 18 h; in the case of naphthol substrates the reaction time was 3 h. After completion, the mixture was poured onto ice water and stirred for 1 – 2 h. In this time a precipitate formed which was filtered and washed with cold water. In some cases, silica gel column chromatography was required to isolate the pure product.

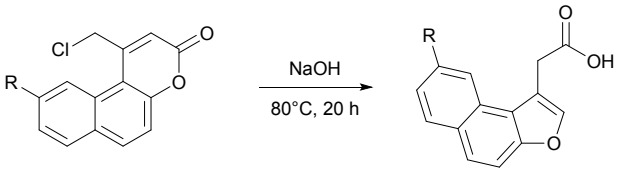
General procedure (III) for the synthesis of substituted benzofuran-3-ylacetic acids **TG20-22**



R^1 = H, Me, OMe
R^2 = H, OMe

In a round bottom flask substituted coumarin (1.00 eq.) was suspended in 1 M $NaOH_{aq}$ and heated under reflux for 1 h. Afterwards, the clear solution was cooled to room temperature, acidified with 1 M HCl_{aq} until pH = 5 – 6 was reached and stirred for 30 minutes. The resulting precipitate was collected by filtration, washed with HCl_{aq} and water and dried in vacuo.

General procedure (IV) for the synthesis of substituted naphthofuran-3-ylacetic acids **TG06** and **TG10**

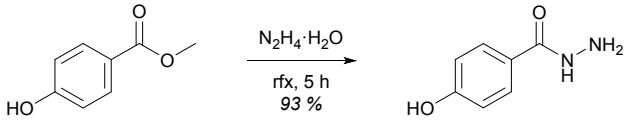


R = H, OMe

In a round bottom flask substituted benzo[*f*]coumarin (1.00 eq.) was suspended in 6 M $NaOH_{aq}$ and heated under reflux for 20 h. Afterwards, the clear solution was acidified with 6 M HCl_{aq} until pH = 5 – 6 was reached and stirred for 30 minutes. The resulting suspension was extracted with ethyl acetate. Then, the organic layer was washed with water and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the corresponding naphthofuranylacetic acid.

4.3 Synthetic Procedures

4-Hydroxybenzohydrazide (TG02)

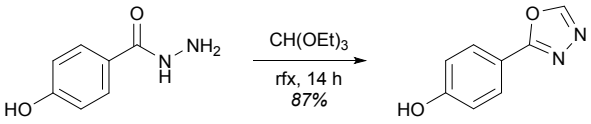


TG02

In a 25 mL round bottom flask hydrazine hydrate (98%, 3.24 g, 68.4 mmol, 4.00 eq.) was added to methyl 4-hydroxybenzoate (2.60 g, 17.1 mmol, 1.00 eq.). After refluxing for 5 h, the resulting solid was collected by filtration and dried in vacuo to afford **TG02** as a white solid (2.42 g, 15.9 mmol, 93%). **^{1}H-NMR** (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 4.36 (br s, 2H), 6.77 (d, 2H, ^3J = 8.8 Hz), 7.68 (d, 2H, ^3J = 8.8 Hz), 9.47 (br s, 1H).**^{13}C-NMR** (DMSO-d_6, 75 MHz, 300 K): δ (ppm) = 114.8, 124.0, 128.8, 156.0, 165.9. **TLC**: R_f = 0.13 (hexane/ethyl acetate = 1:1).

Spectral data are consistent with those published previously.[7]

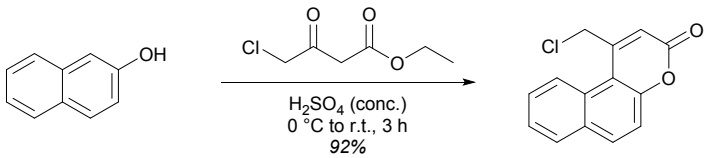
4-(1,3,4-Oxadiazol-2-yl)phenol (TG05)



TG02 **TG05**

Hydrazide **TG02** (1.00 g, 6.57 mmol, 1.00 eq.) and triethyl orthoformate (11.7 g, 78.8 mmol, 12.0 eq.) were mixed in a 50 mL round bottom flask and heated under reflux for 18 h. After cooling to room temperature, the remaining triethyl orthoformate was removed in vacuo. Purification by column chromatography (SiO_2, 160 mL, 4 cm, hexane/ethyl acetate = 1:1) gave phenol **TG05** (0.93 g, 5.73 mmol, 87%) as a white solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 6.95 (d, 2H, ^3J = 8.8 Hz), 7.85 (d, 2H, ^3J = 8.8 Hz), 9.22 (s, 1H), 10.30 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 114.0, 116.2, 128.6, 153.7, 160.8, 163.8. **HRMS** (ESI): *m/z* calcd for $C_8H_6O_2N_2$ $[M+H]^+$: 163.0500, found: 163.0500. **TLC**: R_f = 0.36 (hexane/ethyl acetate = 1:1).

1-(Chloromethyl)-3*H*-benzo[*f*]chromen-3-one (TG04)



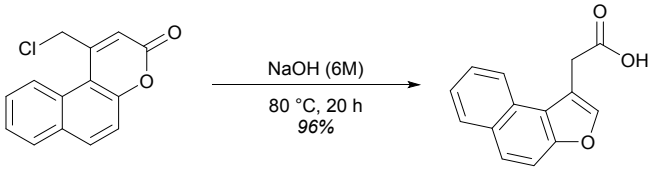
TG04

Following general procedure (II), 2-naphthol (2.02 g, 14.0 mmol, 1.00 eq.) and ethyl 4-chloroacetoacetate (2.63 g, 16.0 mmol, 1.14 eq.) were combined in a 50 mL round bottom flask and cooled to 0 °C. After adding of concentrated H_2SO_4 (98%, 5 mL) over a period of 30 minutes, the reaction mixture was stirred at room temperature for 3 h. Afterwards, the mixture was poured into ice water and stirred for another hour to give an off-white precipitate. The solid was filtered off, washed with cooled

water and ether and dried in vacuo to give **TG04** (3.16 g, 12.9 mmol, 92%). **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 5.07 (s, 2H), 6.75 (s, 1H), 7.50 (d, 1H, ^3J = 8.9 Hz), 7.59 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 6.9 Hz, ^4J = 1.0 Hz), 7.71 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 6.9 Hz, ^4J = 1.5 Hz), 7.95 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.5 Hz), 8.02 (d, 1H, ^3J = 8.9 Hz), 8.42 (d, 1H, ^3J = 8.8 Hz). **^{13}C-NMR** (DMSO-d_6, 75 MHz, 300 K): δ (ppm) = 46.0, 112.7, 117.6, 118.0, 125.1, 126.0, 128.7, 129.0, 130.1, 131.5, 134.5, 151.4, 155.3, 160.1. **TLC**: R_f = 0.86 (hexane/ethyl acetate = 1:2).

Spectral data are consistent with those published previously.[8]

2-(Naphtho[2,1-*b*]furan-1-yl)acetic acid (TG06)

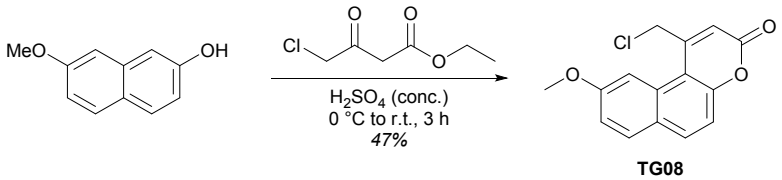


TG04 **TG06**

Following general procedure (IV), a suspension of benzocoumarin **TG04** (3.16 g, 12.9 mmol, 1.00 eq.) in $NaOH_{aq}$ (40 mL, 6 M, 0.24 mol) was stirred at 80 °C for 20 h. After cooling to room temperature, the reaction mixture was acidified with HCl_{aq} (35 mL, 6 M, 0.21 mol) and extracted with ethyl acetate (4 · 80 mL). The organic extracts were washed with 80 mL water and brine respectively, dried over Na_2SO_4 and evaporated under vacuum. Compound **TG06** was obtained as a brown solid (2.80 g, 12.4 mmol, 96%). **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 4.06 (s, 2H), 7.52 (ddd, 1H, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz), 7.61 (ddd, 1H, ^3J = 8.3 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz), 7.78 (d, 1H, ^3J = 8.9 Hz), 7.85 (d, 1H, ^3J = 9.0 Hz), 8.03 (s, 1H, Ha), 8.05 (br d, 1H, ^3J = 8.0 Hz), 8.19 (br d, 1H, ^3J = 7.9 Hz), 12.62 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 30.9, 112.6, 115.7, 121.1, 123.0, 124.3, 125.6, 126.4, 127.9, 128.9, 130.3, 143.6, 152.6, 172,2. **TLC**: R_f = 0.15 (hexane/ethyl acetate = 1:2).

Spectral data match those published previously.[9]

1-(Chloromethyl)-9-methoxy-3*H*-benzo[*f*]chromen-3-one (**TG08**)



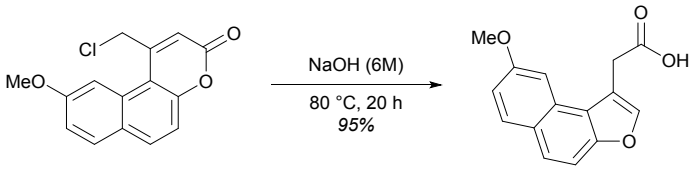
TG08

In a 25 mL round bottom flask, 7-methoxy-2-naphthol (0.50 g, 2.87 mmol, 1.00 eq.) and ethyl 4-chloroacetoacetate (0.54 g, 3.27 mmol, 1.14 eq.) were mixed and cooled to 0 °C. Concentrated H_2SO_4 (98%, 1 mL) was added over a period of 15 min and the reaction mixture was stirred for 3 h at room temperature. Afterwards, the reaction mixture was poured into ice water and stirred for another 3 h. The resulting yellow-brown precipitate was collected by filtration, washed with water and dried in vacuo. The crude product was purified by column chromatography (SiO_2, 300 mL, 8 cm, hexane/ethyl acetate = 2:1 → 1:2) to give pyrone **TG08** (0.37 g, 1.35 mmol, 47%) as a bright yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz,

298 K): δ (ppm) = 4.01 (s, 3H), 5.01 (s, 2H), 6.63 (s, 1H), 7.24 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.3 Hz), 7.34 (d, 1H, ^3J = 8.9 Hz), 7.81 – 7.87 (m, 2H), 7.94 (d, 1H, ^3J = 8.8 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 45.8, 55. 8, 106.0, 112.1, 115.4, 117.3, 117.6, 126.6, 130.5, 131.4, 134.2, 151.2, 156.1, 160.0. **TLC**: R_f = 0.50 (hexane/ethyl acetate = 2:1).

Spectral data match those published previously.[8]

2-(8-Methoxynaphtho[2,1-*b*]furan-1-yl)acetic acid (TG10)

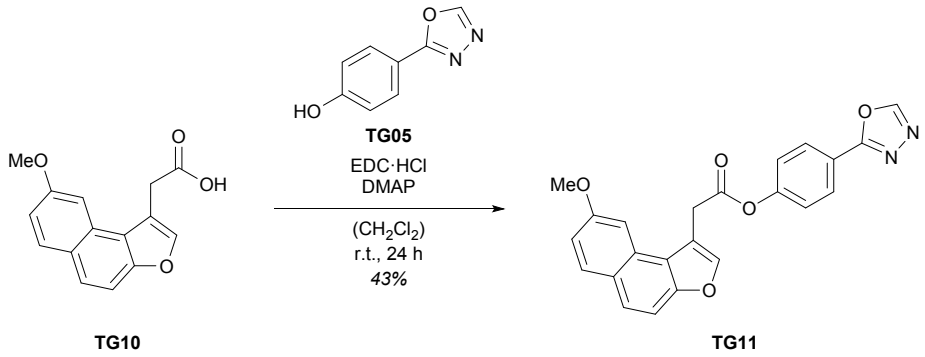


TG08 **TG10**

Following general procedure (IV), a suspension of benzocoumarin **TG08** (324 mg, 1.18 mmol, 1.00 eq.) in $NaOH_{aq}$ (8 mL, 6 M, 48.0 mmol) was heated under reflux for 20 h. Afterwards, the mixture was cooled to room temperature and acidified with HCl_{aq} (10 mL, 6 M, 60.0 mmol) until pH = 5 – 6 was reached. The suspension was extracted with ethyl acetate (4 · 15 mL), the organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. Methoxy substituted naphthofuranylacetic acid **TG10** (288 mg, 1.12 mmol, 95%) was obtained as a brown solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 3.91 (s, 3H), 4.05 (s, 2H), 7.16 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.5 Hz), 7.57 (d, 1H, ^4J = 2.4 Hz), 7.59 (d, 1H, ^3J = 8.9 Hz), 7.76 (d, 1H, ^3J = 8.9 Hz), 7.95 (d, 1H, ^3J = 9.0 Hz), 7.97 (s, 1H) 12.66 (br s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 30.9, 55.0, 103.0, 110.1, 115.6, 115.8, 120.5, 125.2, 125.4, 129.1, 130.4, 143.2, 153.2, 157.7, 172.5. **TLC**: R_f = 0.29 (CH_2Cl_2, 5% CH_3OH).

Spectral data match those published previously.[9]

4-(1,3,4-Oxadiazol-2-yl)phenyl 2 (8-methoxynaphtho[2,1-*b*]furan-1-yl)acetate (TG11)

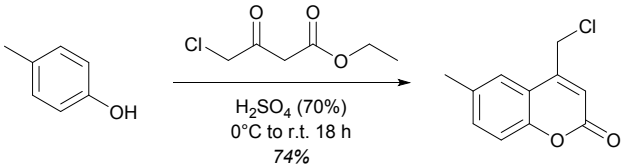


TG10 **TG11**

Following general procedure (I), acid **TG10** (100 mg, 0.39 mmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (4 mL). EDC · HCl (112 mg, 0.59 mmol, 1.50 eq.), DMAP (24.0 mg, 0.20 mmol, 0.50 eq.) and phenol **TG05** (76.0 mg, 0.47 mmol, 1.20 eq.) were added and the resulting mixture was stirred under argon atmosphere at room temperature for 24 h. After this time the reaction mixture was diluted with CH_2Cl_2 (8 mL), washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and evaporated

under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, 160 mL, 4 cm, hexane/ethyl acetate = 1:1) to give phenyl ester **TG11** (67.2 mg, 108 µmol, 43%) as a slightly yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.95 (s, 3H), 4.33 (d, 2H, *J* = 0.9 Hz), 7.16 – 7.22 (m, 3H), 7.53 (d, 1H, ^3J = 9.0 Hz), 7.69 – 7.72 (m, 2H), 7.81 (s, 1H), 7.89 (d, 1H, ^3J = 9.0 Hz), 8.11 (d, 2H, ^3J = 8.9 Hz), 8.44 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 32.3, 55.6, 103.1, 110.5, 114.0, 116.0, 120.3, 121.5, 126.0, 126.2, 128.7, 129.6, 130.9, 142.9, 152.8, 153.5, 154.4, 158.6, 164.2, 169.2. **HRMS** (ESI): *m/z* calcd for $C_{23}H_{16}N_2O_5$ $[M+H]^+$: 401.1121, found: 401.1123. **TLC**: R_f = 0.57 (hexane/ethyl acetate = 2:3).

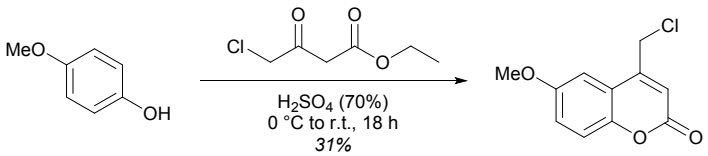
4-(Chloromethyl)-6-methyl-2*H*-chromen-2-one (TG13)



TG13

According to general procedure (II) 4-methylphenol (300 mg, 2.77 mmol, 1.00 eq.) was mixed with ethyl 4-chloroacetoacetate (460 mg, 2.77 mmol, 1.00 eq.) in a 50 mL round bottom flask. H_2SO_4 (70%, 2.5 mL) was added under ice cooling over 15 min. The resulting brown solution was stirred at room temperature for 18 h. Afterwards, the reaction mixture was poured onto ice water to give a greyish precipitate. The solid was filtered off washed with cold water and dried in vacuo to afford compound **TG13** (432 mg, 2.07 mmol) in 74% yield. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 2.44 (s, 3H), 4.67 (d, 2H, ^4J = 0.9 Hz), 6.56 (s, 1H), 7.28 (virt. s, 1H), 7.38 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.8 Hz), 7.43 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 21.2, 41.4, 116.0 117.2, 117.4, 124.0, 133.4, 134.4, 149.5, 152.2, 160.6. **HRMS** (ESI): *m/z* calcd for $C_{11}H_9ClO_2$ $[M+H]^+$: 209.0360, found: 209.0360.

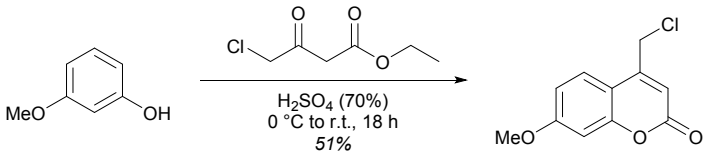
4-(Chloromethyl)-6-methoxy-2*H*-chromen-2-one (TG15)



TG15

Following general procedure (II), 4-methoxyphenol (300 mg, 2.42 mmol, 1.00 eq.) was mixed with ethyl 4-chloroacetoacetate (400 mg, 2.42 mmol, 1.00 eq.) in a 50 mL round bottom flask and cooled to 0 °C. After addition of H_2SO_4 (70%, 2.5 mL) the reaction mixture was allowed to warm to room temperature and stirred for 18 h. After this time the mixture was poured onto ice water with additional stirring for 1 h. The crude product was purified by column chromatography (SiO_2, 190 mL, 4 cm, hexane/ethyl acetate = 2:1) to give compound **TG15** (277 mg, 1.23 mmol, 31%) as a bright yellow solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 3.87 (s, 3H), 4.65 (d, 2H, ^4J = 0.9 Hz), 6.58 (s, 1H), 7.09 (d, 1H, ^4J = 2.8 Hz), 7.15 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.9 Hz), 7.32 (d, 1H, ^3J = 9.0 Hz). **^{13}C-NMR** ($CDCl_3$, 75 MHz, 300 K): δ (ppm) = 41.5, 56.1, 107.4, 116.5, 117.9, 118.6, 119.5, 148.4, 149.2, 156.3, 160.5. **HRMS** (ESI): *m/z* calcd for $C_{11}H_9ClO_3$ $[M+H]^+$: 225.0309, found: 225.0309. **TLC**: R_f = 0.52 (hexane/ethyl acetate = 2:1).

4-(Chloromethyl)-7-methoxy-2*H*-chromen-2-one (TG17)

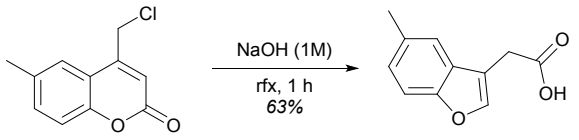


TG17

According to general procedure (II), 3-methoxyphenol (300 mg, 2.42 mmol, 1.00 eq.) was combined with ethyl 4-chloroacetoacetate (400 mg, 2.42 mmol, 1.00 eq.) in a 50 mL round bottom flask. Under ice cooling H_2SO_4 (70%, 3 mL) was added and the reaction mixture was stirred at room temperature for 18 h. Afterwards, the mixture was poured onto ice water and was stirred for 1 h. The crude product was filtered off and recrystallized from ethanol to afford compound **TG17** (276 mg, 1.23 mmol, 51%) as colourless solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 3.87 (s, 3H), 4.99 (d, 2H, ^4J = 0.7 Hz), 6.50 (s, 1H), 7.01 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.5 Hz), 7.04 (d, 1H, ^4J = 2.4 Hz), 7.76 (d, 1H, ^3J = 8.8 Hz). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 41.3, 56.0, 101.1, 110.4, 112.0, 112.3, 126.4, 150.8, 155.2, 160.0, 162.6.

Spectral data match those published previously.[10]

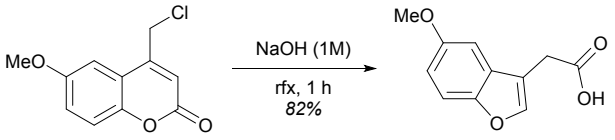
2-(5-Methylbenzofuran-3-yl)acetic acid (TG20)



TG13 **TG20**

According to general procedure (III), furanyl acetic acid **TG13** (427 mg, 2.05 mmol, 1.00 eq.) was suspended in $NaOH_{aq}$ (15 mL, 1 M, 15.0 mmol) and heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was acidified with HCl_{aq} (15 mL, 1 M, 15.0 mmol) and stirred for 1 h. The resulting greyish precipitate was collected by filtration washed with water and dried in vacuo. Compound **TG20** (245 mg, 1.29 mmol, 63%) was obtained as a greyish solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 2.39 (s, 3H), 3.65 (d, 2H, ^4J = 0.9 Hz), 7.12 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.7 Hz), 7.36 – 7.38 (m, 1H), 7.43, (d, 1H, ^3J = 8.4 Hz), 7.83 (s, 1H), 12.45 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 20.9, 29.0, 110.8, 113.7, 119.7, 125.4, 127.8, 131.4, 143.5, 152.9, 171.9. **HRMS** (ESI): *m/z* calcd for $C_{11}H_{10}O_3$ $[M-H]^-$: 189.0557, found: 189.0556.

2-(5-Methoxybenzofuran-3-yl)acetic acid (TG21)

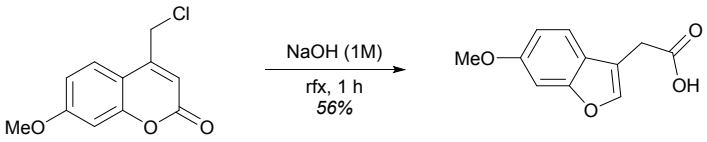


TG15 **TG21**

Following general procedure (III), coumarin **TG15** (272 mg, 1.21 mmol, 1.00 eq.) was suspended in $NaOH_{aq}$ (15 mL, 1 M, 15.0 mmol) and heated under reflux for 1 h. The resulting pale yellow solution was acidified with 1 M HCl_{aq} until pH ≈ 5 was reached. A white precipitate formed which was collected by filtration, washed with water and dried under reduced pressure. Product **TG21** (205 mg, 0.99 mmol, 82%) was isolated as a white solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 3.66 (d, 2H, ^4J = 0.8 Hz), 3.78 (s, 3H), 6.90 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.6 Hz), 7.10 (d, 1H, ^4J = 2.6 Hz), 7.45 (d, 1H, ^3J = 8.9 Hz), 7.84 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 28.9, 55.6, 102.68, 111.7, 112.7, 114.1, 128.4, 144.2, 149.3, 155.4, 171.9. **HRMS** (ESI): *m/z* calcd for $C_{11}H_{10}O_4$ $[M-H]^-$: 205.0506, found: 205.0506.

Spectral data match those published previously.[11]

2-(6-Methoxybenzofuran-3-yl)acetic acid (TG22)

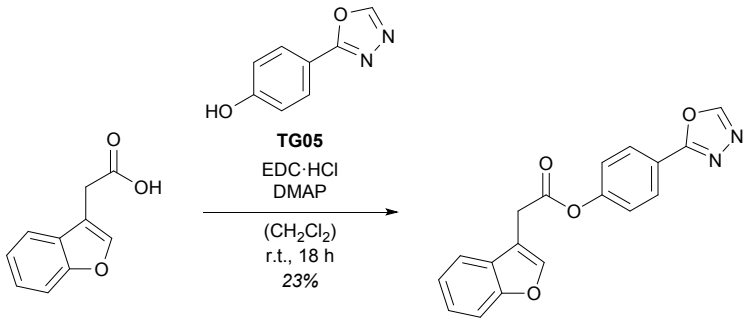


TG17 **TG22**

Following general procedure (III), coumarin **TG17** (206 mg, 0.92 mmol, 1.00 eq.) was suspended in $NaOH_{aq}$ (10 mL, 1 M, 10.0 mmol) and heated under reflux for 1 h. The clear orange solution was cooled to room temperature and acidified with 1 M HCl_{aq}. After stirring for 30 min, the resulting greyish precipitate was filtered off, washed with water and dried in vacuo to give benzofuranyl acetic acid **TG22** (107 mg, 0.52 mmol, 56%). **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K): δ (ppm) = 3.64 (s, 2H), 3.79 (s, 3H), 6.88 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.2 Hz), 7.16 (d, ^4J = 2.1 Hz), 7.46 (d, 1H, ^3J = 8.6 Hz), 7.76 (s, 1H), 12.41 (*br* s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K): δ (ppm) = 29.0, 55.6, 95.9, 111.5, 113.8, 120.2, 120.9, 142.3, 155.5, 157.7, 171.9.

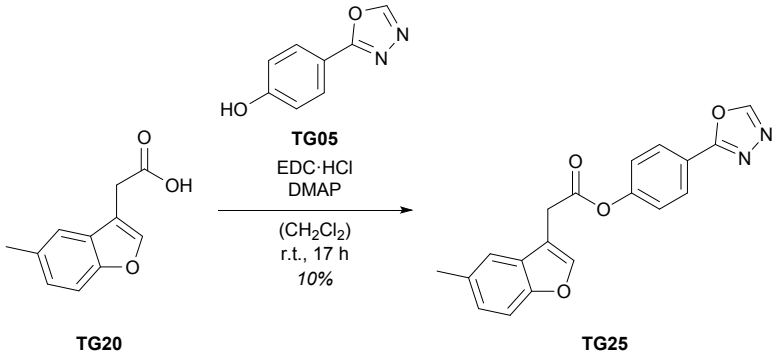
Spectral data match those published previously.[10]

4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(benzofuran-3-yl)acetate (TG24)



According to general procedure (I), acid **TG23** (82.0 mg, 0.47 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (2.5 mL). To this solution EDC · HCl (178 mg, 0.93 mmol, 2.00 eq.), DMAP (28.0 mg, 0.23 mmol, 0.50 eq.) and phenol **TG05** (90.0 mg, 0.56 mmol, 1.20 eq.) were added. Afterwards, the mixture was stirred under argon atmosphere at room temperature for 21 h. Dilution with CH_2Cl_2 (5 mL) gave a yellow solution which was washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Phenyl ester **TG24** (74.4 mg, 232 µmol, 50%) was isolated by column chromatography (SiO_2, 130 mL, 4 cm, hexane/ethyl acetate = 1:1) as a white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 4.00 (d, 2H, ^4J = 1.1 Hz), 7.25 – 7.29 (m, 2H), 7.31 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz), 7.35 (td, 1H, ^3J = 8.2, 7.8 Hz, ^4J = 1.5 Hz), 7.51 – 7.54 (m, 1H), 7.64 – 7.67 (m, 1H), 7.74 (s, 1H), 8.11 (d, 2H, ^3J = 8.9 Hz), 8.46 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 30.2, 111.9, 112.4, 119.7, 121.5, 122.5, 123.0, 124.9, 127.5, 128.7, 143.3, 152.8, 153.5, 155.4, 164.2, 168.8. **HRMS** (ESI): *m/z* calcd for $C_{18}H_{12}N_2O_4$ $[M+H]^+$: 321.0868, found: 321.0868. **TLC**: R_f = 0.51 (hexane/ethyl acetate = 1:1).

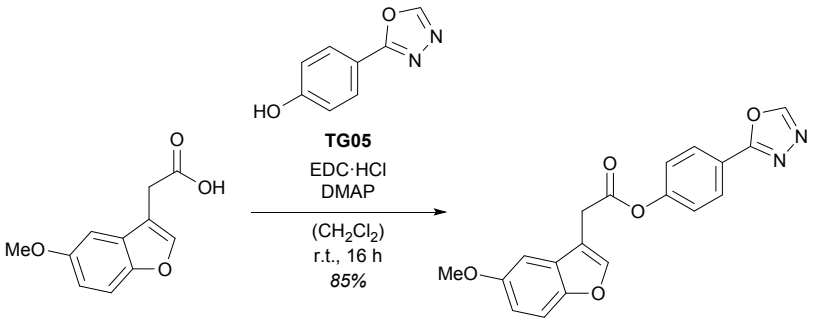
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(5-methylbenzofuran-3-yl)acetate (TG25)



Following general procedure (I), acid **TG20** (100 mg, 0.53 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (4 mL). After addition of EDC · HCl (151 mg, 0.79 mmol, 1.50 eq.), DMAP (32.0 mg, 0.26 mmol, 0.50 eq.) and phenol **TG05** (102 mg, 0.63 mmol, 1.20 eq.) the resulting suspension was stirred at room temperature for 17 h under argon atmosphere. The reaction mixture was diluted with CH_2Cl_2 (12 mL), washed subsequently with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. Afterwards, the solvent was evaporated on a rotavapor under reduced pressure. Purification by column chromatography (SiO_2, 180 mL, 4 cm, hexane/ethyl acetate = 1:1) gave phenyl ester **TG25** (17.0 mg,

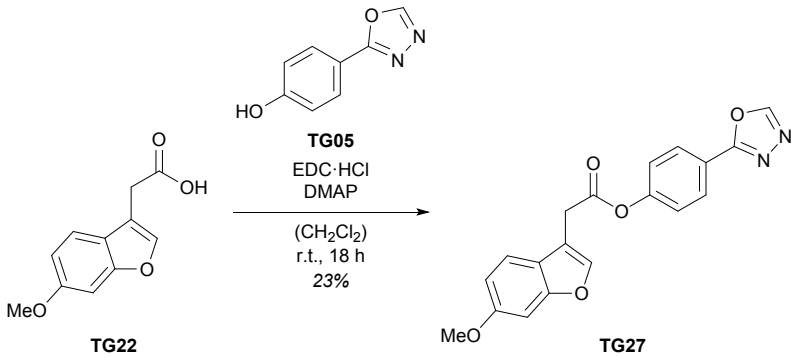
51.0 µmol, 10%) as a pale yellow solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 2.47 (s, 3H), 3.97 (d, 2H, ^4J = 1.0 Hz), 7.15 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.7 Hz), 7.25 – 7.30 (m, 2H), 7.40 (d, 1H, ^3J = 8.6 Hz), 7.41 – 7.43 (m, 1H), 7.69 (s, 1H), 8.11 (d, 2H, ^3J = 8.9 Hz), 8.46 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K): δ (ppm) = 21.6, 30.1, 111.4, 112.0, 119.4, 121.4, 122.6, 126.2, 127.5, 128.7, 132.6, 143.4, 152.8, 153.5, 153.8, 164.2, 168.9. **HRMS** (ESI): *m/z* calcd for $C_{19}H_{14}N_2O_4$ $[M+H]^+$: 335.1023, found: 335.1025. **TLC**: R_f = 0.45 (hexane/ethyl acetate = 1:1).

4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(5-methoxybenzofuran-3-yl)acetate (TG26)



Following general procedure (I), acid **TG21** (50.0 mg, 0.24 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (2 mL). Addition of EDC · HCl (93.0 mg, 0.48 mmol, 2.00 eq.), DMAP (15.0 mg, 0.12 mmol, 0.50 eq.) and phenol **TG05** (47.0 mg, 0.29 mmol, 1.20 eq.) gave a pale yellow solution which was stirred under argon atmosphere at room temperature for 16 h. After this time the reaction mixture was diluted with CH_2Cl_2 (4 mL), washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The organic solvent was removed under reduced pressure and phenyl ester **TG26** (72.6 mg, 0.21 mmol, 85%) was obtained as a pale brown solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.86 (s, 3H), 3.96 (d, 2H, ^4J = 1.0 Hz), 6.95 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.5 Hz), 7.08 (d, 1H, ^4J = 2.5 Hz), 7.25 – 7.29 (m, 2H), 7.41 (dd, 1H, ^3J = 8.8 Hz, ^5J = 0.4 Hz), 7.71 (*br* s, 1H), 8.11 (d, 2H, ^3J = 8.9 Hz), 8.46 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 30.2, 56.2, 102.2, 112.4, 112.4, 113.6, 121.5, 122.5, 128.0, 128.7, 144.1, 150.4, 152.8, 153.5, 156.3, 164.2, 168.7. **HRMS** (ESI): *m/z* calcd for $C_{19}H_{14}N_2O_5$ $[M+H]^+$: 351.0972, found: 351.0973. **TLC**: R_f = 0.44 (hexane/ethyl acetate = 1:1).

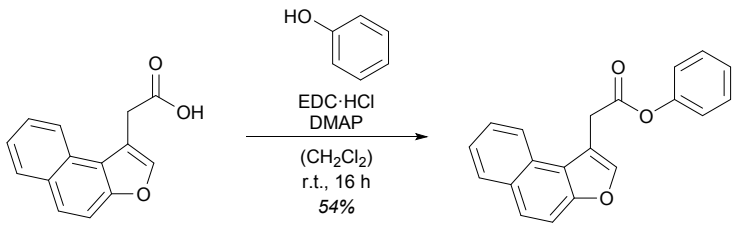
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(6-methoxybenzofuran-3-yl)acetate (TG27)



According to general procedure (I), acid **TG22** (97.0 mg, 0.47 mmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (2.5 mL). After addition of EDC · HCl (180 mg, 0.94 mmol, 2.00 eq.), DMAP (29.0 mg, 0.24 mmol,

0.50 eq.) and phenol **TG05** (91.0 mg, 0.56 mmol, 1.20 eq.), the reaction mixture was stirred under argon atmosphere at room temperature for 18 h. Following that, the mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 130 mL, 4 cm, hexane/ethyl acetate = 1:1) to yield phenyl ester **TG27** (38.1 mg, 109 µmol, 23%) as a white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.87 (s, 3H), 3.96 (d, 2H, ^4J = 0.9 Hz), 6.93 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.2 Hz), 7.05 (d, 1H, ^4J = 2.2 Hz), 7.26 (d, 2H, ^3J = 8.8 Hz), 7.51 (d, 1H, ^3J = 8.6 Hz), 7.63 (s, 1H), 8.10 (d, 2H, ^3J = 8.8 Hz), 8.46 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 298 K): δ (ppm) = 30.2, 55.9, 96.3, 112.2, 112.3, 119.8, 120.8, 121.4, 122.6, 128.7, 142.3, 152.8, 153.5, 156.5, 158.5, 164.2, 168.8. **HRMS** (ESI): *m/z* calcd for $C_{19}H_{14}N_2O_5$ $[M+H]^+$: 351.0971, found: 351.0972. **TLC**: R_f = 0.46 (hexane/ethyl acetate = 1:1).

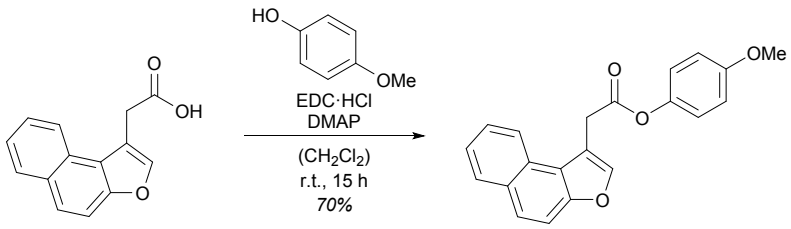
Phenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG28)



TG06 **TG28**

Following general procedure (I), acid **TG06** (30.0 mg, 133 µmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (1 mL). Addition of EDC · HCl (38.1 mg, 0.20 mg, 1.50 eq.), DMAP (8.19 mg, 67.0 µmol, 0.50 eq.) and phenol (15.1 mg, 160 µmol, 1.20 eq.) gave a clear solution which was stirred under argon atmosphere at room temperature for 16 h. Afterwards, CH_2Cl_2 (2 mL) was added and the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting crude product was purified by column chromatography (SiO_2, 150 mL, 4 cm, hexane/ethyl acetates = 3:1) to give phenyl ester **TG28** (21.7 mg, 71.8 µmol, 54%) as a yellow solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 4.34 (d, 2H, ^4J = 1.0 Hz), 7.06 (d, 2H, ^3J = 7.6 Hz), 7.21 (t, 1H, ^3J = 7.4 Hz), 7.33 – 7.37 (m, 2H), 7.51 (ddd, 1H, ^3J = 8.0, 6.8 Hz, ^4J = 0.9 Hz), 7.63 (ddd, 1H, ^3J = 8.2, 6.8 Hz, ^4J = 1.1 Hz), 7.67 (d, 1H, ^3J = 8.9 Hz), 7.76 (d, 1H, ^3J = 8.9 Hz), 7.86 (s, 1H), 7.99 (d, 1H, ^3J = 8.1 Hz), 8.34 (d, 1H, ^3J = 8.3 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 32.1, 112.9, 114.5, 121.1, 121.6, 123.0, 124.5, 126.2, 126.2, 126.7, 128.5, 129.4, 129.6, 131.0, 143.1, 150.8, 153.7, 169.5. **HRMS** (ESI): *m/z* calcd for $C_{20}H_{14}O_3$ $[M+H]^+$: 303.1014, found: 303.1014. **TLC**: R_f = 0.57 (hexane/ethyl acetate = 3:1).

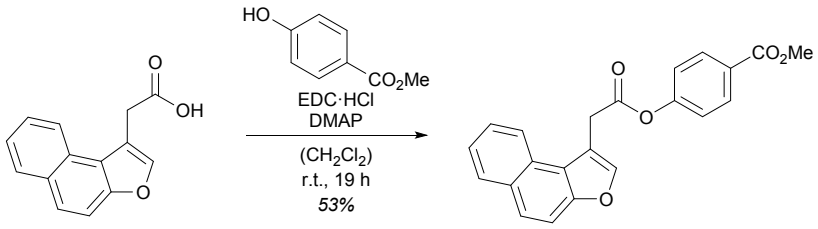
4-Methoxyphenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG29)



TG06 **TG29**

Following general procedure (I), acid **TG06** (30.0 mg, 133 µmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (1 mL) and EDC · HCl (38.3 mg, 0.20 mmol, 1.50 eq.), DMAP (8.19 mg, 67.0 µmol, 0.50 eq.) and 4-methoxyphenol (20.0 mg, 160 µmol, 1.20 eq.) were added. The reaction mixture was stirred under argon atmosphere at room temperature for 15 h. Afterwards, the mixture was diluted with CH_2Cl_2 (2 mL), washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 140 mL, 4 cm, hexane/ethyl acetate = 3:1). Phenyl ester **TG29** (31.0 mg, 93.0 µmol, 70%) was isolated as a pale yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.77 (s, 3H), 4.32 (d, 2H, ^4J = 1.0 Hz), 6.85 (d, 2H, ^3J = 9.2 Hz), 6.97 (d, 2H, ^3J = 9.2 Hz), 7.51 (ddd, 1H, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.62 (ddd, 1H, ^3J = 8.3, 6.9 Hz, ^4J = 1.3 Hz), 7.67 (d, 1H, ^3J = 9.0 Hz), 7.76 (d, 1H, ^3J = 9.0 Hz), 7.85 (s, 1H), 7.98 (*br* d, 1H, ^3J = 8.1 Hz), 8.33 (d, 1H, ^3J = 8.4 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 32.1, 55.7, 112.9, 114.6, 114.6, 121.1, 122.3, 123.0, 124.5, 126.2, 126.7, 128.5, 129.4, 131.0, 143.1, 144.3, 153.6, 157.5, 169.9. **HRMS** (ESI): *m/z* calcd for $C_{21}H_{16}O_4$ $[M+H]^+$: 333.1119, found: 333.1120. **TLC**: R_f = 0.44 (hexane/ethyl acetate = 3:1).

Methyl 4-(2-(naphtho[2,1-*b*]furan-1-yl)acetoxy)benzoate (TG30)

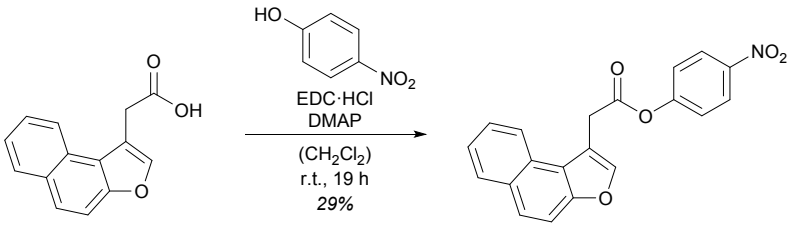


TG06 **TG30**

According to general procedure (I), acid **TG06** (30.0 mg, 133 µmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (1 mL). EDC · HCl (38.3 mg, 0.20 mmol, 1.50 eq.), DMAP (8.19 mg, 67.0 µmol, 0.50 eq.) and methyl 4-hydroxybenzoate (24.3 mg, 160 µmol, 1.20 eq.) were added and the mixture was stirred under argon atmosphere at room temperature for 19 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (2 mL), washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. Purification of the crude product by column chromatography (SiO_2, 130 mL, 4 cm, hexane/ethyl acetates = 3:1) gave phenyl ester **TG30** (25.4 mg, 70.0 µmol, 53%) as a white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.90 (s, 3H), 4.36 (d, 2H, ^4J = 0.9 Hz), 7.14 (d, 2H, ^3J = 8.9 Hz), 7.52 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.62 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.3 Hz), 7.68 (d, 1H, ^3J = 9.0 Hz),

7.77 (d, 1H, ^3J = 9.0 Hz), 7.86 (s, 1H), 7.99 (*br* d, 1H, ^3J = 8.2 Hz), 8.04 (d, 2H, ^3J = 8.9 Hz), 8.31 (br s, 1H, ^3J = 8.3 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 32.1, 52.4, 112.9, 114.2, 121.0, 121.6, 122.9, 124.6, 126.3, 126.8, 128.1, 128.4, 129.5, 131.0, 131.3, 143.1, 153.7, 154.3, 166.4, 169.0. **HRMS** (ESI): *m/z* calcd for $C_{22}H_{16}O_5$ $[M+H]^+$: 361.1071, found: 361.1071. **TLC**: R_f = 0.45 (hexane/ethyl acetate = 3:1).

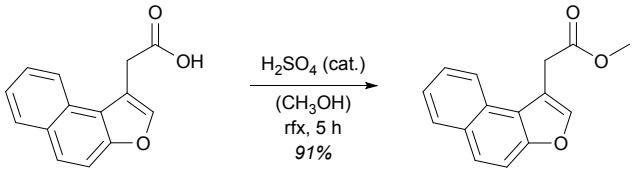
4-Nitrophenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG31)



TG06 **TG31**

Following general procedure (I), acid **TG06** (30.0 mg, 133 µmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (1 mL). Addition of EDC · HCl (38.3 mg, 0.20 mmol, 1.50 eq.), DMAP (8.19 mg, 67.0 µmol, 0.50 eq.) and 4-nitrophenol (22.3 mg, 160 µmol, 1.20 eq.) gave a clear solution which was stirred under argon atmosphere at room temperature for 19 h. After this time the reaction mixture was diluted with CH_2Cl_2 (2 mL), washed with saturated aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. After purification by column chromatography (SiO_2, 130 mL, 4 cm, hexane/ethyl acetate = 3:1), phenyl ester **TG31** (13.3 mg, 38.0 µmol, 29%) was isolated as yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 4.38 (d, 2H, ^4J = 0.9 Hz), 7.24 (d, 2H, ^3J = 9.2 Hz), 7.53 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.63 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.4 Hz), 7.69 (d, 1H, ^3J = 9.0 Hz), 7.79 (d, 1H, ^3J = 9.0 Hz), 7.86 (s, 1H), 8.00 (*br* d, 1H, ^3J = 8.1 Hz), 8.24 (d, 2H, ^3J = 9.2 Hz), 8.29 (*br* d, 1H, ^3J = 8.4 Hz). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K): δ (ppm) = 32.1, 113.0, 113.9, 120.8, 122.5, 122.7, 124.7, 125.4, 126.4, 126.8, 128.3, 129.6, 131.0, 143.2, 145.6, 153.7, 155.4, 168.7. **HRMS** (APCI): *m/z* calcd for $C_{20}H_{13}NO_5$ $[M+H]^+$: 348.0866, found: 348.0867. **TLC**: R_f = 0.44 (hexane/ethyl acetate = 3:1).

Methyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG36)

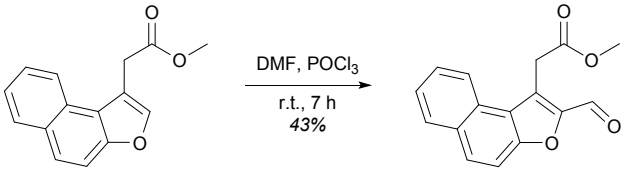


TG06 **TG36**

CH_3OH (5 mL) was cooled to 0 °C and concentrated H_2SO_4 (1.25 mL) was added dropwise. To the resulting clear solution was added acid **TG06** (1.00 g, 4.42 mmol, 1.00 eq.) and the mixture was heated under reflux for 5 h. After cooling to room temperature the mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (2 · 40 mL). The organic layer was washed with aqueous $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. After removing the solvent under reduced pressure methyl ester **TG36** (0.97 g, 4.02 mmol, 91%) was obtained as a brownish oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) =

3.75 (s, 3H), 4.09 (d, 2H, ^4J = 0.9 Hz), 7.49 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.59 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.4 Hz), 7.65 (d, 1H, ^3J = 8.9 Hz), 7.74 (d, 1H, ^3J = 9.0 Hz), 7.76 (s, 1H), 7.96 (*br* d, 1H, ^3J = 8.1 Hz), 8.21 (*br* d, 1H, ^3J = 8.4 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 31.8, 52.5, 112.8, 114.9, 121.2, 123.0, 124.4, 126.0, 126.6, 128.5, 129.3, 130.9, 142.9, 153.6, 171.4. **HRMS** (APCI): *m/z* calcd for $C_{15}H_{12}O_3$ $[M+H]^+$: 241.0859, found: 241.0860. **TLC**: R_f = 0.29 (hexane/ethyl acetate = 10:1).

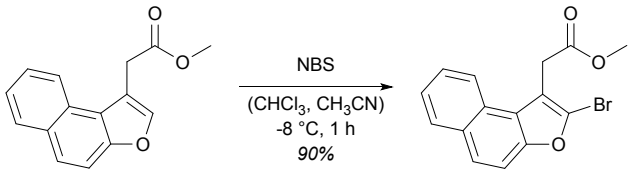
Methyl 2-(2-formylnaphtho[2,1-*b*]furan-1-yl)acetate (TG37)



TG36 **TG37**

In a 10 mL round bottom flask compound **TG36** (150 mg, 0.62 mmol, 1.00 eq.) was dissolved in dry DMF (1.11 mL) and cooled to 0 °C. After addition of phosphoryl trichloride (0.55 g, 3.60 mmol, 5.80 eq.) the reaction mixture was allowed to warm to room temperature and stirred for 7 h. The solution was then diluted with DMF (2.5 mL) and poured onto a mixture of saturated sodium acetate solution and ice water. After 30 min the mixture was extracted with ethyl acetate (3 · 15 mL), the organic layer was washed with water and brine and dried over Na_2SO_4. The organic solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 230 mL, hexane/ethyl acetate = 5:1). Product **TG37** (72.1 mg, 0.27 mmol, 43%) was isolated as an orange solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.73 (s, 3H), 4.57 (s, 2H), 7.57 (ddd, 1H, ^3J = 8.1, 7.1 Hz, ^4J = 1.2 Hz), 7.65 – 7.70 (m, 2H), 7.95 (d, 1H, ^3J = 9.1 Hz), 7.99 (*br* d, 1H, ^3J = 8.1 Hz), 8.24 (*br* d, 1H, ^3J = 8.2 Hz), 10.1 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 31.1, 52.8, 113.0, 122.1, 123.1, 124.3, 125.7, 128.0, 129.0, 129.9, 131.3, 131.6, 148.8, 154.8, 170.1, 180.7. **HRMS** (APCI): *m/z* calcd for $C_{16}H_{12}O_4$ $[M+H]^+$: 269.0808, found: 269.0809. **TLC**: R_f = 0.25 (hexane/ethyl acetate = 5:1).

Methyl 2-(2-bromonaphtho[2,1-*b*]furan-1-yl)acetate (TG38)

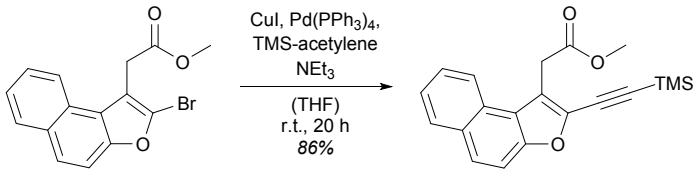


TG36 **TG38**

In a 25 mL round bottom flask methyl ester **TG36** (440 mg, 1.85 mmol, 1.00 eq.) was dissolved in $CHCl_3$ (8 mL) and cooled to **–** 8 °C. In another round bottom flask *N*-bromosuccinimide (360 mg, 2.02 mmol, 1.09 eq.) was dissolved in CH_3CN (8 mL) and was added dropwise to the stirring solution of **TG36** in $CHCl_3$. After 1 h at – 8 °C the reaction mixture was allowed to warm to room temperature and was then diluted with water (30 mL). This mixture was extracted with $CHCl_3$ (2 · 20 mL), the resulting organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography (SiO_2, 180 mL, 4 cm, hexane/ethyl acetate

= 10:1) gave compound **TG38** (0.53 g, 1.65 mmol, 90%) as a pale brown solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 3.72 (s, 3H), 4.04 (s, 2H), 7.50 (ddd, 1H, ^3J = 8.2, 6.9 Hz, ^4J = 1.2 Hz), 7.59 (*virt.* td, 1H, ^3J = 7.4, 7.0 Hz, ^4J = 1.5 Hz), 7.61 (d, 1H, ^3J = 8.9 Hz), 7.72 (d, 1H, ^3J = 9.0 Hz), 7.94 (*br* d, 1H, ^3J = 8.1 Hz), 8.15 (*br* d, 1H, ^3J = 8.4 Hz). **^{13}C-NMR** ($CDCl_3$, 75 MHz, 300 K): δ (ppm) = 32.45, 52.62, 77.16, 112.05, 114.59, 122.08, 122.81, 124.89, 126.04, 126.94, 127.43, 127.78, 129.32, 130.98, 153.50, 170.59. **HRMS** (APCI): *m/z* calcd for $C_{15}H_{11}BrO_3$ $[M+H]^+$: 318.9964, found: 318.9966. **TLC**: R_f = 0.37 (hexane/ethyl acetate = 10:1).

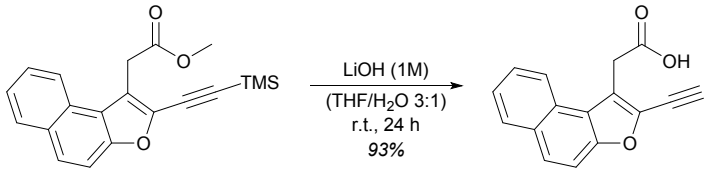
Methyl 2-(2-((trimethylsilyl)ethynyl)naphtho[2,1 *b*] furan-1-yl)acetate (TG40)



TG38 **TG40**

In a 50 mL Schlenk tube compound **TG38** (1.50 g, 4.70 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (66.0 mg, 94.0 µmol, 0.018 eq.) and CuI (36.0 mg, 189 µmol, 0.27 eq.) were dissolved in dry THF (5 mL). Then, the resulting yellow solution was degassed by repeated freeze-pump-thaw cycles. Ethynyltrimethylsilane (951 mg, 9.40 mmol, 2.00 eq.) and triethylamine (508 mg, 5.17 mmol, 1.10 eq.) were added and the mixture was stirred at room temperature for 20 h. Afterwards, the reaction was diluted with EtOAc (25 mL) and subsequently washed with water and brine (20 mL each). The organic layer was dried over Na_2SO_4 and the residual solvent was removed by evaporation under reduced pressure. The resulting sticky brownish oil was purified by flash chromatography (SiO_2, 280 mL, 4 cm, hexane/ethyl acetate = 20:1) yielding compound **TG40** (1.36 g, 4.05 mmol, 86%) as brown solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 0.32 (s, 9H), 3.72 (s, 3H), 4.15 (s, 2H), 7.49 (ddd, 1H ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz,), 7.58 (d, 1H ^3J = 9.0 Hz,), 7.62 – 7.56 (m, 1H), 7.78 (d, 1H ^3J = 9.0 Hz,), 7.94 (d, 1H ^3J = 8.1 Hz,), 8.13 (d, 1H ^3J = 8.2 Hz,). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 298 K): δ (ppm) = -0.09, 32.35, 52.55, 93.26, 105.37, 112.51, 120.28, 121.29, 122.99, 124.85, 127.02, 127.77, 128.11, 129.36, 131.09, 137.41, 152.75, 170.90. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{20}O_3Si$ $[M+H]^+$: 337.1255, found: 337.1256. **TLC**: R_f = 0.45 (hexane/ethyl acetate = 10:1).

2-(2-Ethynylnaphtho[2,1-*b*]furan-1-yl)acetic acid (TG41)

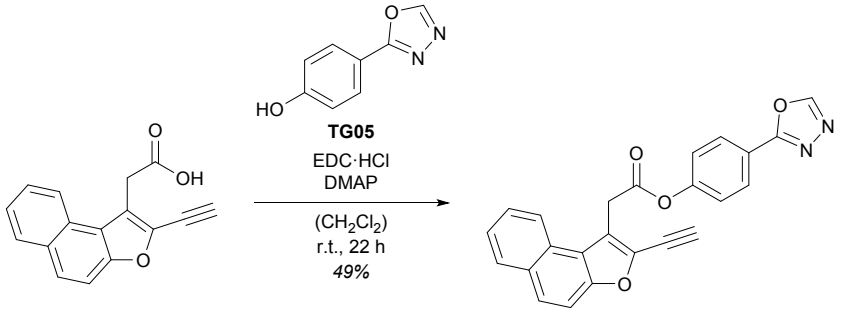


TG40 **TG41**

In a round bottom flask compound **TG40** (1.36 g, 4.05 mmol, 1.00 eq.) was dissolved in THF (24 mL). $LiOH_{aq}$ (4.86 mL, 1 M, 4.86 mmol) and water (7.1 mL) were added and the resulting solution was stirred at room temperature for 24 h. The organic solvent was removed under reduced pressure and the remaining residue was acidified with 1 M HCl_{aq}. The resulting suspension was extracted with EtOAc

(3 · 20 mL), the organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Compound **TG41** (938 mg, 3.75 mmol, 93%) was isolated as brown solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K) δ (ppm) = 4.10 (s, 2H), 5.13 (s, 1H), 7.56 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.66 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.4 Hz), 7.78 (d, 1H, ^3J = 9.0 Hz), 7.96 (d, 1H, ^3J = 9.0 Hz), 8.08 (d, 1H, ^3J = 7.9 Hz), 8.19 (d, 1H, ^3J = 8.4 Hz), 12.83 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 300 K) δ (ppm) = 31.50, 72.75, 90.49, 112.26, 120.68, 121.64, 122.99, 124.96, 126.99, 127.35, 127.83, 129.09, 130.49, 135.75, 151.90, 171.18. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{10}O_3$ $[M-H]^-$: 249.0557, found: 249.0564. **TLC**: R_f = 0.11 (hexane/ethyl acetate = 5:1 + 2 drops AcOH).

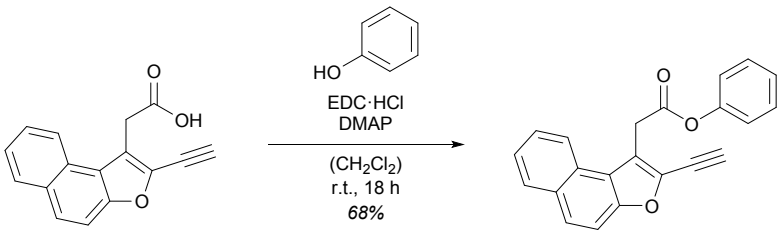
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG42)



TG41 **TG42**

Following general procedure (I), acid **TG41** (100 mg, 400 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (2 mL) and EDC · HCl (115 mg, 600 µmol, 1.50 eq.), DMAP (24.9 mg, 200 µmol, 0.50 eq.) and 4-(1,3,4-oxadiazol-2-yl)phenol (77.8 mg, 480 µmol, 1.20 eq.) were added. The resulting mixture was stirred at room temperature under argon atmosphere for 18 h and afterwards diluted with CH_2Cl_2 (2 mL). The organic phase was extracted with saturated $NaHCO_3$ solution, water and brine (10 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2, 250 mL, 4 cm, hexane/ethyl acetate = 2:1). Phenyl ester **TG42** (77.5 mg, 197 µmol, 49%) was isolated as pale yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K): δ (ppm) = 3.78 (s, 1H), 4.44 (s, 2H), 7.21 (d, 2H, ^3J = 8.9 Hz), 7.55 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.63 (d, 1H, ^3J = 9.0 Hz), 7.66 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.3 Hz), 7.84 (d, 1H, ^3J = 9.0 Hz), 7.99 (*br* d, 1H, ^3J = 8.1 Hz), 8.06 (d, 2H, ^3J = 9.0 Hz), 8.29 (*br* d, 1H, ^3J = 8.2 Hz), 8.44 (s, 1H).**^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K): δ (ppm) = 32.5, 73.1, 87.0, 112.6, 120.1, 120.9, 121.4, 122.5, 122.7, 125.2, 127.3, 127.9, 128.2, 128.6, 129.6, 131.2, 136.9, 152.8, 153.0, 153.5, 168.3. **HRMS** (ESI): *m/z* calcd for $C_{24}H_{14}N_2O_4$ $[M+H]^+$: 395.1019, found: 395.1019. **TLC**: R_f = 0.25 (hexane/ethyl acetate = 2:1).

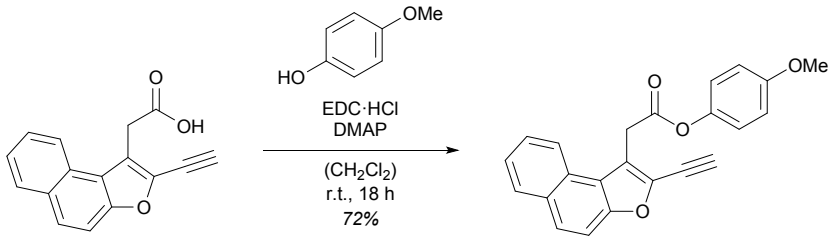
Phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG49)



TG41 **TG49**

According to general procedure (I), **TG41** (50.0 mg, 200 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (1 mL). Addition of EDC · HCl (57.5 mg, 300 µmol, 1.50eq.), DMAP (12.2 mg, 100 µmol, 0.50 eq.) and phenol (18.8 mg, 240 µmol, 1.20 eq.) gave a light brown solution which was stirred at room temperature under argon atmosphere for 18 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and washed saturated $NaHCO_3$ solution, water and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 250 mL, 4 cm, hexane/ethyl acetate = 10:1) gave **TG49** (44.7 mg, 137 µmol, 68%) as pale-brown solid. **^{1}H-NMR** ($CDCl_3$, 500 MHz, 298 K) δ (ppm) = 3.77 (s, 1H), 4.40 (s, 2H), 7.01 – 7.03 (m, 2H), 7.17 – 7.20 (m, 1H), 7.29 – 7.32 (m, 2H), 7.53 (ddd, 1H, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.62 (d, 1H, ^3J = 9.0 Hz), 7.65 (ddd, 1H, ^3J = 8.3, 7.0 Hz, 1.4 Hz), 7.82 (d, 1H, ^3J = 9.0 Hz), 7.97 (d, 1H, ^3J = 8.2 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 298 K) δ (ppm) = 32.50, 73.22, 76.84, 77.16, 77.36, 77.48, 86.84, 112.57, 120.59, 121.05, 121.53, 122.94, 125.06, 126.13, 127.21, 128.05, 128.10, 129.50, 129.53, 131.15, 136.81, 150.78, 153.01, 168.77. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{14}O_3$ $[M+H]^+$: 327.1016, found: 327.1015. **TLC**: R_f = 0.33 (hexane/ethyl acetate = 10:1).

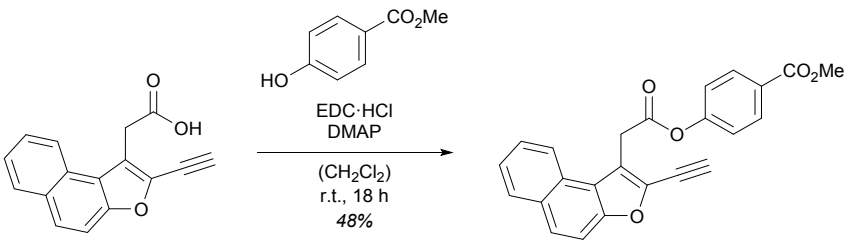
4-Methoxyphenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG50)



TG41 **TG50**

Following general procedure (I), **TG41** (50.0 mg, 200 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (1 mL). Addition of EDC · HCl (57.5 mg, 300 µmol, 1.50 eq.), DMAP (12.0 mg, 100 µmol, 0.50 eq.) and 4-methoxyphenol (29.8 mg, 240 µmol, 1.20 eq.) led to a clear brown solution which was stirred at room temperature under argon atmosphere for 18 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and extracted with saturated $NaHCO_3$ solution, water and brine (10 mL). After drying over Na_2SO_4 the organic solvent was evaporated under reduced pressure. Purification by column chromatography (SiO_2, 250 mL, 4 cm, hexane/ethyl acetate = 10:1) yielded **TG50** (51.3 mg, 144 µmol, 72%) as pale brown solid. **^{1}H-NMR** ($CDCl_3$, 500 MHz, 298 K) δ (ppm) = 3.78 (s, 3H), 3.79 (s, 1H), 4.40 (s, 2H), 6.86 – 6.82 (m, 2H), 6.97 – 6.94 (m, 2H), 7.55 (ddd, 1H, ^3J = 8.2, 6.9 Hz, ^4J = 1.2 Hz), 7.64 (d, 1H, ^3J = 8.9 Hz), 7.66 (ddd, 1H, ^3J = 8.4, 6.9 Hz, ^4J = 1.4 Hz), 7.84 (d, 1H, ^3J = 9.0 Hz), 7.99 (dd, 1H, ^3J = 8.1 Hz, ^4J =1.5 Hz), 8.32 (dd, 1H, ^3J = 8.4 Hz, ^3J = 1.0 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K) δ (ppm) = 32.44, 55.71, 73.23, 86.81, 112.57, 114.54, 120.67, 121.07, 122.28, 122.96, 125.04, 127.19, 128.05, 128.08, 129.49, 131.14, 136.77, 144.29, 153.00, 157.49, 169.14. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{16}O_4$ $[M+H]^+$: 357.1121, found: 357.1121. **TLC**: R_f = 0.22 (hexane/ethyl acetate = 10:1).

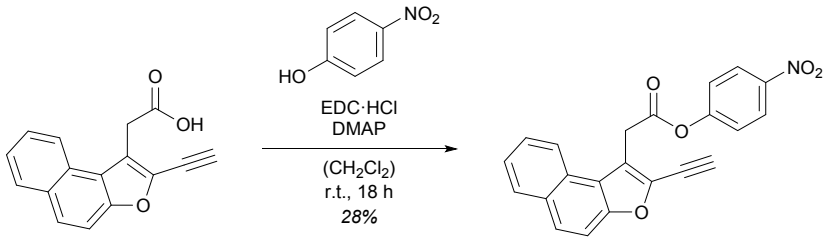
Methyl 4-(2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetoxy)benzoate (TG51)



TG41 **TG51**

Following general procedure (I), **TG41** (50.0 mg, 200 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (1 mL). After addition of EDC · HCl (57.5 mg, 300 µmol, 1.50 eq.), DMAP (12.2 mg, 100 µmol, 0.50 eq.) and Methyl-4-hydroxybenzoate (36.5 mg, 240 µmol, 1.20 eq.) the mixture was stirred at room temperature under argon atmosphere for 18 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and extracted with saturated $NaHCO_3$ solution, water and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. **TG51** (37.2 mg, 96.8 µmol, 48%) was isolated after column chromatography (SiO_2, 250 mL, 4 cm, hexane/ethyl acetate = 9:1) as off-white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 3.77 (s, 1H), 3.89 (s, 3H), 4.42 (s, 2H), 7.07 – 7.14 (m, 2H), 7.54 (ddd, 1H, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.63, d, 1H, ^3J = 8.9 Hz), 7.64 (ddd, 1H, ^3J = 8.3, 6.9 Hz, ^4J = 1.3 Hz), 7.83 (d, 1H, ^3J = 9.0 Hz), 7.98 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.2 Hz), 7.97 – 8.04 (m, 2H), 8.28 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.1 Hz). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K) δ (ppm) = 32.49, 52.37, 73.10, 86.98, 112.59, 120.19, 120.90, 121.58, 122.75, 125.13, 127.26, 127.93, 128.03, 128.19, 129.59, 131.14, 131.27, 136.83, 153.01, 154.27, 166.34, 168.29. **HRMS** (ESI) *m/z* calcd for $C_{24}H_{16}O_5$ $[M+H]^+$: 385.1071, found: 385.1070. **TLC**: R_f = 0.16 (hexane/ethyl acetate = 9:1).

4-Nitrophenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG52)

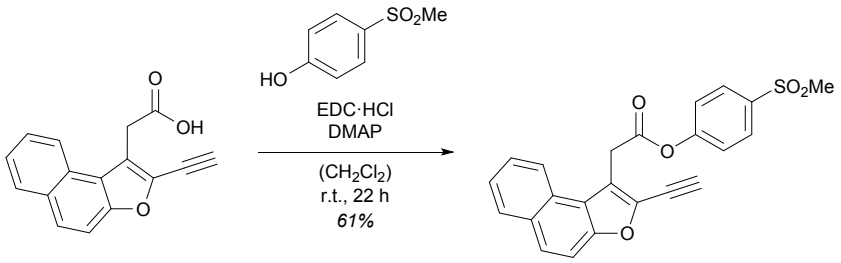


TG41 **TG52**

Following general procedure (I), **TG41** (50.0 mg, 200 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (1 mL) and EDC · HCl (57.5 mg, 300 µmol, 1.50 eq.), DMAP (12.2 mg, 100 µmol, 0.50 eq.) and 4-nitrophenol (33.4 mg, 240 µmol, 1.20 eq.) were added. The resulting mixture was stirred at room temperature under argon atmosphere for 18 h. After this time, CH_2Cl_2 (1 mL) was added and the organic phase was extracted with saturated $NaHCO_3$ solution, water and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 250 mL, 4 cm, hexane/ethyl acetate = 17:3) yielded **TG52** (21.0 mg, 56.6 µmol, 28%) as pale yellow solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 3.79 (s, 1H), 4.45 (s, 2H), 7.16 – 7.25 (m, 2H), 7.55 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.64 (d, 1H, ^3J = 8.9 Hz), 7.62 – 7.69 (m, 1H), 7.84 (d, 1H, ^3J = 9.0 Hz), 7.99 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.2 Hz), 8.17 – 8.25 (m, 2H), 8.25 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.1 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K) δ (ppm) = 32.35, 72.87, 86.97, 112.50, 119.66, 120.64,

122.34, 122.43, 125.07, 125.20, 127.17, 127.72, 128.17, 129.56, 131.04, 135.27, 136.76, 152.91, 155.18, 167.79. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{13}NO_5$ [M-H]$^-$: 370.0721, found: 370.0721. **TLC**: R_f = 0.33 (hexane/ethyl acetate = 17:3).

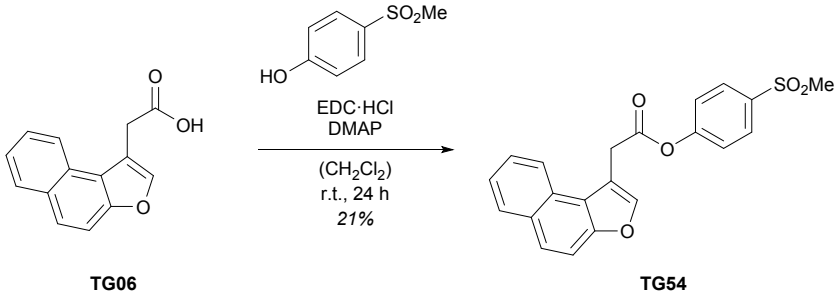
4-(Methylsulfonyl)phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG53)



TG41 **TG53**

Following general procedure (I), acid **TG41** (102 mg, 408 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (5 mL), EDC · HCl (117 mg, 612 µmol, 1.50 eq.), DMAP (24.9 mg, 204 µmol, 0.50 eq.) and 4-(methylsulfonyl)phenol (84.4 mg, 490 µmol, 1.20 eq.) were added and the resulting brown solution was stirred at room temperature under argon atmosphere for 22 h. Afterwards, CH_2Cl_2 (10 mL) was added and the organic phase was washed with saturated $NaHCO_3$ solution, water and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography yielded **TG53** (101 mg, 250 µmol, 61%) as brown solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 3.01 (s, 3H), 3.78 (s, 1H), 4.44 (s, 2H), 7.22 – 7.26 (m, 2H), 7.54 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.64 (d, 1H, ^3J = 9.0 Hz), 7.60 – 7.69 (m, 1H), 7.84 (d, 1H, ^3J = 9.0 Hz), 7.89 – 7.93 (m, 2H), 8.26 (ddd, 1H, ^3J = 8.4 Hz, ^4J = 1.9, 0.7 Hz). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K) δ (ppm) = 32.47, 44.77, 73.02, 87.09, 112.63, 119.87, 120.79, 122.60, 122.70, 125.18, 127.28, 127.86, 128.28, 129.34, 129.68, 131.16, 136.87, 138.17, 153.04, 154.65, 168.14. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{16}SO_5$ [M+H]$^+$: 405.0791, found: 405.0794. **TLC**: R_f = 0.49 (hexane/ethyl acetate = 1:1).

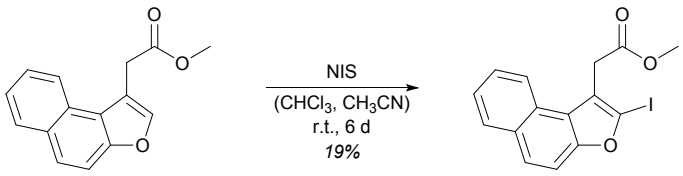
4-(Methylsulfonyl)phenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG54)



TG06 **TG54**

According to general procedure (I), **TG06** (100 mg, 442 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (3 mL) and EDC · HCl (127 mg, 663 µmol, 1.50 eq.), DMAP (27.0 mg, 221 mmol, 0.50 eq.) and 4-(methylsulfonyl) phenol (91.3 mg, 530 µmol, 1.20 eq.) were added. The resulting brown solution was stirred at room temperature under argon atmosphere for 24 h and then diluted with CH_2Cl_2 (10 mL). The organic phase was washed with saturated $NaHCO_3$ solution, water and brine (10 mL) and dried over Na_2SO_4. After evaporation of the organic solvent the crude product was purified by column chromatography (SiO_2, 220 mL, 4 cm, hexane/ethyl acetate = 3:1). Phenyl ester **TG54** (34.8 mg, 91.0 µmol, 21%) was isolated as yellow-brown solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 3.03 (s, 3H), 4.38 (d, 2H, ^4J = 1.0 Hz), 7.25 – 7.29 (m, 2H), 7.52 (ddd, 1H, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.62 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.4 Hz), 7.68 (d, 1H, ^3J = 9.0 Hz), 7.78 (d, 1H, ^3J = 9.0 Hz), 7.92 – 7.96 (m, 2H), 7.98 – 8.01 (m, 1H), 8.29 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.1 Hz). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K) δ (ppm) = 32.08, 44.78, 112.96, 113.92, 120.86, 122.70, 122.73, 124.65, 126.39, 126.78, 128.32, 129.40, 129.54, 130.99, 138.19, 143.17, 153.72, 154.69, 168.86. **HRMS** (ESI) *m/z* calcd for $C_{21}H_{16}SO_5$ $[M+H]^+$: 381.0791, found: 381.0788. **TLC**: R_f = 0.22 (hexane/ethyl acetate = 2:1).

Methyl 2-(2-iodonaphtho[2,1-*b*]furan-1-yl)acetate (TG67)

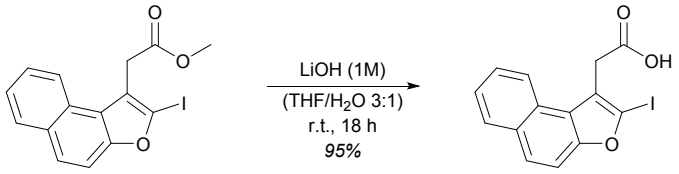


TG36 **TG67**

To a solution of ester **TG36** (314 mg, 1.31 mmol, 1.00 eq.) in 3 mL $CHCl_3$ a solution of *N*-iodosuccinimide (322 mg, 1.43 mmol, 1.10 eq.) in 3 mL CH_3CN was added under argon atmosphere at -10 °C. The solution was allowed to warm to room temperature and stirred for six days in the dark. Afterwards, the reaction mixture was diluted with 20 mL $CHCl_3$, extracted with saturated Na_2SO_3 solution and subsequently washed with water and brine (30 mL). The organic solvent was evaporated and the crude material was purified by flash chromatography (SiO_2, 200 mL, 3 cm, hexane/ethyl acetate = 20:1 → 15:1). **TG67** (91.2 mg, 0.25 mmol, 19%) was isolated as white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) =3.75 (s, 3H), 4.09 (d, 2H, ^4J = 1.0 Hz), 7.49 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.1 Hz), 7.59 (ddd, 1H, ^3J = 8.3, 7.0 Hz, ^4J = 1.3 Hz), 7.65 (d, 1H, ^3J = 8.9 Hz), 7.74 (d, 1H, ^3J = 9.0 Hz), 7.76 (s, 1H), 7.96 (d, 1H, ^3J = 8.3 Hz), 8.22 – 8.19 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K); 34.24, 52.65, 99.43, 112.16,

121.74, 122.03, 122.82, 124.84, 126.11, 126.98, 127.09, 129.25, 130.79, 156.77, 170.75. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{11}IO_3$ $[M+H]^+$: 366.9826, found: 366.9219. **TLC**: R_f = 0.28 (hexane/ethyl acetate = 10:1).

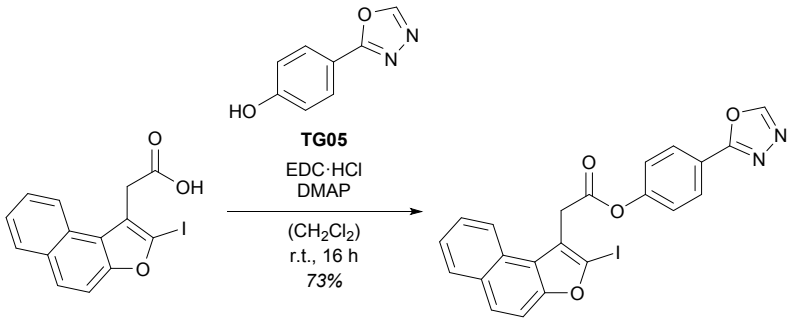
2-(2-Iodonaphtho[2,1-*b*]furan-1-yl)acetic acid (TG68)



TG67 **TG68**

To a solution of **TG67** (88.8 mg, 242 µmol, 1.00 eq.) in 1.6 mL dry THF were added 0.29 mL aqueous solution of LiOH (1 M, 291 µmol) and 0.52 mL water. The resulting mixture was stirred at room temperature for 18 h. Afterwards, the reaction mixture was concentrated and acidified with HCl_{aq} (1 M) extracted with EtOAc (2 · 10 mL) and the combined organic layers were washed with water and brine (30 mL) dried over Na_2SO_4 and concentrated under reduced pressure. **TG68** (81.3 mg, 231 µmol, 95%) was isolated as white solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K) δ (ppm) = 3.96 (s, 2H), 7.53 (ddd, 1H, ^3J = 8.1, 6.9 Hz, ^4J = 1.1 Hz), 7.63 (ddd, 1H, ^3J = 8.3, 7.0 Hz, 1.4 Hz), 7.79 (d, 1H, ^3J = 9.0 Hz), 7.82 (d, 1H, ^3J= 9.1 Hz), 8.05 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.3 Hz), 8.19 (d, 1H, ^3J = 8.3 Hz), 12.76 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 126 MHz, 300 K) δ (ppm) = 33.59, 103.37, 112.04, 121.42, 122.46, 122.94, 124.79, 125.71, 126.50, 126.76, 128.99, 130.29, 155.72, 171.45. **HRMS** (ESI) *m/z* calcd for $C_{14}H_9IO_3$ $[M-H]^-$: 350.9524, found: 350.9523. **TLC**: R_f = 0.07 (hexane/ethyl acetate = 3:1 + 2 drops AcOH).

4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-iodonaphtho[2,1-*b*]furan-1-yl)acetate (TG69)

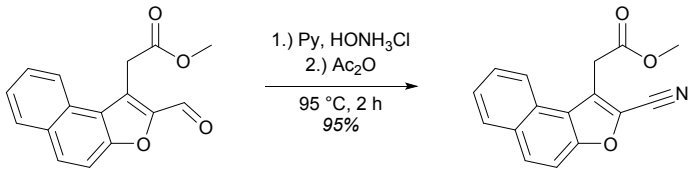


TG68 **TG69**

Following general procedure (I), acid **TG68** (51.4 mg, 146 µmol, 1.00 eq.) was dissolved in 2 mL dry CH_2Cl_2. EDC · HCl (42.0 mg, 219 µmol, 1.50 eq.), DMAP (8.91 mg, 73.0 µmol, 0.50 eq.) and phenol **TG05** (28.4 mg, 175 µmol, 1.20 eq.) were added and the resulting mixture was stirred at room temperature under argon atmosphere for 16 h. After this time 10 mL CH_2Cl_2 were added and the reaction mixture was washed with saturated $NaHCO_3$ solution water and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 110 mL, 2.5 cm, hexane/ethyl acetate = 2:1) yielded **TG69** (53.0 mg, 107 µmol, 73%) as white solid. **^{1}H-NMR** ($CDCl_3$, 400 Hz, 298 K) δ (ppm) = 4.30 (s, 2H), 7.19 – 7.23(m, 2H), 7.53 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.1 Hz), 7.62 – 7.68 (m, 1H), 7.66 (d,1H ^3J = 9.0 Hz), 7.72 (d, 1H, ^3J = 8.9 Hz), 7.96 –

7.99 (m, 1H), 8.03 – 8.07 (m, 2H), 8.30 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.0 Hz), 8.44 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K) δ (ppm) = 34.59, 99.85, 112.26, 121.35, 121.43, 121.58, 122.53, 122.60, 125.04, 126.37, 126.97, 127.14, 128.64, 129.50, 130.89, 152.79, 153.44, 156.92, 164.16, 168.32. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{14}IN_2O_4$ $[M+H]^+$: 496.9993, found: 496.9993. **TLC**: R_f = 0.35 (hexane/ethyl acetate = 1:1).

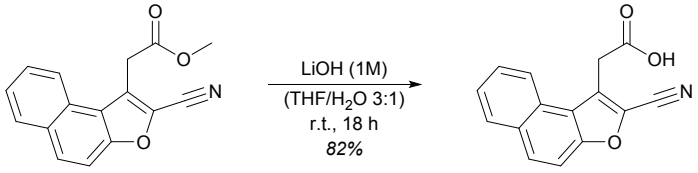
Methyl 2-(2-cyanonaphtho[2,1-*b*]furan-1-yl)acetate (TG76)



TG37 **TG76**

In a Schlenk tube, ester **TG37** (101 mg, 0.38 mmol, 1.00 eq.), hydroxylamine hydrochloride (53.4 mg, 753 µmol, 6.22 eq.) and pyridine (282 mg, 3.57 mmol, 9.47 eq.) were combined and heated to 90 °C. Acetic anhydride (239 mg, 2.34 mmol, 2.00 eq.) was slowly added and the reaction mixture was stirred for additional 2 h at 95 °C. After this time, the mixture was poured on ice water. The resulting precipitate was taken up in EtOAc, and the aqueous phase was extracted with EtOAc (3 · 10 mL). The combined organic layers were washed with water and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography gave **TG76** (94.6 mg, 366 µmol, 95%) as white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 3.75 (s, 3H), 4.22 (s, 2H), 7.58 (ddd, 1H, ^3J = 8.2, 7.0 Hz, ^4J = 1.2 Hz), 7.64 (d, 1H, ^3J = 9.1 Hz), 7.67 (ddd,1H, ^3J = 8.4, 7.1 Hz, ^4J = 1.4 Hz), 7.93 (dt, 1H, ^3J = 9.1 Hz, ^4J = 0.6 Hz), 7.99 (ddt, 1H, ^3J = 8.1 Hz, ^4J = 1.3, 0.6 Hz), 8.15 (ddd, 1H, ^3J = 8.3 Hz, ^4J = 1.3, 0.7 Hz). **^{13}C-NMR** ($CDCl_3$, 101 MHz, 300 K) δ (ppm) = 31.93, 52.95, 111.62, 112.52, 120.20, 122.82, 125.86, 126.37, 127.49, 128.00, 128.11, 129.68, 130.85, 131.24, 154.78, 169.24. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{11}NO_3$ $[M+H]^+$: 266.0812, found: 266.0767. **TLC**: R_f = 0.26 (hexane/ethyl acetate = 10:1).

2-(2-Cyanonaphtho[2,1-*b*]furan-1-yl)acetic acid (TG77)

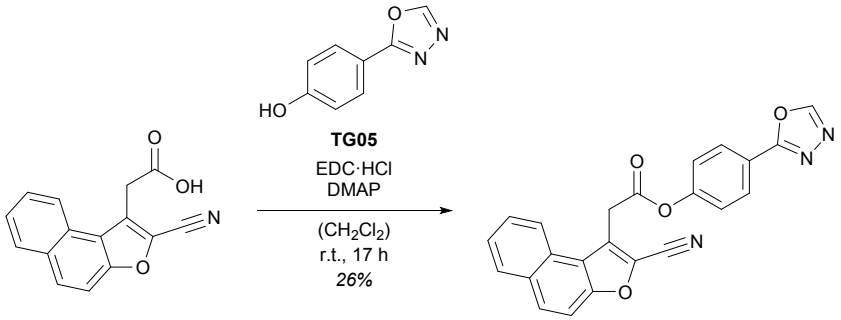


TG76 **TG77**

Methyl ester **TG76** (76.6 mg, 289 µmol, 1.00 eq.) was dissolved in dry THF (1.9 mL). $LiOH_{aq}$ (346 µL, 1 M, 0.35 mmol, 1.20 eq.) and water (0.6 mL) were added and the resulting mixture was stirred for 18 h at room temperature. Then, the mixture was diluted with EtOAc (5 mL), acidified with HCl_{aq} (1 M) and extracted with EtOAc (3 · 10 mL). The combined organic layers were washed with water and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. After column chromatography (SiO_2, 100 mL, 2.5 cm, hexane/ethyl acetate = 1:2 + 1% AcOH) compound **TG77** (59.3 mg, 236 µmol, 82%) was isolated as yellow-brown solid. **^{1}H-NMR** (DMSO-d_6, 400 MHz, 298 K) δ (ppm) = 4.26 (s, 2H),

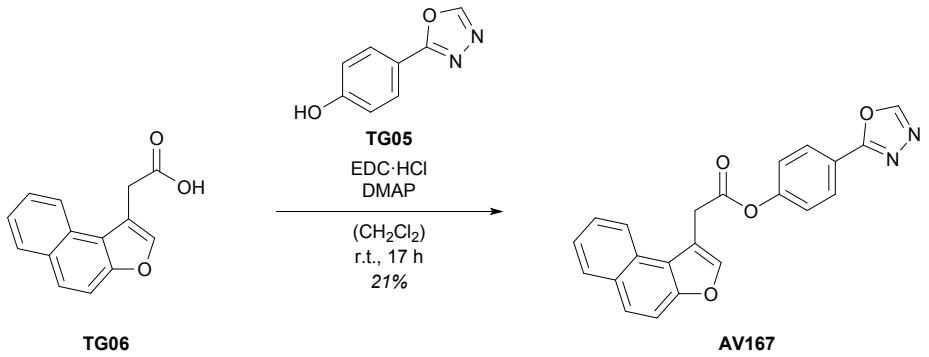
7.65 (ddd, 1H, ^3J = 8.0, 6.9 Hz, ^4J = 1.0 Hz), 7.75 (ddd, 1H, ^3J = 8.3, 7.1 Hz, ^4J = 1.3 Hz), 7.89 (d, 1H, ^3J = 9.1 Hz), 8.15 (d, 1H, ^3J = 8.5 Hz), 8.15 (d, 1H, ^3J = 9.3 Hz), 8.26 (d, 1H, ^3J = 8.2 Hz), 13.12 (s, 1H). **^{13}C-NMR** (DMSO-d_6, 101 MHz, 298 K) δ (ppm) = 31.44, 111.56, 112.47, 119.67, 123.03, 124.98, 125.83, 127.30, 127.92, 129.17, 129.40, 130.67, 130.94, 154.06, 170.15. **HRMS** (ESI) *m/z* calcd for $C_{15}H_9NO_3$ $[2M+H]^+$: 501.1092, found: 501.1090. **TLC**: R_f = 0.29 (hexane/ethyl acetate = 1:2 + 1% AcOH).

4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-cyanonaphtho[2,1-*b*]furan-1-yl)acetate (TG78)



According to general procedure (I), acid **TG77** (34.3 mg, 137 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (0.7 mL). Addition of EDC · HCl (41.8 mg, 218 µmol, 1.50 eq.), DMAP (8.75 mg, 71.6 µmol, 0.50 eq.) and phenol **TG05** gave a yellow solution, which was stirred at room temperature under argon atmosphere for 17 h. After this time, 10 mL CH_2Cl_2 were added, the organic phase was extracted with saturated $NaHCO_3$ solution, water and brine (10 mL) and dried over Na_2SO_4. The organic solvent was evaporated and the crude product was purified by column chromatography (SiO_2, 100 mL, 2.5 cm, hexane/ethyl acetate = 3:2). Compound **TG78** (14.3 mg, 36.2 µmol, 26%) was isolated as white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz, 298 K) δ (ppm) = 4.51 (s, 2H), 7.21 – 7.24 (m, 2H), 7.63 (ddd, 1H, ^3J = 8.2, 7.0 Hz, ^4J = 1.2 Hz), 7.68 (d, 1H, ^3J = 9.1 Hz), 7.73 (ddd, 1H, ^3J = 8.4, 7.0 Hz, ^4J = 1.4 Hz), 7.98 (dt, 1H, ^3J = 9.0 Hz, ^4J = 0.6 Hz), 8.03 (ddt, 1H, ^3J = 8.1 Hz, ^4J = 1.2, 0.6 Hz), 8.06 – 8.09 (m, 2H), 8.28 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.0 Hz), 8.45 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 126 MHz, 300 K) δ (ppm) = 32.22, 111.55, 112.65, 120.02, 121.73, 122.42, 122.57, 126.10, 126.56, 126.63, 127.82, 128.27, 128.74, 129.95, 131.13, 131.32, 152.82, 153.14, 154.92, 164.06, 166.92. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{13}N_3O_4$ $[M+H]^+$: 396.0979, found: 396.0977. **TLC**: R_f = 0.28 (hexane/ethyl acetate = 1:1).

4-(1,3,4-Oxadiazol-2-yl)phenyl-2-(naphtho[2,1-*b*]furan-1-yl)acetate (AV167)



Following general procedure (I), acid **TG06** (200 mg, 0.88 mmol, 1.00 eq.) was suspended in dry CH_2Cl_2 (5 mL). Addition of EDC · HCl (224 mg, 1.17 mmol, 1.32 eq.), DMAP (54.0 mg, 0.44 mmol, 0.50 eq.) and then phenol **TG05** (172 mg, 1.06 mmol, 1.20 eq.) gave a clear solution which was stirred at room temperature for 17 h. The mixture was diluted with CH_2Cl_2 (10 mL) and subsequently washed with saturated $NaHCO_3$ solution, water and brine. The organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Purification by column chromatography (SiO_2, 180 mL, 4 cm, hexane/ethyl acetate = 1:1) gave phenyl ester **AV167** (70.1 mg, 0.19 mmol, 21%) as a brown solid. **^{1}H-NMR** ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 4.37 (d, 2H, ^4J = 0.9 Hz), 7.21 – 7.26 (m, 2H), 7.52 (ddd, 1H, ^3J = 8.1, 7.0 Hz, ^4J = 1.2 Hz), 7.64 (ddd, 1H, ^3J = 8.4, 7.0 Hz, ^4J = 1.4 Hz), 7.68 (d, 1H, ^3J = 9.0 Hz), 7.78 (d, 1H, ^3J = 9.0 Hz), 7.86 (s, 1H), 8.00 (*br* d, 1H, ^3J = 8.1 Hz), 8.07 (d, 2H, ^3J = 8.9 Hz), 8.32 (*br* d, 1H, ^3J = 8.4 Hz), 8.44 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 32.1, 112.9, 114.1, 121.0, 121.5, 122.6, 122.8, 124.6, 126.3, 126.8, 128.4, 128.7, 129.5, 131.0, 143.1, 152.8, 153.5, 153.7, 169.0. **HRMS** (ESI): *m/z* calcd for $C_{22}H_{14}N_2O_4$ $[M+H]^+$: 371.1023, found: 371.1026. **TLC**: R_f = 0.46 (hexane/ethyl acetate = 1:1).

5. Supplementary References

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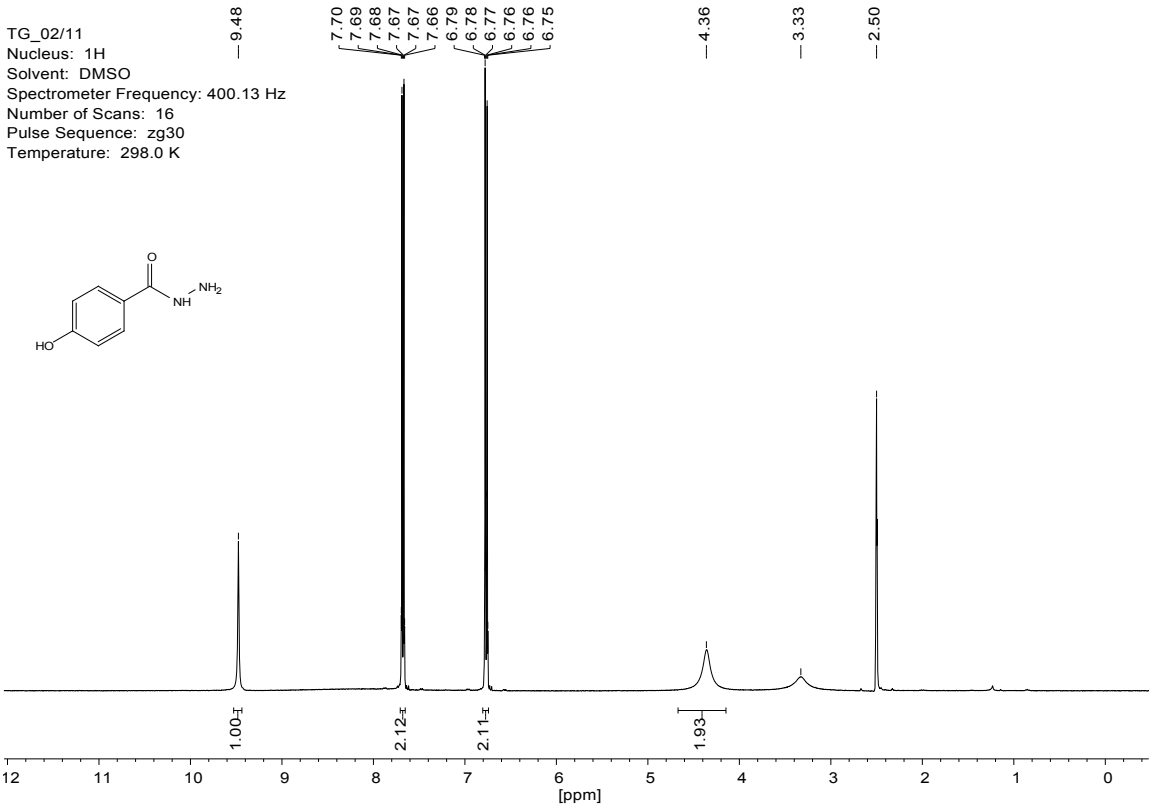
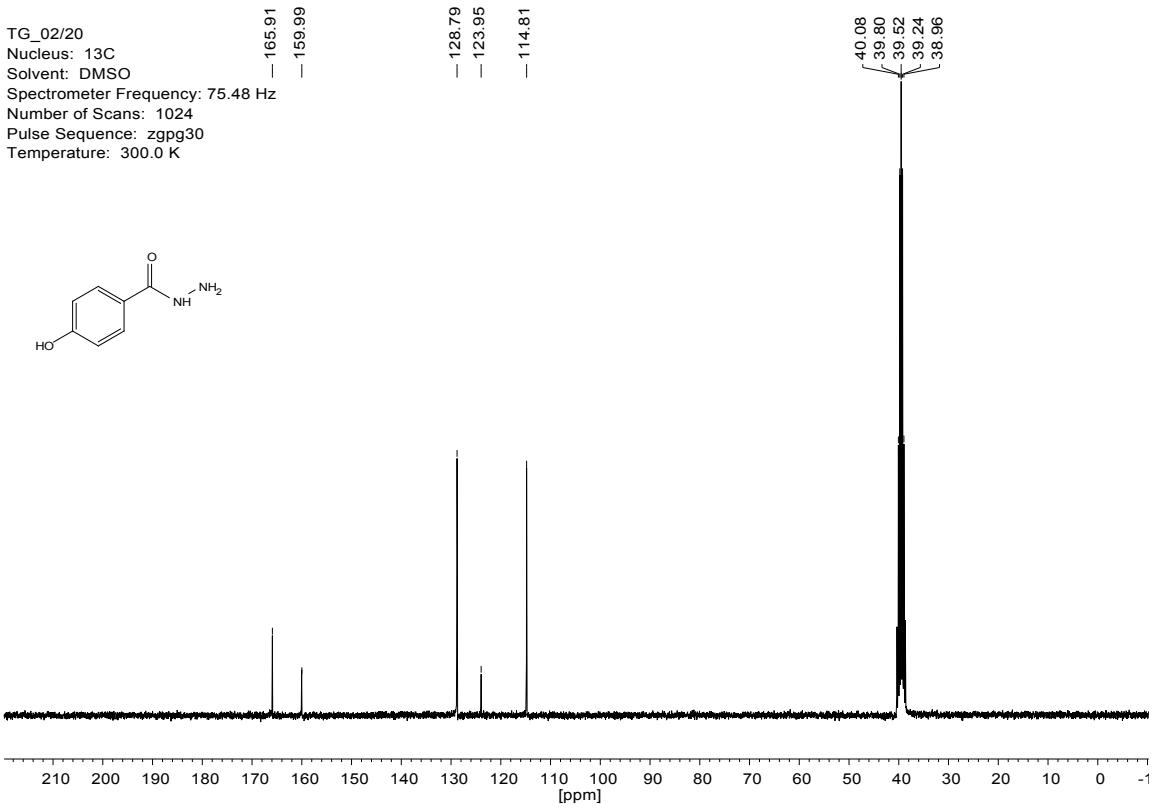
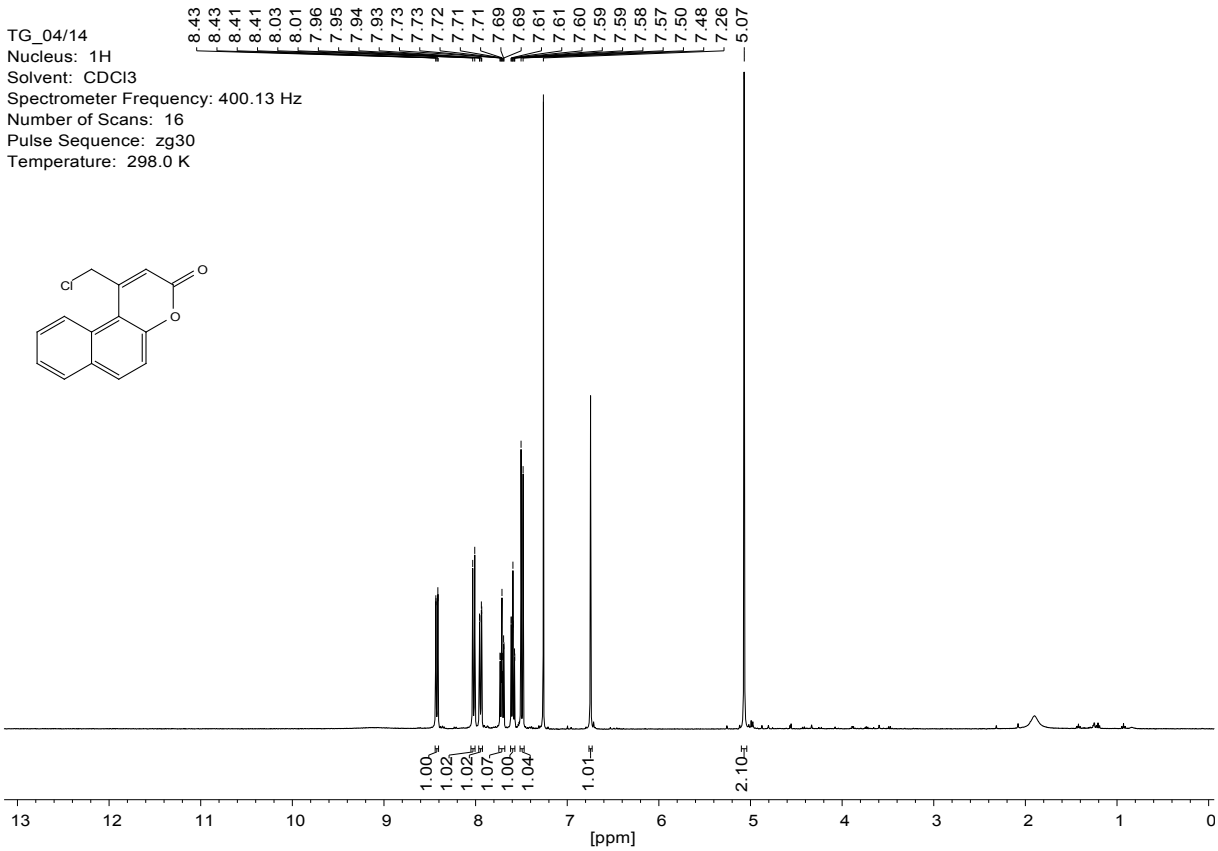
6. NMR spectra

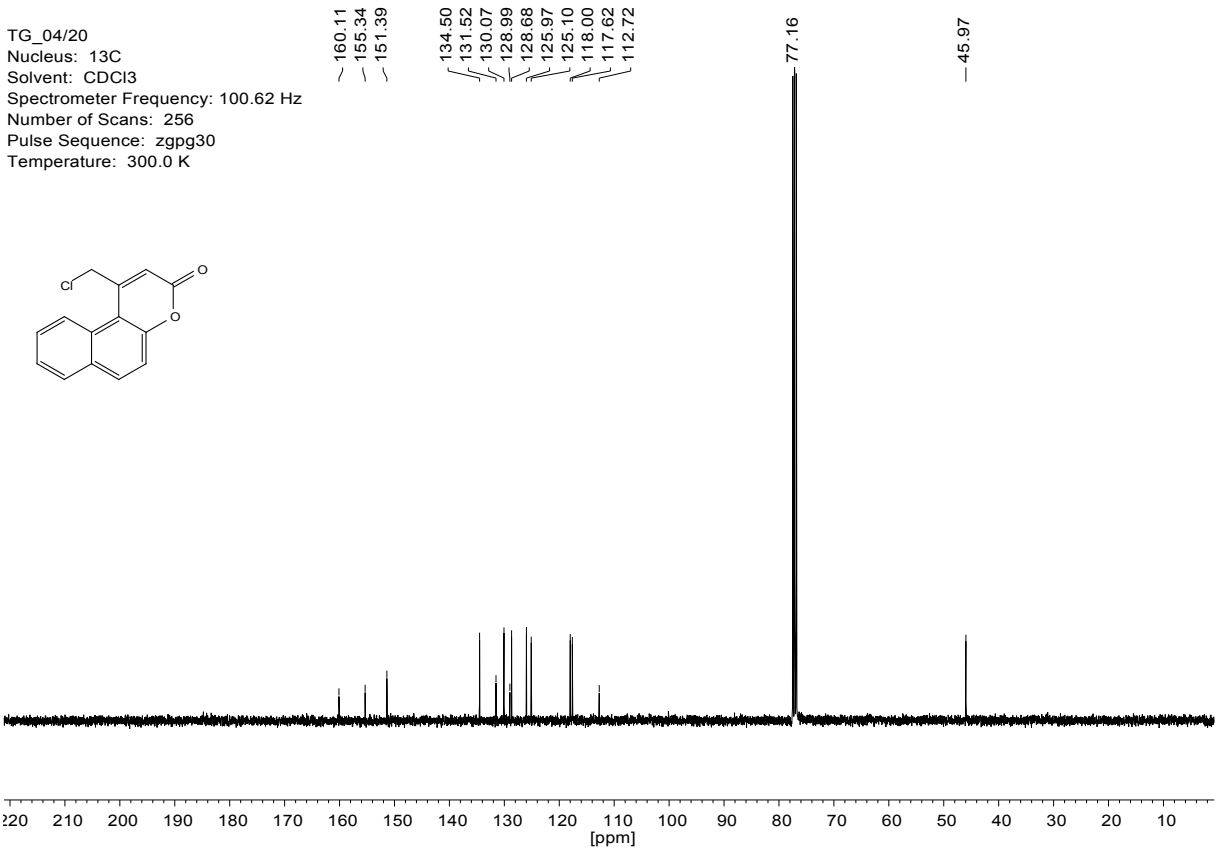
4-Hydroxybenzohydrazide (TG02)



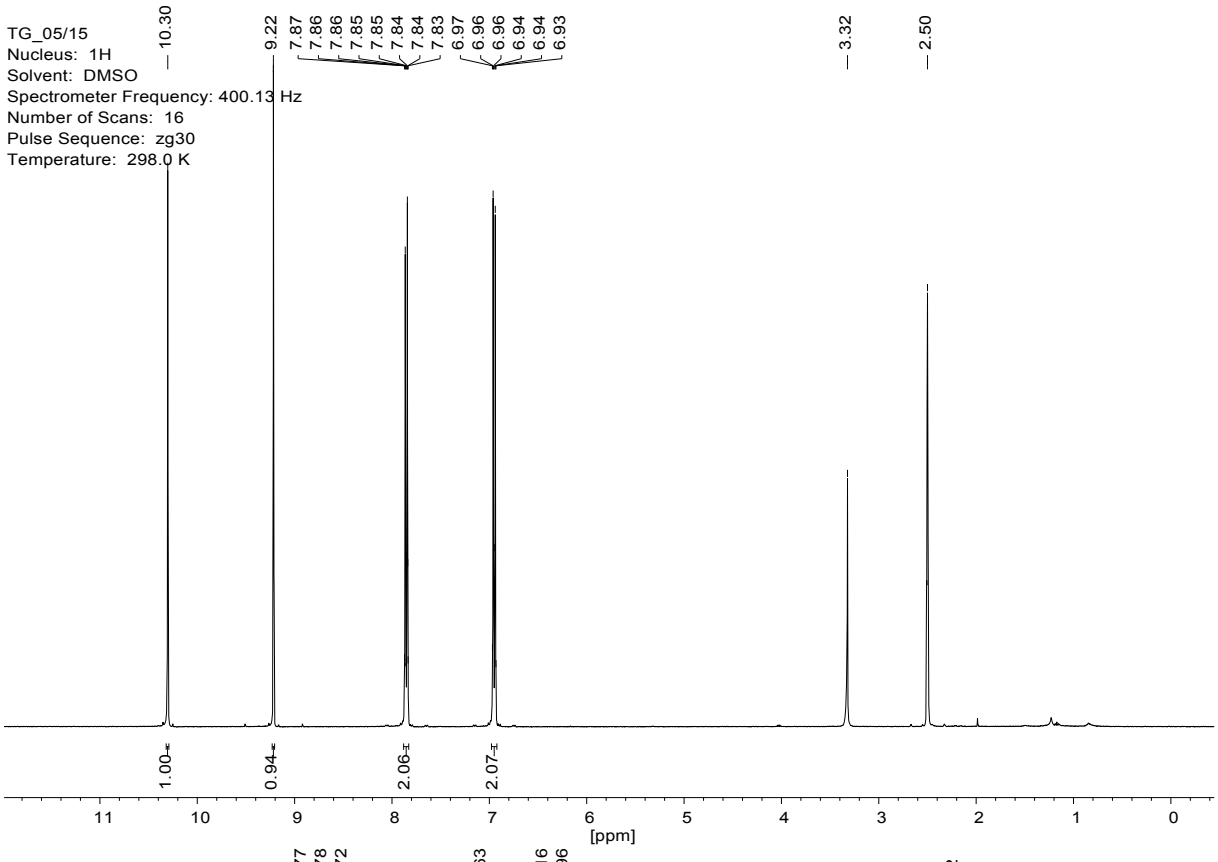


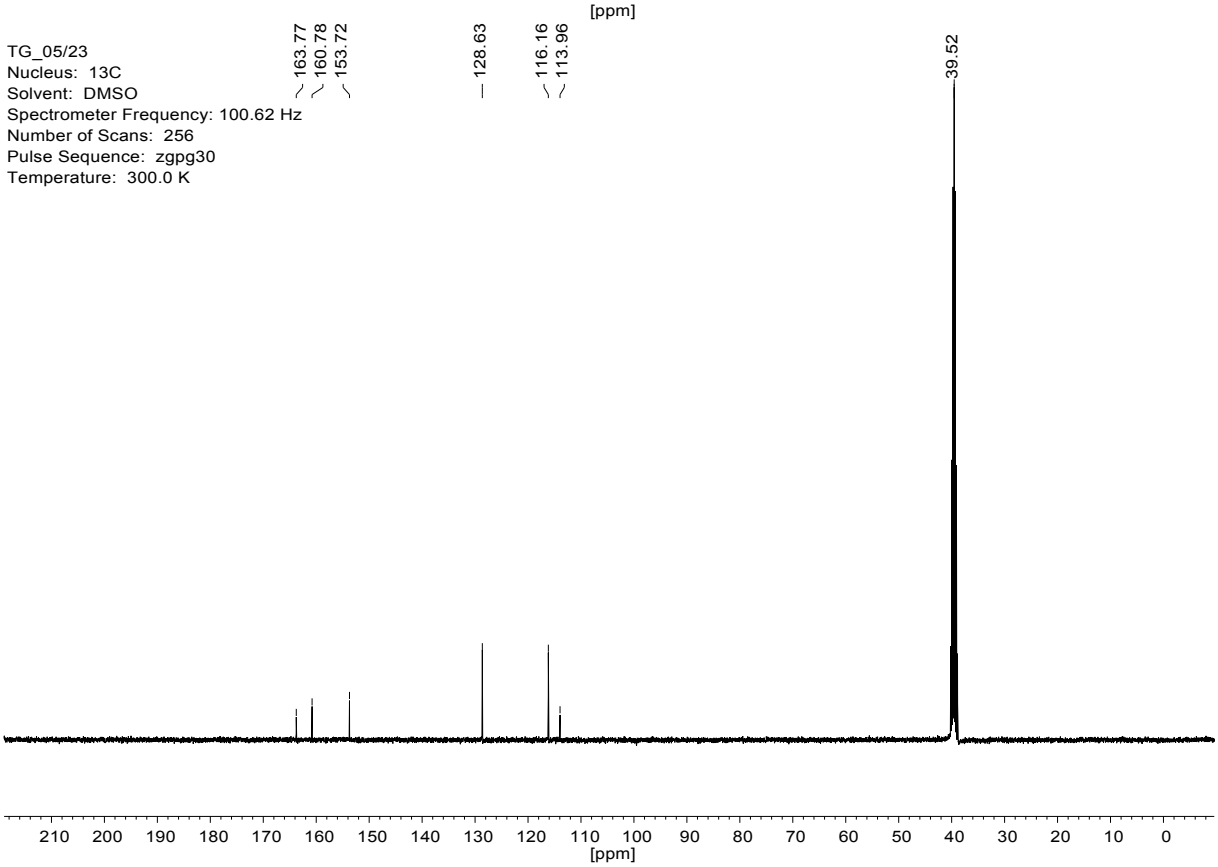
1-(Chloromethyl)-3*H*-benzo[*f*]chromen-3-one (TG04)



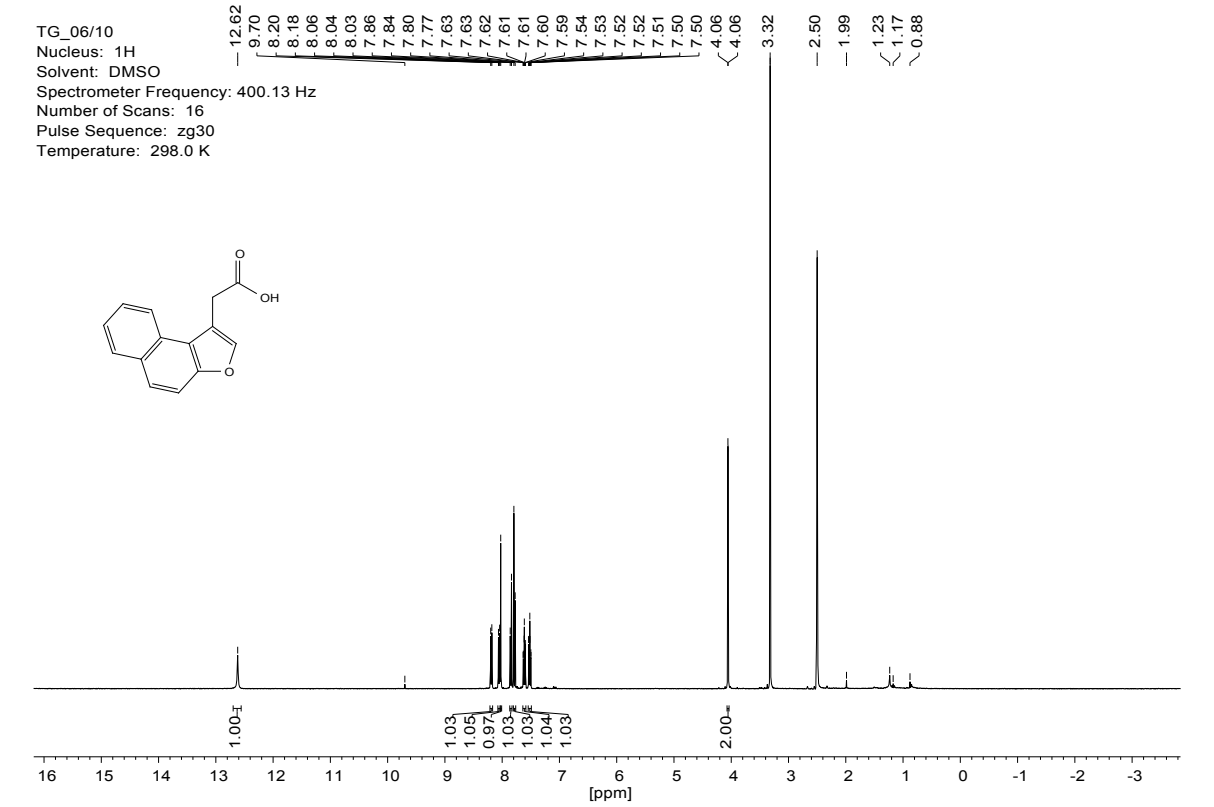


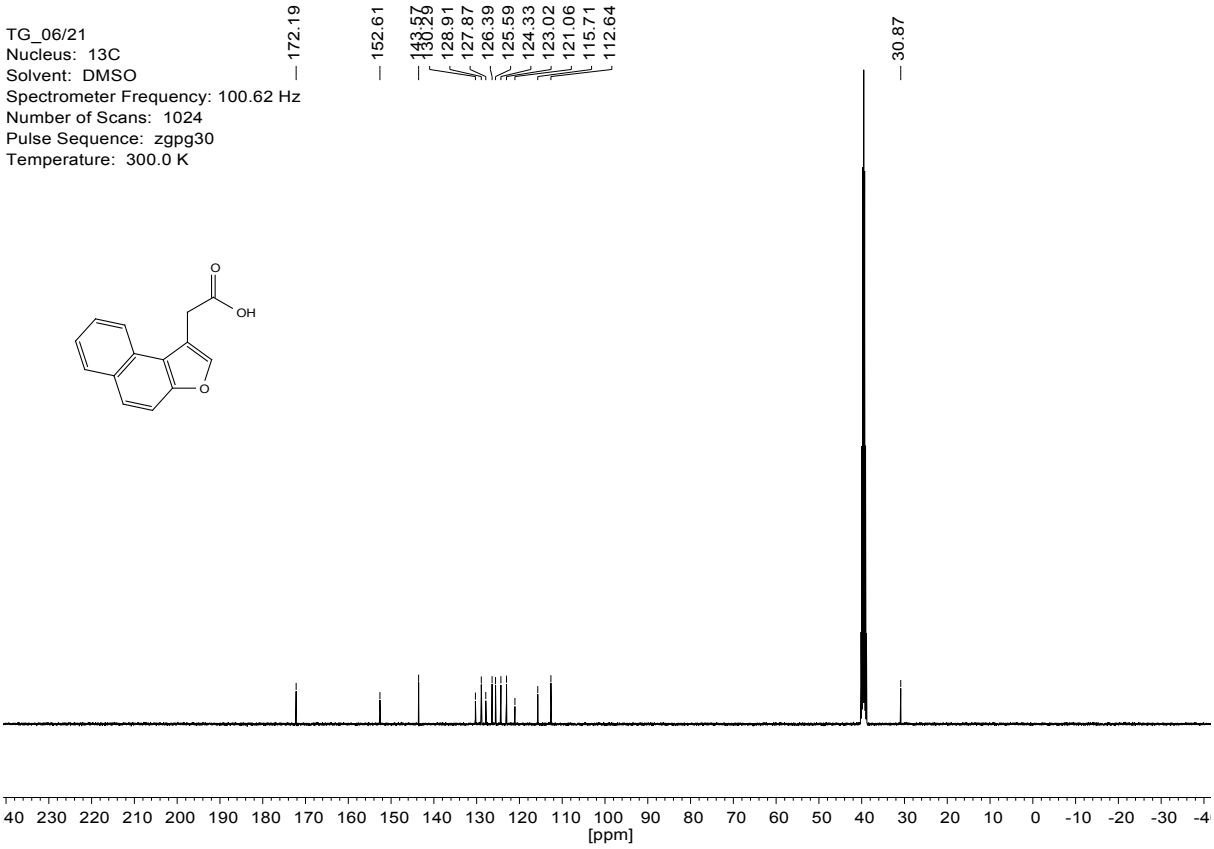
4-(1,3,4-Oxadiazol-2-yl)phenol (TG05)



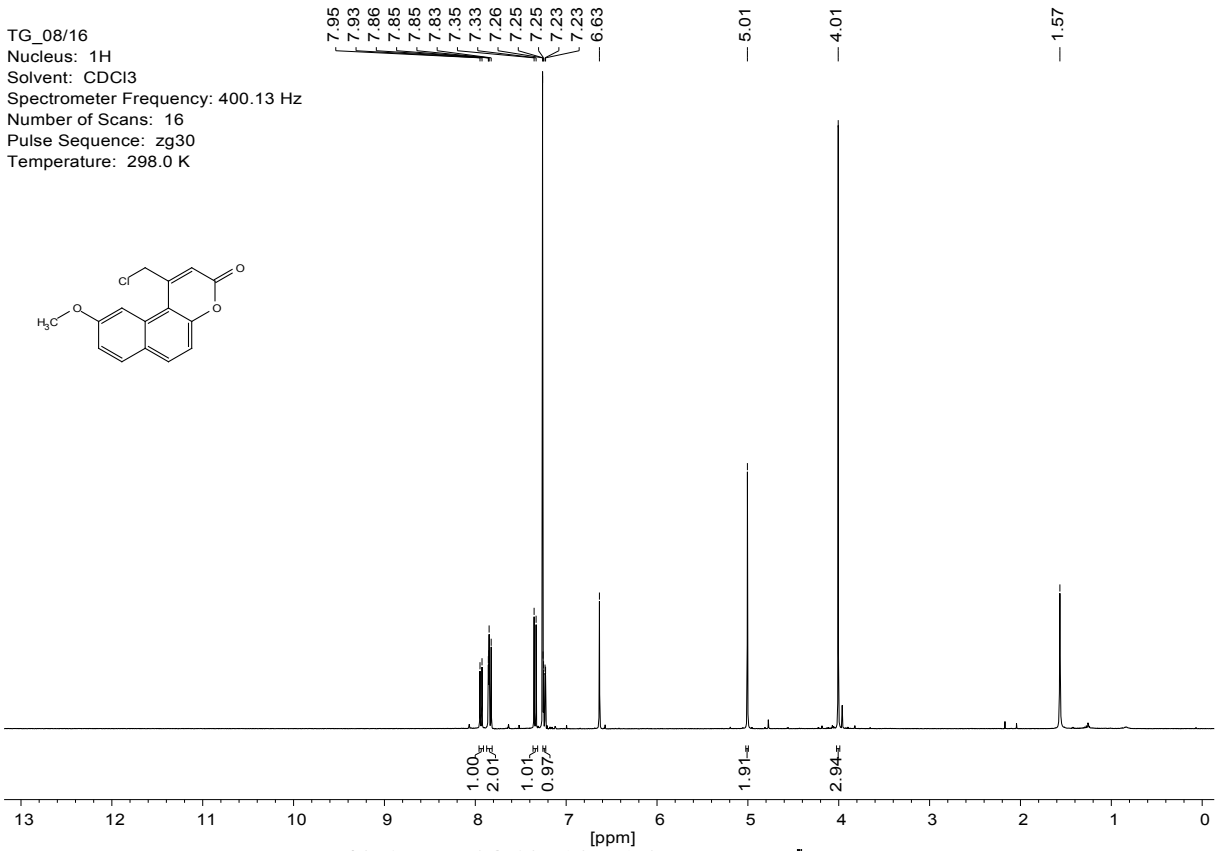


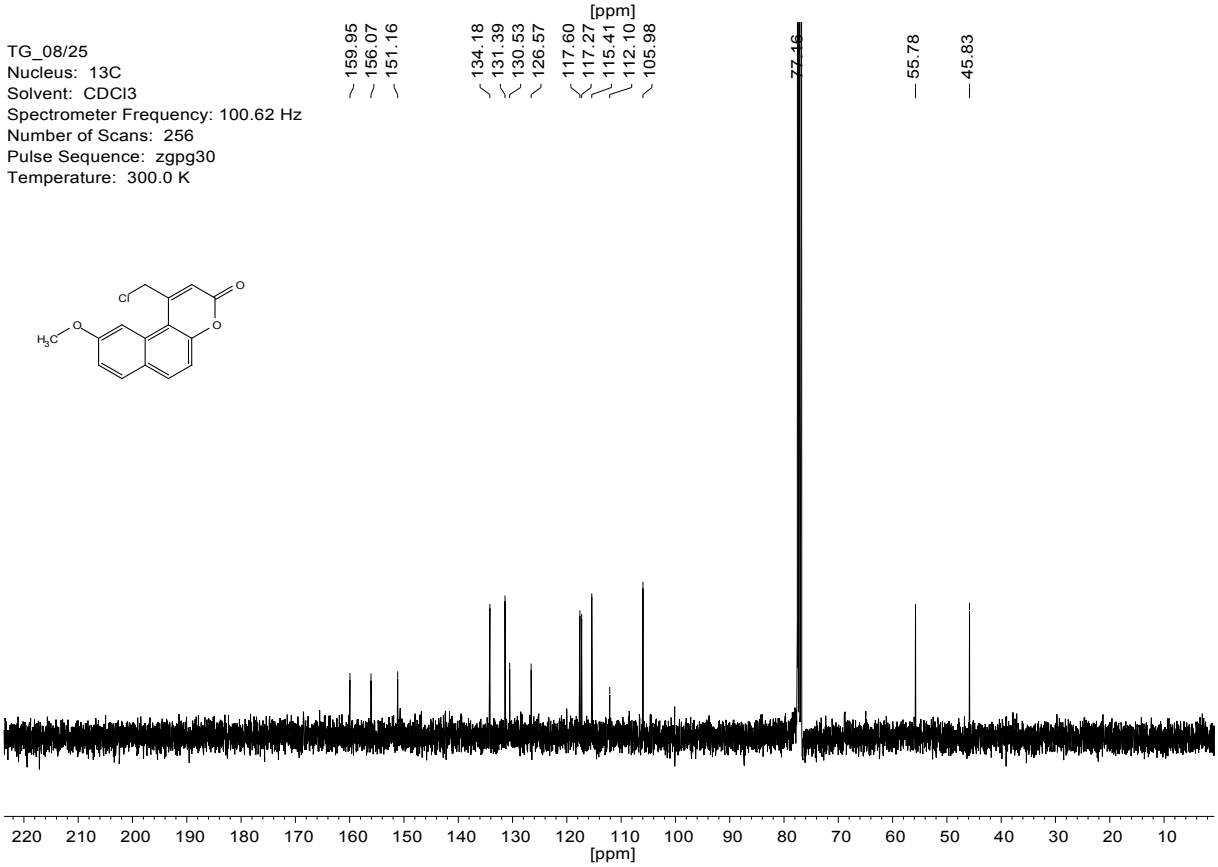
2-(Naphtho[2,1-*b*]furan-1-yl)acetic acid (TG06)



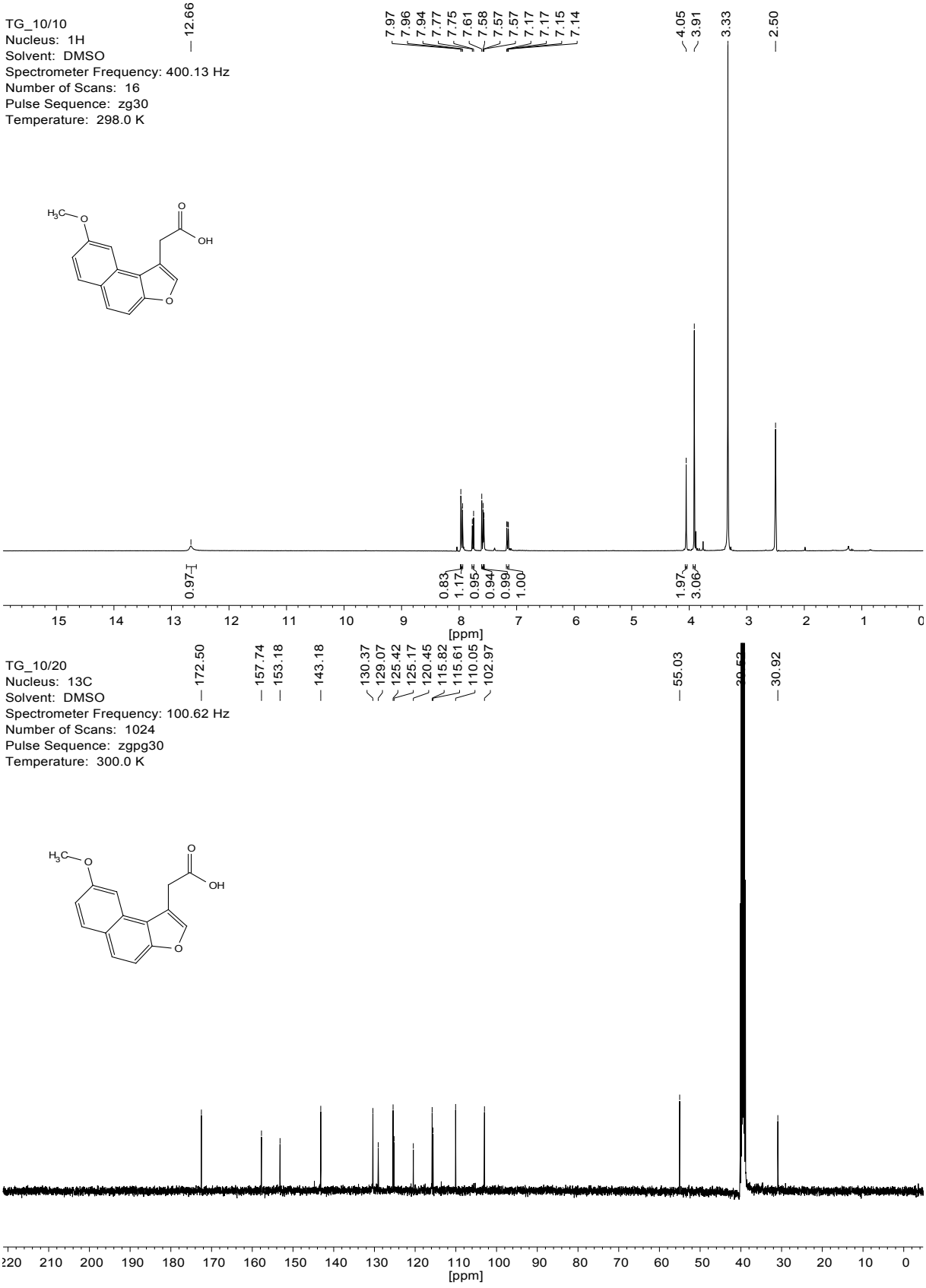


1-(Chloromethyl)-9-methoxy-3*H*-benzo[*f*]chromen-3-one (TG08)

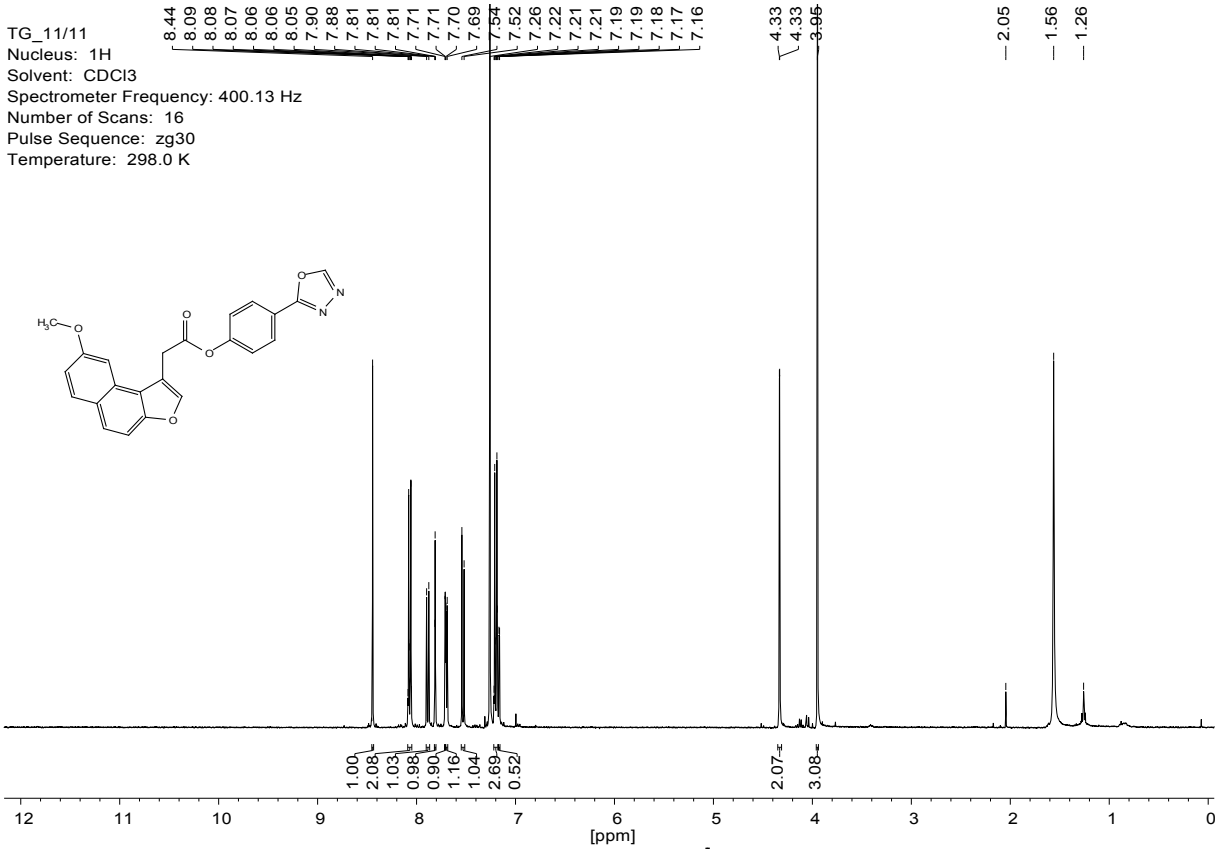


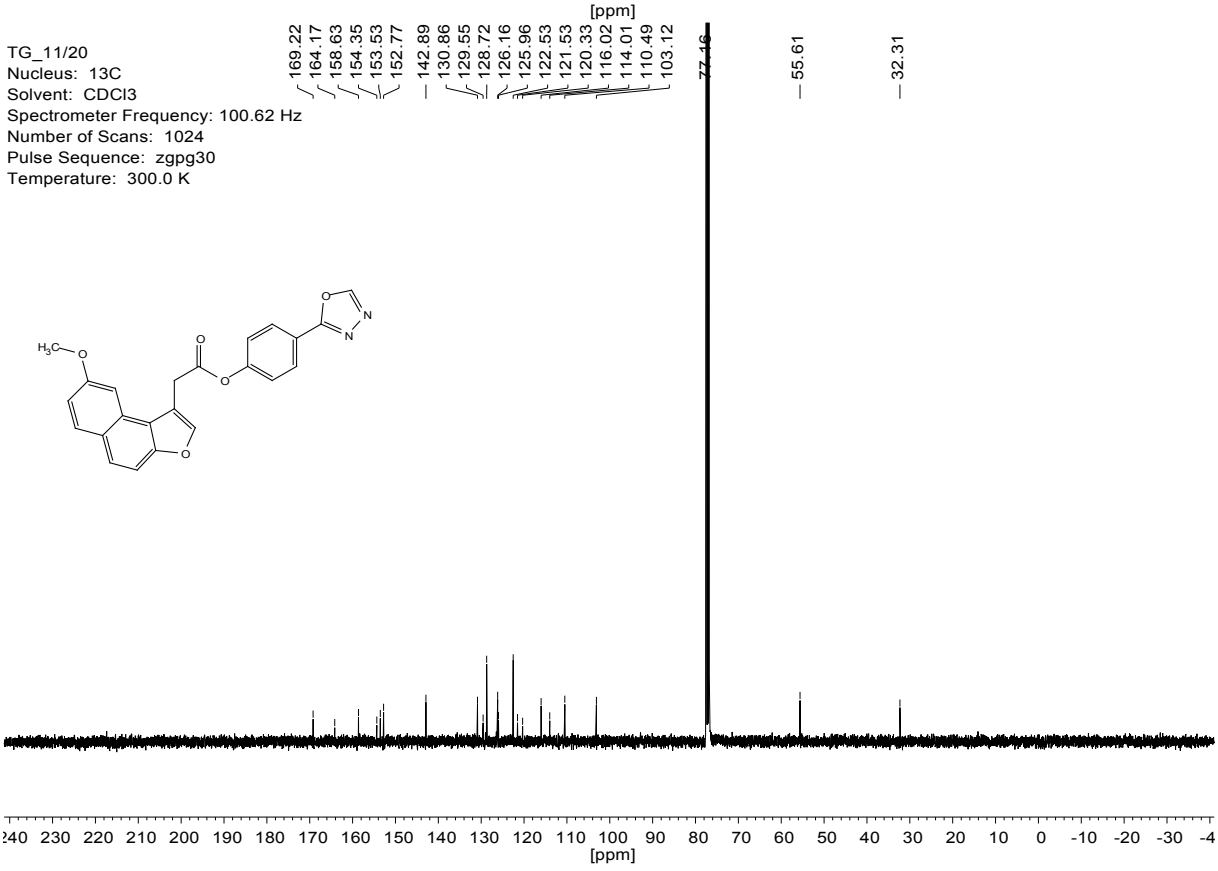


2-(8-Methoxynaphtho[2,1-*b*]furan-1-yl)acetic acid (TG10)

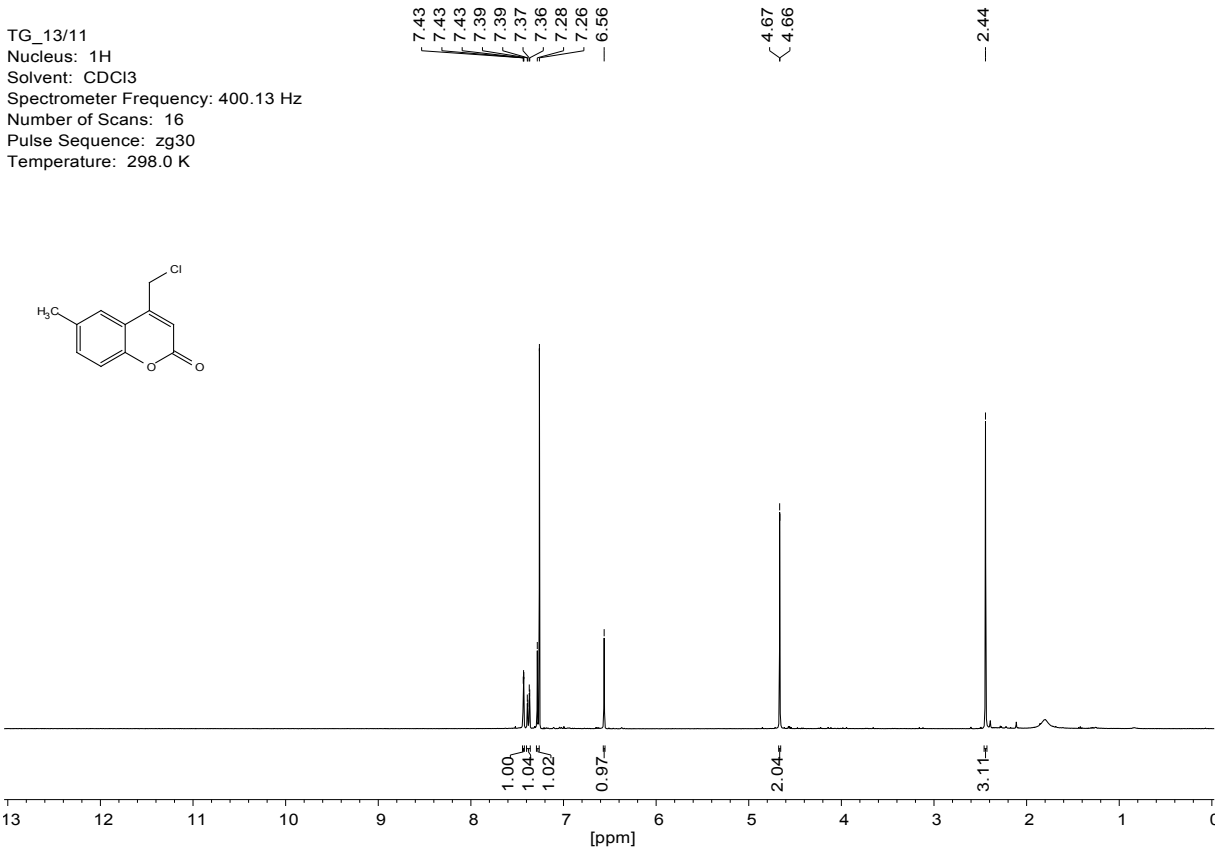


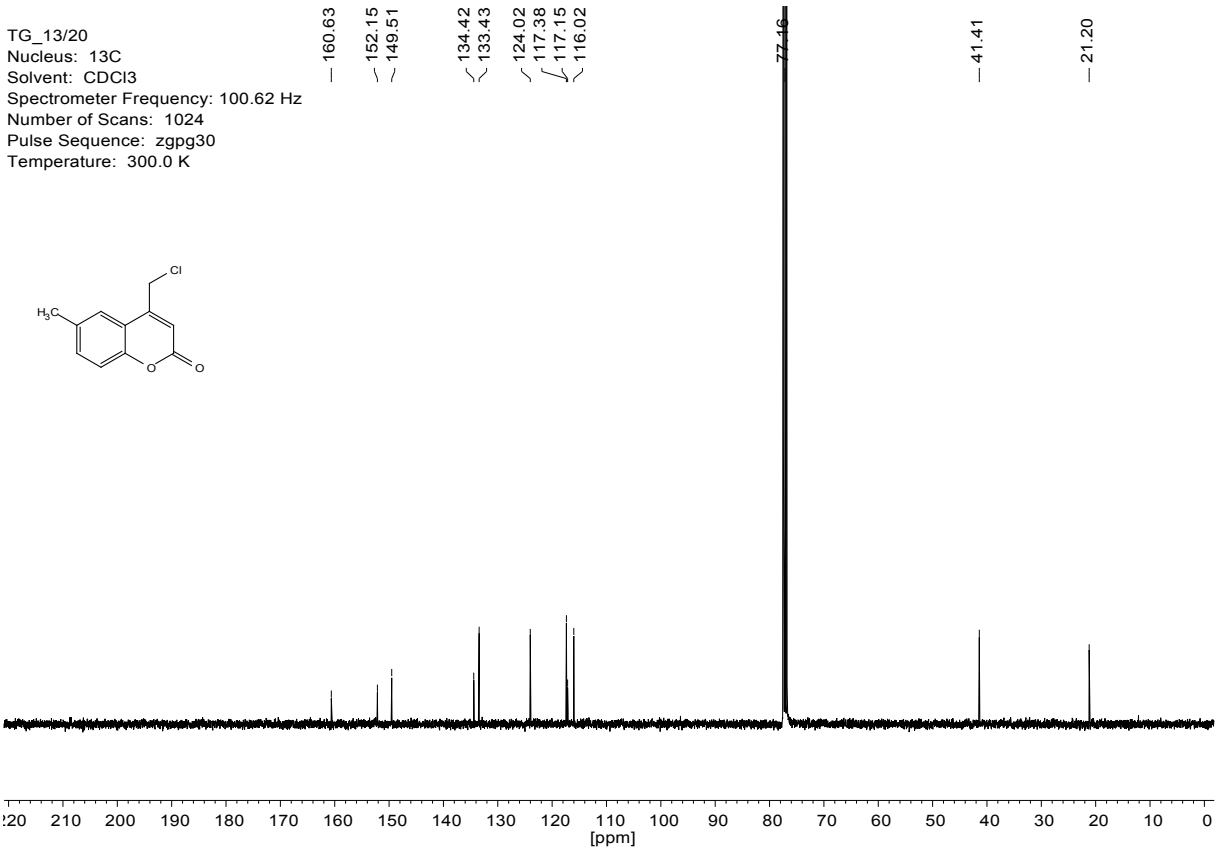
4-(1,3,4-Oxadiazol-2-yl)phenyl-2-(8-methoxynaphtho[2,1-*b*]furan-1-yl)acetate (TG11)



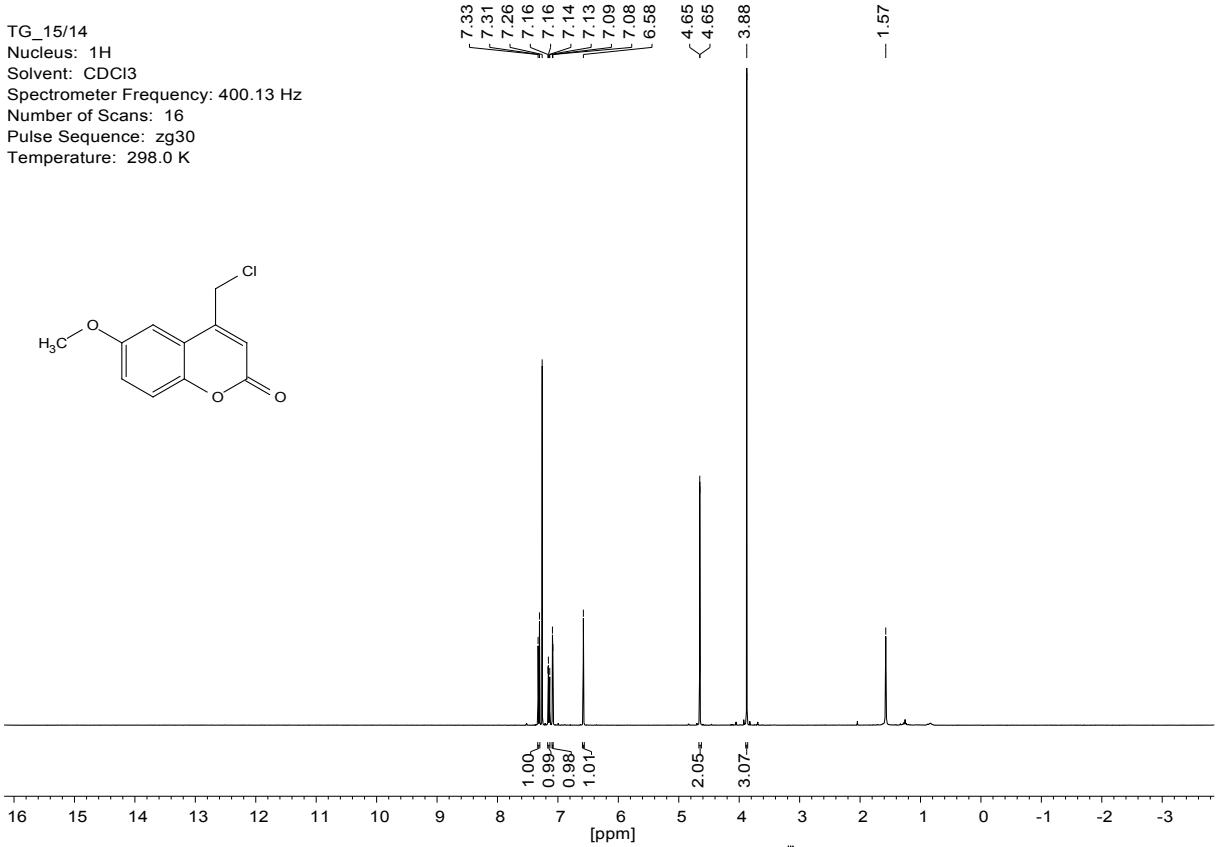


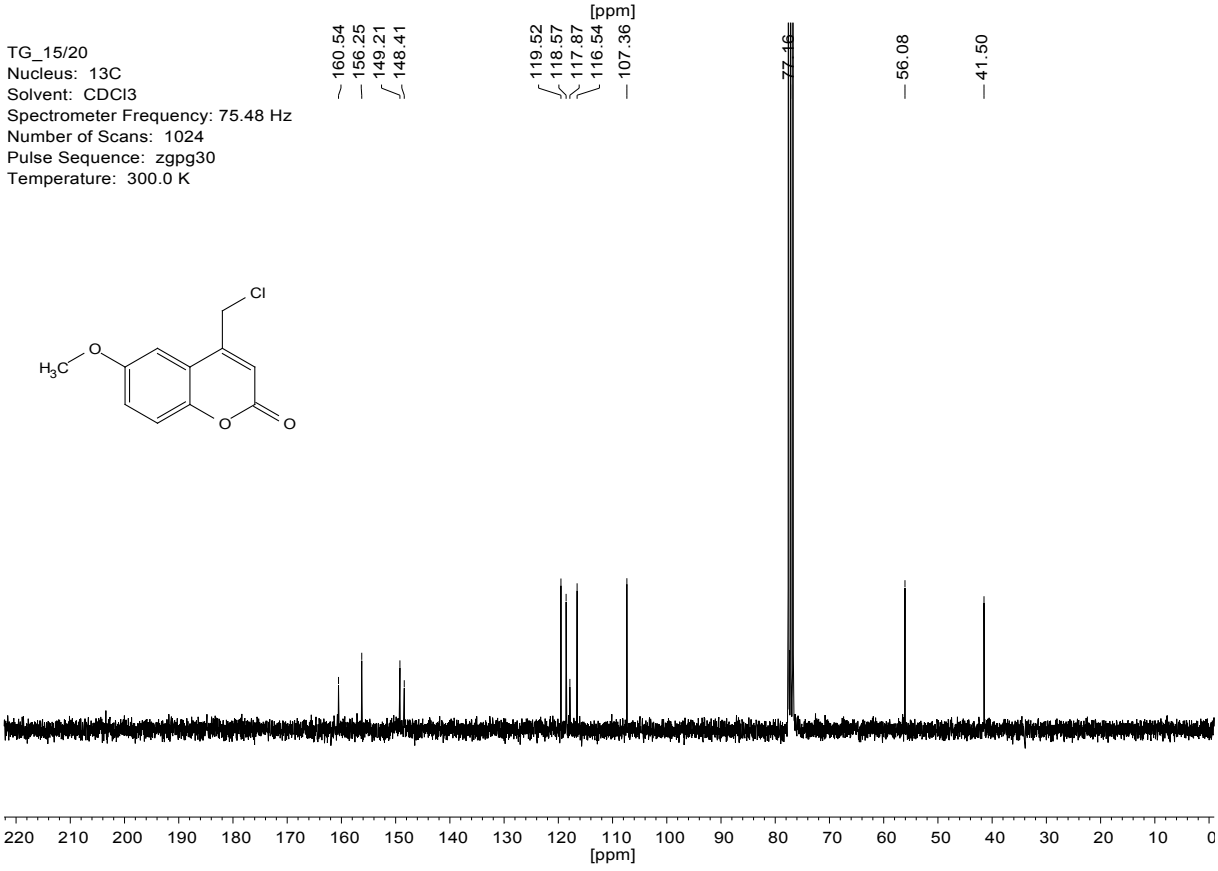
4-(Chloromethyl)-6-methyl-2*H*-chromen-2-one (TG13)



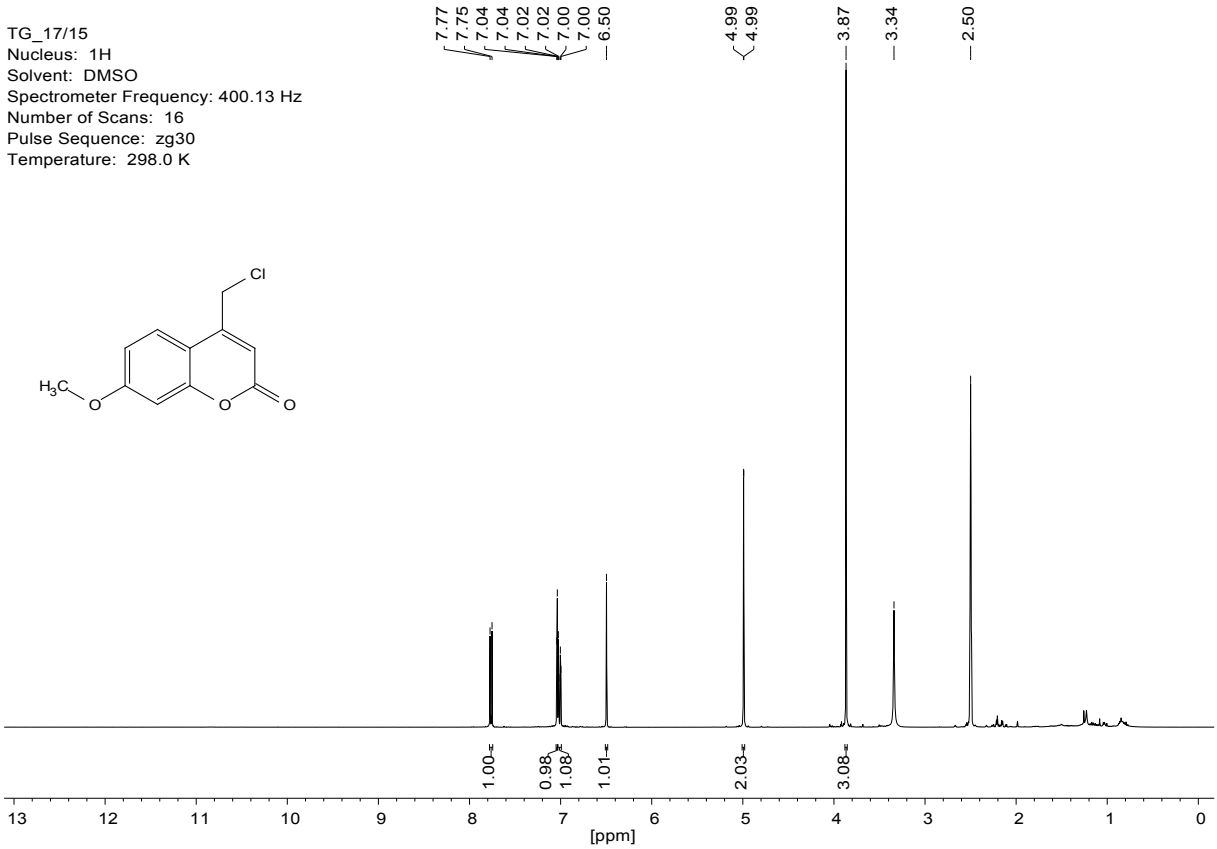


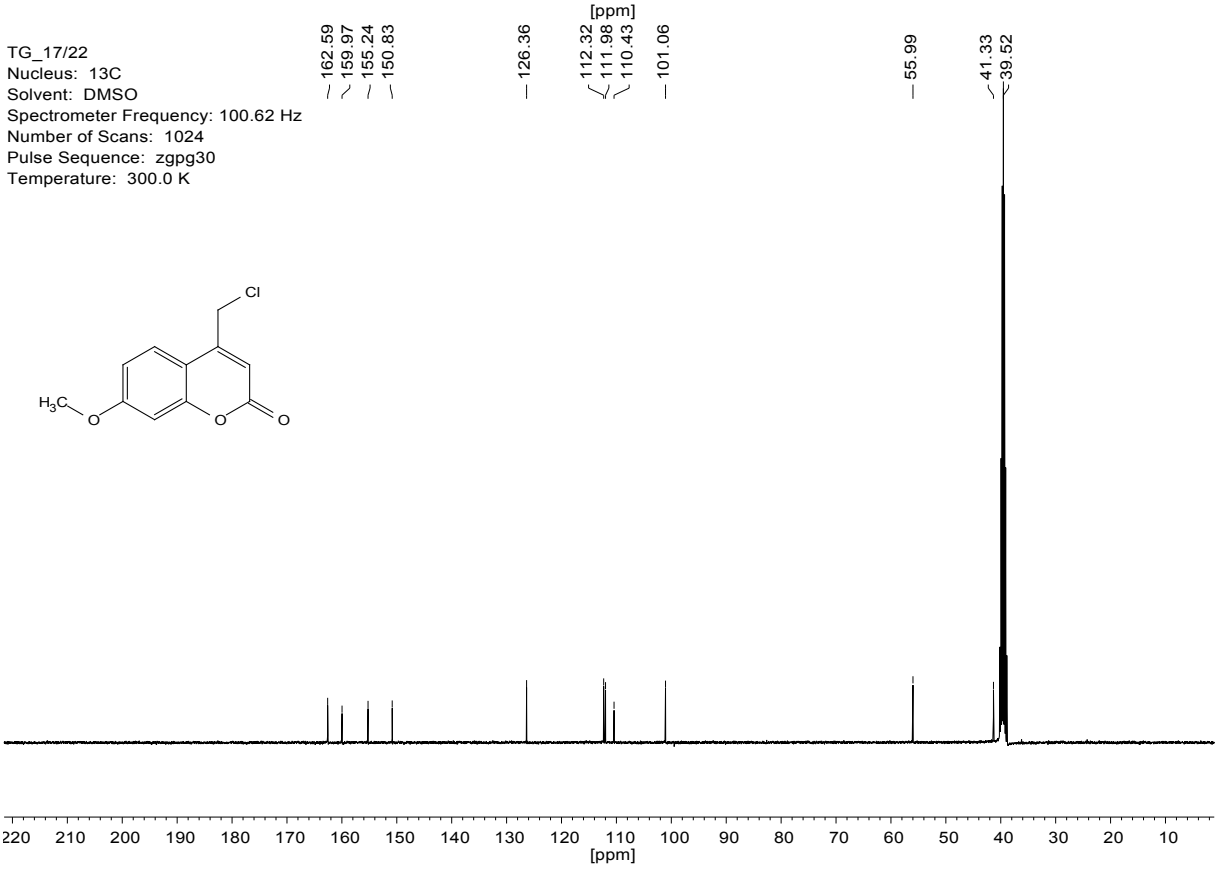
4-(Chloromethyl)-6-methoxy-2*H*-chromen-2-one (TG15)



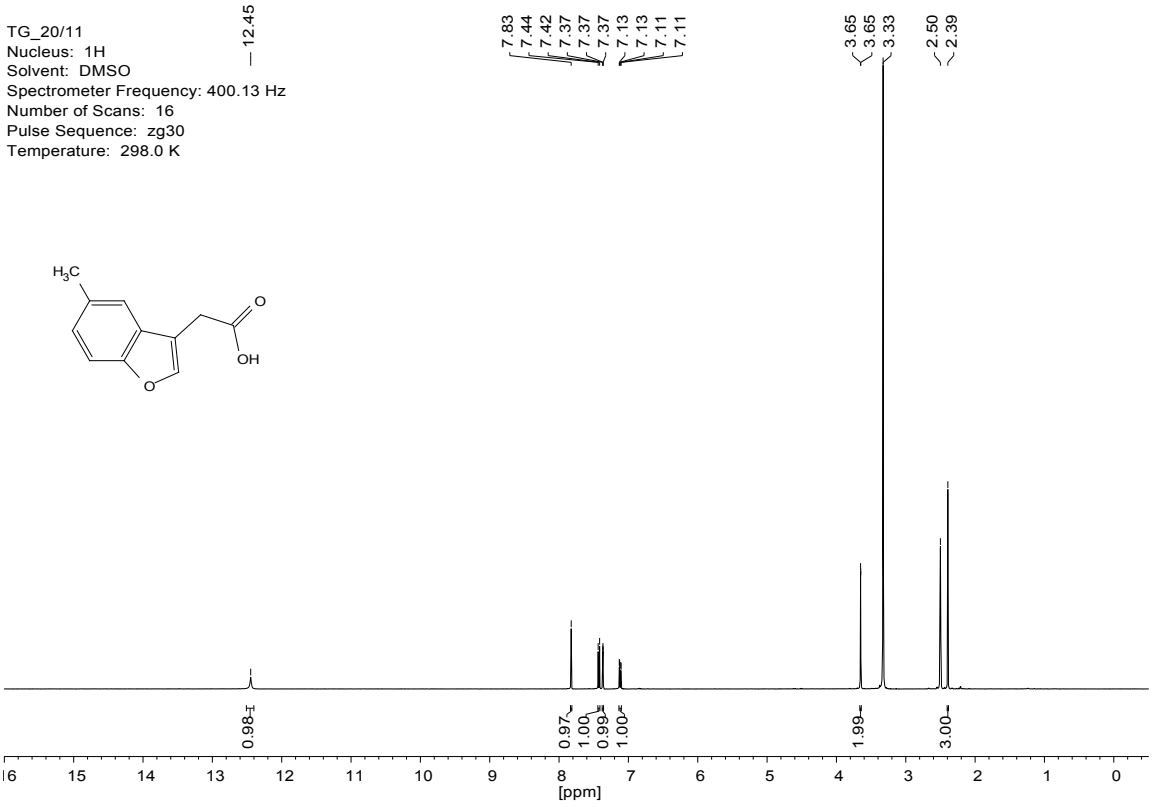


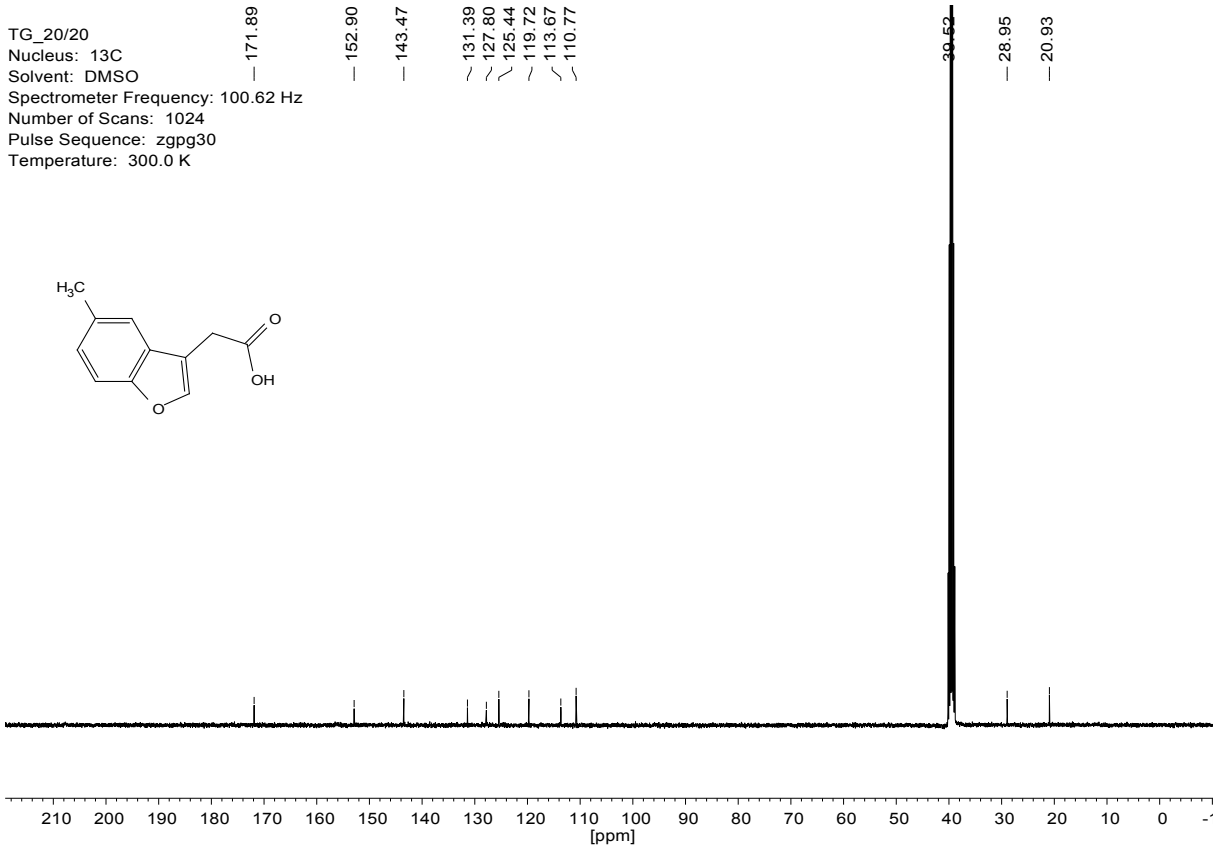
4-(Chloromethyl)-7-methoxy-2*H*-chromen-2-one (TG17)



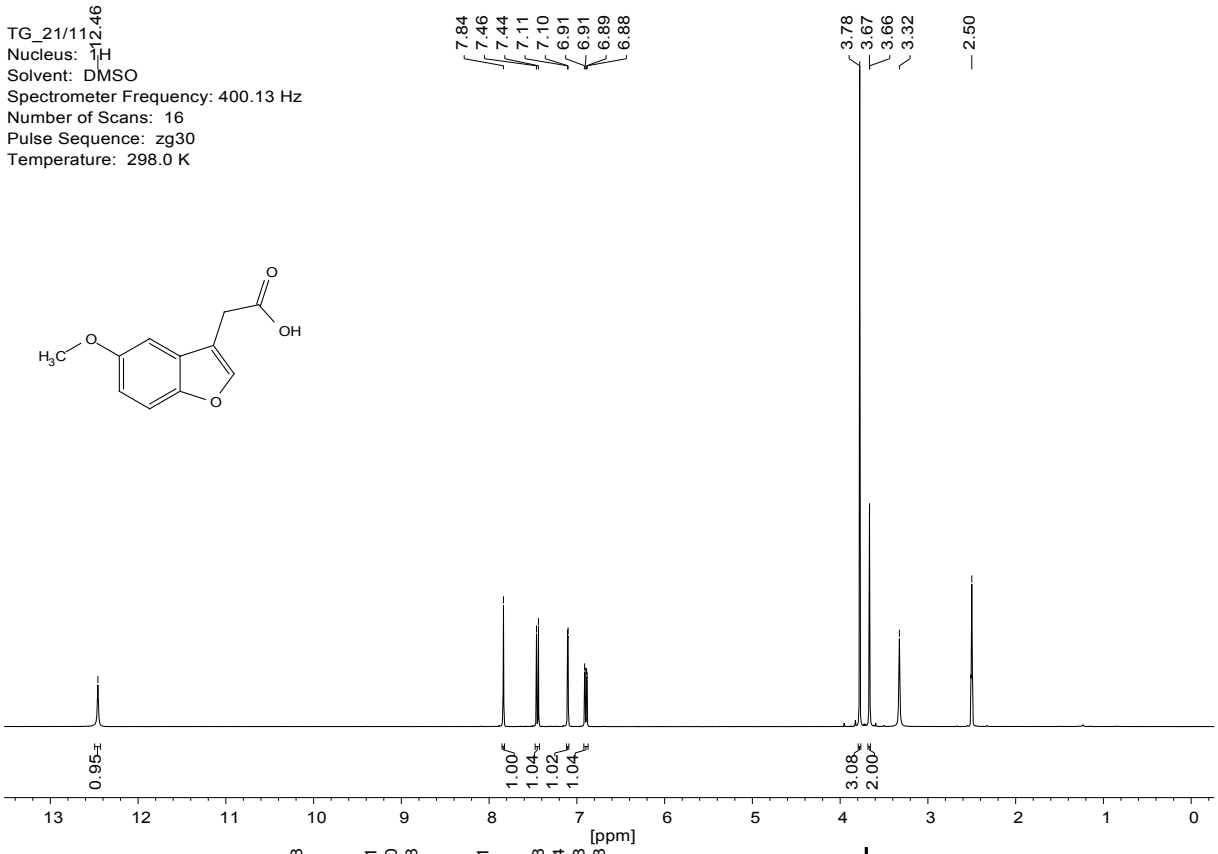


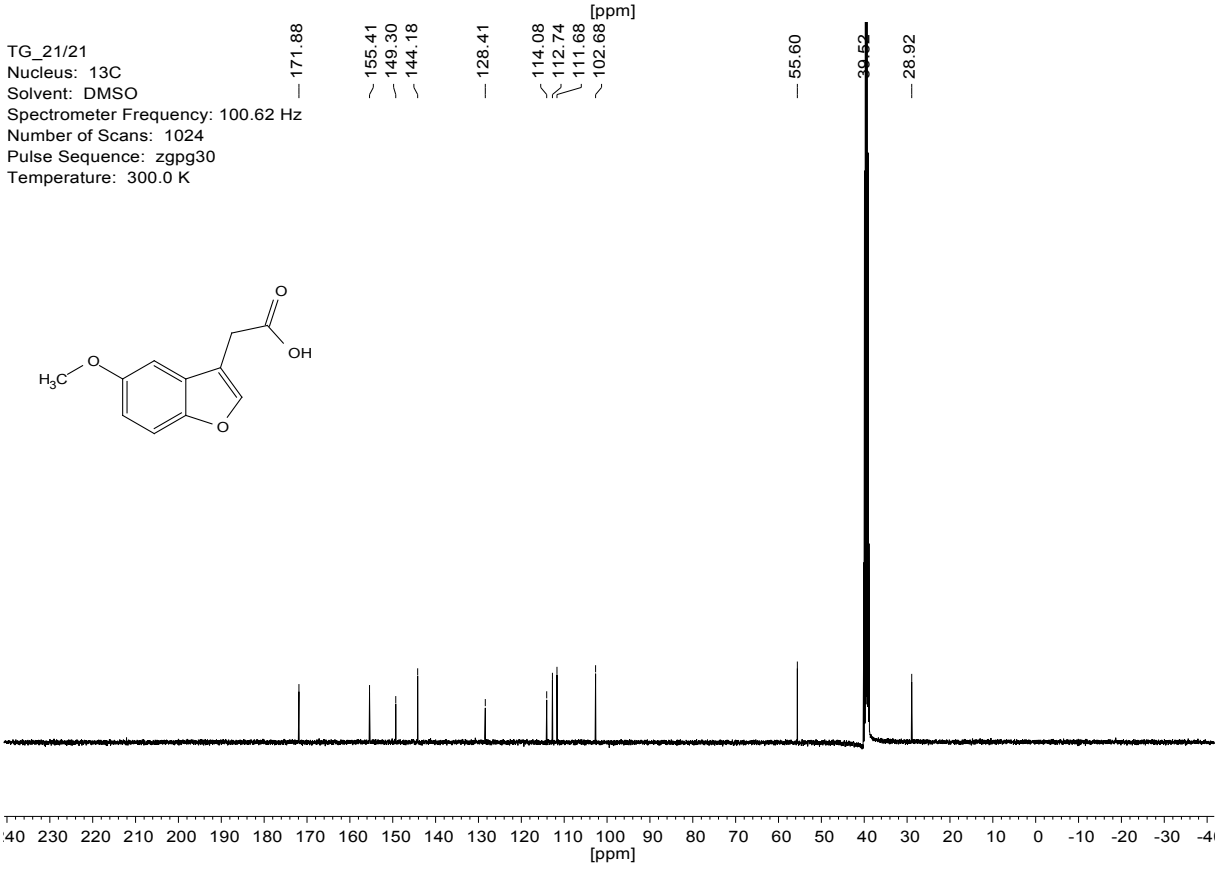
2-(5-Methylbenzofuran-3-yl)acetic acid (TG20)



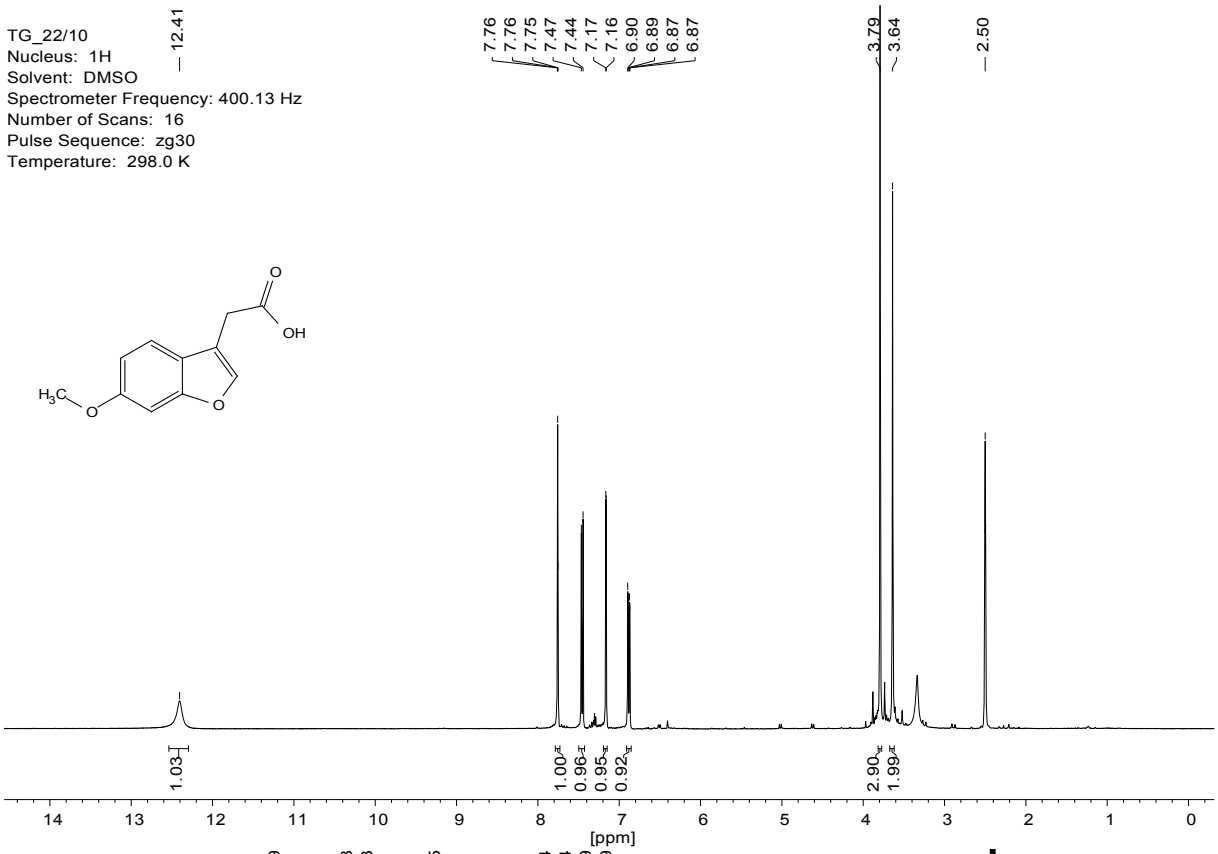


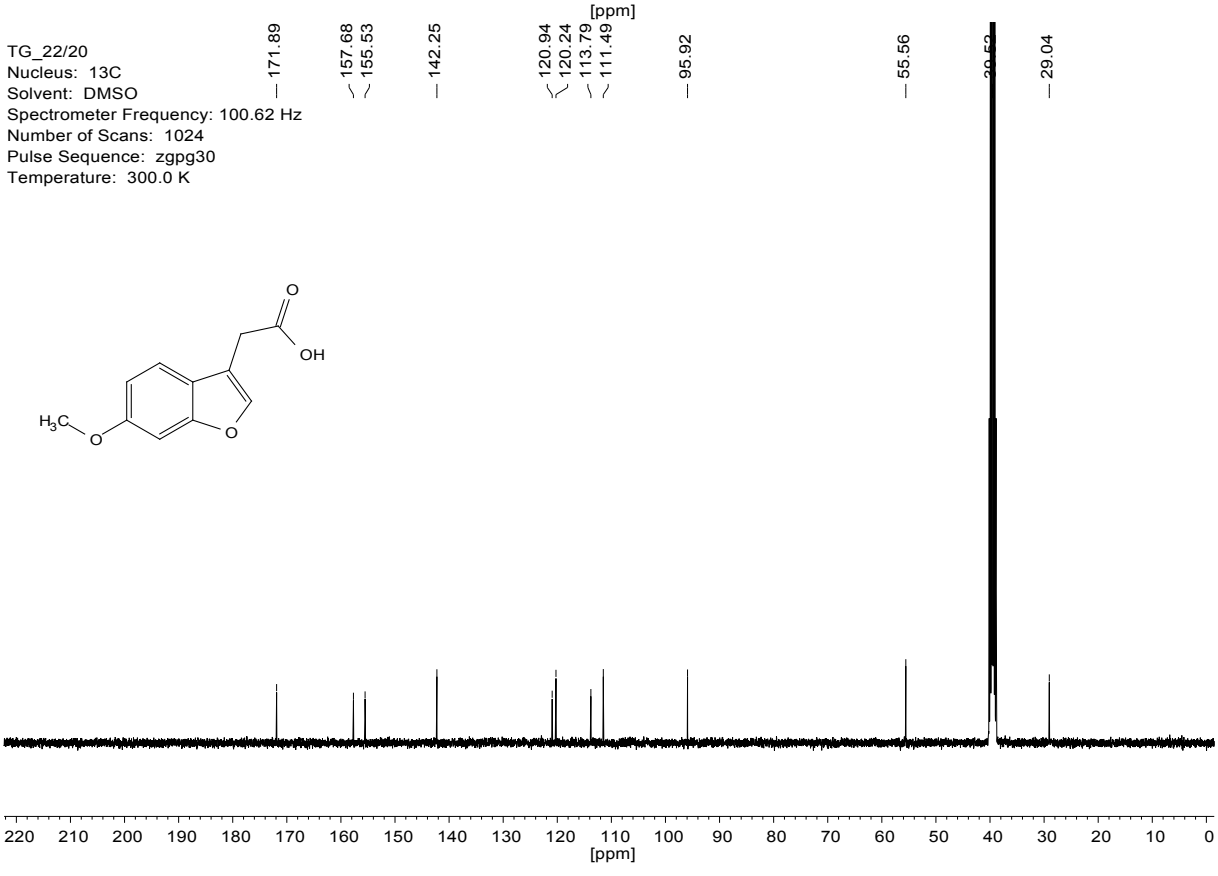
2-(5-Methoxybenzofuran-3-yl)acetic acid (TG21)



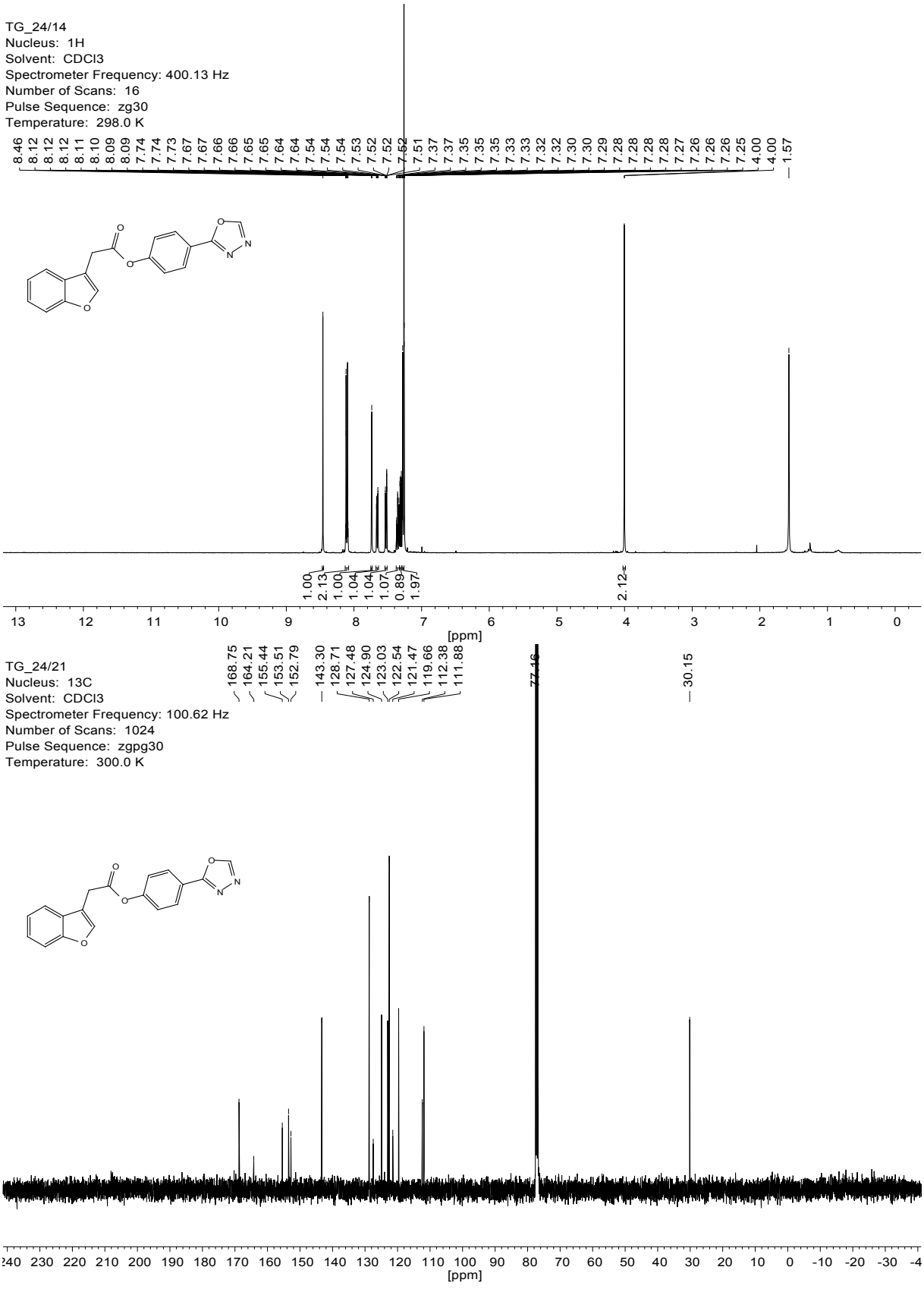


2-(6-Methoxybenzofuran-3-yl)acetic acid (TG22)

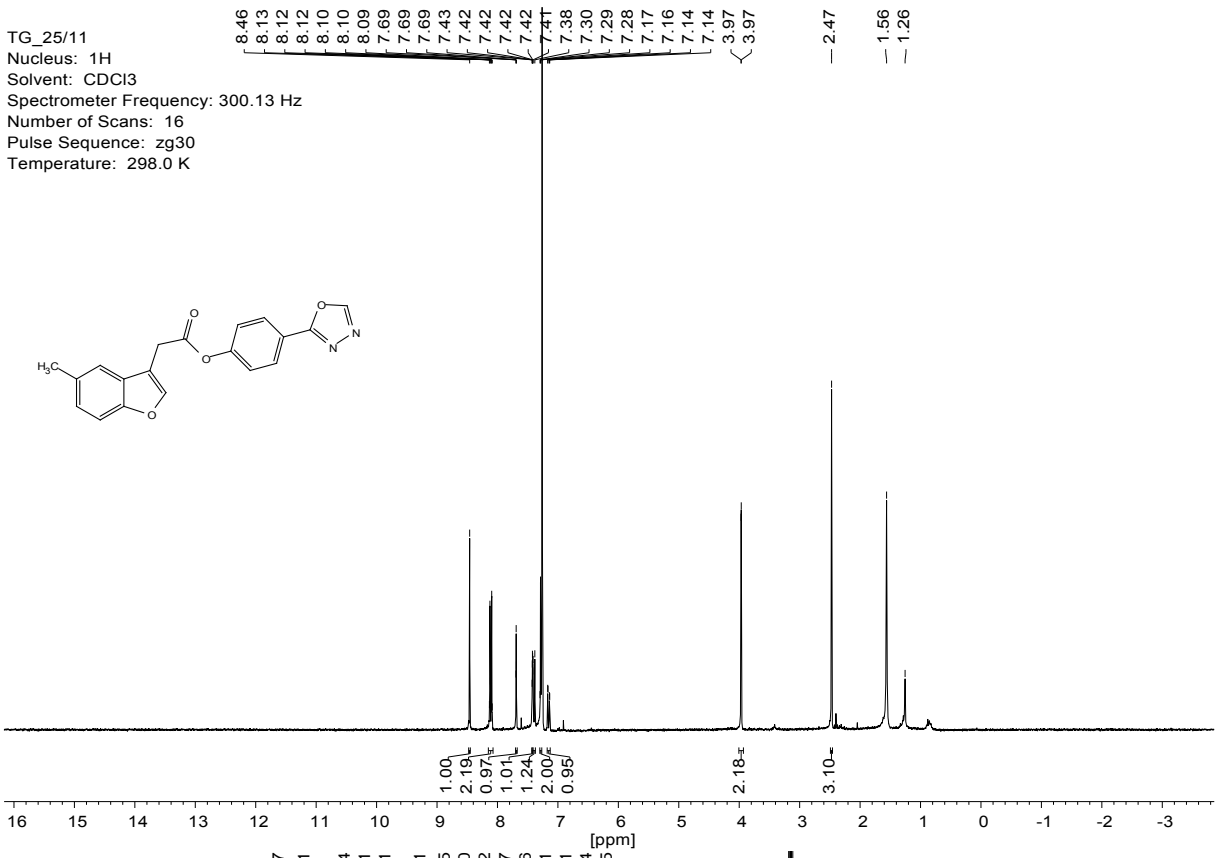


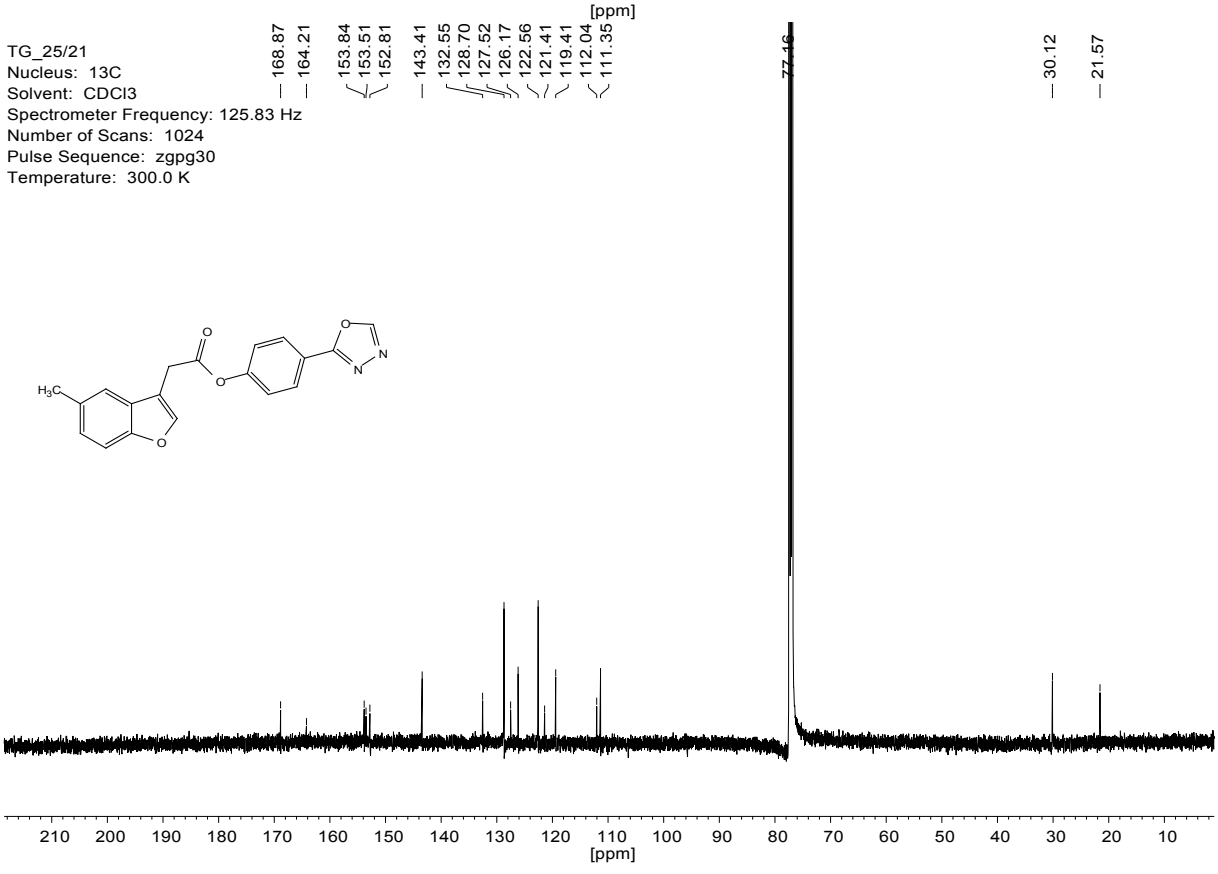


4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(benzofuran-3-yl)acetate (TG24)

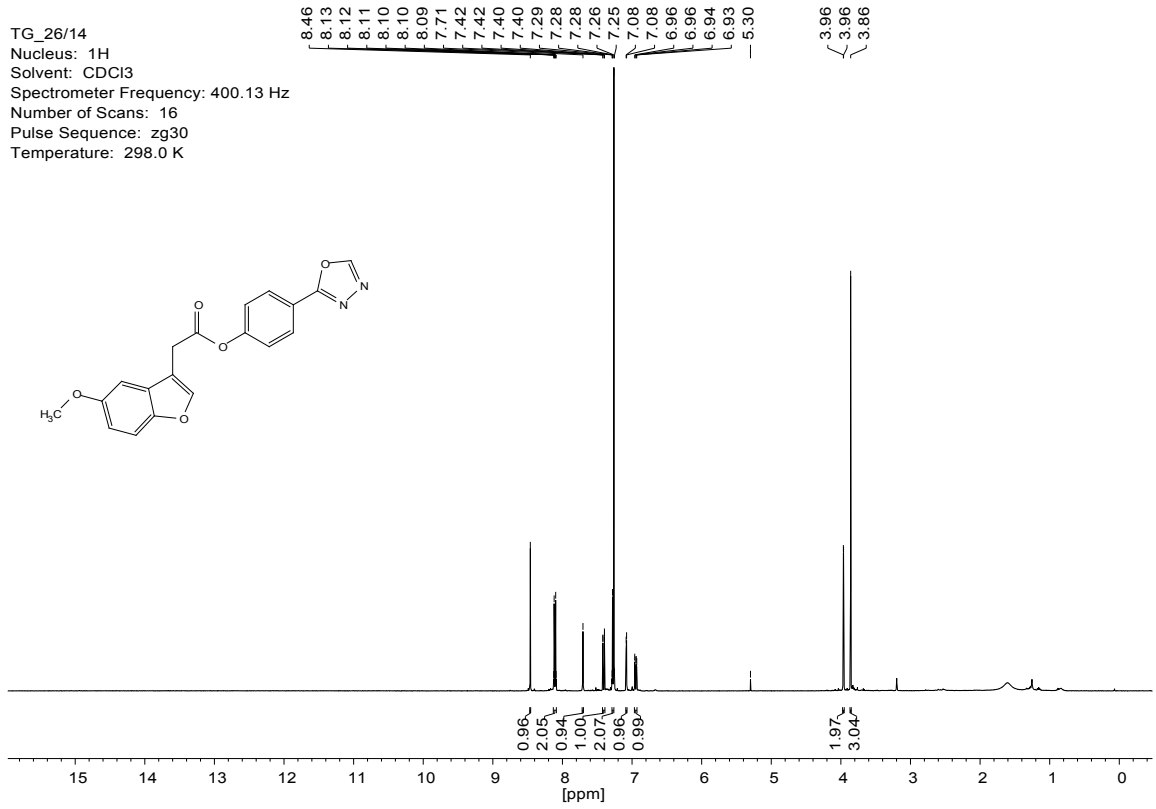


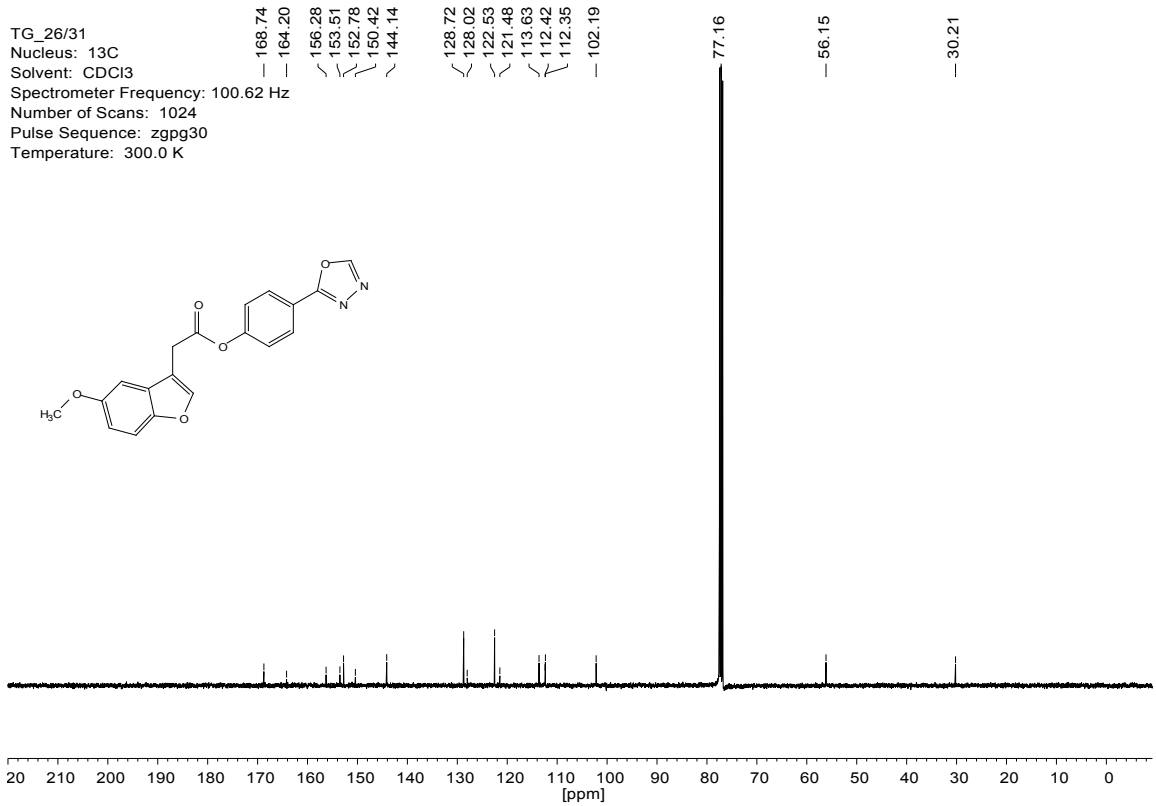
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(5-methylbenzofuran-3-yl)acetate (TG25)



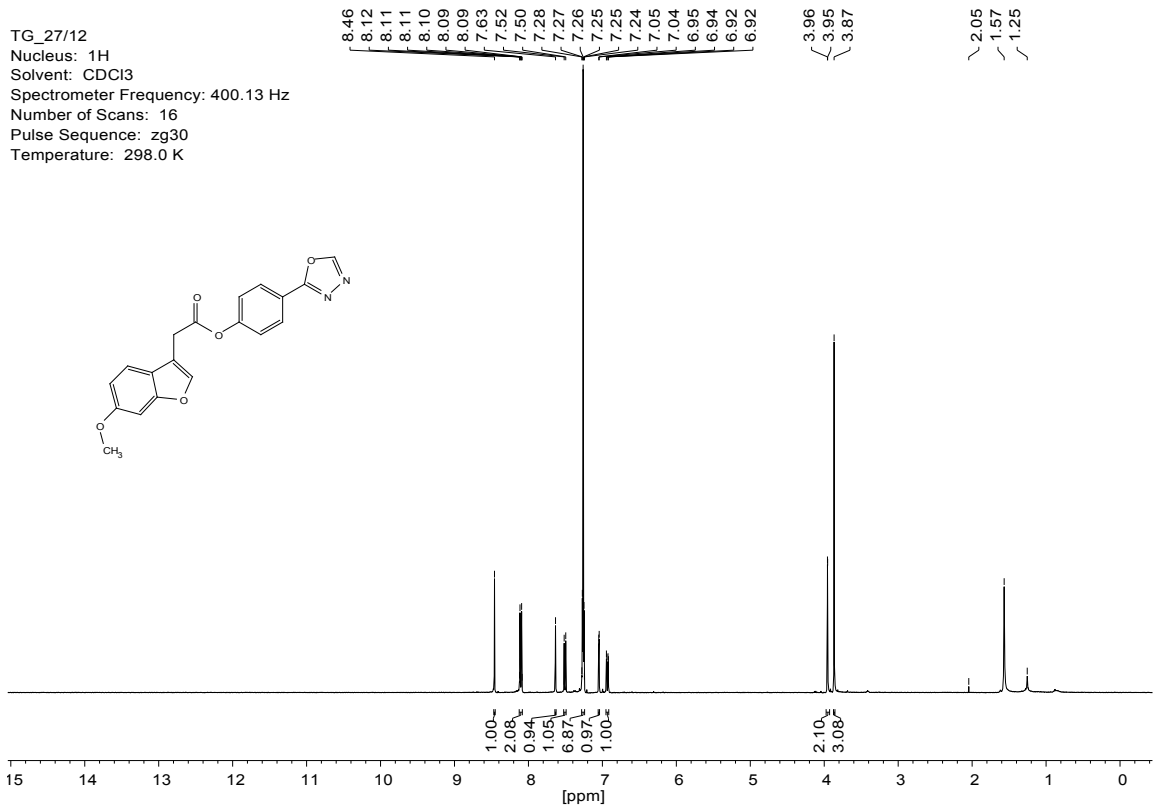


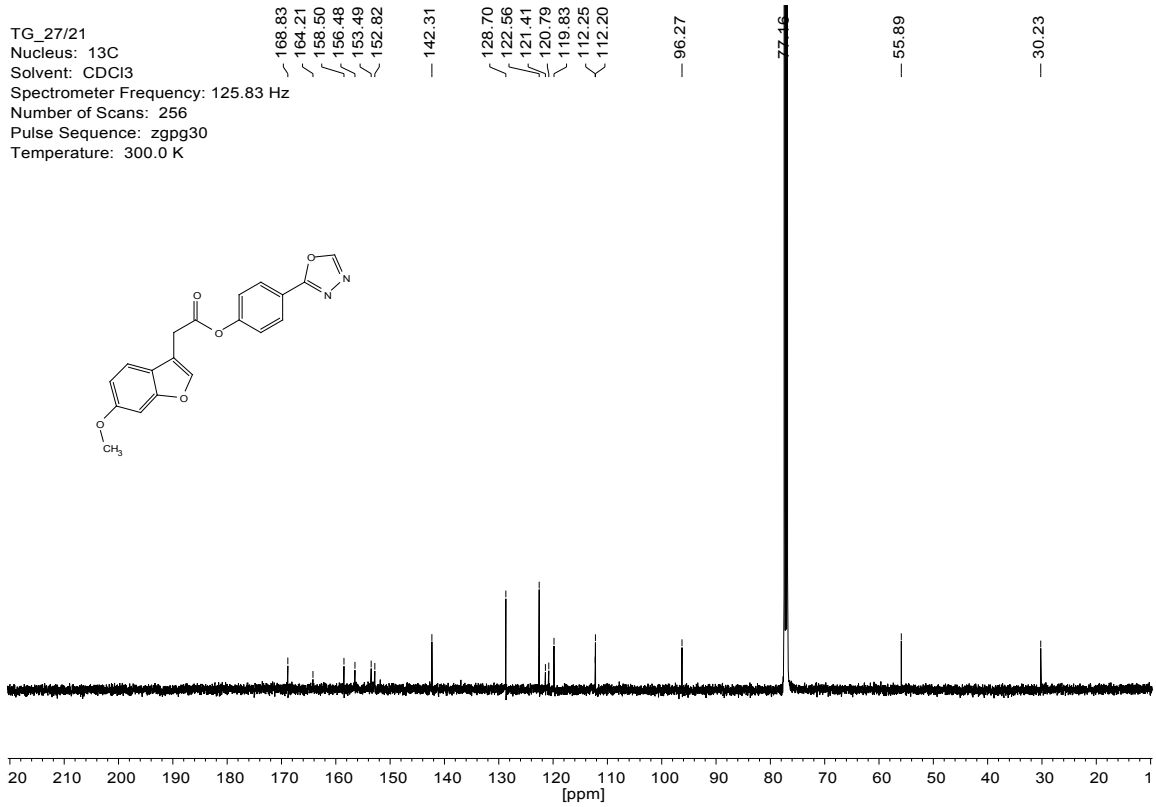
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(5-methoxybenzofuran-3-yl)acetate (TG26)



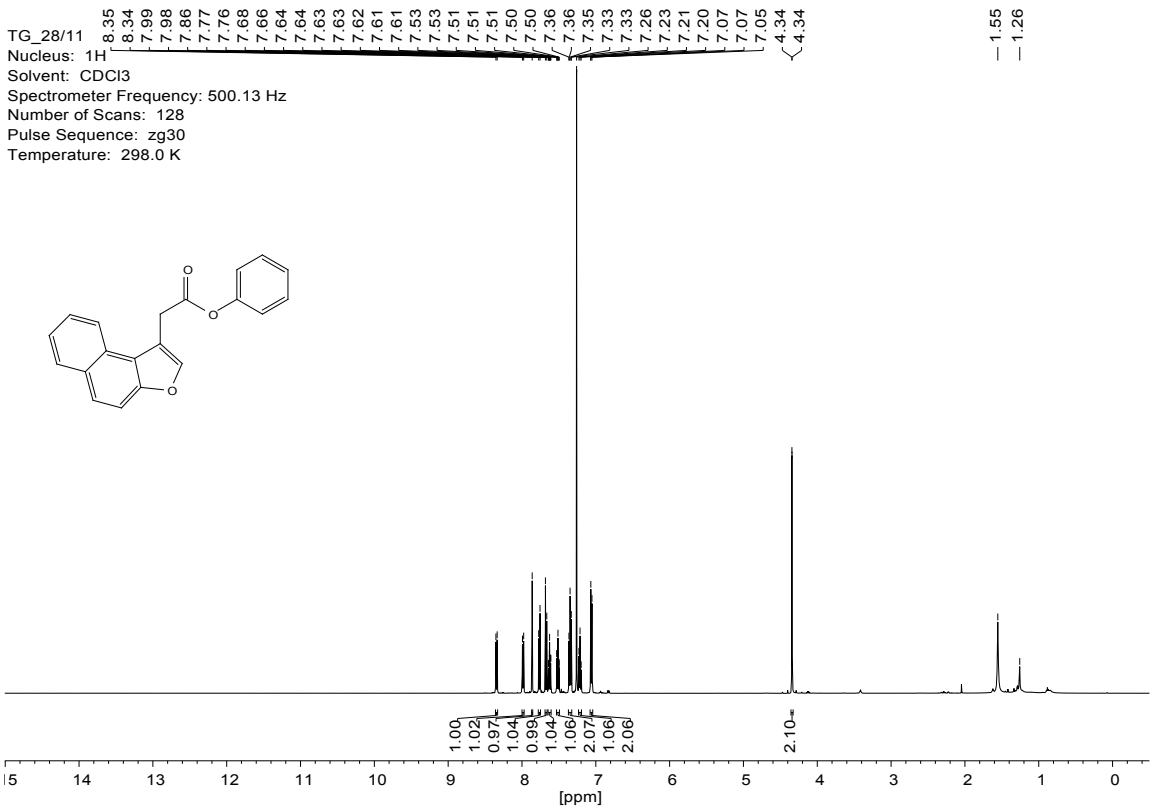


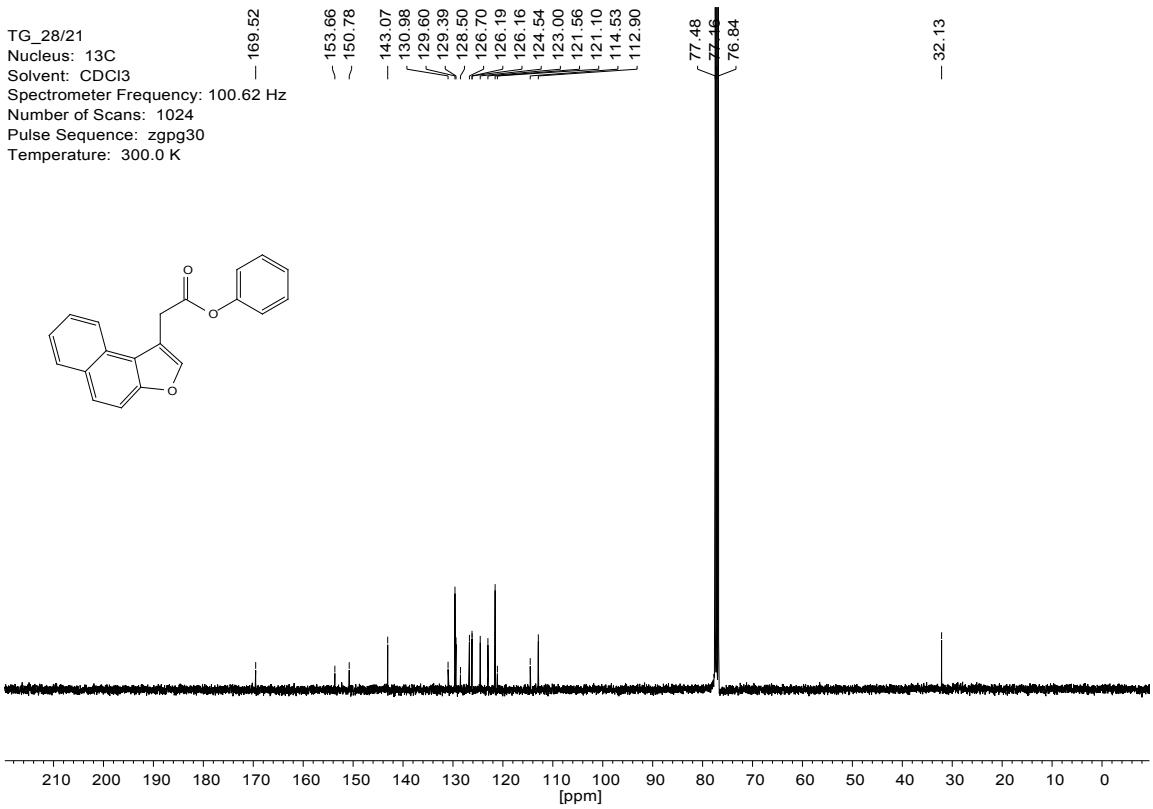
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(6-methoxybenzofuran-3-yl)acetate (TG27)



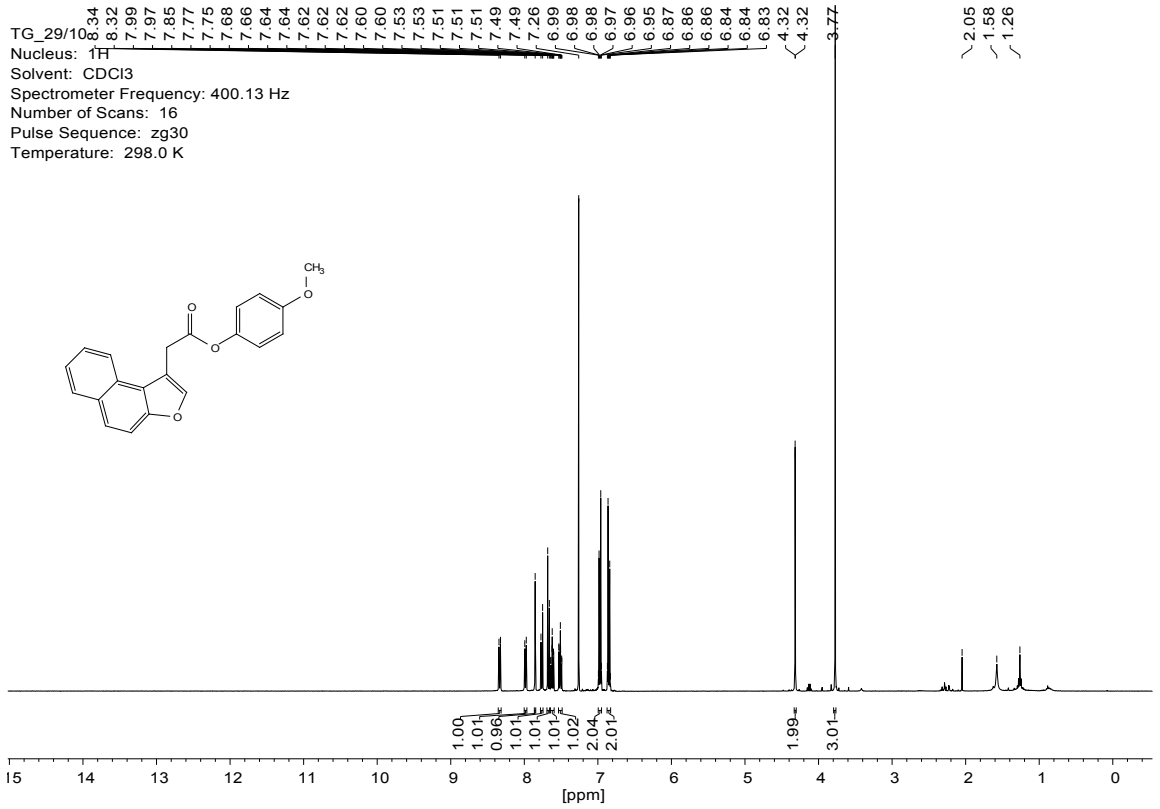


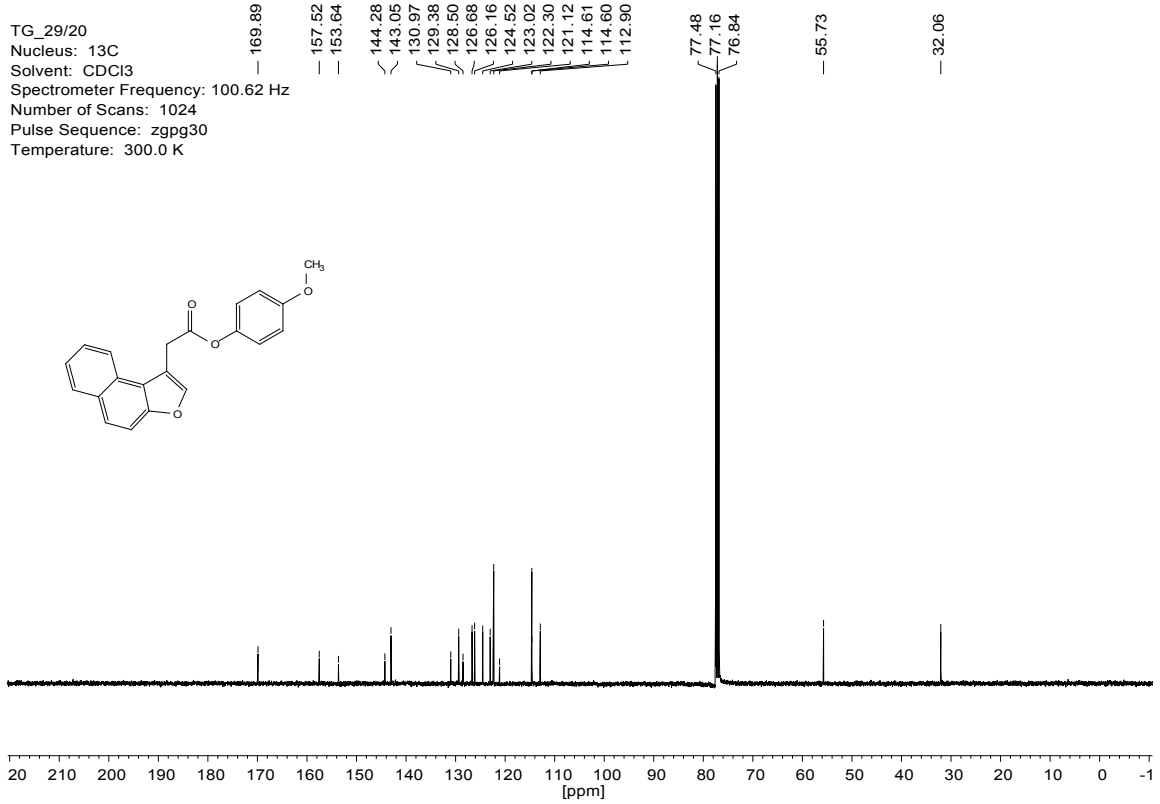
Phenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG28)



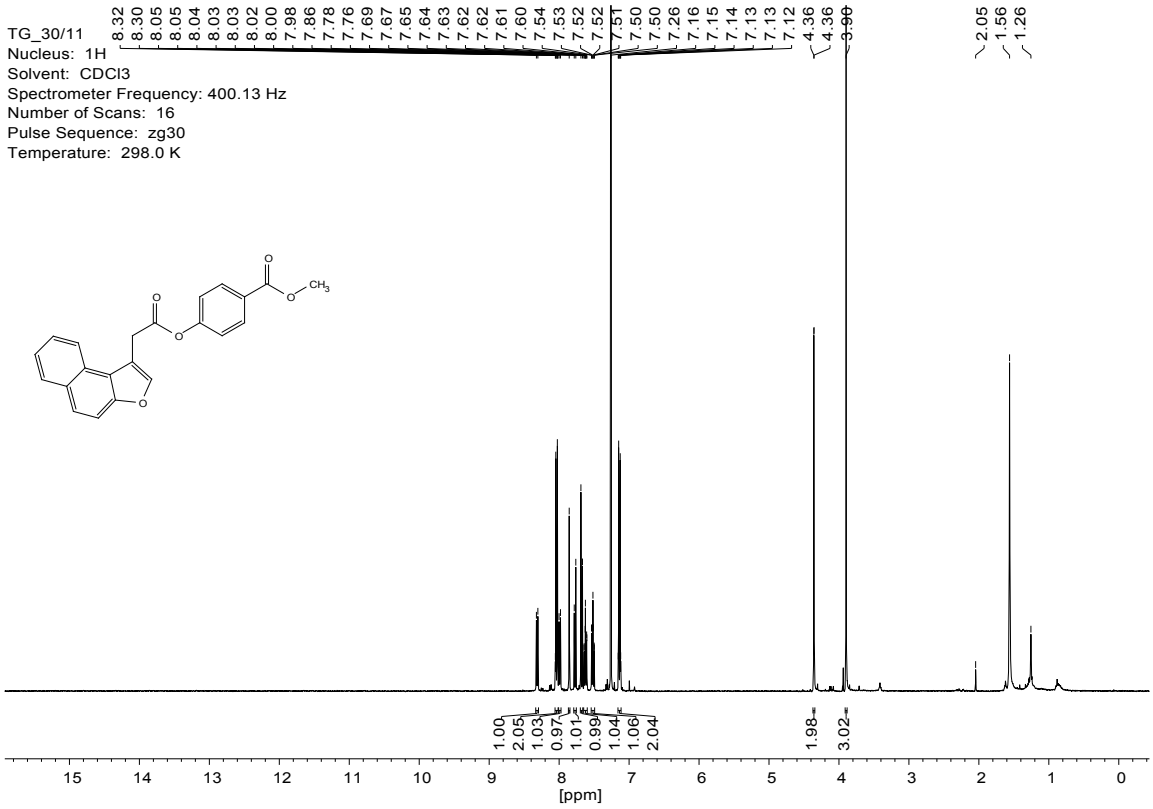


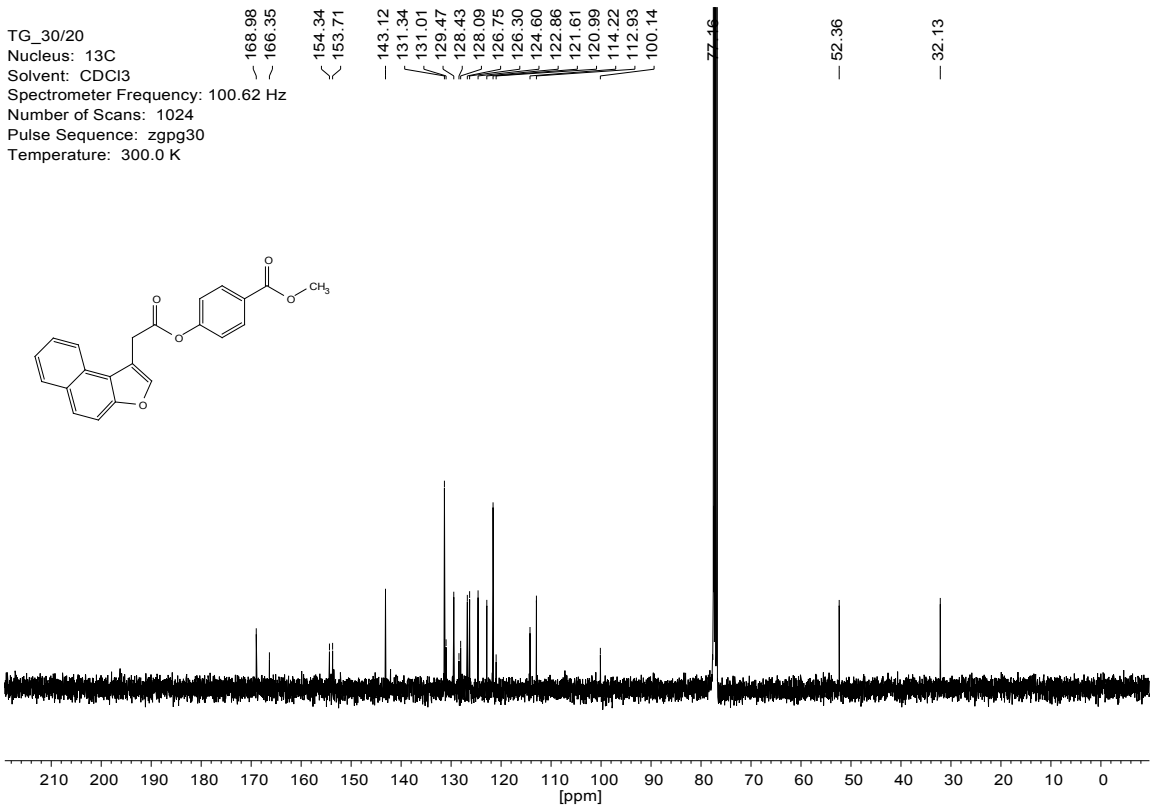
4-Methoxyphenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG29)



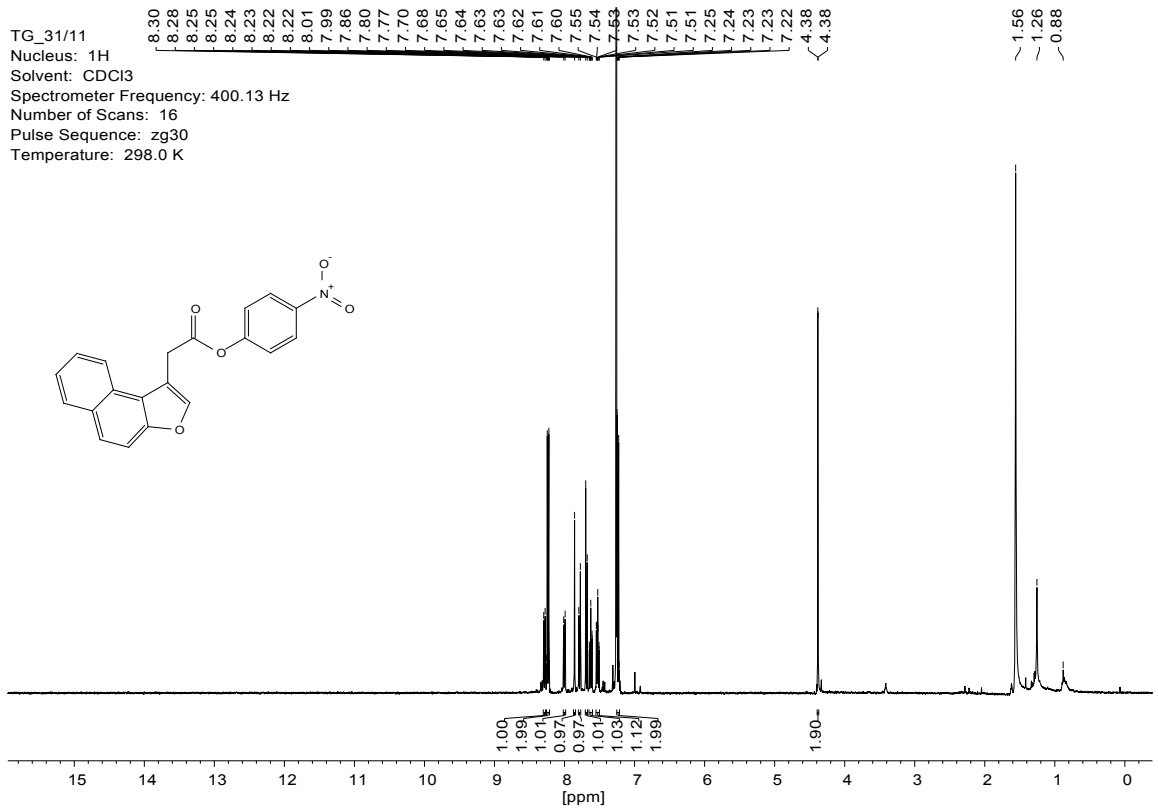


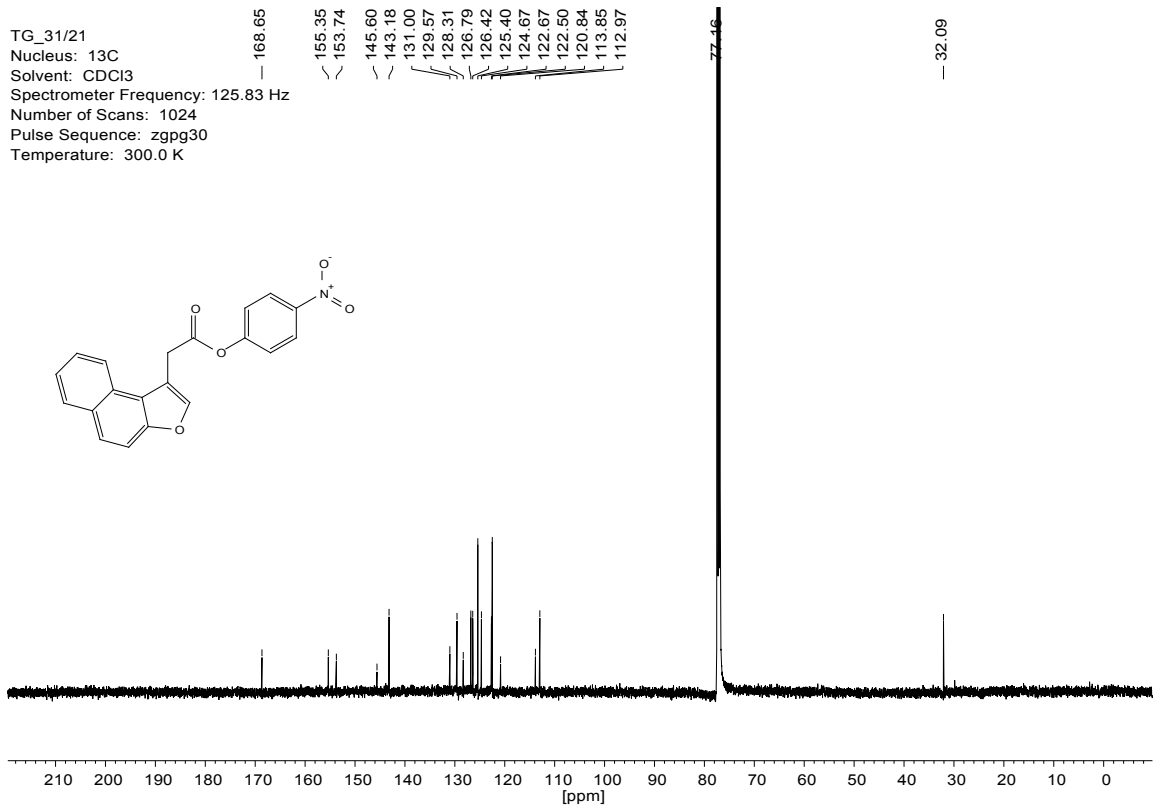
Methyl 4-(2-(naphtho[2,1-*b*]furan-1-yl)acetoxy)benzoate (TG30)



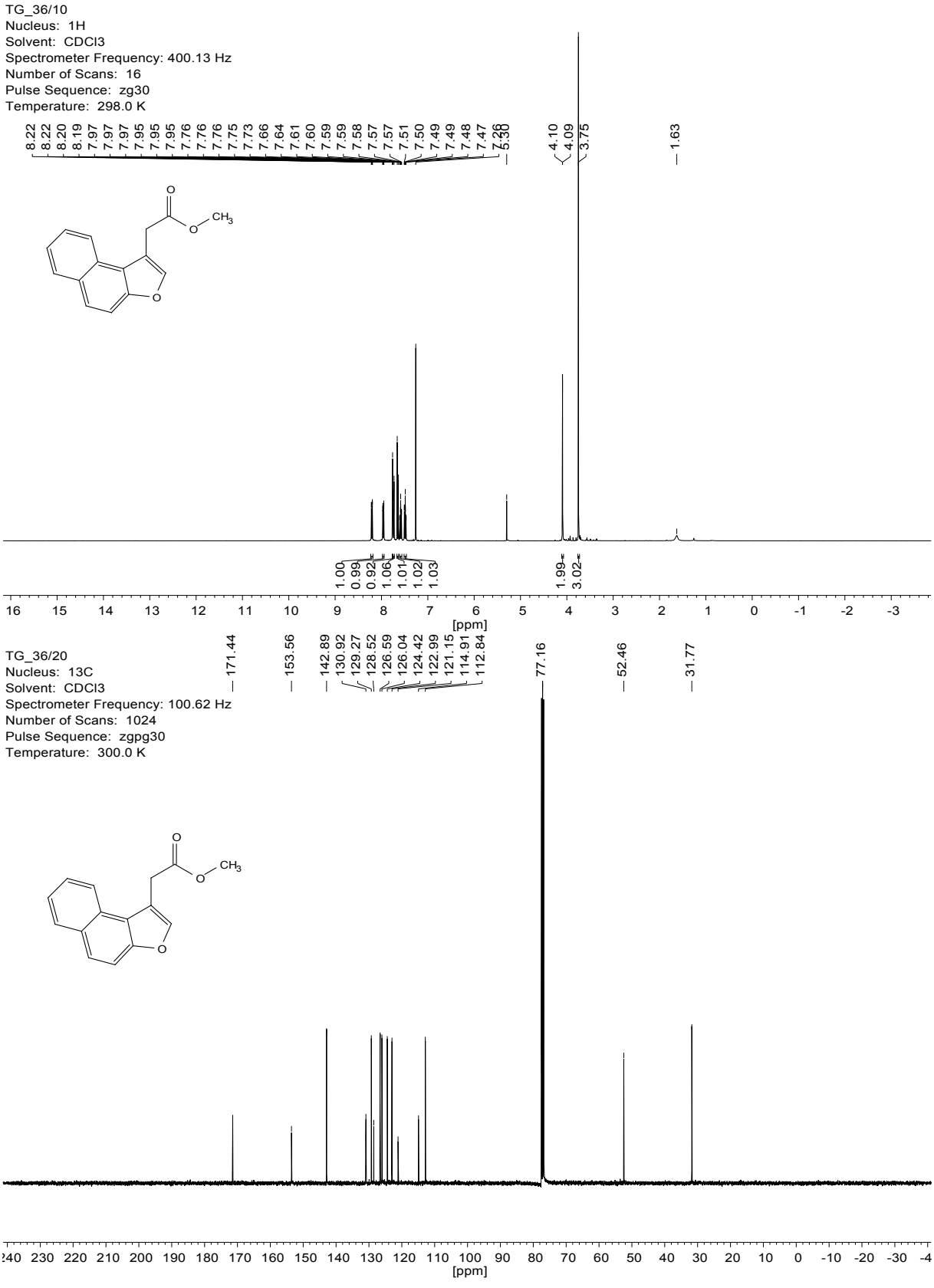


4-Nitrophenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG31)

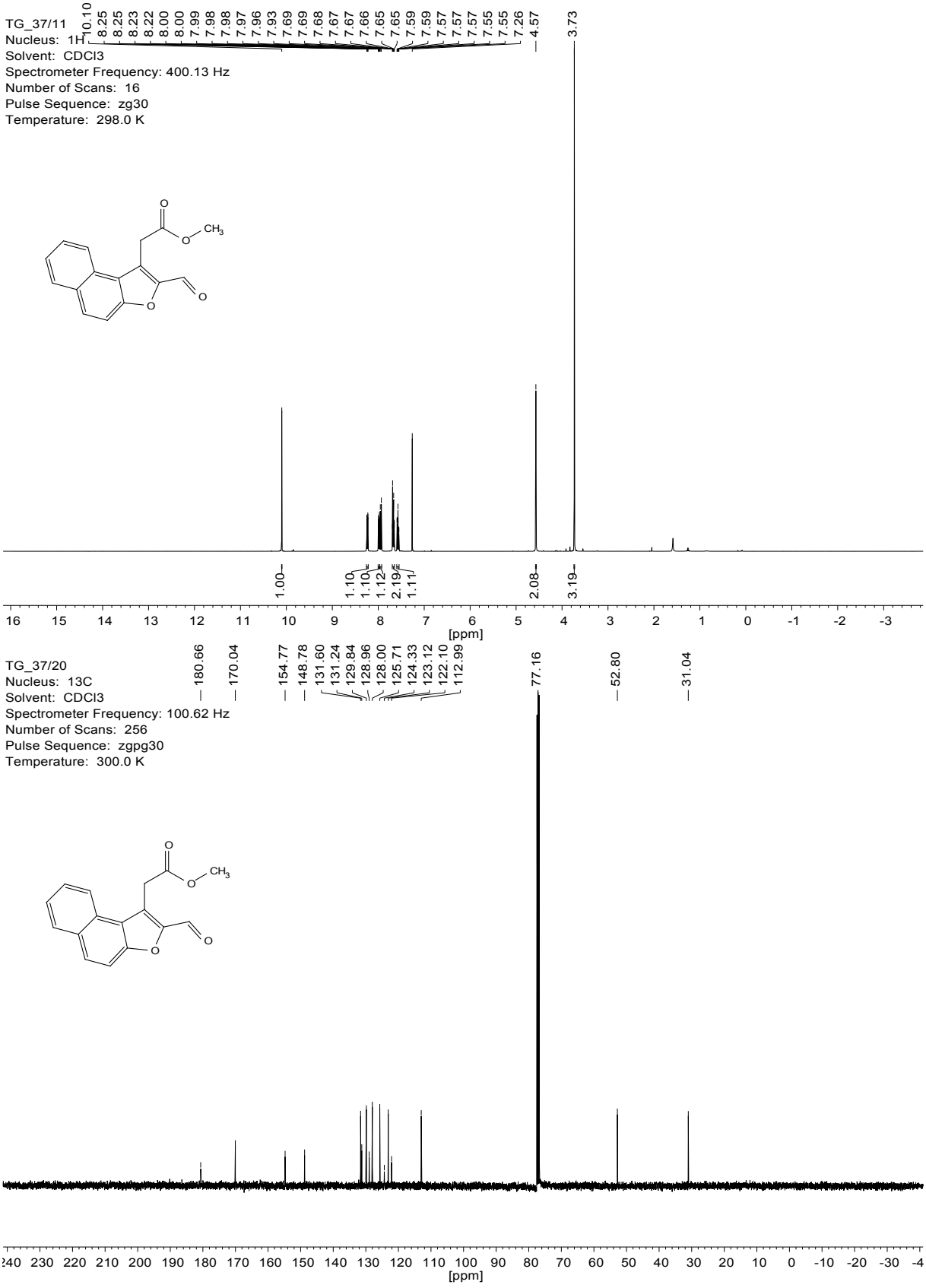




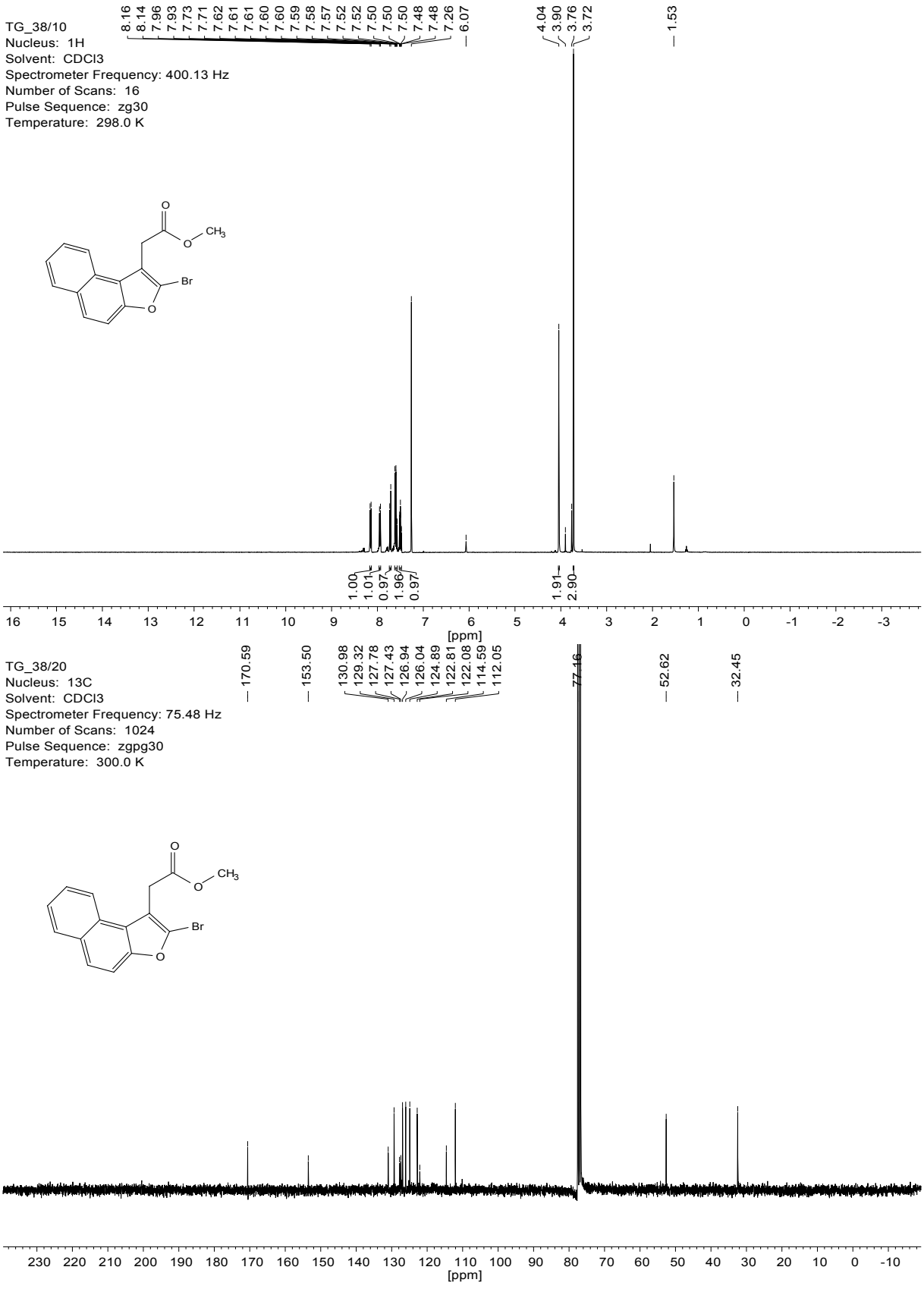
Methyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG36)



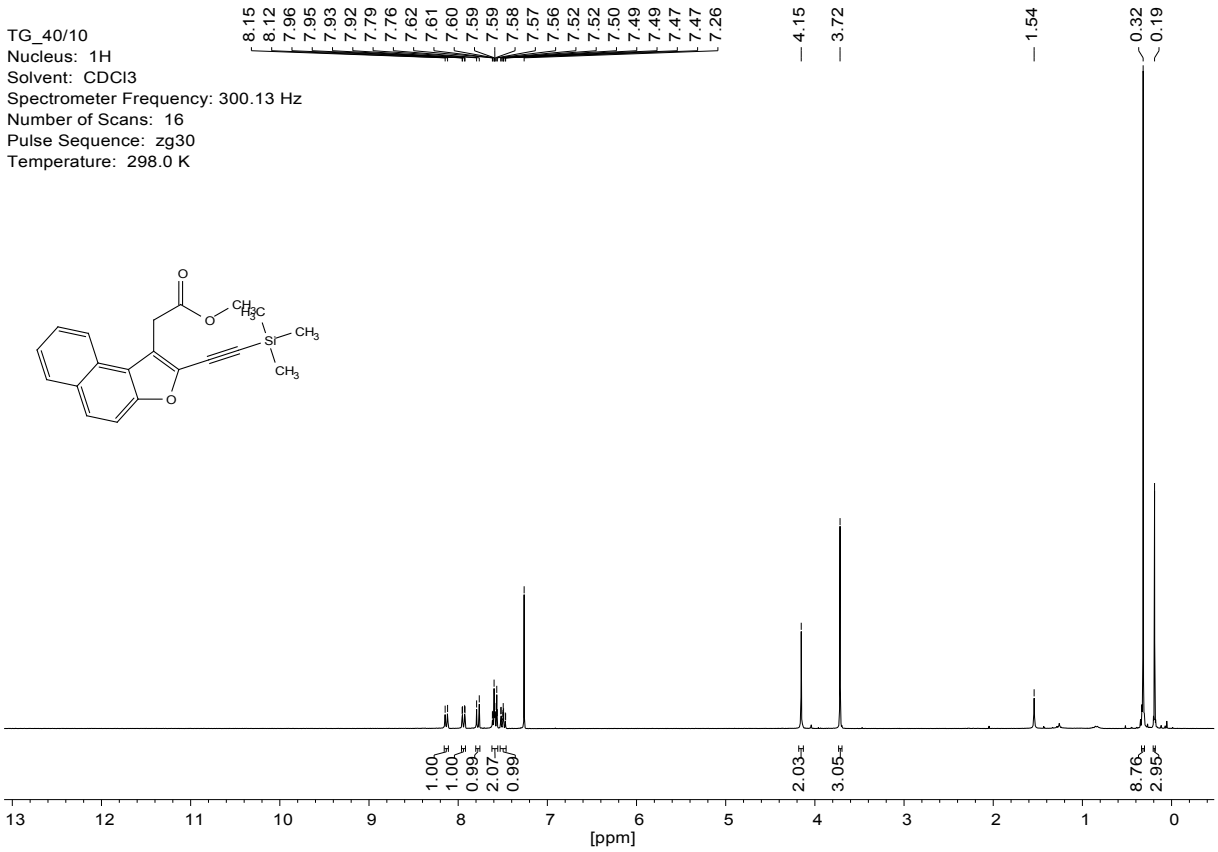
Methyl 2-(2-formylnaphtho[2,1-*b*]furan-1-yl)acetate (TG37)

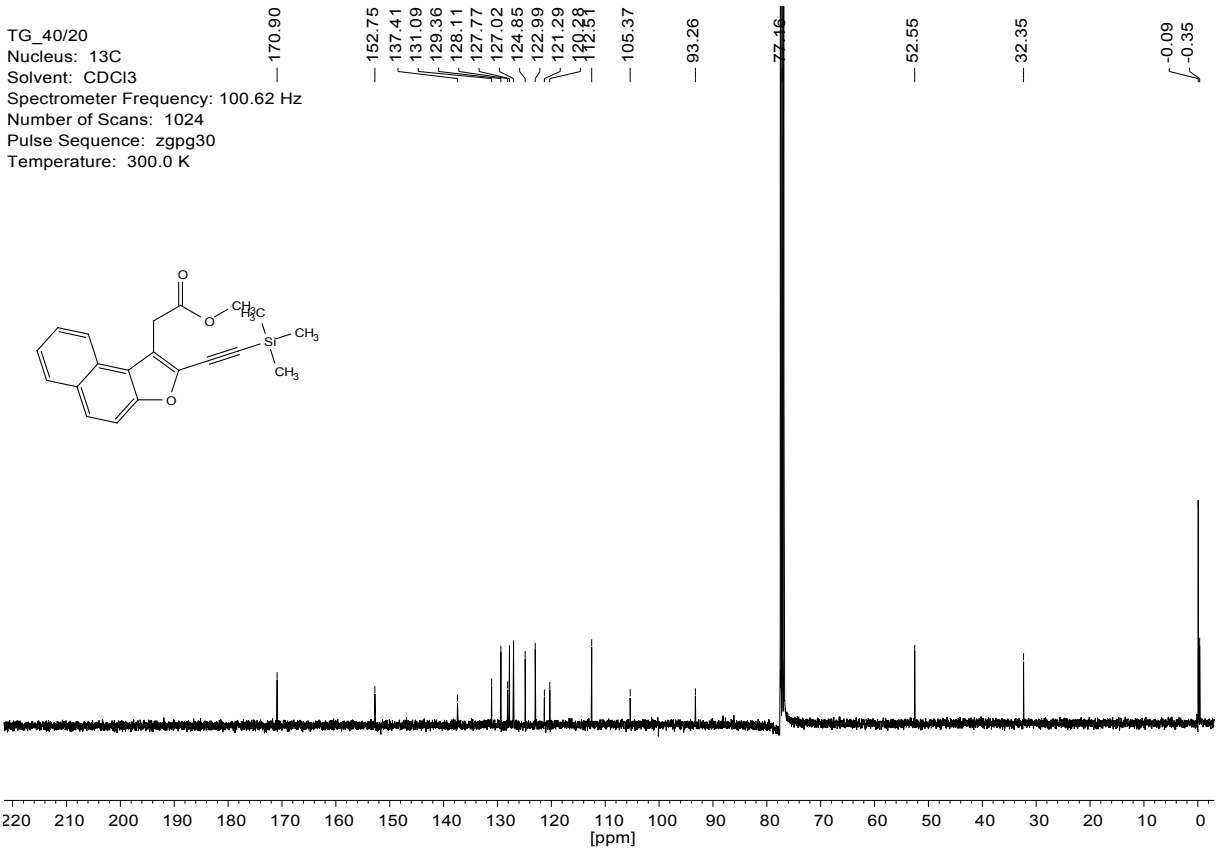


Methyl 2-(2-bromonaphtho[2,1-*b*]furan-1-yl)acetate (TG38)

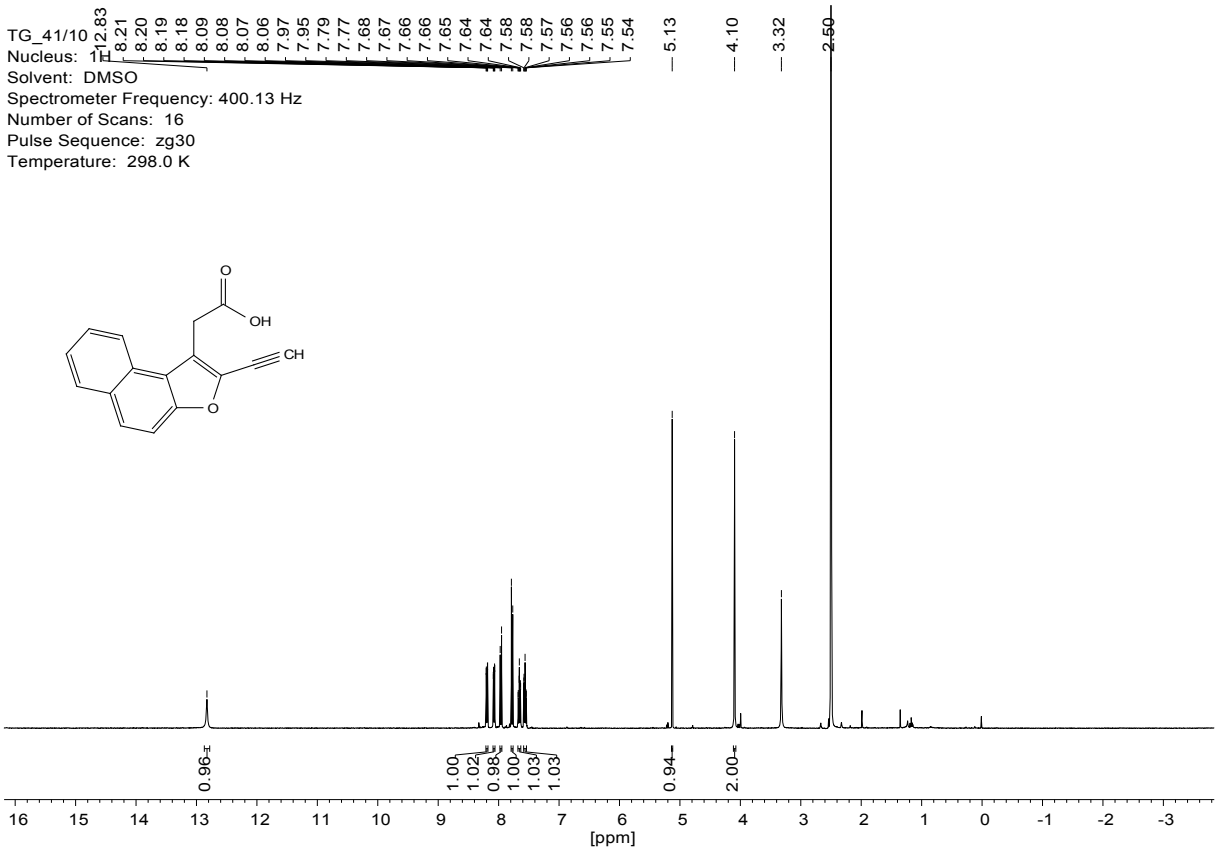


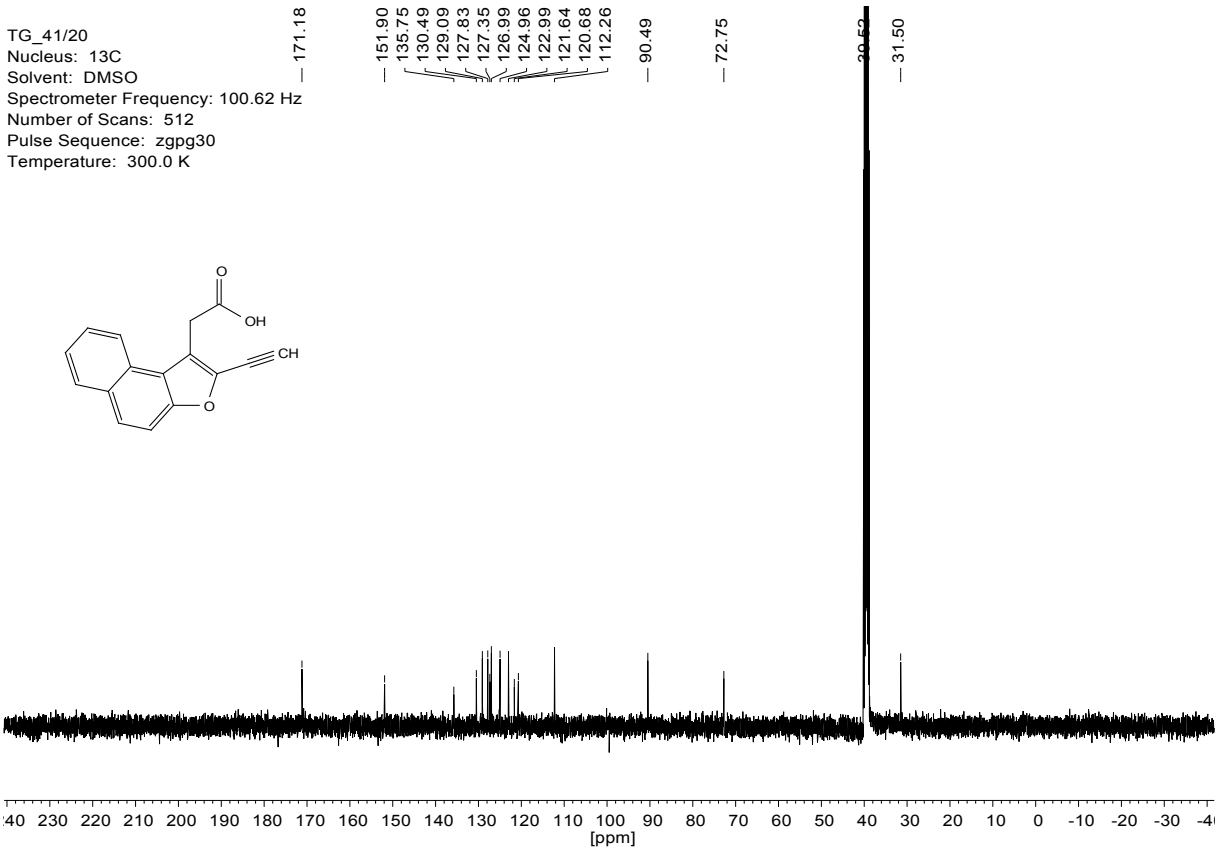
Methyl 2-(2-((trimethylsilyl)ethynyl)naphtho[2,1 *b*] furan-1-yl)acetate (TG40)



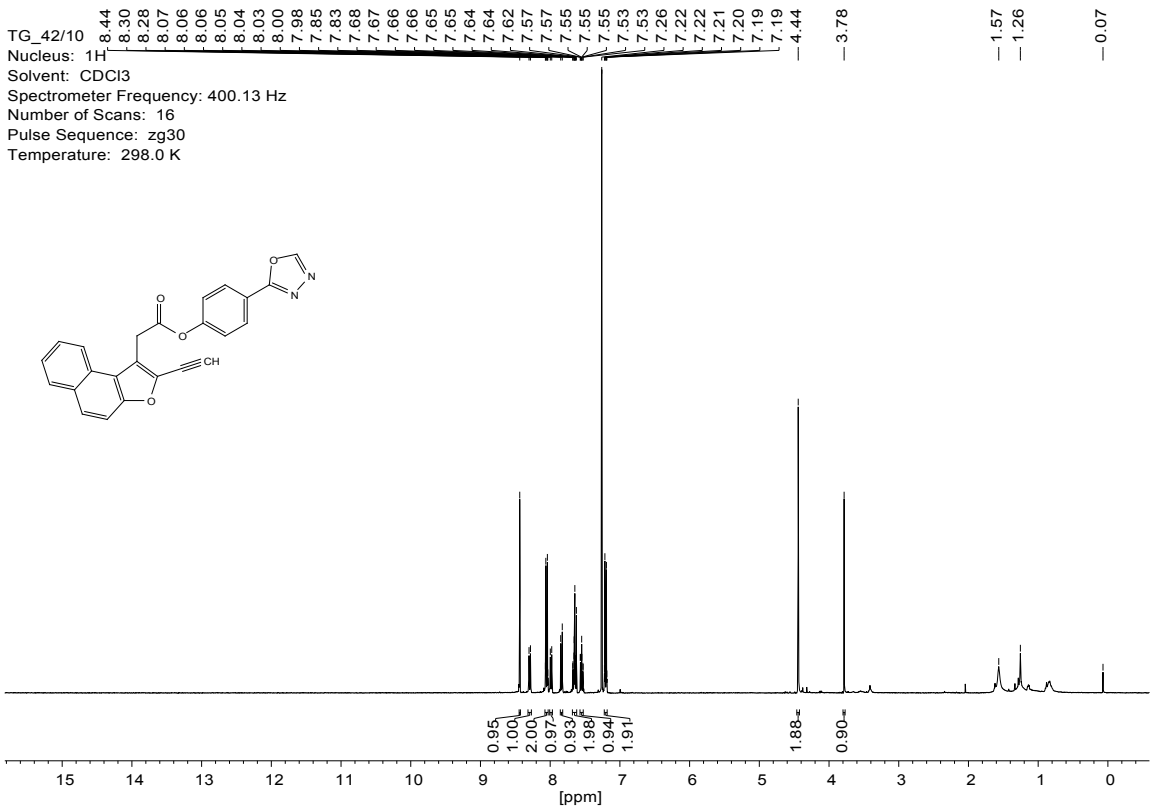


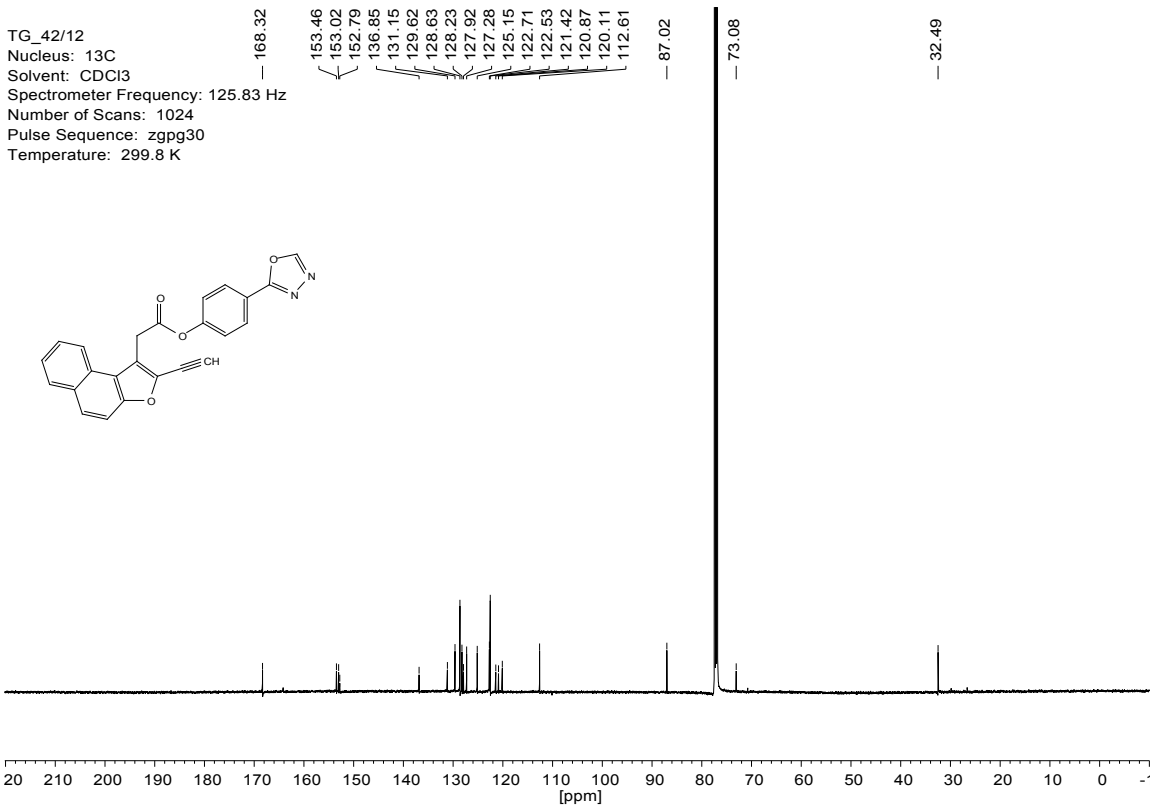
2-(2-Ethynylnaphtho[2,1-*b*]furan-1-yl)acetic acid (TG41)



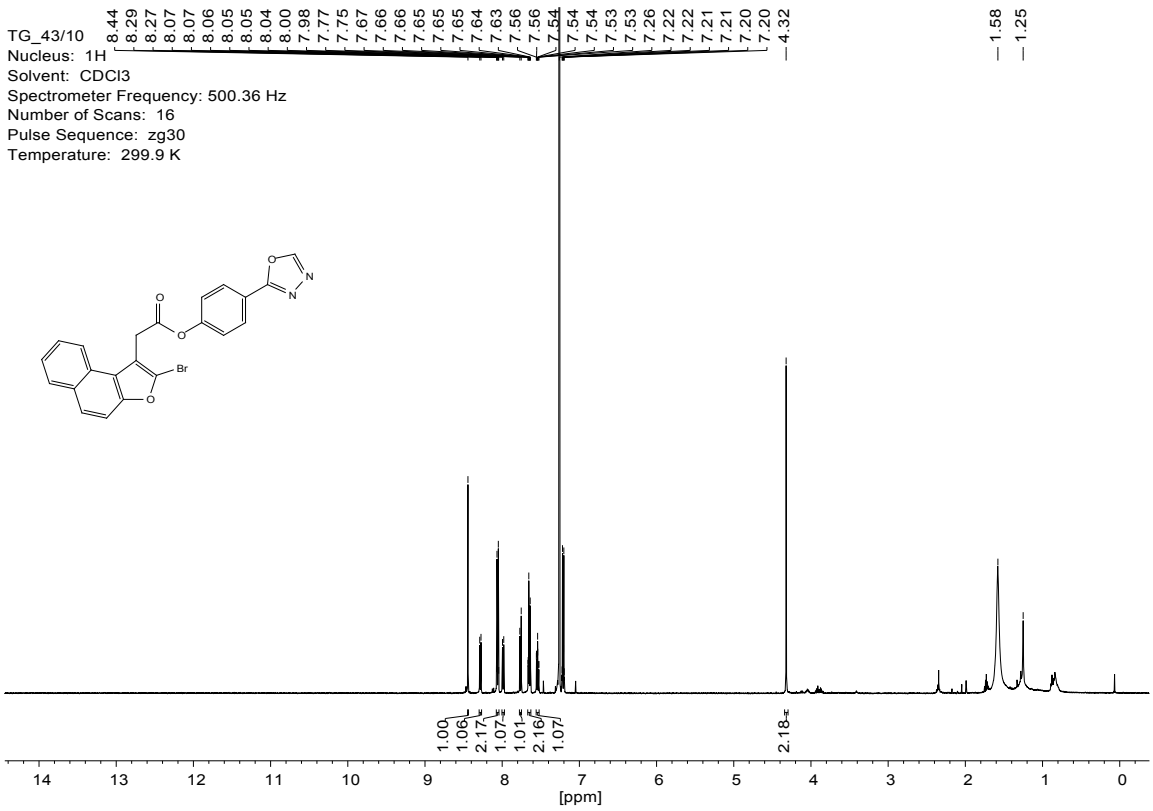


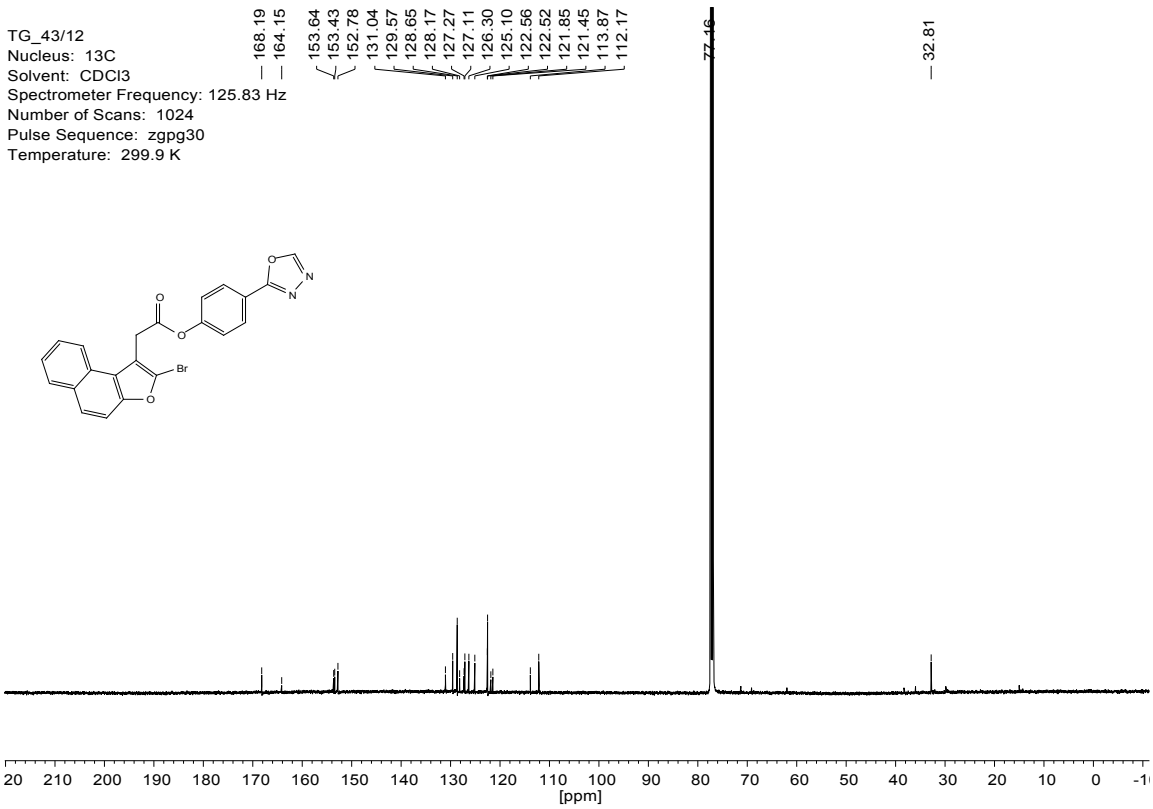
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG42)



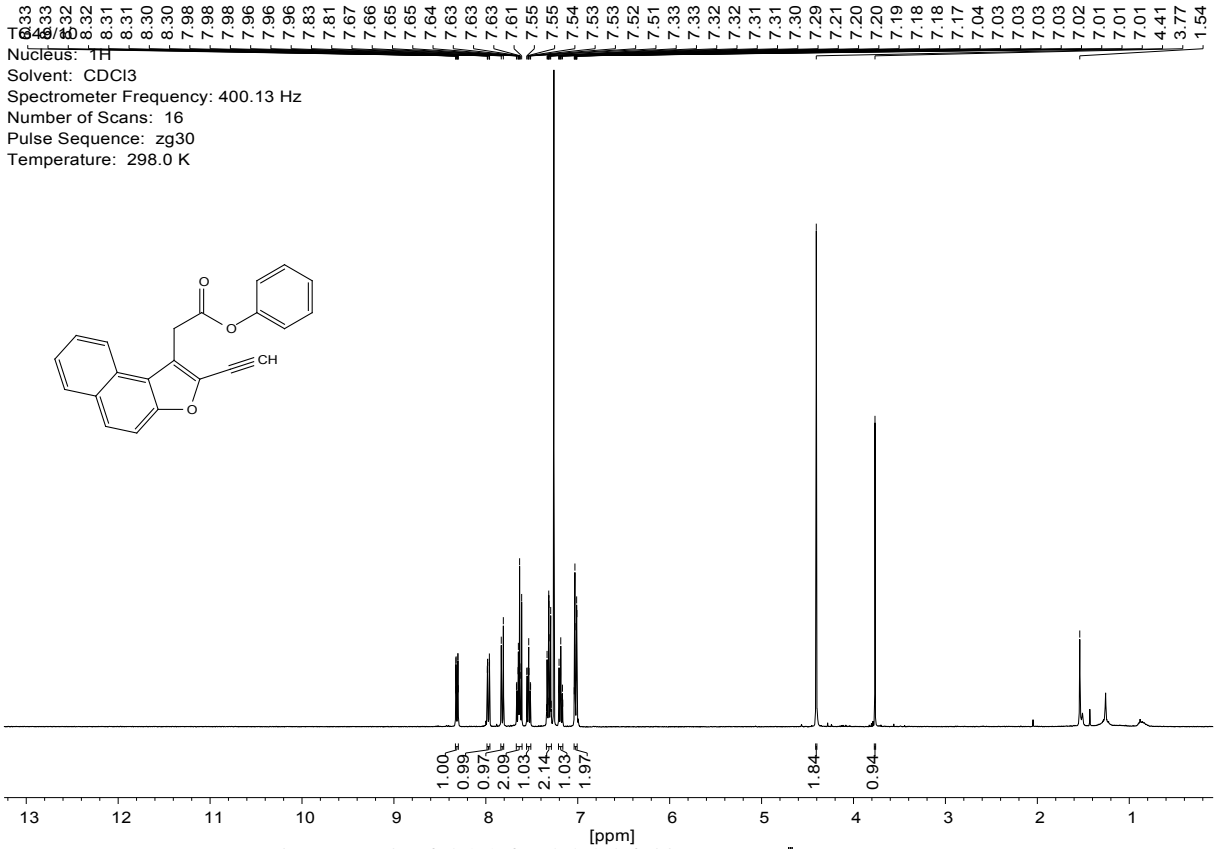


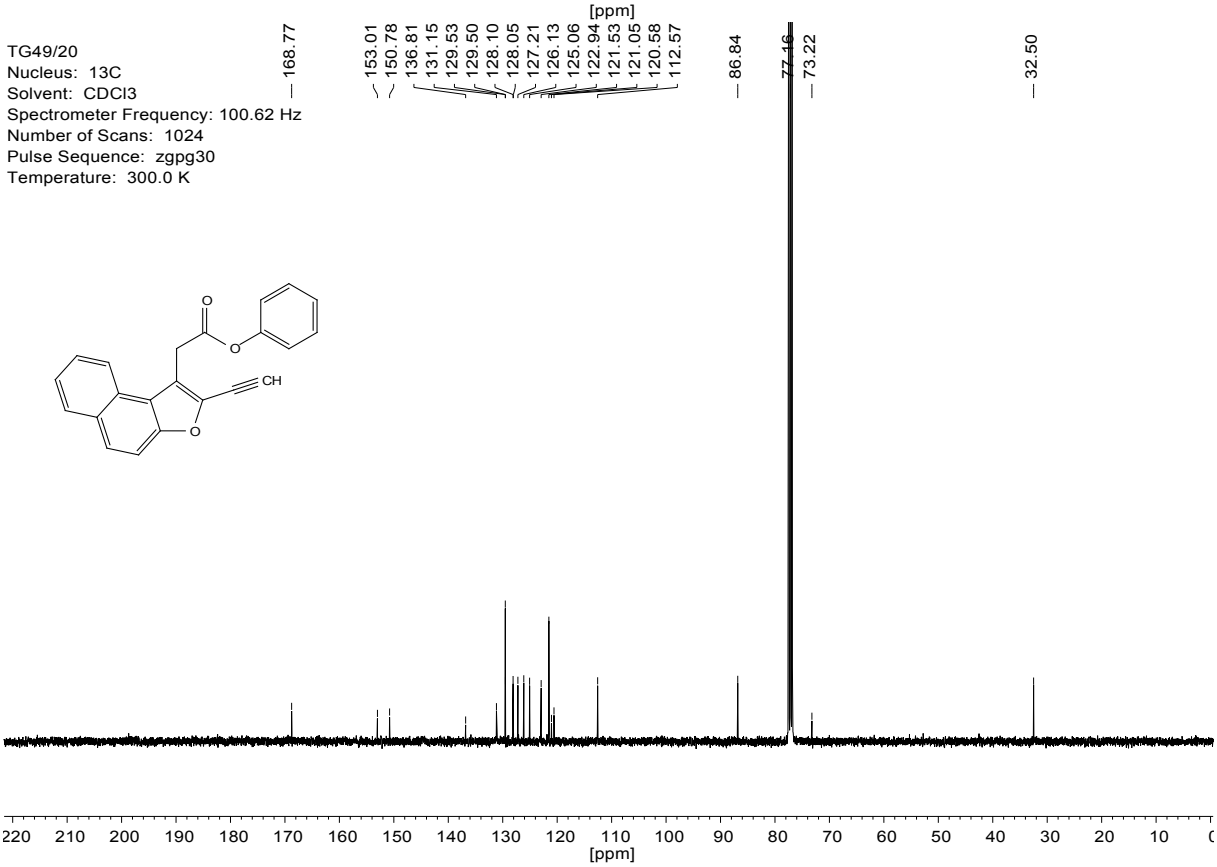
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-bromonaphtho[2,1-*b*]furan-1-yl)acetate (TG43)



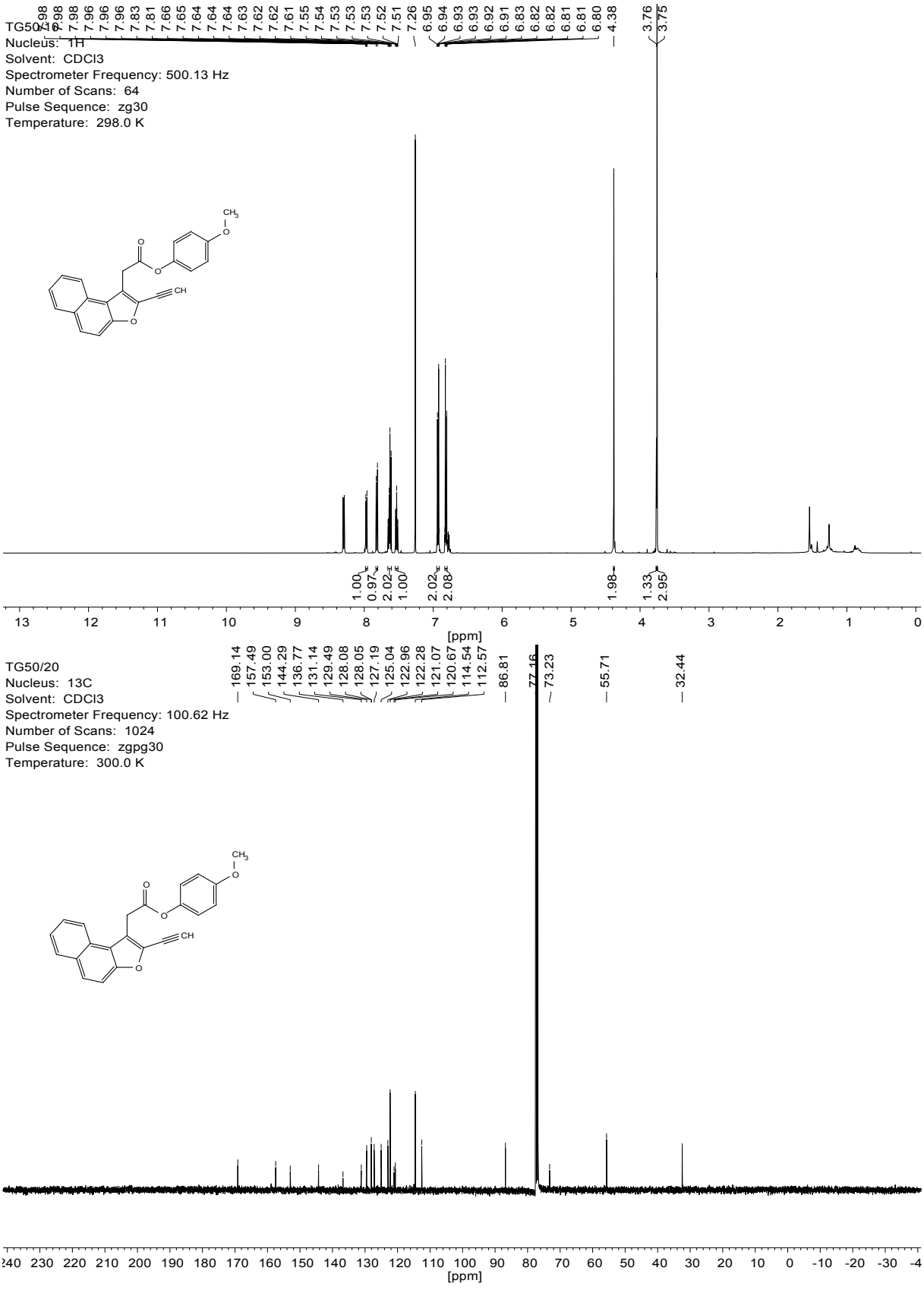


Phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG49)

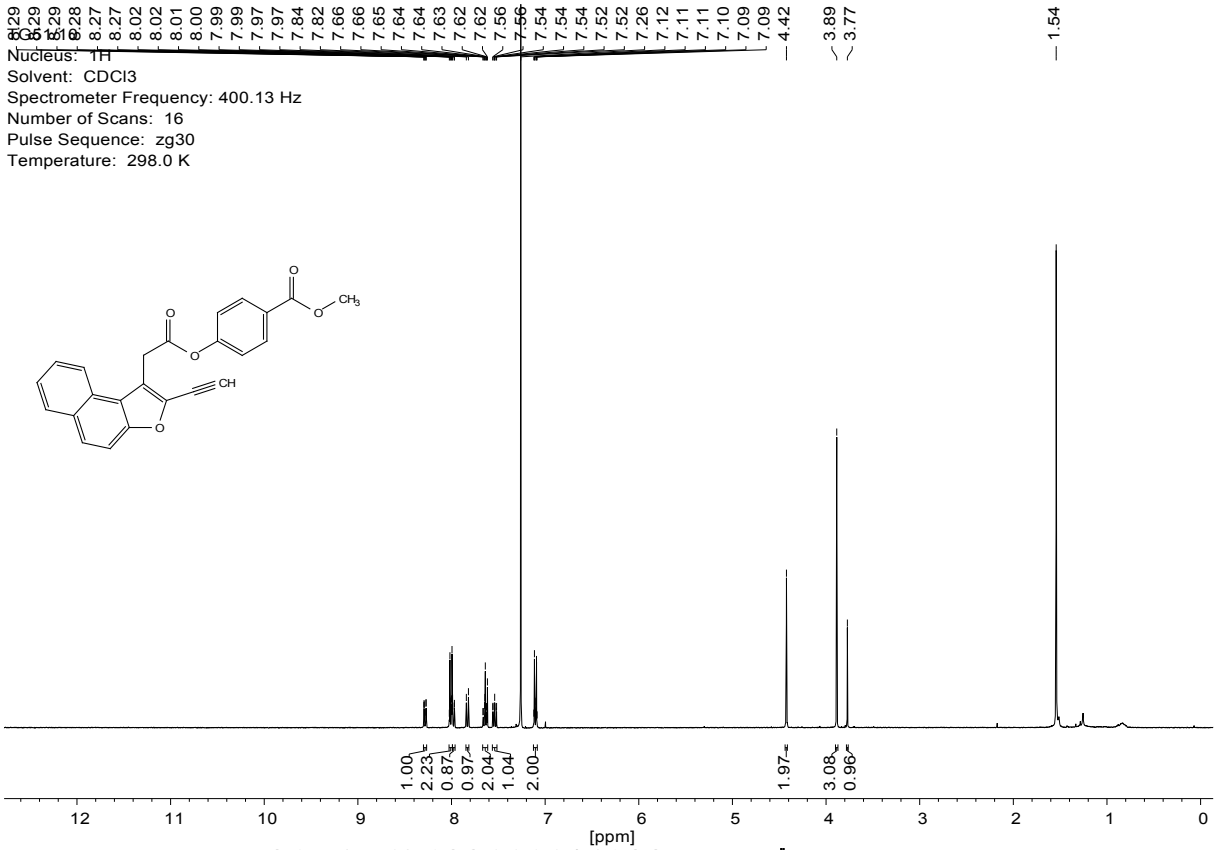


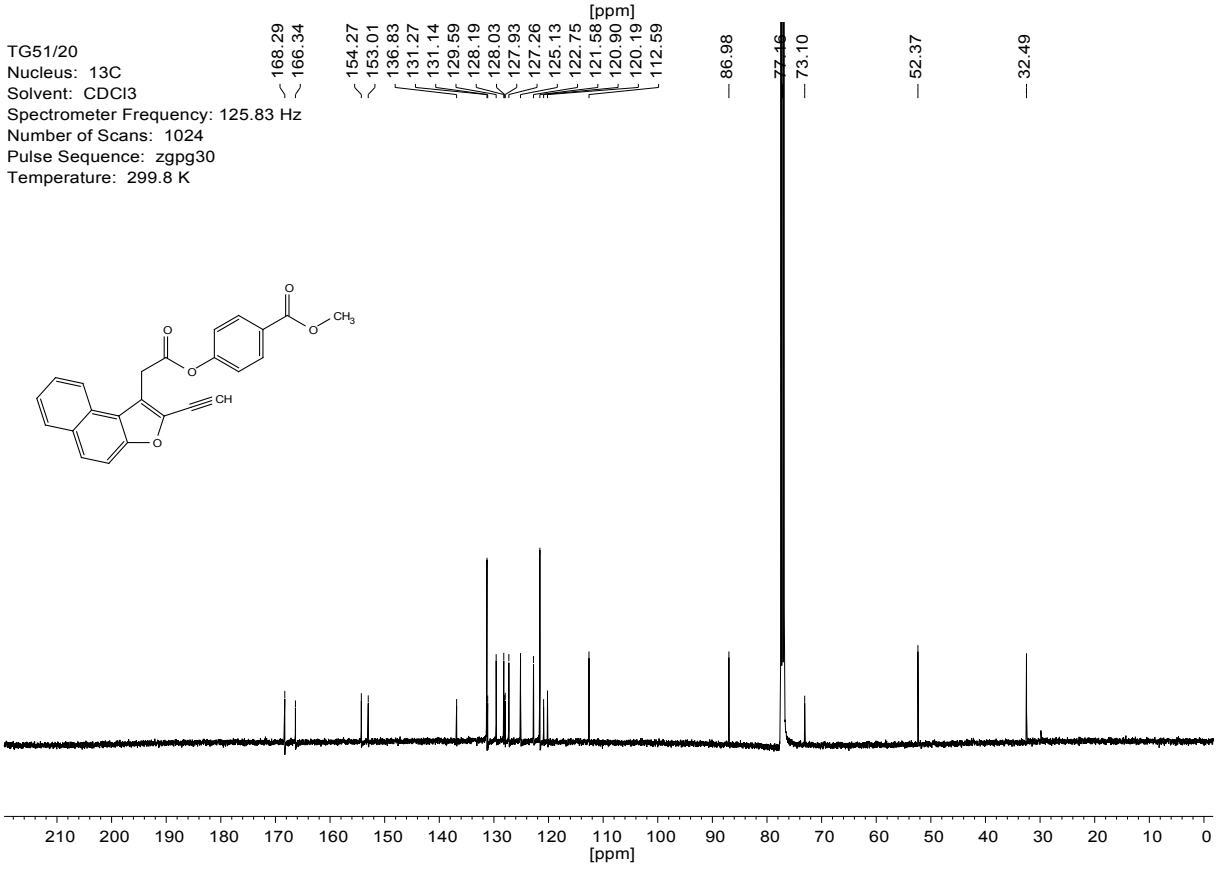


4-Methoxyphenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG50)

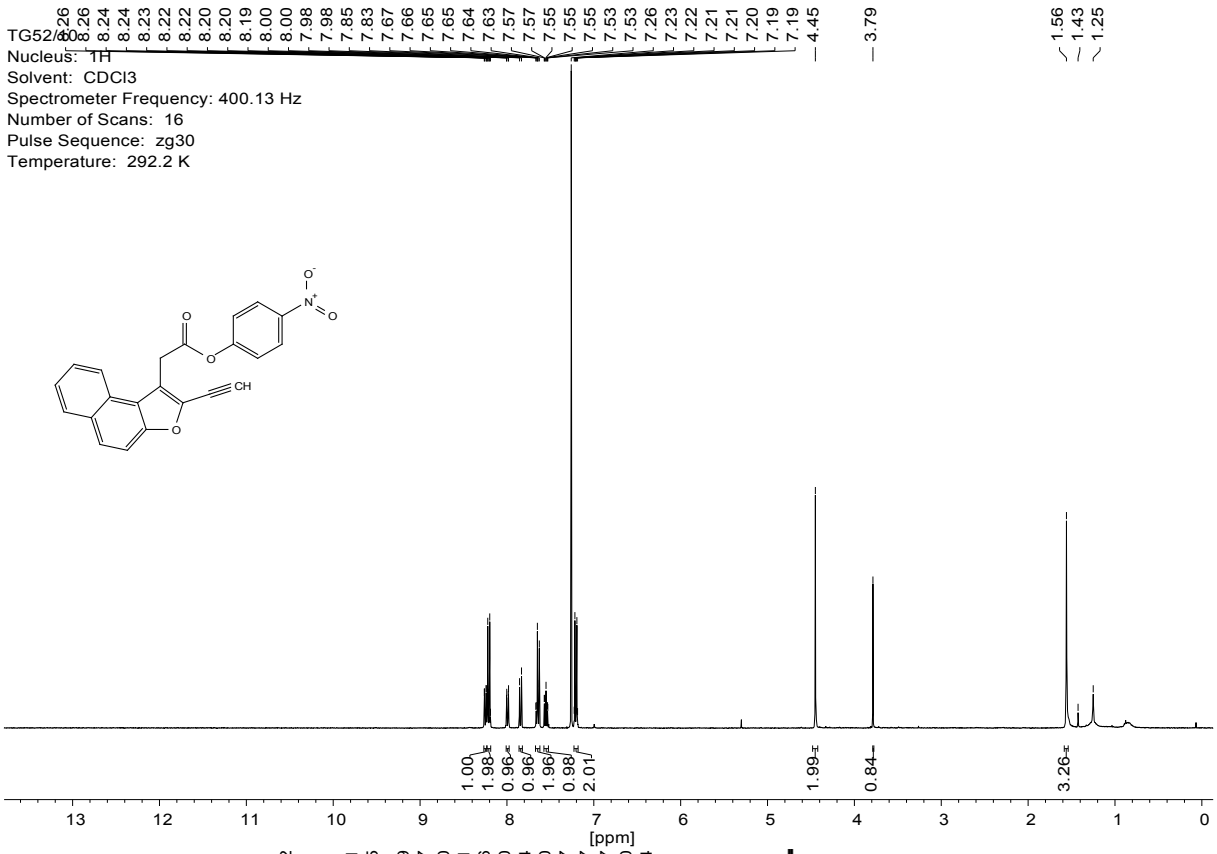


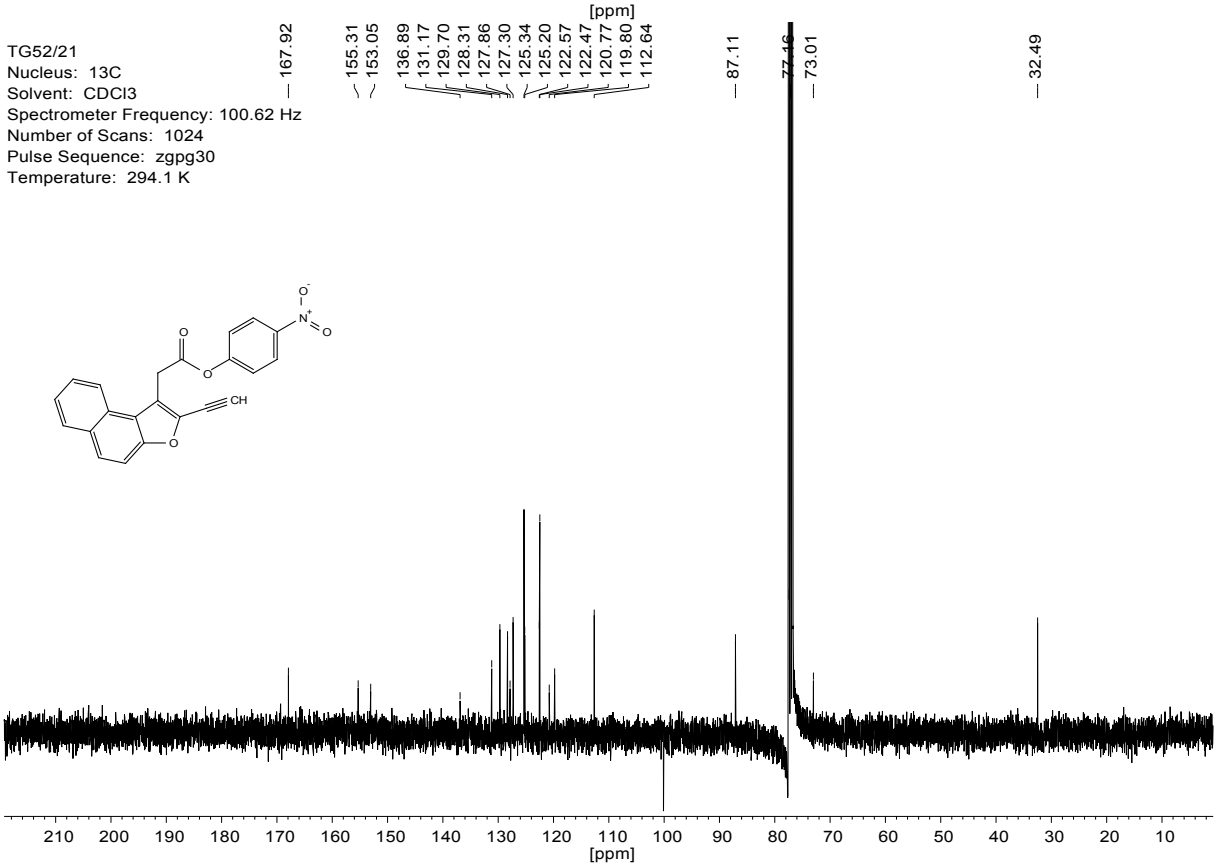
Methyl 4-(2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetoxy)benzoate (TG51)



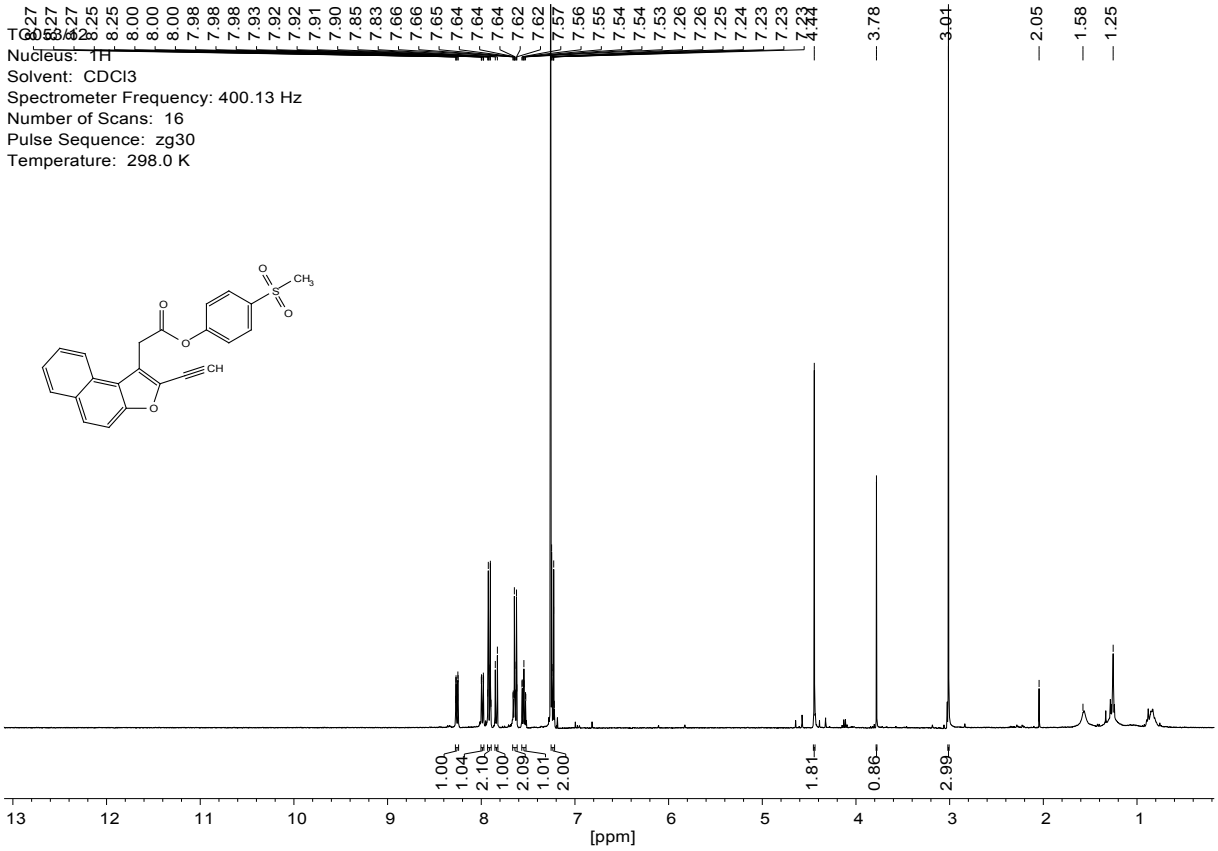


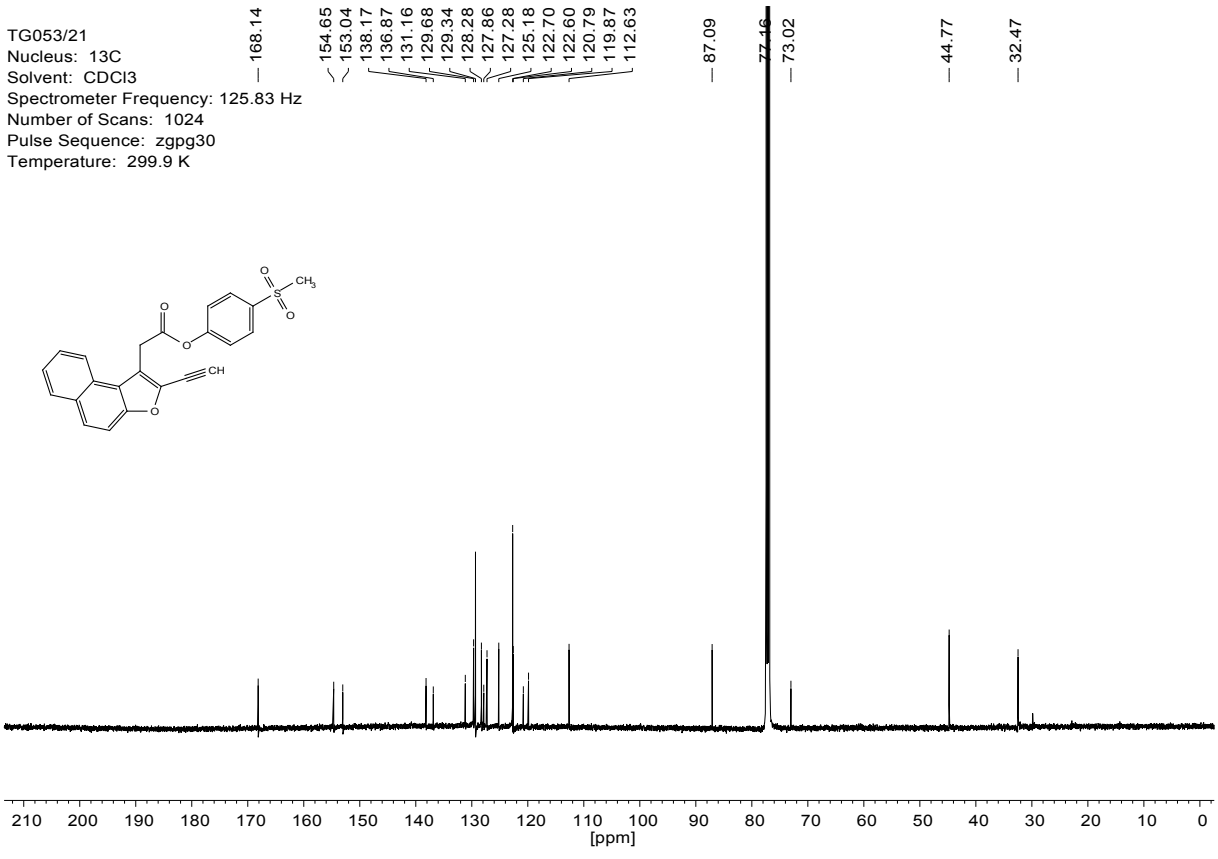
4-Nitrophenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG52)



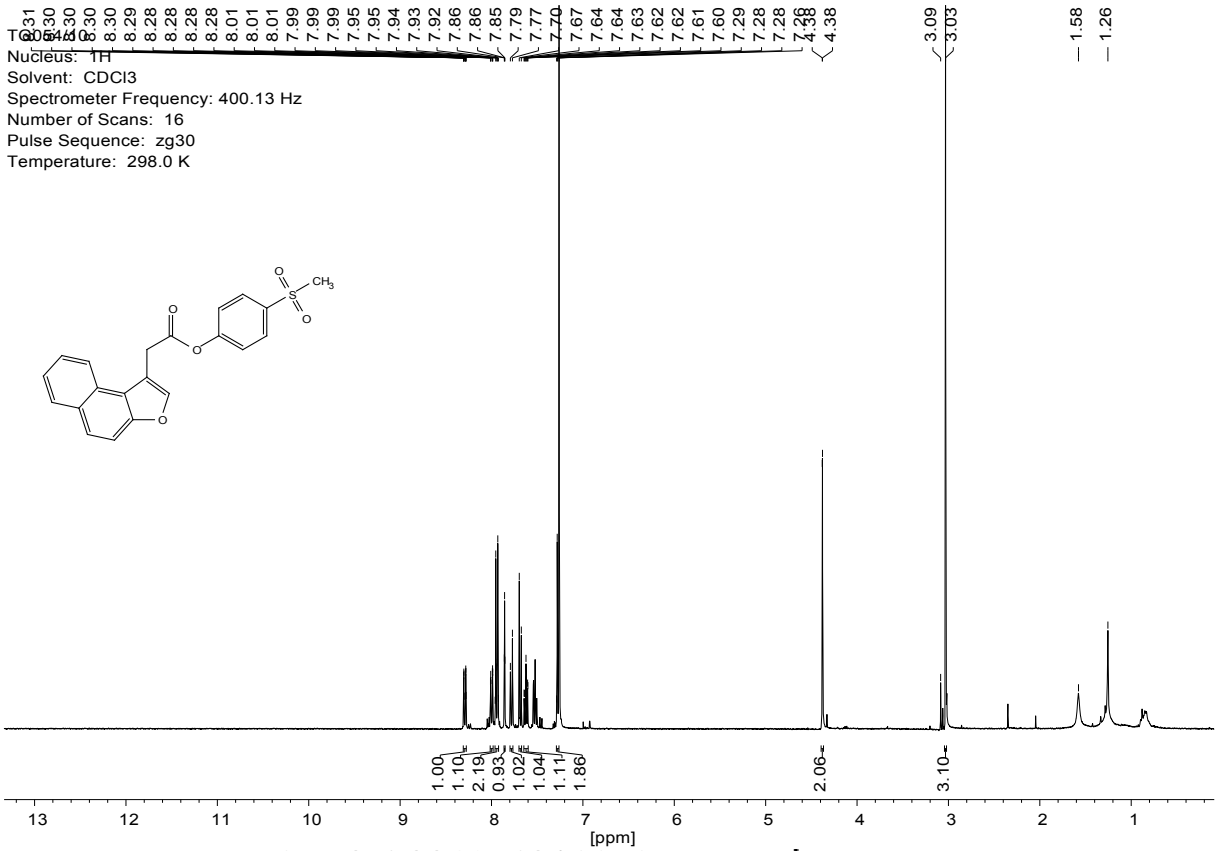


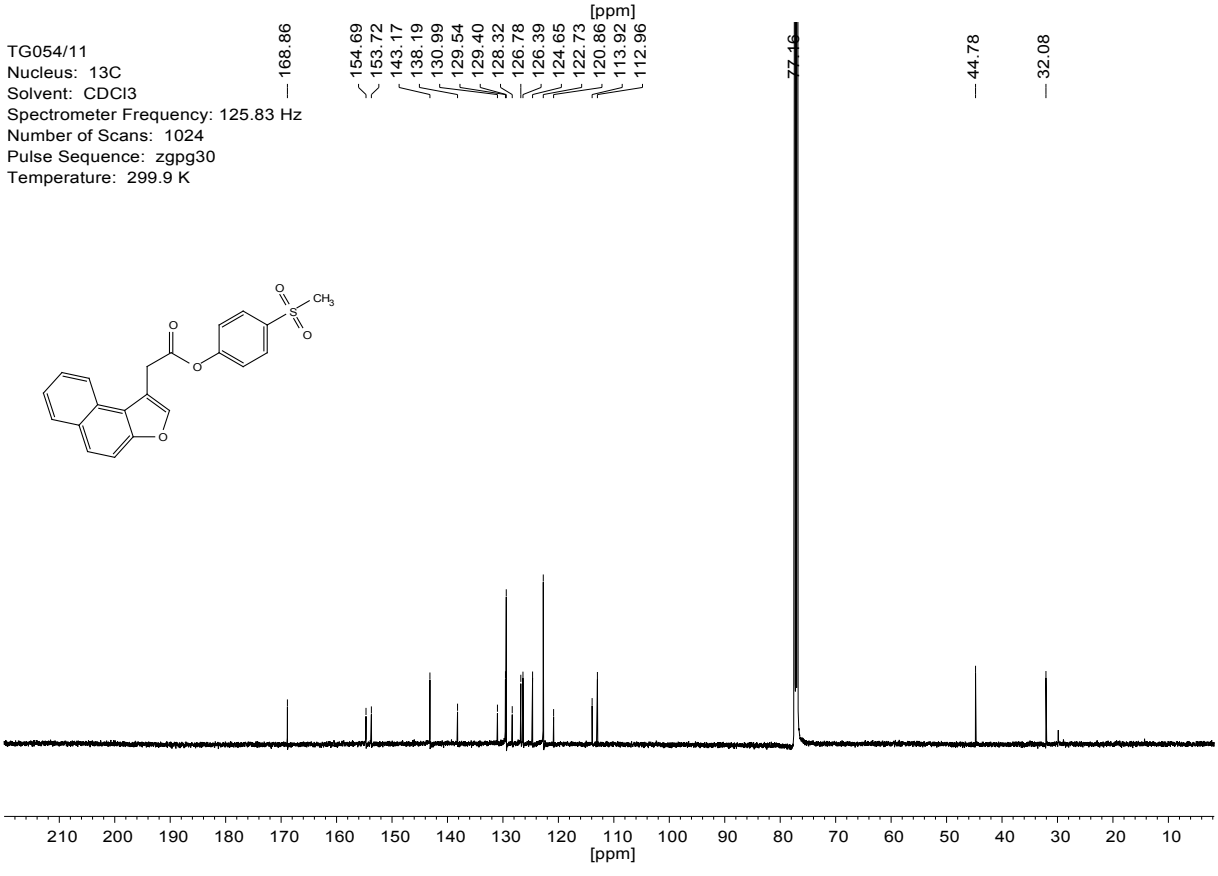
4-(Methylsulfonyl)phenyl 2-(2-ethynylnaphtho[2,1-*b*]furan-1-yl)acetate (TG53)



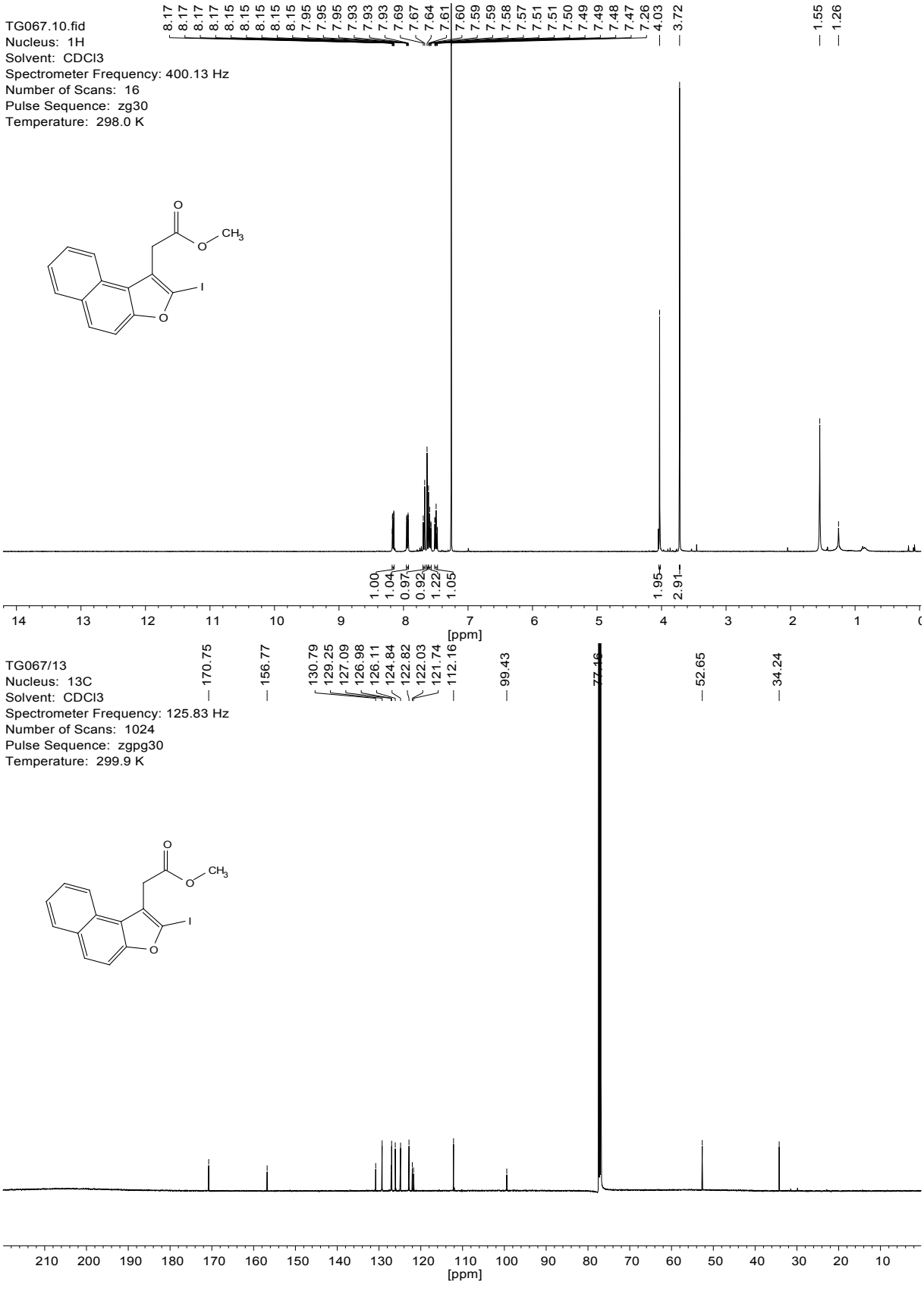


4-(Methylsulfonyl)phenyl 2-(naphtho[2,1-*b*]furan-1-yl)acetate (TG54)

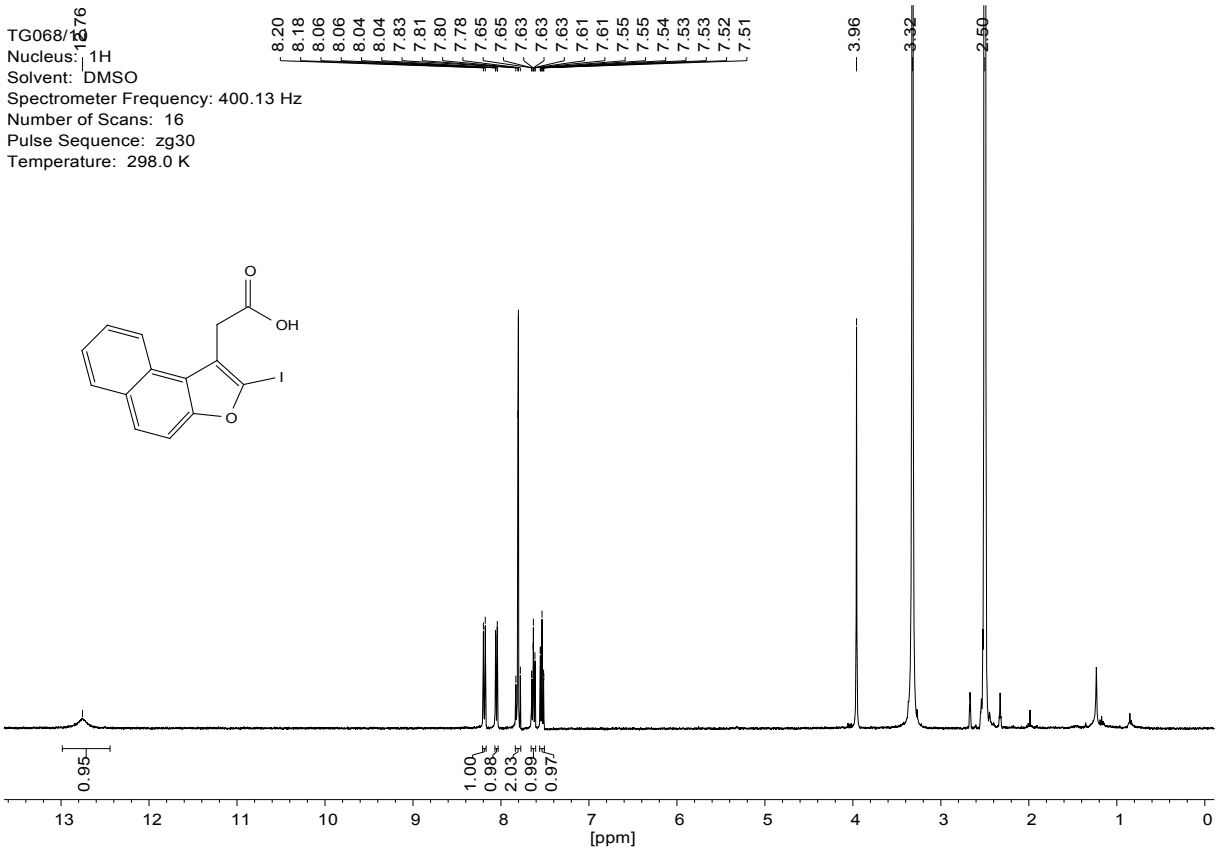


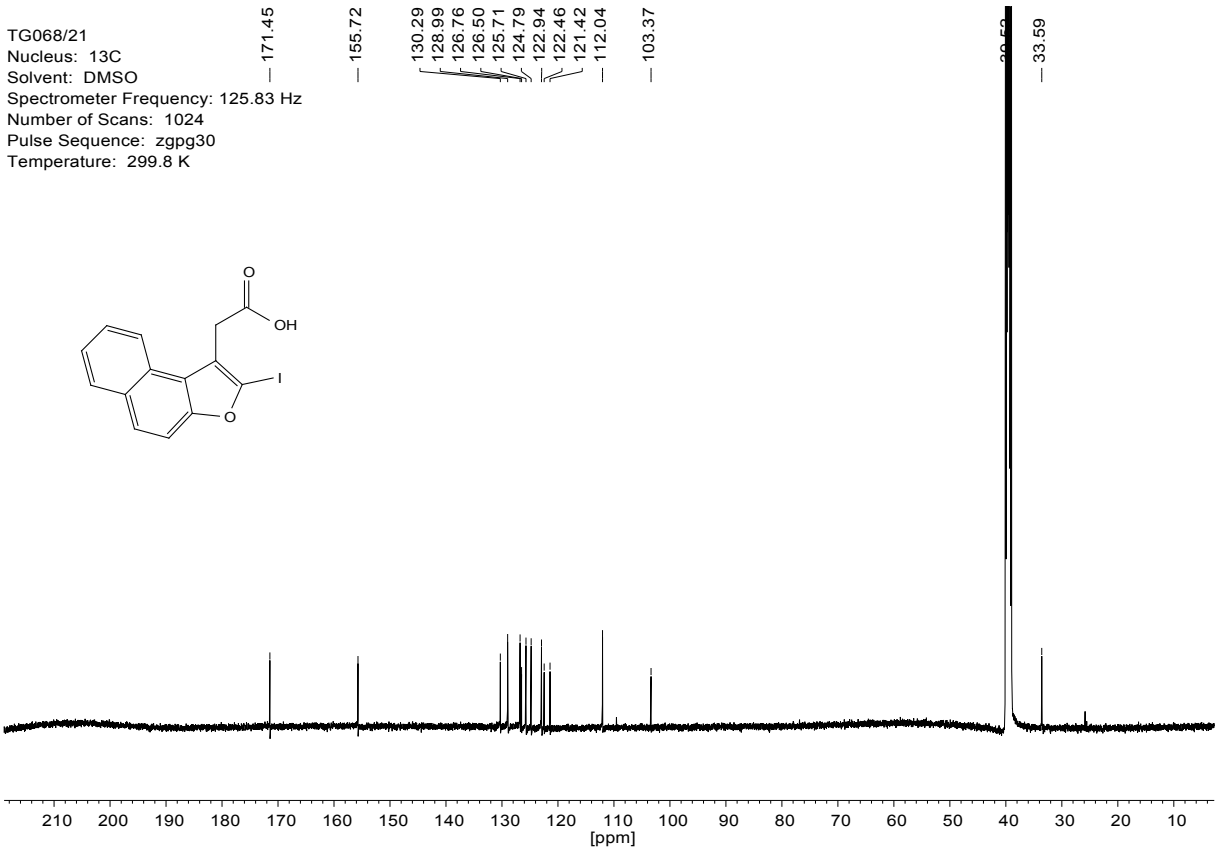


Methyl 2-(2-iodonaphtho[2,1-*b*]furan-1-yl)acetate (TG67)

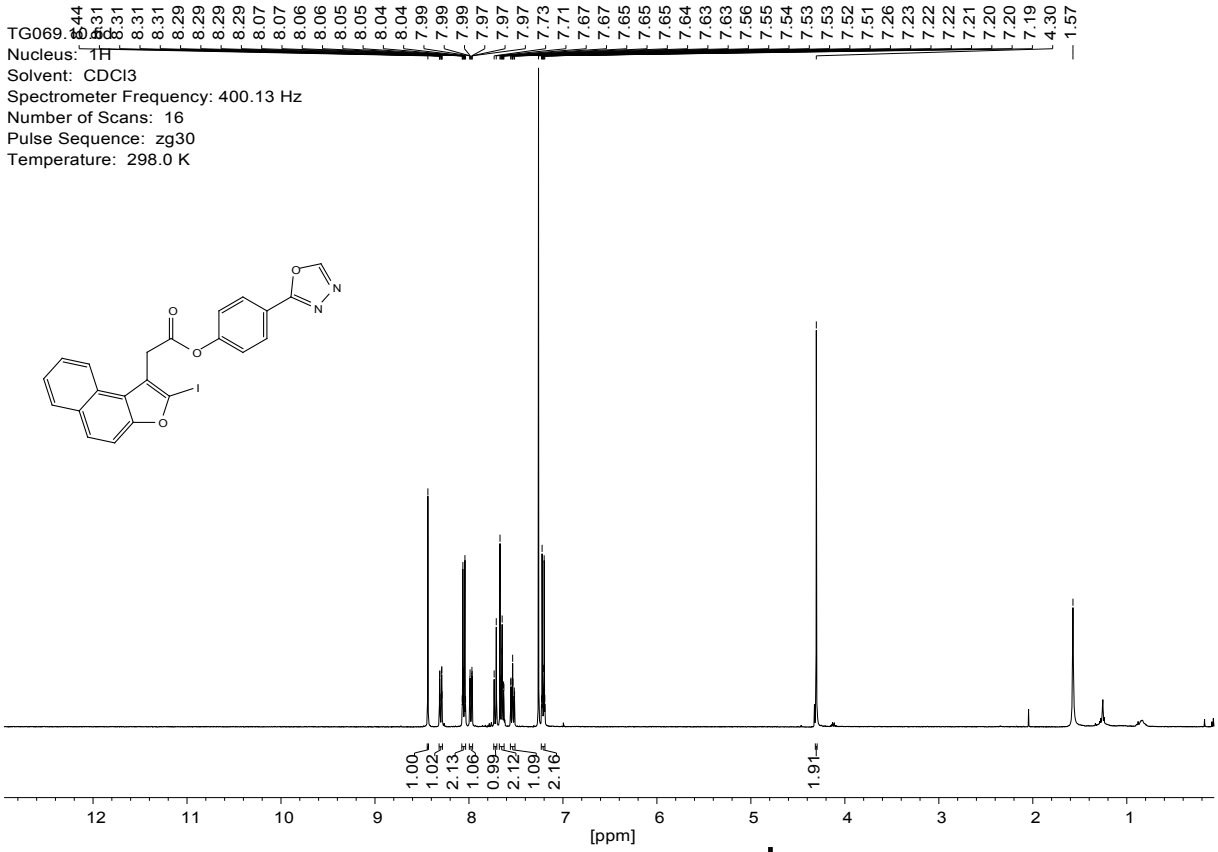


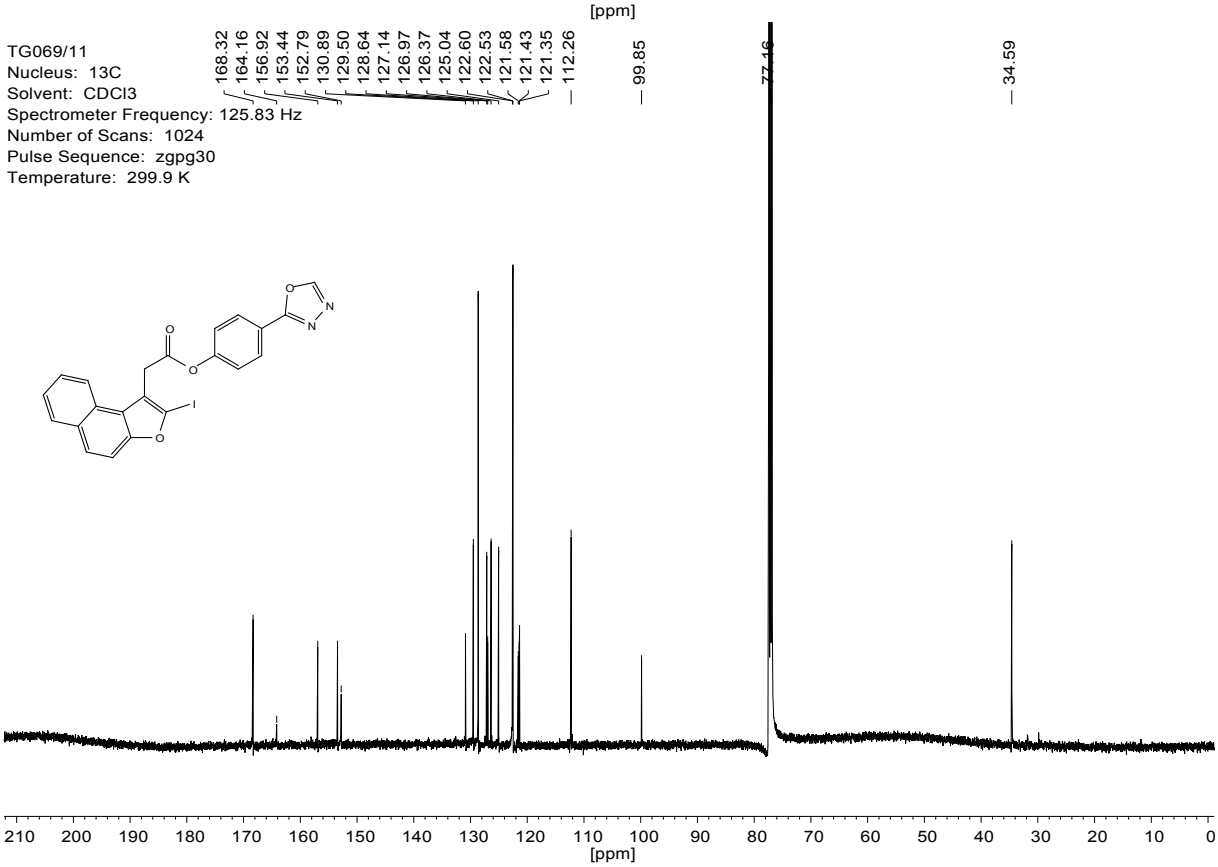
2-(2-Iodonaphtho[2,1-*b*]furan-1-yl)acetic acid (TG68)



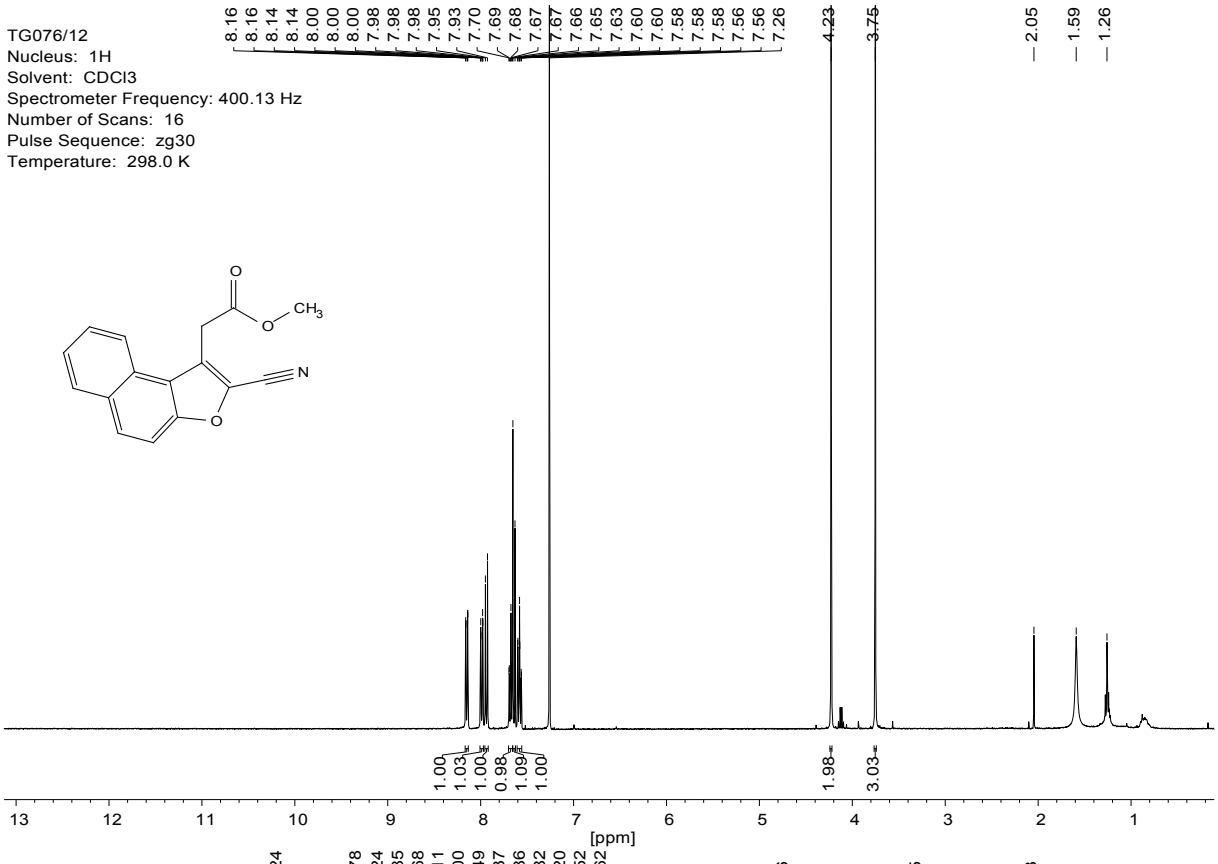


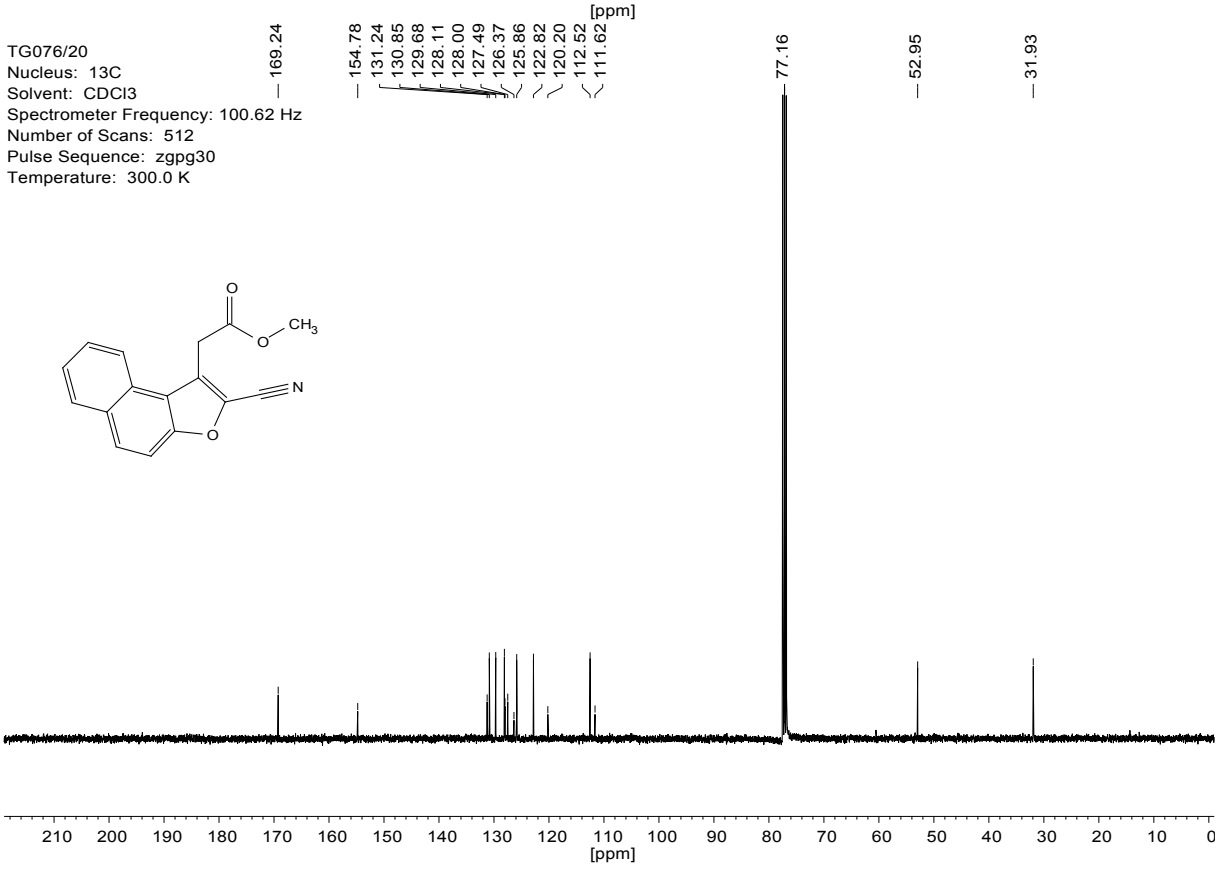
4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-iodonaphtho[2,1-*b*]furan-1-yl)acetate (TG69)



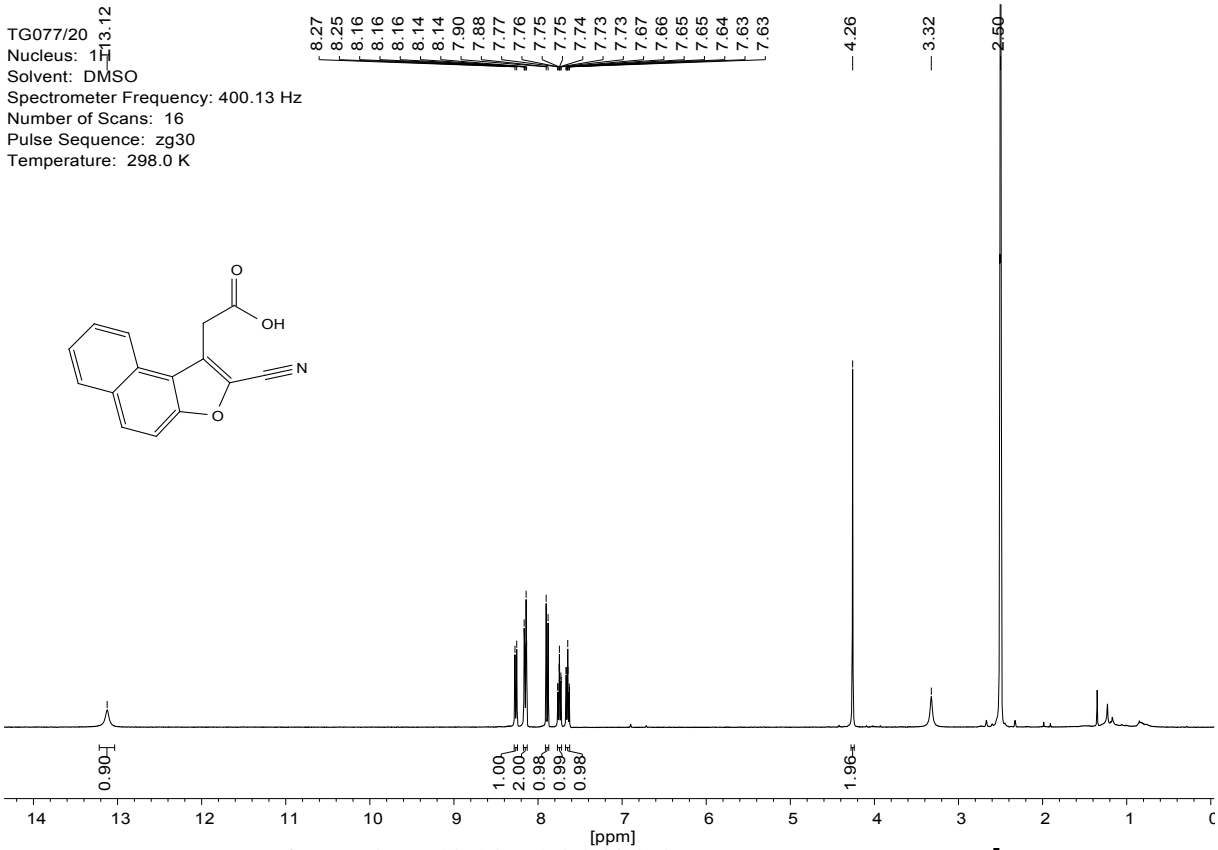


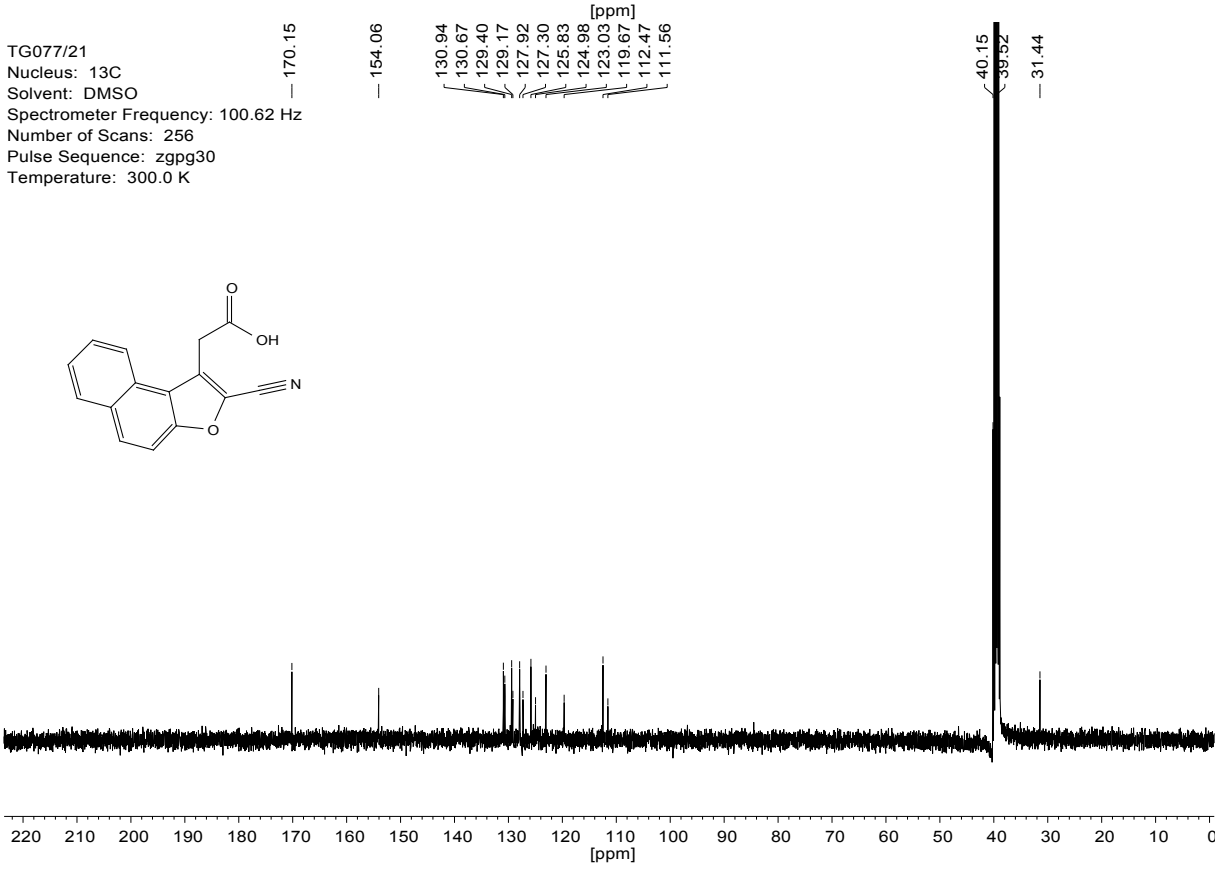
Methyl 2-(2-cyanonaphtho[2,1-*b*]furan-1-yl)acetate (TG76)



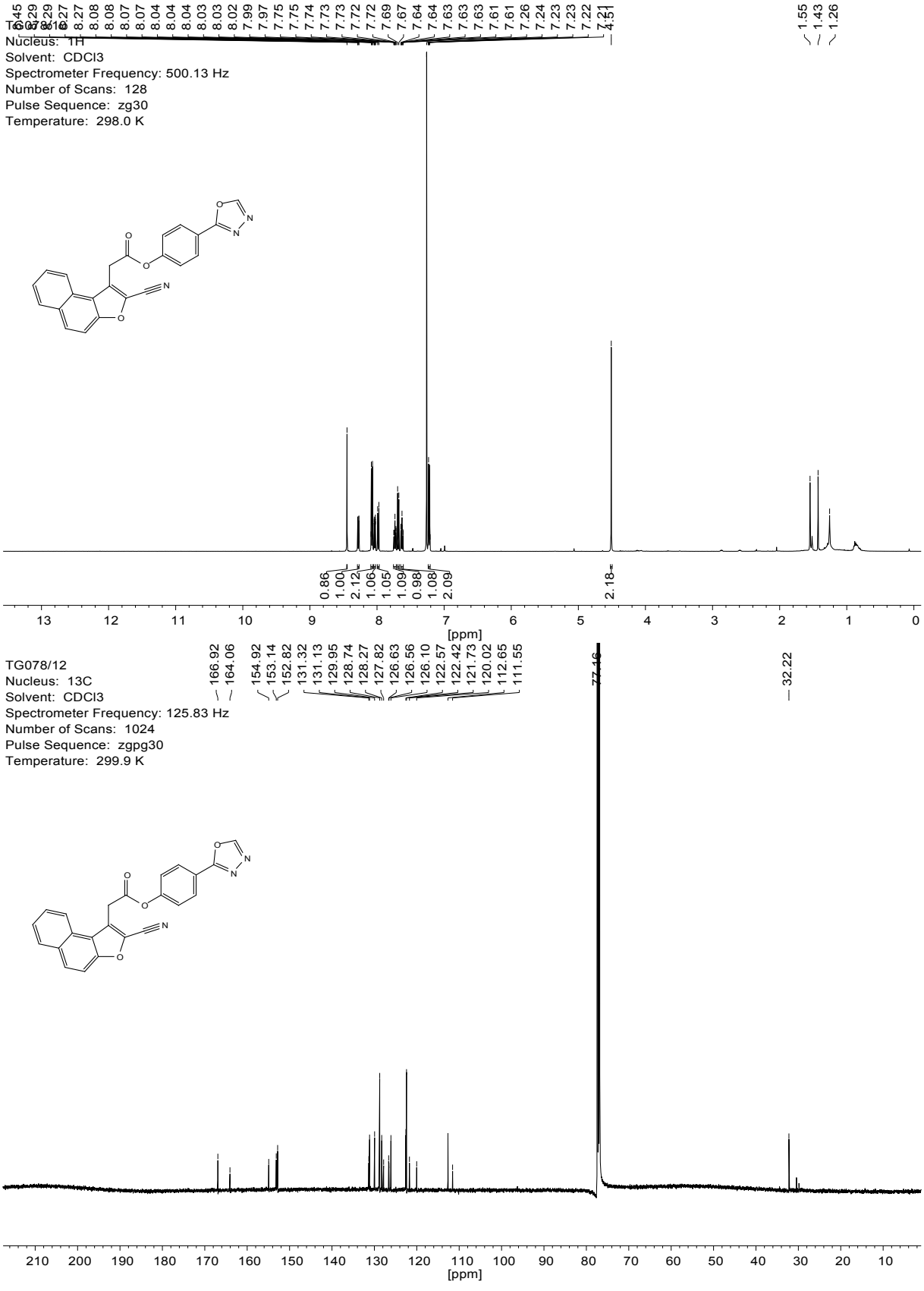


2-(2-Cyanonaphtho[2,1-*b*]furan-1-yl)acetic acid (TG77)





4-(1,3,4-Oxadiazol-2-yl)phenyl 2-(2-cyanonaphtho[2,1-*b*]furan-1-yl)acetate (TG78)



4-(1,3,4-Oxadiazol-2-yl)phenyl-2-(naphtho[2,1-*b*]furan-1-yl)acetate (AV167)