

Supplementary Data A

(Detailed synthetic protocols, compound characterization data and copies of NMR spectra)

Quantum Mechanics-Driven Structure-Activity Relationship Study of PEX5-PEX14 Protein-Protein Interaction Inhibitors Based On a Dibenzo[*b,e*]azepin-6(6*H*)-one Scaffold

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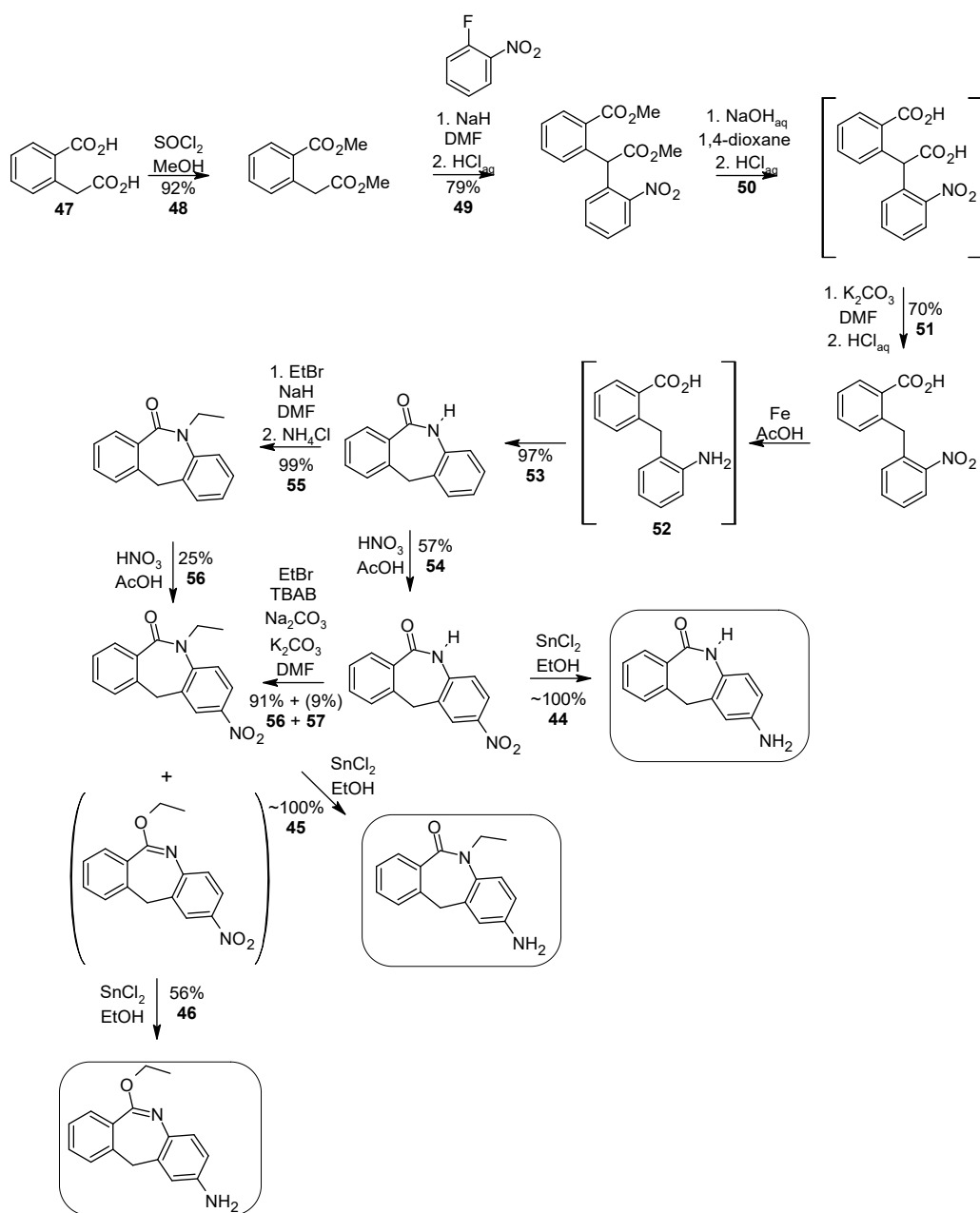
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General remarks

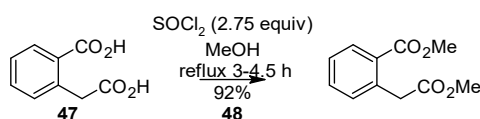
Thin layer chromatography (TLC) was carried out on Merck TLC 60 aluminium sheets (silica gel and RP-18). Normal-phase flash column chromatography (CC) was performed using Merck silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh ASTM). Reverse-phase CC separations were conducted using cartridge columns (12 g or 24g SiliCycle SiliaSep™ C18). LC-MS analyses were performed on an Agilent 1220 Infinity II Gradient LC System coupled with an Agilent LC/MSD single-quadrupole detector (column: Poroshell 120, EC-C18, 3.0 × 50 mm, 2.7 μm; gradient: water/MeCN containing 0.1% formic acid (v/v), 5–95% MeCN; UV detection at 220 and 254 nm). NMR data were recorded on Agilent 400 MHz 400-MR DD2 or Varian NMR System (500 MHz) instruments. ¹H NMR peaks are reported as follows: chemical shift (δ) in parts per million (ppm) relative to residual non-deuterated solvent as the internal standards, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, m = multiplet and br = broad signal), coupling constant (in Hz), number of nuclei and proton assignment. The compounds having a methylene group in the central seven-membered ring often occur as pairs of atropisomers which is a known phenomenon eg. in 1,4-benzodiazepines [1, 2] and 1*H*-dibenzo[*b,e*]-azepine derivatives [3]. If an additional stereogenic center is present in the dibenzo[*b,e*]azepin-6(6*H*)-one derivatives obtained herein, pairs of diastereoisomers of atropisomers are seen in the respective ¹H, ¹³C, (¹⁹F and ³⁵P if concerns) NMR spectra (*see additional comments in the respective NMR peaklists*). Optical rotation analysis was performed with a Perkin Elmer 241 polarimeter using a sodium lamp (λ = 589 nm, D-line), at 20 °C. The specific rotation [α]_D values are reported in 10⁻¹ deg cm² g⁻¹, the concentrations (*c*) are in g/100 mL. The final compounds were ≥95% pure, as determined by ¹H NMR.

Reagents and solvents were purchased from commercial suppliers and used without further purification. Some of the reactions (especially for key substrates) were repeated on various scales. In such cases, the most representative protocols were described.

Synthesis of key building blocks for target 5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one inhibitors.



Methyl 2-(2-methoxy-2-oxoethyl)benzoate (**48**)



Two similar, literature-adapted procedures[4] were employed for synthesis of diester **48**:

Method A

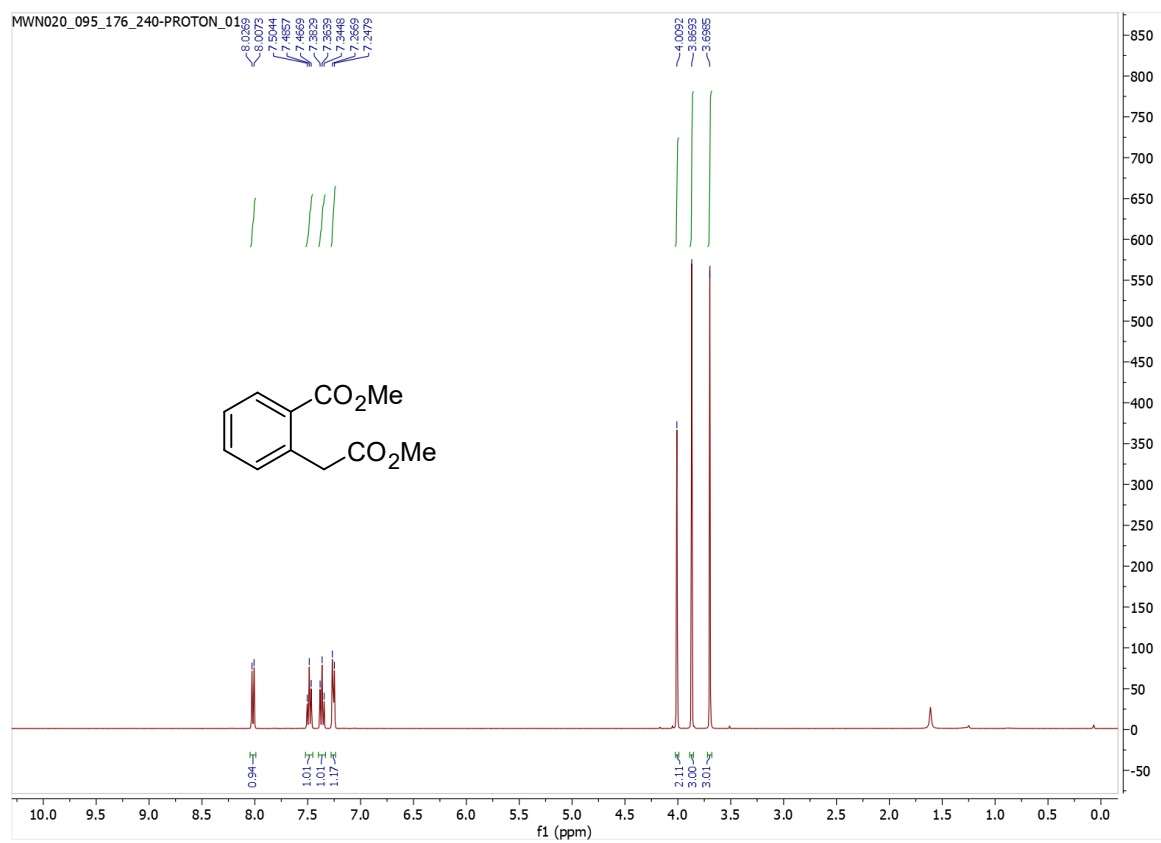
Homophthalic acid **47** (10.00 g, 55.5 mmol, 1 equiv) was dissolved in MeOH (200 mL) and thionyl chloride (5.5 mL, 62.0 mmol, 2.75 equiv) was added dropwise. The resulting solution was heated under reflux for 3 h and concentrated in vacuo. The volatiles were evaporated, and the residue was dissolved in AcOEt (150 mL) and washed with saturated aqueous solution of NaHCO_3 (1 x 40 mL, 2 x 20 mL) and brine. All aqueous extracts were re-extracted one-by-one with the same portion of AcOEt (50 mL). Organic extracts were combined, dried over Na_2SO_4 , evaporated to give 10.63 g (92%) of product **48** as a yellowish oil. The product was used in the next step without further purification.

Method B

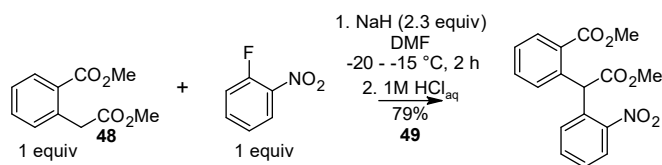
Homophthalic acid **47** (14.00 g, 77.7 mmol) was dissolved in MeOH (280 mL) and thionyl chloride (15.6 mL, 213.0 mmol) was added dropwise. The solution was heated under reflux for 4.5 h and concentrated in vacuo. The volatiles were evaporated, the residue was dissolved in AcOEt (100 mL), saturated aqueous NaHCO_3 solution (50 mL) was added, and the mixture was stirred at rt for 15 min. The phases were separated, and the aqueous one was extracted with AcOEt (5 x 50 mL). All organic extracts were filtrated, washed with brine (50 mL), and the brine was re-extracted with AcOEt (50 mL). All organic extracts were combined, dried over Na_2SO_4 , evaporated to give 14.88 g (92%) of product **48**, as a yellowish oil. The product was used in the next step without further purification.

^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 7.8$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.26 (d, $J = 7.6$ Hz, 1H) overlapping with residual CHCl_3 , 4.01 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.70 (s, 3H, CH_3). LR-MS (m/z): 209 $[\text{M}+\text{H}]^+$.

The ^1H NMR data is in agreement with the one reported in the literature.[4]



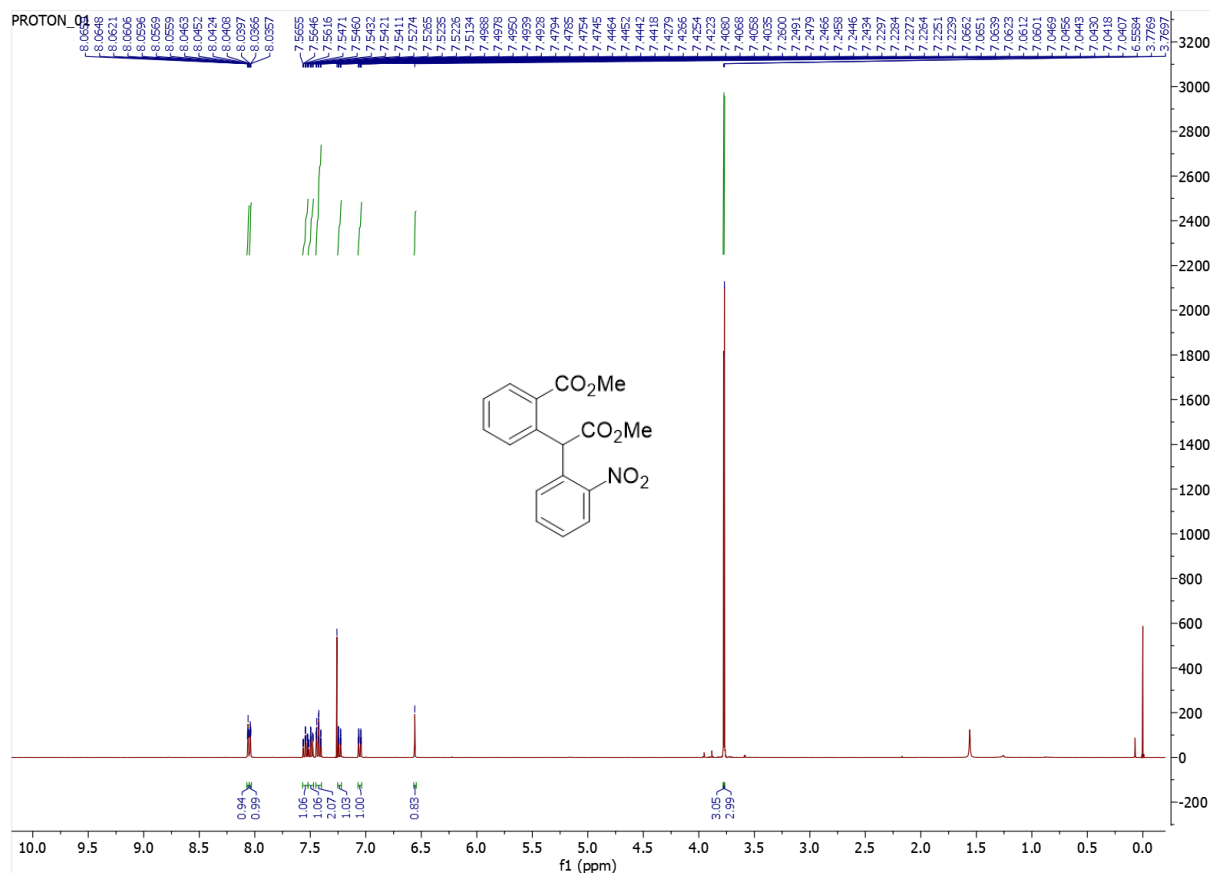
Methyl 2-[2-methoxy-1-(2-nitrophenyl)-2-oxoethyl]benzoate (**49**)



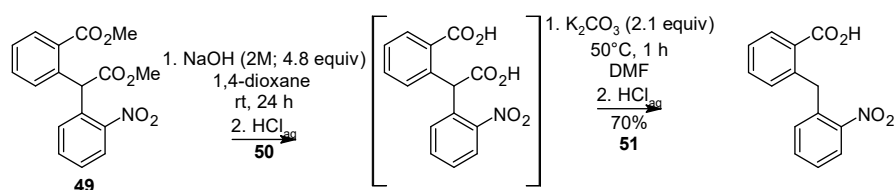
An oven-dried, two-neck, round-bottom bulb equipped with a thermometer was charged with anhydrous DMF (120 mL), cooled to -20°C and NaH (60% dispersion in oil; 6.577 g, 164.42 mmol, 2.3 equiv) was added in one portion. A solution of dimethylhomophthalate **48** (14.884 g, 71.49 mmol, 1 equiv) and 1-fluoro-2-nitrobenzene (10.087 g, 71.49 mmol, 1 equiv) in DMF (60 mL) was added dropwise over 25 min, maintaining the temperature below -5°C. The mixture was further stirred for 2 h. at -20 - -15 °C and quenched with 1M HCl (150 mL). Water (50 mL) and Et₂O (50 mL) were added and the resulting yellowish solid was filtrated, washed with water (2 x 20 mL) and Et₂O (3 x 20 mL), to give 18.54 g (79%) of product **49**.

¹H NMR (400 MHz, CDCl₃) δ 8.07-8.05 (m, 1H), 8.05-8.03 (m, 1H), 7.57-7.52 (m, 1H), 7.52-7.47 (m, 2H), 7.45-7.40 (m, 2H), 7.25-7.22 (m, 1H), 6.58 (s, 1H, CH), 3.78 (m, 3H, OCH₃), 3.77 (m, 3H, OCH₃). LR-MS (m/z): 330 [M+H]⁺.

The ¹H NMR spectrum is in agreement with the one previously reported.[5]



2-[(2-Nitrophenyl)methyl]benzoic acid (**51**)



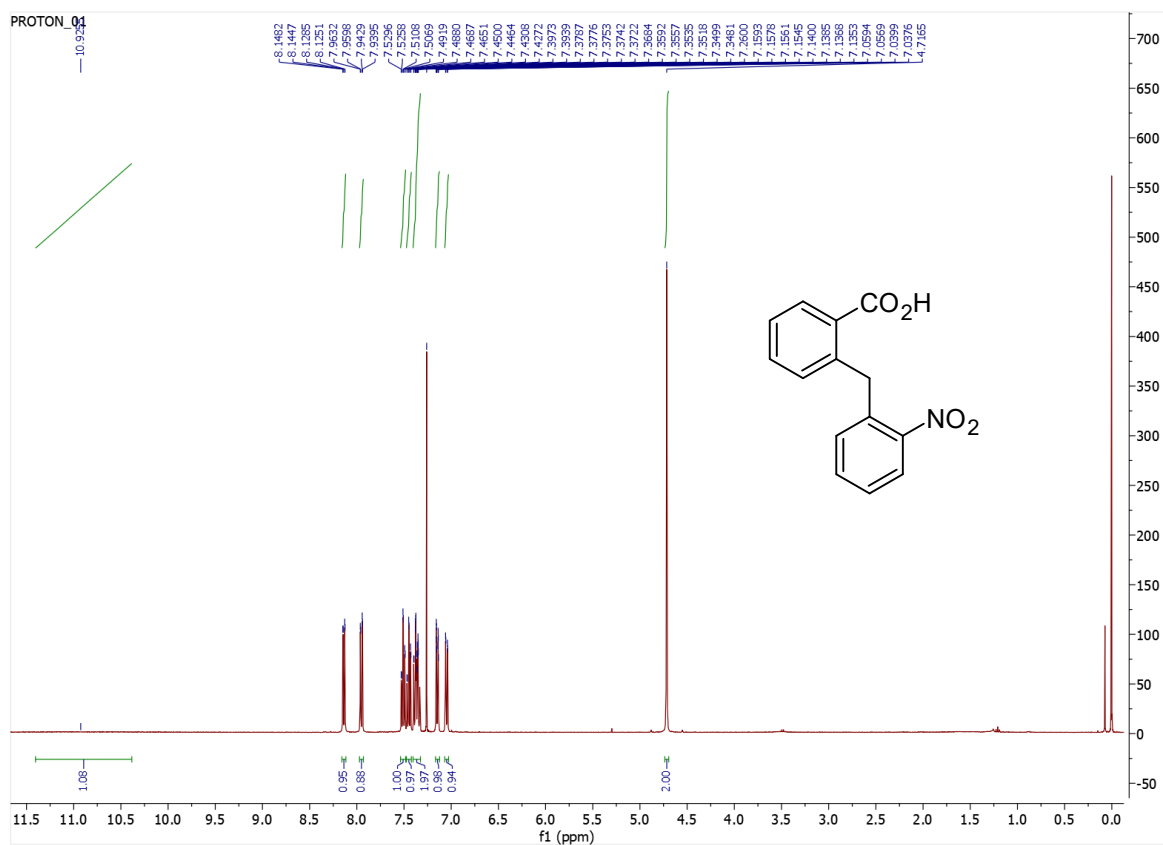
The product was obtained according to slightly modified literature procedure.[5]

A round-bottom bulb was charged with methyl 2-[2-methoxy-1-(2-nitrophenyl)-2-oxoethyl]benzoate **49** (10.773 g, 32.72 mmol, 1 equiv) and 1,4-dioxane (140 mL). To the resulting solution was added 2 M aqueous NaOH (6.281 g, 157.03 mmol, 4.8 equiv, 80 mL) and the mixture was stirred at rt for 24 h. The organic solvent was removed under vacuum, and the residual aqueous solution was acidified to pH 2 using 3 M aqueous HCl (~ 90 mL). Et₂O (100 mL) was added and the phases were separated. The aqueous layer was extracted with Et₂O (4 x 50 mL). The organic extracts were combined, washed with water (50 mL) and brine (100 mL). The aqueous extracts were separately re-extracted with the same portion of Et₂O (50 mL). The combined organic phase was dried over Na₂SO₄, filtrated and evaporated to obtain the crude product **50**. LR-MS (m/z): 240 [M-OH]⁺, 324 [M+Na]⁺, 625 [2M+H]⁺.

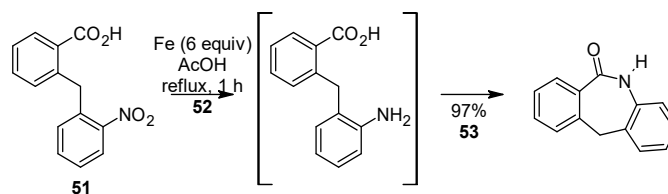
The crude product **50** was dissolved in anhydrous DMF (100 mL). Anhydrous K₂CO₃ (9.495 g, 68.70 mmol, 2.1 equiv) was added and the suspension was stirred at 50 °C for 1 h. The suspension was cooled to rt and acidified with 1 M aqueous HCl (~220 mL), then with 3 M HCl (~50 mL). Et₂O (150 mL) was added, and the phases were separated. The aqueous layer was extracted with Et₂O (4 x 50 mL). The organic fractions were combined, washed with 1 M aqueous HCl (50 mL), water (50 mL) and brine (100 mL). All aqueous extracts were separately re-extracted one-by-one with the same portion of Et₂O (50 mL). The combined organic extracts were dried over Na₂SO₄, filtrated and evaporated. The residue was triturated with Et₂O (20 mL) and washed with cooled Et₂O (3 x 5 mL) to give 4.760 g of **51** as a white solid. The filtrate was evaporated, the residue was dissolved in DCM (30 mL), followed by precipitation using rotary evaporator. The mixture was left in the refrigerator overnight. The precipitated solid was filtered and washed with a cooled DCM/cyclohexane 1:1 (3 x 5 mL) mixture to give an additional batch of 1.129 g of product **51**. Overall yield was 5.889 g (70%).

¹H NMR (400 MHz, CDCl₃) δ 10.93 (br s, 1 H, CO₂H), 8.14 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.95 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40-7.33 (m, 2H), 7.17-7.13 (m, 1H), 7.07-7.03 (m, 1H), 4.72 (s, 2H, CH₂). LR-MS (m/z): 240 [M-OH]⁺.

The ¹H NMR spectrum is in agreement with the one previously reported.[5]



5,11-Dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (**53**)

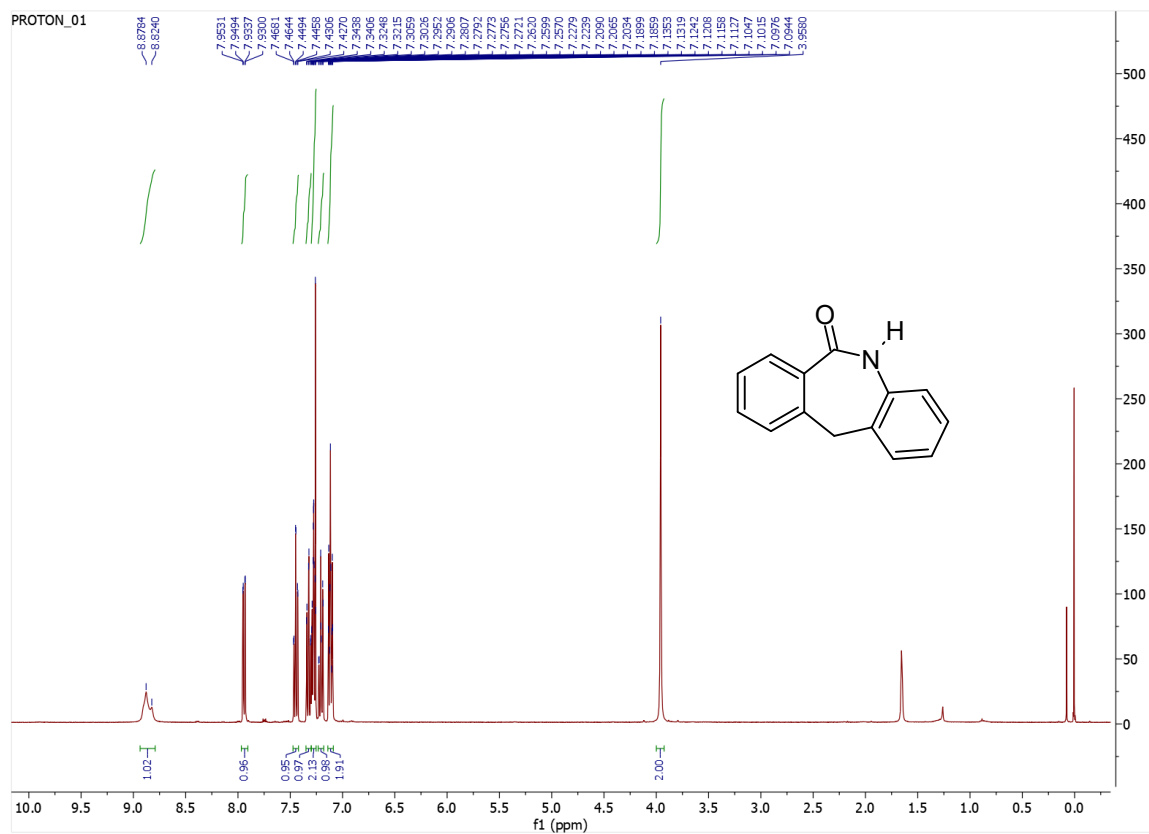


The product was obtained according to slightly modified literature procedure.[6]

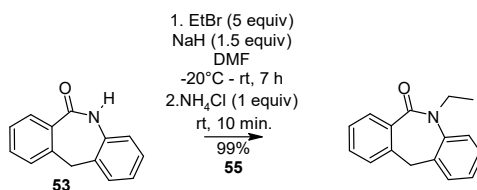
To a solution of 2-[(2-nitrophenyl)methyl]benzoic acid **51** (4.879 g, 18.97 mmol, 1 equiv) in acetic acid (150 mL), in round-bottom bulb, was added Fe (powder, 6.356 g, 113.81 mmol, 6 equiv) and the resulting suspension was stirred at reflux for 1 h. The reaction mixture was cooled to rt, filtered through cotton and the solids were extensively washed with AcOEt (~150 mL). The filtrate was evaporated, and the residue was dissolved in AcOEt (200 mL), washed with water (50 mL), aqueous saturated solution of NaHCO₃ (75 mL) and brine (100 mL). All aqueous extracts were separately re-extracted with the same portion of AcOEt (50 mL) and the organic extracts were combined, dried over Na₂SO₄, filtrated and evaporated to give 3.969 g (97%) of product **53** as a white powder. The product was used in the next step without additional purification.

¹H NMR (400 MHz, CDCl₃) δ 8.93-8.80 (m, 1H, *NH*), 7.94 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H), 7.32 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30-7.25 (m, 2H), overlapped by residual CHCl₃, 7.23-7.18 (m, 1H), 7.14-7.09 (m, 2H), 3.96 (s, 2H, *CH*₂). LR-MS (*m/z*): 210 [M+H]⁺.

The ¹H NMR spectrum is in agreement with previously reported in the literature.[6]

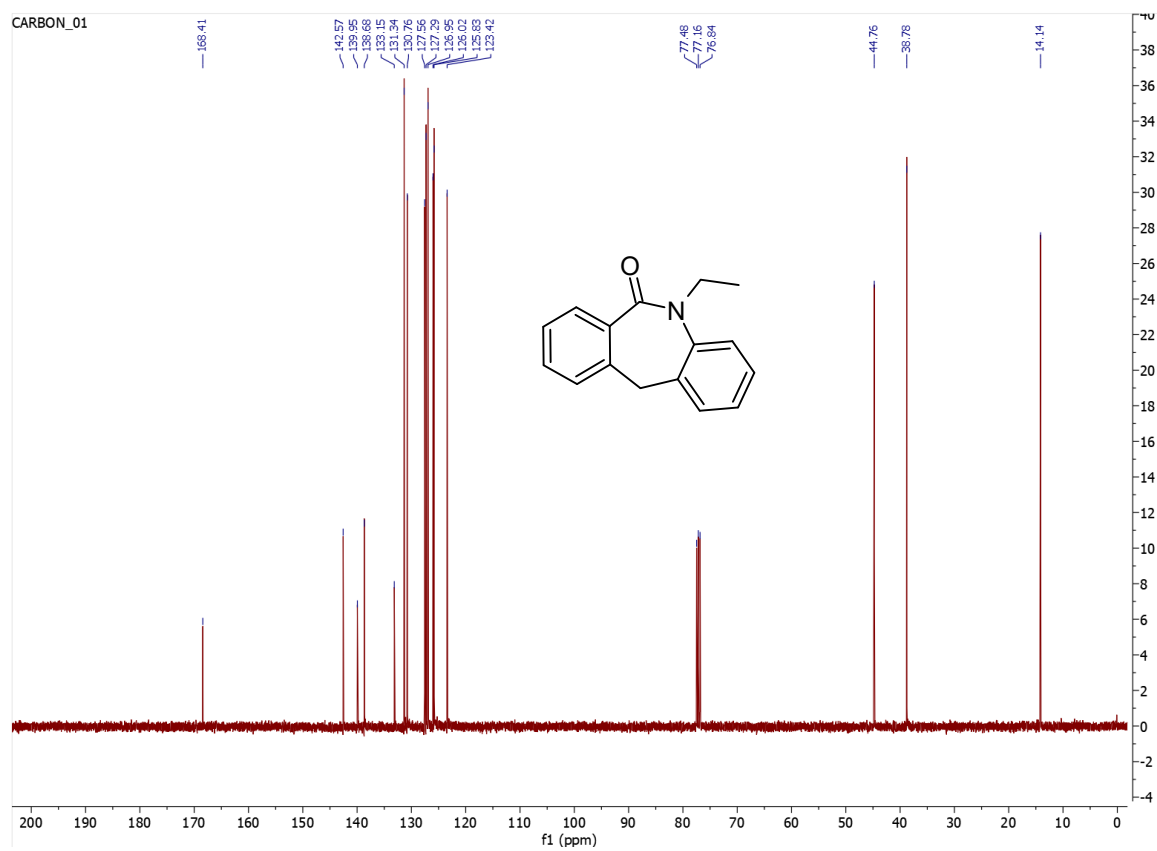
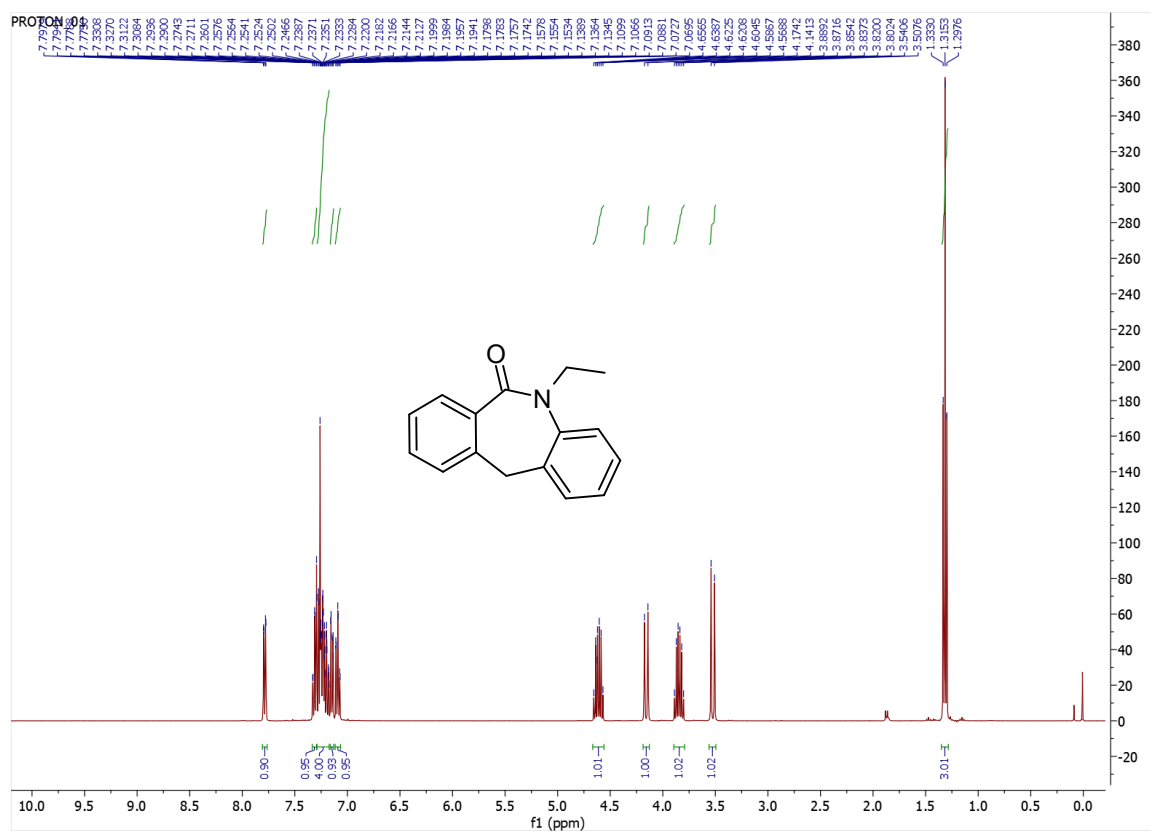


5-Ethyl-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one (55)

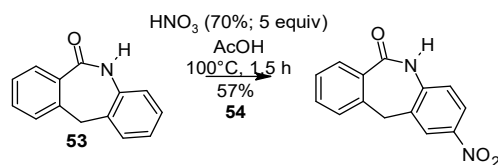


An oven-dried, round-bottom bulb was charged with anhydrous DMF (5 mL) and cooled to -20°C. NaH (60% dispersion in mineral oil, 0.918 g, 22.94 mmol, 1.5 equiv) was added. 5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one **53** (3.200 g, 15.29 mmol, 1 equiv) was dissolved in anhydrous DMF (30 mL) and added dropwise to the reaction flask, followed by EtBr (5.7 mL, 76.47 mmol, 5 equiv). The reaction mixture was allowed to warm slowly to rt and was stirred overall for 7 h at rt. NH₄Cl (0.818 g, 15.29 mmol, 1 equiv) was added, the mixture was stirred for 10 min, and the volatiles were evaporated. The residue was additionally evaporated with PhMe (2 x 30 mL), filtered through a plug of silica (to remove oil from NaH) eluting with cyclohexane, then AcOEt/cyclohexane 1:8, and finally DCM/MeOH 1%. The volatiles were evaporated to give 3.595 g (99%) of product **55** as a yellowish oil that solidified to a white solid upon adding *n*-hexane and standing in the fridge.

¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.31 (td, *J* = 7.4, 1.5 Hz, 1H) overlapping 7.29-7.17 (m, 4H) overlapped by residual CHCl₃, 7.15 (d, *J* = 7.5 Hz, 1H), 7.09 (td, *J* = 7.4, 1.3 Hz, 1H), 4.66-4.56 (m, 1H, ½ CH₂CH₃), 4.16 (d, *J* = 13.2 Hz, 1H, ½ ArCH₂Ar'), 3.90-3.80 (m, 1H, ½ CH₂CH₃), 3.52 (d, *J* = 13.2 Hz, 1H, ½ ArCH₂Ar'), 1.32 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 168.4 (CO), 142.6, 140.0, 138.7, 133.2, 131.3, 130.8, 127.6, 127.3, 126.9, 126.0, 125.8, 123.4, 44.8, 38.8, 14.1 (CH₃). LR-MS (*m/z*): 238 [M+H]⁺.



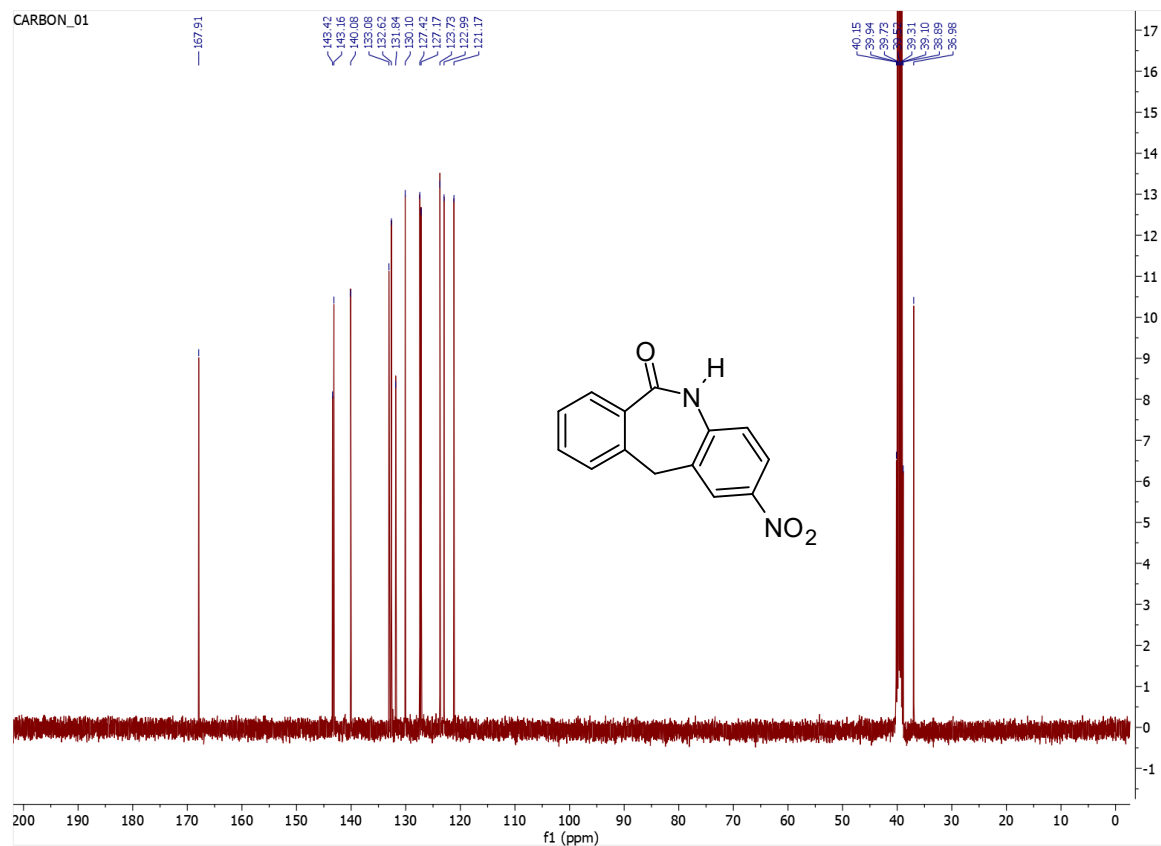
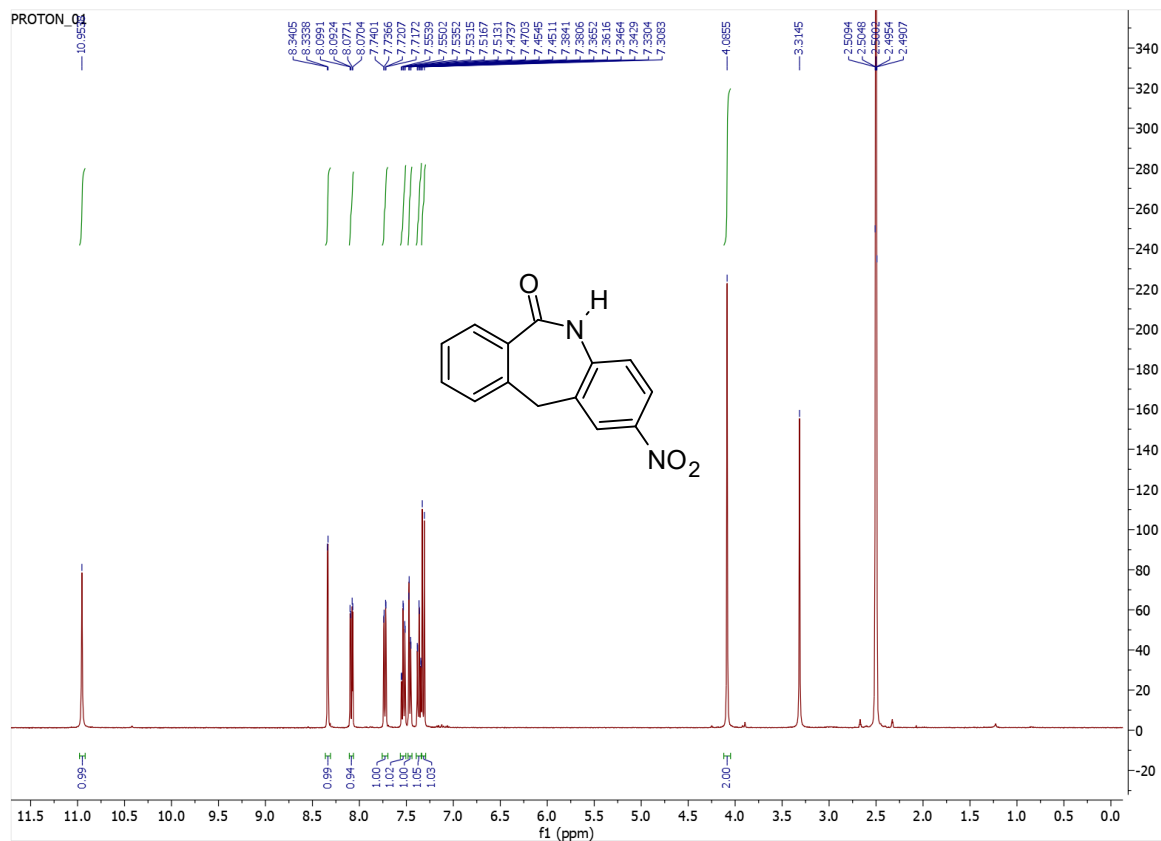
2-Nitro-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one (**54**)



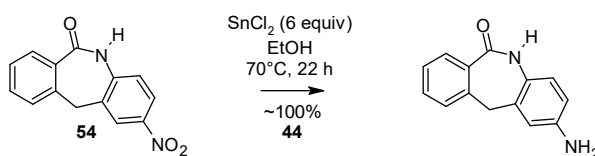
A round-bottom bulb was charged with 5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one **53** (4.546 g, 21.73 mmol, 1 equiv) and AcOH (36 mL) and HNO₃ (~70%[‡]; 7.1 mL, 108.64 mmol, 5 equiv) was added dropwise. The resulting solution was stirred at 100°C for 1.5 h, cooled to rt, the solid was washed with chilled AcOH and cooled MeCN to give 3.127 g (57%) of target product **54** as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.95 (s, 1H, CONH), 8.34 (d, *J* = 2.7 Hz, 1H, C¹H), 8.08 (dd, *J* = 8.8, 2.7 Hz, 1H, C³H), 7.73 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (td, *J* = 7.4, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H, C⁴H), 4.09 (s, 2H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 167.9 (CONH), 143.4, 143.2, 140.1, 133.1, 132.6, 131.8, 130.1, 127.4, 127.2, 123.7, 123.0, 121.2, 37.0 (CH₂). LR-MS (*m/z*): 255 [M+H]⁺.

[‡] Attempting to re-synthesize compound **54**, we discovered that after 20 months after opening of the reagent bottle there was a need to use 10-20 equiv of HNO₃ (calculated as fresh ~70%) to carry out nitration to obtain the comparable yield (53%). We suggest that if not further conversion of starting intermediate **53** is observed, more HNO₃ may be added in portions – every 15 minutes, until first crystals of the precipitating product **54** are observed.

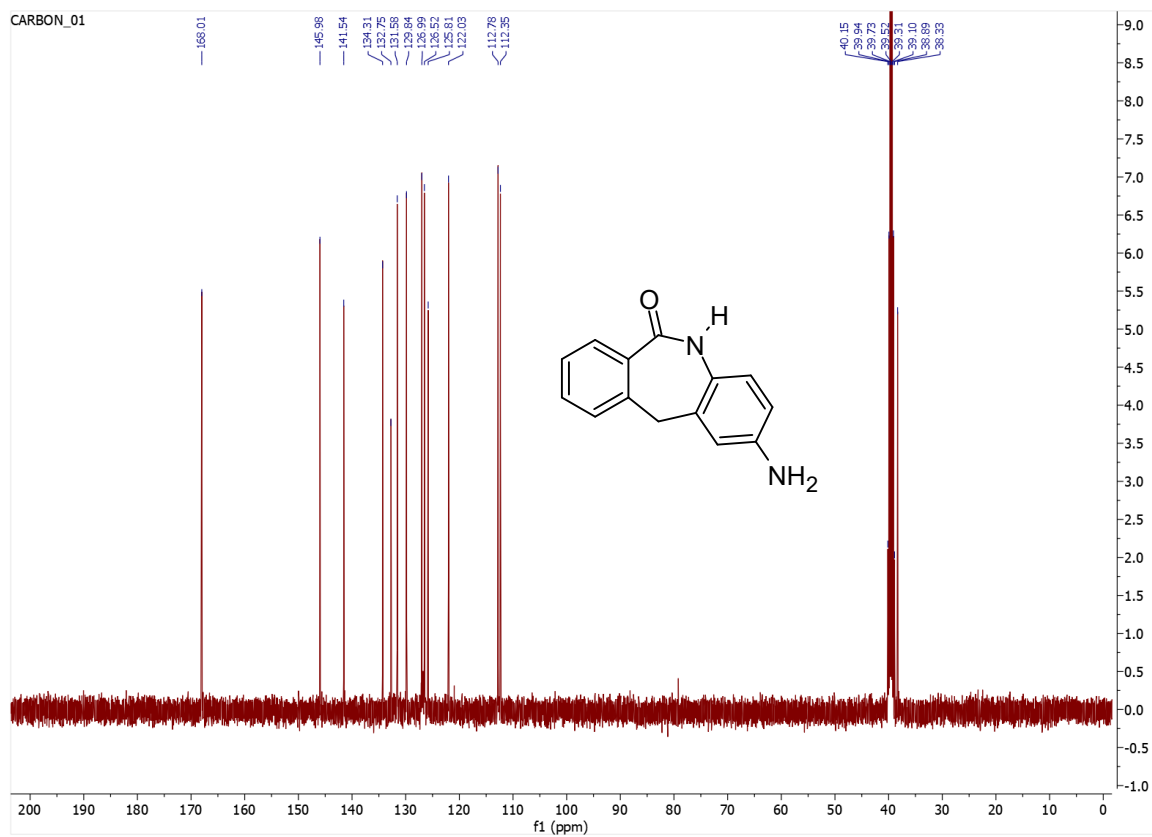
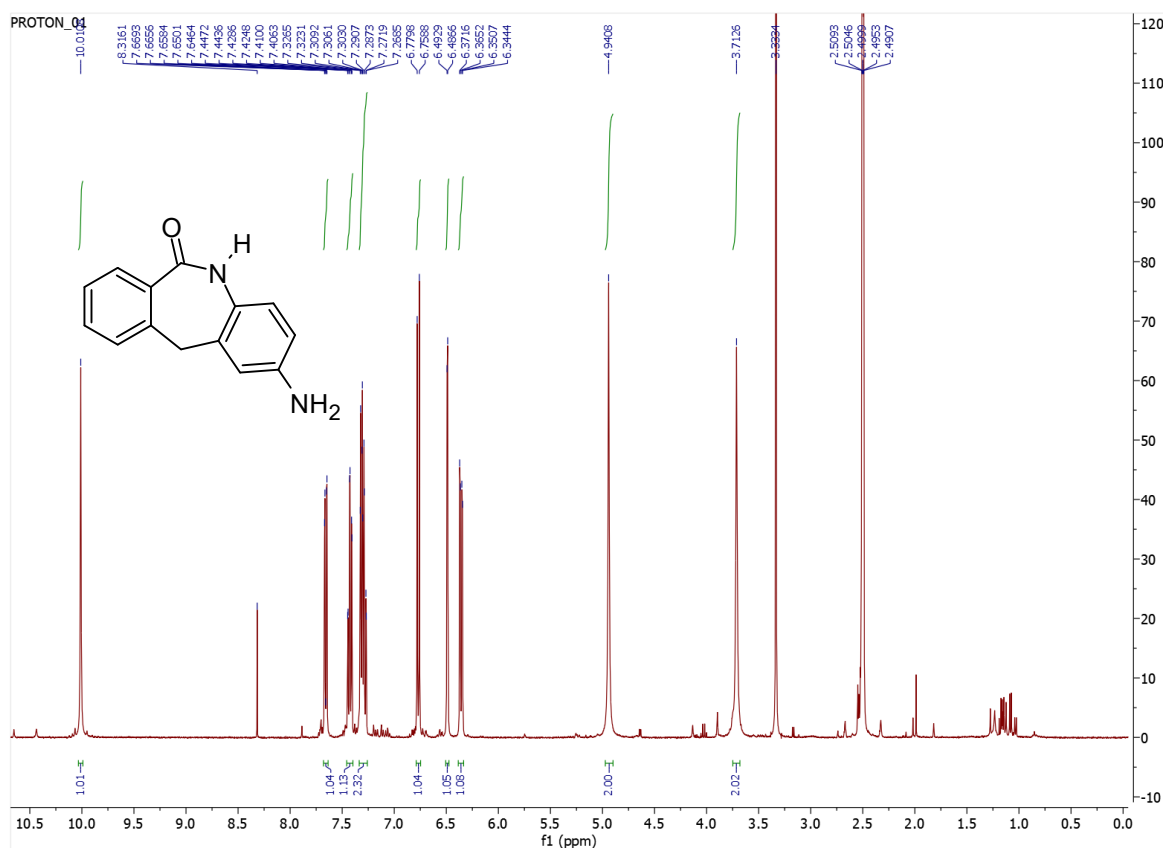


2-Amino-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one (**44**)



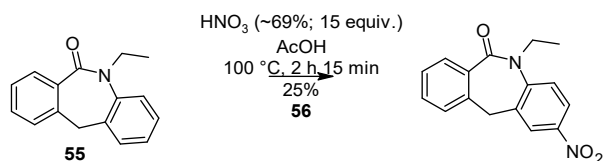
Anhydrous SnCl₂ (8.698 g, 45.88 mmol, 6 equiv) was added to a suspension of 2-nitro-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one **54** (1.944 g, 7.65 mmol, 1 equiv) in an anhydrous EtOH (95 mL). The mixture was stirred at 70°C for 22 h, concentrated to about 25 mL, diluted with AcOEt (250 mL). Saturated aqueous solution of NaHCO₃ (100 mL) was added dropwise. The resulting suspension was filtered and the liquid phases of the filtrate were separated in a separatory funnel. The aqueous layer was extracted with AcOEt (5 x 25 mL) and all organic extracts were combined. The filtrated solid was transferred to the round-bottom bulb, AcOEt (50 mL) was added and the suspension was stirred for 30 min. The filtrate was decanted and combined with the previously collected organic extracts. AcOEt (50 mL) was added again to the solid residue and the procedure was repeated until there was no longer product in the filtrate (determined using TLC). All organic extracts were combined, washed with brine (100 mL), dried over Na₂SO₄, filtrated and evaporated to yield 1.813 g (quant.) of the target product **44** as a white solid, which was used in the next step without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.01 (s, 1H, CONH), 7.66 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.43 (td, *J* = 7.4, 1.5 Hz, 1H), 7.33–7.26 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H, C⁴H), 6.49 (d, *J* = 2.5 Hz, 1H, C¹H), 6.36 (dd, *J* = 8.3, 2.6 Hz, 1H, C³H), 4.94 (s, 2H, NH₂), 3.71 (s, 2H, CH₂); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 168.0 (CONH), 146.0, 141.5, 134.3, 132.8, 131.6, 129.8, 127.0, 126.5, 125.8, 122.0, 112.8, 112.3, 38.3 (CH₂). LR-MS (*m/z*): 225 [M+H]⁺.



5-Ethyl-2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (**56**)

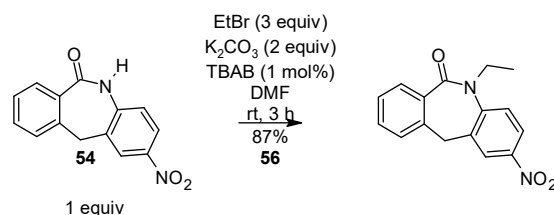
(Method A)



A round-bottom bulb was charged with 5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **55** (2.878 g, 12.13 mmol, 1 equiv), AcOH (18.2 mL) and ~69% HNO₃ (181.29 mmol, 15 equiv). The resulting solution was heated at 100°C for 2 h 15 min. and cooled to 0°C. Solid Na₂CO₃ (9.641 g, 90.96 mmol, 7.5 equiv) was added portionwise and the volatiles were evaporated. The residue was portioned between saturated NaHCO₃ solution (50 mL) and AcOEt (50 mL). Additional portions of solid Na₂CO₃ were added to basify the aqueous phase. Phases were separated and the aqueous layer was extracted with AcOEt (3 x 50 mL). The combined organic extracts were washed with brine, and the brine was re-extracted with AcOEt (50 mL). The organic extracts were dried over Na₂SO₄, filtrated and evaporated. The crude was macerated with Et₂O (25 mL) and stirred overnight. The resulting solid was collected, washed with Et₂O, and recrystallized from MeOH to obtain 0.562 g of product **56** as a white solid. The filtrate was evaporated and re-crystallized from MeOH to give an additional batch 0.280 g of product **56**. Overall yield was 0.842 g (25%).

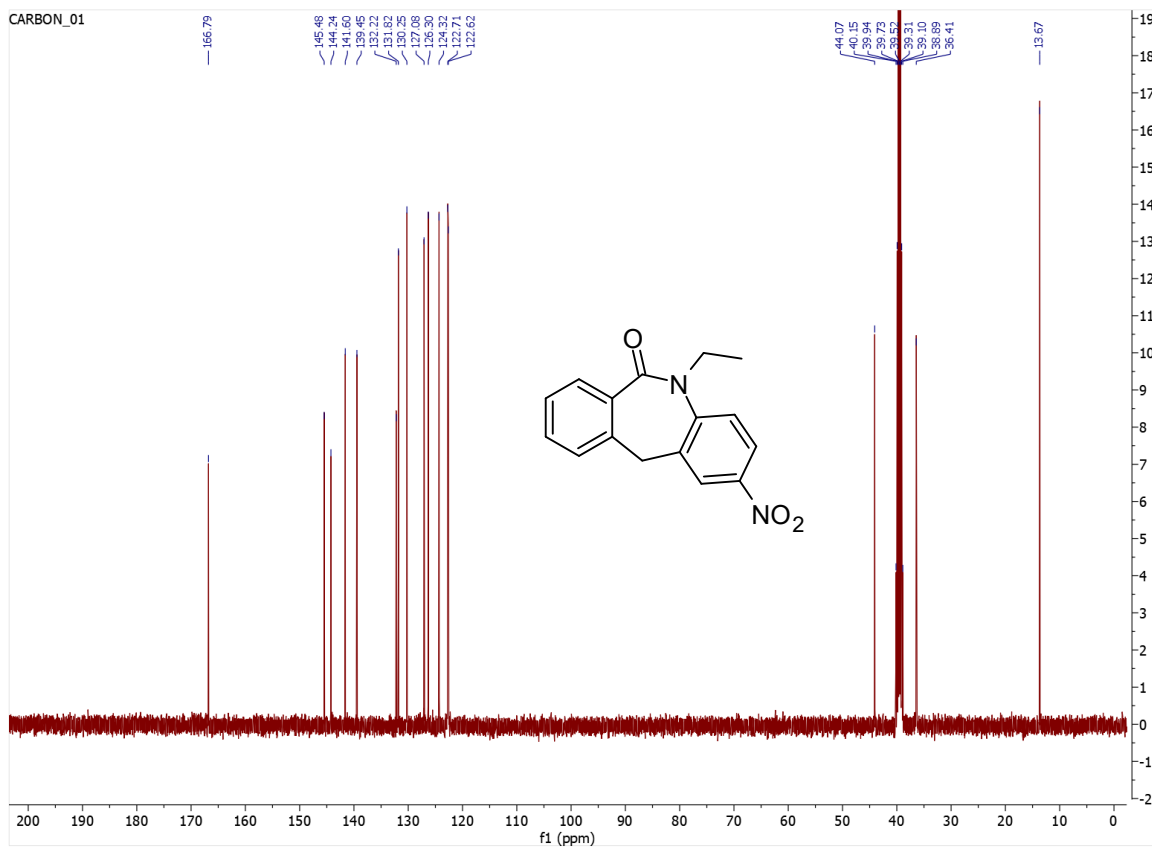
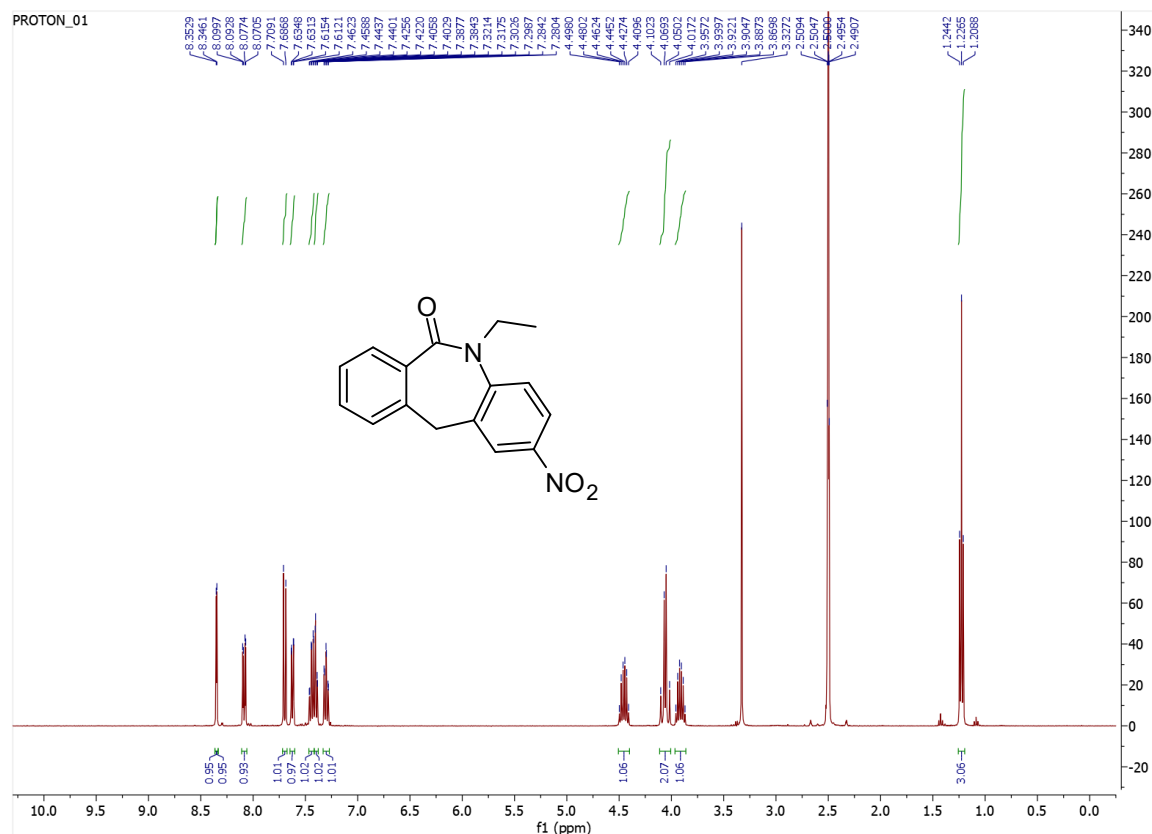
5-Ethyl-2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (**56**)

(Method B)



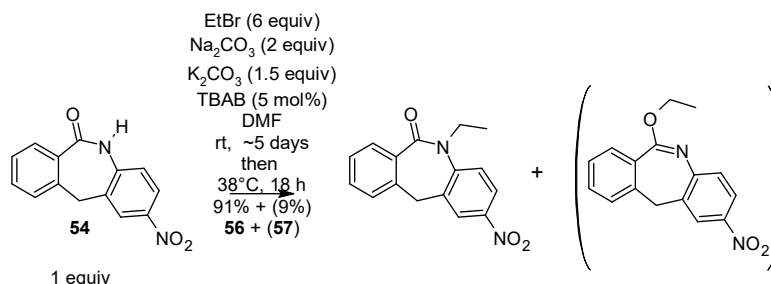
An oven-dried pressure tube was charged with 2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **54** (1.100 g, 4.33 mmol, 1 equiv), TBAB (28 mg, 0.09 mmol, 1 mol%), anhydrous DMF (3.5 mL), K₂CO₃ (1.196 g, 8.65 mmol, 2 equiv) and EtBr (962 μ L, 12.98 mmol, 3 equiv). The resulting suspension was stirred at rt for 3.5 h. The reaction mixture was diluted with water (80 mL) and cooled to rt. The liquid phase was decanted into a separatory funnel and the oil which remained in the bulb was washed with water (2 x 10 mL) and triturated with Et₂O (50 mL). After 30 min of standing at rt, a solid was formed, which was then filtered and washed with Et₂O to give 447 mg of product **56** as a white solid. The aqueous phase in the separatory funnel was extracted with Et₂O (4 x 50 mL), washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over Na₂SO₄, filtrated, combined with the filtrate obtained previously and evaporated. The residue was dissolved in DCM, cyclohexane was added, and the DCM was slowly evaporated using rotary evaporator. The oily residue was triturated with cyclohexane, and the resulting white solid was filtered and washed with cyclohexane (3 times) to give an additional batch 616 mg of product **56**. Overall yield was 1.063 g (87%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (d, *J* = 2.7 Hz, 1H, C¹*H*), 8.09 (dd, *J* = 8.9, 2.8 Hz, 1H, C³*H*), 7.70 (d, *J* = 8.9 Hz, 1H, C⁴*H*), 7.62 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.44 (td, *J* = 7.7, 0.7 Hz, 1H), 7.40 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 (td, *J* = 7.4, 1.5 Hz, 1H), 4.50-4.40 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 4.11-4.01 (m, 2H, ArCH₂Ar'), 3.6-3.86 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 1.23 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.8 (CONH), 145.5, 144.2, 141.6, 139.5, 132.2, 131.8, 130.2, 127.1, 126.3, 124.3, 122.7, 122.6, 44.1 (CH₂CH₃), 36.4 (ArCH₂Ar'), 13.7 (CH₃). LR-MS (*m/z*): 283 [M+H]⁺.



[Method C (with isolation of the *O*-alkyl regioisomer (57))]

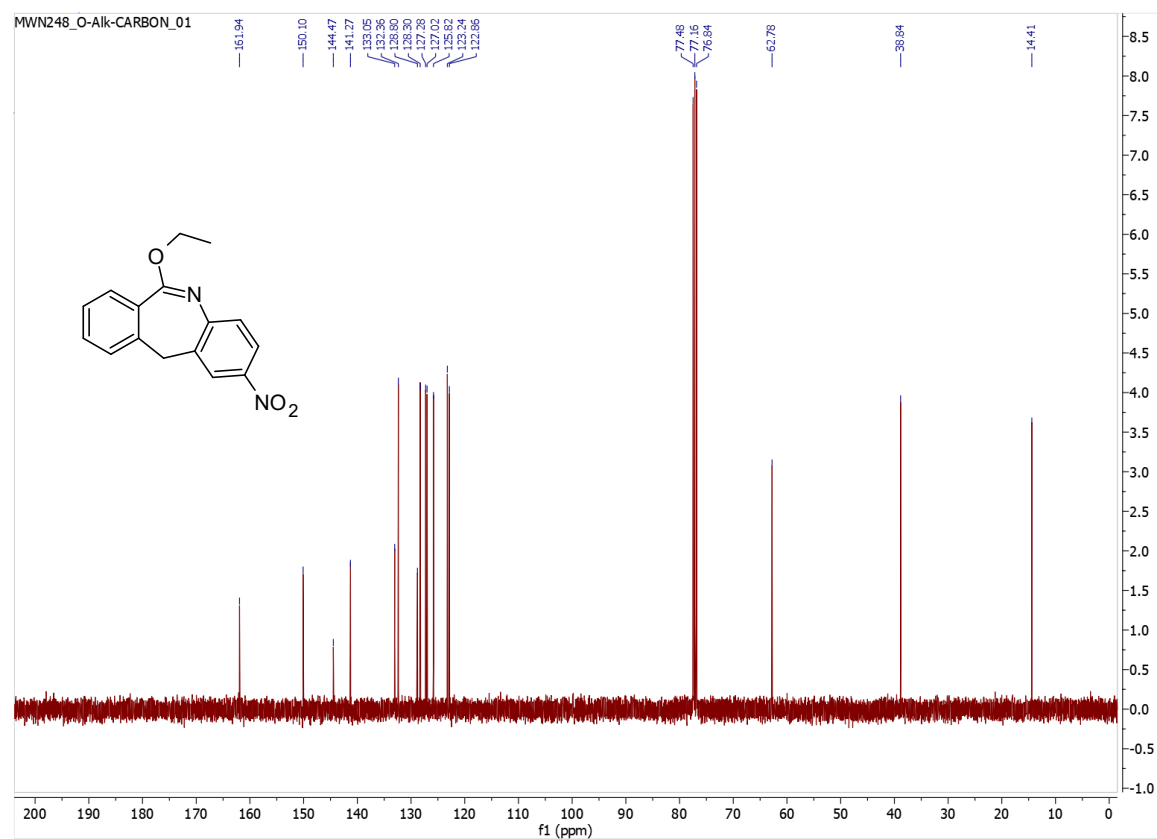
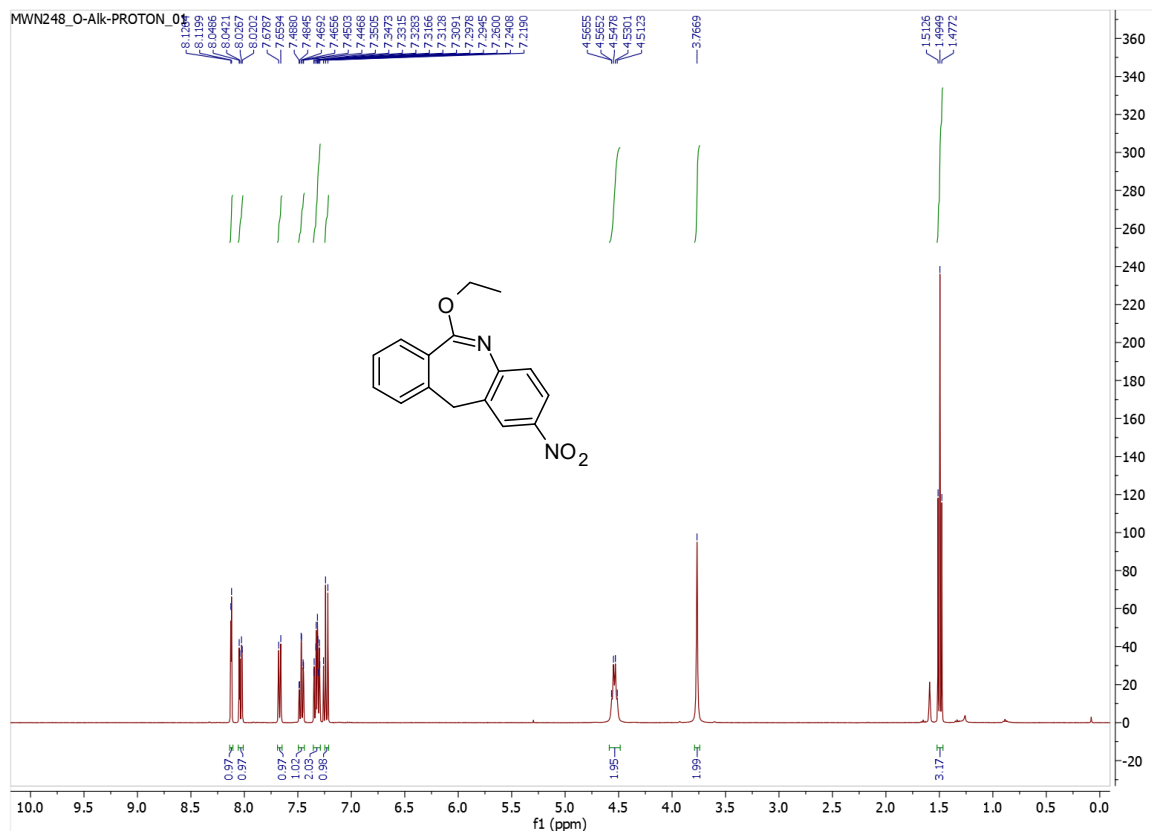
5-Ethyl-2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one and 6-ethoxy-2-nitro-11*H*-dibenzo[*b,e*]azepine (57)



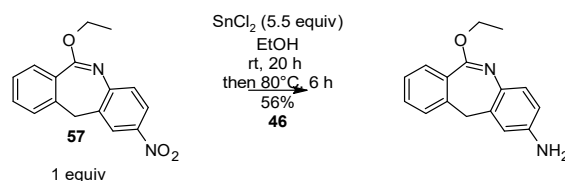
An oven-dried, round-bottom bulb was charged with 2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **54** (1.400 g, 5.51 mmol, 1 equiv) and anhydrous DMF (42 mL). To the resulting suspension was added calcinated, milled Na₂CO₃ (1.167 g, 11.01 mmol, 2 equiv), EtBr (1.63 mL, 22.03 mmol, 4 equiv) and the mixture was stirred at rt for 71 h. Another aliquots of calcinated milled K₂CO₃ (1.142 g, 8.26 mmol, 1.5 equiv) and EtBr (0.82 mL, 11.01 mmol, 2 equiv) were added, followed by stirring for additional 21 h. TBAB (89 mg, 0.28 mmol, 5 mol%) was added and the reaction was stirred for an additional 30 h, and then heated at 38°C for 18 h. The volatiles were evaporated and the residue was subjected to column chromatography (silica; DCM/cyclohexane: 33-100% to give 139 mg (9%) of 6-ethoxy-2-nitro-11*H*-dibenzo[*b,e*]azepine **57** as a white solid) and then MeOH/DCM 3% to obtain 1.411 g (91%) of 5-ethyl-2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **56** as a white solid).

6-ethoxy-2-nitro-11*H*-dibenzo[*b,e*]azepine (57)

¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 2.6 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.67 (br d, *J* = 7.7 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H, OCH₂), 3.77 (s, 2H, ArCH₂Ar), 1.49 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 161.9, 150.1, 144.5, 141.3, 133.0, 132.4, 128.8, 128.3, 127.3, 127.0, 125.8, 123.2, 122.9, 62.8 (OCH₂), 38.8 (ArCH₂Ar'), 14.4 (CH₃). LR-MS (*m/z*): 283 [M+H]⁺.



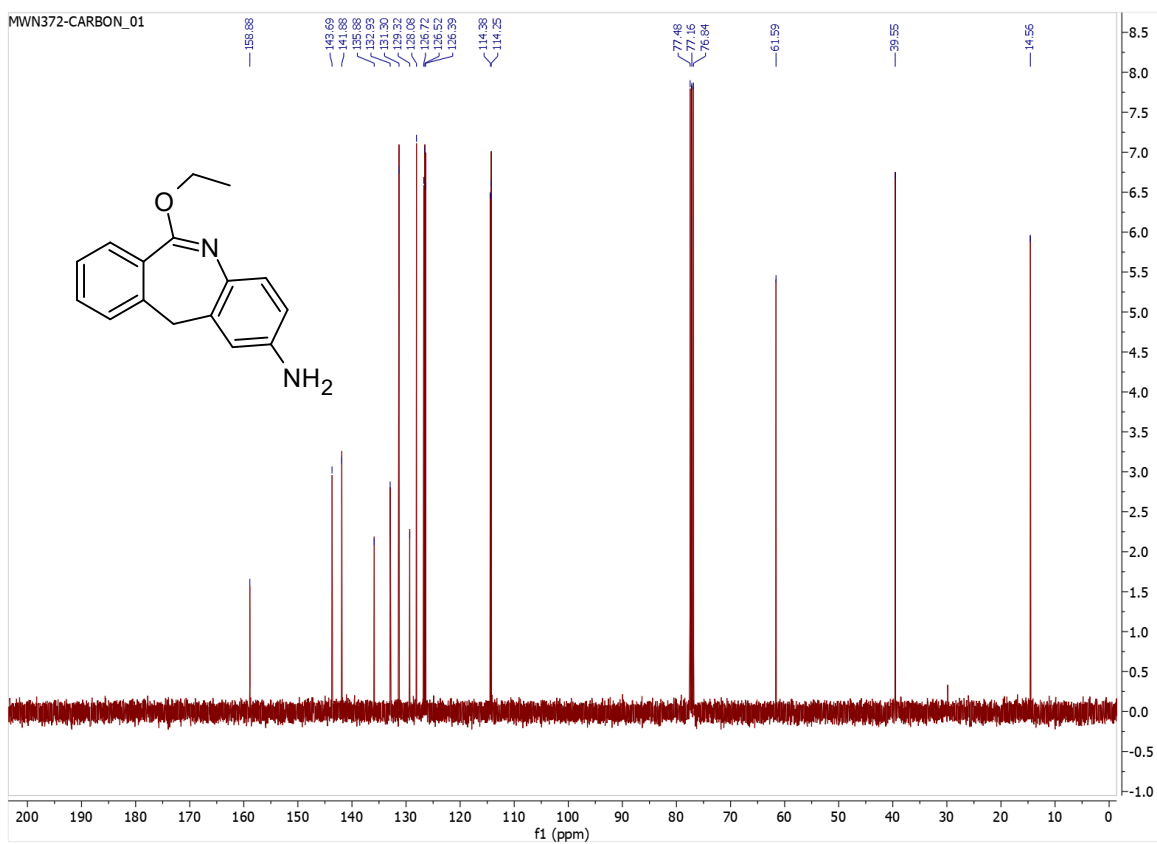
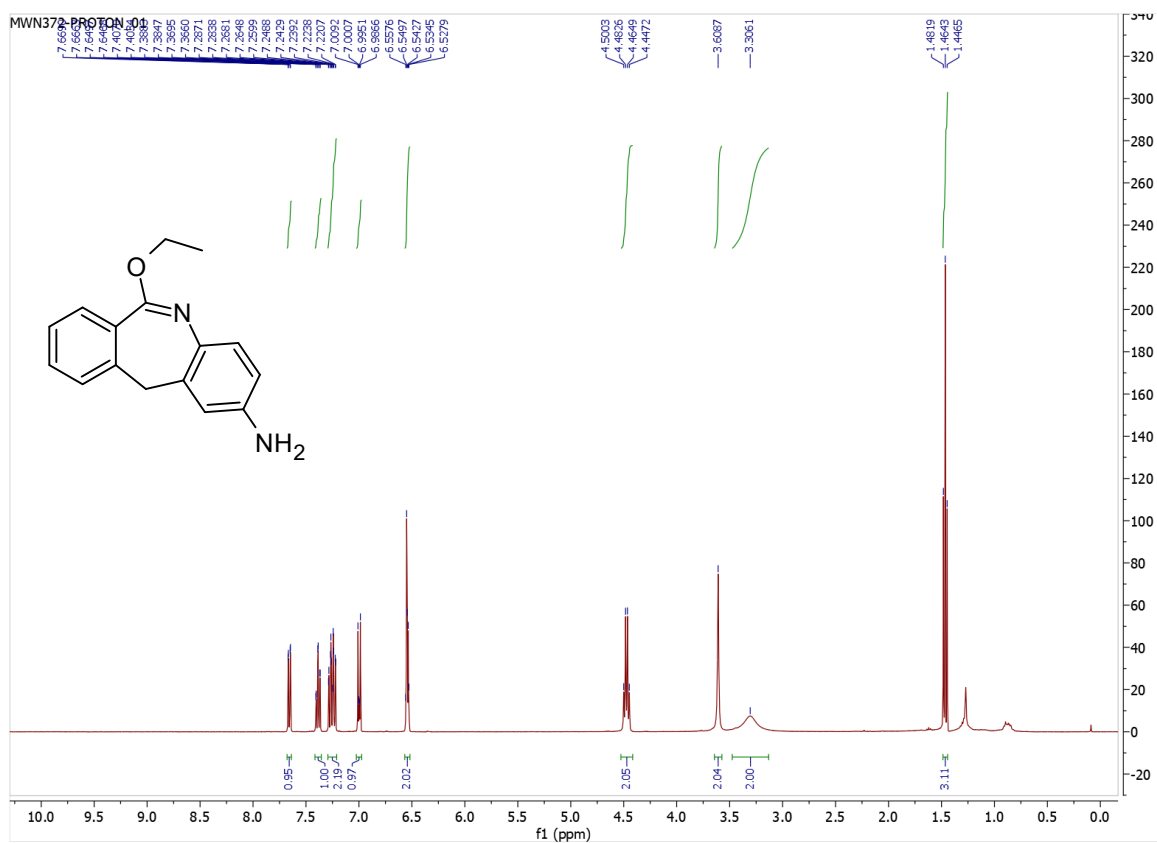
6-Ethoxy-11*H*-dibenzo[*b,e*]azepin-2-amine (46)



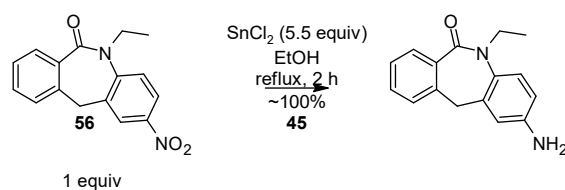
A screw-capped vial was charged with 6-ethoxy-2-nitro-11*H*-dibenzo[*b,e*]azepine **57** (129 mg, 0.46 mmol, 1 equiv), EtOH (12 mL), anhydrous SnCl₂ (477 mg, 2.51 mmol, 5.5 equiv). The resulting suspension was stirred at rt for 20 h and 80°C for 6 h. The mixture was concentrated on rotary evaporator to 1/3 volume. Saturated aqueous solution of NaHCO₃ (2 mL) was added dropwise and the volatiles were evaporated. The residue was subjected to column chromatography (silica; AcOEt/cyclohexane: 0-25%). The product was precipitated from the mixture DCM/*n*-hexane using rotary evaporator[§] and the resulting white solid was washed with *n*-hexane (2 times), to give 64 mg (56%) of pure product **46**.

¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.7, 1.1 Hz, 2H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29-7.21 (m, 2H) overlapping residual CHCl₃, 7.01-6.98 (m, 1H), 6.56-6.52 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H, CH₂CH₃), 3.61 (s, 2H, ArCH₂Ar'), 3.31 (br s, 2H, NH₂), 1.46 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.9 (C=N), 143.7, 141.9, 135.9, 132.9, 131.3, 129.3, 128.1, 126.7, 126.5, 126.4, 114.4, 114.3, 61.6 (OCH₂), 39.5 (ArCH₂Ar'), 14.6 (CH₃). LR-MS (*m/z*): 253 [M+H]⁺.

[§] Due to the fact that commercial solvents of HPLC purity were used without additional purification (distillation), in order to remove the trace amount of the grease, To obtain some of the target compounds (mainly final inhibitors) in a crystalline form, without a loss chemical yield, the procedure of final 'precipitation' of the products was applied: The compounds were dissolved in a small quantity of DCM, *n*-hexane was added in the quantity that did not cause the precipitation, and the mixture was slowly evaporated using a rotary evaporator, without immersing the bulb in the heating bath, allowing the DCM to be evaporated, which decreases the polarity of the solvent mixture and cools it down at the same time, which caused precipitation of the product. The solids were transferred into the (small) Schott funnel using the widened part of a previously cut Pasteur pipette, or the filtrate was collected using a syringe with a needle with a crushed tip by cutting it off with scissors and additionally crushed with a spoon, and the solid was washed with *n*-hexane (2-3 times). In the case of the products 'precipitating' as oils or viscous solids, a syringe with a needle was used, which sharpened the tip (lancet) to carefully separate the filtrate; the residue was washed with *n*-hexane (2-3 times) – in every case, the filtrate was removing with the aforementioned syringe. Despite using high-purity grade solvents (HPLC and p.a.) for column chromatography, we have found the above procedure suitable for removing residual 'grease'/other impurities which occasionally remained in the chromatographically purified samples.

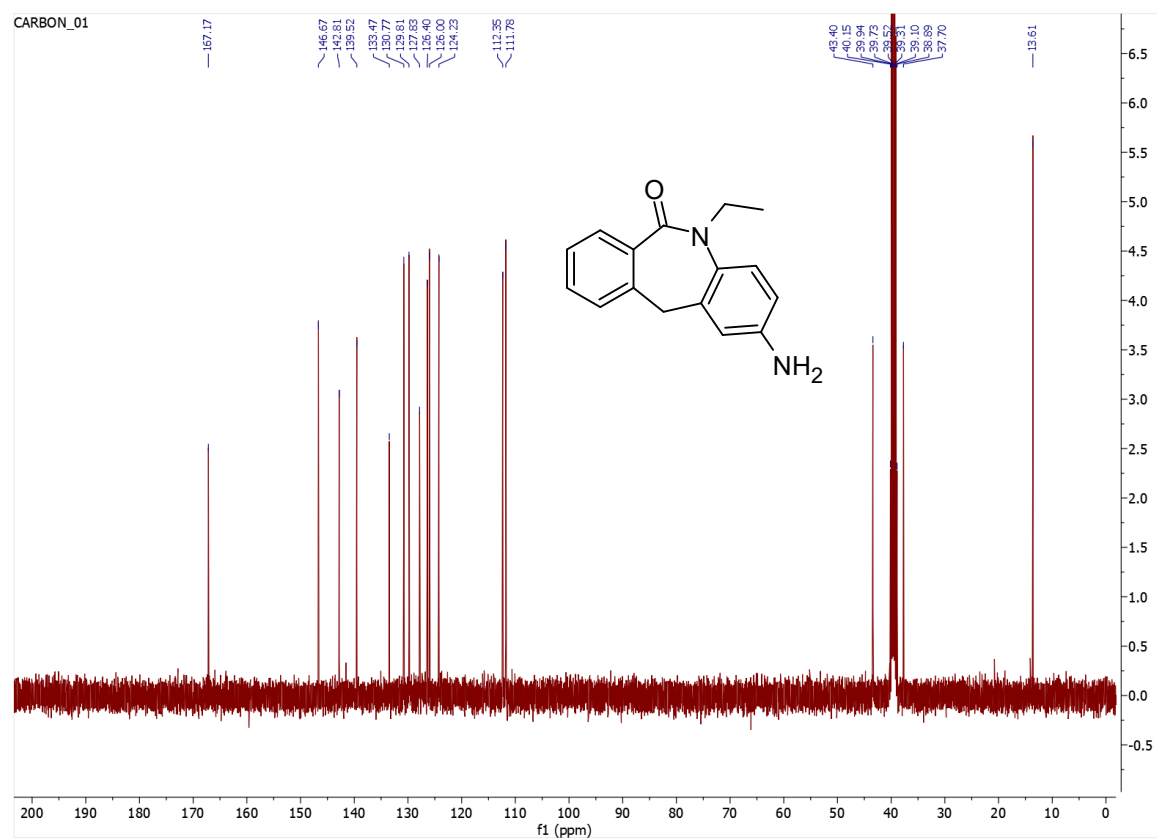
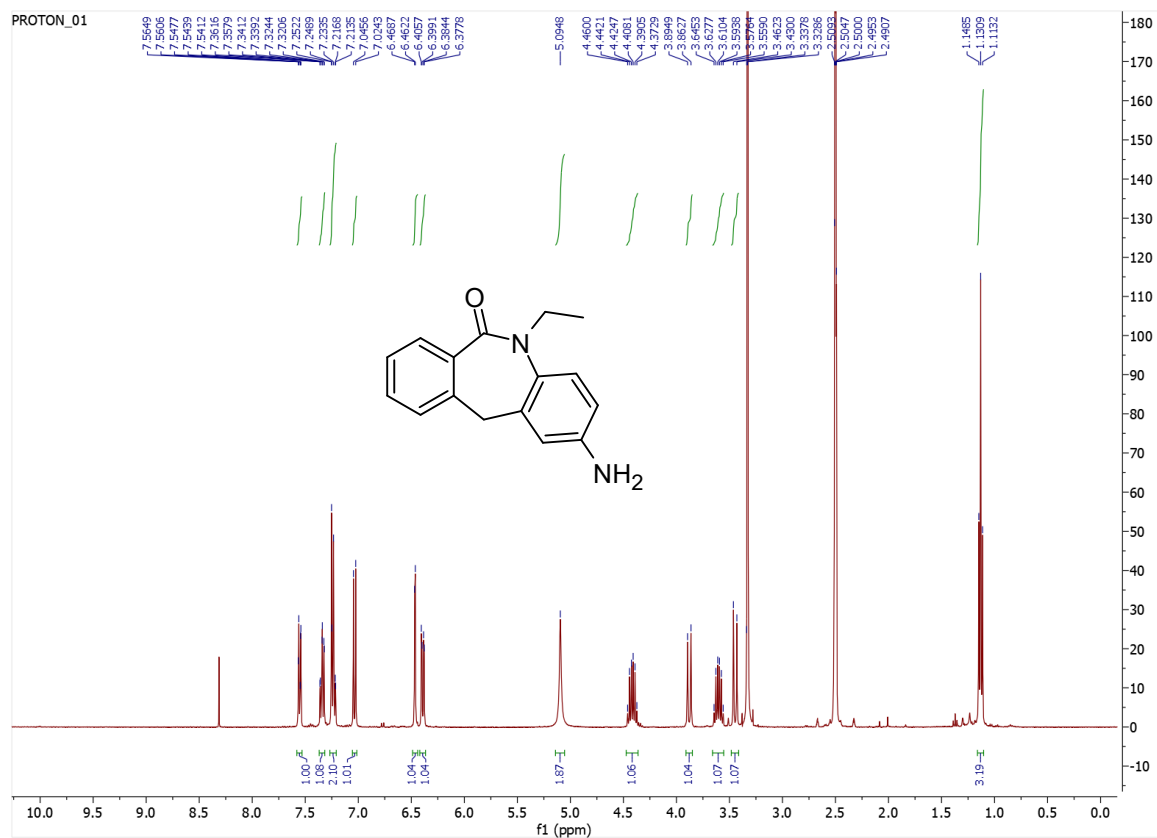


2-Amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (45)

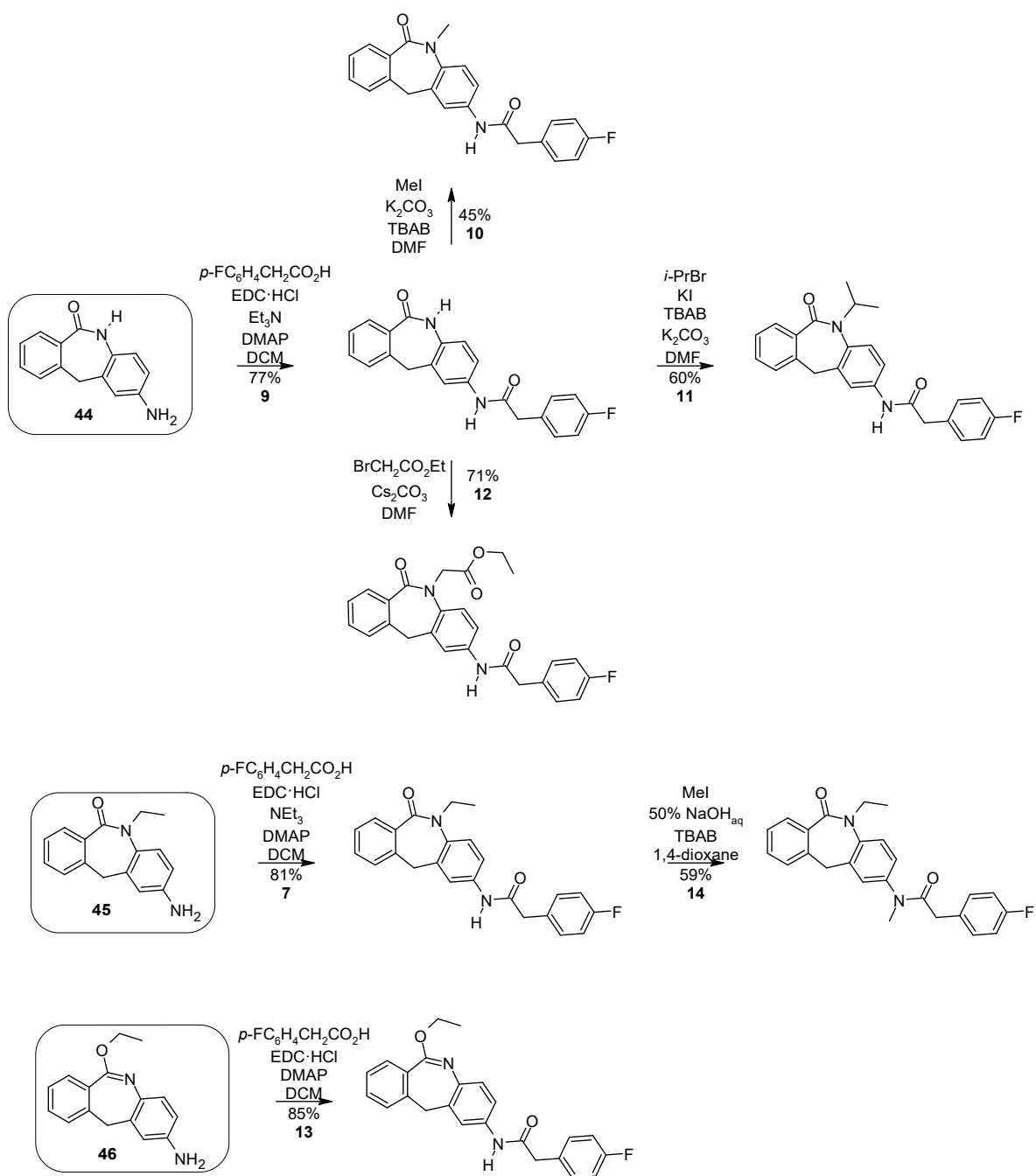


A round bottom bulb was charged with 5-ethyl-2-nitro-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **56** (1.040 g, 3.68 mmol, 1 equiv), anhydrous EtOH (55 mL) and anhydrous SnCl₂ (3.842 g, 20.26 mmol, 5.5 equiv). The suspension was stirred at 70°C for 2 h. The reaction mixture was concentrated using rotary evaporator to about 10 mL, then AcOEt (250 mL) of and NaHCO₃ saturated aqueous solution (100 mL) were added, and the suspension was stirred for 15 min at rt. The inorganic solid was filtrated, and the aqueous phase was extracted with AcOEt (5 x 25 ml). The inorganic solid was washed with each of the organic extracts. The solid was additionally washed with AcOEt (4 x 50 mL) until no more product was detected (TLC) in the filtrate. All organic extracts were combined, washed with brine (100 mL) and the brine was re-extracted with AcOEt (50 mL). The organic extracts were combined, dried over Na₂SO₄ and evaporated to give 1.714 g (quant.) of pure product **45** as a white solid, which was directly used in the next step.

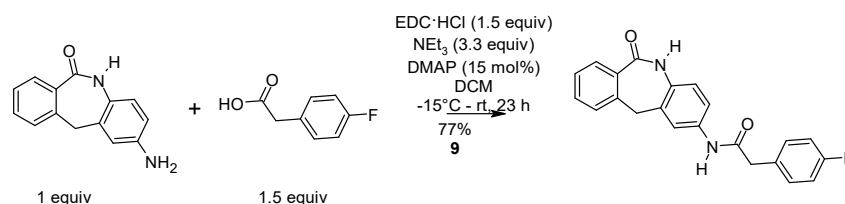
¹H NMR (400 MHz, DMSO- *d*₆) δ 7.57-7.53 (m, 1H), 7.36-7.31 (m, 1H), 7.27-7.21 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H, C⁴*H*), 6.47 (d, *J* = 2.6 Hz, 1H, C¹*H*), 6.39 (dd, *J* = 8.5, 2.6 Hz, 1H, C³*H*), 4.94 (s, 2H, NH₂), 4.47-4.36 (m, 1H, ½ CH₂CH₃) 3.88 (d, *J* = 12.9 Hz, 1H, ½ ArCH₂Ar'), 3.65-3.55 (m, 1H, ½ CH₂CH₃), 3.45 (d, *J* = 12.9 Hz, 1H, ½ ArCH₂Ar'), 1.13 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, DMSO- *d*₆) δ 167.2 (CONH), 146.7, 142.8, 139.5, 133.5, 130.8, 129.8, 127.8, 126.4, 126.0, 124.2, 112.3, 111.8, 43.4 (CH₂CH₃), 37.7 (CH₂), 13.6 (CH₃). LR-MS (*m/z*): 253 [M+H]⁺.



Synthesis of *N*-alkylated 5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one derivatives 7, 9-12, 14

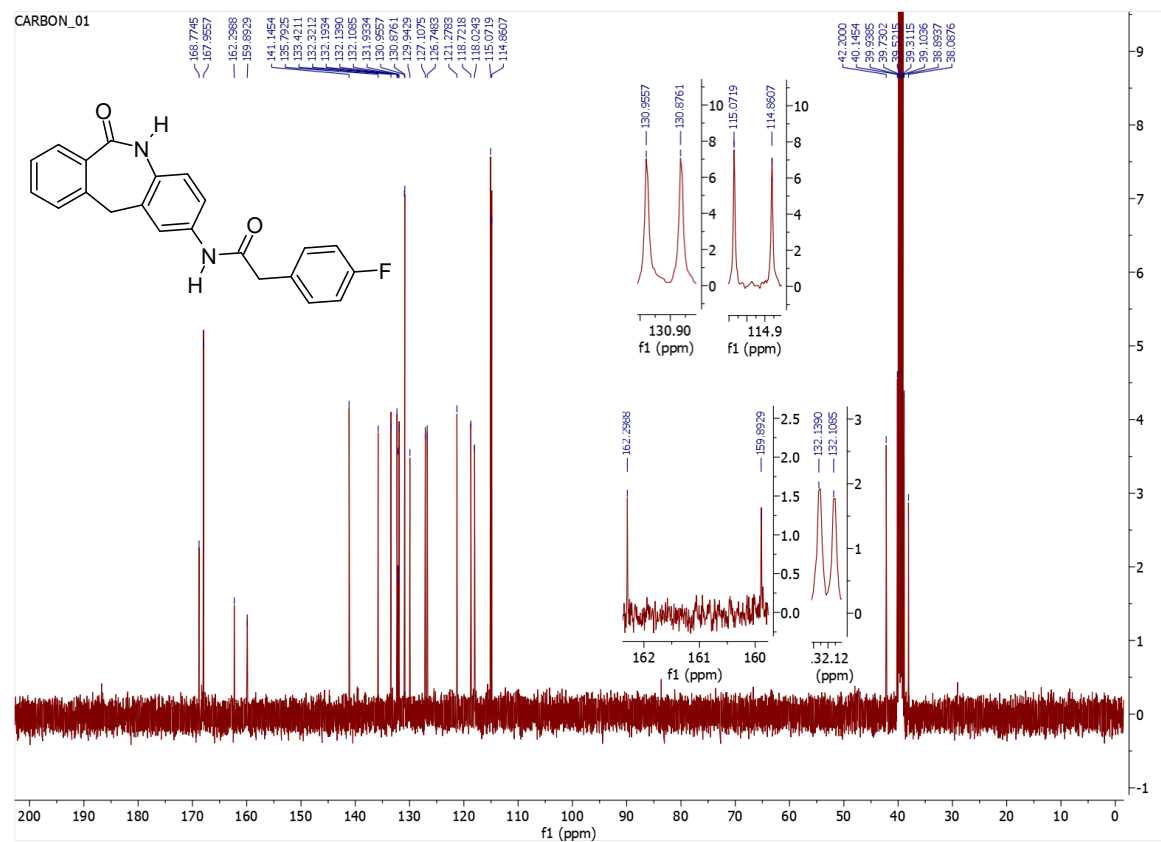
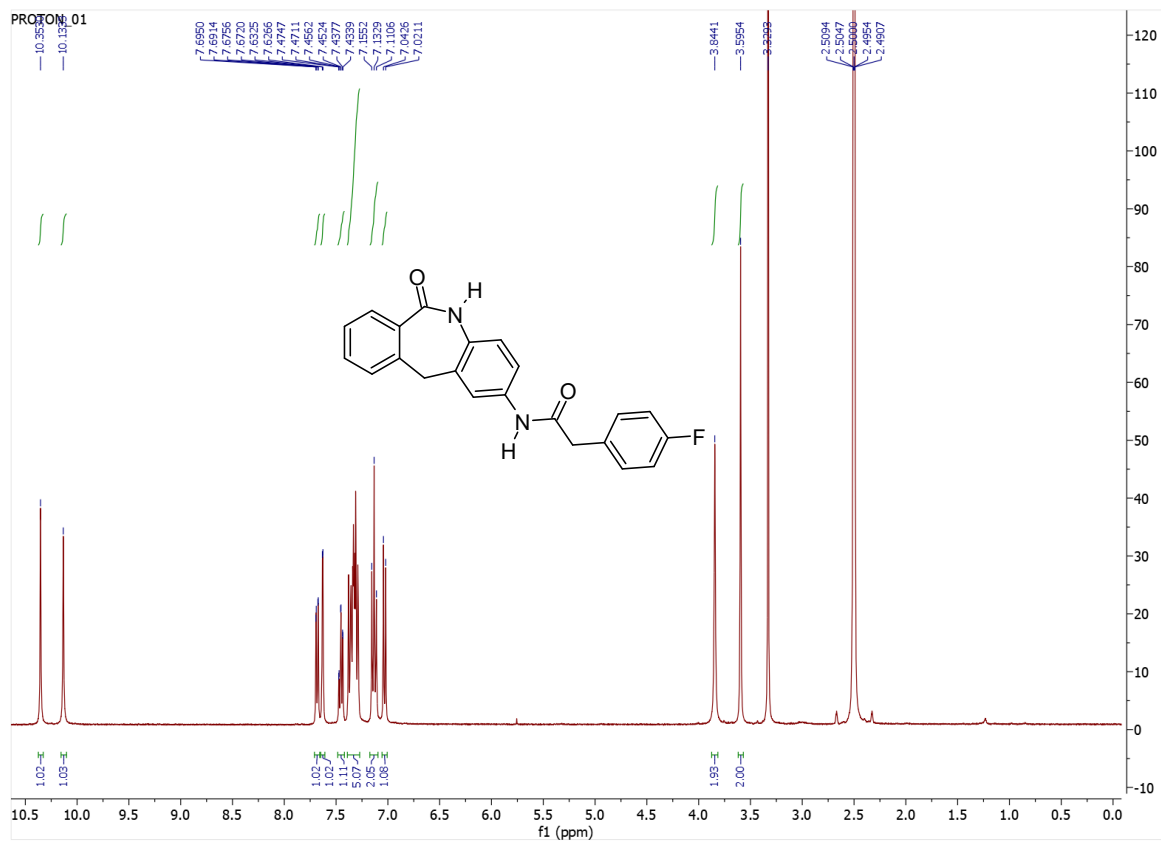


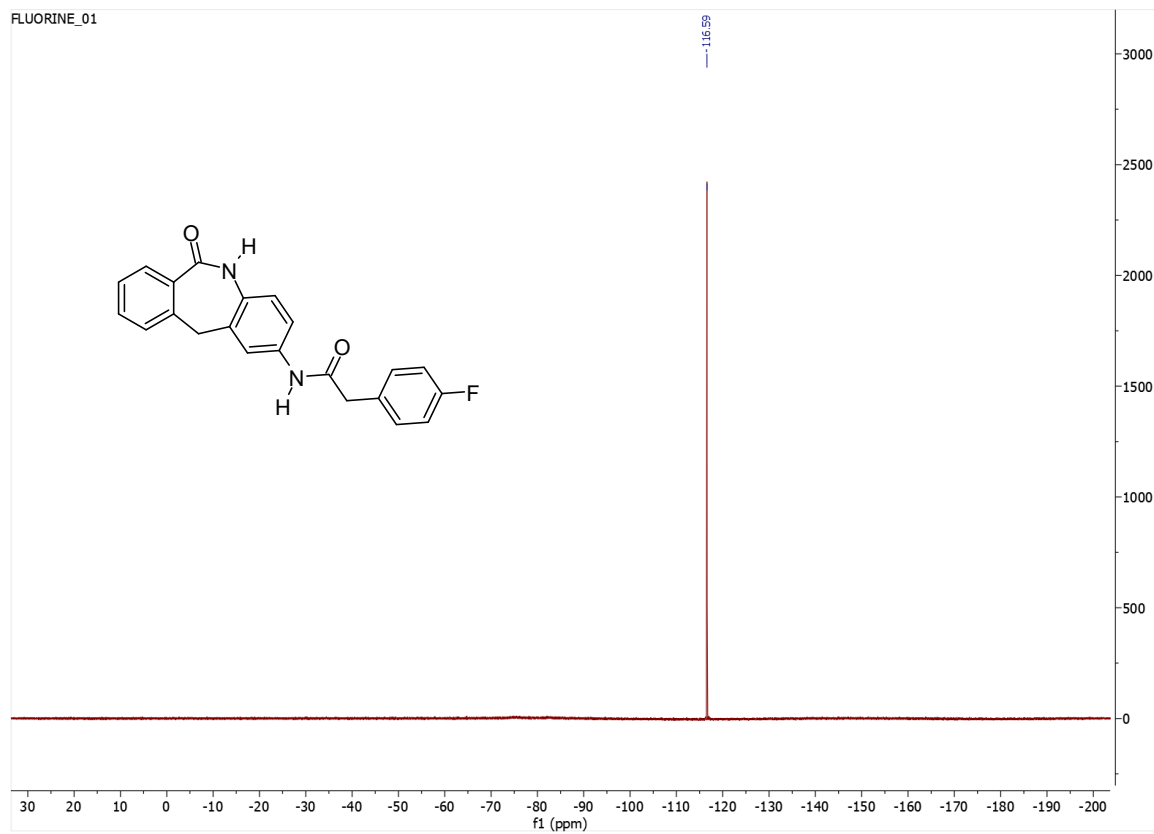
2-(4-Fluorophenyl)-N-(6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)acetamide (9)



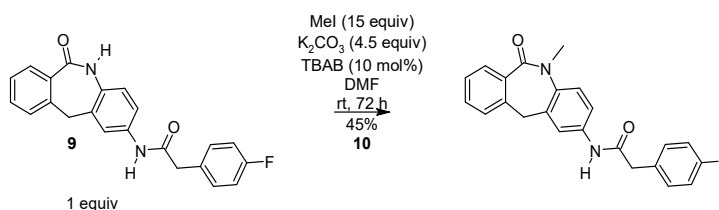
An oven-dried, round-bottom bulb was charged with 2-amino-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one **44** (750 mg, 3.34 mmol, 1 equiv), 4-fluorophenylacetic acid (773 mg, 5.02 mmol, 1.5 equiv) and anhydrous DCM (40 mL). The resulting suspension was cooled down to -15°C. DMAP (61 mg, 0.5 mmol, 15 mol%) and EDC·HCl (967 mg, 5.02 mmol, 1.5 equiv) were added in one portion and Et₃N (1.54 mL, 11.04 mmol, 3.3 equiv) was added dropwise, while stirring. The reaction mixture was allowed to warm slowly to rt by allowing the cooling bath to warm to rt overnight. The reaction mixture was stirred overall for 22.5 h. Water (20 mL) was added dropwise to the resulting suspension, and the mixture was stirred for 10 min, and filtrated. The filtrate was washed with water and DCM to give 812 mg of the product **9** as a white solid. The filtrate was re-extracted with DCM (10 x 25 mL) and the organic phase was dried over Na₂SO₄, filtrated and evaporated. The residue was heated with DCM, filtered and washed with DCM to obtain additional 111 mg of product **9**. Overall yield was 923 mg (77%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.35 (s, 1H, *NH*), 10.13 (s, 1H, *NH*), 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.45 (td, *J* = 7.4, 1.5 Hz, 1H), 7.39-7.27 (m, 5H), 7.13 (t, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 2H, *CH*₂), 3.60 (s, 2H, *CH*₂); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 168.8 (CONH), 168.0 (CONH), 161.1 (d, ¹*J*_{CF} = 241.9 Hz), 141.1, 135.8, 133.4, 132.3, 132.2, 132.1 (d, ⁴*J*_{CF} = 3.1 Hz), 131.9, 130.9 (d, ³*J*_{CF} = 8.0 Hz), 129.9, 127.1, 126.7, 121.3, 118.7, 118.0, 115.0 (d, ²*J*_{CF} = 21.2 Hz), 42.2 (*CH*₂), 38.1 (*CH*₂). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -116.6. LR-MS (*m/z*): 361 [M+H]⁺.



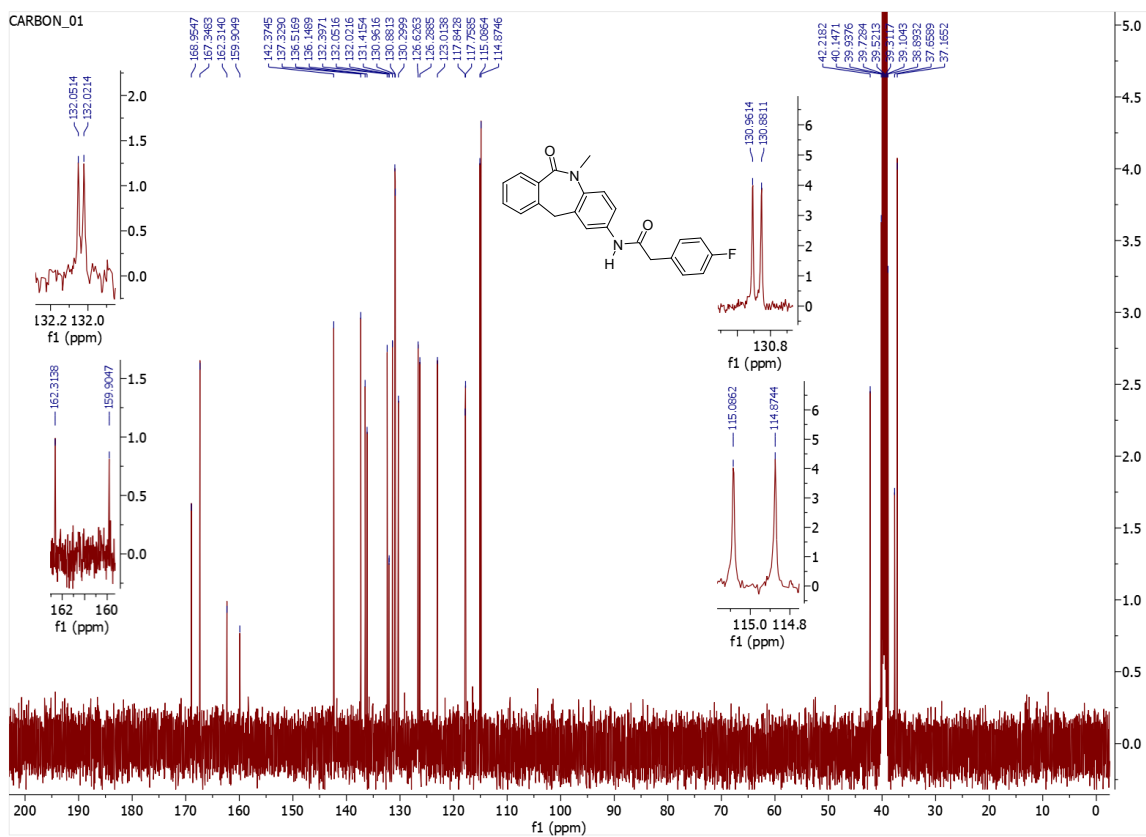
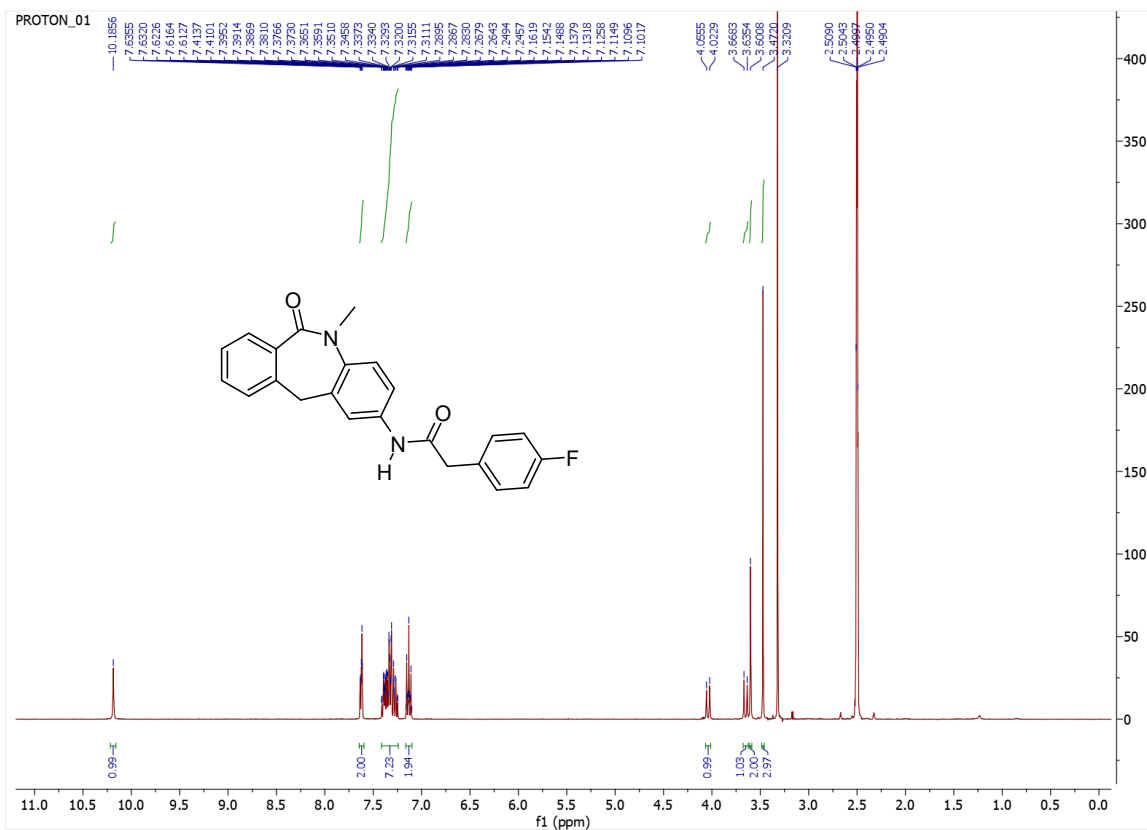


2-(4-Fluorophenyl)-*N*-(5-methyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)acetamide (10)

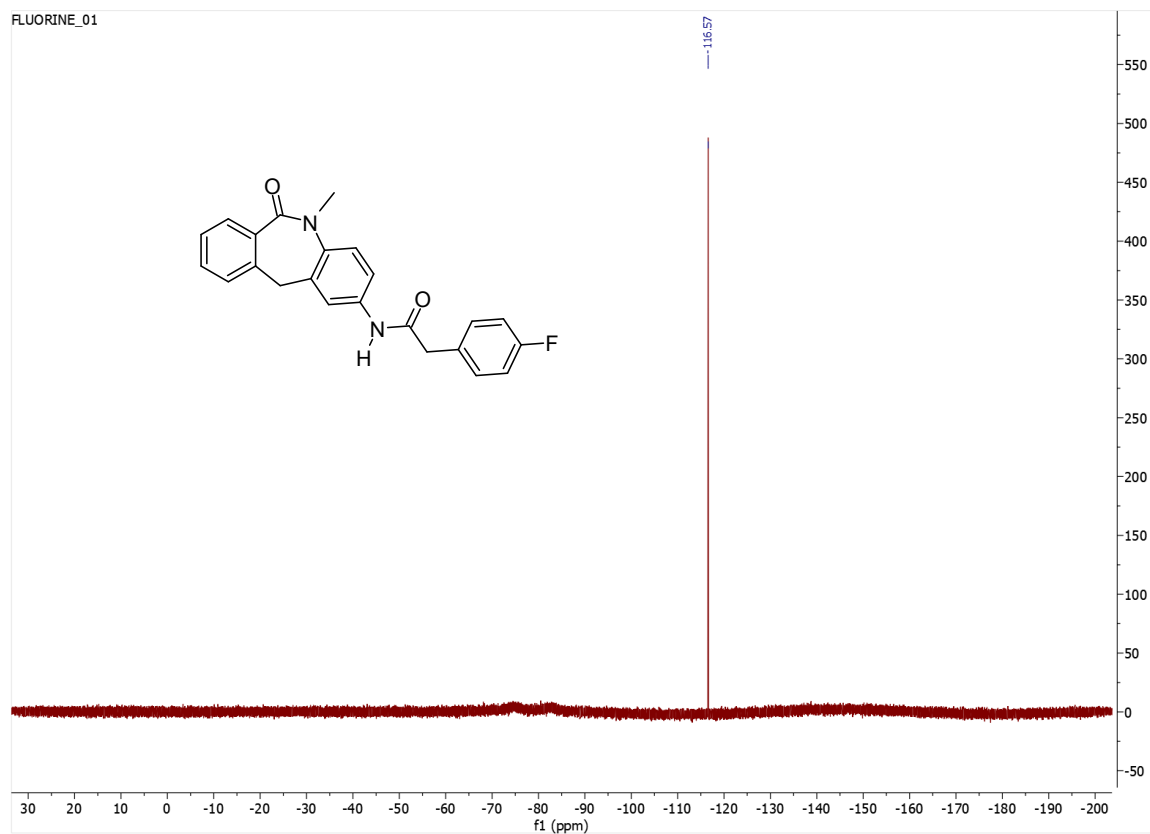


An oven-dried, screw-capped vial was charged with 2-(4-fluorophenyl)-*N*-(6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)acetamide **9** (120 mg, 0.33 mmol, 1 equiv), calcinated, milled K₂CO₃ (69 mg, 0.50 mmol, 1.5 equiv), TBAB (11 mg, 0.03 mmol, 10 mol%), anhydrous DMF (1.2 ml) and MeI (104 μ l, 1.66 mmol, 5 equiv), and the resulting mixture was stirred at rt for 24 h. Additional portions of calcinated, milled K₂CO₃ (69 mg, 0.5 mmol, 1.5 equiv) and MeI (104 μ l, 1.66 mmol, 5 equiv) were added after 24 h and again after 48 h. The mixture was stirred at rt for overall 72 h and the volatiles were evaporated. The residue was subjected to column chromatography (silica; acetone/DCM: 2-8%) to obtain 56 mg (45%) of product **10** as a bright-yellow foam.

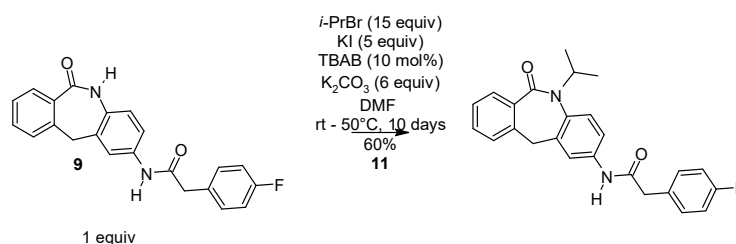
¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H, CONH), 7.64-7.59 (m, 2H), 7.41-7.24 (m, 7H), 7.16-7.10 (m, 2H), 4.04 (d, *J* = 13.0 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 3.65 (d, *J* = 13.1 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 3.60 (s, 2H, CH₂CONH), 3.47 (s, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.0 (CON), 167.3 (CON), 161.1 (d, ¹*J*_{CF} = 242.3 Hz), 142.4, 137.3, 136.5, 136.1, 132.4, 132.0 (d, ⁴*J*_{CF} = 3.0 Hz), 131.4, 131.0 (d, ³*J*_{CF} = 8.1 Hz), 130.3, 126.6, 126.3, 123.0, 117.8 (x 2), 115.0 (d, ²*J*_{CF} = 21.3 Hz), 42.2, 37.7, 37.2; ¹⁹F NMR (376 MHz, DMSO) δ -116.6. LR-MS (*m/z*): 375 [M+H]⁺.



FLUORINE_01

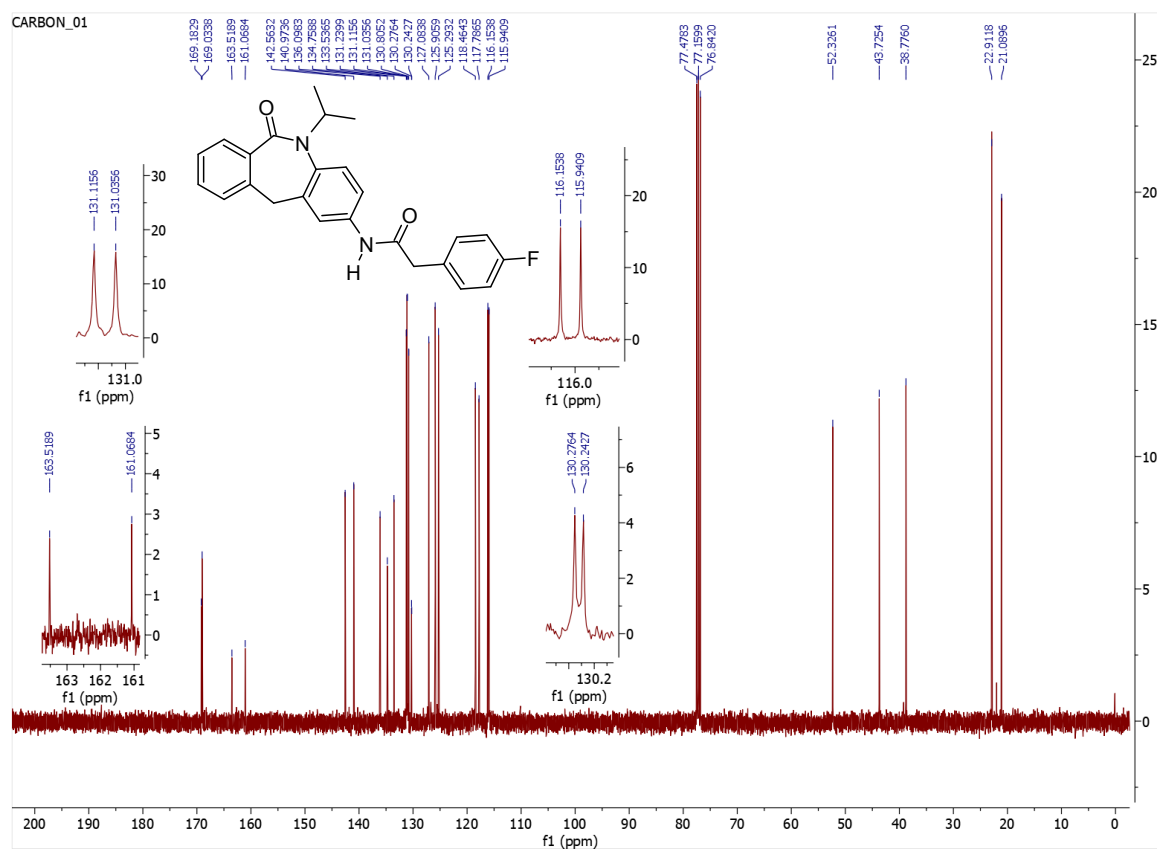
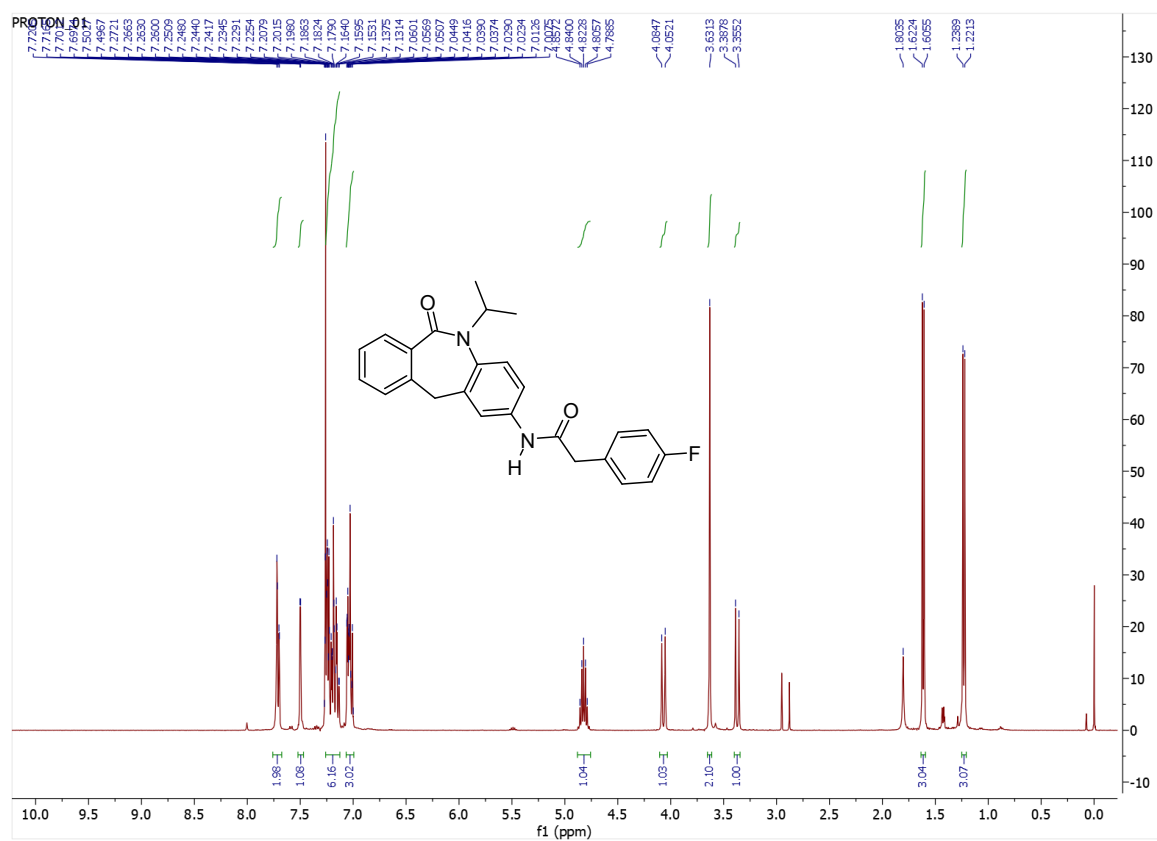


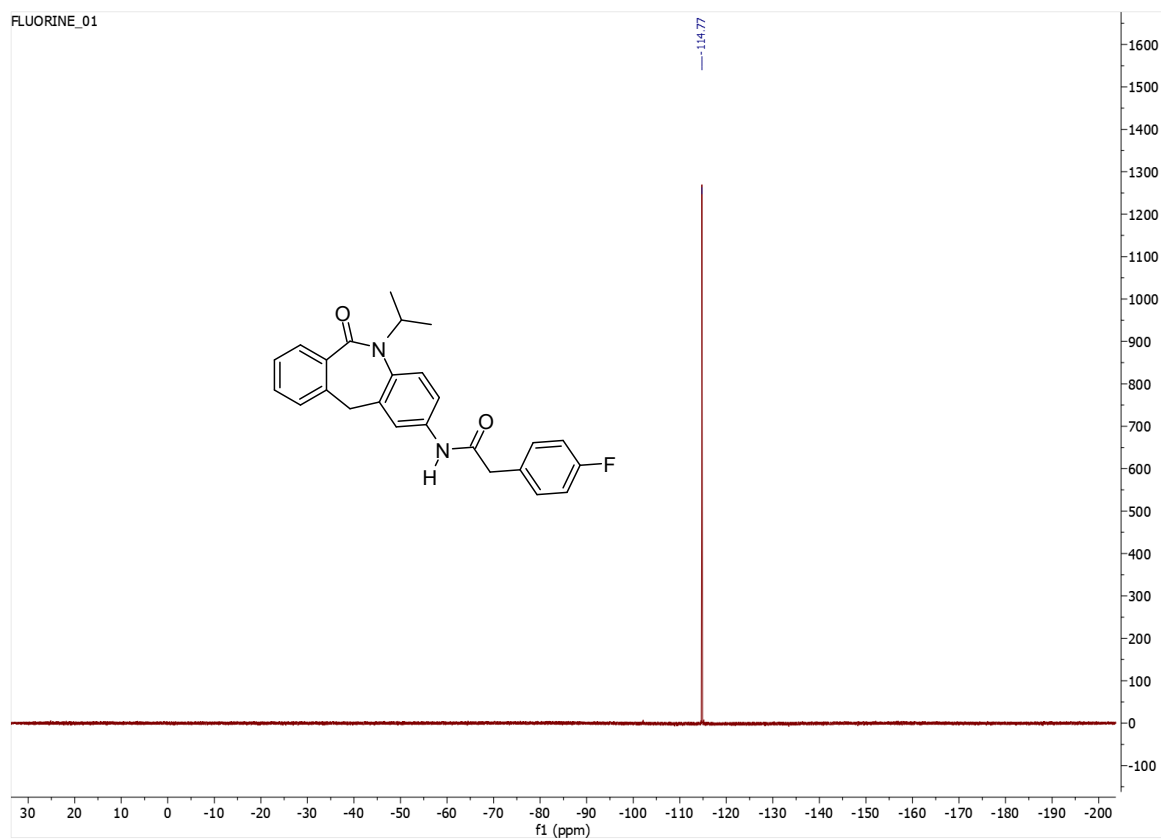
2-(4-fluorophenyl)-*N*-(5-isopropyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)acetamide (11)



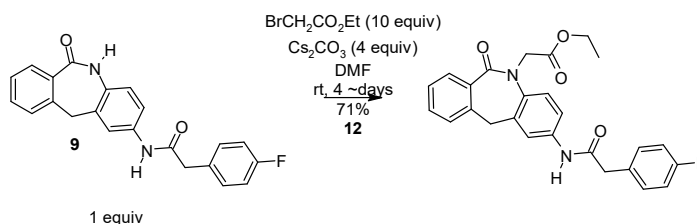
An oven-dried, round-bottom bulb was charged with 2-(4-fluorophenyl)-*N*-(6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)acetamide **9** (120 mg, 0.33 mmol, 1 equiv), calcinated, milled K₂CO₃ (92 mg, 0.67 mmol, 2 equiv), TBAB (11 mg, 0.03 mmol, 10 mol%), anhydrous DMF (1.8 mL) and *i*-PrBr (144 µl, 1.66 mmol, 5 equiv), and the resulting mixture was stirred at rt for 24 h. KI (55 mg, 0.33 mmol, 1 equiv) was added and the mixture was stirred at rt for additional 48 h. Further portions of calcinated, milled K₂CO₃ (92 mg, 0.67 mmol, 2 equiv) and *i*-PrBr (144 µl, 1.66 mmol, 5 equiv) were added and the mixture was stirred at 50°C for additional 48 h. Additional portions of KI (221 mg, 1.33 mmol, 4 equiv), calcinated, milled K₂CO₃ (92 mg, 0.67 mmol, 2 equiv) and *i*-PrBr (144 µl, 1.66 mmol, 5 equiv) were added and the mixture was stirred at rt for further 7 days. The volatiles were evaporated and the residue was subjected to column chromatography (silica; DCM/cyclohexane: 25-100%, then MeOH/DCM 0-0.5%). The compound was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, and the precipitate was washed with *n*-hexane (2 times) to give 80 mg (60%) of a product **11** as a yellow foam.

¹H NMR (400 MHz, CDCl₃) δ 7.76-7.67 (m, 2H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.26-7.13 (m, 6H) overlapped with residual CHCl₃, 7.07-6.99 (m, 3H), 4.82 [m, 1H, CH(CH₃)₂], 4.07 (d, *J* = 13.0 Hz, 1H, ½ ArCH₂Ar'), 3.63 (s, 2H, CH₂CONH), 3.37 (d, *J* = 13.0 Hz, 1H, ½ ArCH₂Ar'), 1.61 (d, *J* = 6.7 Hz, 3H, CH₃), 1.23 (d, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.2 (CON), 169.0 (CON), 162.3 (d, ¹*J*_{C-F} = 246.3 Hz), 142.6, 141.0, 136.1, 134.8, 133.5, 131.2, 131.1 (d, ³*J*_{C-F} = 8.0 Hz), 130.8, 130.3 (d, ⁴*J*_{C-F} = 3.4 Hz), 127.1, 125.9, 125.3, 118.5, 117.8, 116.0 (d, ²*J*_{C-F} = 21.4 Hz), 52.3, 43.7, 38.8, 22.9 (CH₃), 21.1 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.8. LR-MS (*m/z*): 403 [M+H]⁺.



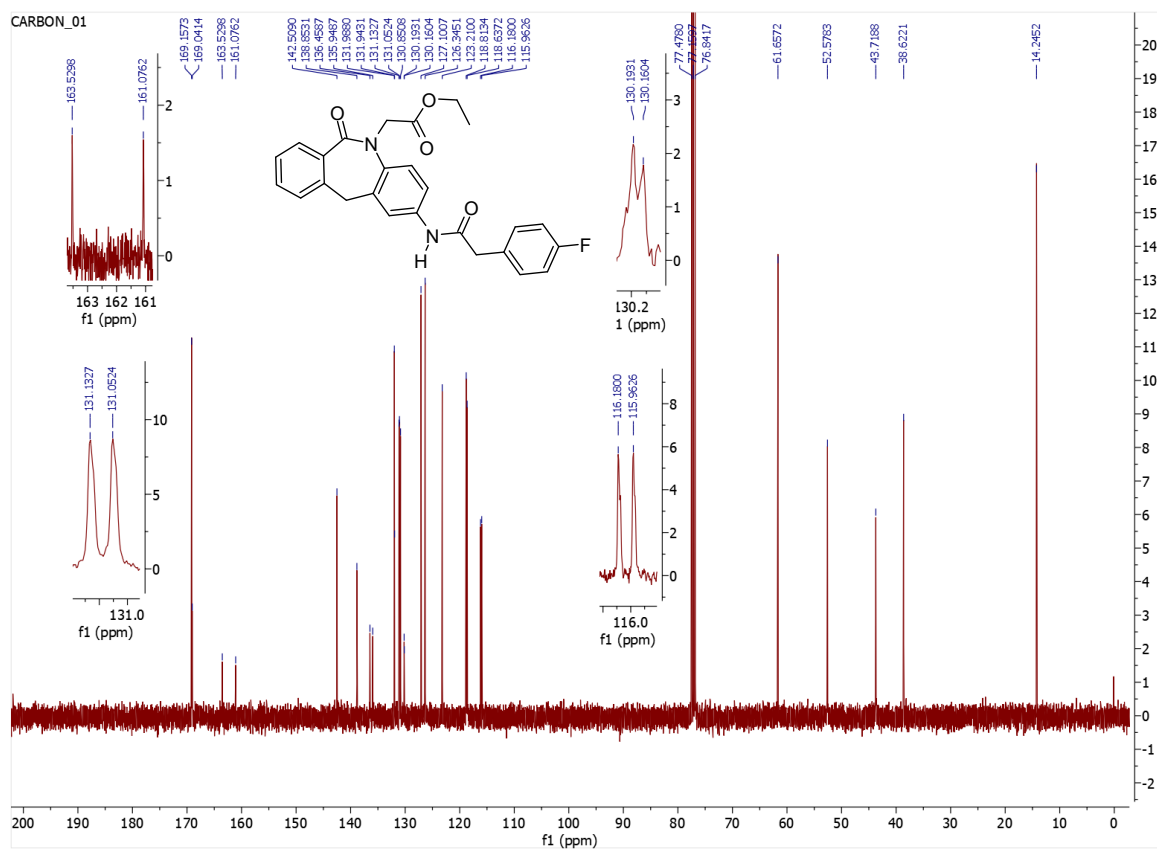
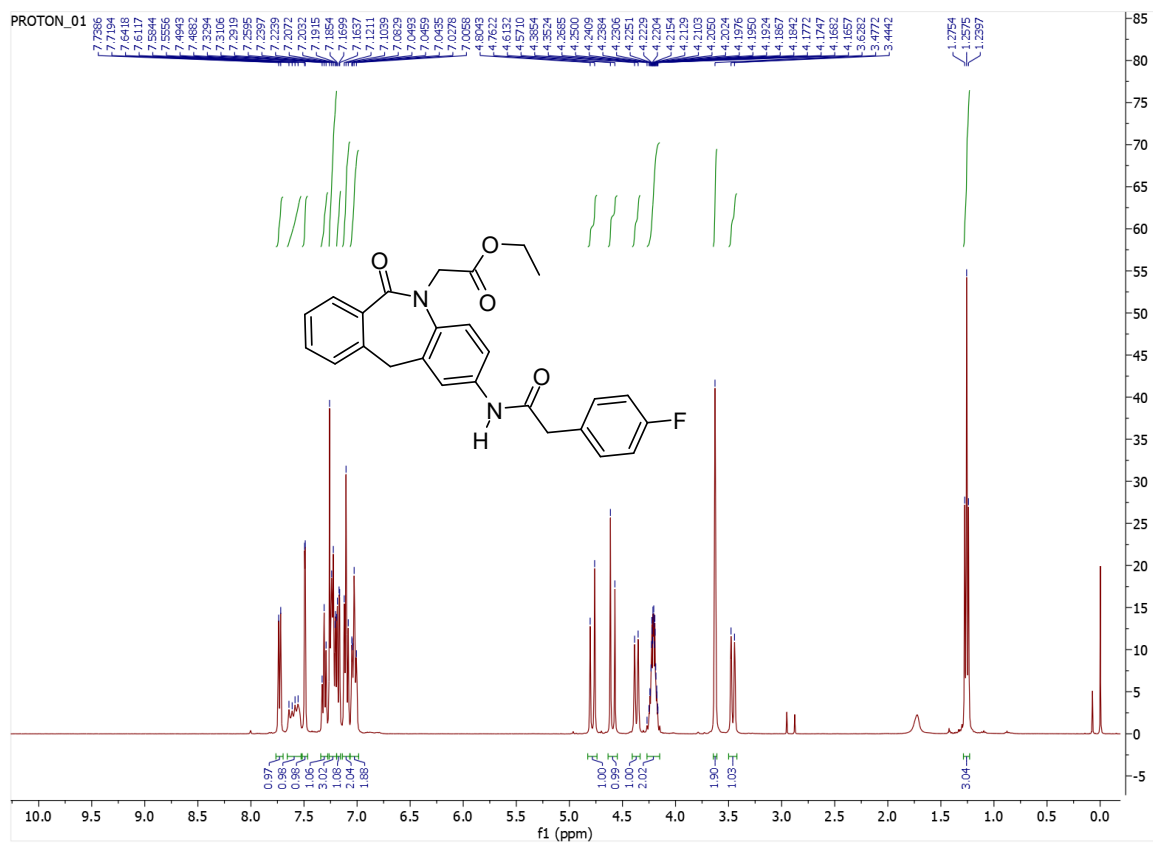


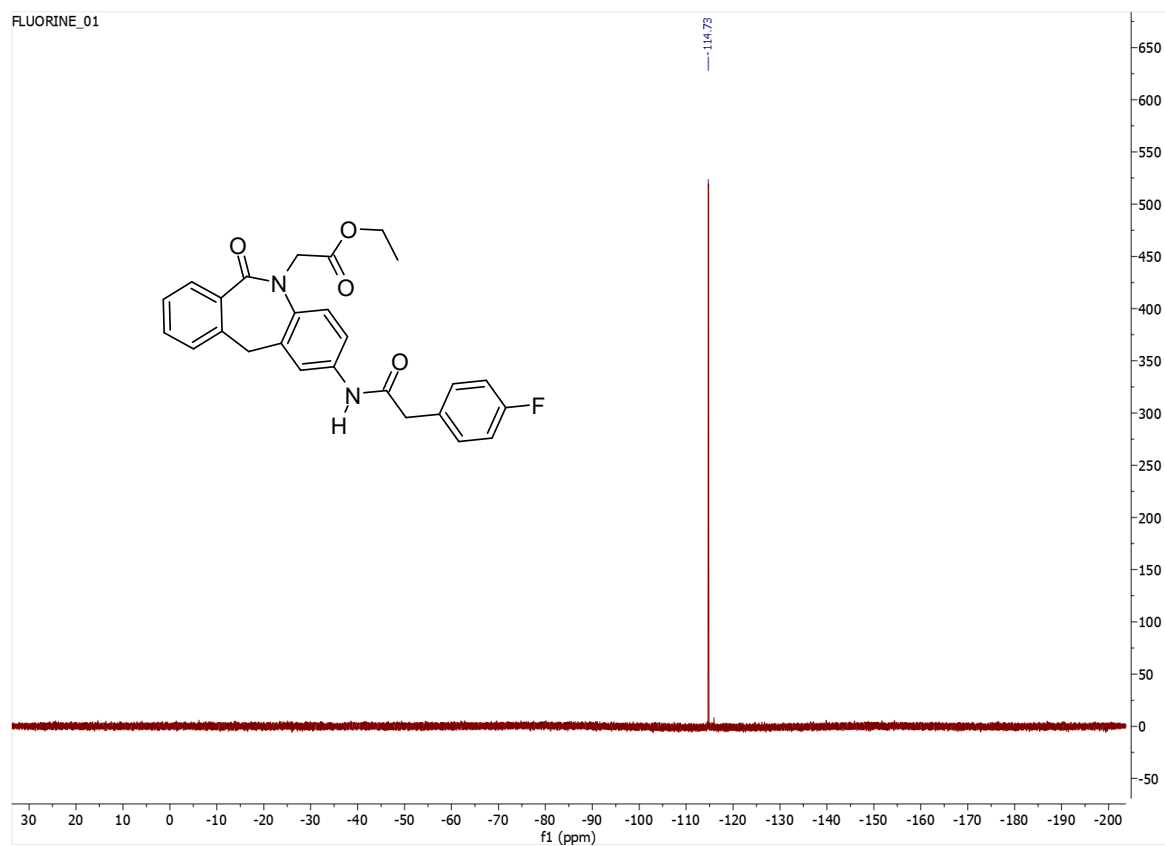
Ethyl 2-(2-(2-(4-fluorophenyl)acetamido)-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-5-yl)acetate (12)



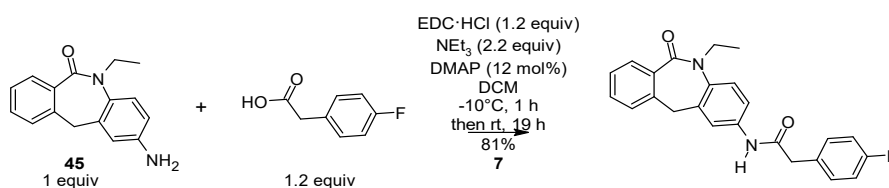
An oven-dried, screw-capped vial was charged with 2-(4-fluorophenyl)-*N*-(6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)acetamide **9** (120 mg, 0.33 mmol, 1 eq.), anhydrous Cs₂CO₃ (92 mg, 0.67 mmol, 2 equiv), anhydrous DMF (2 ml) and BrCH₂CO₂Et (157 μ l, 1.66 mmol, 5 equiv). After stirring at rt for 24 h, additional portions of anhydrous Cs₂CO₃ (92 mg, 0.67 mmol, 2 equiv) and BrCH₂CO₂Et (157 μ l, 1.66 mmol, 5 equiv) were added and the mixture was stirred at rt for additional 70 h. The volatiles were evaporated, and the residue was subjected to column chromatography (silica; MeOH/DCM: 0-0.5%). The obtained yellowish oil was triturated with Et₂O (3 mL) at rt for 3 h. The precipitate was filtered and washed with chilled Et₂O to obtain 105 g (71%) of product **12** as a white viscous solid.

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.66-7.53 (m, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.27-7.20 (m, 3H) overlapping with residual CHCl₃, 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 2H), 7.07-6.98 (m, 2H), 4.78 (d, *J* = 16.8 Hz, 1H, $\frac{1}{2}$ CONCH₂COO), 4.59 (d, *J* = 16.9 Hz, 1H, $\frac{1}{2}$ CONCH₂COO), 4.37 (d, *J* = 13.2 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 4.27-4.15 (m, 2H, COOCH₂CH₃), 3.63 (s, 2H, CH₂CONH), 3.46 (d, *J* = 13.2 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 1.26 (t, *J* = 7.1 Hz, 3H, COOCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.2 (2 x CO), 169.0 (CO), 162.3 (d, ¹*J*_{CF} = 246.6 Hz), 142.5, 138.9, 136.5, 135.9, 132.0, 131.9, 131.1 (d, ³*J*_{C-F} = 8.0 Hz), 130.9, 130.2 (d, ⁴*J*_{CF} = 3.3 Hz), 127.1, 126.3, 123.2, 118.8, 118.6, 116.1 (d, ²*J*_{C-F} = 21.8 Hz), 61.7 (CO₂CH₂CH₃), 52.6, 43.7, 38.6, 14.2 (CO₂CH₂CH₃); (one CAr missing); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.7. LR-MS (*m/z*): 447 [M+H]⁺.



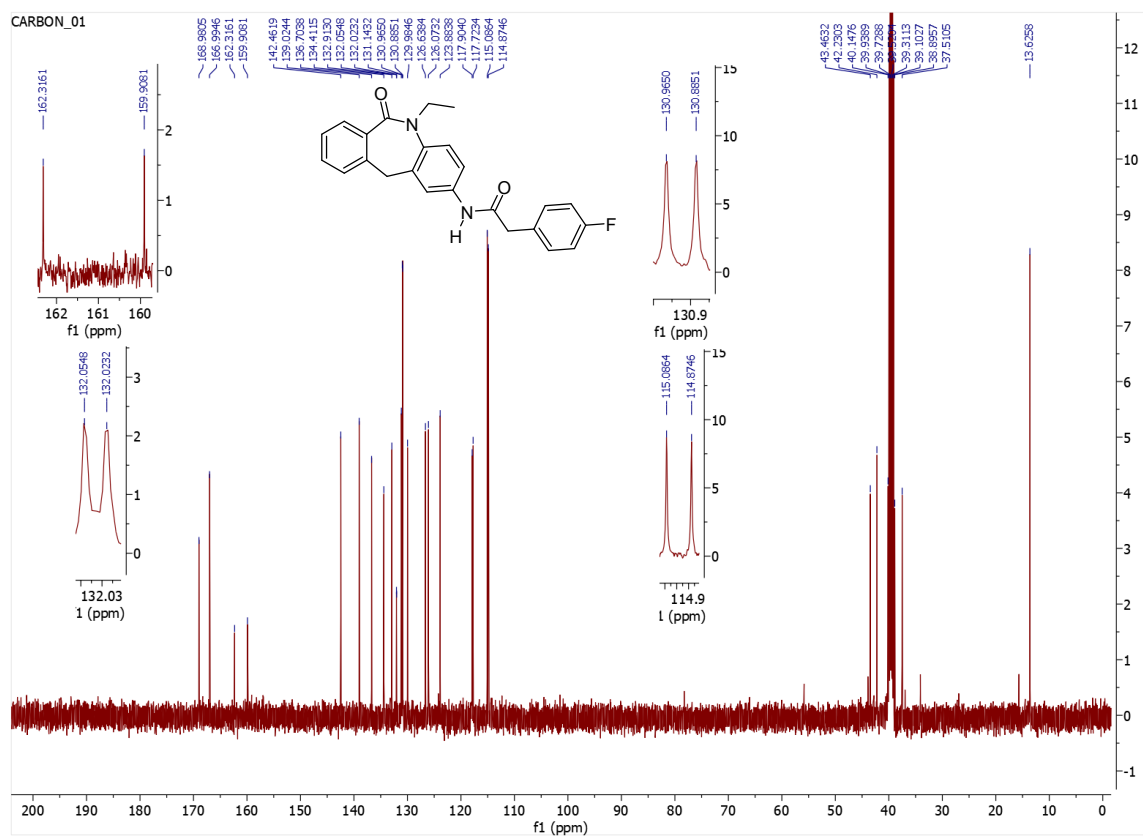
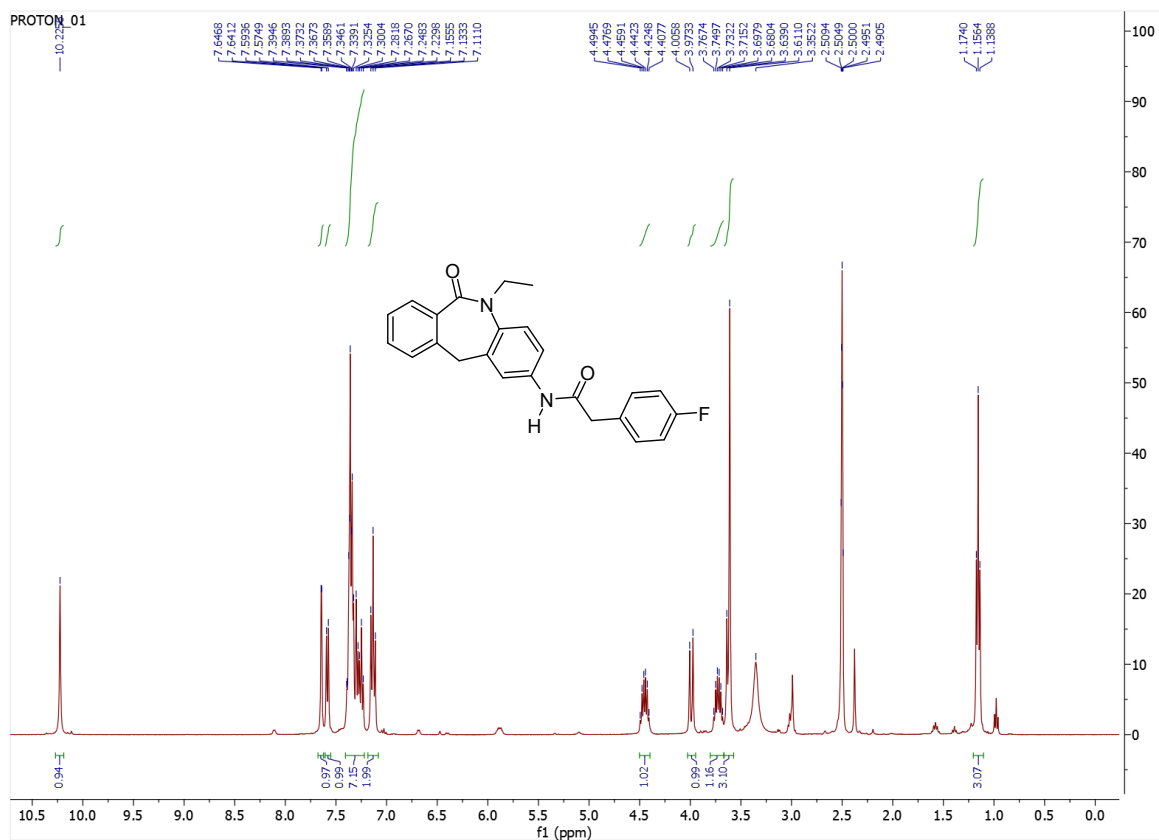


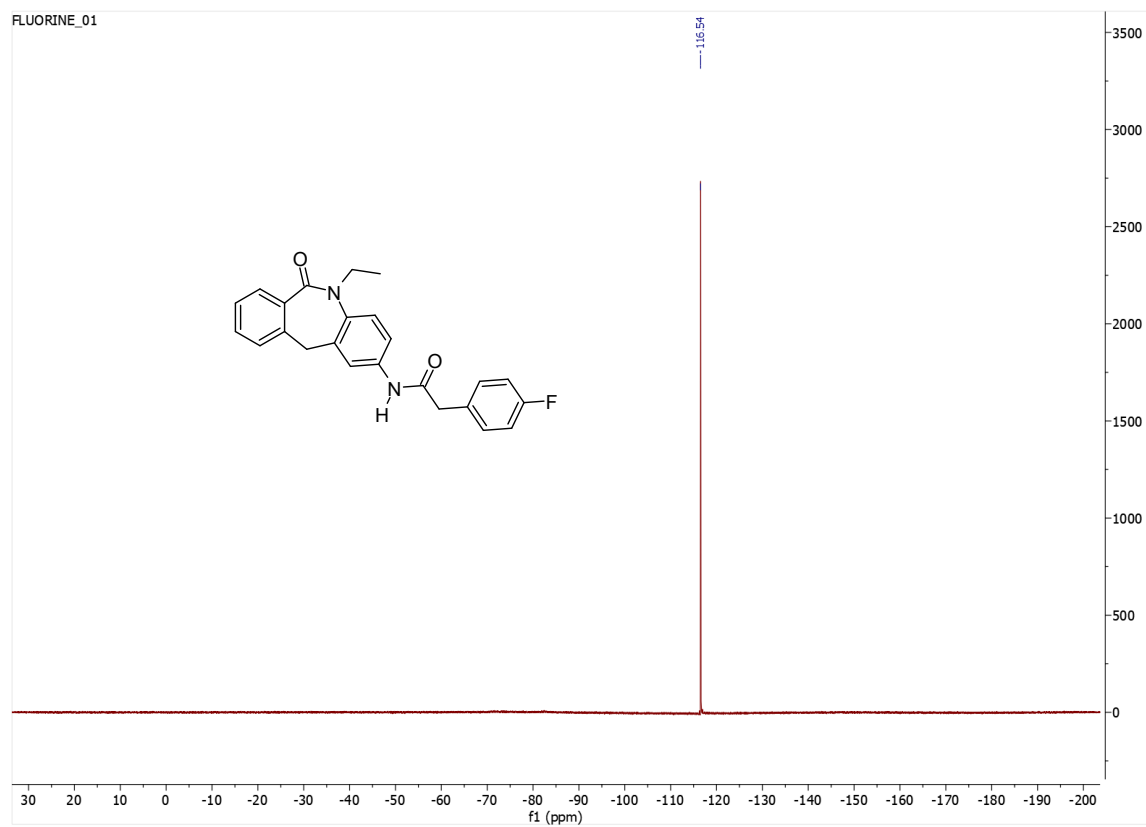
***N*-(5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)acetamide (7)**



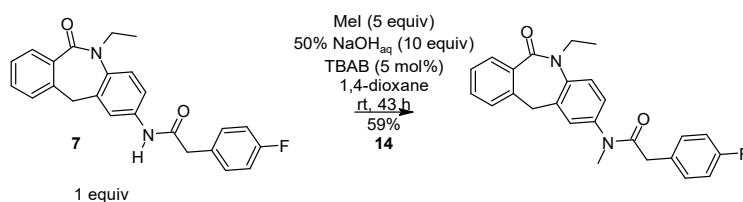
An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (100 mg, 0.40 mmol, 1 equiv), 4-fluorophenylacetic acid (73 mg, 0.48 mmol, 1.2 equiv) and anhydrous DCM (5 mL). After stirring for 10 min, the suspension was cooled down to -10°C. DMAP (6 mg, 0.05 mmol, 12 mol%), EDC·HCl (92 mg, 0.48 mmol, 1.2 equiv) and NEt₃ (122 μ L, 0.87 mmol, 2.2 equiv) were added. The suspension was stirred at -10°C for 1 h and then at rt for 19 h. Saturated aqueous solution of NH₄Cl (10 mL) and water (1 mL) were added. The suspension was stirred for 10 min, and the phases were separated. The aqueous one was extracted with DCM (4 x 10 mL), washed with brine (15 mL), dried over Na₂SO₄, filtrated and evaporated. The crude was dissolved in DCM, *n*-hexane was added and the solid was precipitated using rotary evaporator and washed with *n*-hexane (2 times). The procedure of the precipitation was repeated to give 154 mg (81%) of target product **7** as a beige solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.23 (s, 1H, NH), 7.67-7.62 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.41-7.21 (m, 7H), 7.13 (t, *J* = 8.9 Hz, 1H), 4.51-4.39 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 3.99 (d, *J* = 13.0 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 3.78-3.67 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 3.66-3.58 (m, 1H, $\frac{1}{2}$ ArCH₂Ar') overlapped with 3.61 [s, 2H, N(O)CCH₂], 1.16 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.0 (CONH), 167.0 (CONH), 161.1 (d, ¹*J*_{CF} = 242.1 Hz), 142.5, 139.0, 136.7, 134.4, 132.9, 132.0 (d, ⁴*J*_{CF} = 3.2 Hz), 131.1, 130.9 (d, ³*J*_{CF} = 8.0 Hz), 130.0, 126.6, 126.1, 123.9, 117.9, 117.7, 115.0 (d, ²*J*_{CF} = 21.3 Hz), 43.5 (CH₂), 42.2 (CH₂), 37.5 (CH₂), 13.6 (CH₃). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -116.5. LR-MS (*m/z*): 389 [M+H]⁺.



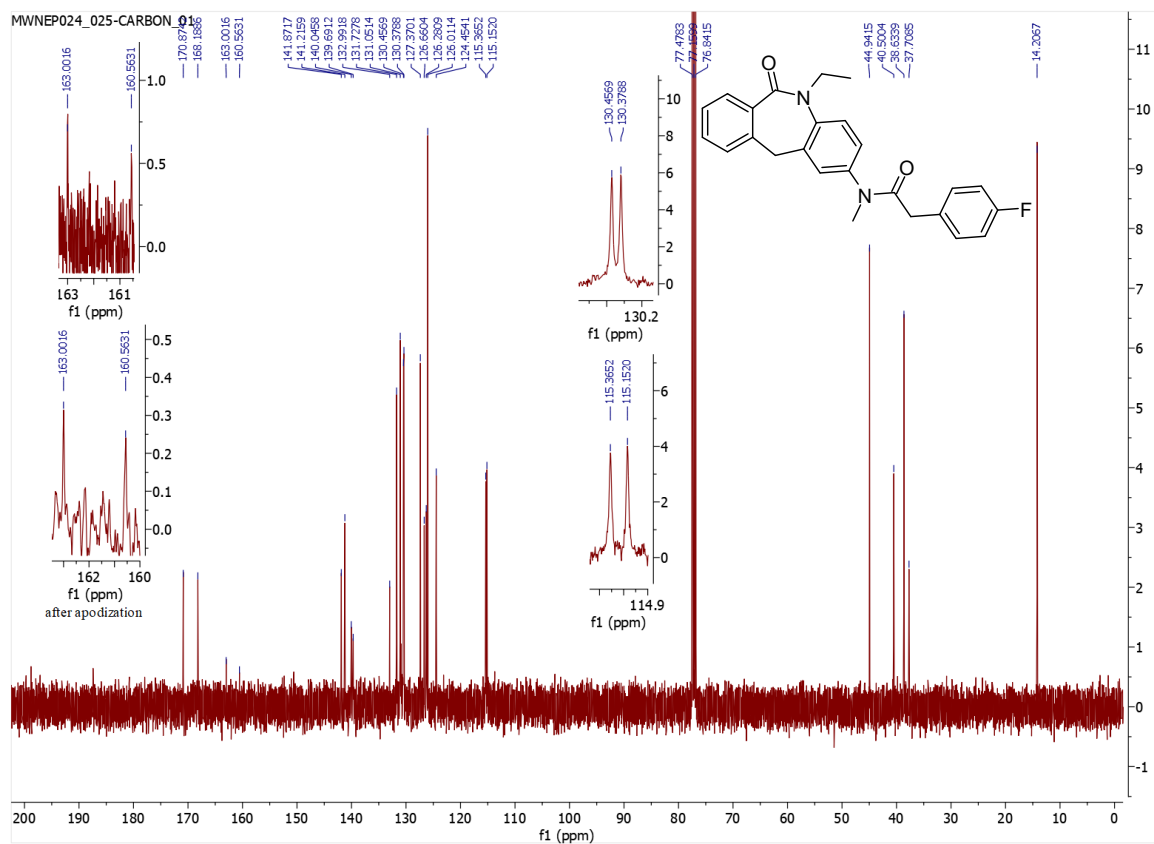
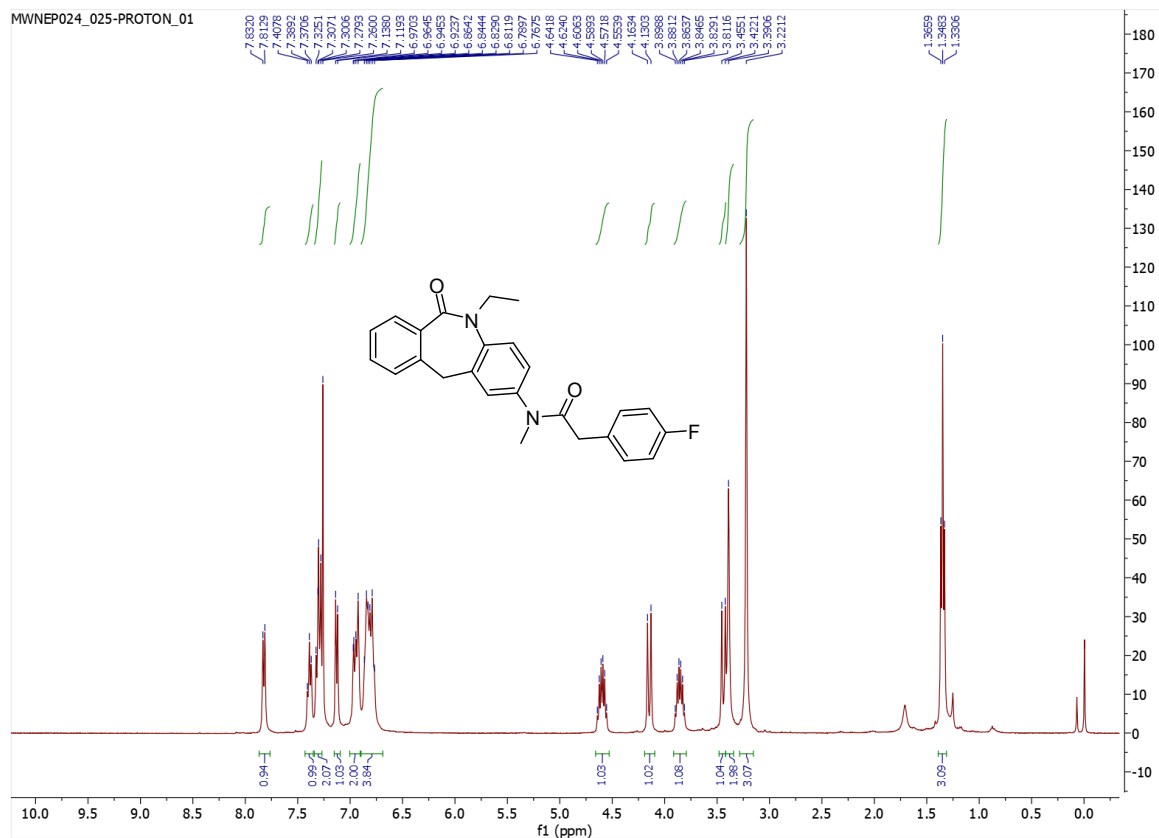


***N*-(5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)-*N*-methylacetamide (**14**)**

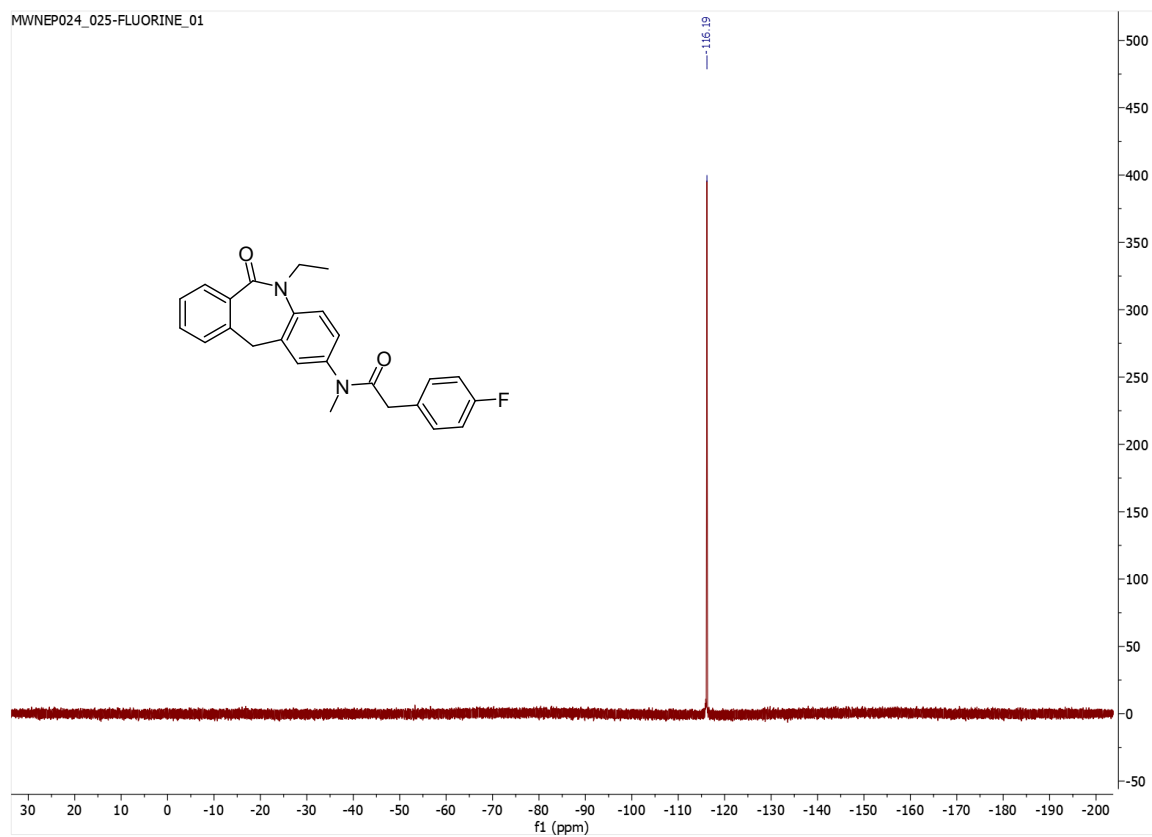


The screw-cap vial was charged with *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)acetamide **7** (80 mg, 0.21 mmol, 1 equiv), TBAB (3 mg, 0.01 mmol, 5 mol%), 1,4-dioxane (4 ml) and 50% aqueous solution of NaOH (106 μ l, 2.06 mmol, 10 equiv of solid NaOH) and MeI (64 μ l, 1.03 mmol, 5 equiv). The mixture was stirred at rt for 43 h. Solid NH₄Cl (165 mg, 3.09 mmol, 15 equiv) was added followed by water (dropwise, 0.5 ml) and the mixture was stirred for further 15 min. The volatiles were evaporated, and the residue was subjected to column chromatography (silica; MeOH/DCM: 0-1.5%). The compound was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator and the resulting white solid was washed with *n*-hexane (2 times) to give 49 mg (59%) of product **14**.

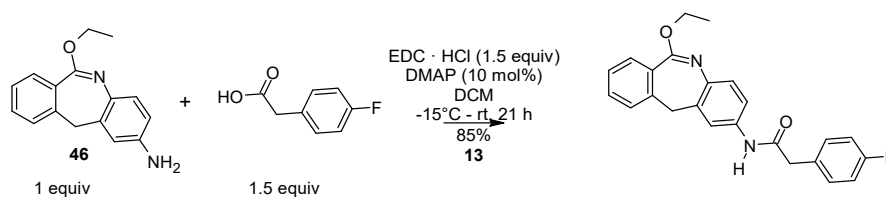
¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.34-7.26 (m, 2H) overlapping with residual CHCl₃, 7.13 (d, *J* = 7.5 Hz, 1H), 7.00-6.89 (m, 2H), 6.88-6.69 (m, 4H), 4.66-4.54 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 4.15 (d, *J* = 13.2 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 3.91-3.80 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 3.44 (d, *J* = 13.2 Hz, 1H, ArCH₂Ar'), overlapping with 3.39 (s, 2H, CH₂C₆H₄F), 3.22 (s, 3H, NCH₃), 1.35 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 170.9 (CON), 168.2 (CON), 161.8 (d, ¹*J*_{CF} = 245.1 Hz), 141.9, 141.2, 140.0, 139.7, 133.0, 131.7, 131.1, 130.9, 130.4 (d, ³*J*_{CF} = 7.9 Hz), 127.4, 126.7, 126.3, 126.0, 124.5, 115.3 (d, ²*J*_{C-F} = 21.4 Hz), 44.9, 40.5, 38.6, 37.7, 14.2 (CH₂CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -116.2. LR-MS (*m/z*): 423 [M+H]⁺.



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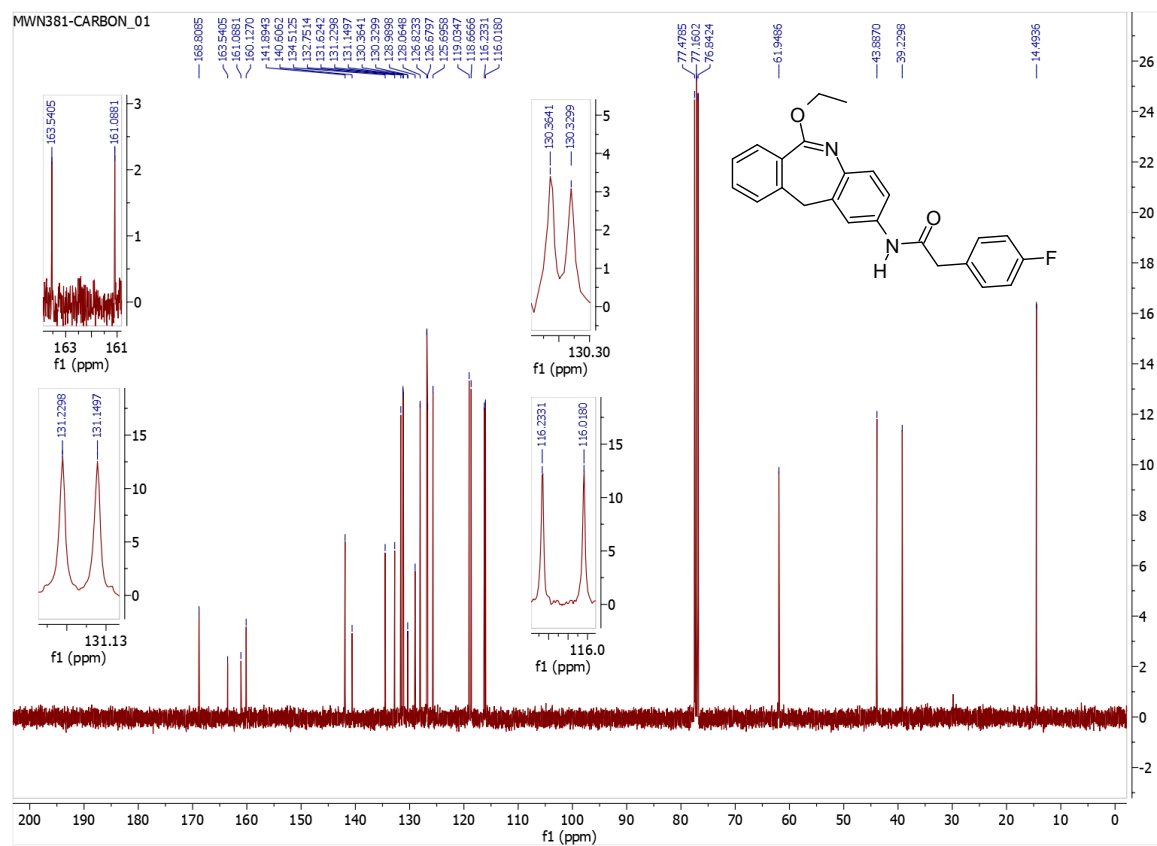
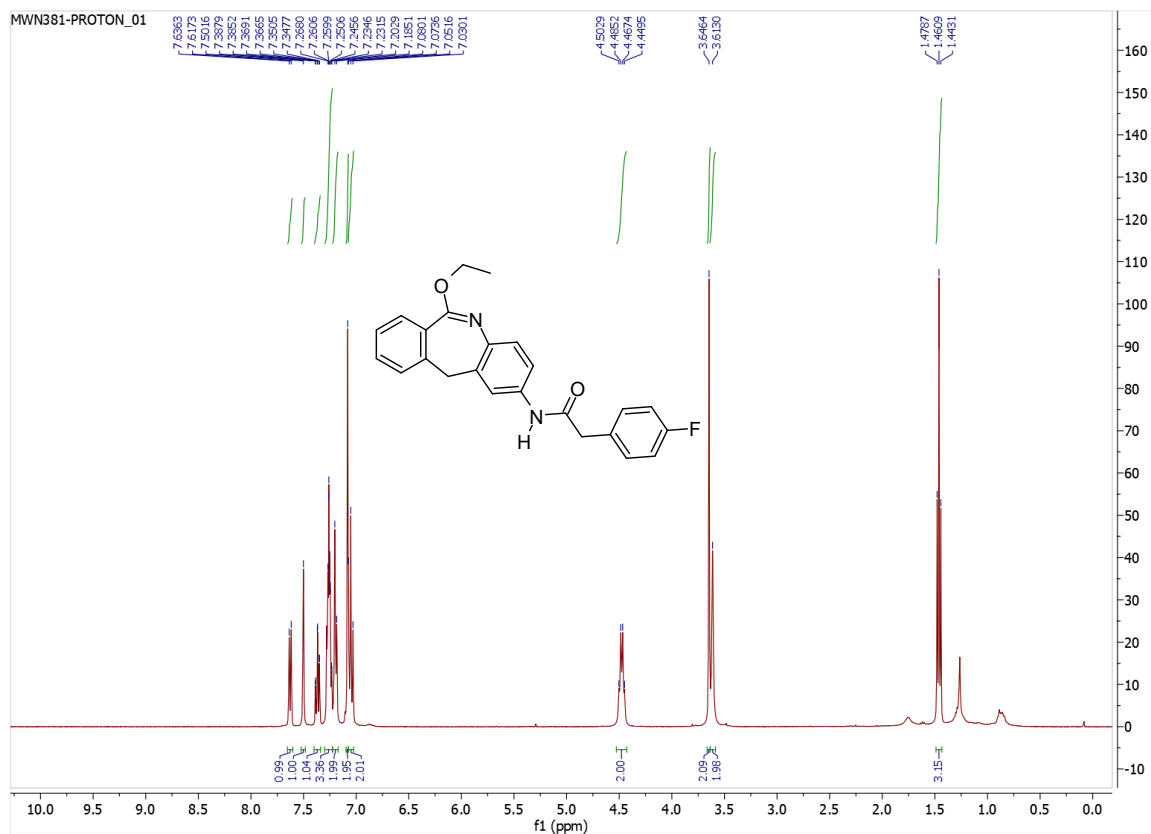


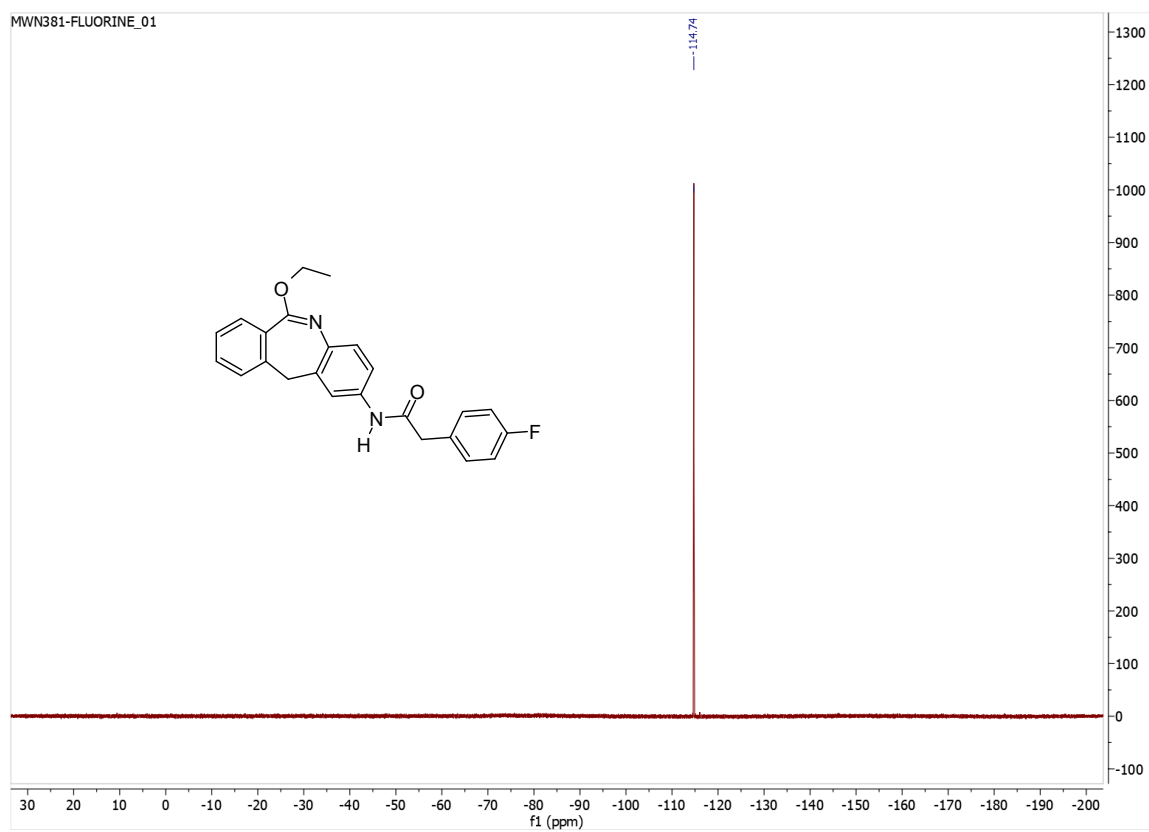
***N*-(6-ethoxy-11*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)acetamide (**13**)**



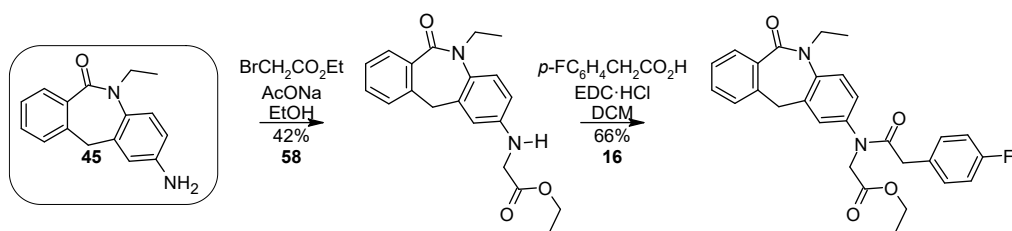
An oven-dried, screw-capped vial was charged with 6-ethoxy-11*H*-dibenzo[*b,e*]azepin-2-amine **46** (40 mg, 0.16 mmol, 1 equiv), 4-fluorophenylacetic acid (37 mg, 0.24 mmol, 1.5 equiv), DMAP (2 mg, 0.02 mmol, 10 mol%) and anhydrous DCM (2 mL). The solution was cooled down to -15° C and EDC·HCl (46 mg, 0.24 mmol, 1.5 equiv) was added. The reaction was allowed to warm slowly to rt by allowing the cooling bath to warm to rt overnight. The reaction mixture was stirred overall for 21 h and the volatiles were evaporated. The crude was subjected to column chromatography (silica; acetone/DCM: 0.5-1%) to obtain 53 mg (85%) of product **13** as a white solid. The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, and the resulting solid was washed with *n*-hexane (2 times).

¹H NMR (400 MHz, CDCl₃) δ 7.63 (br d, *J* = 7.6 Hz, 1H), 7.50 (br s, 1H, NH), 7.37 (td, *J* = 7.5, 0.5 Hz, 1H), 7.29-7.23 (m, 3H), 7.22-7.17 (m, 2H), 7.09-7.07 (m, 2H) overlapping 7.05 (t, *J* = 8.7 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H, CH₂CH₃), 3.65 (s, 2H, CH₂), 3.61 (s, 2H, CH₂), 1.46 (t, *J* = 7.1 Hz, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 168.8 (C=O), 162.3 (d, ¹*J*_{CF} = 246.5 Hz), 160.1 (C=N), 141.9, 140.6, 134.5, 132.8, 131.6, 131.2 (d, ³*J*_{CF} = 8.0 Hz), 130.3 (d, ⁴*J*_{CF} = 3.4 Hz), 129.0, 128.1, 126.8, 126.7, 125.7, 119.0, 118.7, 116.1 (d, ²*J*_{CF} = 21.6 Hz), 61.9 (CH₂CH₃), 43.9, 39.2, 14.5 (CH₃). ¹⁹F NMR (376 MHz, CDCl₃) δ -114.7. LR-MS (*m/z*): 389 [M+H]⁺.

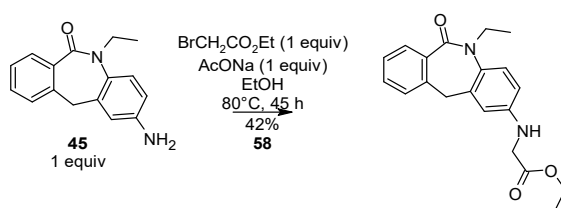




Synthesis of ethyl *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-*N*-(2-(4-fluorophenyl)acetyl)glycinate 16.

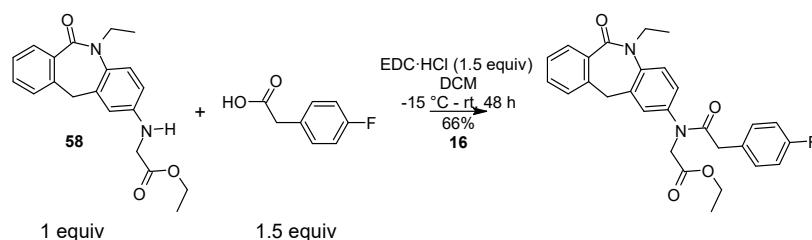


Ethyl [(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino]acetate (58**)**



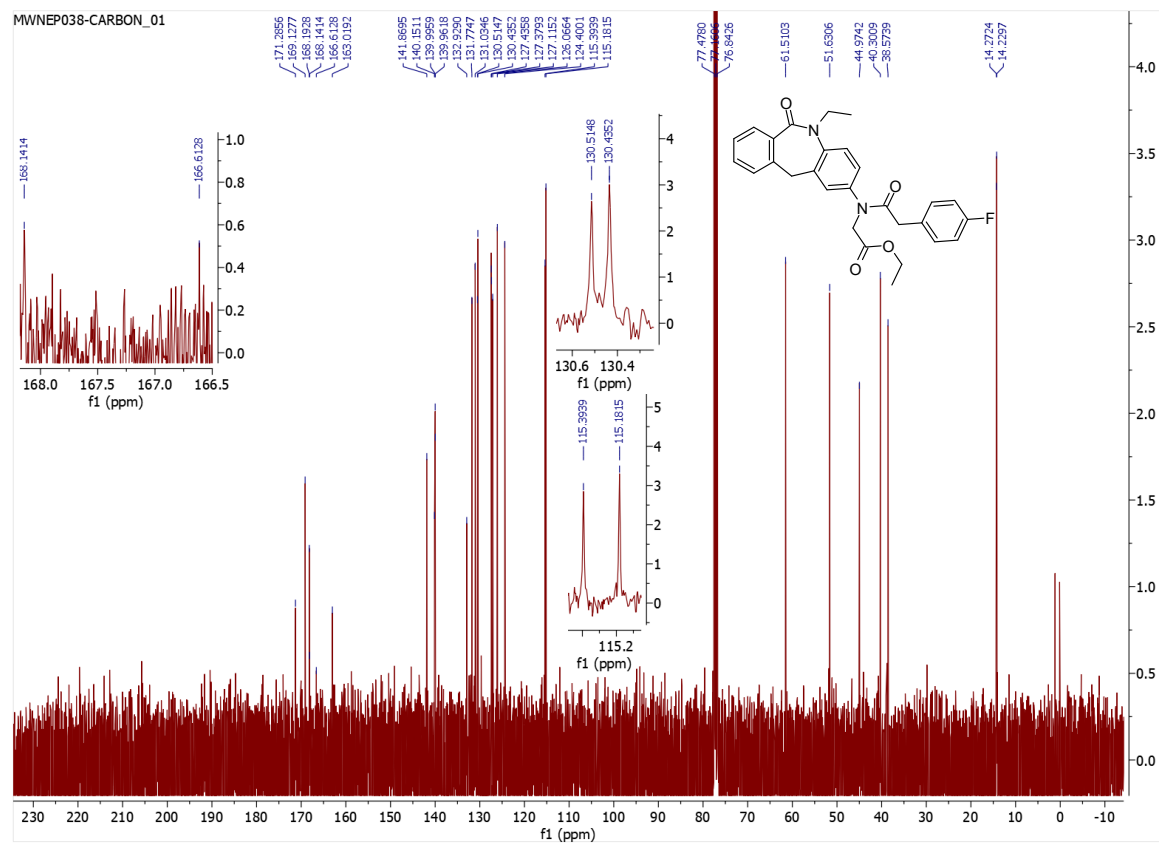
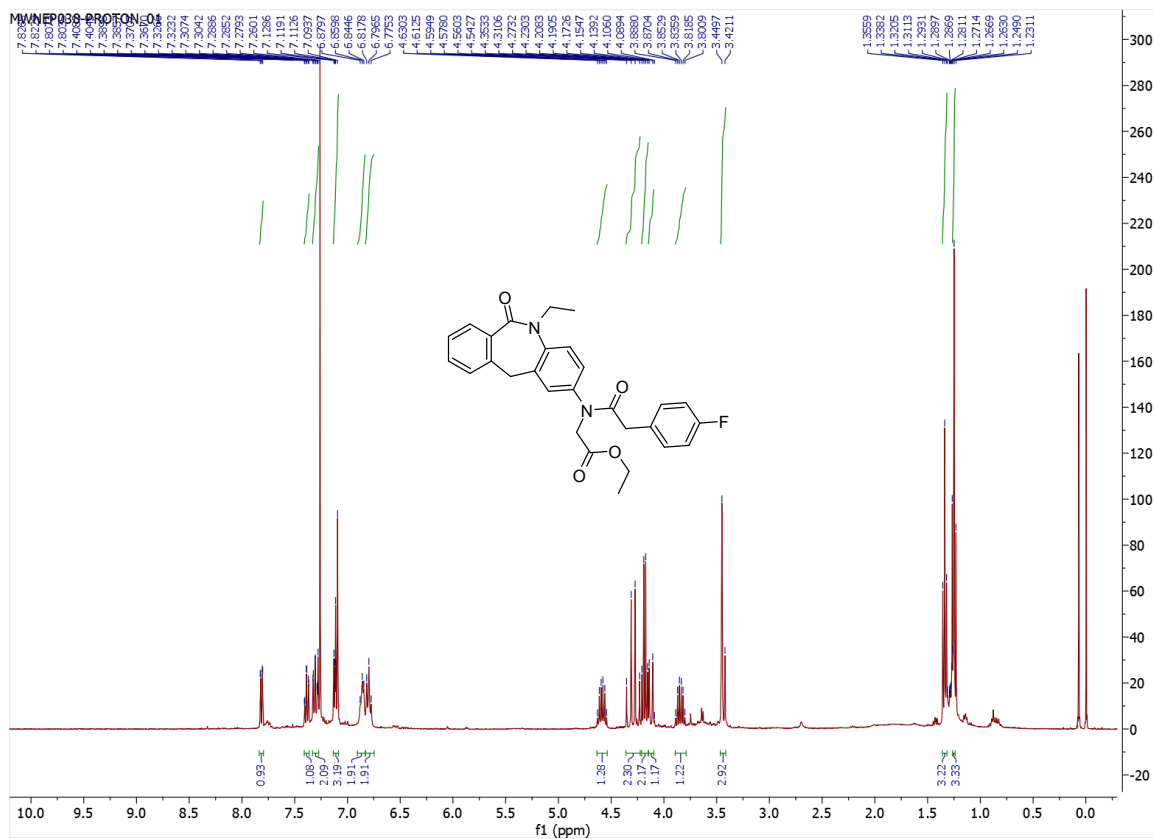
An oven-dried, screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (80 mg, 0.32 mmol, 1 equiv), AcONa (26 mg, 0.32 mmol, 1 equiv), anhydrous EtOH (0.5 mL) and ethyl bromoacetate (35 μ L, 0.32 mmol, 1 equiv). The mixture was stirred at 80°C for 45 h. NaHCO₃ (53 mg, 0.63 mmol, 2 equiv) was added and the volatiles were evaporated. The crude was subjected to column chromatography (silica; AcOEt/cyclohexane: 1:5 – 1:4) to obtain 45 mg (42%) of product **58** as a yellowish viscous solid that was used in the next step without further purification.

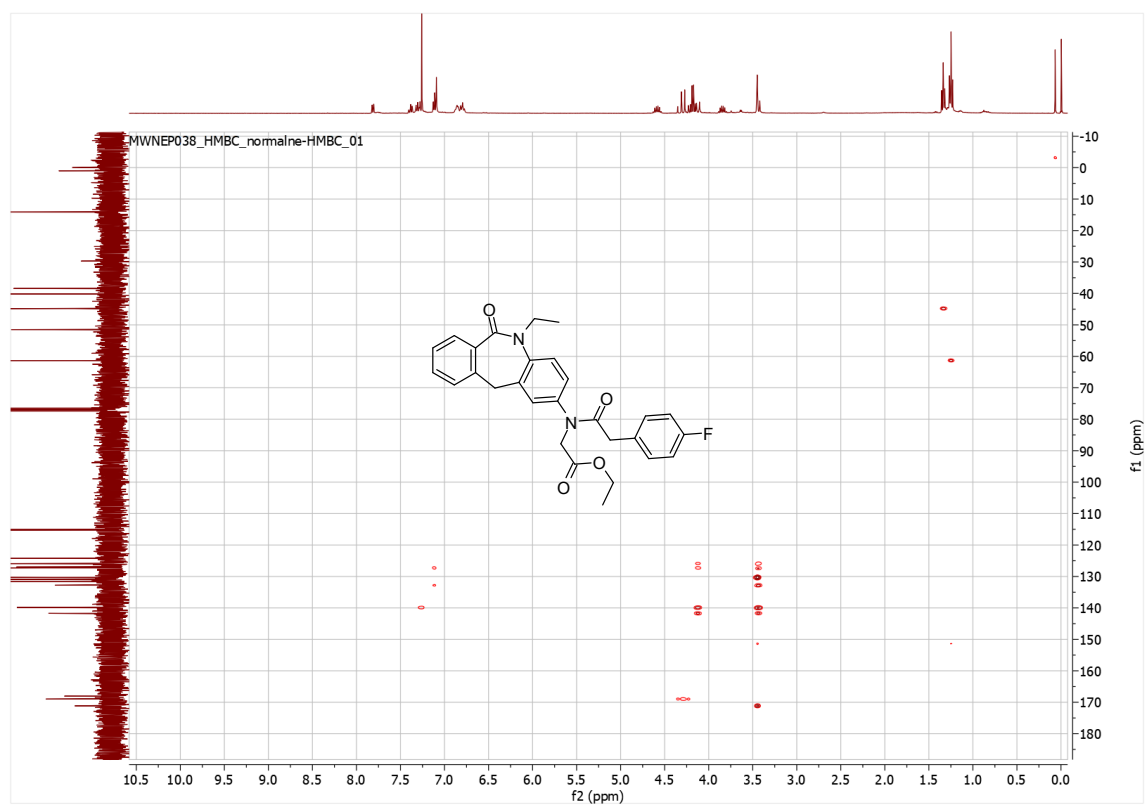
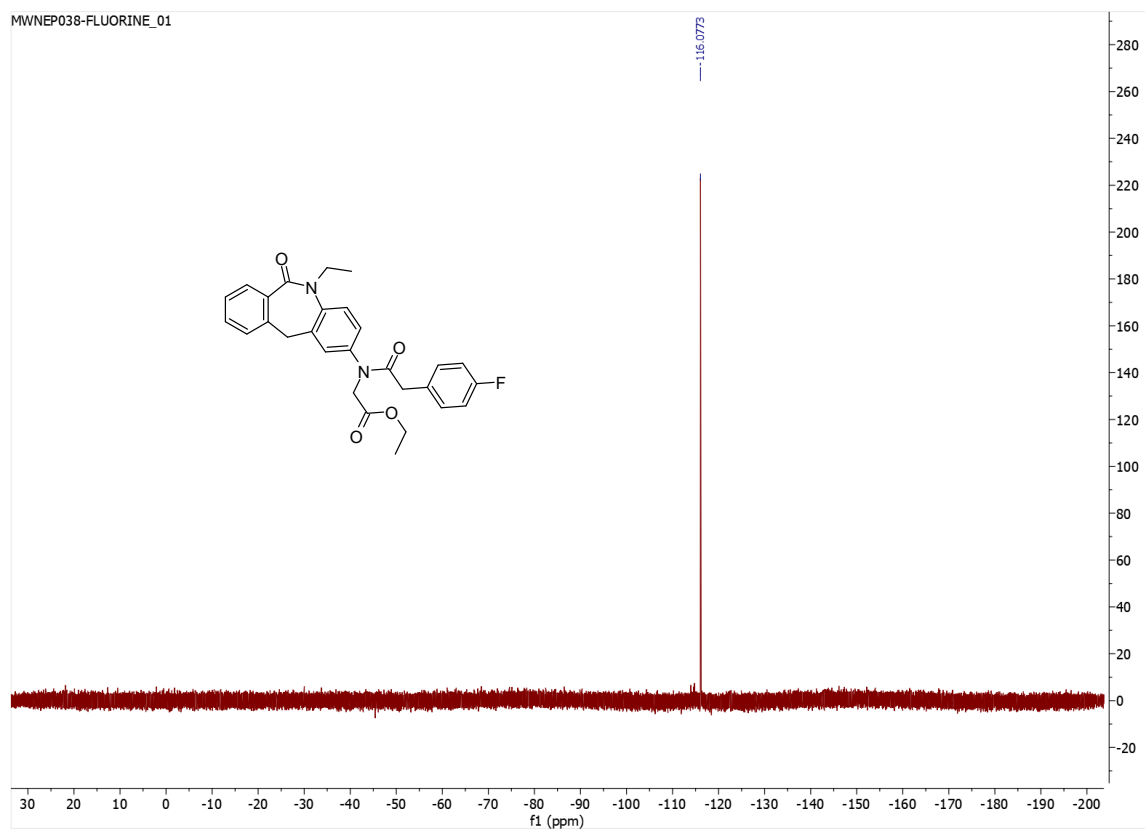
Ethyl *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-*N*-(2-(4-fluorophenyl)acetyl)glycinate (16**)**

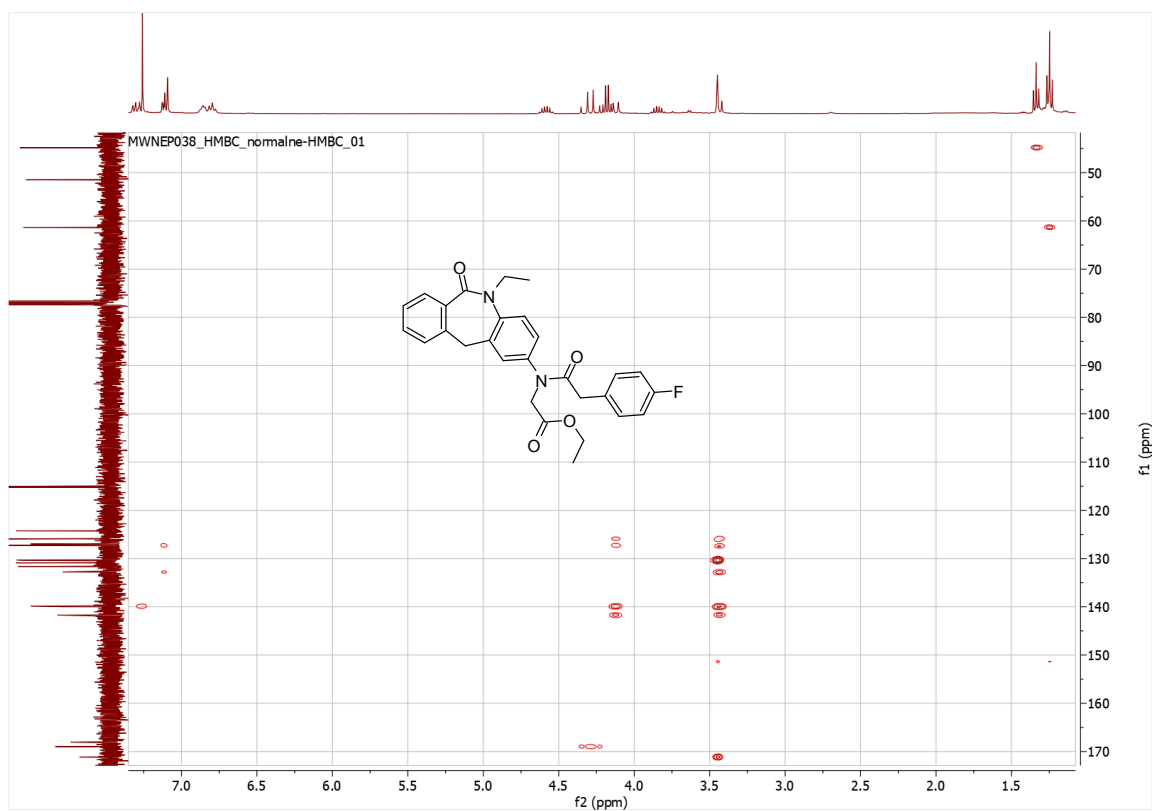


An oven-dried, screw-cap vial was charged with ethyl [(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino]acetate **58** (44 mg, 0.13 mmol, 1 equiv), 4-fluorophenylacetic acid (30 mg, 0.20 mmol, 1.5 equiv) and anhydrous DCM (2 ml). The solution was cooled to -15°C (NaCl_{aq} – solid CO₂ bath) and EDC·HCl (38 mg, 0.2 mmol, 1.5 equiv) was added. The reaction mixture was allowed to warm slowly to rt and stirred overall for 48 h. The volatiles were evaporated, and the crude was subjected to column chromatography (C-18; MeCN/H₂O: 35-50%). The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator and the resulting yellowish solid was washed with *n*-hexane (2 times), to obtain 40 mg (65%) of product **16**.

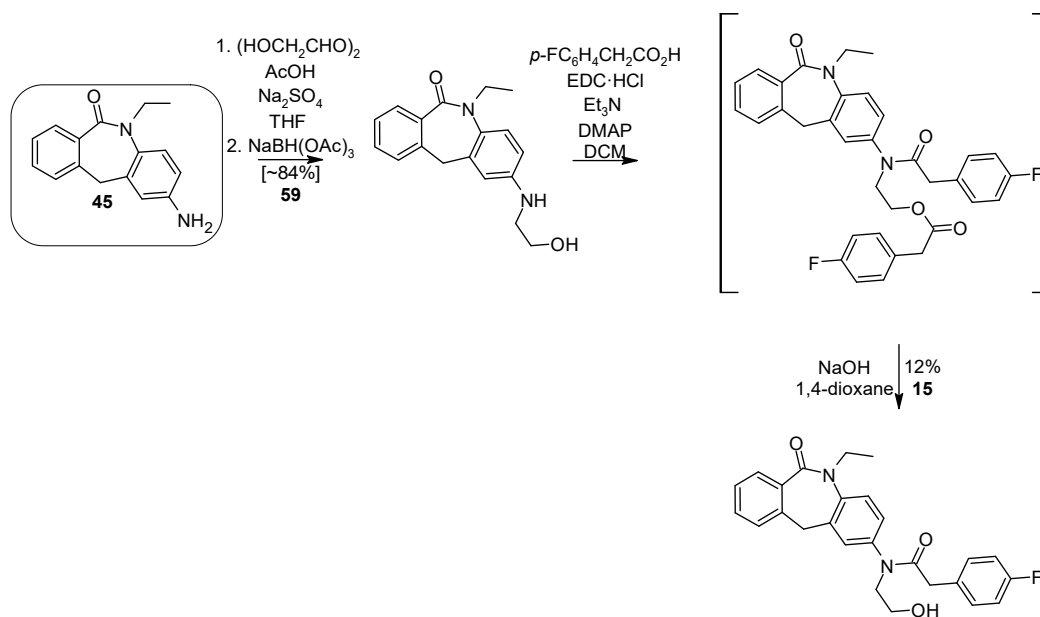
¹H NMR (400 MHz, CDCl₃) δ 7.82 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 -7.27 (m, 2H), 7.14-7.08 (m, 3H), 6.90-6.83 (m, 2H), 6.83-6.76 (m, 2H), 4.63-4.54 (m, 1H, ½ NCH₂CH₃), [4.33 (d, *J* = 17.1 Hz, 1H, ½ NCH₂CO₂Et), 4.25 (d, *J* = 17.1 Hz, 1H, NCH₂CO₂Et)], 4.18 (q, *J* = 7.1 Hz, 2H, CH₂), 4.12 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 3.89-3.79 (m, 1H, ½ NCH₂CH₃), 3.46-4.41 (m, 1H, ½ ArCH₂Ar') overlapping 3.45 (s, 2H, NCOCH₂C₆H₄F), 1.34 (t, *J* = 7.1 Hz, 3H, CH₃, OCH₂CH₃), 1.25 (t, *J* = 7.1 Hz, 3H, CH₃, NCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.3 (CH₂CONAr), 169.1 (CO₂), 168.2 (CONCH₂CH₃), 167.4 (d, ¹*J*_{CF} = 153.6 Hz), 163.0, 141.9, 140.2, 140.0 (x 2), 132.9, 131.8, 131.0, 130.5 (d, ³*J*_{CF} = 8.0 Hz), 127.4 (x 2), 127.1, 126.1, 124.4, 115.3 (d, ²*J*_{CF} = 21.3 Hz), 61.5 (OCH₂), 51.6, 45.0 (NCH₂), 40.3, 38.6, 14.3 (OCH₂CH₃), 14.2 (NCH₂CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -116.1. LR-MS (*m/z*): 475 [M+H]⁺.



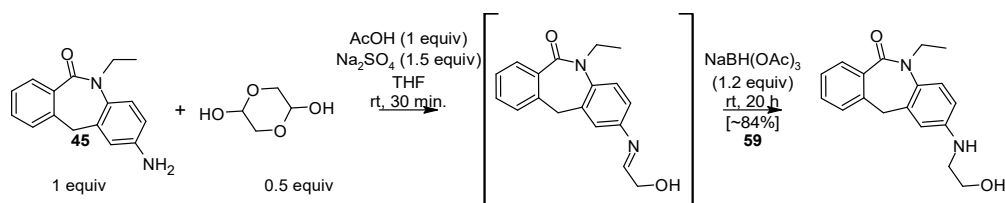




Synthesis of *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)-*N*-(2-hydroxyethyl)acetamide **15.**

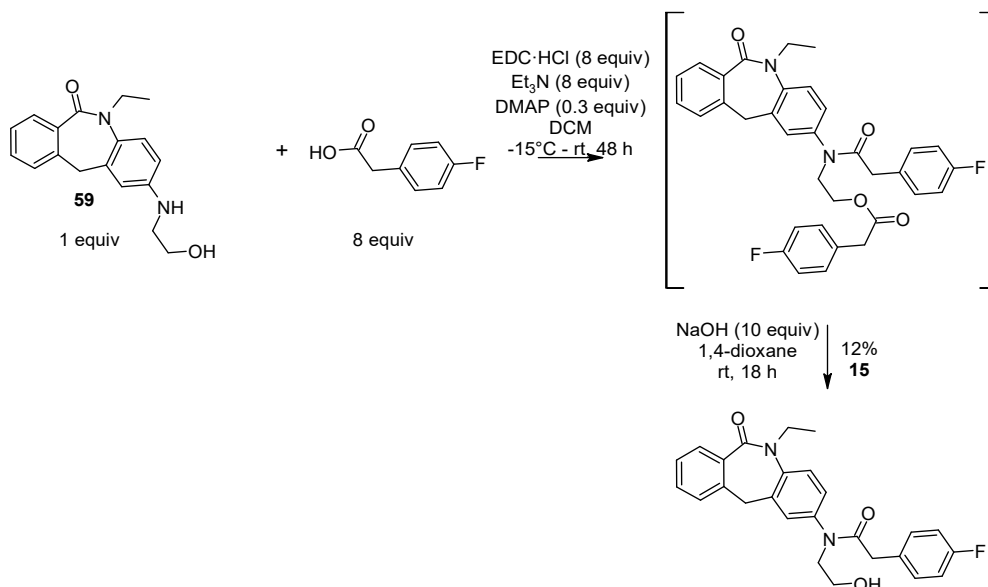


5-Ethyl-2-[(2-hydroxyethyl)amino]-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (**59**)



An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (130 mg, 0.52 mmol, 1 equiv), glycolaldehyde dimer (31 mg, 0.26 mmol, 0.5 equiv) and anhydrous THF (2 ml). The mixture was stirred at rt for 10 min and AcOH (29 μ l, 0.52 mmol, 1 equiv) and anhydrous Na₂SO₄ (110 mg, 0.77 mmol, 1.5 equiv) were added. After 30 min, NaBH(OAc)₃ (131 mg, 0.62 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt for 20 h. To the reaction mixture was added K₂CO₃ (356 mg, 2.58 mmol, 5 equiv). The volatiles were evaporated and the residue was subjected to column chromatography (silica; MeOH/DCM: 0-0.5%) to collect 128 mg (~84%) of product **59** as a brown oil, that was used directly in the next step without further purification. LR-MS (*m/z*): 297 [M+H]⁺.

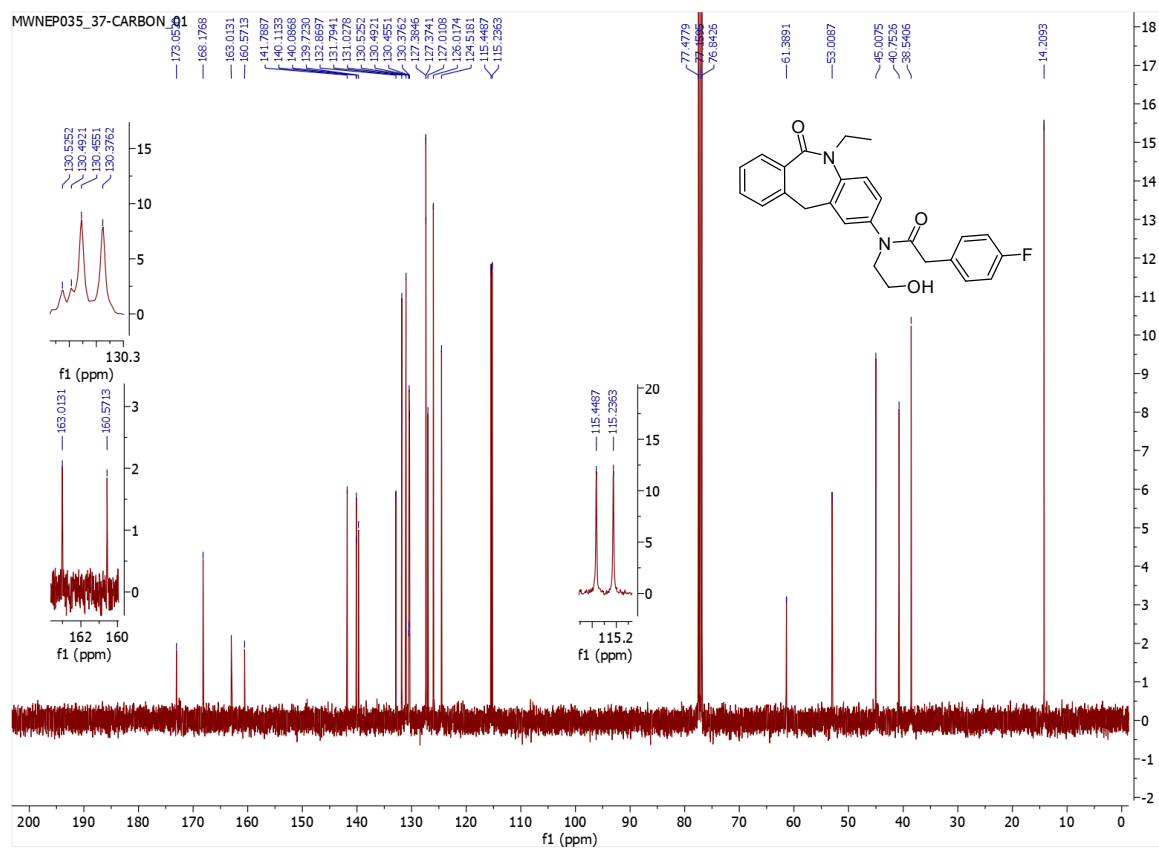
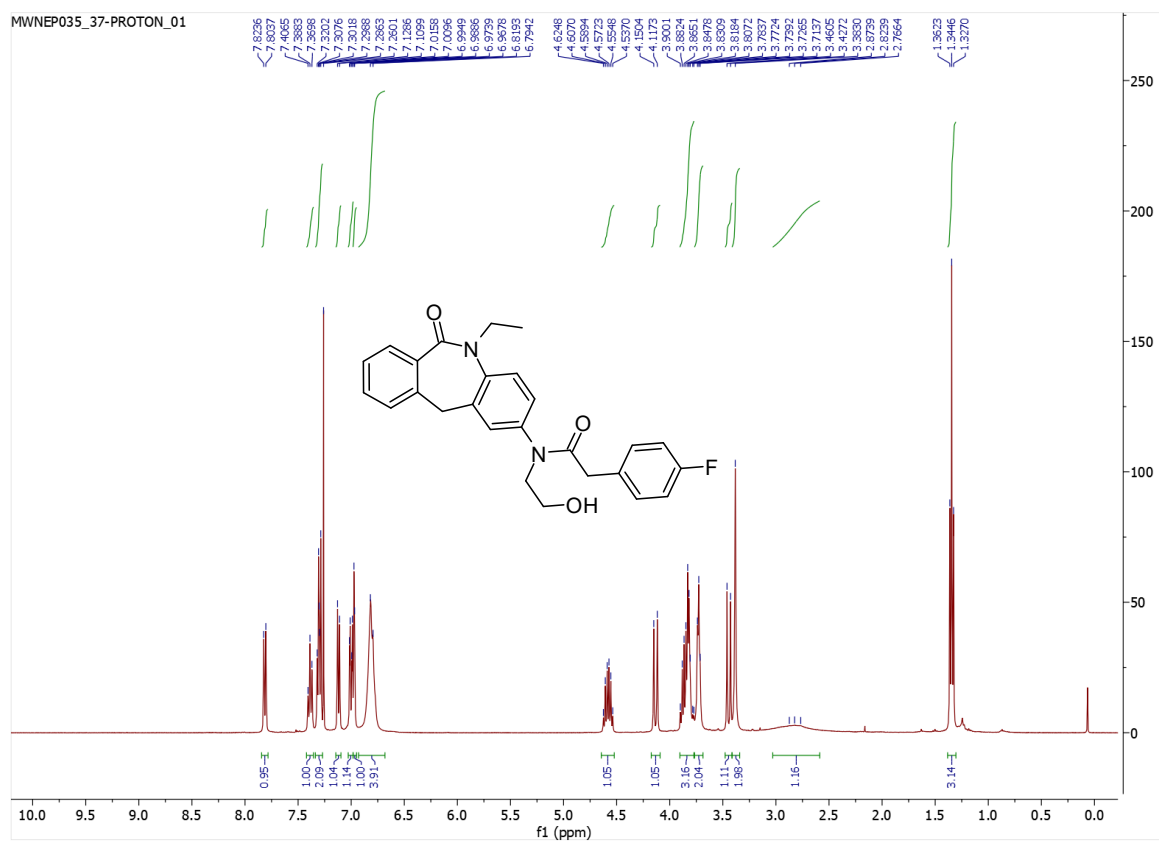
***N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-(4-fluorophenyl)-*N*-(2-hydroxyethyl)acetamide (**15**)**



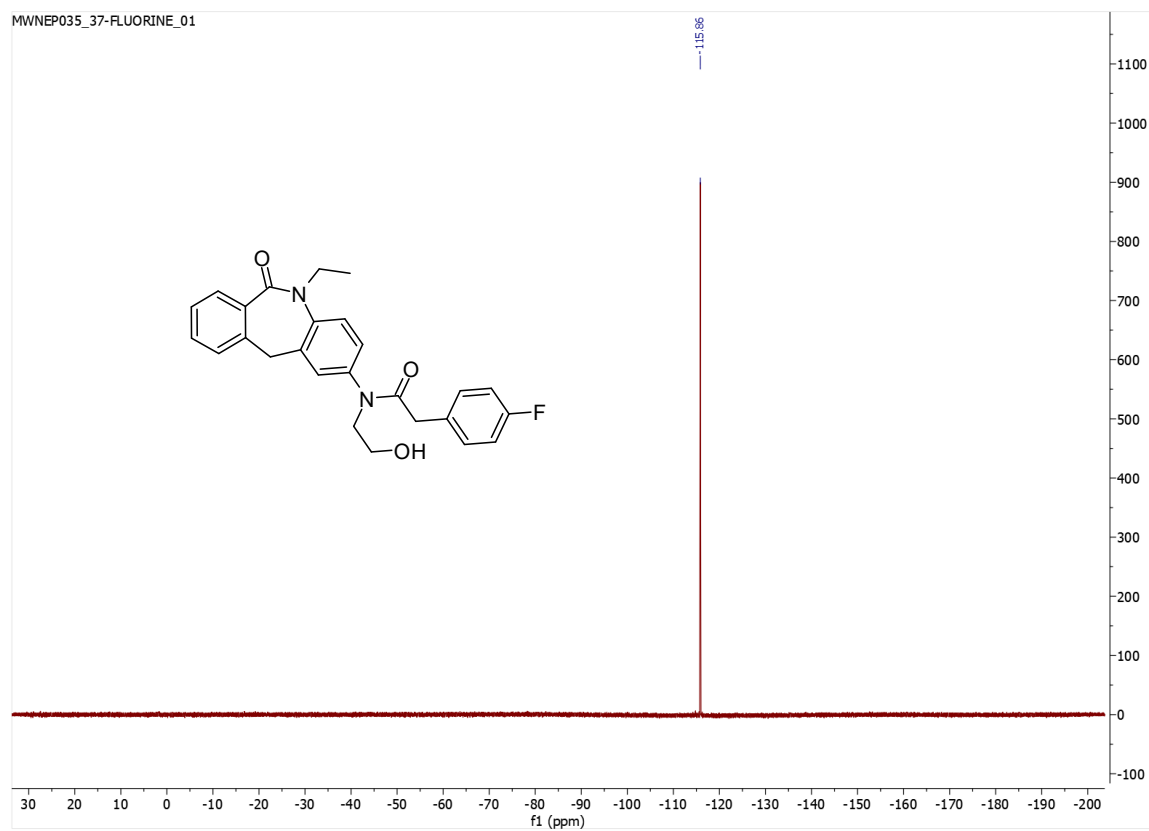
An oven-dried, round-bottom bulb was charged with 5-ethyl-2-[(2-hydroxyethyl)amino]-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **59** (128 mg, 0.43 mmol, 1 equiv), 4-fluorophenylacetic acid (266 mg, 1.73 mmol, 4 equiv), DMAP (16 mg, 0.13 mmol, 0.3 equiv) and anhydrous DCM (5 ml). The resulting suspension was stirred at rt for 30 min, cooled to -15 °C (NaCl_{aq} – CO₂ bath), and EDC·HCl (323 mg, 1.73 mmol, 4 equiv) was added. The reaction mixture was allowed to warm to rt overnight and stirred in total for 24 h. Additional portion of 4-fluorophenylacetic acid (266 mg, 1.73 mmol, 4 equiv) was added, and the reaction mixture was cooled to -15°C. Subsequently EDC·HCl (323 mg, 1.73 mmol, 4 equiv) and Et₃N – dropwise – (482 µl, 3.46 mmol, 8 equiv) were added. The reaction was once again gradually warmed by allowing the cooling bath to warm up to rt overnight. The reaction mixture was stirred for 24 h in total and the volatiles were evaporated. The residue was subjected to column chromatography (silica; MeOH/DCM: 0-2%). The obtained fractions containing double acylated product were combined, evaporated, and dissolved in 1,4-dioxane (6 mL) and aqueous 2 M solution of NaOH (2.15 mL, 4.30 mmol, 10 equiv). The mixture was stirred at rt for 18 h, adjusted to pH = ~ 7 using aqueous 1 M solution of HCl (~ 4 mL) and the volatiles were evaporated. The residue was subjected to column chromatography (silica; MeOH/DCM: 0.5-2%). The fractions containing expected product were collected, evaporated and additionally subjected to reverse phase column chromatography (C-18; MeCN/H₂O: 30-40%). The compound was additionally purified by precipitation from the cold mixture of DCM and *n*-hexane using rotary evaporator and the resulting crystals were washed with *n*-hexane (2 times), to obtain 23 mg (12%) of the target product **15** as a white solid.

¹H NMR (400 MHz, CDCl₃-*d*) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.33-7.27 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.98-6.95 (m, 1H), 6.92-6.68 (m, 4H), 4.63-4.52 (m, 1H, 1/2 CH₂CH₃), 4.13 (d, *J* = 13.2 Hz, 1H, 1/2 ArCH₂Ar'), 3.91-3.77 (m, 3H, 1/2 CH₂CH₃, CH₂)

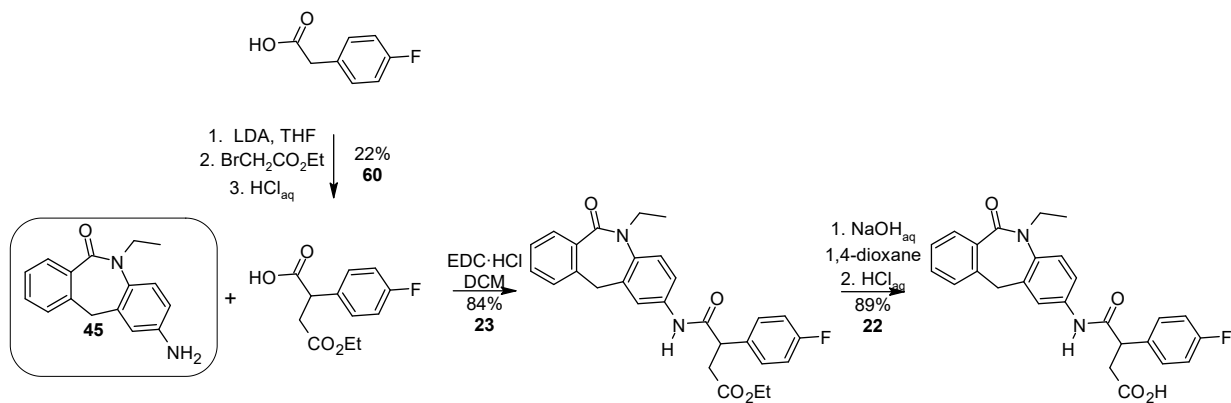
overlapping 3.77-3.68 (m, 2H, CH₂), 3.44 (d, $J = 13.3$ Hz, 1H, 1/2 ArCH₂Ar'), 3.38 (s, 2H, NCOCH₂C₆H₄F), 3.18-2.44 (m, 1H, OH), 1.34 (t, $J = 7.0$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 173.1 (CO), 168.2 (CO), 161.8 [d, $^1J_{\text{CF}} = 245.4$ Hz], 141.8, 140.1, 140.1, 139.7, 132.9, 131.8, 131.0, 130.5 (d, $^4J_{\text{CF}} = 3.3$ Hz), 130.4 (d, $^3J_{\text{CF}} = 7.9$ Hz), 127.4, 127.4, 127.0, 126.0, 124.5, 115.3 (d, $^2J_{\text{CF}} = 21.3$ Hz), 61.4 (OCH₂), 53.0, 45.0, 40.8, 38.5, 14.2 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) -115.9. LR-MS (m/z): 433 [M+H]⁺



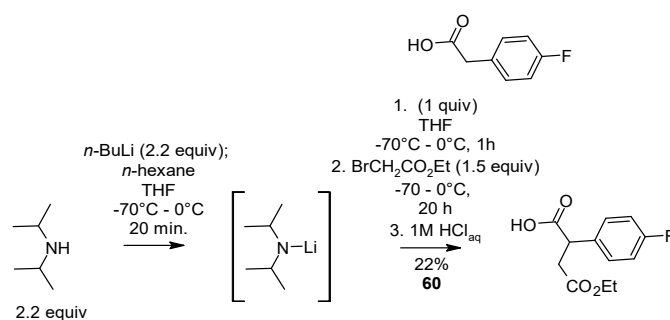
MWNEP035_37-FLUORINE_01



Synthesis of 4-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(4-fluorophenyl)-4-oxobutanates **22 and **23**:**

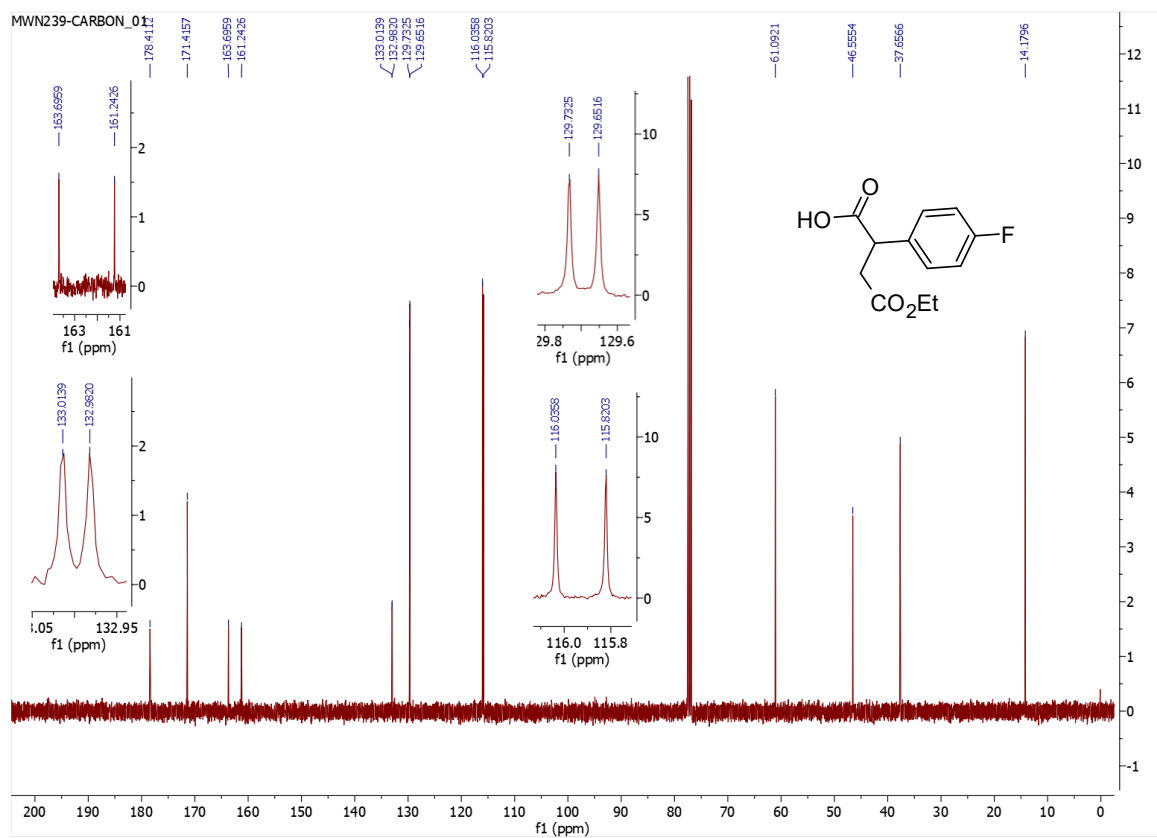
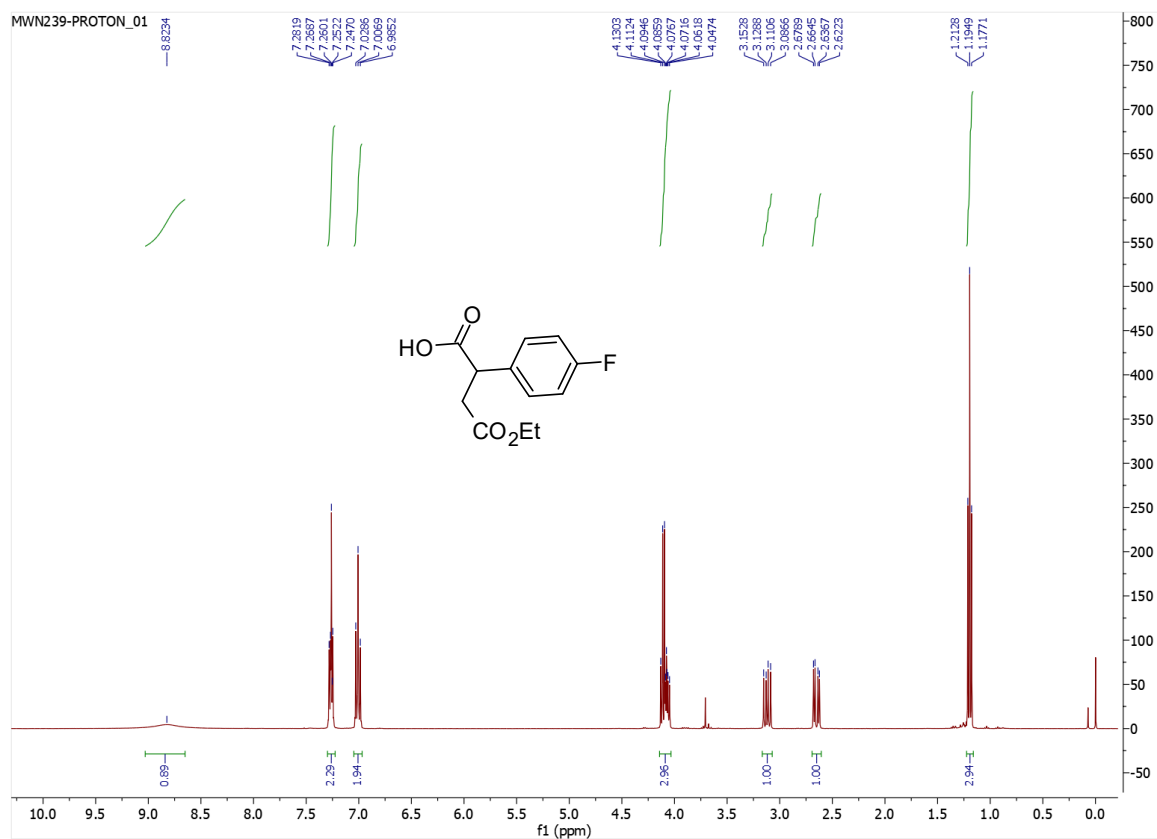


4-Ethoxy-2-(4-fluorophenyl)-4-oxobutanoic acid (**60**)

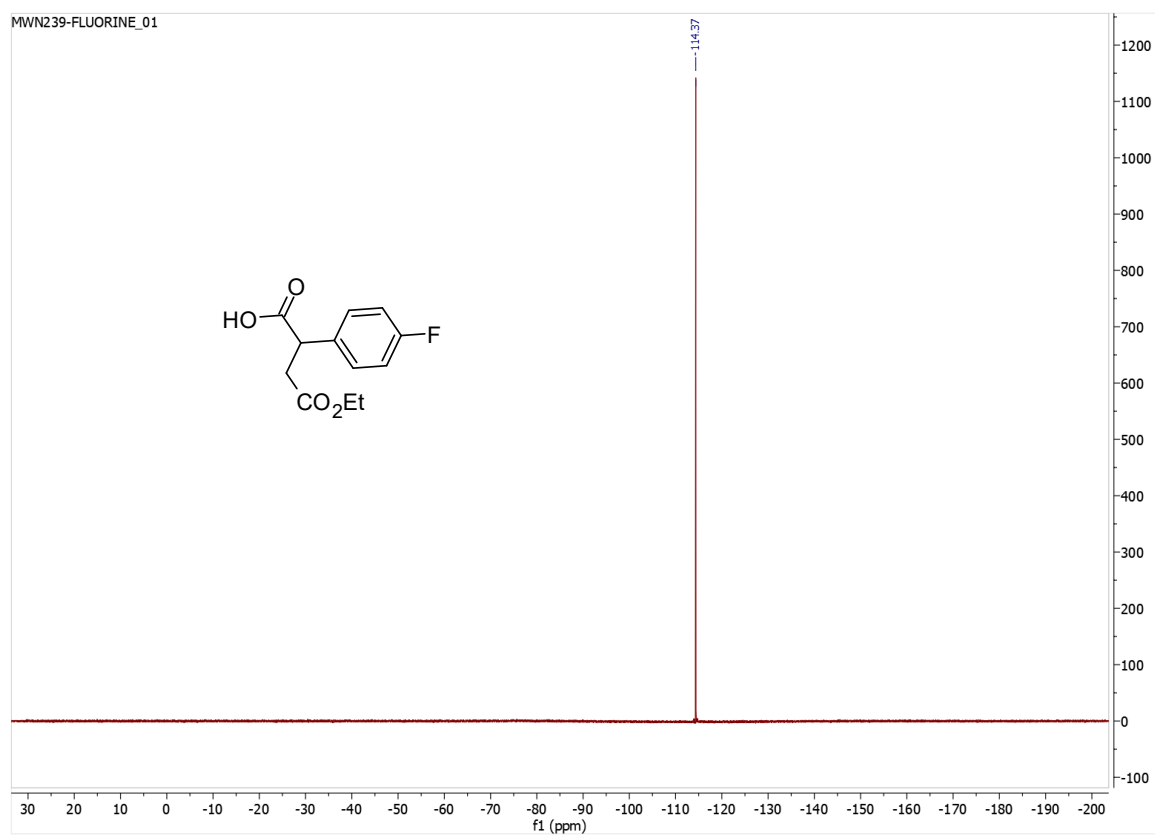


An oven-dried, round-bottom bulb was charged with anhydrous THF (8 mL) and diisopropylamine (0.80 mL, 5.71 mmol, 2.2 equiv) and cooled to -70°C . Subsequently, 2.5 M solution of $n\text{-BuLi}$ in THF (2.30 mL, 5.71 mmol, 2.2 equiv) was added dropwise. The solution was warmed to 0°C , and after 20 min cooled to -70°C . 4-Fluorophenyl)acetic acid (400 mg, 2.6 mmol, 1 equiv) dissolved in anhydrous THF (2 mL) was added dropwise to the reaction flask. The solution was warmed to 0°C , and after 1 h cooled to -70°C . Ethyl bromoacetate (0.43 mL, 3.90 mmol, 1.3 equiv) was added dropwise. The cooling bath was removed, and the mixture was stirred for 20 h at rt. The reaction mixture was diluted with 1M aqueous HCl (25 mL) and extracted with AcOEt (3 x 25 mL). All organic extracts were combined, washed with brine (15 mL) and the brine was reextracted with AcOEt (25 mL). All organic extracts were combined, dried over Na_2SO_4 , filtrated and evaporated. The crude was subjected to reverse phase column chromatography (C-18; MeCN/ H_2O : 20-40%) to obtain 139 mg (22%) of the product **60** as a yellowish viscous solid.

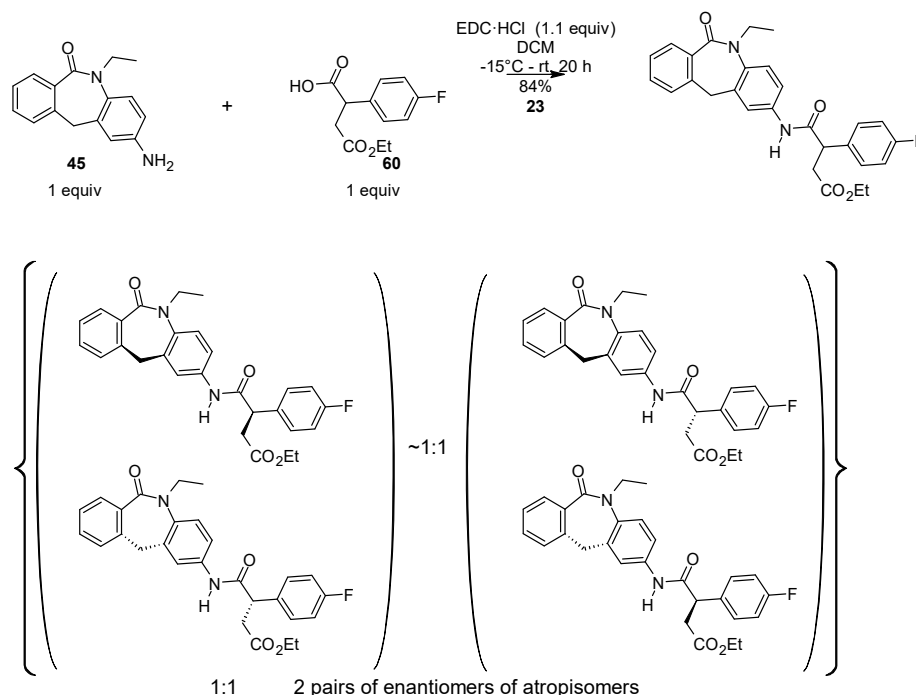
^1H NMR (400 MHz, CDCl_3) δ 8.82 (br s, 1H, CO_2H), 7.29-7.24 (m, 2H) overlapping residual CHCl_3 , 7.03-6.98 (m, 2H), 4.10 (q, $J = 7.1$ Hz, 2H, OCH_2) overlapping 4.07 (dd, $J = 9.7, 5.7$ Hz, 1H, CH), 3.12 (dd, $J = 16.9, 9.6$ Hz, 1H, $1/2 \text{CH}_2\text{CO}_2\text{Et}$), 2.65 (dd, $J = 16.9, 5.8$ Hz, 1H, $1/2 \text{CH}_2\text{CO}_2\text{Et}$), 1.19 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 178.4 (CO_2H), 171.4 (CO_2Et), 162.5 (d, $^1J_{\text{CF}} = 246.7$ Hz), 133.0 (d, $^4J_{\text{CF}} = 3.2$ Hz), 129.7 (d, $^3J_{\text{CF}} = 8.1$ Hz), 115.9 (d, $^2J_{\text{CF}} = 21.7$ Hz), 61.1 (OCH_2), 46.6 (CHAr), 37.7 ($\text{CH}_2\text{CO}_2\text{Et}$), 14.2 (CH_3). ^{19}F NMR (376 MHz, CDCl_3) δ -114.37. LR-MS (m/z): 241 $[\text{M}+\text{H}]^+$.



MWN239-FLUORINE_01

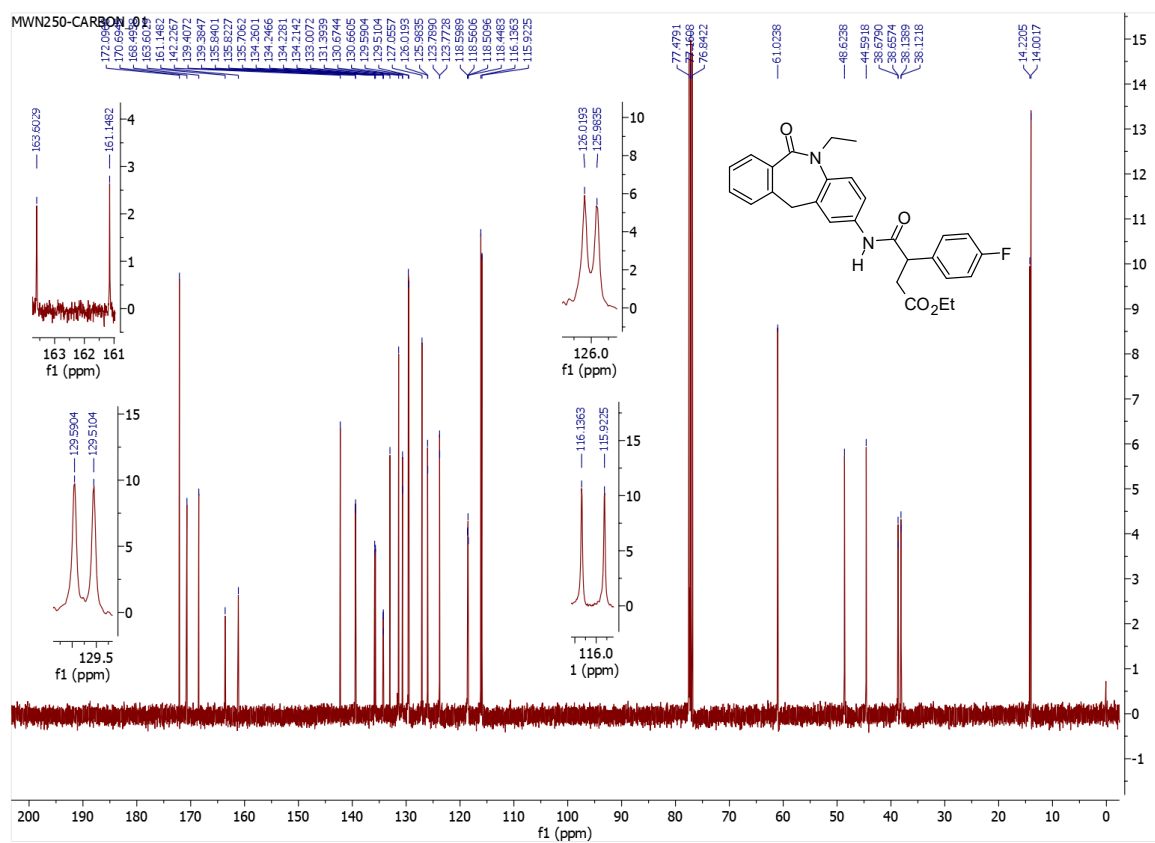
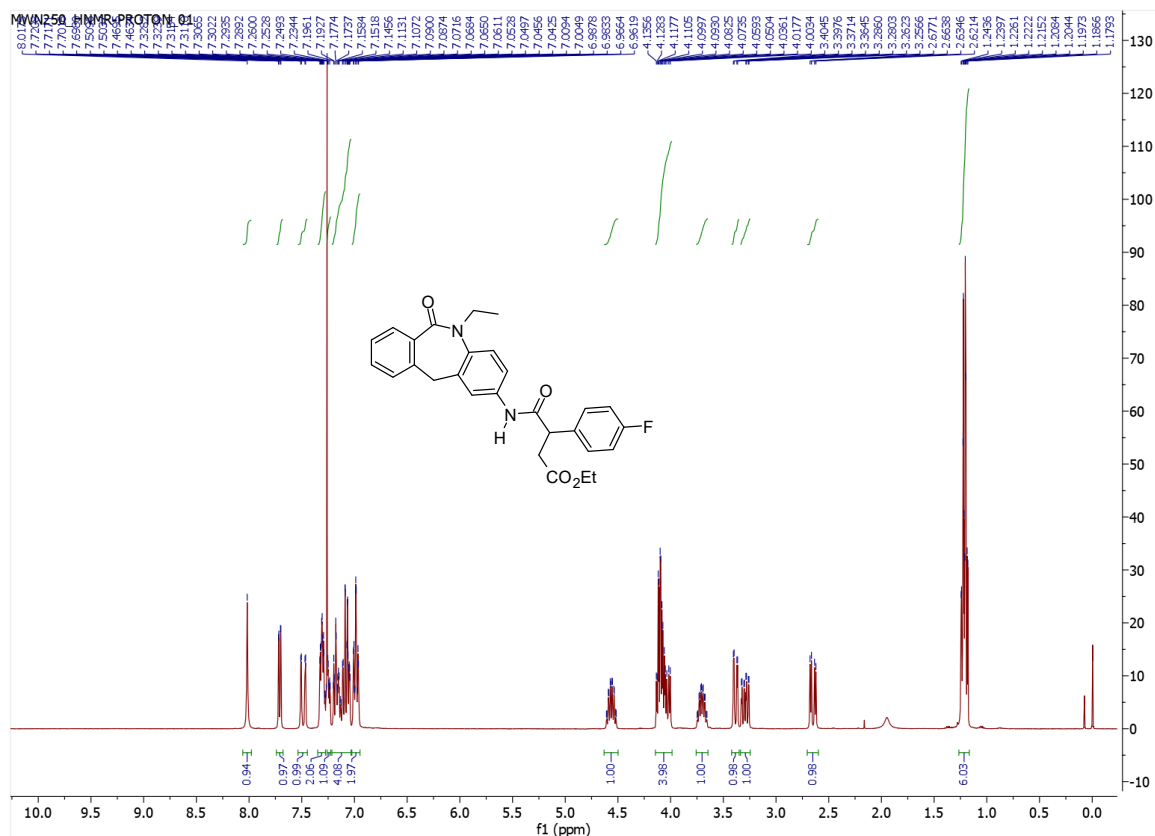


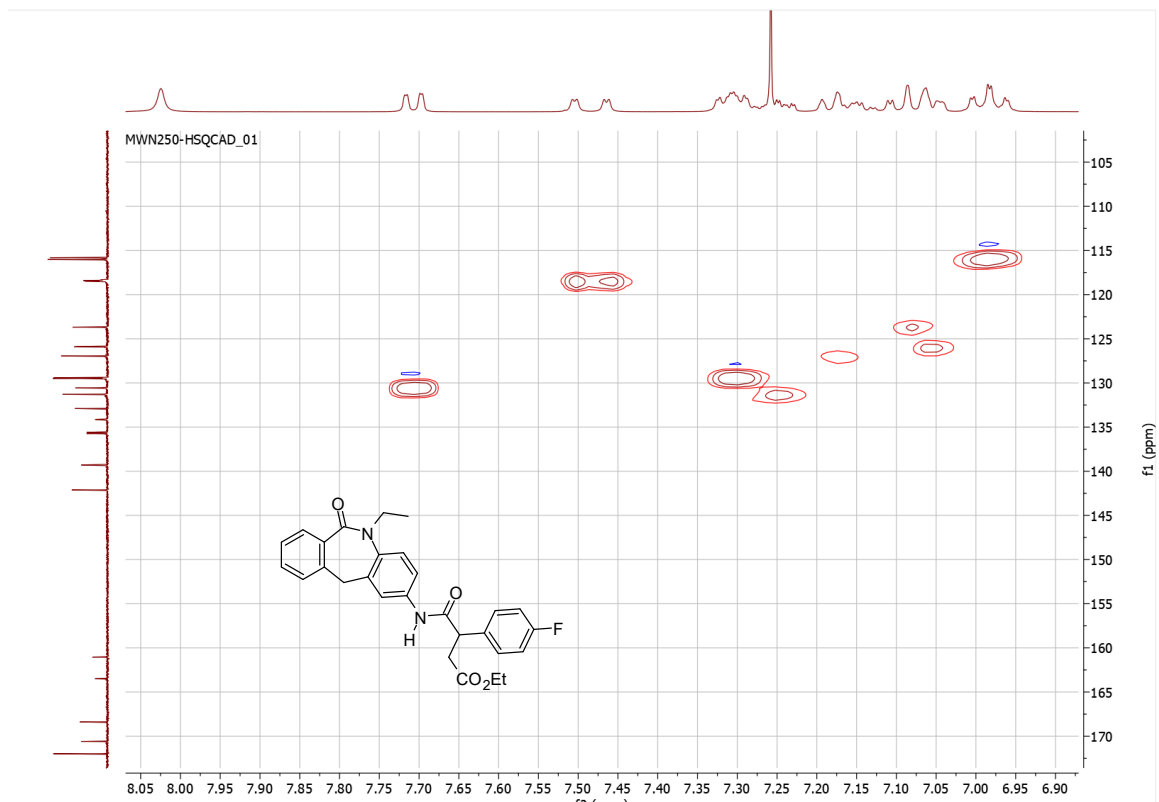
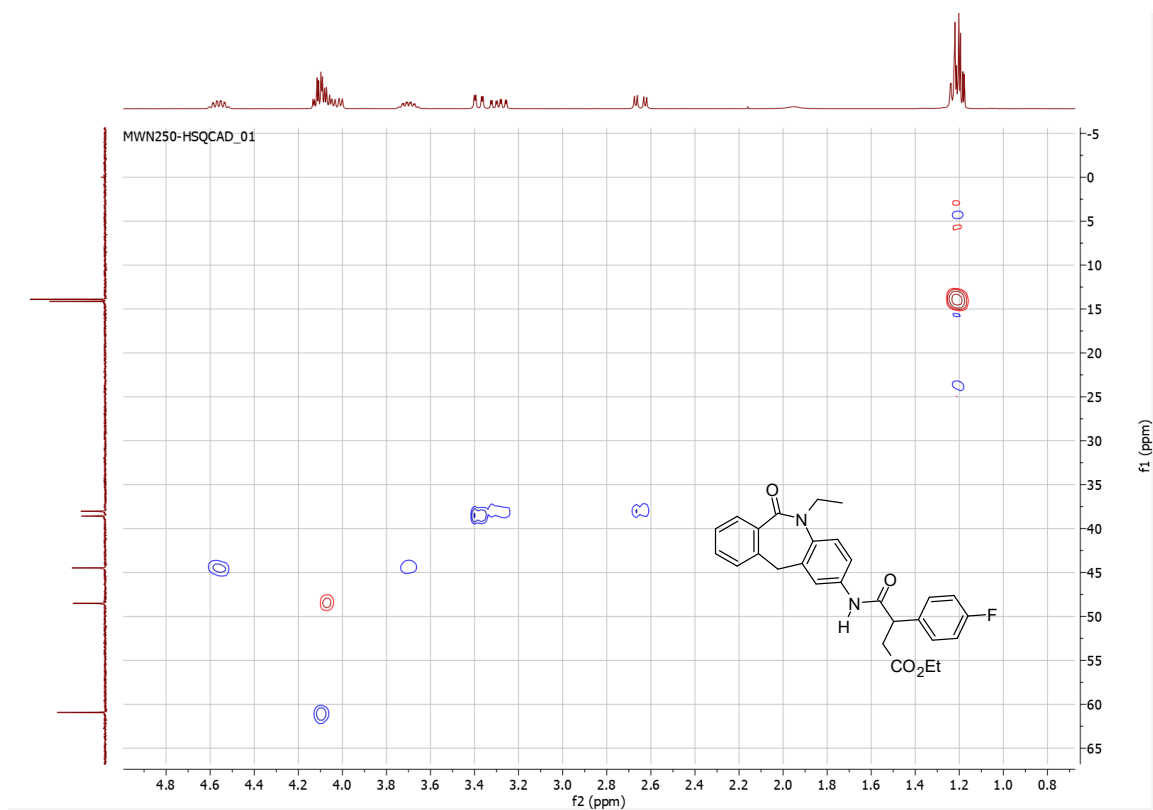
Ethyl 4-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(4-fluorophenyl)-4-oxobutanoate (23**)**



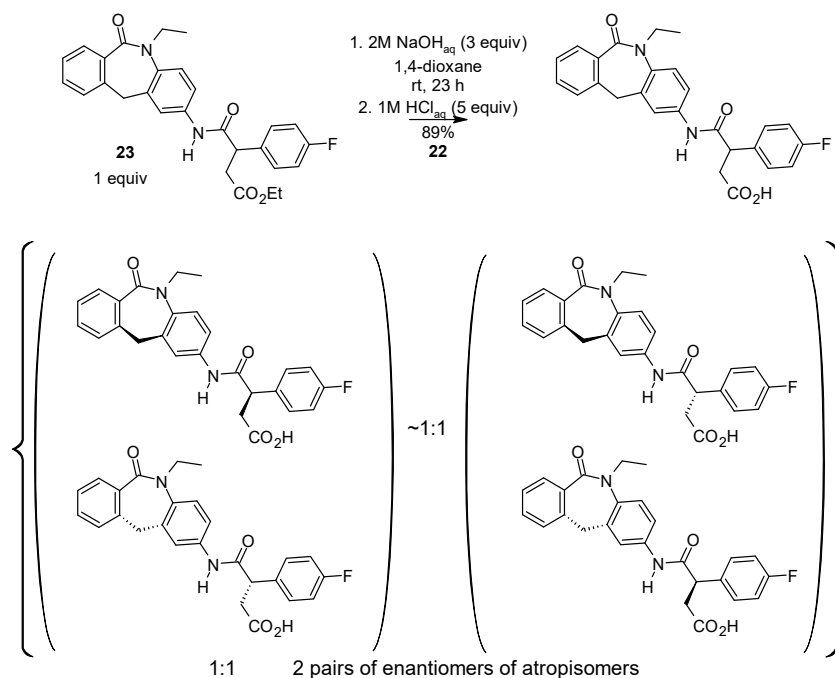
An oven-dried screw-cap vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (110 mg, 0.44 mmol, 1 equiv) and 4-ethoxy-2-(4-fluorophenyl)-4-oxobutanoic acid **60** (105 mg, 0.44 mmol, 1 equiv) and anhydrous DCM (3 mL). The solution was cooled down to -15°C and EDC·HCl (92 mg, 0.48 mmol, 1.1 equiv) was added. The reaction was allowed to warm slowly to rt by allowing the cooling bath to warm to rt overnight. The reaction mixture was stirred overall for 20 h. The volatiles were evaporated and the crude was subjected to column chromatography (C-18; using MeCN/H₂O: 40-60%). The product was then precipitated as oil from the mixture of DCM and *n*-hexane using rotary evaporator and washed with *n*-hexane (2 times), to obtain 173 mg (84%) of target product **23** as a white foam.

¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1 H, NH), 7.73-7.69 (m, 1H), 7.52-7.45 (m, 1H), 7.52-7.45 (m, 1H), 7.34-7.28 (m, 2H), 7.27-7.23 (m, 1H) overlapped by residual CHCl₃, 7.21-7.03 (m, 4H), 7.02-6.95 (m, 1H), 4.62-4.51 (m, 1H, ½ NCH₂CH₃), 4.15-3.99 (m, 4H, FC₆H₄CH, CO₂CH₂CH₃, ½ ArCH₂Ar'), dd, 3.76-3.64 (m, 1H, ½ NCH₂CH₃), 3.45-3.42 (m, 1H, ½ ArCH₂Ar'), 3.33-3.25 (m, 1H, ½ CH₂CO), 2.69-2.61 (m, 1H, ½ CH₂CO), 1.26-1.17 (m, 6H, 2 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.1 (CO), 170.7 (CO), 168.5 (CO), 162.4 (d, ¹J_{CF} = 246.8 Hz), 142.2, [139.4 (x 2)], [135.8 (x 2)], 135.7, [134.3, 134.2], [134.2 (x 2)], 133.0, 131.4, [130.7 (x 2)], 129.6 (d, ³J_{CF} = 8.0 Hz), 127.1, 126.0 (d, ⁴J_{CF} = 3.6 Hz), [123.8 (x 2)], [118.6 (x 2)], [118.5, 118.4], 116.0 (d, ²J_{CF} = 21.5 Hz), 61.0 (CO₂CH₂CH₃), 48.6 (FC₆H₄CH), 44.6 (NCH₂CH₃), [38.7 (x 2); ArCH₂Ar'], [38.1 (x 2); CH₂CO], 14.2 (CH₃), 14.0 (CH₃); some signals are doubled due to the presence of atropisomers and/or dynamic effects; LR-MS (m/z): 475 [M+H]⁺.





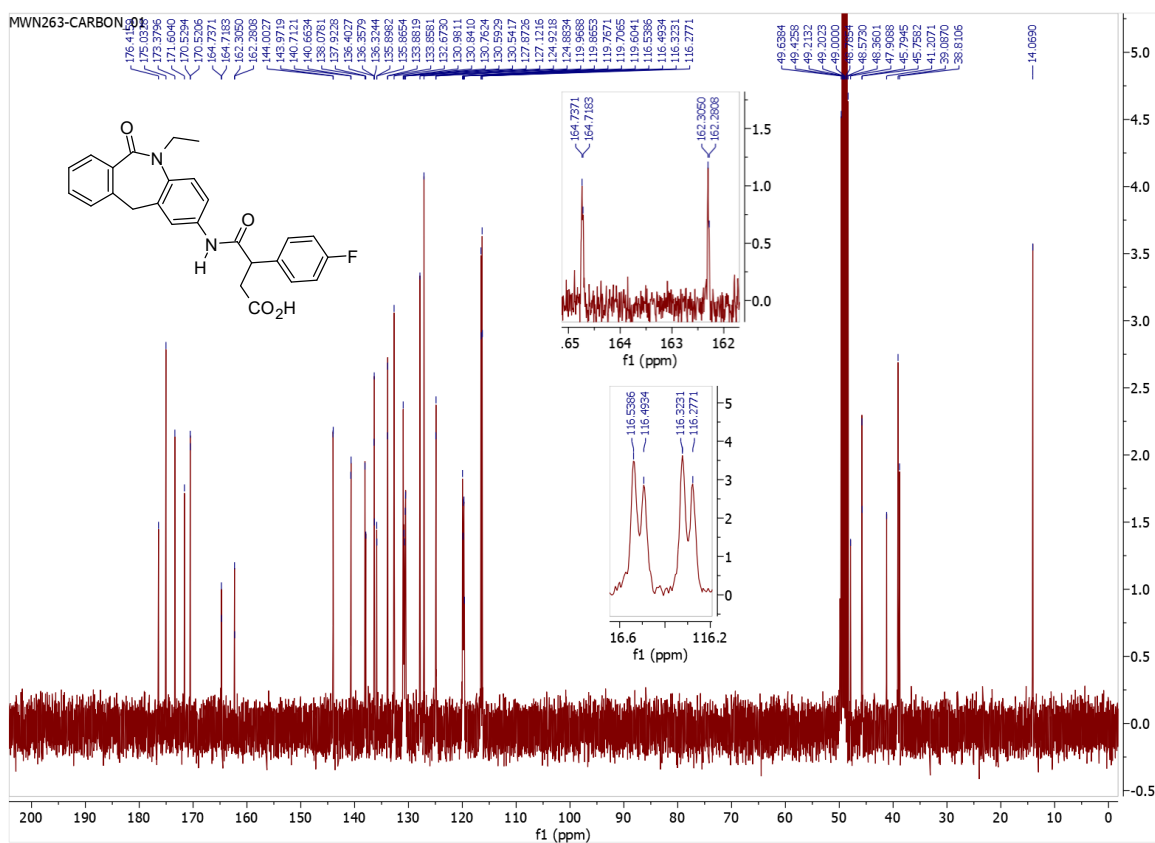
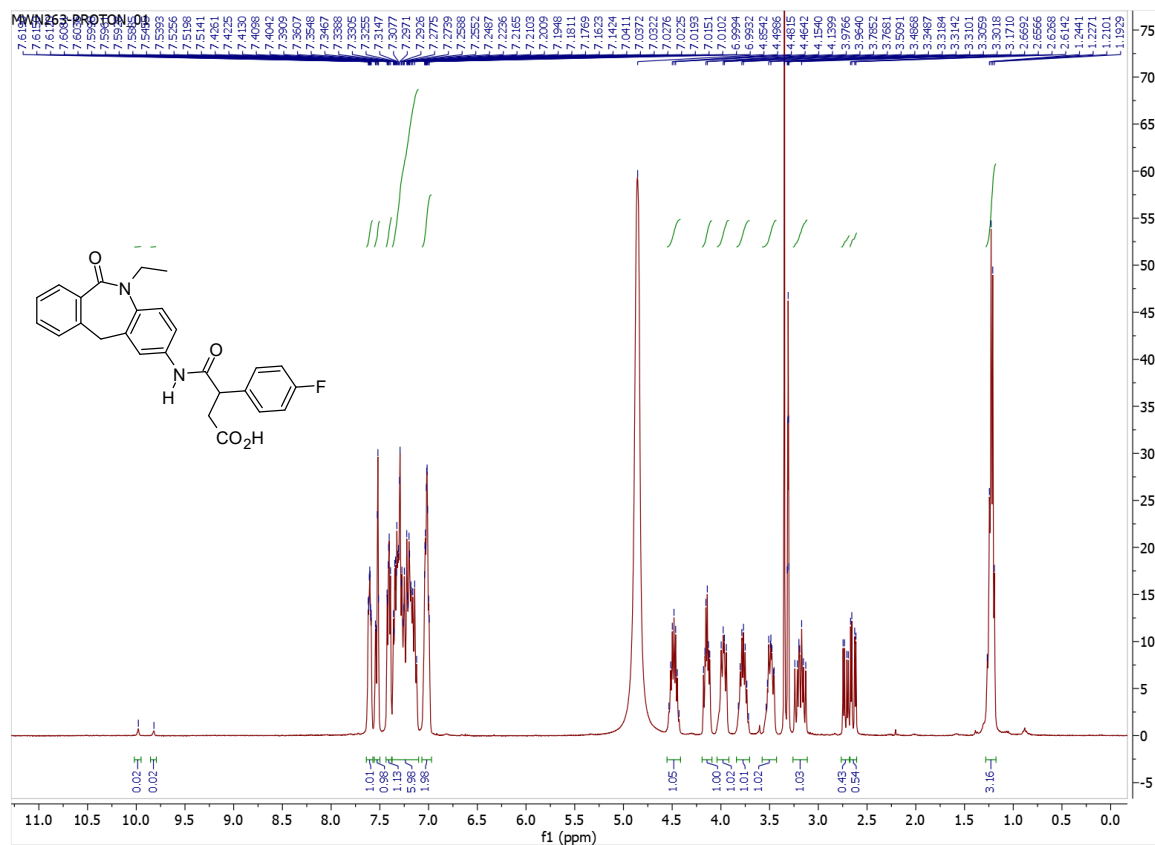
4-((5-Ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)amino)-3-(4-fluorophenyl)-4-oxobutanoic acid (22**)**



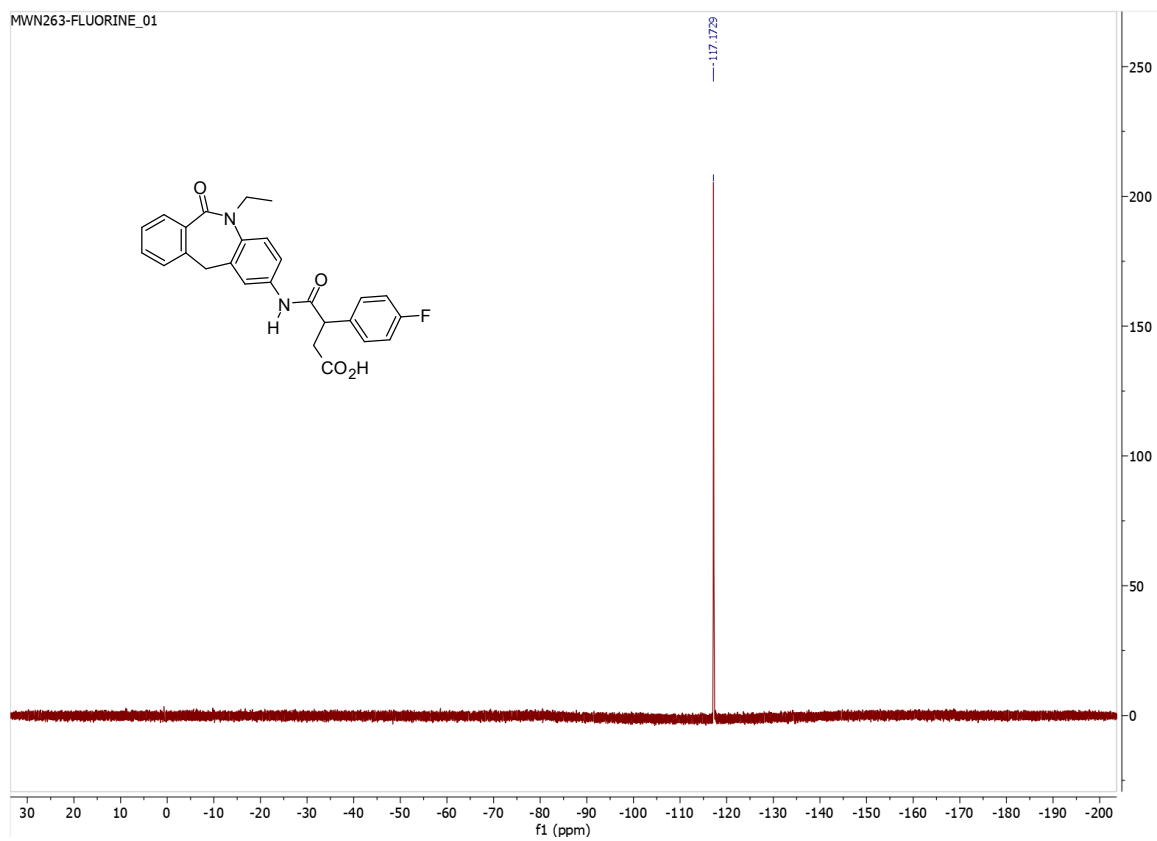
An oven-dried, screw-capped vial was charged with ethyl 4-((5-ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)amino)-3-(4-fluorophenyl)-4-oxobutanoate **23** (75 mg, 0.16 mmol, 1 equiv), 1,4-dioxane (0.7 mL) and 2M NaOH aqueous solution (237 μ L, 3 equiv NaOH). The mixture was stirred at rt for 23 h. 1M HCl aqueous solution (790 μ L, 0.79 mmol, 5 equiv HCl) was added to the solution and the volatiles were evaporated. To the residue was added DCM and the resulting suspension was dried over anhydrous Na₂SO₄, filtrated and evaporated. To the residue was added a mixture of DCM and *n*-hexane, and DCM was removed using rotary evaporator. The residue was washed with *n*-hexane (2 times) to obtain 63 mg (89%) of product **22** as a yellowish viscous foam.

¹H NMR (400 MHz, CD₃OD) δ 9.98 [s, ~0H, (CO₂H)'; almost completely exchanged into deuterium], 9.82 [s, ~0H, (CO₂H)"; almost completely exchanged into deuterium], 7.64-7.58 (m, 1H), 7.56-7.50 (m, 1H), 7.44-7.38 (m, 1H), 7.37-7.11 (m, 6H), 7.07-6.97 (m, 2H), 4.55-4.42 (m, 1H, 1/2 CH₂CH₃), 4.19-4.09 (m, 1H), 4.04-3.92 (m, 1H), 3.83-3.71 (m, 1H, 1/2 CH₂CH₃), 3.57-3.43 (m, 1H), 3.25-3.11 (m, 1H), 2.72 (dd, *J* = 15.6, 6.0 Hz, 0.5H, (CH₂CO₂H)'''), 2.64 [dd, *J* = 17.0, 5.0 Hz, 0.5H, (CH₂CO₂H)'], 1.28-1.18 (m, 3H, CH₃); (hydrogen of NH group is exchanged into deuterium); ¹³C NMR (101 MHz, CD₃OD) δ 176.4 (C=O), 175.0 (C=O), 173.4 (C=O), 171.6 (C=O), [170.5 (x 2), C=O], 163.5 (d, ¹*J*_{CF} = 244.6 Hz), 163.5 (d, ¹*J*_{CF} = 246.2 Hz), [144.0 (x 2)], [140.7 (x 2)], [138.1, 137.9], [136.4 (x 2), 136.3], [135.9 (x 2)], [133.9 (x 2)], 132.7, 131.0, 130.8 (x 2), 130.6, 130.5, 127.9, 127.1, [124.9 (x 2)], 124.9, 120.0, 119.9, 119.8, 119.7, 119.6, 116.4 (d, ²*J*_{CF} = 21.7 Hz), 116.4 (d, ²*J*_{CF} = 21.9 Hz), 47.9, [45.8 (x 2)], 41.2, 39.1, 38.8, 14.1 (CH₃); (some of the signals are multiplied due to the presence of atropisomers and

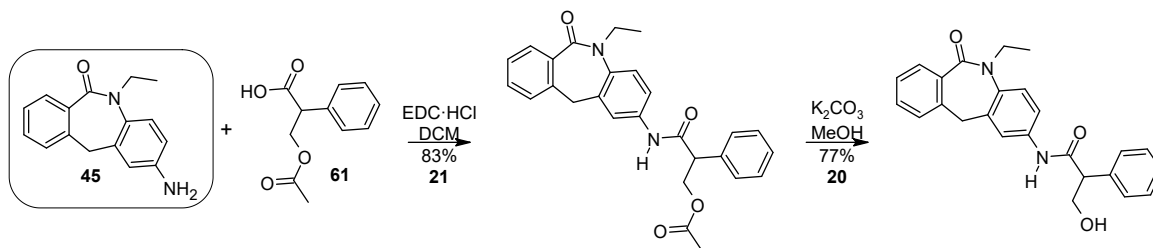
C-F coupling and broadened and/or jagged because of dynamic effects). ^{19}F NMR (376 MHz, CD_3OD) δ -117.2 (br). LR-MS (m/z): 447 $[\text{M}+\text{H}]^+$.



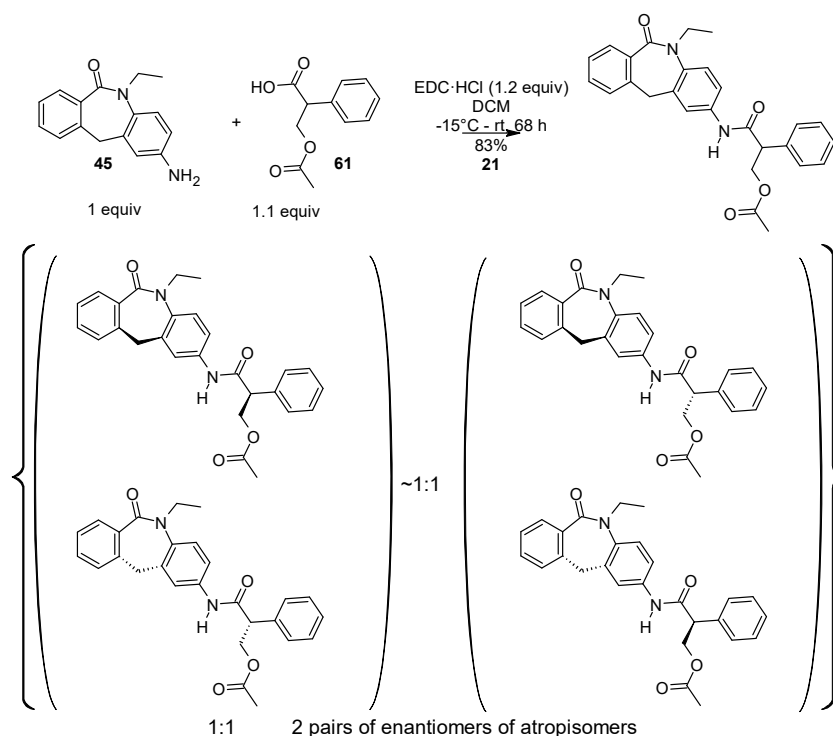
MWN263-FLUORINE_01



The synthesis of *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-3-hydroxy-2-phenylpropanamide **20** and its ester **21**:

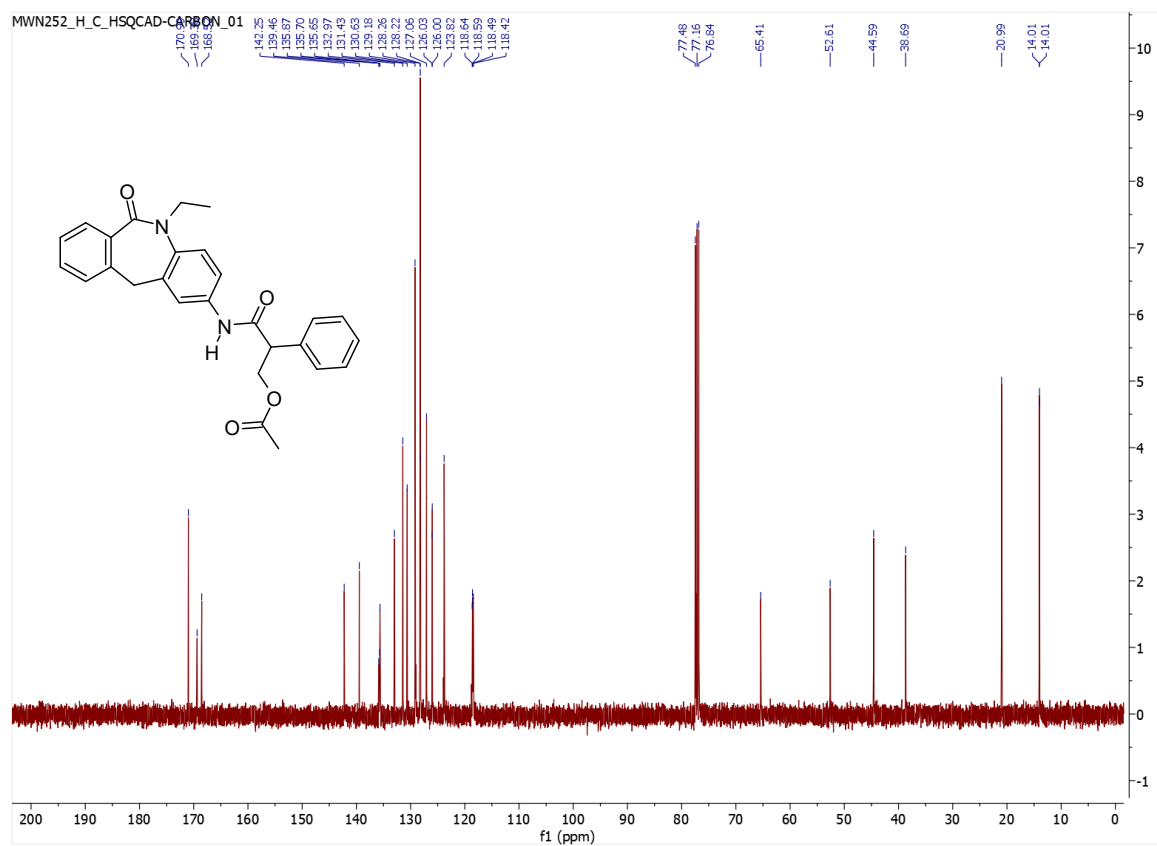
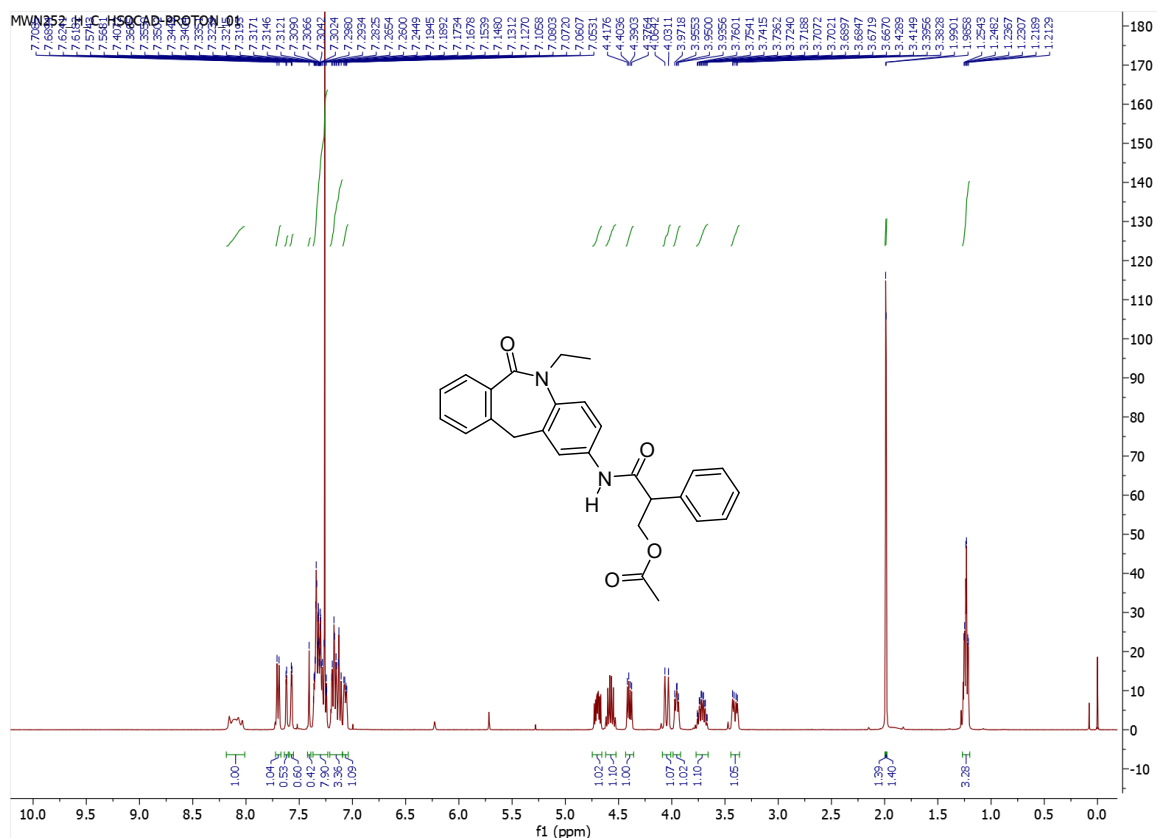


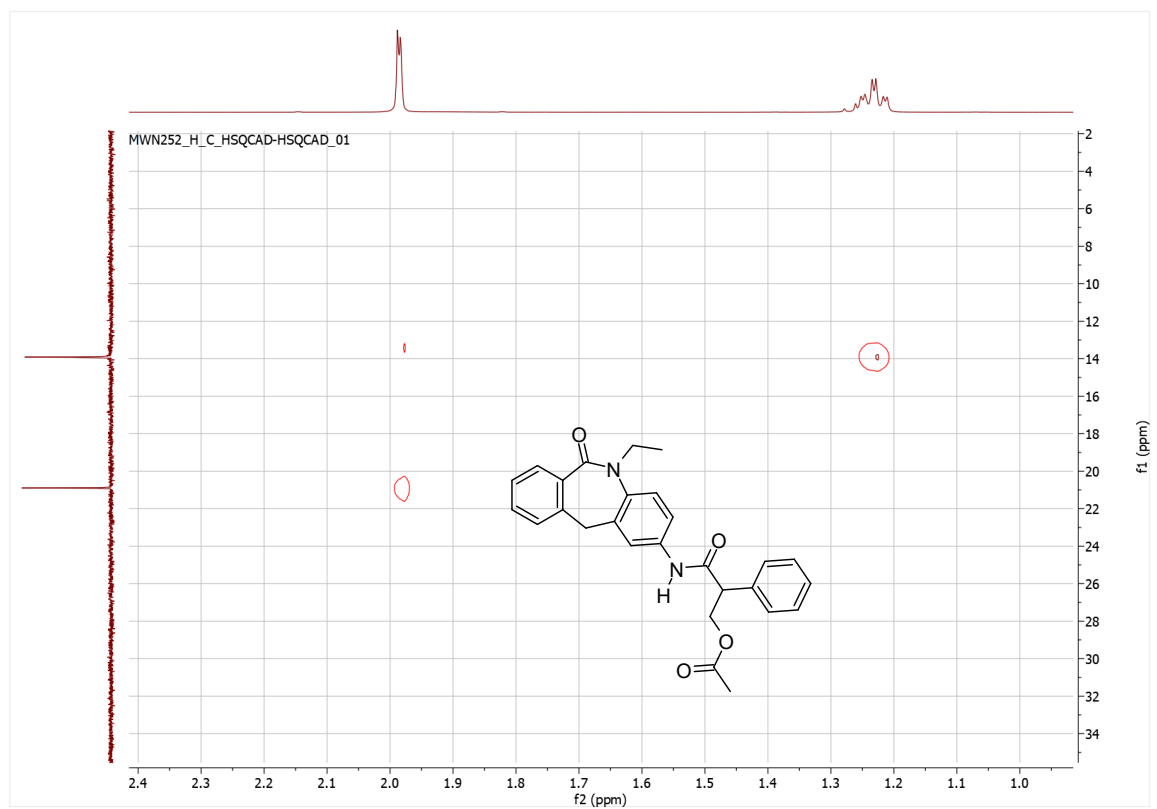
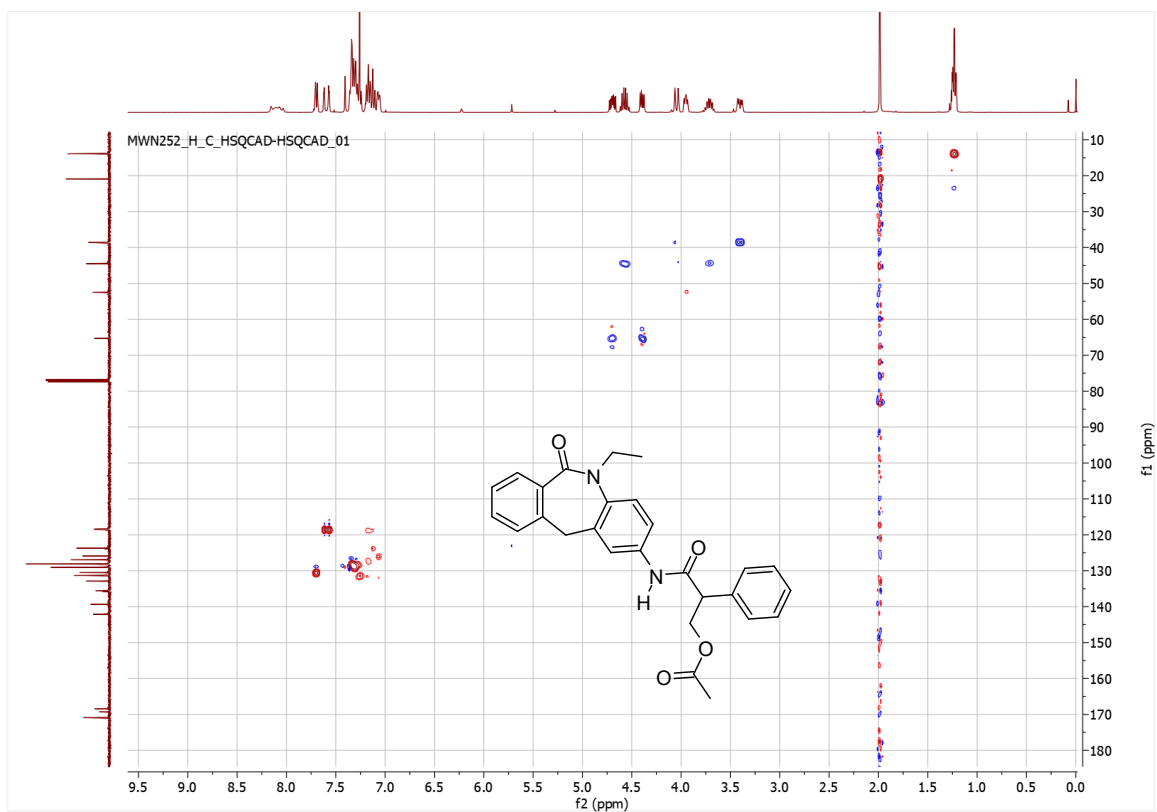
3-((5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-oxo-2-phenylpropyl acetate (21)

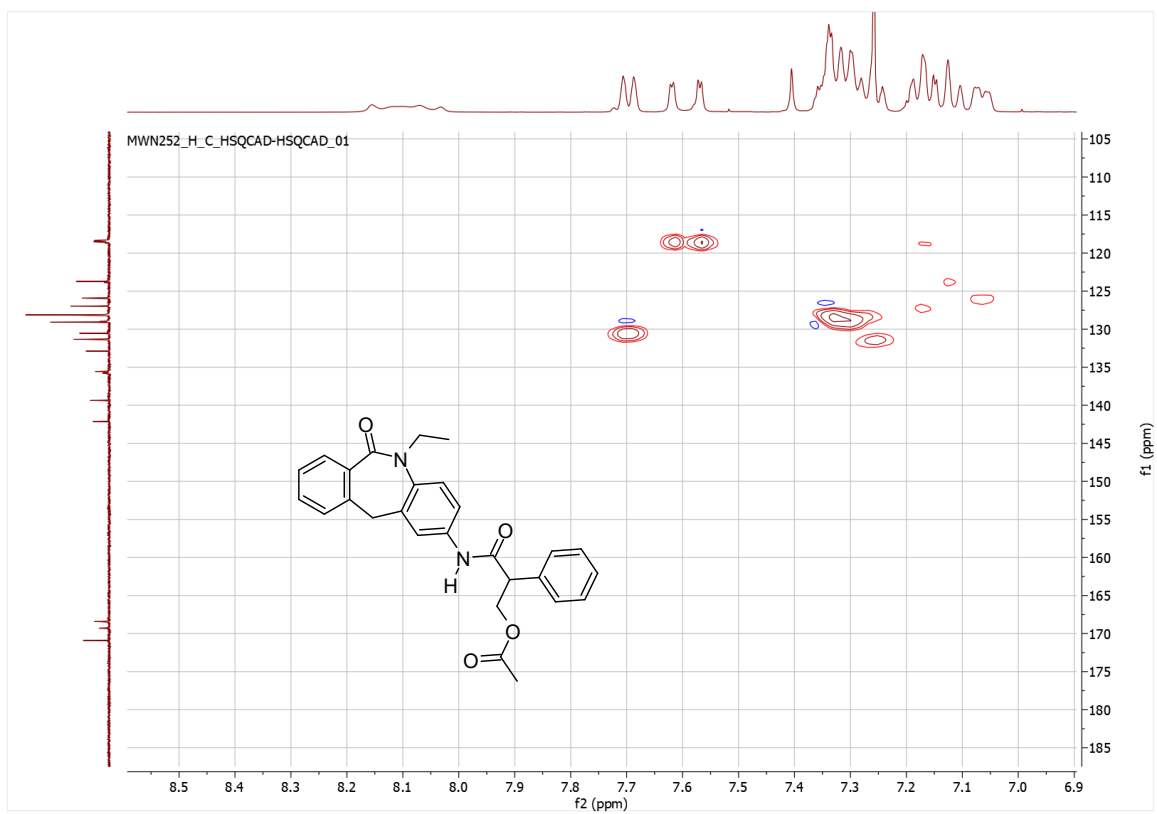
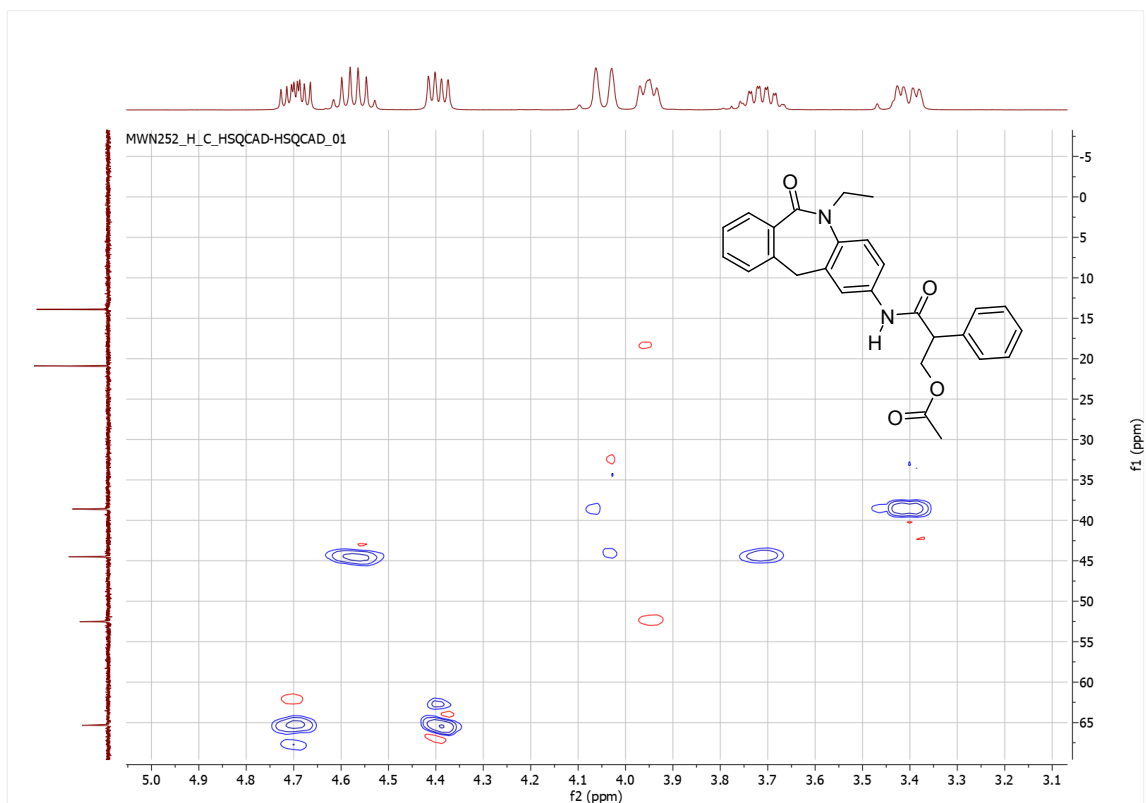


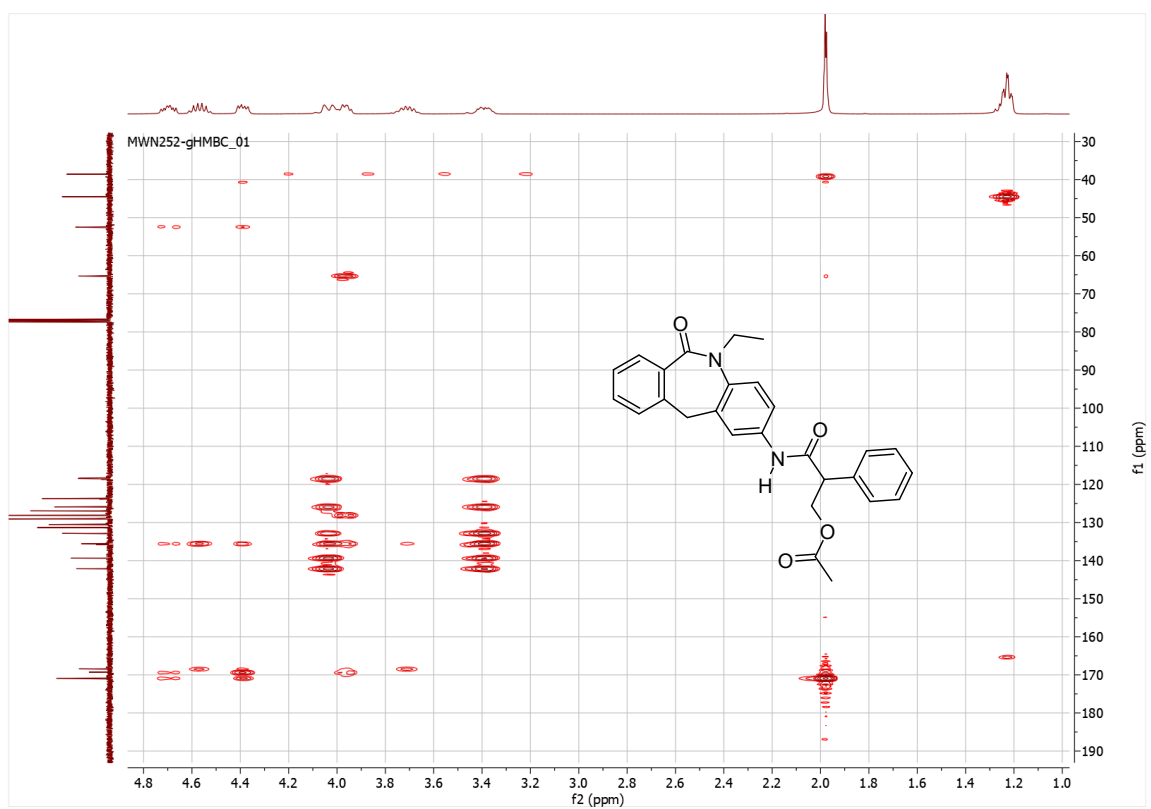
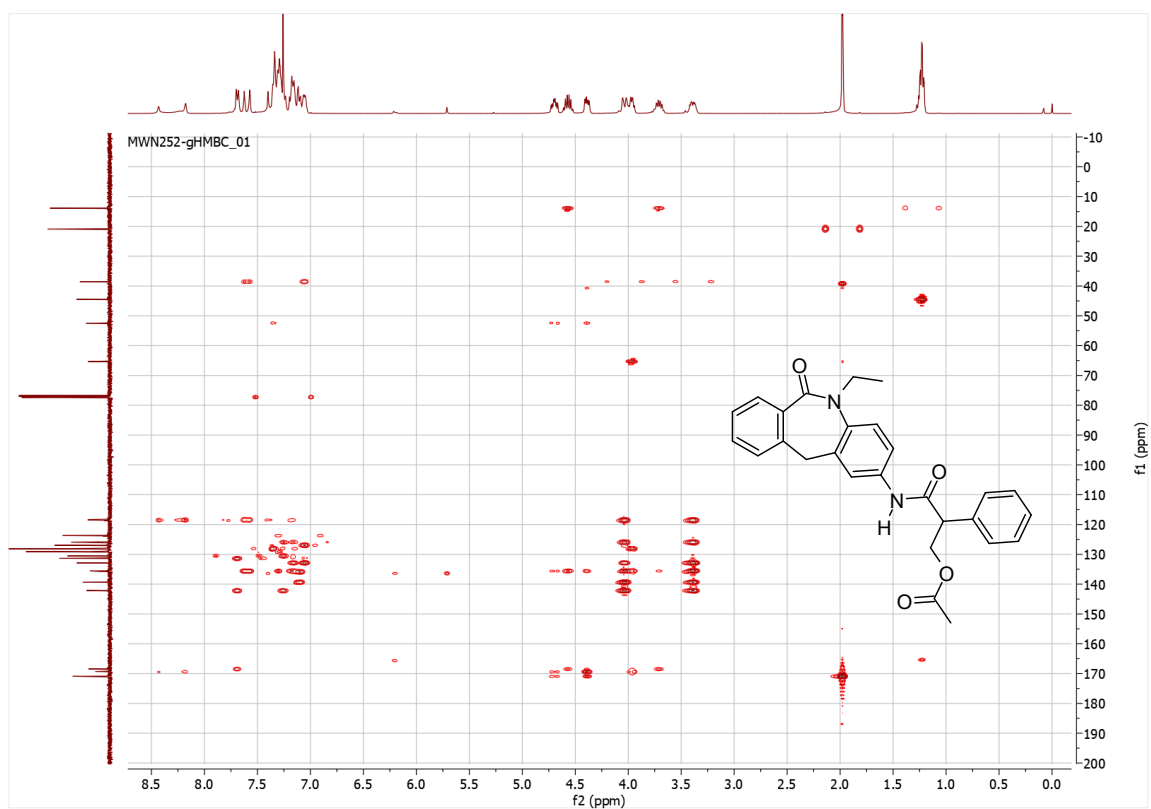
An oven-dried, screw-cap vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (120 mg, 0.48 mmol, 1 equiv) and 3-(acetyloxy)-2-phenylpropanoic acid **61** (109 mg, 0.52 mmol, 1.1 equiv) and anhydrous DCM (3 mL). The solution was cooled down to -15°C and EDC·HCl (109 mg, 0.57 mmol, 1.2 equiv) was added. The reaction was allowed to warm slowly to rt and stirred for 68 h. The volatiles were evaporated and the crude was subjected to column chromatography (C-18; using MeCN/H₂O: 40-55%). The product was precipitated as oil from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times). This gave 175 mg (83%) of target product **21** as a yellowish foam.

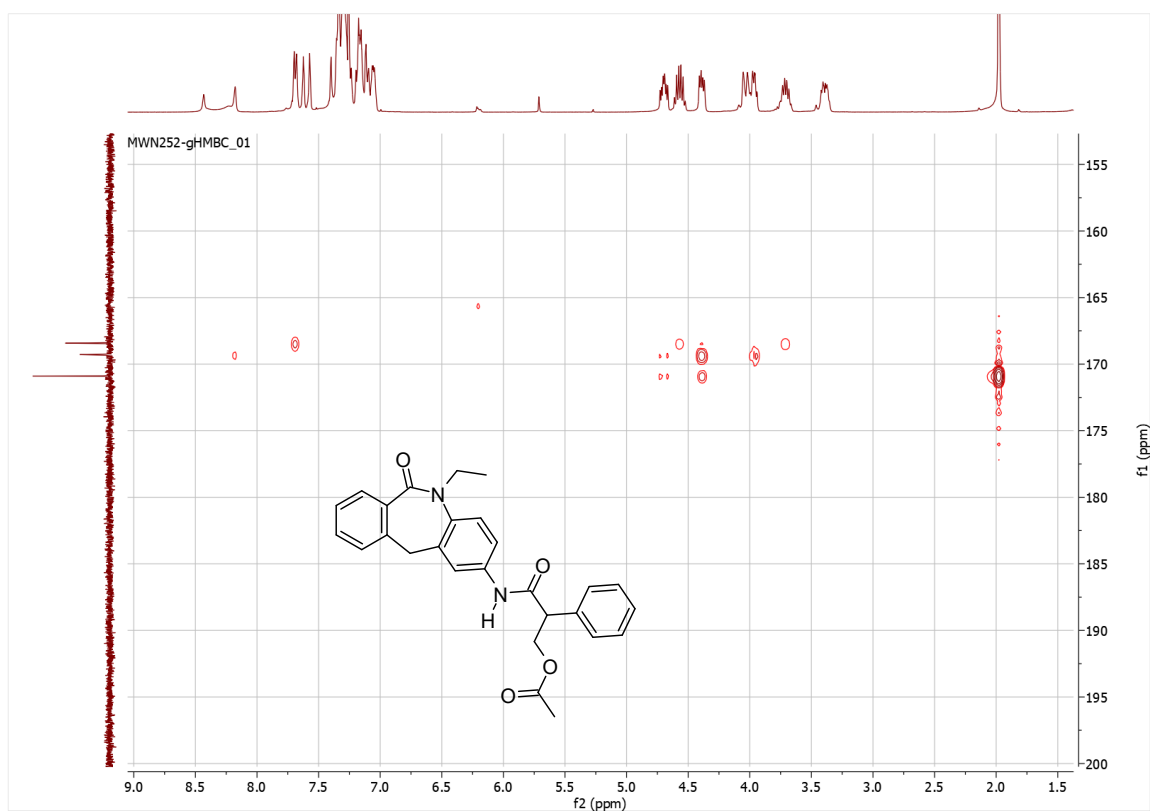
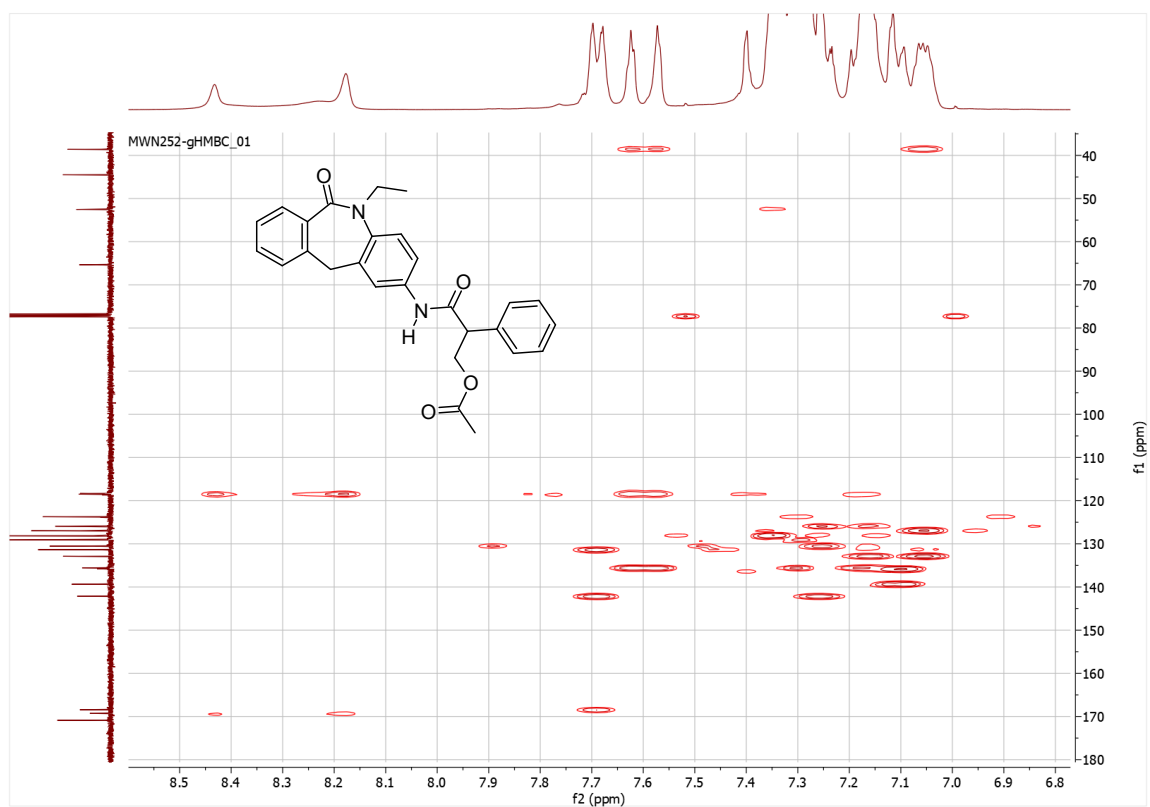
¹H NMR (400 MHz, CDCl₃) δ 8.1-8.01 (m, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 2.3 Hz, 0.5H), 7.57 (d, *J* = 2.5 Hz, 0.5H), 7.41 (s, 0.5H), 7.37-7.23 (m, 5.5H) overlapping residual CHCl₃, 7.21-7.10 (m, 3H), 7.09-7.04 (m, 1H), 4.74-4.66 (m, 1H, ½ OCH₂), 4.63-4.52 (m, 1H, 1/2 CH₂CH₃), 4.43-4.36 (m, 1H, ½ OCH₂), 4.05 (d, *J* = 13.2 Hz, 1H, ½ ArCH₂Ar'), 3.99-3.92 (m, 1H, ArCHCH₂), 3.77-3.66 (1H, ½ CH₂CH₃), 3.45-3.37 (m, 1H, ½ ArCH₂Ar'), 1.99 [s, 1.5H, (CH₃CO)'] overlapping 1.99 [s, 1.5H, (CH₃CO)"], 1.24 [t, *J* = 7.1 Hz, 1.5H, (CH₂CH₃)'] overlapping 1.23 [t, *J* = 7.1 Hz, 1.5H (CH₂CH₃)"]; ¹³C NMR (101 MHz, CDCl₃) δ 171.0 (CO₂), 169.4 (CHCON), 168.5 (CONEt), 142.2, 139.5, 135.9, 135.7, 135.7, 133.0, 131.4, 130.6, 129.2, 128.3, 128.2, 127.1, 126.0 (x 2) 123.8, 118.6 (x 2) 118.5, 118.4, 65.4 (OCH₂), 52.6 (ArCHCH₂), 44.6 (NCH₂), 38.7 (ArCH₂Ar'), 21.0 (COCH₃), [14.0 (x 2), CH₂CH₃]; some peaks are doubled due to the presence of atropisomers and/or dynamic effects. LR-MS (*m/z*): 443 [M+H]⁺.



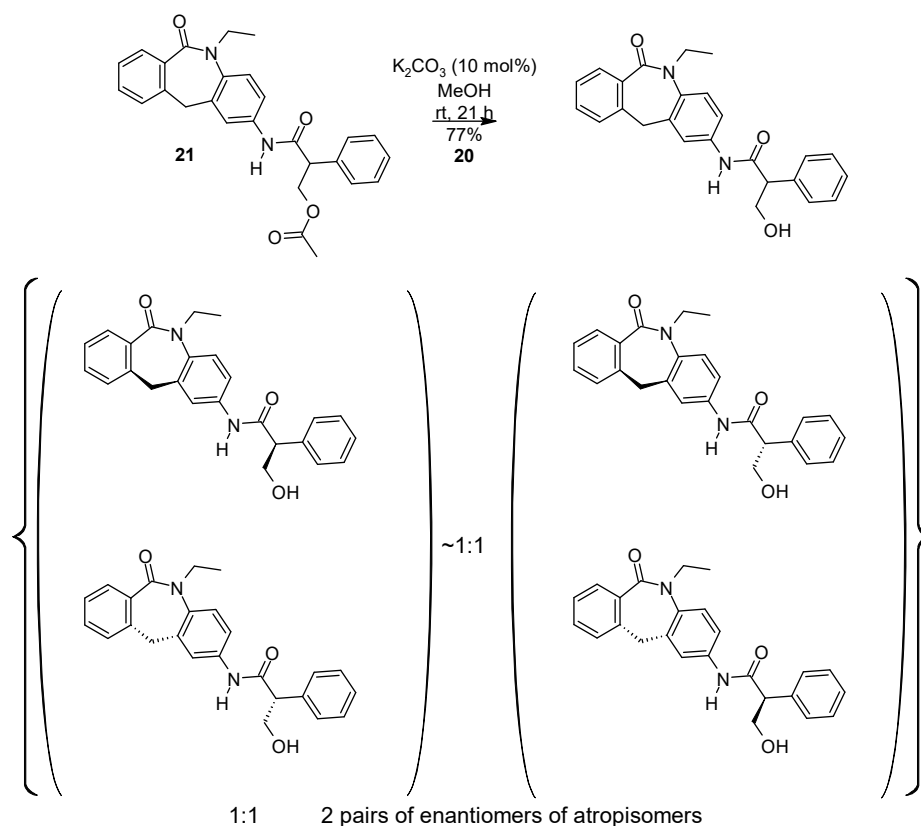






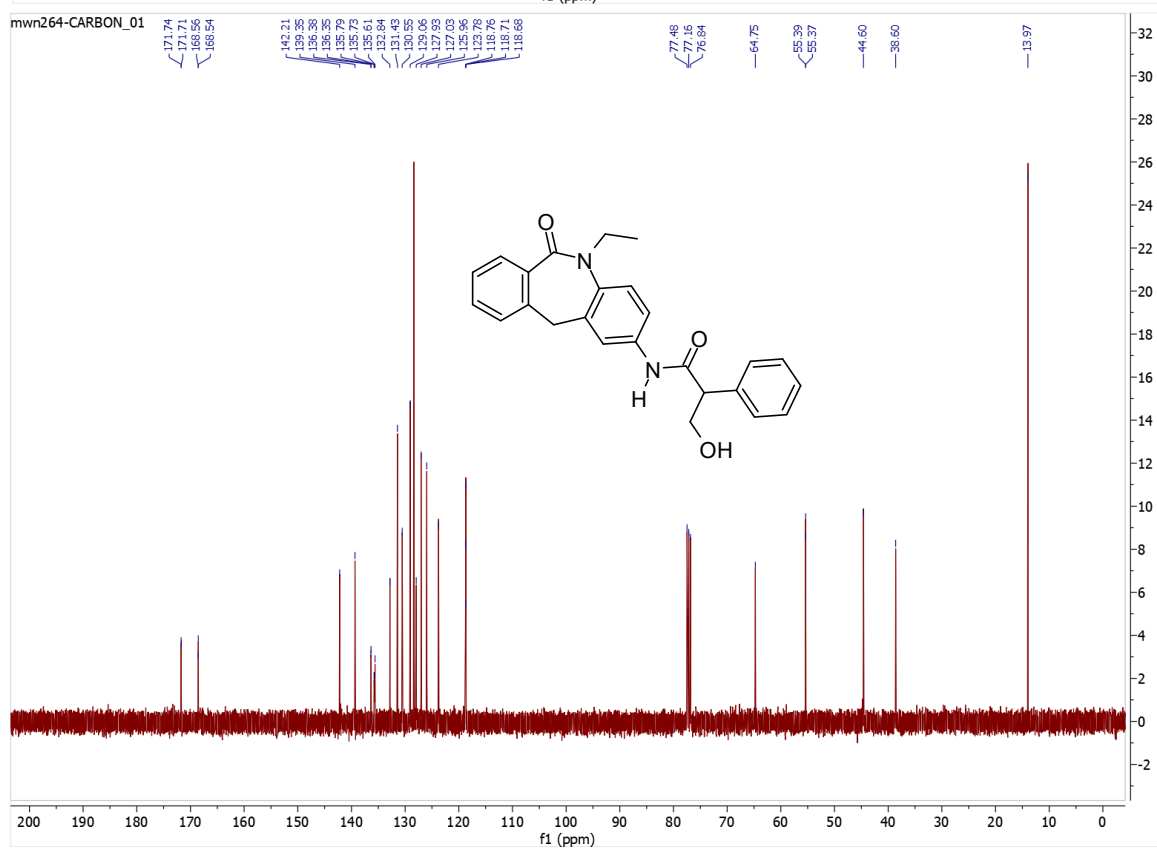
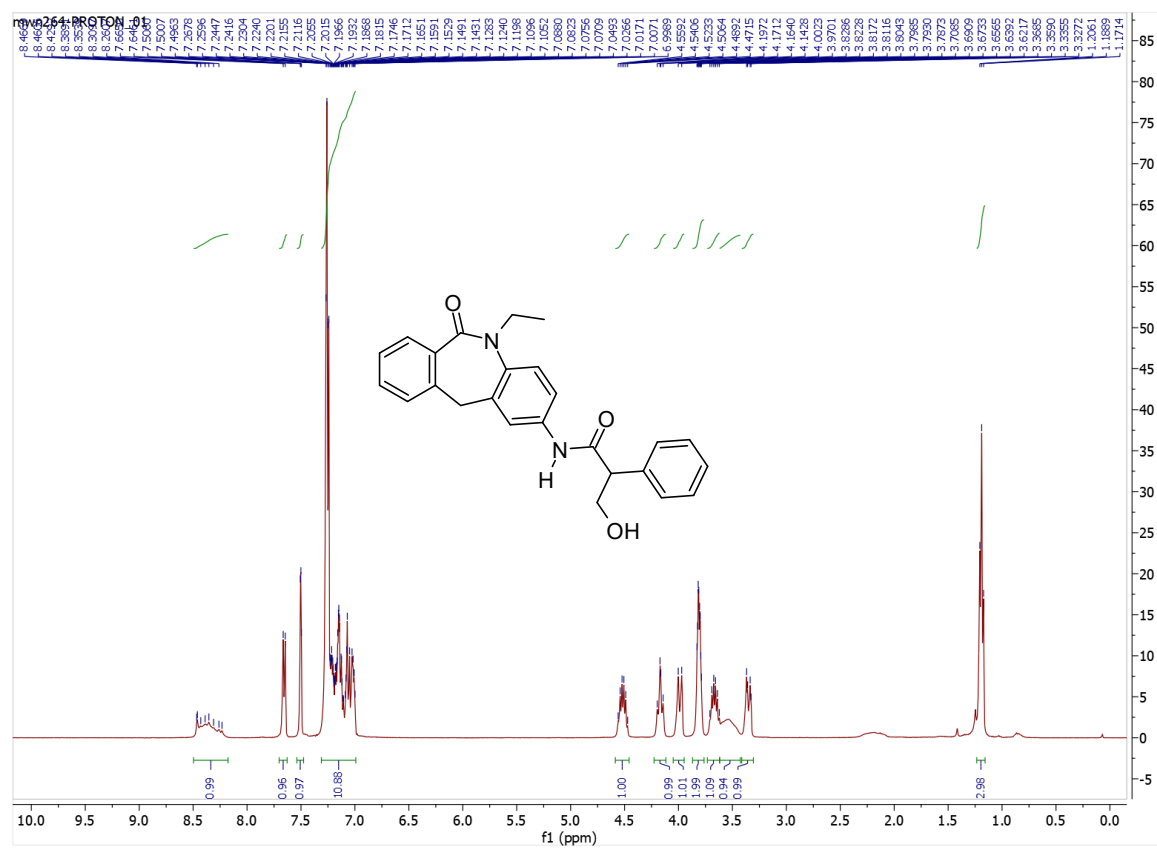


***N*-(5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-3-hydroxy-2-phenylpropanamide
(20)**

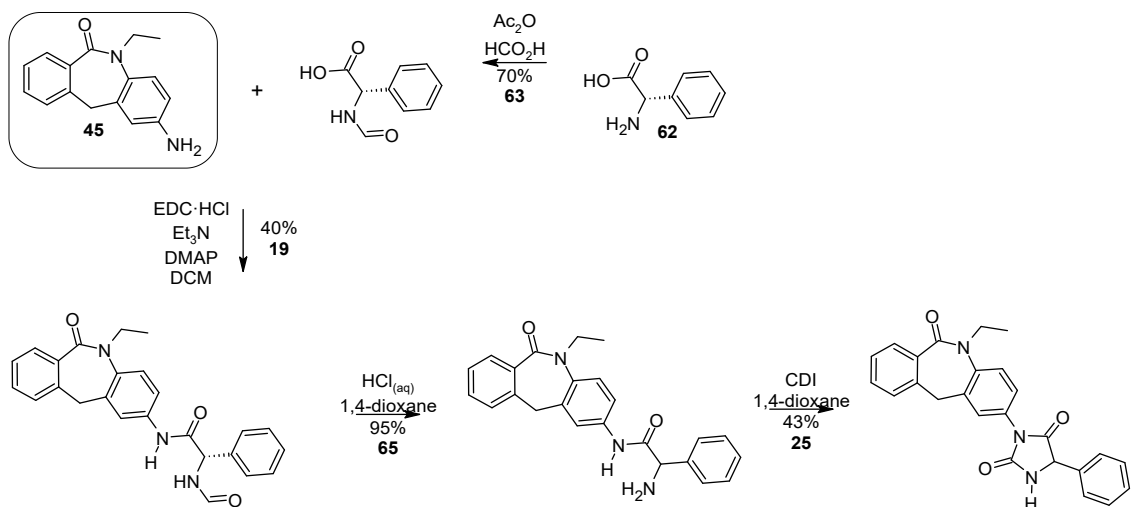


A screw-capped vial was charged with 3-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-oxo-2-phenylpropyl acetate **21** (75 mg, 0.17 mmol, 1 equiv), MeOH (2 mL) and K₂CO₃ (2 mg, 0.02 mmol, 10 mol%). The resulting solution was stirred at rt for 21 h, concentrated and subjected to column chromatography (silica; using MeOH/DCM: 0.5-3%). The product was precipitated as an oil from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times) and dried. This gave 52 mg (77%) of target product **20** as a white foam.

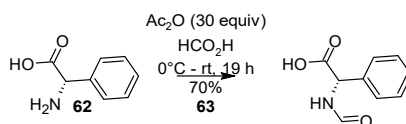
¹H NMR (400 MHz, CDCl₃) δ 8.52-8.16 (m, 1H), 7.70-7.62 (m, 1H), 7.52 (br s, 1H), 7.31-6.99 (m, 10H) overlapping residual CHCl₃, 4.59-4.46 (m, 1H, ½ NCH₂CH₃), 4.22-4.12 (m, 1H), 3.99 (br d, *J* = 12.9 Hz, 1H, ½ ArCH₂Ar'), 3.87-3.76 (m, 2H), 3.73-3.61 (m, 1H, ½ NCH₂CH₃) overlapping 3.65-3.42 (m, 1H, OH), 3.41-3.31 (m, 1H ArCH₂Ar'), 1.19 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [171.7 (x 2); NCO], [168.6, 168.5], 142.2, 139.3, [(136.4 (x 2))], [135.8, 135.7], 135.6 (br), 132.8, 131.4, 130.5, 129.1, 128.4, 127.9, 127.0, 126.0, 123.8, 118.8, 118.7, 118.7 (x 2), 64.8, [55.4 (x 2)], 44.6 (NCH₂), 38.6 (ArCH₂Ar'), 14.0 (CH₃). LR-MS (*m/z*): 401 [M+H]⁺.



The synthesis of 3-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-5-phenylimidazolidine-2,4-dione **25**.



(2S)-Formamido(phenyl)acetic acid (**63**)

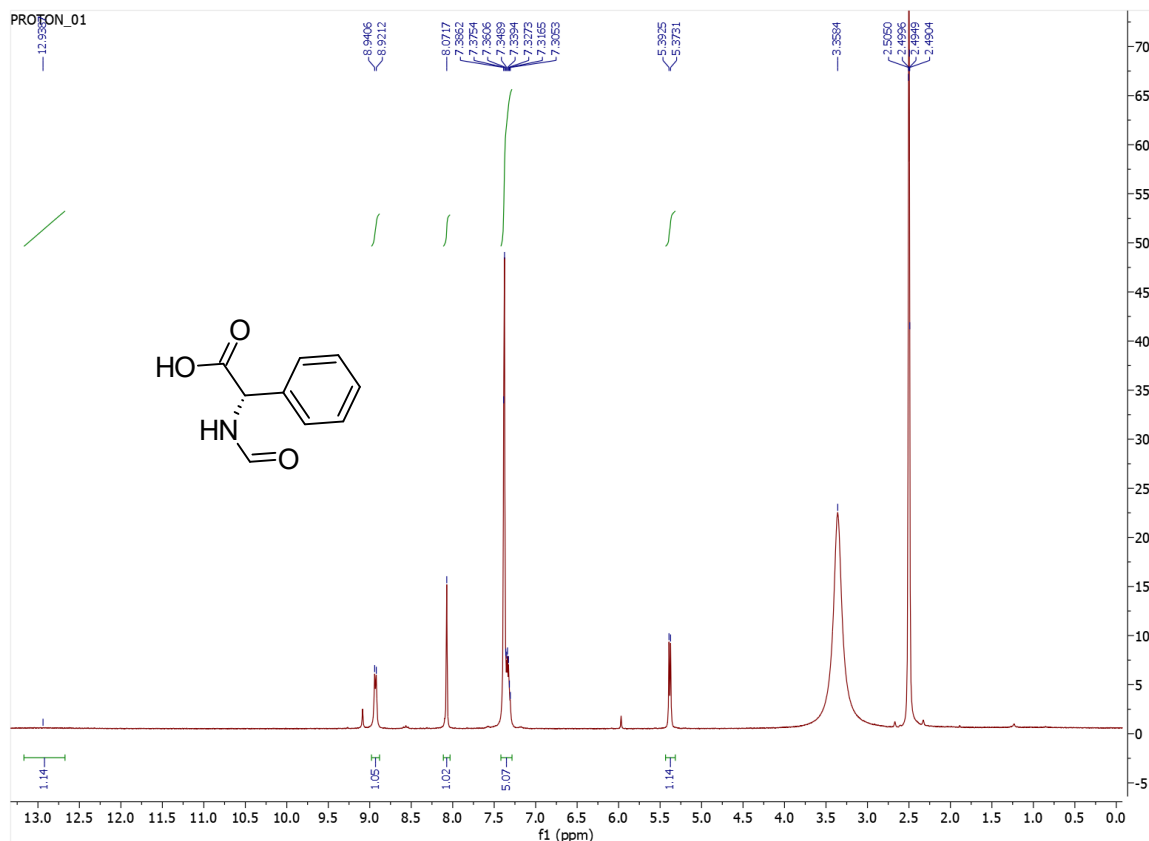


The product was obtained according to slightly modified literature procedure.[7]

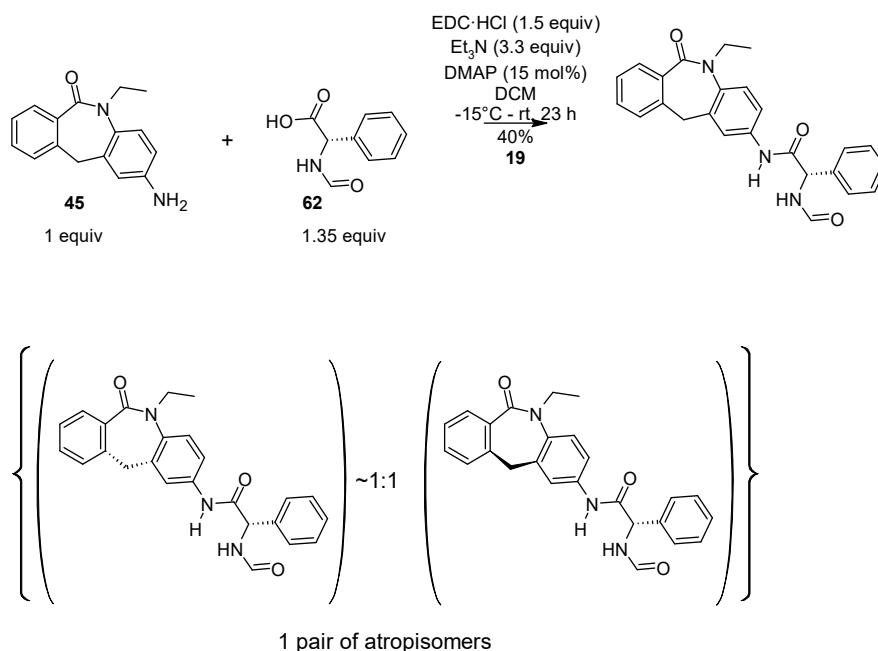
An oven-dried, round-bottom bulb was charged with (2S)-amino(phenyl)acetic acid **62** (1.210 g, 8.00 mmol, 1 equiv) and formic acid (60.5 mL). The solution was cooled to 0°C, and acetic anhydride (22.7 mL, 240.14 mmol, 30 equiv) was added dropwise. The cooling bath was removed and the solution was stirred at rt for 19 h. Water (42 mL) was added dropwise and the volatiles were evaporated. The crude was crystallized from water (20 mL), filtrated and washed with cold water to obtain 0.998 g (70%, in three crops) of product **63** as white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 12.94 (br s, 1H, CO_2H), 8.93 (d, $J = 7.7$ Hz, 1H, NH), 8.07 (s, 1H, CHO), 7.42-7.28 (m, 5H), 5.38 (d, $J = 7.7$ Hz, 1H, CHPh). LR-MS (m/z): 180 $[\text{M}+\text{H}]^+$.

The ^1H NMR spectrum is in agreement with the one previously reported in the literature.[8]

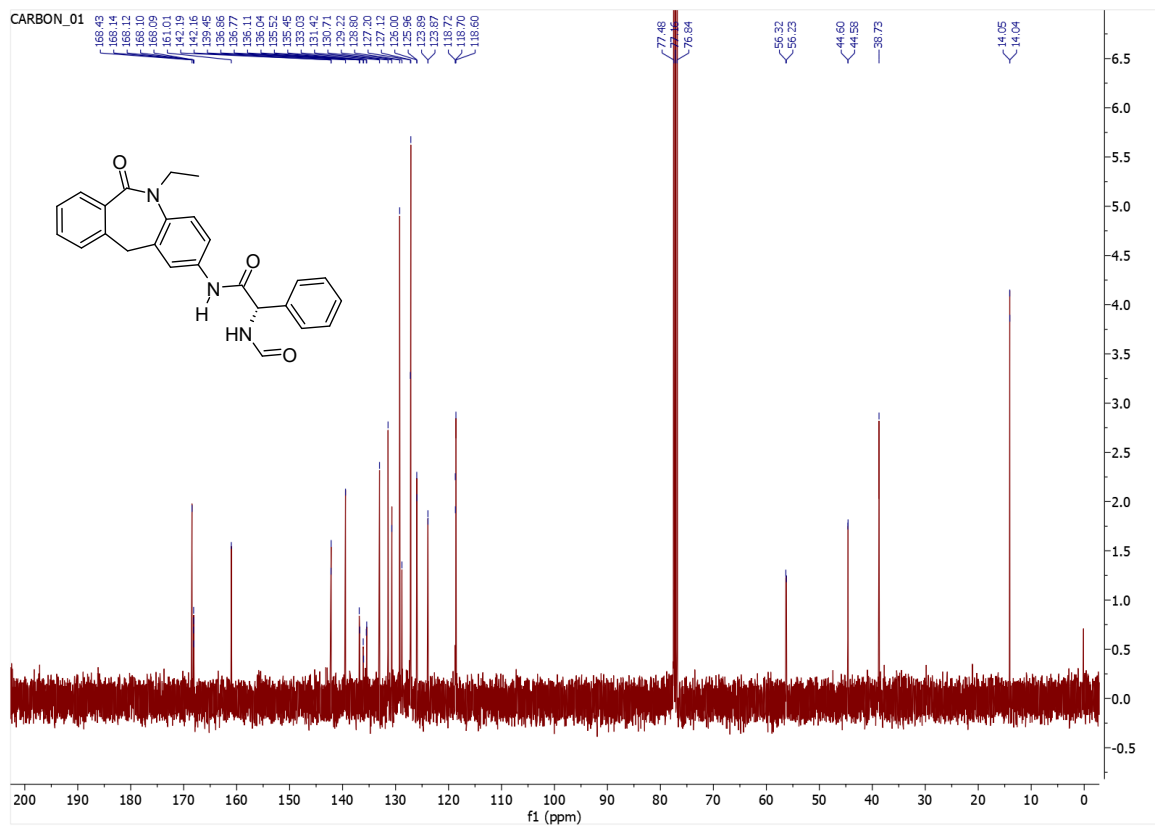
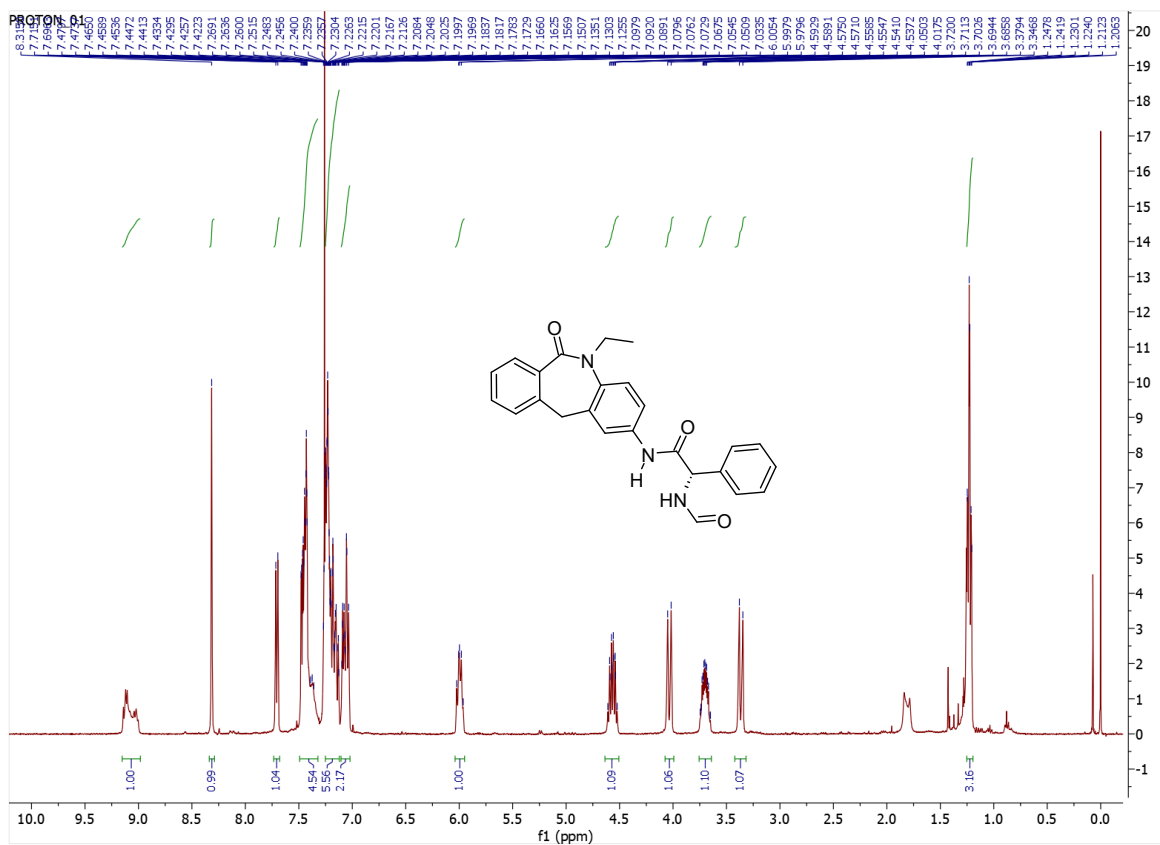


(S)-N-(5-ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)-2-formamido-2-phenylacetamide (19)

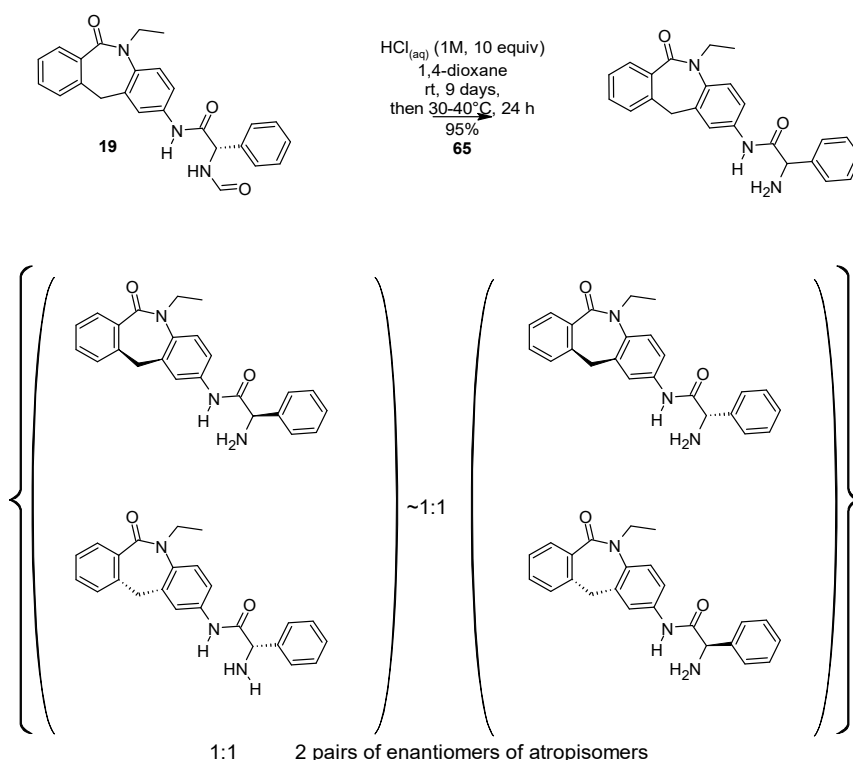


An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (350 mg, 1.24 mmol, 1 equiv), (2*S*)-formamido(phenyl)acetic acid **62** (333 mg, 1.87 mmol, 1.35 equiv) and anhydrous DCM (20 mL). The resulting suspension was cooled down to -15°C and DMAP (22 mg, 0.18 mmol, 13 mol%), EDC·HCl (361 mg, 1.87 mmol, 1.35 equiv) and Et₃N (dropwise, 0.58 mL, 4.16 mmol, 3 equiv) were added. The reaction was allowed to warm slowly to rt and stirred overall for 26 h. The volatiles were evaporated and the crude was subjected to column chromatography (silica; using MeOH/DCM: 0-3%). The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (3 times) to obtain 232 mg (40%) of target product **19** as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.16-8.98 (m, 1H), 8.32 (s, 1 H, CHO), 7.72-7.68 (m, 1H), 7.50-7.31 (m, 4.5H), 7.29-7.12 (m, 1H, 5.5H) overlapped with residual CHCl₃, 7.11-7.02 (m, 2H), 6.04-5.95 (m, 1H, CHPh), 4.62-4.51 (m, 1H, ½ CH₂CH₃), 4.03 (d, *J* = 13.1 Hz, 1H, ½ ArCH₂Ar'), 3.75-3.64 (m, 1H, ½ CH₂CH₃), 3.36 (d, *J* = 13.1 Hz, 1H, ½ ArCH₂Ar'), 1.27-1.20 (m, 3H, CH₃); ¹³C NMR (101 MHz, CHCl₃) δ 168.4 (CON), [168.1 (x 4); (CON')], 161.0 (CON''), [142.2 (x 2)], 139.5, [136.9, 136.8], [136.1, 136.0], [135.5, 135.4], 133.0, 131.4, 130.7, 129.2, 128.8, 127.2, 127.1, [126.0 (x 2)], [123.9 (x 2)], [118.7 (x 2)], 118.6, [56.3, 56.2; (CHPh)], [44.6 (x 2)]; (NCH₂), 38.7 (ArCH₂Ar'), [14.0 (x 2); (CH₃)]; some peaks are multiplied due to the presence of atropisomers and/or dynamic effects. LR-MS (*m/z*): 414 [M+H]⁺.

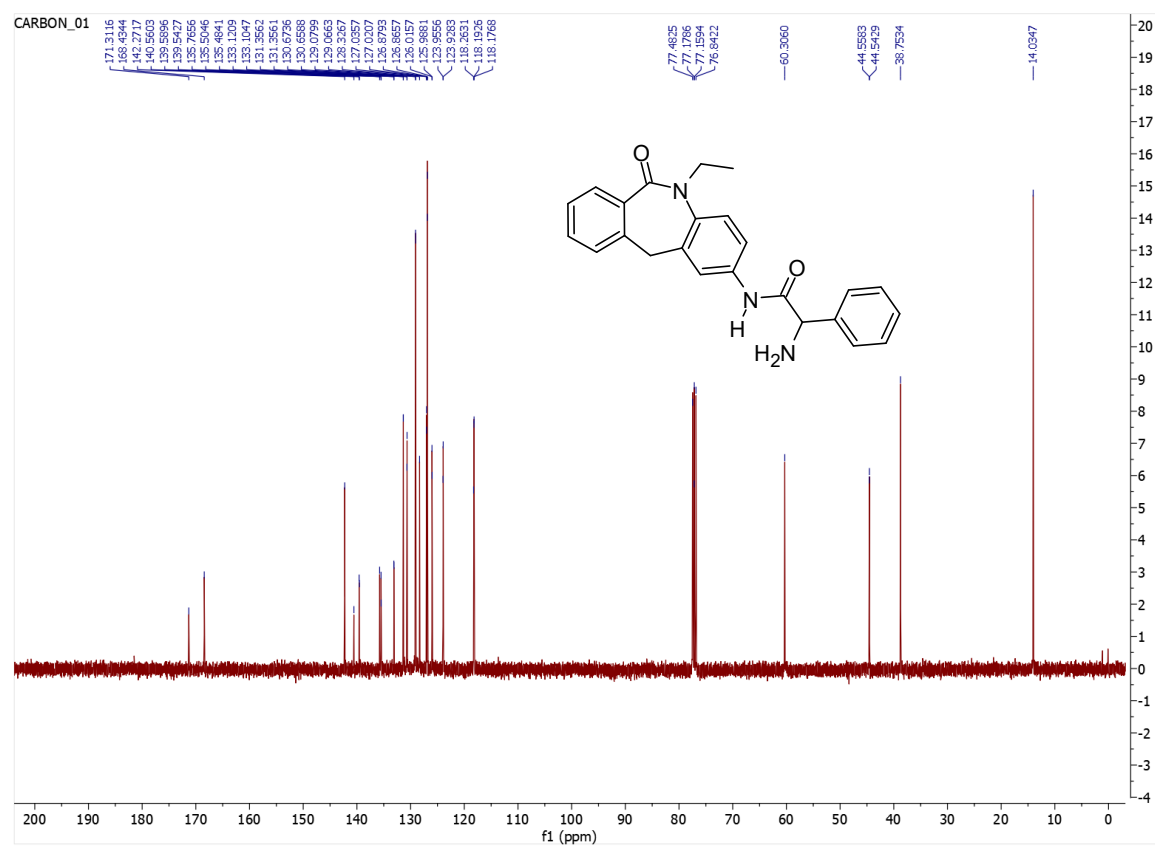
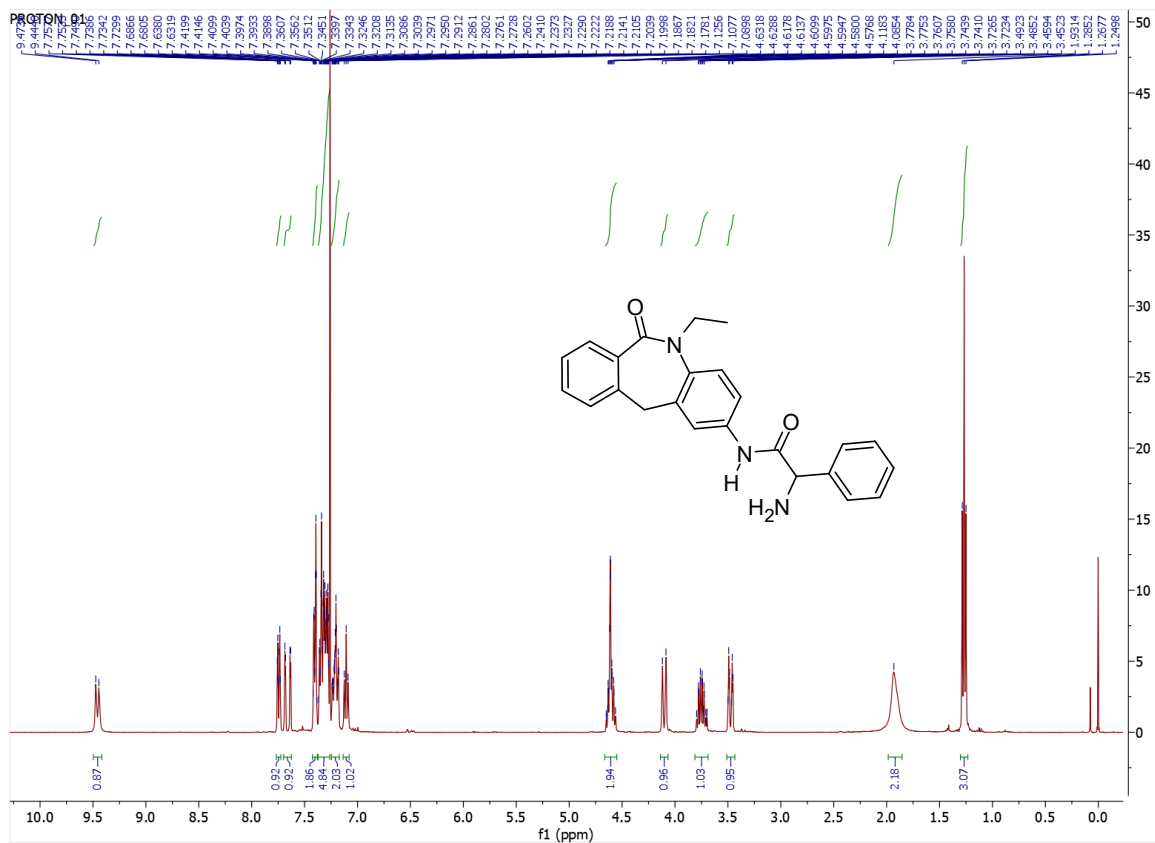


2-Amino-*N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-phenylacetamide (**63**)

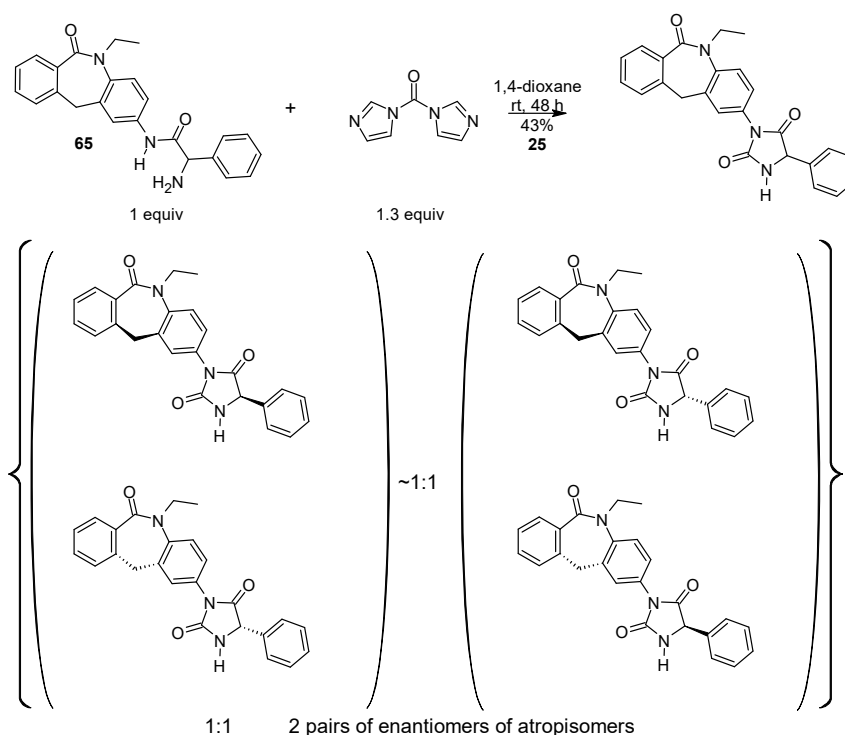


A round-bottom bulb was charged with (*S*)-*N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-formamido-2-phenylacetamide **19** (211 mg, 0.51 mmol, 1 equiv) and 1,4 dioxane (5.1 mL). To the solution was added $\text{HCl}_{(\text{aq})}$ (1 M; 5.1 mL, 5.1 mmol, 10 equiv). The mixture was stirred at rt for 9 days and at 30-40 °C for 24 h. Subsequently, saturated aqueous solution of NaHCO_3 (10 mL) and DCM (15 mL) were added to the mixture and the phases were separated. The aqueous one was extracted with DCM (2 x 15 mL). The organic extracts were combined, washed with brine (10 mL) and the brine was re-extracted with DCM (15 mL). The combined organic extract was dried over anhydrous Na_2SO_4 , filtrated and evaporated. The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (3 times). This gave 186 mg (95%) of product **65** as a yellowish foam.

^1H NMR (400 MHz, CDCl_3) δ [9.47 (s, 0.5H, $\frac{1}{2}$ ArNH), 9.44 (s, 0.5H, $\frac{1}{2}$ ArNH)], 7.77-7.72 (m, 1H), 7.70-7.62 (m, 1H), 7.43-7.38 (m, 2H), 7.37-7.26 (m, 5 H) overlapped by residual CHCl_3 , 7.25-7.17 (m, 2H), 7.14-7.08 (m, 1H), 4.66-4.55 (m, 2H, $\frac{1}{2}$ CH_2CH_3 , CHPh), 4.10 (d, $J = 13.1$ Hz, 1H, $\frac{1}{2}$ $\text{ArCH}_2\text{Ar}'$), 3.81-3.70 (m, 1H, $\frac{1}{2}$ CH_2CH_3), 3.51-3.44 (m, 1H, $\frac{1}{2}$ $\text{ArCH}_2\text{Ar}'$), 1.93 (br s, 2H, NH_2) overlapped by residual water, 1.27 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CHCl_3) δ 171.3 (CON), 168.4 (CON)', 142.3, 140.6, [139.6, 139.5], 135.8, 135.5 (x 2), [133.1 (x 2)], [131.4 (x 2)], [130.7 (x 2)], [129.1 (x 2)], 128.3, [127.0 (x 2)], [126.9 (x 2)], [126.0 (x 2)], [124.0, 123.9], 118.3, [118.2 (x 2)], 60.3, [44.6, 44.5], 38.8, 14.0 (CH_3); (some signals are doubled due to the presence of atropisomers). LR-MS (m/z): 386 [$\text{M}+\text{H}$] $^+$.

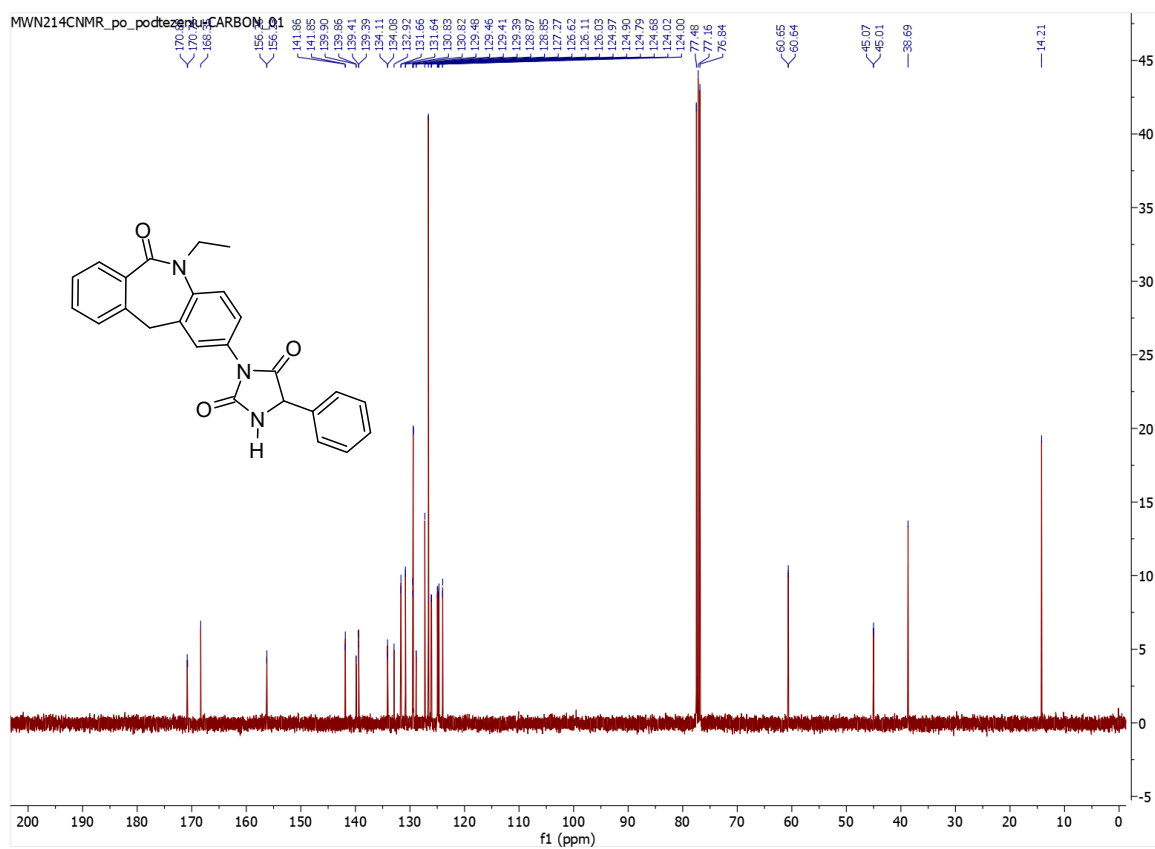
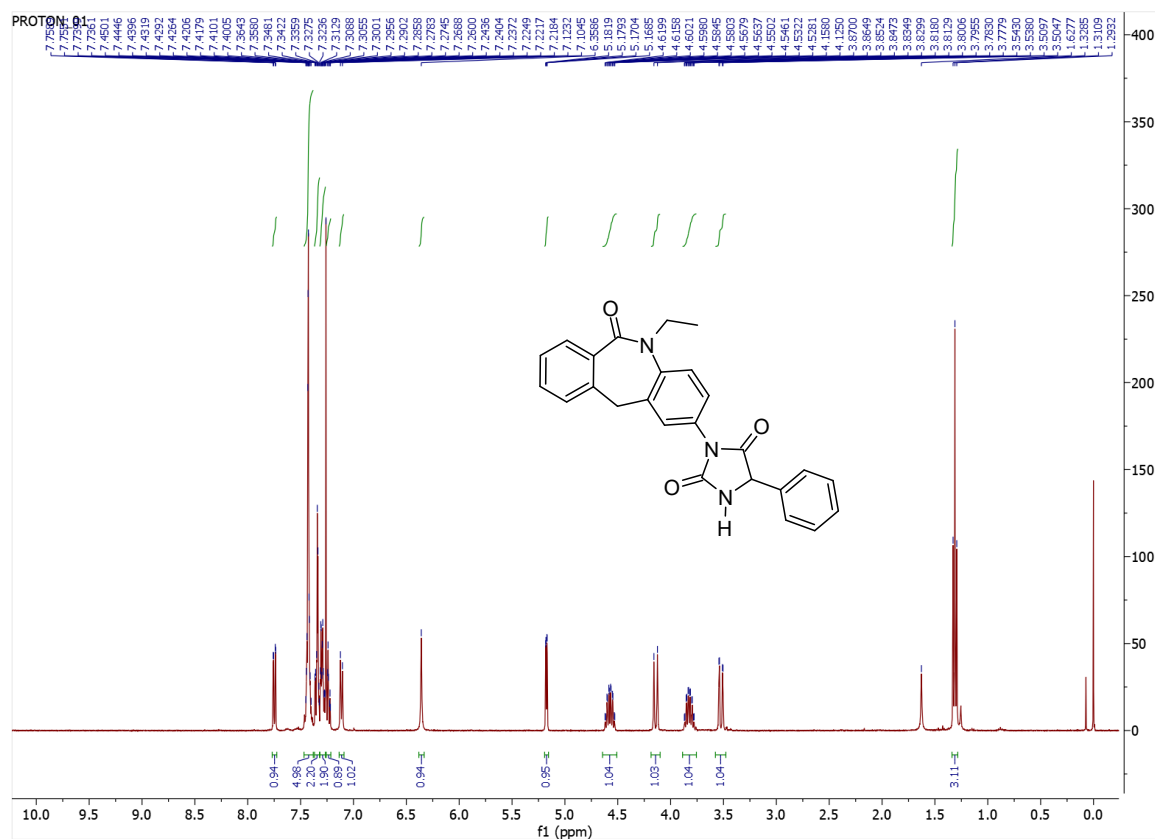


3-(5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-5-phenylimidazolidine-2,4-dione (25)

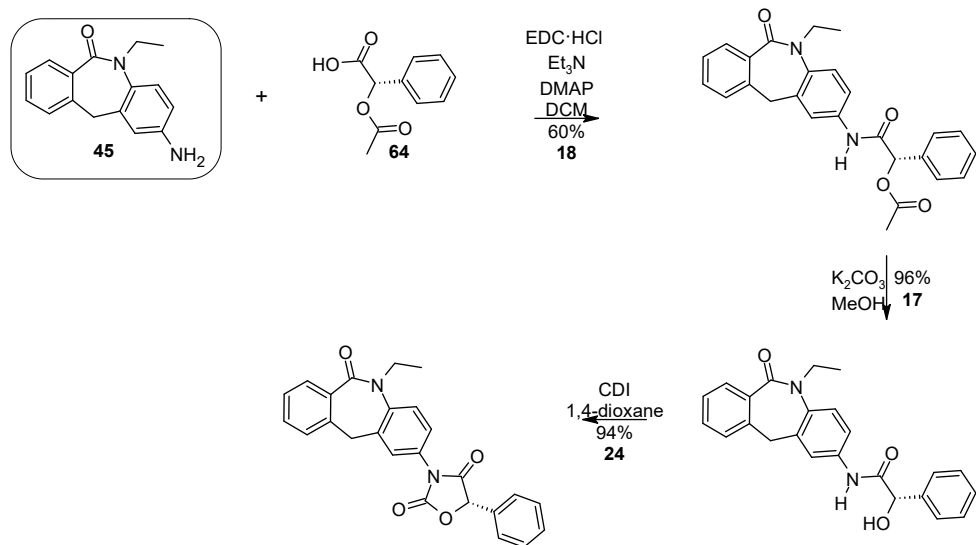


An oven-dried, screw-capped vial was charged with 2-amino-*N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-phenylacetamide **65** (65 mg, 0.17 mmol, 1 equiv), anhydrous 1,4-dioxane (2.8 mL), carbonyldiimidazole (36 mg, 0.22 mmol, 1.3 equiv), and the resulting suspension was stirred at rt for 48 h. To the reaction mixture was added aqueous HCl (1 M, 1 mL, 1 mmol) and the volatiles were evaporated. The residue was subjected to column chromatography (silica; using MeOH/DCM: 0.5-2%). The product was precipitated, as an oil, from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (3 times) and dried. This gave 30 mg (43%) of the target product **25** as a white solid.

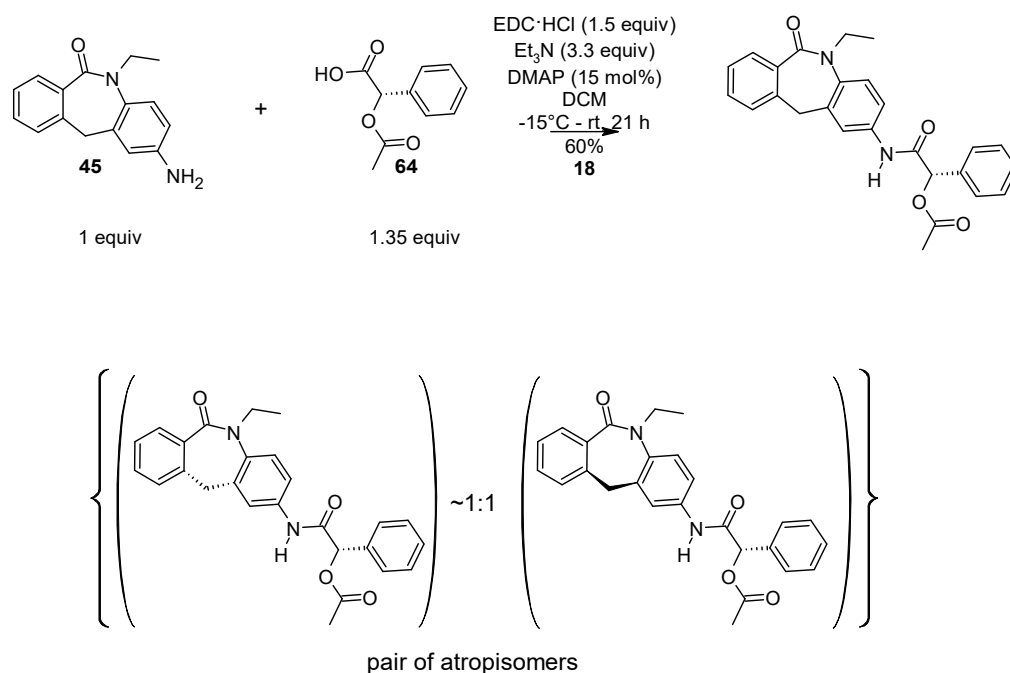
¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.47-7.48 (m, 5H), 7.37-7.21 (m 5H) overlapped by residual CHCl₃, 7.11 (br d, *J* = 7.5 Hz, 1H), 6.36 (s, 1H, CONH), 5.19-5.16 (m, *J* = 4.5, 1.2 Hz, 1H, CHPh), 4.63-4.52 (m, 1H, ½ CH₂CH₃), 4.14 (d, *J* = 13.2 Hz, 1H, ArCH₂Ar'), 3.88-3.77 (m, ½ CH₂CH₃, 1H), [3.53 (*J* = 13.3 Hz, 0.5 H, ArCH₂Ar') overlapping 3.52 (*J* = 13.3 Hz, 0.5 H, ArCH₂Ar')], 1.31 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [170.8 (x 2); (CON)], 168.4 ((CON), [156.3, 156.2, (CON)], [141.9, 141.8], [139.9 (x 2)], [139.4 (x 2)], [134.1 (x 2)], 132.9, [131.7, 131.6], [130.8 (x 2)], [129.5 (x 2)], [129.4 (x 2)], [128.9 (x 2)], 127.3, 126.6, [126.1, 126.0], [125.0, 124.9], [124.8, 124.7], [124.0 (x 2)], [60.7, 60.6, CHPh], [45.1, 45.0, NCH₂], 38.7 (ArCH₂Ar'), 14.2 (CH₃); (doubled signals are caused by the presence of atropisomers). LR-MS (*m/z*): 412 [M+H]⁺.



The synthesis of (*S*)-3-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-5-phenyloxazolidine-2,4-dione **24**.

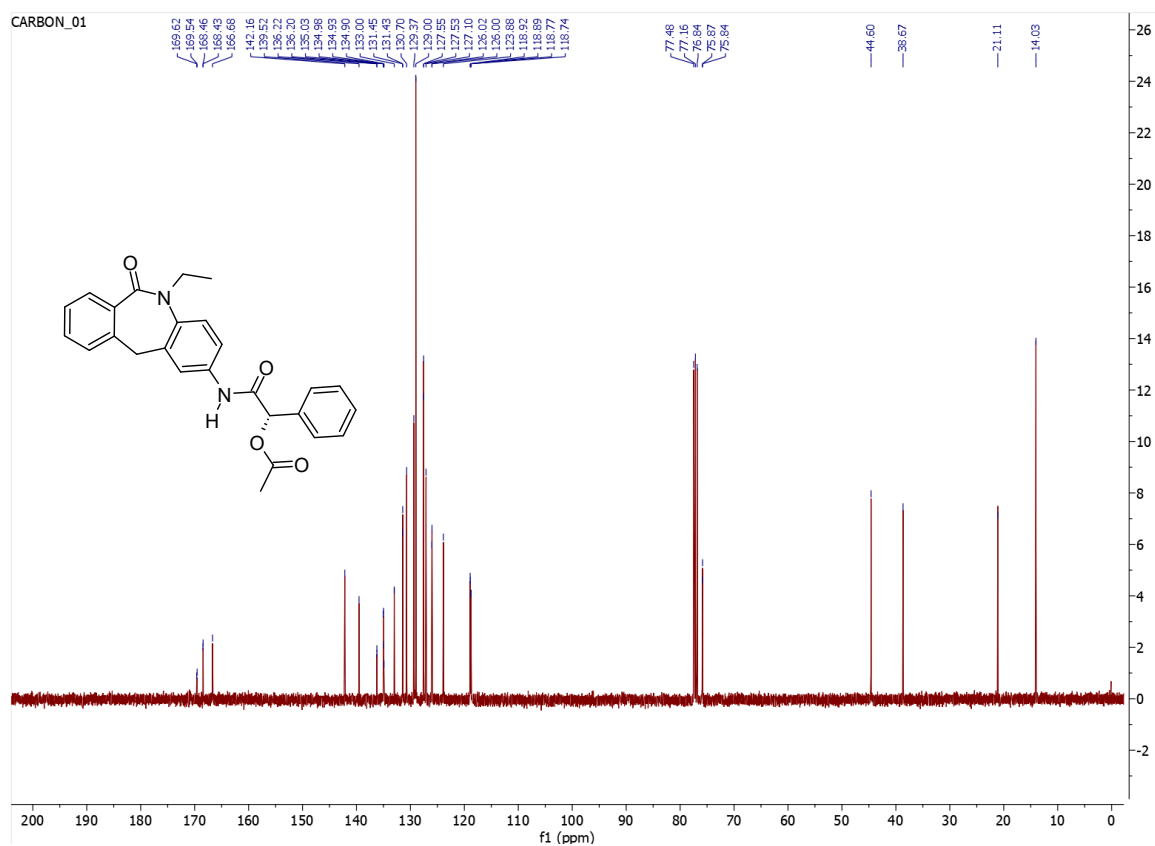
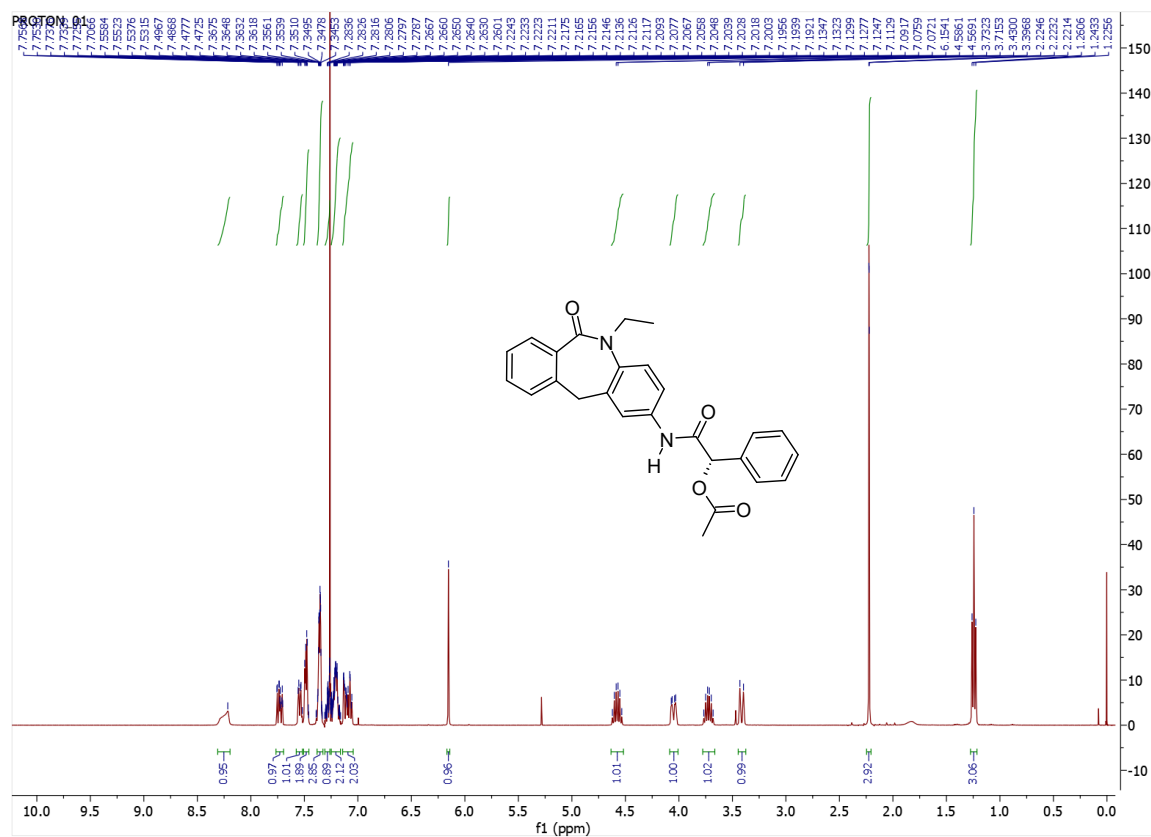


(*S*)-2-((5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-2-oxo-1-phenylethyl acetate (18**)**

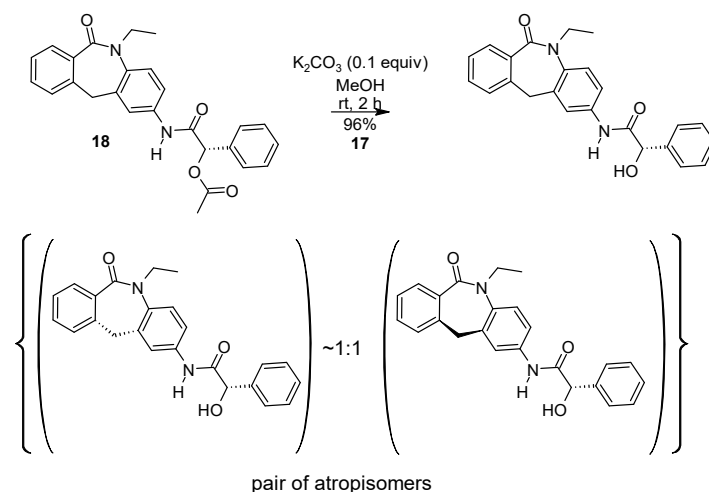


An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (350 mg, 1.24 mmol, 1 equiv), (*S*)-2-(acetyloxy)(phenyl)acetic acid **64** (364 mg, 1.87 mmol, 1.35 equiv) and anhydrous DCM (20 mL). The resulting suspension was cooled down to -15°C and DMAP (22 mg, 0.18 mmol, 13 mol%), EDC·HCl (361 mg, 1.87 mmol, 1.35 equiv) and Et₃N (dropwise, 0.58 mL, 4.16 mmol, 3 equiv) were added. The reaction was allowed to warm slowly to rt, stirred for 21 h and evaporated. The crude was filtrated through the plug of silica using acetone/DCM 0-4%, evaporated and subjected to reverse-phase column chromatography (C-18; using MeCN/H₂O: 25-50%). The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator as colorless oil, washed with *n*-hexane (3 times), to obtain 355 mg (60%) of target product **18** as a white foam.

¹H NMR (400 MHz, CDCl₃) δ 8.31-8.19 (m, 1H), 7.76-7.70 (m, 1H), 7.57-7.52 (m, 1H), 7.51-7.45 (m, 2H), 7.38-7.33 (m, 3H), 7.31-7.16 (m, 3H), 7.14-7.04 (m, 2H), 6.15 (s, 1H, *CH*Ph), 4.63-4.52 (m, 1H, ½ *CH*₂CH₃), 4.09-4.01 (m, 1H, ½ *ArCH*₂*Ar*'), 3.78-3.67 (m, 1H, ½ *CH*₂CH₃), 3.41 (d, *J* = 13.3 Hz, 1H, ½ *ArCH*₂*Ar*'), 2.23-2.21 (m, 3H, COCH₃), 1.24 (t, *J* = 7.0 Hz, 3H, CH₂CH₃); ¹³C NMR (101 MHz, CHCl₃) δ [169.6, 169.5; (CO)], [168.5, 168.4; (CO)], 166.7 (CO), 142.2, 139.5, [136.2 (x 2)], [135.0 (x 2)], [134.9 (x 2)], 133.0, [131.4 (x 2)], 130.7, 129.4, 129.0, [127.6, 127.5], 127.1, 126.0 (x 2), 123.9, [118.9 (x 2)], [118.8, 118.7], [75.9, 75.8; (PhCH)], 44.6 (NCH₂), 38.7 [*ArCH*₂*Ar*'], 21.1 [COCH₃], 14.0 (CH₂CH₃); (some signals are doubled due to the presence of atropisomers). LR-MS (*m/z*): 429 [M+H]⁺.

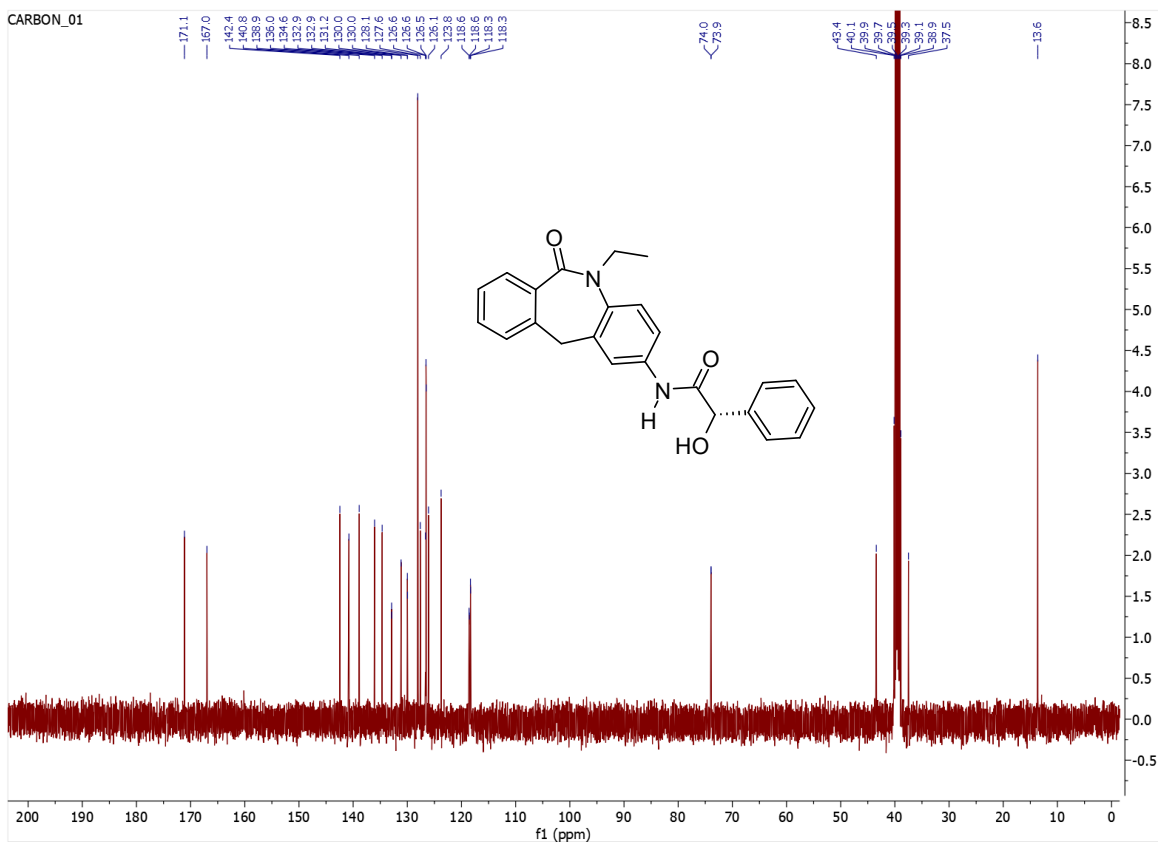
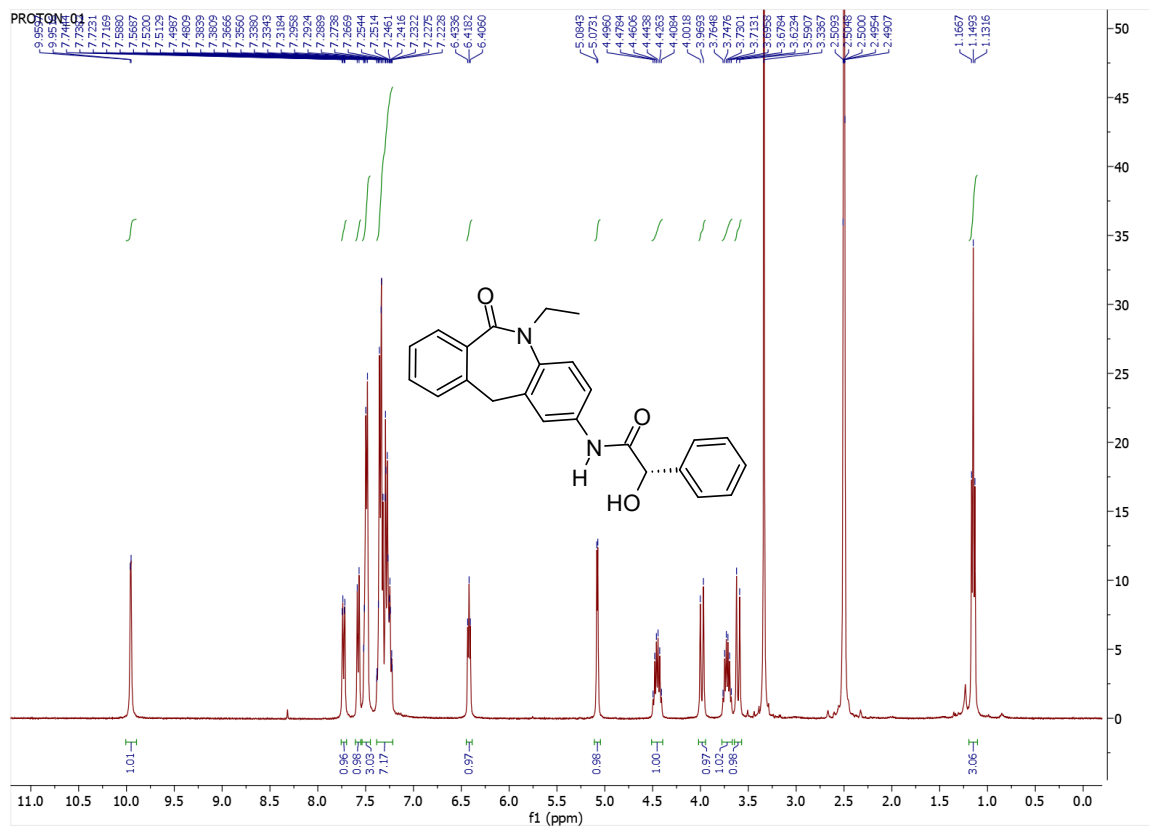


(S)-N-(5-Ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)-2-hydroxy-2-phenylacetamide
(17)

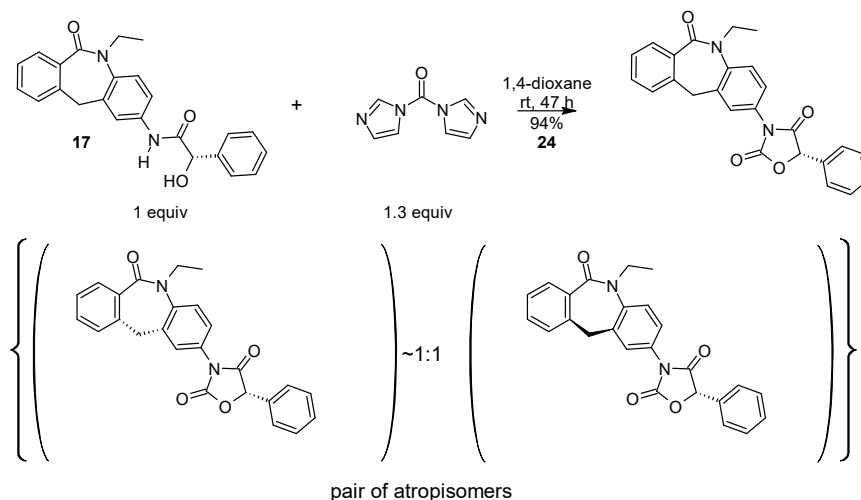


A screw-capped vial was charged with (*S*)-2-((5-ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)amino)-2-oxo-1-phenylethyl acetate **18** (271 mg, 0.63 mmol, 1 equiv), pulverized K₂CO₃ (9 mg, 0.06 mmol, 0.1 equiv) and MeOH (9.5 mL), and the resulting suspension was stirred at rt for 2 h. The solid was filtrated and washed with chilled MeOH (2 times), to obtain 203 mg of product **17** as a white solid. To the filtrate was added aqueous HCl (1 M, 0.5 mL) and the volatiles were evaporated. The residue was macerated with MeOH (1 mL) and filtrated to obtain additional 32 mg of product **17**. The overall yield was 96%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.96 (d, *J* = 3.2 Hz, 1H, CONH), 7.73 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.54-7.46 (m, 3H), 7.39-7.21 (m, 7 H), 6.44-6.39 (m, 1H), 5.08 (d, *J* = 4.5 Hz, 1H), 4.51-4.39 (m, 1H, ½ CH₂CH₃), 3.99 (d, *J* = 13.0 Hz, 1H, ½ ArCH₂Ar'), 3.77-3.67 (m, 1H, ½ CH₂CH₃), 3.61 (d, *J* = 13.1 Hz, 1H, ½ ArCH₂Ar'), 1.15 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 171.1 (CON), 167.0 (CON), 142.4, 140.8, 138.9, 136.0, 134.6, [132.9 (x 2)], 131.2, [130.0 (x 2)], 128.1, 127.6, 126.6, [126.6, 126.5], 126.1, 123.8, [118.6 (x 2)], [118.3 (x 2)], [74.0, 73.9, CHOH], 43.4 (NCH₂), 37.5 (ArCH₂Ar'), 13.6 (CH₃); (some signals are doubled due to the presence of atropisomers). LR-MS (*m/z*): 387 [M+H]⁺, 795 [2M+Na]⁺.

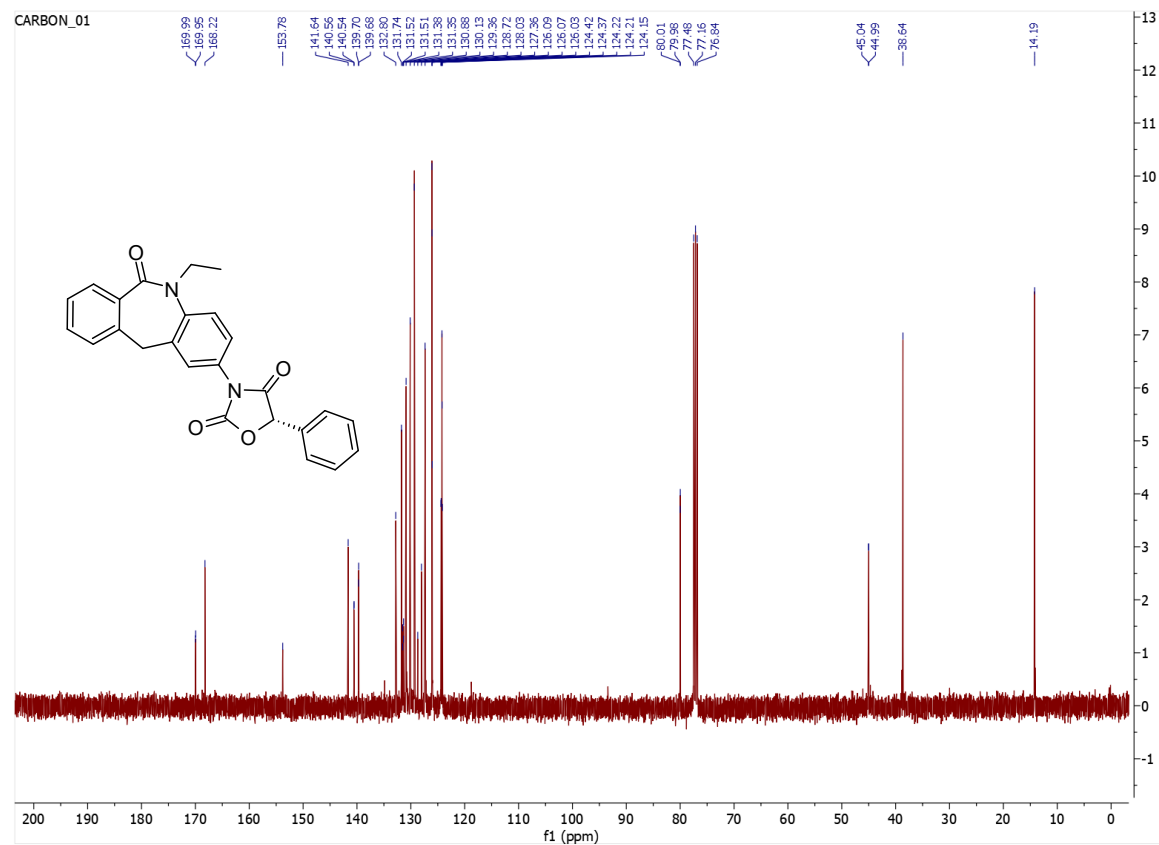
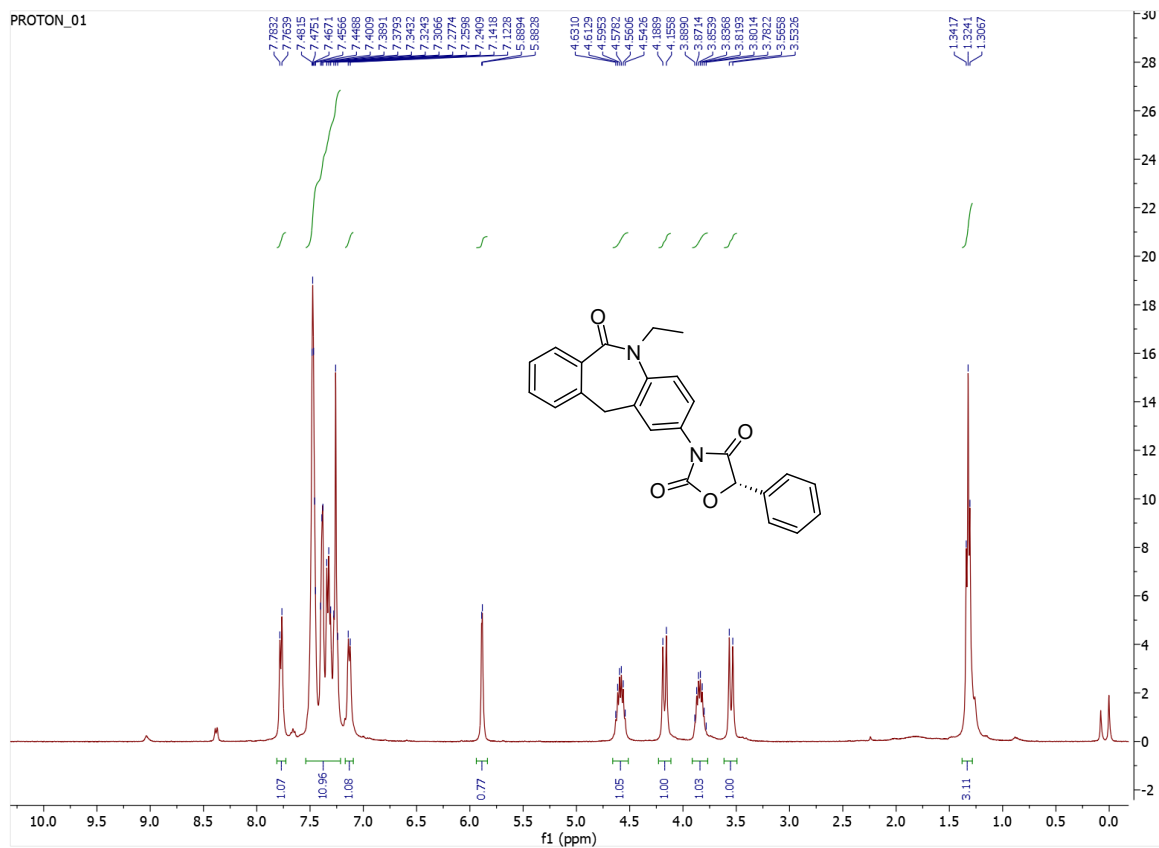


(S)-3-(5-ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)-5-phenyloxazolidine-2,4-dione
(24)

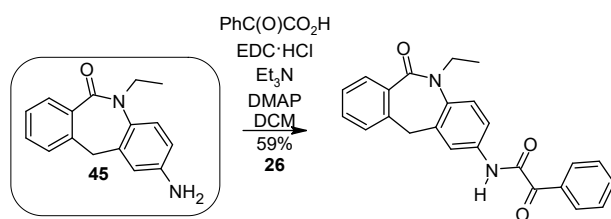


An oven-dried, screw-capped vial was charged with (*S*)-*N*-(5-ethyl-6-oxo-6,11-dihydro-5H-dibenzo[*b,e*]azepin-2-yl)-2-hydroxy-2-phenylacetamide **17** (67 mg, 0.17 mmol, 1 equiv), anhydrous 1,4-dioxane (3 mL) and carbonyldiimidazole (37 mg, 0.23 mmol, 1.3 equiv), and the resulting suspension was stirred at rt for 47 h. The volatiles were evaporated and the residue was portioned between AcOEt (25 mL) and HCl aqueous solution (1 M, 2 mL). The phases were separated, and the organic one was washed with water (2 x 2 mL) and brine 5 mL, dried over Na₂SO₄, filtrated and evaporated. The product was precipitated, as an oil, from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (3 times) and dried to obtain 67 mg (94%) of target product **24** as a yellowish foam.

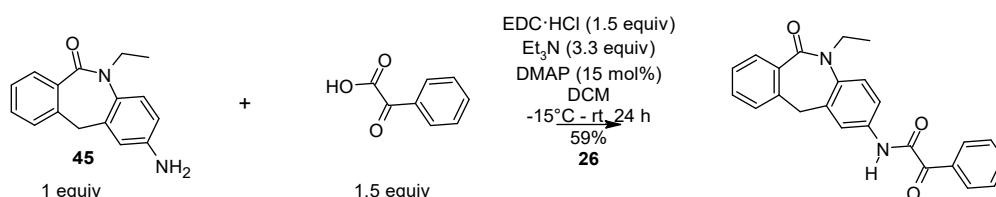
¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.54-7.21 (m, 11H), 7.13 (d, *J* = 7.6 Hz, 1H), 5.91-5.86 (m, 1H, CHPh) (m, 1H), 4.67-4.52 (m, 1H, ½ CH₂CH₃), 4.17 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 3.91-3.78 (m, 1H, ½ CH₂CH₃), 3.55 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 1.32 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [170.0, 169.9; (CON)], 168.2 (CON'), 153.8 (OCON), 141.6, [140.6, 140.5], [139.7 (x 2)], 132.8, 131.7, [131.5 (x 2)], [131.4 (x 2)], 130.9, 130.1, 129.4, 128.7, 128.0, 127.4, 126.1 (x 2), 126.0, [124.4 (x 2)], 124.2 (x 2), 124.1, [80.0 (x 2), CHPh], 45.0 (x 2, NCH₂), 38.6 (ArCH₂Ar'), 14.2 (CH₂); some signals are doubled due to the presence of atropisomers). LR-MS (*m/z*): 413 [M+H]⁺, 847 [2M+Na]⁺.



Synthesis of *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-oxo-2-phenylacetamide **26.**

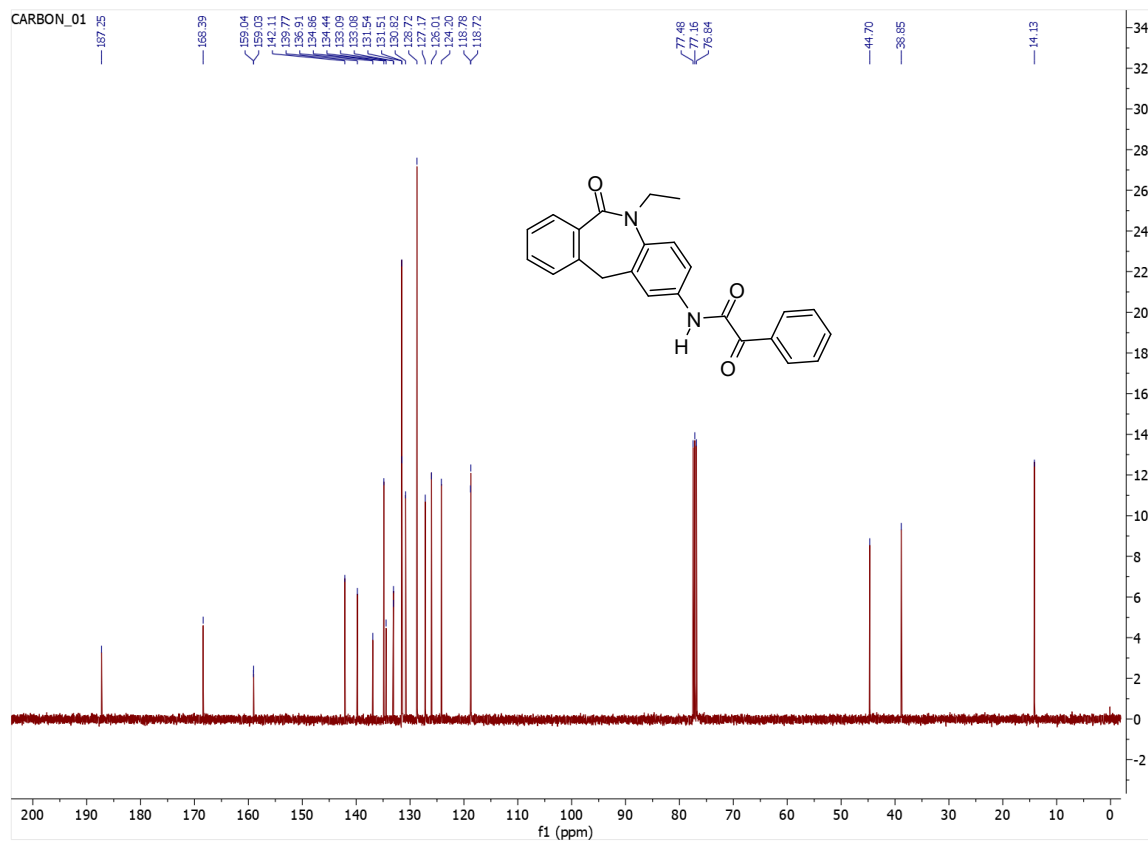
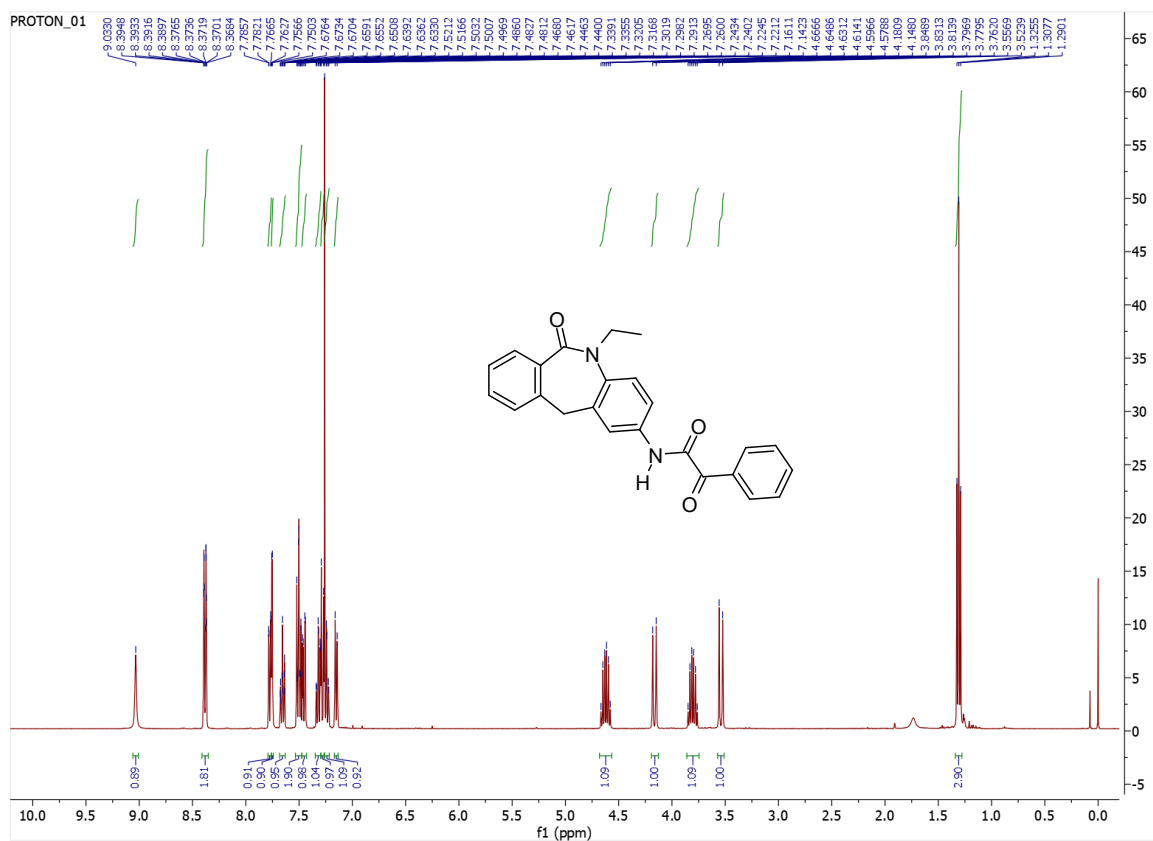


***N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)-2-oxo-2-phenylacetamide (**26**)**

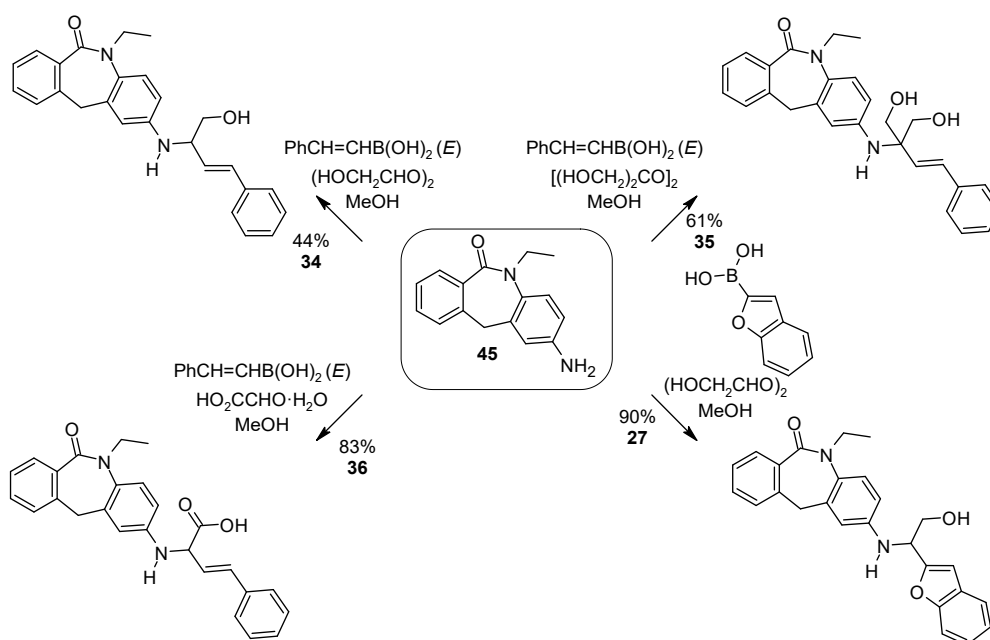


An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (75 mg, 0.30 mmol, 1 equiv), oxo(phenyl)acetic acid (67 mg, 0.45 mmol, 1.5 equiv) and anhydrous DCM (5 mL). The suspension was cooled down to -15 °C and DMAP (5 mg, 0.04 mmol, 15 mol%), EDC·HCl (86 mg, 0.45 mmol, 1.5 equiv) and Et₃N (dropwise, 0.14 mL, 0.98 mmol, 3.3 equiv) were added. The reaction was allowed to warm slowly to rt, stirred for 24 h and evaporated. The crude was filtrated through a plug of silica using MeOH/DCM: 0-0.5% evaporated and subjected to column chromatography (C-18; using MeCN/H₂O: 35-55%). The product **26** was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (3 times), to obtain 67 mg (59%) of yellow solid.

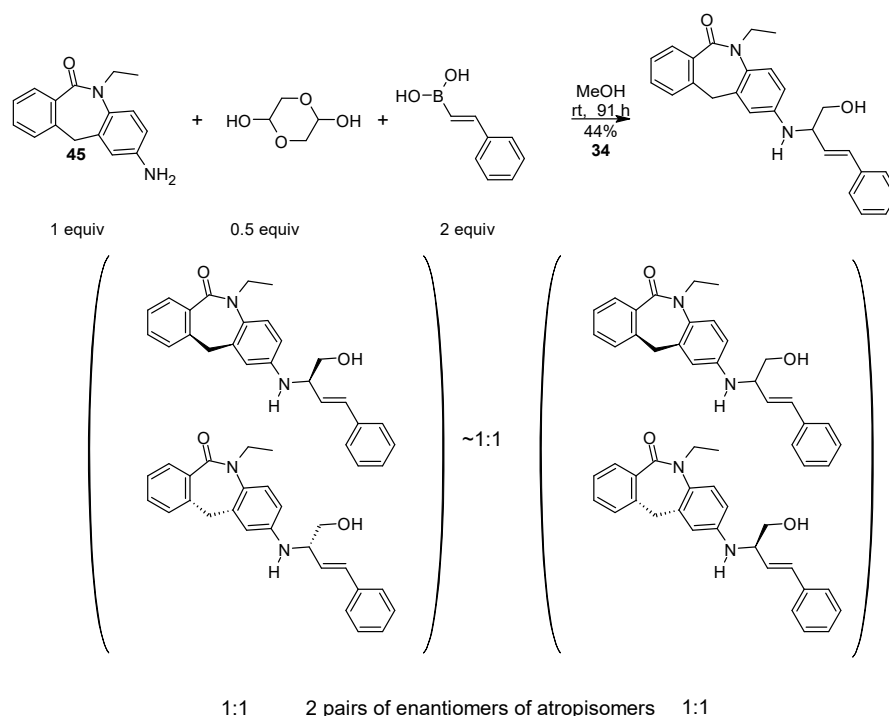
¹H NMR (400 MHz, CDCl₃) δ 9.03 (br s, 1H, NH), 8.40-8.36 (m, 2H), 7.77 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.68-7.63 (m, 1H), 7.53-7.49 (m, 2H), 7.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.26-7.22 (m, 1H) overlapped by residual CHCl₃, 7.15 (d, *J* = 7.5 Hz, 1H), 4.68-4.57 (m, 1H, ½ CH₂CH₃), 4.16 (d, *J* = 13.2 Hz, 1H, ½ ArCH₂Ar'), 3.86-3.75 (m, 1H, ½ CH₂CH₃), 3.54 (d, *J* = 13.2 Hz, 1H, ½ ArCH₂Ar'), 1.31 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 187.3 (CO), 168.4 (CON), [159.0 (x 2), CON⁺], 142.1, 139.8, 136.9, 134.9, 134.4, 133.1, 133.1, 131.5 (x 2), 130.8, 128.7, 127.2, 126.0, 124.2, 118.8, 118.7, 44.7 (NCH₂), 38.8 (ArCH₂Ar'), 14.1 (CH₃). LR-MS (*m/z*): 385 [M+H]⁺, 791 [2M+Na]⁺.



Synthesis of 2-[(3*E*)-1-hydroxy-4-phenylbut-3-en-2-yl]amino}-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one derivatives 27, 34-36 using Petasis MCR.

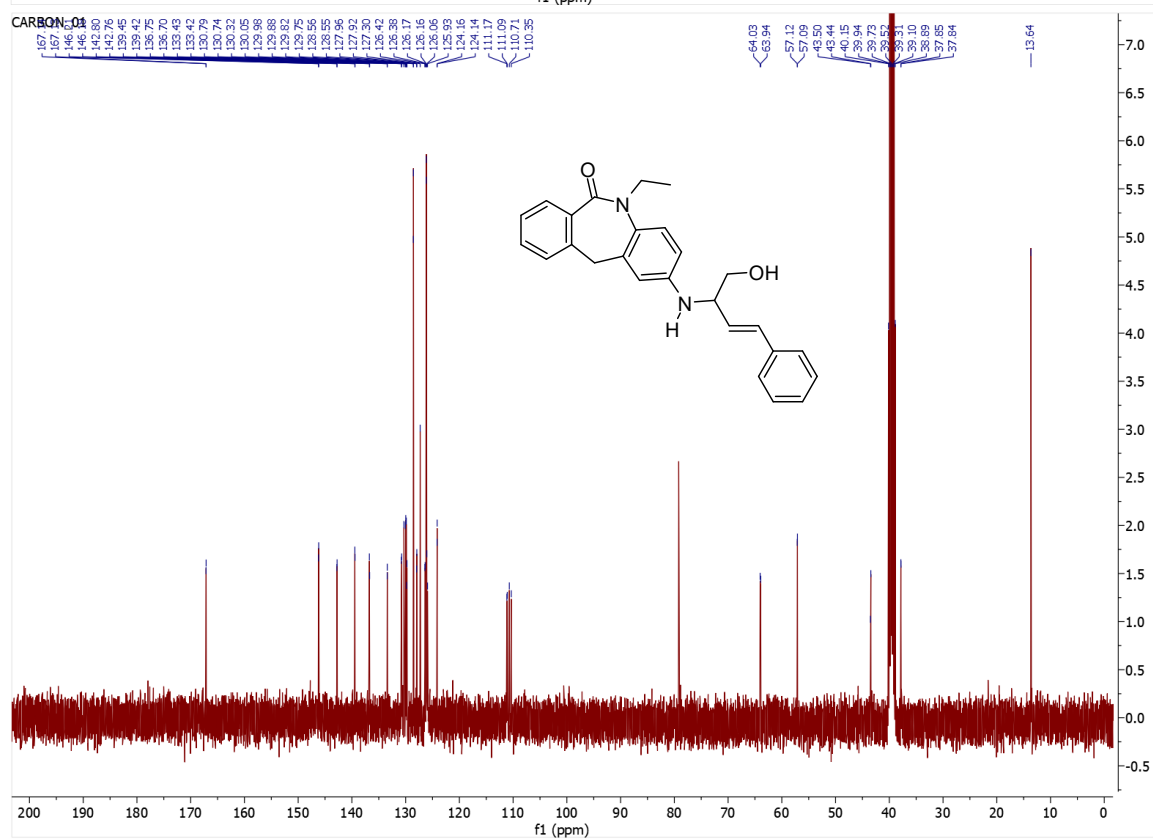
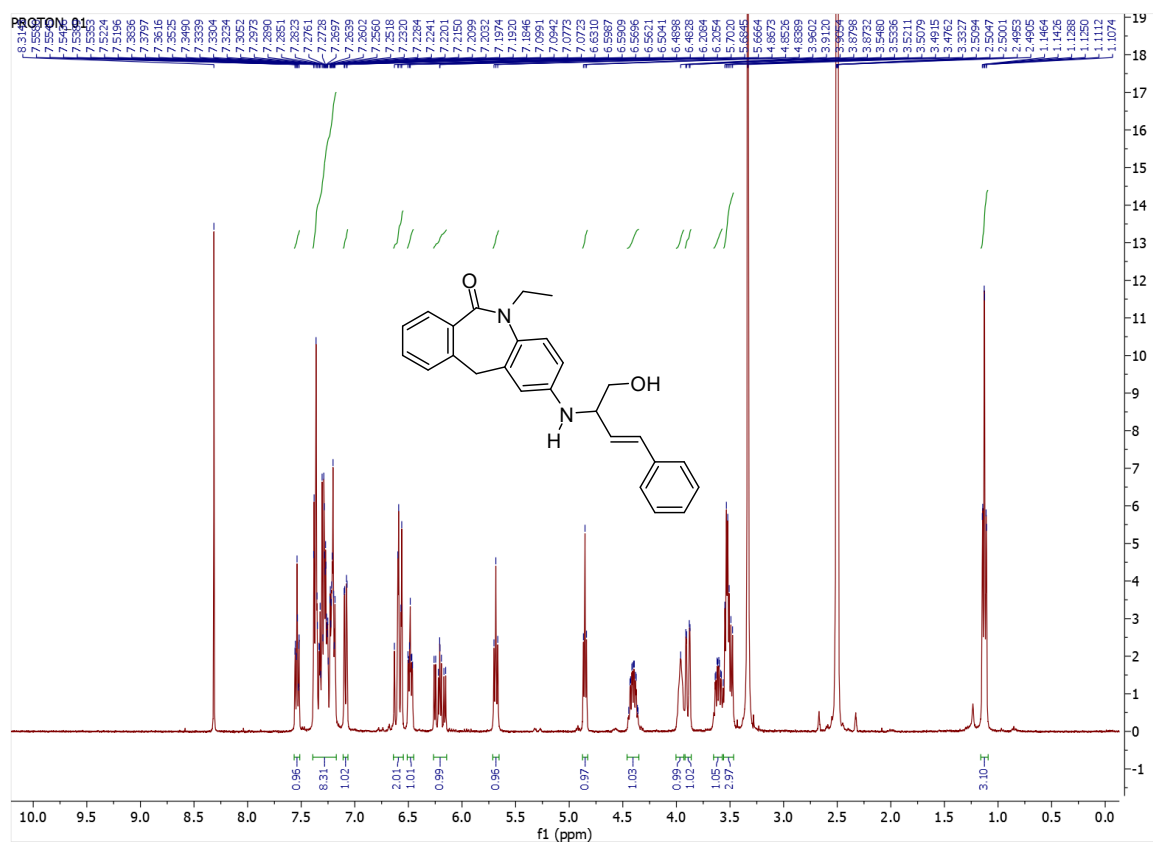


(*E*)-5-Ethyl-2-((1-hydroxy-4-phenylbut-3-en-2-yl)amino)-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (34)

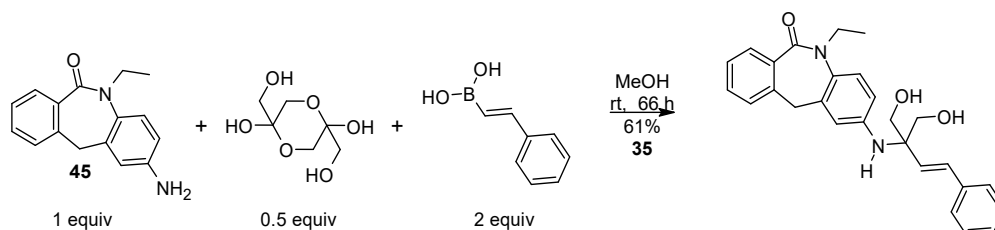


A screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (100 mg, 0.40 mmol, 1 equiv), *trans*-2-phenylvinylboronic acid (117, 0.79 mmol, 2 equiv), glycolaldehyde dimer (24 mg, 0.5 equiv) and MeOH (2 mL), and the resulting mixture was stirred at rt for 91 h. The volatiles were evaporated, and the crude was subjected to column chromatography (silica; using MeOH/DCM: 0-1%) and then reverse phase chromatography (C-18; using MeCN/H₂O: 10-40%), to obtain 67 mg (44%) of the target product **34** as a yellowish viscous solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56-7.51 (m, 1H), 7.40-7.17 (m, 8H), 7.11-7.06 (m, 1H), 6.64-6.65 (m, 2H), 6.51-6.45 (m, 1H), 6.27-6.14 (m, 1H, CH=CHCH), [5.69 (d, *J* = 7.0 Hz, 0.5H, NH) overlapping 5.68 (d, *J* = 7.3 Hz, 0.5H, NH)], 4.85 (t, *J* = 5.7 Hz, 1H, OH), 4.46-4.35 (m, 1H, ½ CH₂CH₃), 4.00-3.93 (m, 1H, CHCH₂), 3.92-3.86 (m, 1H, ½ ArCH₂Ar'), 3.66-3.56 (m, ½ CH₂CH₃) overlapped by 3.57-3.46 (m, 3H, ½ ArCH₂Ar', CH₂OH), 1.16-1.09 (m, 3H, CH₃); ¹³C NMR (100 MHz, DMSO- *d*₆) δ [167.1 (x 2); (CONH)], [146.2 (x 2)], [142.8 (x 2)], [139.5, 139.4], [136.7 (x 2)], [133.4 (x 2)], [130.8, 130.7], 130.3, [130.0 (x 2)], 129.9, [129.8 (x 2)] [128.6, 128.5], [128.0, 127.9], 127.3, [126.4 (x 2)], [126.2 (x 2)], [126.1, 125.9], [124.2, 124.1], [111.2, 111.1], [110.7, 110.3], [64.0, 63.9, (CH₂OH)], [57.1 (x 2); (NCH)], [43.5, 43.4; (NCH)], [37.8 (x 2); (ArCH₂Ar')], 13.6 (CH₃); (due to the presence of atropisomers almost every signal is doubled);. LR-MS (*m/z*): 253 [M-{PhCH=CHCHCH₂OH}+2H]⁺, 399 [M+H]⁺.

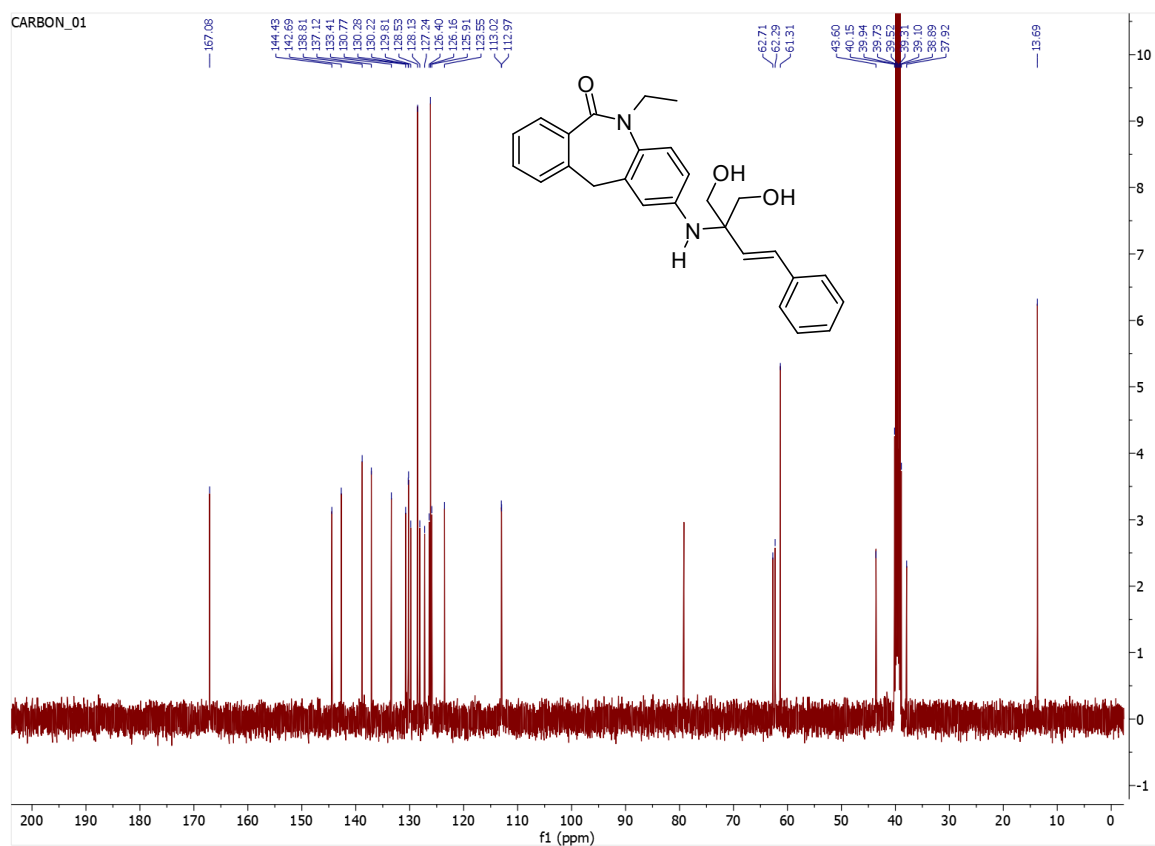
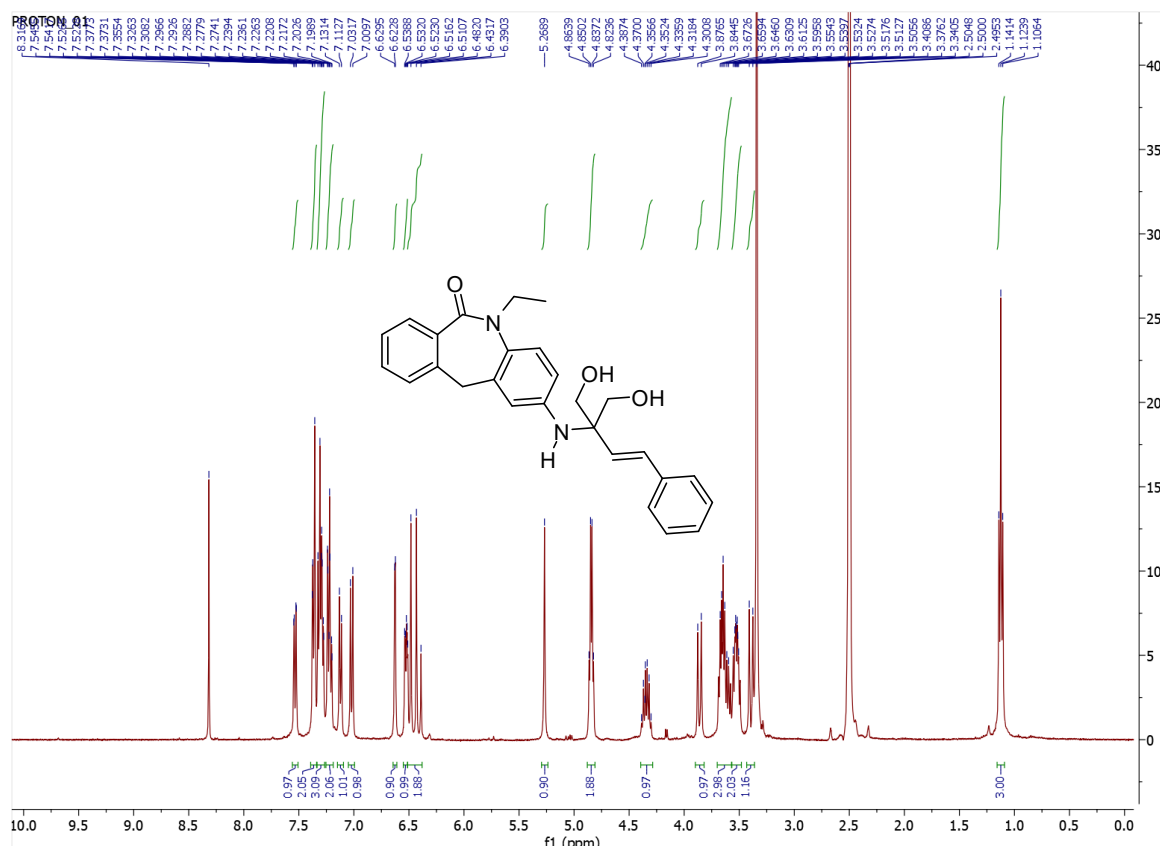


(*E*)-5-ethyl-2-((1-hydroxy-2-(hydroxymethyl)-4-phenylbut-3-en-2-yl)amino)-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (35)

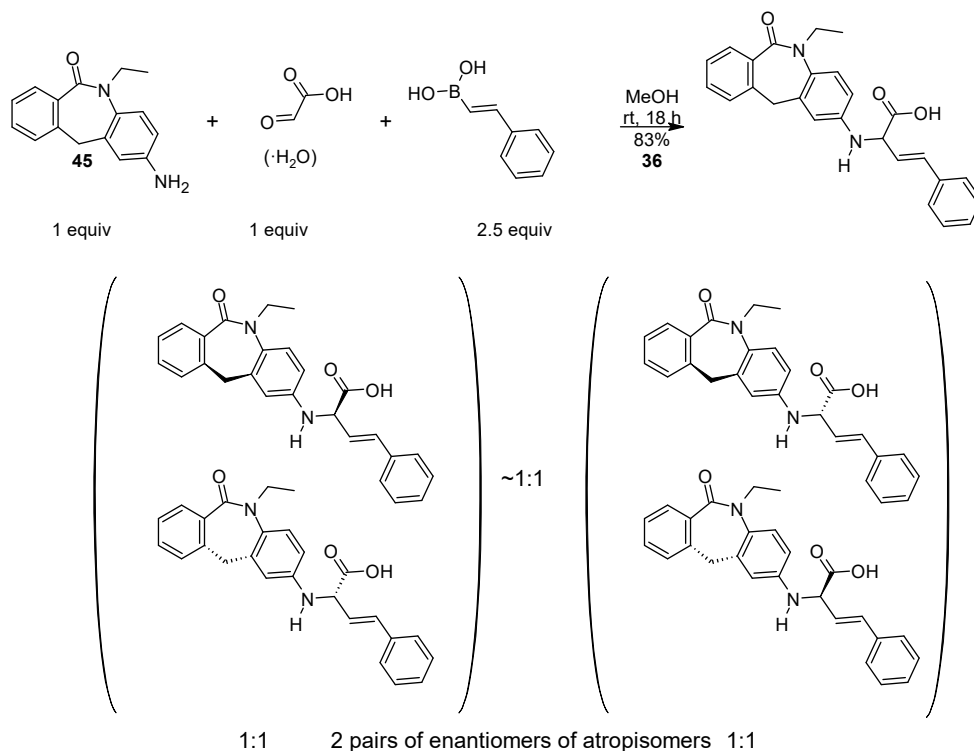


A round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (80 mg, 0.32 mmol, 1 equiv), *trans*-2-phenylvinylboronic acid (95 mg, 0.63 mmol, 2 equiv), 1,3-dihydroxyacetone dimer (29 mg, 0.16 mmol, 0.5 equiv) and MeOH (1.5 mL). The mixture was stirred at rt for 66 h. The volatiles were evaporated and the residue was subjected to column chromatography (silica; AcOEt/cyclohexane: 1:2 - 2:1). The compound was additionally triturated with Et₂O (3 x 1.5 mL) to obtain 82 mg (61%) of the target product **35** as a yellowish solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.5 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.39-7.34 (m, 2H), 7.33-7.27 (m, 3H), 7.25-7.19 (td, *J* = 7.4, 1.4 Hz, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.52 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.50 (d, *J* = 16.4 Hz, 1H, HC=CH_{trans}), 6.41 (*J* = 16.6 Hz, 1H HC=CH_{trans}), 5.27 (s, 1H, NH), 4.87-4.81 (m, 2H, 2 x OH), 4.40-4.29 (m, 1H, ½ CH₂CH₃), 3.86 (d, *J* = 12.8 Hz, 1H, ArCH₂Ar'), 3.70-3.57 (m, 3H, ½ CH₂CH₃, CH₂OH), 3.56-3.48 (2H, CH₂OH), 3.39 (d, *J* = 12.9 Hz, 1H, ½ ArCH₂Ar'), 1.12 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.1, 144.4, 142.7, 138.8, 137.1, 133.4, 130.8, 130.3, 130.2, 129.8, 128.5, 128.1, 127.2, 126.4, 126.2, 125.9, 123.6, 113.0 (x 2), 113.0, 62.7, 62.3, 61.3, 43.6 (CH₂CH₃), 37.9 (ArCH₂Ar'), 13.7 (CH₃); LR-MS (*m/z*): 253 [M - {PhCH=CHC(CH₂OH)₂} + 2H]⁺, 879 [2M + Na]⁺.

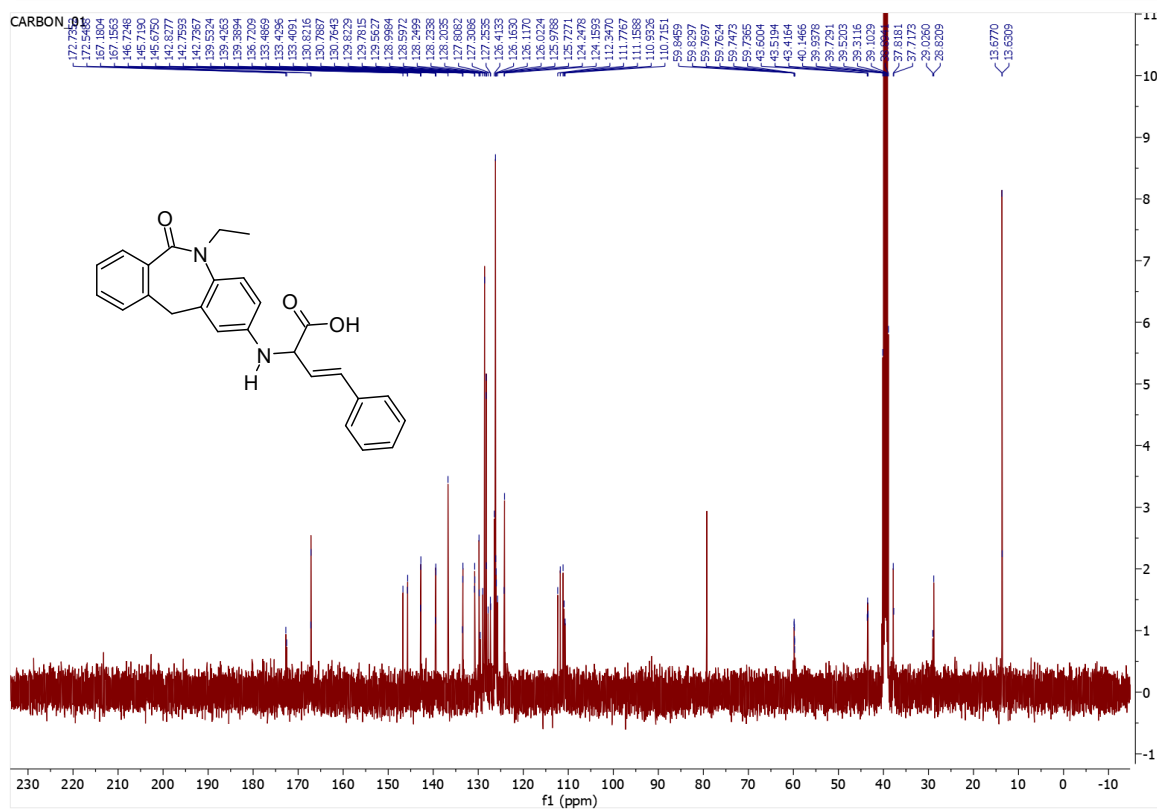
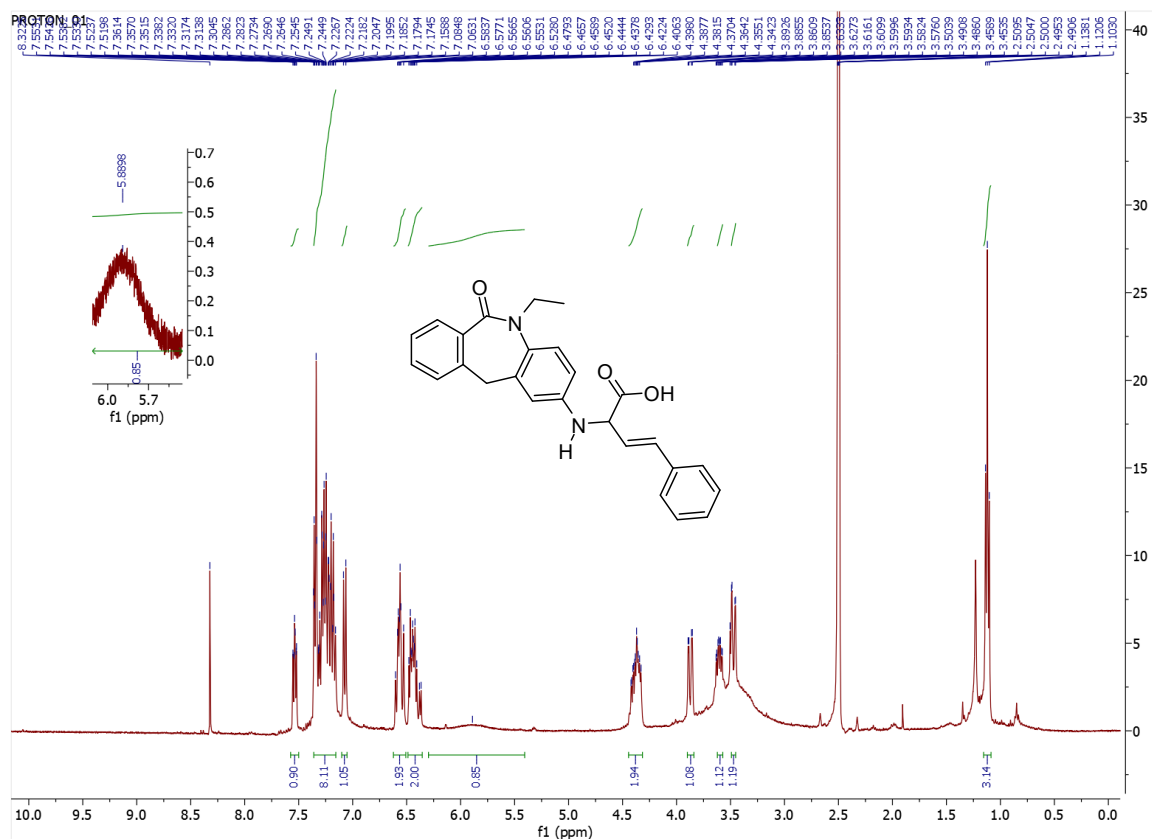


(*E*)-2-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-4-phenylbut-3-enoic acid
(36)

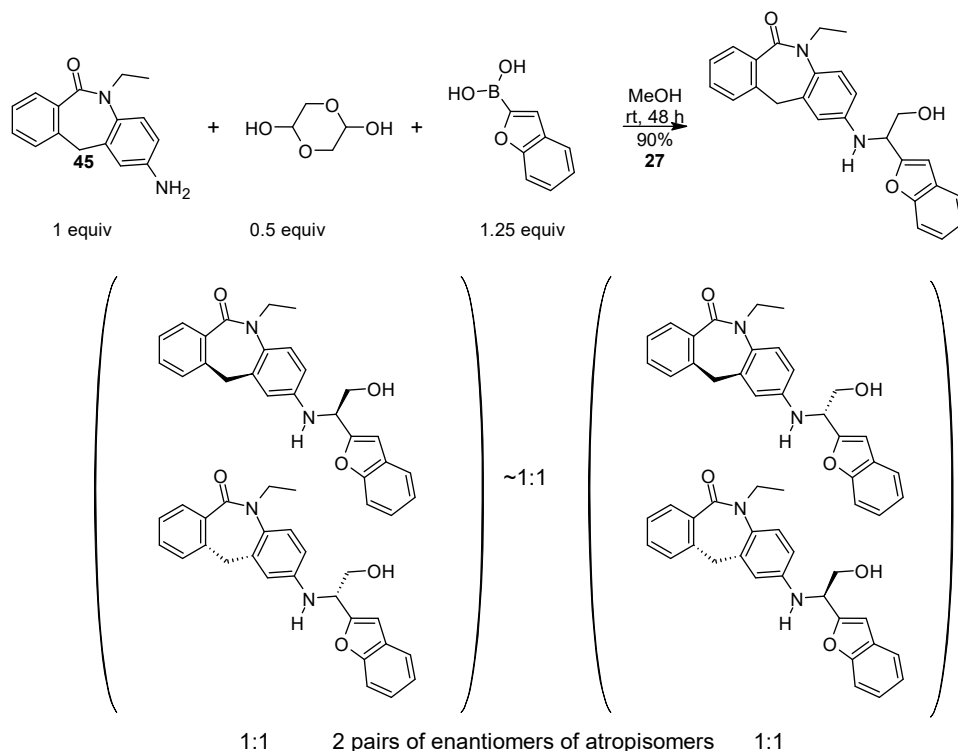


A round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (80 mg, 0.32 mmol, 1 equiv), *trans*-2-phenylvinylboronic acid (119 mg, 0.79 mmol, 2.5 equiv), glyoxalic acid monohydrate (29 mg, 0.32 mmol, 1 equiv) and MeOH (2 mL). The mixture was stirred at rt for 18 h, and the volatiles were evaporated. The crude was subjected to column chromatography (silica; using AcOEt/cyclohexane: 1:1, then MeOH/AcOEt (0-30%)) to obtain 108 mg (83%) of product **36** as a brownish solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56-7.51 (m, 1H), 7.37-7.15 (m, 8H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.61-6.51 (m, 2H), 6.49-6.38 (m, 2H), 5.89 (br s, 1H, NH), 4.45-4.31 (m, 2H, ½ CH₂CH₃, CHNH), [3.88 (d, *J* = 12.7, 0.5H, ½ ArCH₂Ar'), overlapping 3.87 (d, *J* = 12.7, 0.5H, ½ ArCH₂Ar')], 3.65-3.55 (m, 1H, ½ CH₂CH₃) overlapped by water from DMSO, 3.47 (d, *J* = 12.8 Hz, 0.5H, ½ ArCH₂Ar') overlapped 3.47 (d, *J* = 13.0 Hz, 0.5H, ½ ArCH₂Ar')] overlapped by water from DMSO, 1.12 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ [172.7, 172.5, (CO₂)], [167.2 (x 2), NCO], 146.7, [145.7, 145.7], [142.8 (x 2), 142.7], [139.5, 139.4 (x 2)], 136.7, [133.5, 133.4 (x 2)], [130.8 (x 3)], [129.8 (x 2)], 129.6, 129.0, 128.6, [128.2 (x 3)], 127.8, [127.3 (x 2)], 126.4, 126.2, 126.1, [126.0 (x 2)], 125.7, 124.2, 124.2, [112.3, 111.8], 111.2, [110.9, 110.7], [59.8 (x 4), 59.7 (x 2)], [43.6, 43.5, 43.4], [29.0, 28.8], [13.7, 13.6, (CH₃)]; multiplied signals are caused by the presence of atropisomers. 253 [M-{PhCH=CHCHCO₂H}+2H]⁺, 413 [M+H]⁺.

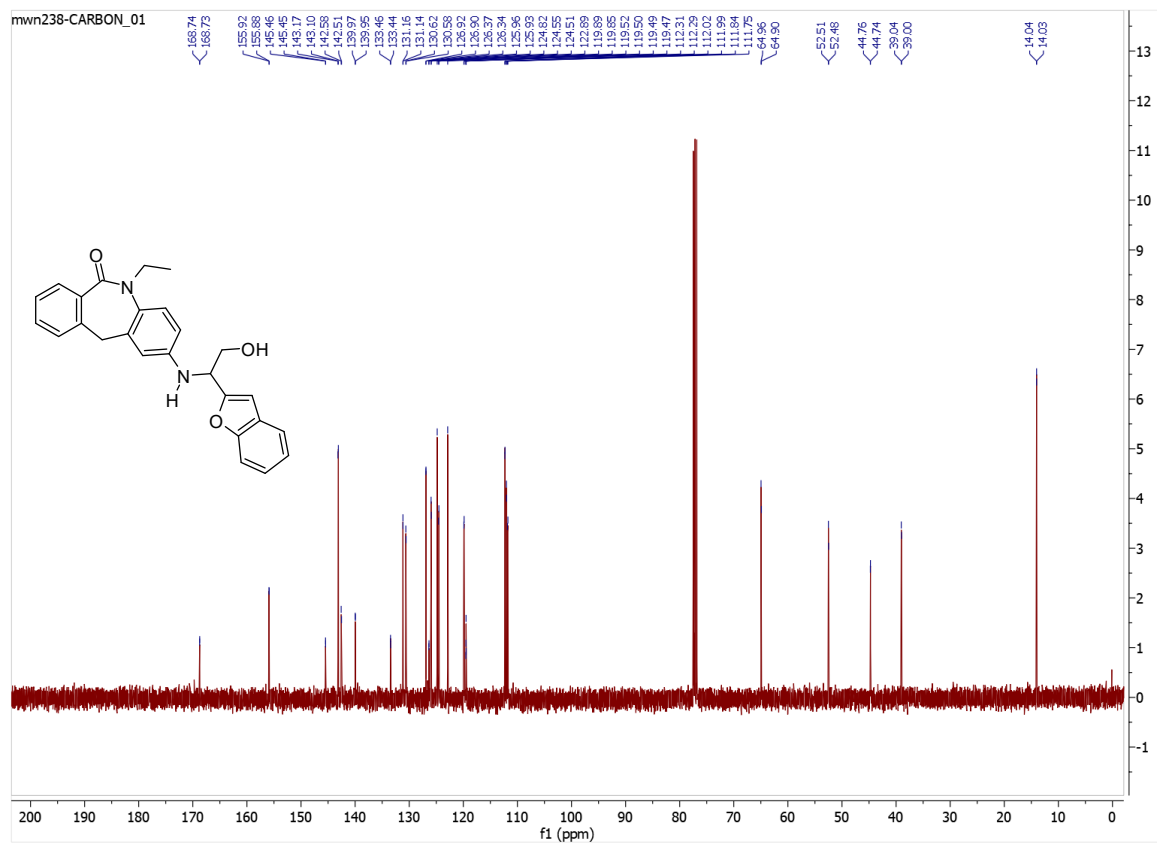
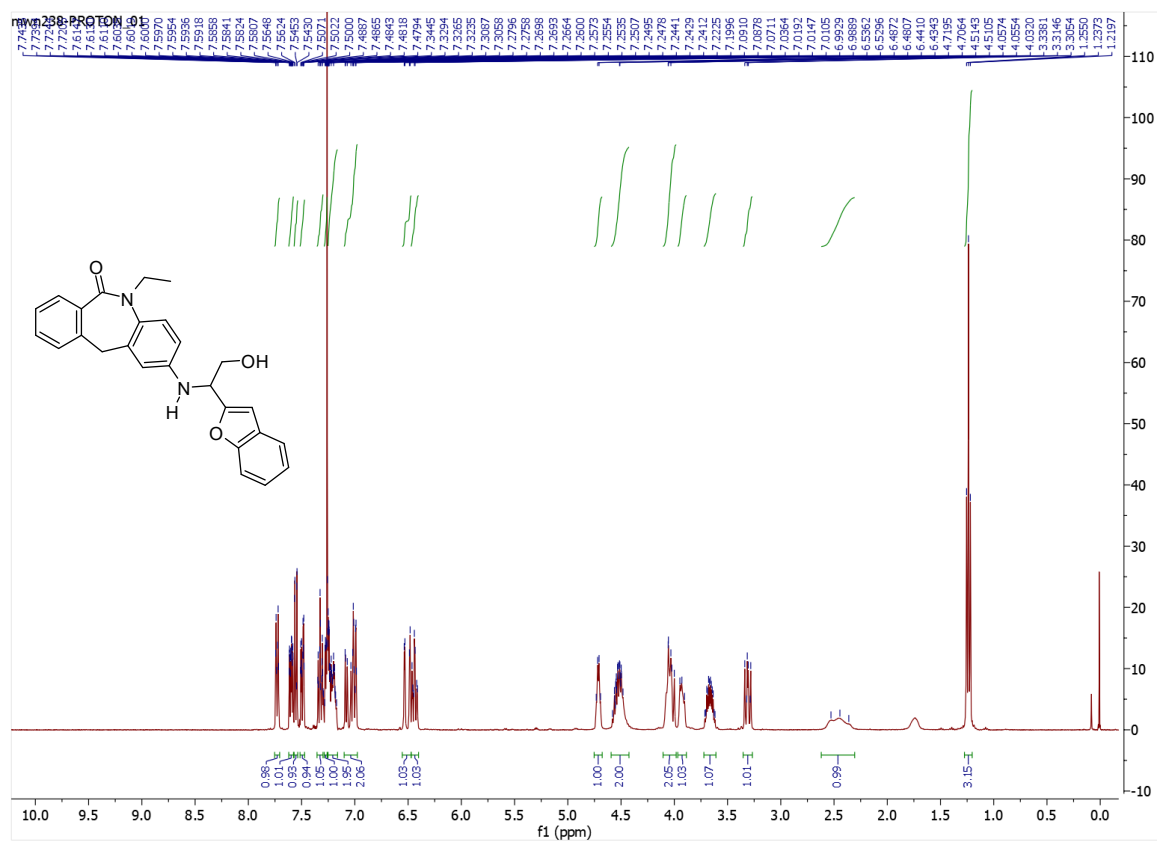


2-((1-(Benzofuran-2-yl)-2-hydroxyethyl)amino)-5-ethyl-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one (27)

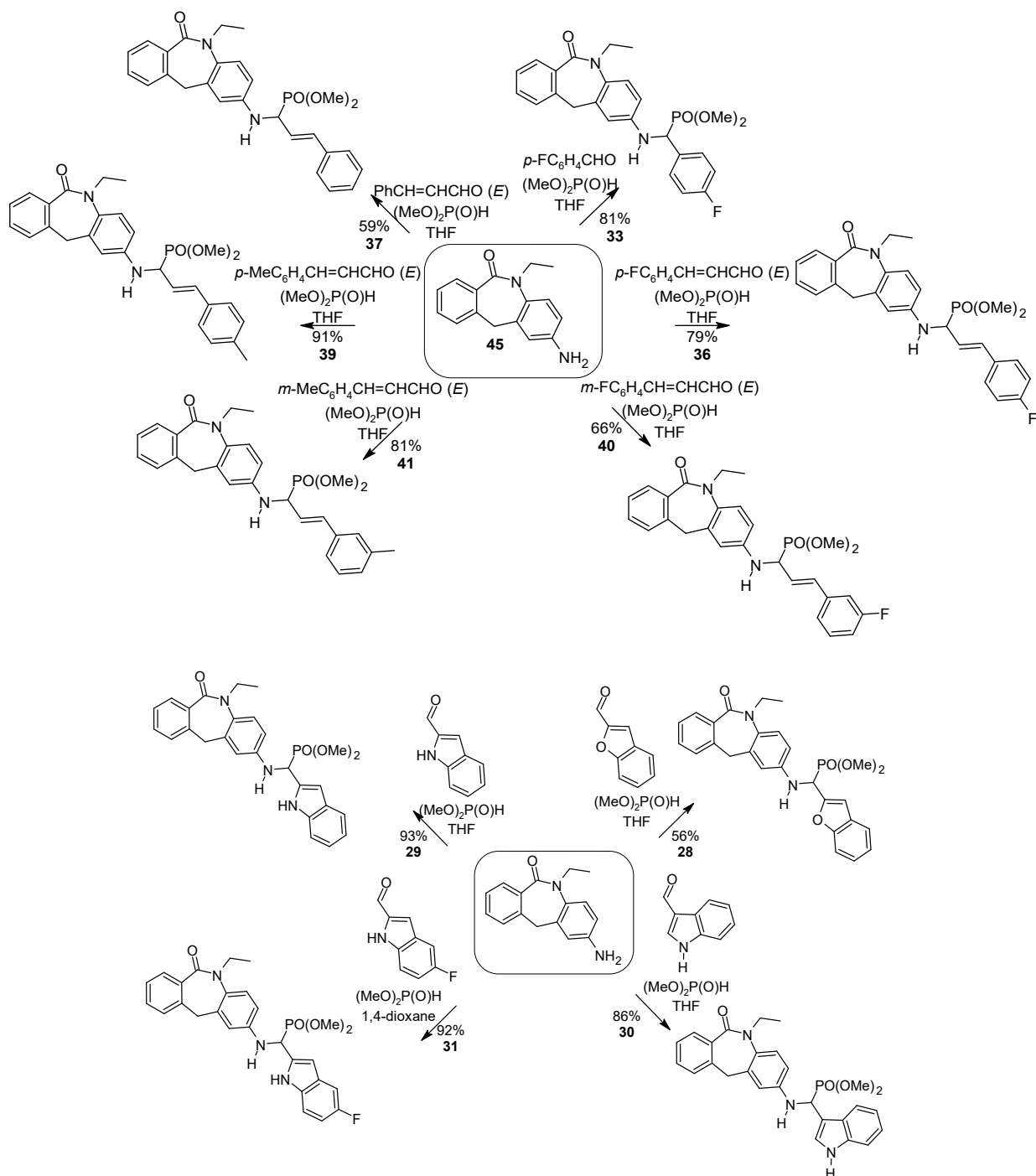


A screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6H-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.24 mmol, 1 equiv), benzo[*b*]furan-2-boronic acid (48 mg, 0.30 mmol, 1.25 equiv), glycolaldehyde dimer (14 mg, 0.12 mmol, 0.5 equiv) and MeOH (1 mL). The mixture was stirred at rt for 48 h and the volatiles were evaporated. The crude was subjected to reverse phase column chromatography (C-18; MeCN/H₂O: 30-50%). The product was precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times), to give 88 mg (90%) of product **27** as a yellowish foam.

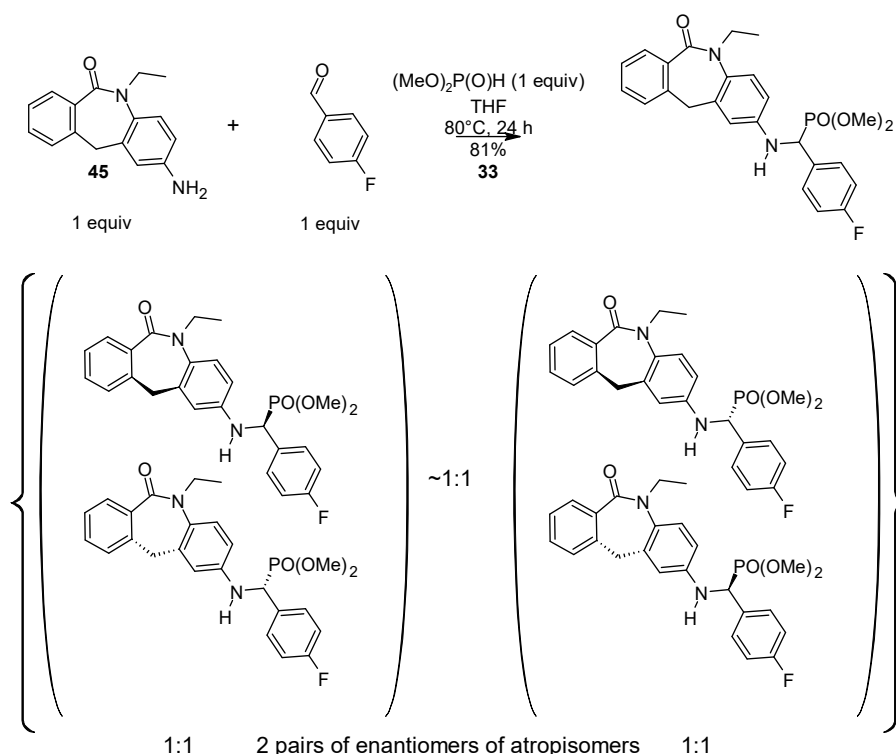
¹H NMR (400 MHz, CDCl₃) δ 7.75-7.71 (m, 1H), 7.62-7.58 (m, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.35-7.30 (m, 1H), 7.29-7.16 (m, 3H) overlapped with residual CDCl₃, 7.10-6.98 (m, 2H), 6.55-6.47 (m, 1H), 6.47-6.41 (m, 1H), 4.75-4.68 (m, 1H), 4.59-4.42 (m, 2H), 4.10-3.98 (m, 2H), 3.96-3.89 (m, 1H), 3.32 (d, *J* = 13.1 Hz, 0.5 H, ArCH₂Ar'), 3.30 (d, *J* = 13.1 Hz, 0.5 H, ArCH₂Ar'), 2.61-2.30 (m, 1H, OH), 1.24 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ [168.7 (x 2)], [155.9 (x 2)], [145.5, 145.4], [143.2, 143.1], [142.6, 142.5], [140.0 (x 2)], [133.5, 133.4], [131.2, 131.1], [130.6 (x 2)], [126.9 (x 2)], [126.4, 126.3], [126.0, 125.9], 124.8, [124.6, 124.5], 122.9, [119.9, 119.8], 119.5 (x 4), [112.3 (x 2)], [112.0, 112.0 (x 2)], [111.8 (x 2)], [65.0, 64.9, CH₂OH], [52.5 (x 2)], [44.8, 44.7], [39.0 (x 2), ArCH₂Ar'], [14.0 (x 2), CH₃]; (most of the signals are multiplied due to the presence of atropisomers). LR-MS (*m/z*): 413 [M+H]⁺.



Synthesis of 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one derivatives 28-31, 33, 36, 37, 39-41 using Kabachnik–Fields MCR.



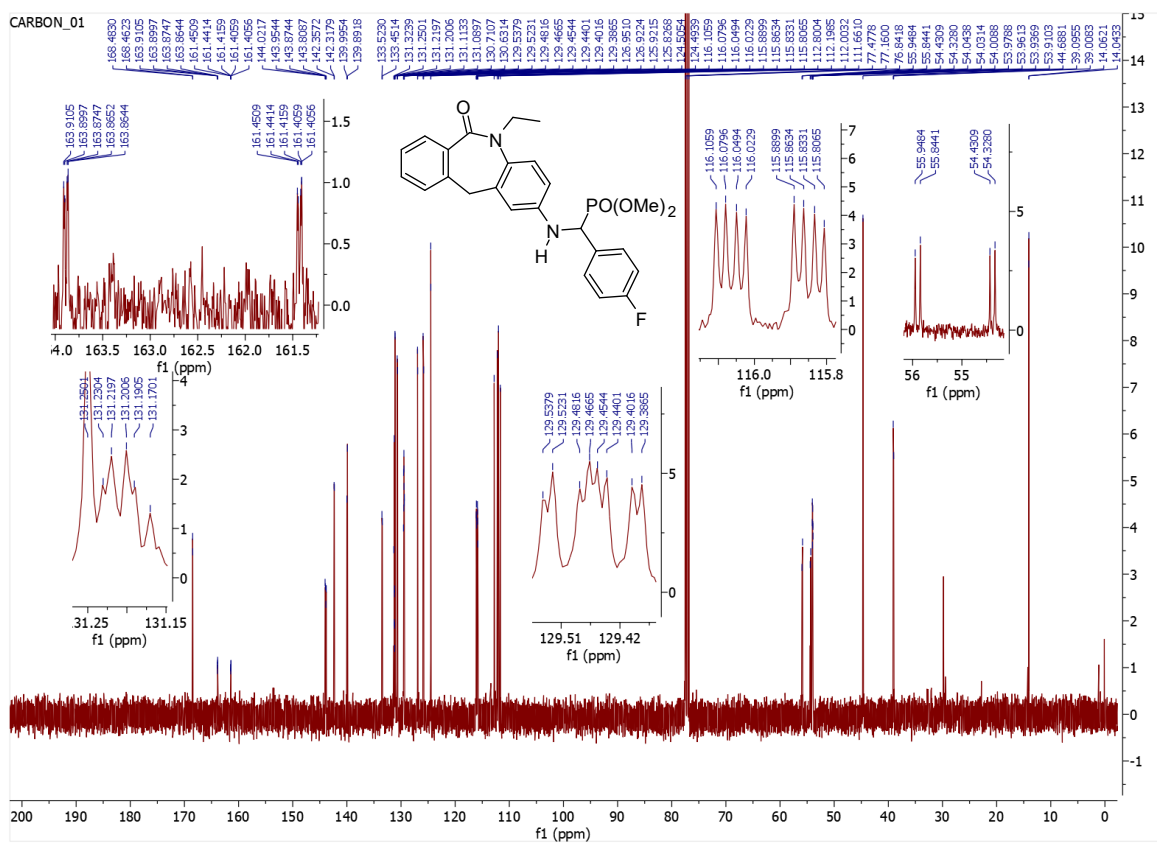
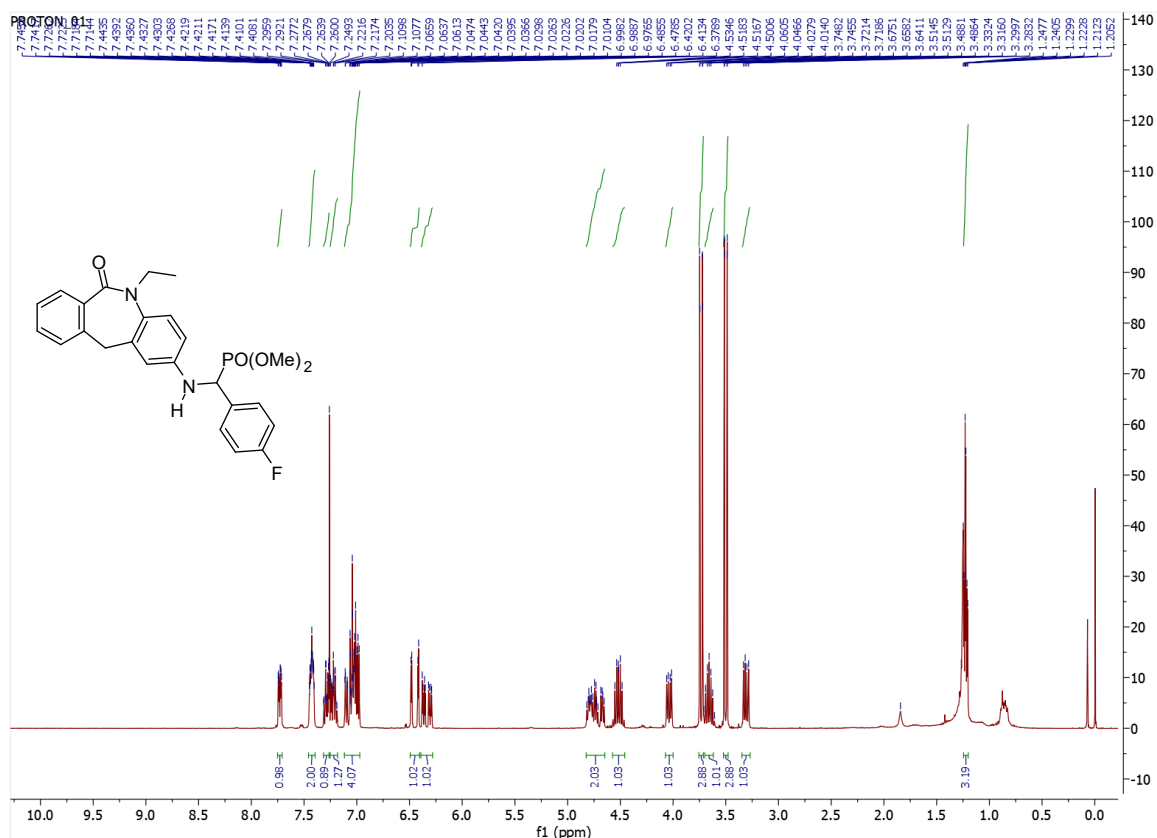
Dimethyl (((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)(4-fluorophenyl)methyl)phosphonate (33**)**

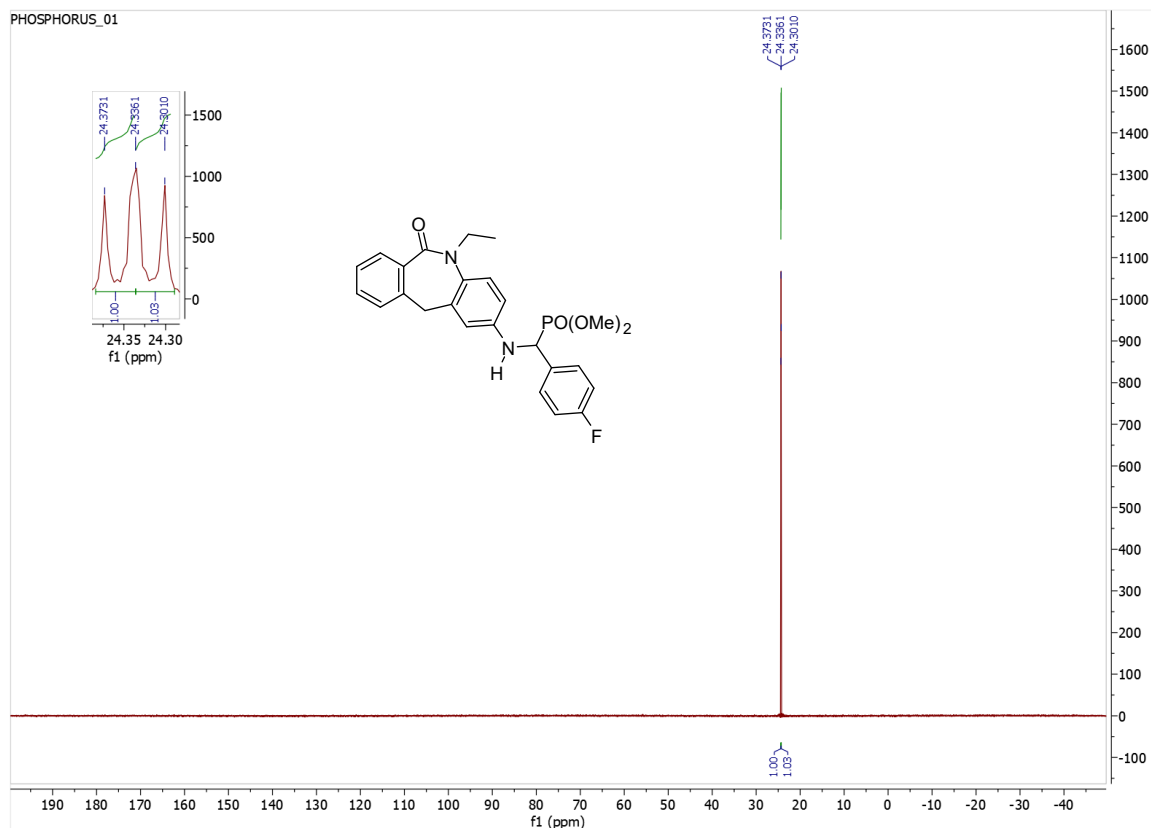
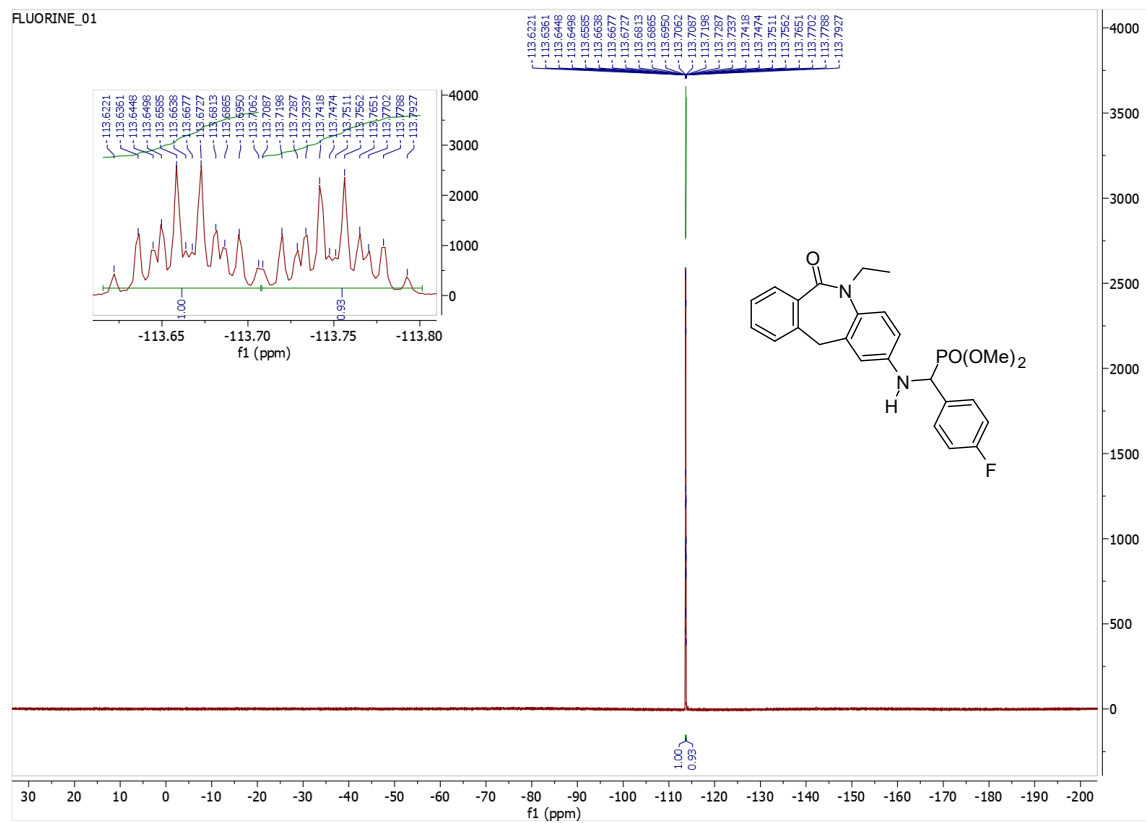


An oven-dried, screw-cap vial was charged with 4-fluorobenzaldehyde (37 mg, 0.30 mmol, 1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (75 mg, 0.30 mmol, 1 equiv), anhydrous THF (1 mL) and dimethylphosphite (27 μL , 0.30 mmol, 1 equiv). The resulting solution was stirred at 80°C for 24 h. The volatiles were evaporated, and the crude was subjected to column chromatography (silica; AcOEt/cyclohexane: 0-75%) to give 113 mg (81%) of product **33** as a yellowish solid.

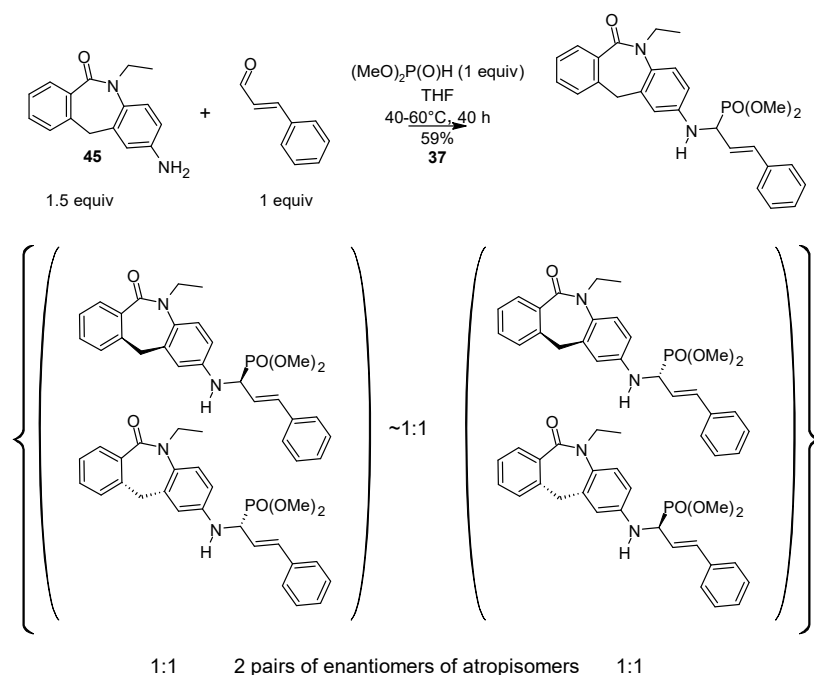
^1H NMR (400 MHz, CDCl_3) δ 7.75-7.71 (m, 1H), 7.45-7.39 (m, 2H), 7.32-7.18 (m, 2H) overlapping by residual CHCl_3 , 7.12-6.97 (m, 4H), 6.49-6.41 (m, 1H), 6.39-6.28 (m, 1H), 4.83-4.64 (m, 2H, NHCH , NHCHP), 4.58-4.46 (m, 1H, $1/2 \text{CH}_2\text{CH}_3$), [4.04 (d, $J = 13.0$ Hz, 0.5H, $\text{ArCH}_2\text{Ar}'$) overlapping 4.03 (d, $J = 13.0$ Hz, 0.5 H, $\text{ArCH}_2\text{Ar}'$)], [3.73 (d, $^3J_{\text{HP}} = 10.7$ Hz, 1.5H, OCH_3) overlapping 3.73 (d, $^3J_{\text{HP}} = 10.7$ Hz, 1.5H, OCH_3)], 3.70-3.60 (m, 1H, $1/2 \text{CH}_2\text{CH}_3$), 3.50 (d, $^3J_{\text{HP}} = 10.6$ Hz, 1.5H, OCH_3) overlapping 3.50 (d, $^3J_{\text{HP}} = 10.6$ Hz, 1.5H, OCH_3), [3.32 (d, $J = 13.1$ Hz, 0.5 H, $\text{ArCH}_2\text{Ar}'$) overlapping 3.30 (d, $J = 13.1$ Hz, 0.5 H, $\text{ArCH}_2\text{Ar}'$)], [1.23 (t, $J = 7.1$ Hz, 1.5 H, CH_2CH_3) overlapping 1.22 (t, $J = 7.1$ Hz, 1.5 H, CH_2CH_3)]; ^{13}C NMR (101 MHz, CDCl_3) δ [168.5 (x 2), (NCO)], [163.9 (x 4), 161.5, 161.4 (x 3), (CF)], [144.0 (x 2), 143.9, 143.8], [142.4, 142.3], [140.0, 139.9], [133.5 (x 2)], [131.3 (x 2)] overlapping [131.2 (x 3), 131.1, 131.1, (F-C=CH-CH=C-CH-P)], [130.7, 130.6], [129.5 (x 4), 129.4 (x 3), (F-C=CH-CH=C-CH-P)], [127.0, 126.9], [125.9, 125.8], [124.5 (x 2)], [116.1 (x 2), 116.0 (x 2), 115.9 (x 2), 115.8 (x 2), (F-C=CH)], 112.8, [112.2, 112.0], 111.7, [55.2 ($^1J_{\text{CP}} = 153.3$ Hz, CHP), 55.1 ($^1J_{\text{CP}} = 153.1$ Hz, CHP)], [54.0 (x 5), 53.9 (x 2) (2 x OCH_3)], 44.7 (NCH_2), [39.1, 39.0, ($\text{ArCH}_2\text{Ar}'$)], [14.1, 14.0, (CH_2CH_3)]; (almost all signals are multiplied due to the presence of atropisomers as well as CP and CF

couplings); ^{19}F NMR (376 MHz, CDCl_3) δ -113.7 (dt, $^6J_{\text{FP}} = 5.3$ Hz; $^3J_{\text{HF}} = 8.4$ Hz, $^4J_{\text{HF}} = 5.3$, $\sim 0.5\text{F}$), -113.7 (dt, $^6J_{\text{FP}} = 5.4$ Hz; $^3J_{\text{HF}} = 8.4$ Hz, $^4J_{\text{CF}} = 5.2$ Hz; $\sim 0.5\text{F}$); ^{31}P NMR (162 MHz, CDCl_3) δ 24.4 (d, $^6J_{\text{FP}} = \sim 6.0$ Hz) overlapping 24.3 (d, $^6J_{\text{FP}} = \sim 5.7$ Hz). LR-MS (m/z): 469 $[\text{M}+\text{H}]^+$.





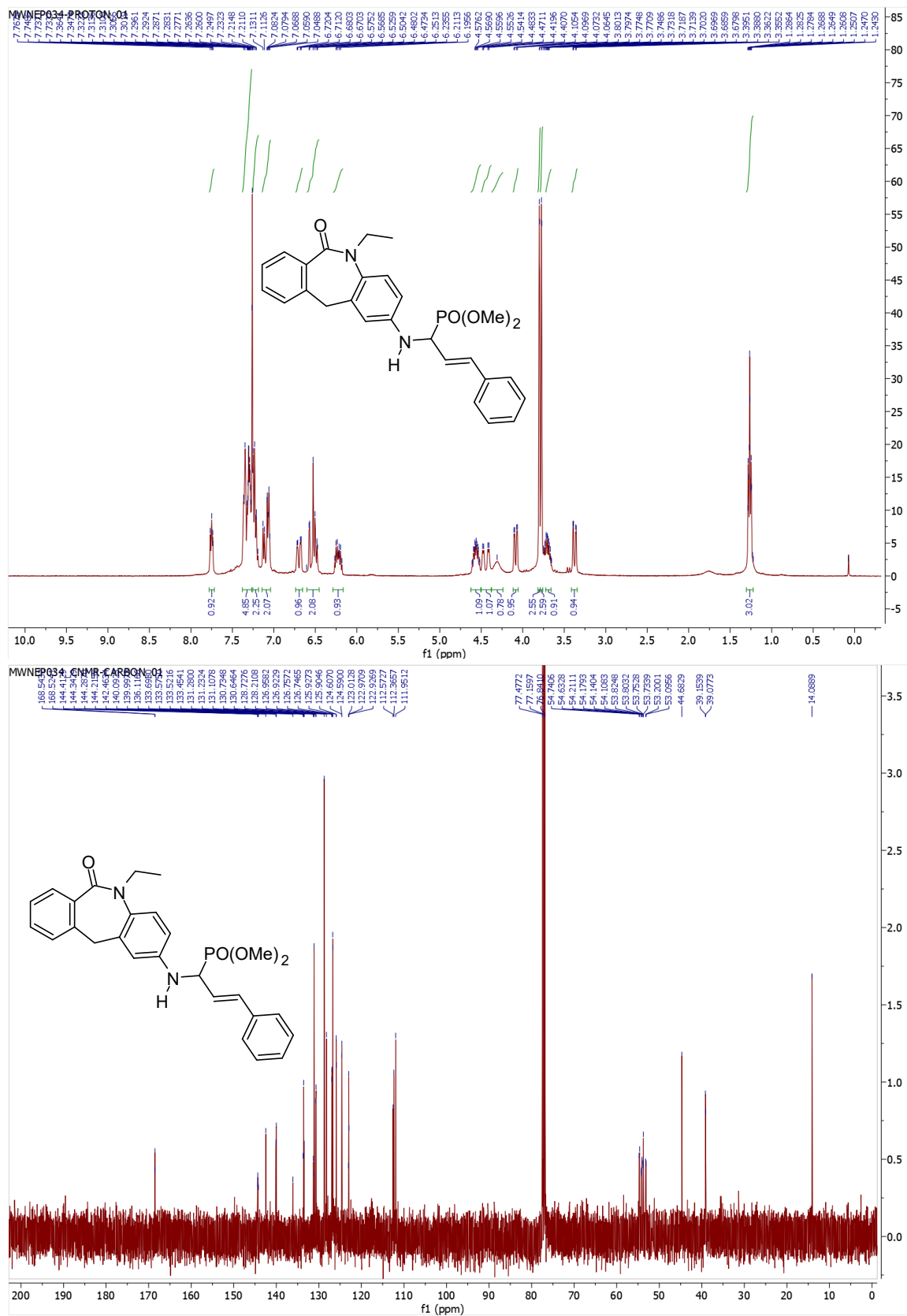
Dimethyl (*E*)-(1-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-phenylallyl)phosphonate (37**)**



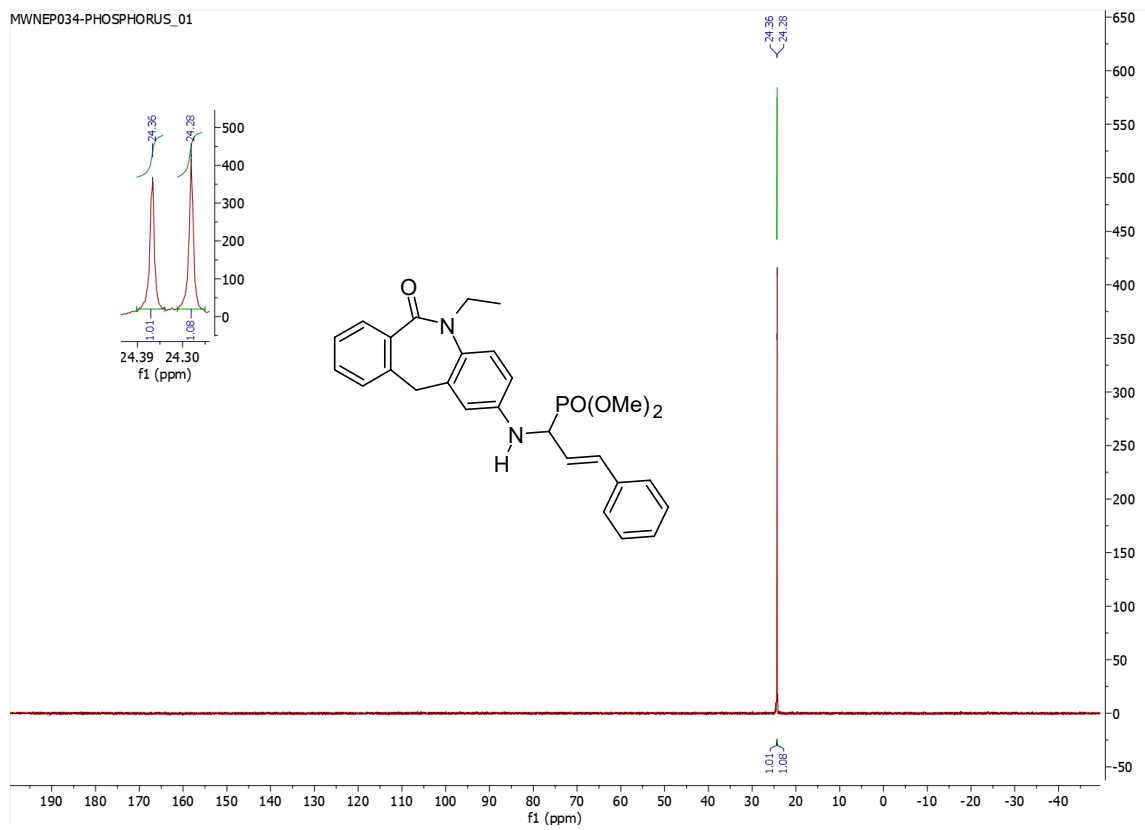
An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.24 mmol, 1.5 equiv), anhydrous THF (2 mL), *trans*-cinnamaldehyde (23 μ L, 0.16 mmol, 1 equiv) and dimethylphosphite (15 μ L, 0.16 mmol, 1 equiv). The reaction mixture was stirred at 40°C for 24 h, and then at 60°C for 16 h. The volatiles were evaporated and the residue was subjected to column chromatography (AcOEt/cyclohexane: 50-100%). The collected product was additionally precipitated as an oil from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times) to obtain 44 mg (59%) of the product **37** as an orange oil.

¹H NMR (400 MHz, CDCl₃) δ 7.78-7.72 (m, 1H), 7.38-7.18 (m, 7H) overlapped with residual CHCl₃, 7.14-7.04 (m, 2H), 6.74-6.65 (m, 1H), 6.60-6.45 (m, 2H), 6.29-6.16 (m, 1H), 4.63-4.51 (m, 1H, $\frac{1}{2}$ CH₂CH₃), [4.45 (d, ²J_{HP} = 25.5 Hz, 0.5H, *CHP*) overlapping 4.44 (d, ²J_{HP} = 25.6 Hz, 0.5H, *CHP*)], 4.31 (br s, 1H, NH), [4.09 (d, *J* = 12.9 Hz, 0.5H, $\frac{1}{2}$ ArCH₂Ar') overlapping 4.08 (d, *J* = 13.0 Hz, 0.5H, $\frac{1}{2}$ ArCH₂Ar')], [3.79 (d, ³J_{HP} = 10.6 Hz, 3H, OCH₃) overlapping 3.78 (d, ³J_{HP} = 10.6 Hz, 3H, OCH₃)], 3.72-3.66 (m, 1H, $\frac{1}{2}$ CH₂CH₃), [3.38 (d, *J* = 13.2 Hz, 0.5H, $\frac{1}{2}$ ArCH₂Ar') overlapping 3.37 (d, *J* = 13.1 Hz, 0.5H, $\frac{1}{2}$ ArCH₂Ar')], 1.30-1.22 (m, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [168.5 x2 (CO)], [144.4, (144.3 x 2) 144.2], 142.5, [140.1, 140.0], 136.1, 133.7, 133.6, 133.5, 133.5, [131.3, 131.2], 131.1, [130.7, 130.6], 128.7, 128.2, [127.0, 126.9], 126.8, 126.7, [125.9 x2], [124.6 x2], (123.0 x2), 122.9, 112.6, 112.4, 112.0, [54.7, 54.6 and 53.2, 53.1; C'HP] overlapping {(54.2 x 2), (54.1 x 2); POC'H₃}, [(53.8 x 3), 53.7; POCH₃], , 44.7 (NCH₂), [39.2, 39.1 (ArCH₂Ar)], 14.1 (CH₃); (the multiplied peaks

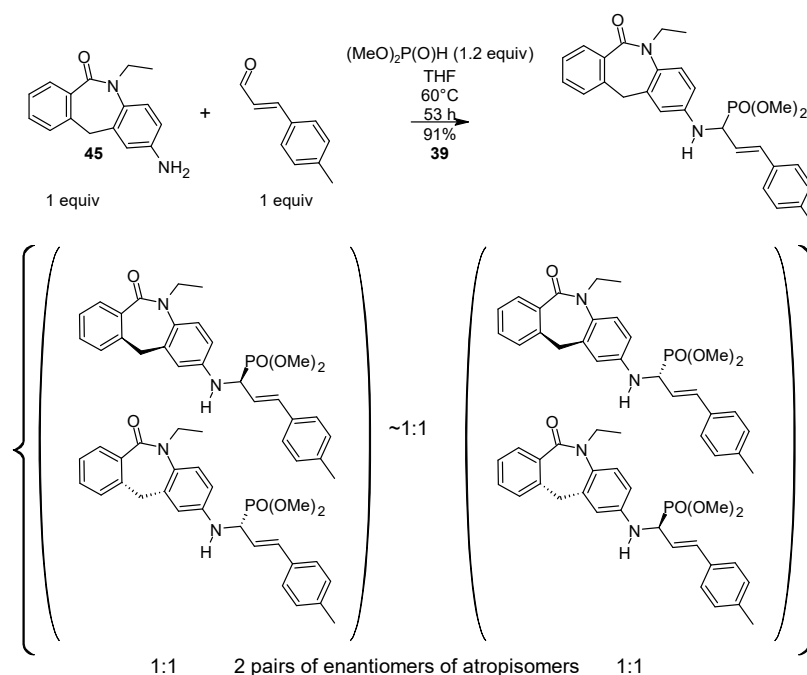
are due to the presence of atropisomers and C-P coupling); ^{31}P NMR (162 MHz, CDCl_3) δ 24.4, 24.3. LR-MS (m/z): 477 $[\text{M}+\text{H}]^+$, 499 $[\text{M}+\text{Na}]^+$, 975 $[2\text{M}+\text{Na}]^+$.



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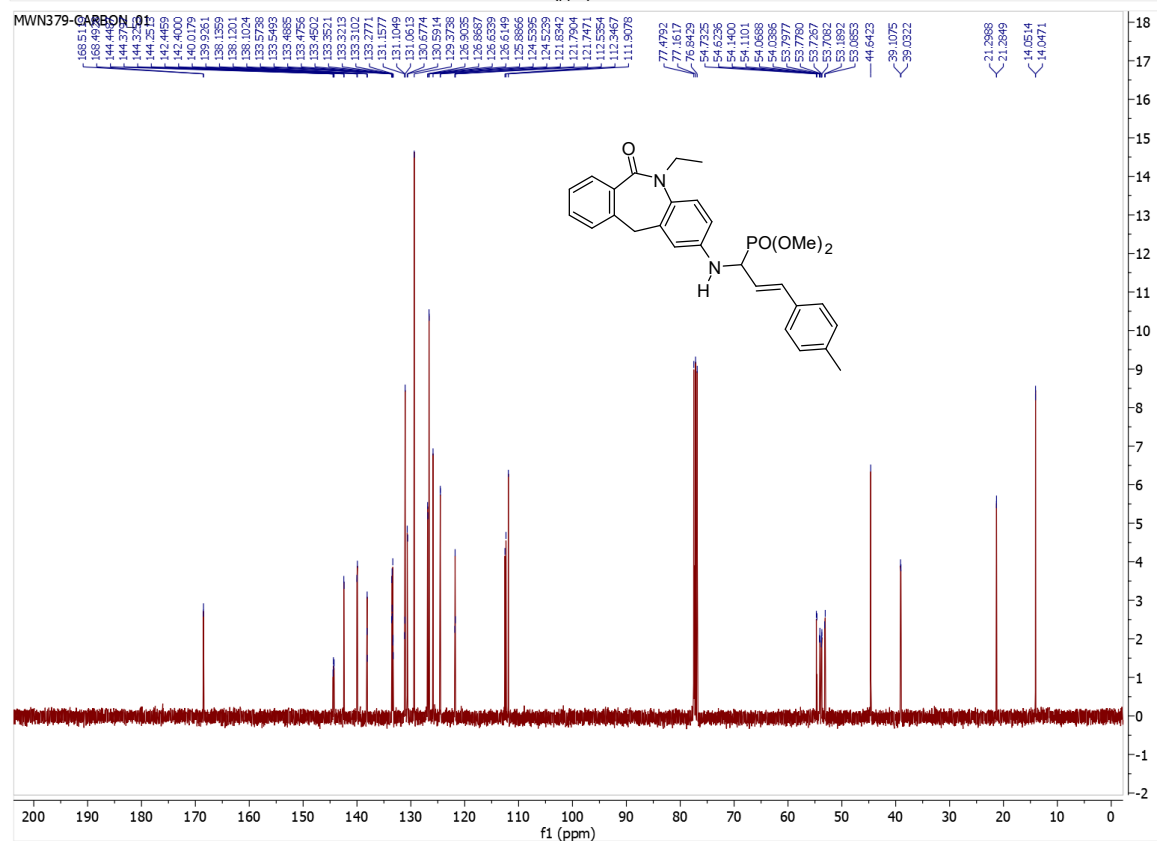
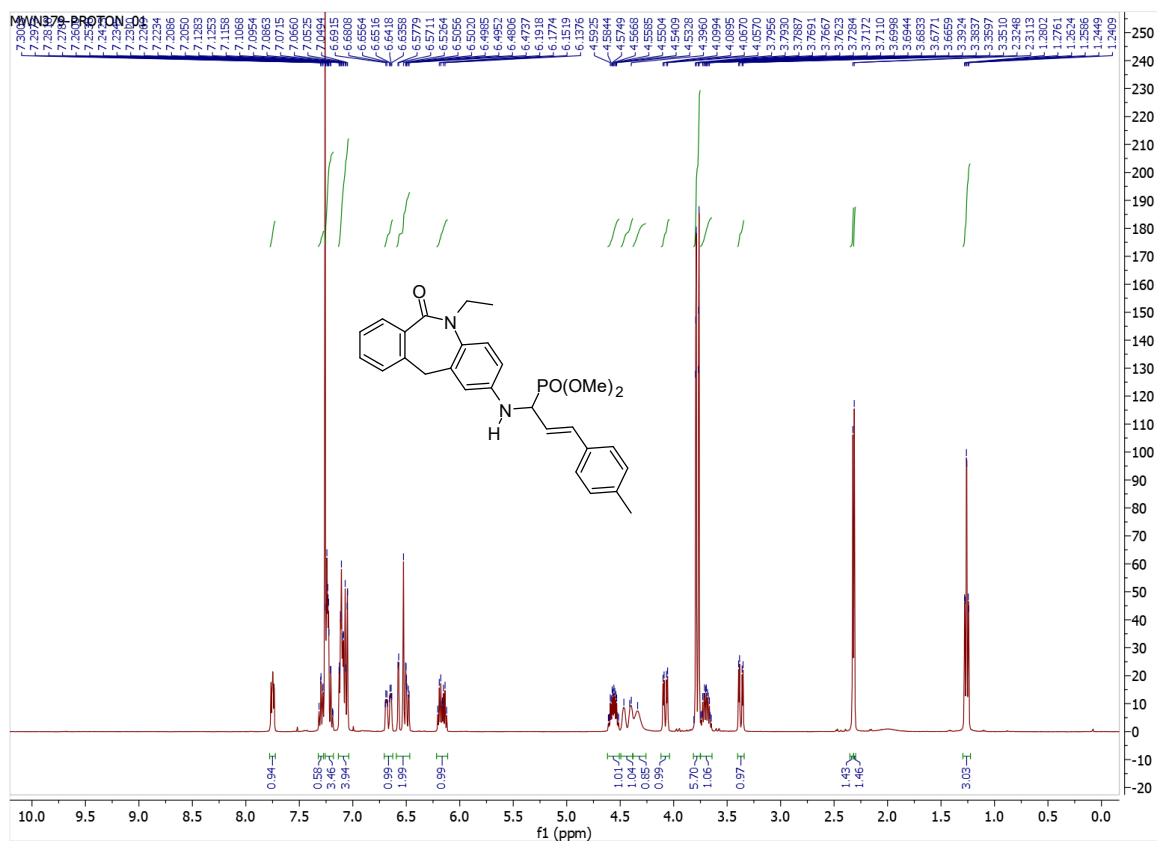


Dimethyl (*E*)-(1-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(*p*-tolyl)allyl)phosphonate (39**)**

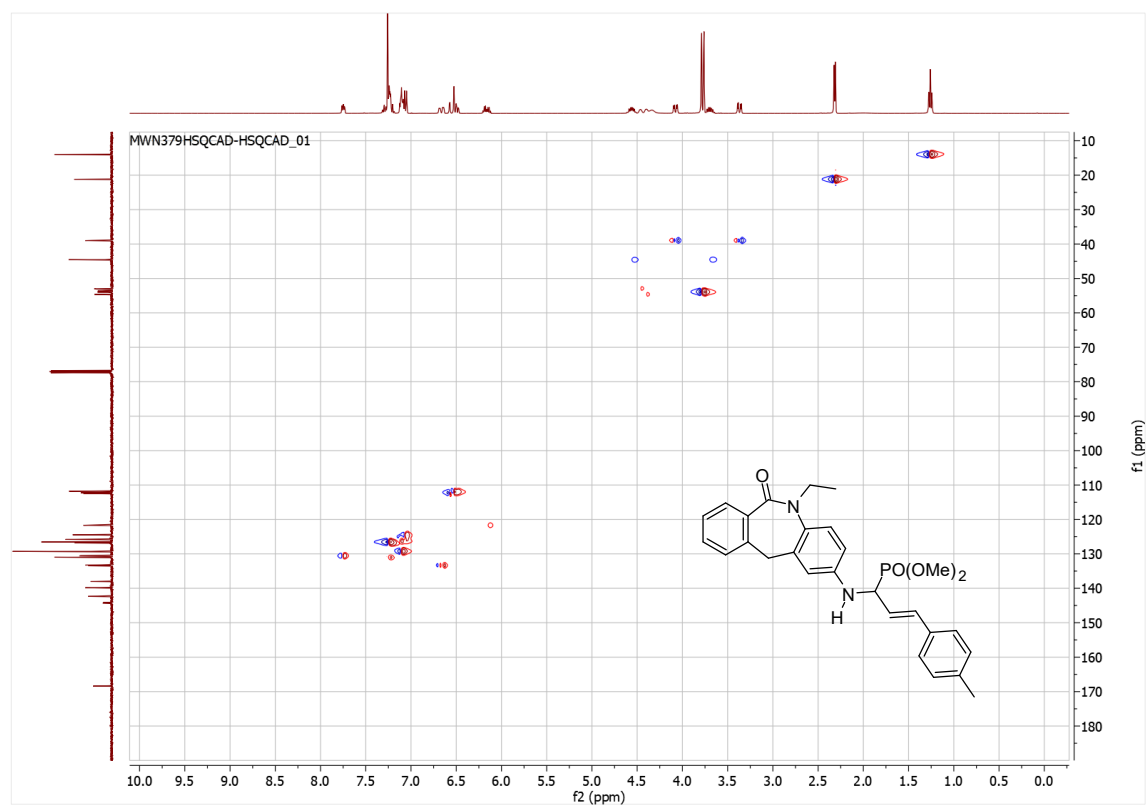
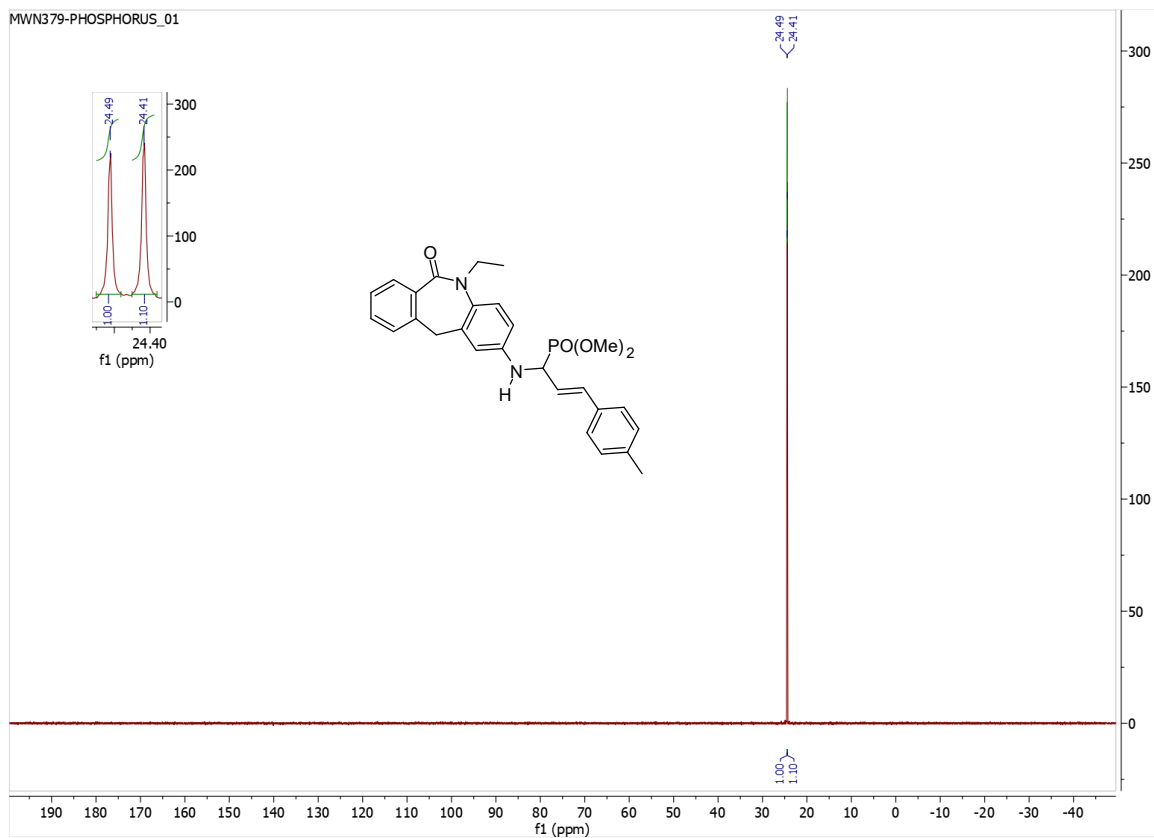


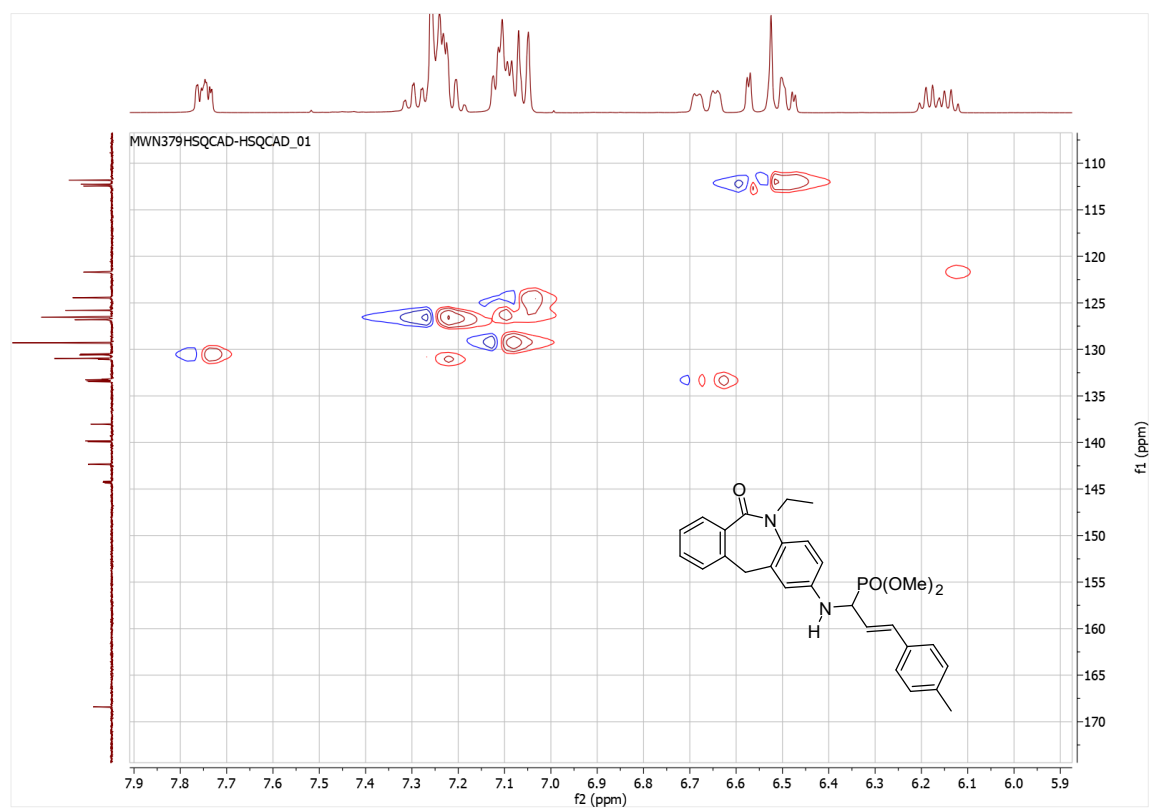
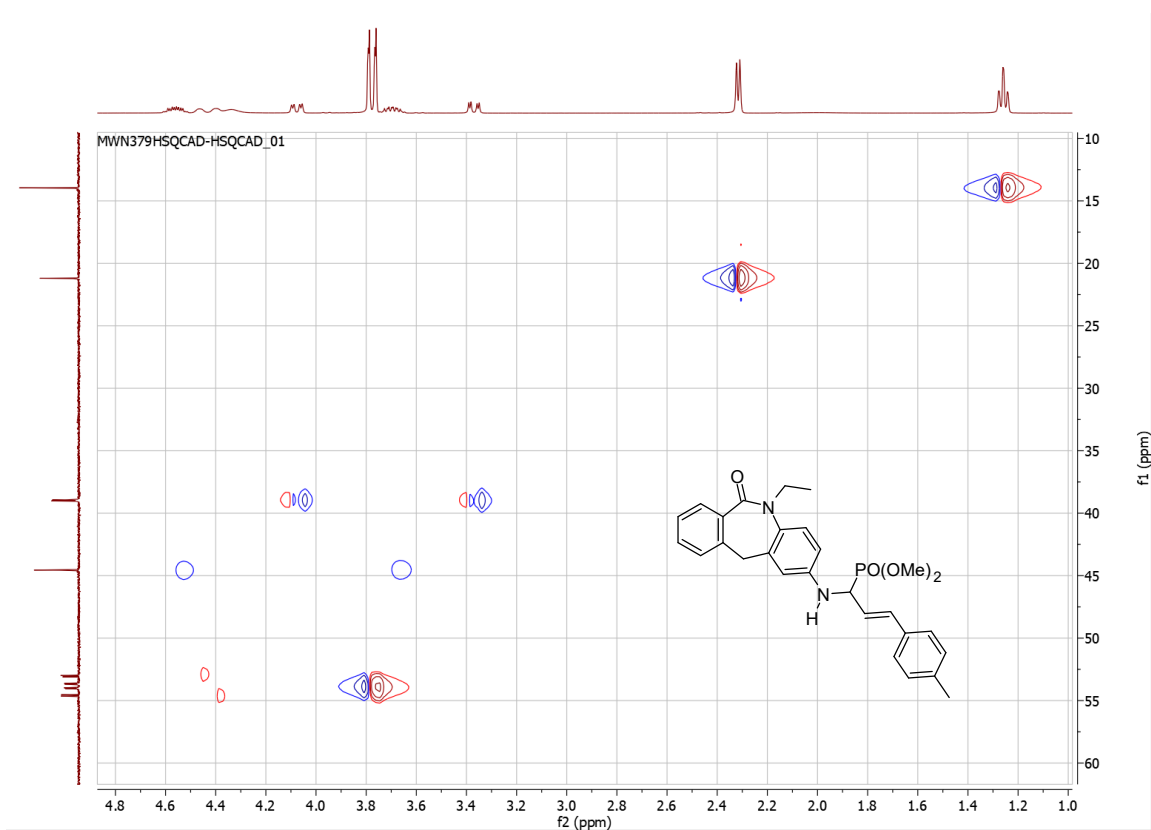
An oven-dried, screw-capped vial was charged with (*E*)-3-(*p*-tolyl)acrylaldehyde (29 mg, 0.20 mmol, 1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (50 mg, 0.20 mmol, 1 equiv), dimethylphosphite (20 μL mg, 0.22 mmol, 1.1 equiv) and anhydrous THF (1.5 mL). The solution was stirred at 60°C for 53 h. The volatiles were evaporated and the crude was subjected to reverse phase column chromatography (C-18; using MeCN/H₂O: 45%) to give 90 mg (92%) of product **39** as a yellowish viscous solid. The product was additionally precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times) to obtain yellowish foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78-7.72 (m, 1H), 7.29 (td, *J* = 7.4, 1.2 Hz, 0.5H), 7.26-7.18 (m, 3.5 H), 7.14-7.04 (m, 4H), 6.71-6.62 (m, 1H), 6.59-6.46 (m, 2H), 6.22-6.11 (m, 1H), 4.62-4.50 (m, 1H, 1/2 CH₂CH₃), 4.50-4.37 (m, 1H), 4.34 (br s, 1H, NH), 4.08 [d, *J* = 13.0 Hz, 0.5H, 1/2 (ArCH₂Ar')], overlapping 4.07 [d, *J* = 13.0 Hz, 0.5H, 1/2 (ArCH₂Ar')], 3.81-3.75 (m, 6H, 2 x OCH₃), 3.74-3.64 (m, 1H, 1/2 CH₂CH₃), 3.38 (d, *J* = 13.1 Hz, 0.5 H, 1/2 (ArCH₂Ar')], 3.37 [d, *J* = 13.1 Hz, 0.5H, 1/2 (ArCH₂Ar')], 2.32 [s, 1.5H, (ArCH₃)] overlapping 2.31 [s, 1.5H, (ArCH₃)], 1.26 [t, *J* = 7.0 Hz, 1.5 H, (CH₃)] overlapping 1.26 [t, *J* = 7.1 Hz, 1.5 H, (CH₃)]; ¹³C NMR (101 MHz, CDCl₃) δ [168.5 (x 2), C=O], [144.4 (x 2), 144.3 (x 2)], [142.4 (x 2)], [140.0, 139.9], [138.1 (x 3)], 133.6, 133.5 (x 4), 133.4, 133.3 (x 2), [131.2, 131.1], 131.1, [130.7, 130.6], 129.4, [126.9 (x 2)], [126.6 (x 2)], 125.9, [124.5 (x 2)], [121.8 (x 2), 121.7], [112.5, 112.3], 111.9, [54.7, 54.6, 53.2, 53.1, (CHP)] overlapping [54.1 (x 3), 54.0, OCH₃] and [53.8 (x 2), 53.7 (x 2), OCH₃], 44.6 (CH₂CH₃), [39.1, 39.0, (ArCH₂Ar')], [21.3 (x 2), (ArCH₃)], [14.1, 14.0, (CH₃)] (multiplied peaks are due to the presence of atropisomers and C-P coupling); ³¹P NMR (162 MHz, CDCl₃) δ 24.5, 24.4. LR-MS (*m/z*): 491 [M+H]⁺, 513 [M+Na]⁺.

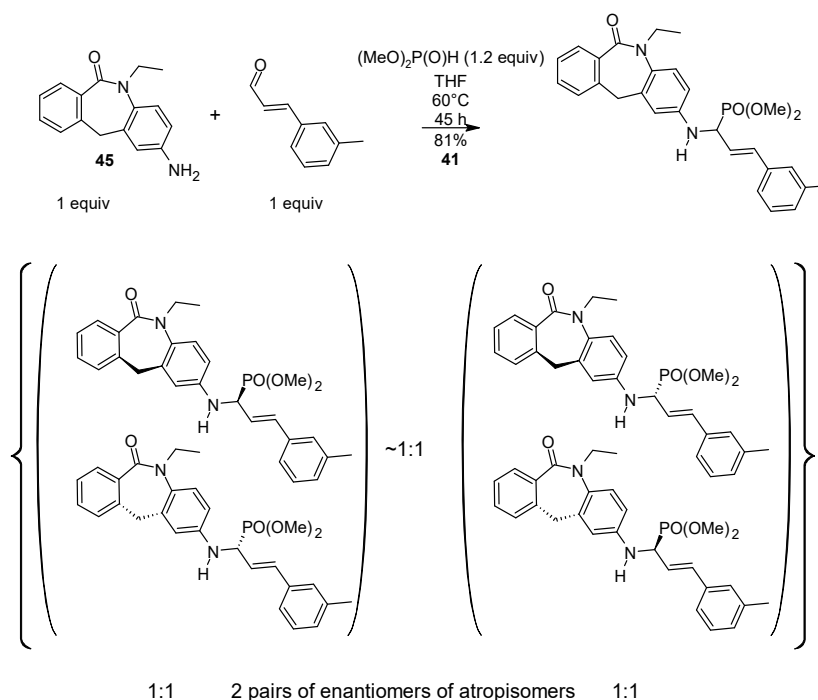


MWN379-PHOSPHORUS_01





Dimethyl (*E*)-(1-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(*m*-tolyl)allyl)phosphonate (41**)**



An oven-dried, screw-capped vial was charged with (*E*)-3-(*m*-tolyl)acrylaldehyde (29 mg, 0.20 mmol, 1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (50 mg, 0.20 mmol, 1 equiv), dimethylphosphite (20 μ L mg, 0.22 mmol, 1.1 equiv) and anhydrous THF (1.5 mL). The resulting solution was stirred at 60°C for 45 h. The volatiles were evaporated and the crude was subjected to reverse phase column chromatography (C-18; using MeCN/H₂O: 45-50%) to obtain 79 mg (81%) of product **41** as a yellowish viscous solid. The product was additionally precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times) to obtain yellowish foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78-7.73 (m, 1H), 7.30 (t, *J* = 7.2 Hz, 0.5H), 7.26-7.10 (m, 5H) overlapped by residual CHCl₃, 7.09-7.03 (m, 2.5H), 6.71-6.63 (m, 1H), 6.59-6.47 (m, 2 H), 6.26-6.16 (m, 1H), 4.62-4.51 (m, 0.5 + 0.5 H, 1/2 CH₂CH₃), 4.50-4.38 (m, 1H) overlapping 4.36 (br s, 1H, NH), {4.08 [(d, *J* = 12.9 Hz, 0.5H, 1/2 (ArCH₂Ar')] overlapping 4.08 [d, *J* = 12.9 Hz, 0.5 H 1/2 (ArCH₂Ar')]}, [3.79 (d, *J* = 10.6 Hz, 3H, OCH₃') overlapping 3.78 (d, *J* = 10.6 Hz, 3H, OCH₃)], 3.75-3.64 (m, 1H, 2 x 0.5 H, 1/2 CH₂CH₃), {3.38 (d, *J* = 13.2 Hz, 0.5 H, 1/2 (ArCH₂Ar')]}, 3.37 (d, *J* = 13.2 Hz, 0.5 H, 1/2 (ArCH₂Ar')]}, {2.32 (s, 1.5H, (ArCH₃')), 2.31 (s, 1.5H, (ArCH₃'))}, 1.26 (t, *J* = 6.9 Hz, 3H, CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [168.5, 168.5, (C=O)], [144.4, (144. x 2), 144.2], [142.4, 142.4], [140.0, 139.9], 138.3, [(136.0 x 3), 135.9], [133.8, 133.5] overlapping [133.6, 133.5], [(131.1 x 2)], 131.1, [130.7, 130.6], [129.0, 128.6], [127.4, 127.4, 127.3], [126.9 (x 2)], [125.9 (x 2)], [124.5 (x 2)], [123.9 (x 2)], [122.7, 122.6 (x 2)], [112.5, 112.3], 111.9, [54.2, 54.1 (x 3), (POCH₃)], 53.9 [d, *J* = 155.9 Hz, (CHP)], 53.8 (d, *J* = 155.3 Hz, (CHP))], [53.8 (x 2), 53.7 (x 2), (POCH₃)], 44.6 (CH₂CH₃), [39.1, 39.0,

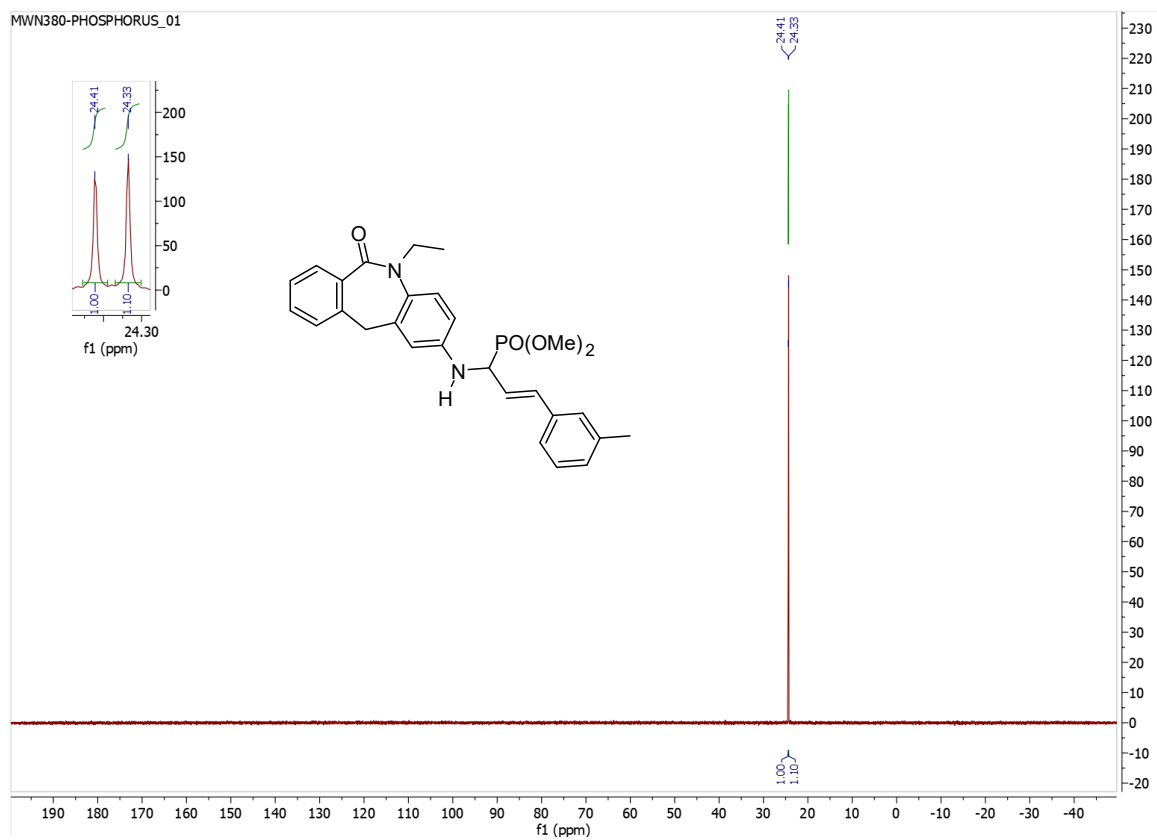
1H NMR (CDCl₃) spectrum of compound **10**. The chemical structure of **10** is shown above the spectrum.

The spectrum displays peaks in the aromatic region (7.0-7.8 ppm), a methine region (6.5-6.8 ppm), a methoxy region (3.7-3.8 ppm), and a methyl region (2.3-2.4 ppm). Integration values are provided below the peaks.

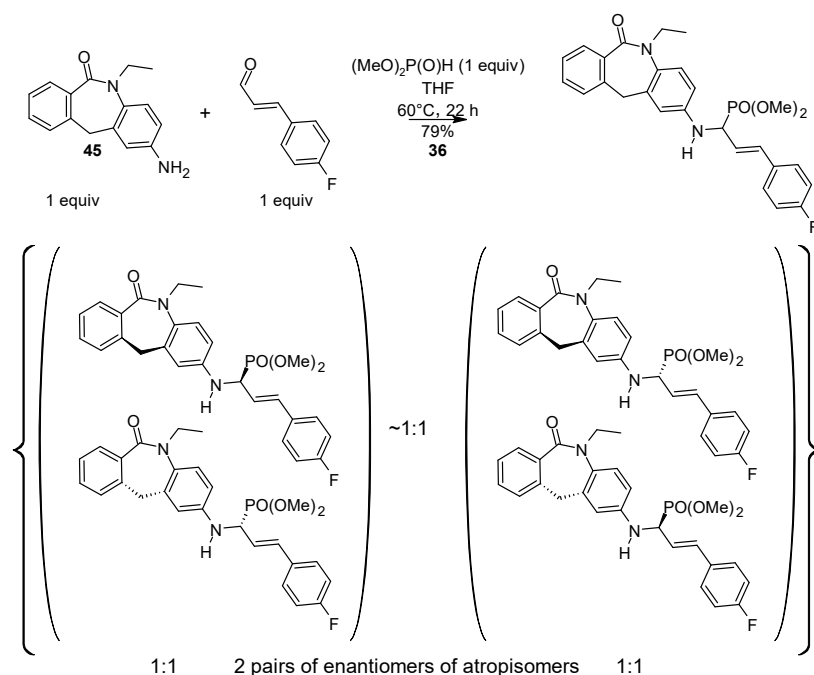
Chemical structure of **10**: CC1=CC=C(C=C1N2C(=O)c3ccccc3CC2)C(=C(C=Cc4ccc(C)cc4)COP(=O)(OC)OC)N

Peak list (ppm): 7.766, 7.765, 7.755, 7.749, 7.735, 7.732, 7.730, 7.728, 7.726, 7.723, 7.720, 7.718, 7.716, 7.714, 7.712, 7.710, 7.708, 7.706, 7.704, 7.702, 7.700, 7.698, 7.696, 7.694, 7.692, 7.690, 7.688, 7.686, 7.684, 7.682, 7.680, 7.678, 7.676, 7.674, 7.672, 7.670, 7.668, 7.666, 7.664, 7.662, 7.660, 7.658, 7.656, 7.654, 7.652, 7.650, 7.648, 7.646, 7.644, 7.642, 7.640, 7.638, 7.636, 7.634, 7.632, 7.630, 7.628, 7.626, 7.624, 7.622, 7.620, 7.618, 7.616, 7.614, 7.612, 7.610, 7.608, 7.606, 7.604, 7.602, 7.600, 7.598, 7.596, 7.594, 7.592, 7.590, 7.588, 7.586, 7.584, 7.582, 7.580, 7.578, 7.576, 7.574, 7.572, 7.570, 7.568, 7.566, 7.564, 7.562, 7.560, 7.558, 7.556, 7.554, 7.552, 7.550, 7.548, 7.546, 7.544, 7.542, 7.540, 7.538, 7.536, 7.534, 7.532, 7.530, 7.528, 7.526, 7.524, 7.522, 7.520, 7.518, 7.516, 7.514, 7.512, 7.510, 7.508, 7.506, 7.504, 7.502, 7.500, 7.498, 7.496, 7.494, 7.492, 7.490, 7.488, 7.486, 7.484, 7.482, 7.480, 7.478, 7.476, 7.474, 7.472, 7.470, 7.468, 7.466, 7.464, 7.462, 7.460, 7.458, 7.456, 7.454, 7.452, 7.450, 7.448, 7.446, 7.444, 7.442, 7.440, 7.438, 7.436, 7.434, 7.432, 7.430, 7.428, 7.426, 7.424, 7.422, 7.420, 7.418, 7.416, 7.414, 7.412, 7.410, 7.408, 7.406, 7.404, 7.402, 7.400, 7.398, 7.396, 7.394, 7.392, 7.390, 7.388, 7.386, 7.384, 7.382, 7.380, 7.378, 7.376, 7.374, 7.372, 7.370, 7.368, 7.366, 7.364, 7.362, 7.360, 7.358, 7.356, 7.354, 7.352, 7.350, 7.348, 7.346, 7.344, 7.342, 7.340, 7.338, 7.336, 7.334, 7.332, 7.330, 7.328, 7.326, 7.324, 7.322, 7.320, 7.318, 7.316, 7.314, 7.312, 7.310, 7.308, 7.306, 7.304, 7.302, 7.300, 7.298, 7.296, 7.294, 7.292, 7.290, 7.288, 7.286, 7.284, 7.282, 7.280, 7.278, 7.276, 7.274, 7.272, 7.270, 7.268, 7.266, 7.264, 7.262, 7.260, 7.258, 7.256, 7.254, 7.252, 7.250, 7.248, 7.246, 7.244, 7.242, 7.240, 7.238, 7.236, 7.234, 7.232, 7.230, 7.228, 7.226, 7.224, 7.222, 7.220, 7.218, 7.216, 7.214, 7.212, 7.210, 7.208, 7.206, 7.204, 7.202, 7.200, 7.198, 7.196, 7.194, 7.192, 7.190, 7.188, 7.186, 7.184, 7.182, 7.180, 7.178, 7.176, 7.174, 7.172, 7.170, 7.168, 7.166, 7.164, 7.162, 7.160, 7.158, 7.156, 7.154, 7.152, 7.150, 7.148, 7.146, 7.144, 7.142, 7.140, 7.138, 7.136, 7.134, 7.132, 7.130, 7.128, 7.126, 7.124, 7.122, 7.120, 7.118, 7.116, 7.114, 7.112, 7.110, 7.108, 7.106, 7.104, 7.102, 7.100, 7.098, 7.096, 7.094, 7.092, 7.090, 7.088, 7.086, 7.084, 7.082, 7.080, 7.078, 7.076, 7.074, 7.072, 7.070, 7.068, 7.066, 7.064, 7.062, 7.060, 7.058, 7.056, 7.054, 7.052, 7.050, 7.048, 7.046, 7.044, 7.042, 7.040, 7.038, 7.036, 7.034, 7.032, 7.030, 7.028, 7.026, 7.024, 7.022, 7.020, 7.018, 7.016, 7.014, 7.012, 7.010, 7.008, 7.006, 7.004, 7.002, 7.000, 6.998, 6.996, 6.994, 6.992, 6.990, 6.988, 6.986, 6.984, 6.982, 6.980, 6.978, 6.976, 6.974, 6.972, 6.970, 6.968, 6.966, 6.964, 6.962, 6.960, 6.958, 6.956, 6.954, 6.952, 6.950, 6.948, 6.946, 6.944, 6.942, 6.940, 6.938, 6.936, 6.934, 6.932, 6.930, 6.928, 6.926, 6.924, 6.922, 6.920, 6.918, 6.916, 6.914, 6.912, 6.910, 6.908, 6.906, 6.904, 6.902, 6.900, 6.898, 6.896, 6.894, 6.892, 6.890, 6.888, 6.886, 6.884, 6.882, 6.880, 6.878, 6.876, 6.874, 6.872, 6.870, 6.868, 6.866, 6.864, 6.862, 6.860, 6.858, 6.856, 6.854, 6.852, 6.850, 6.848, 6.846, 6.844, 6.842, 6.840, 6.838, 6.836, 6.834, 6.832, 6.830, 6.828, 6.826, 6.824, 6.822, 6.820, 6.818, 6.816, 6.814, 6.812, 6.810, 6.808, 6.806, 6.804, 6.802, 6.800, 6.798, 6.796, 6.794, 6.792, 6.790, 6.788, 6.786, 6.784, 6.782, 6.780, 6.778, 6.776, 6.774, 6.772, 6.770, 6.768, 6.766, 6.764, 6.762, 6.760, 6.758, 6.756, 6.754, 6.752, 6.750, 6.748, 6.746, 6.744, 6.742, 6.740, 6.738, 6.736, 6.734, 6.732, 6.730, 6.728, 6.726, 6.724, 6.722, 6.720, 6.718, 6.716, 6.714, 6.712, 6.710, 6.708, 6.706, 6.704, 6.702, 6.700, 6.698, 6.696, 6.694, 6.692, 6.690, 6.688, 6.686, 6.684, 6.682, 6.680, 6.678, 6.676, 6.674, 6.672





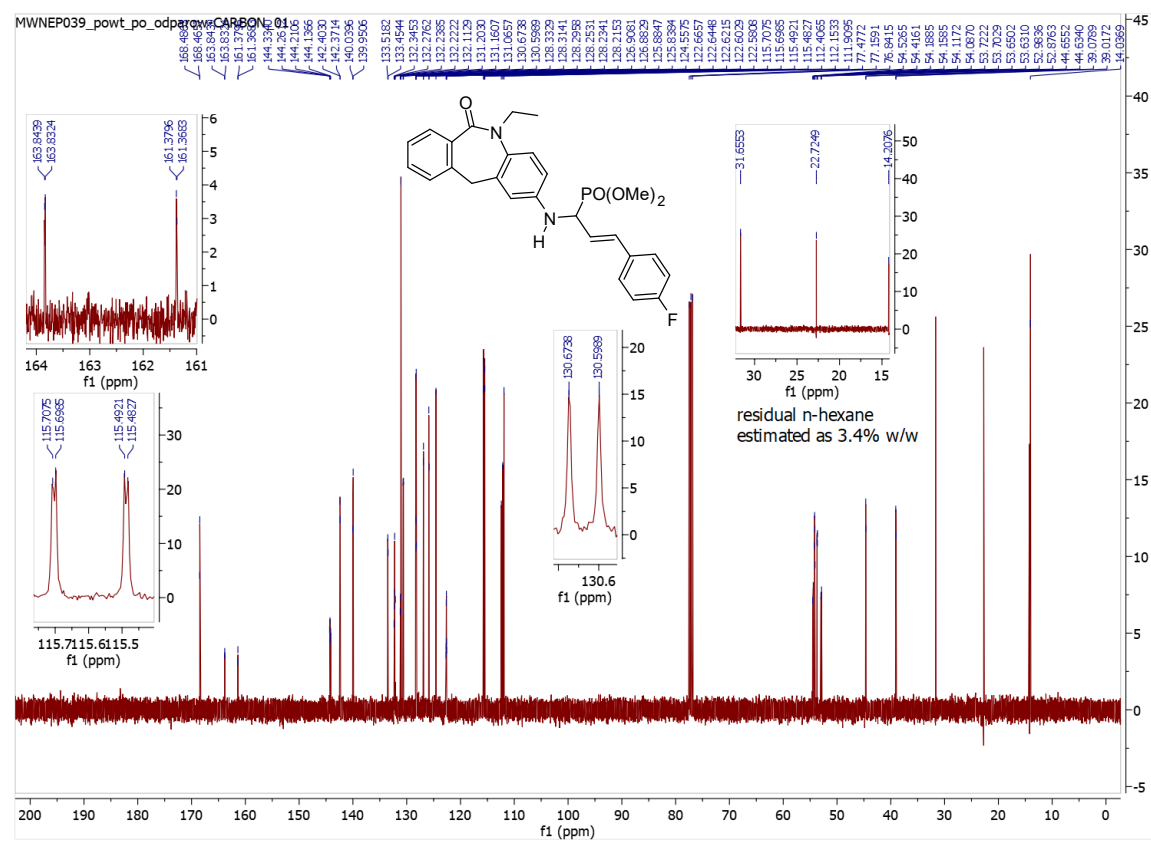
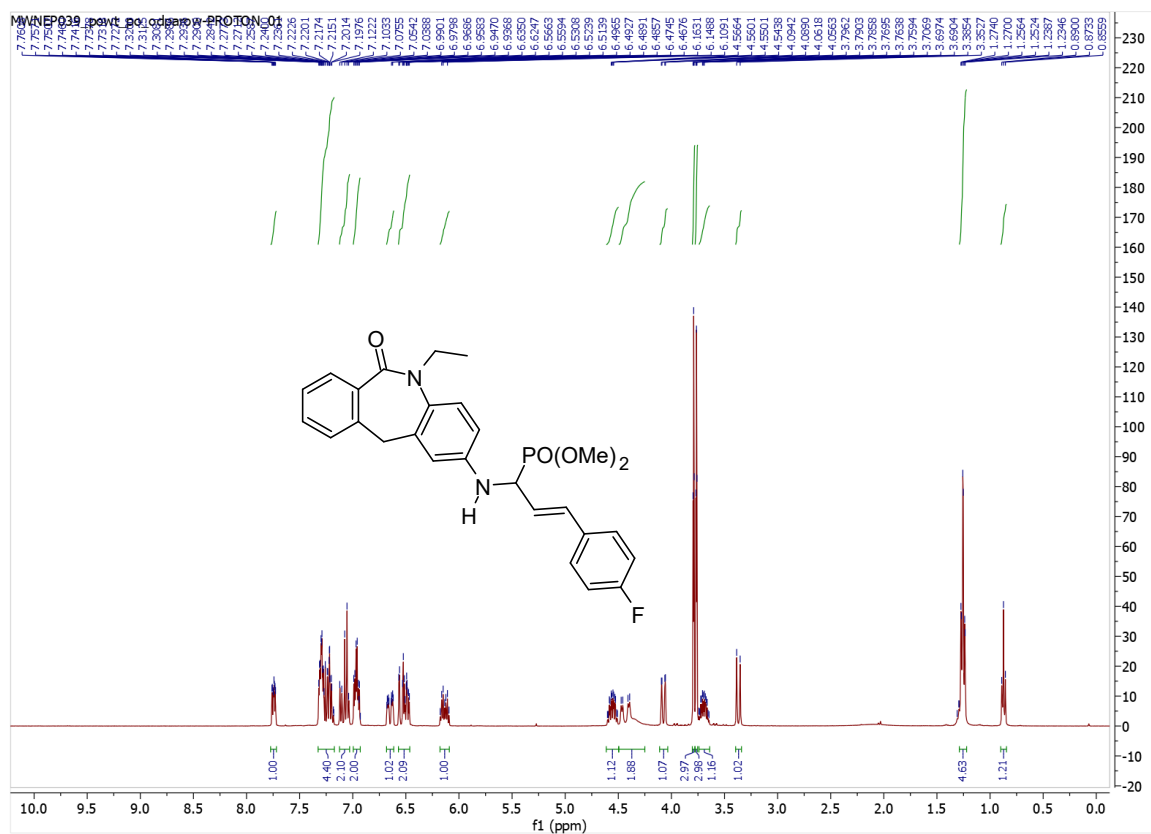
Dimethyl (*E*)-(1-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(4-fluorophenyl)allyl)phosphonate (36**)**

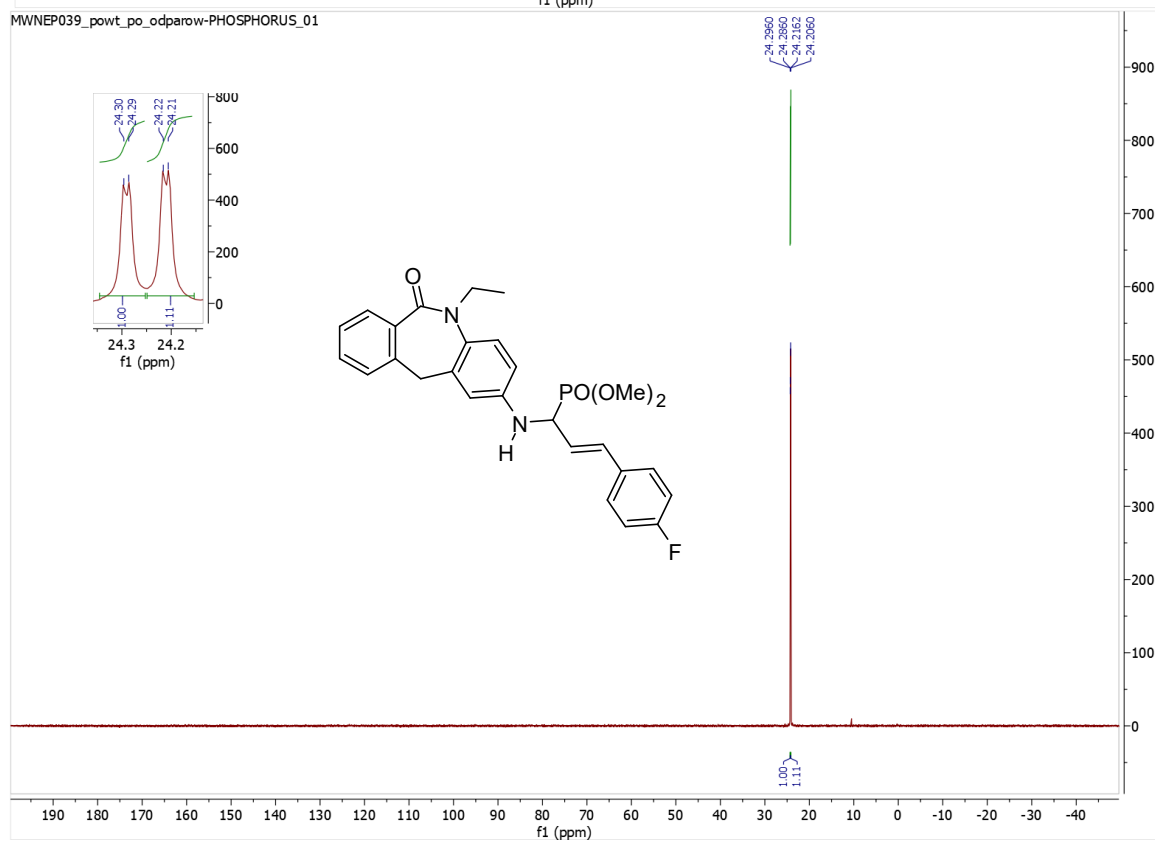
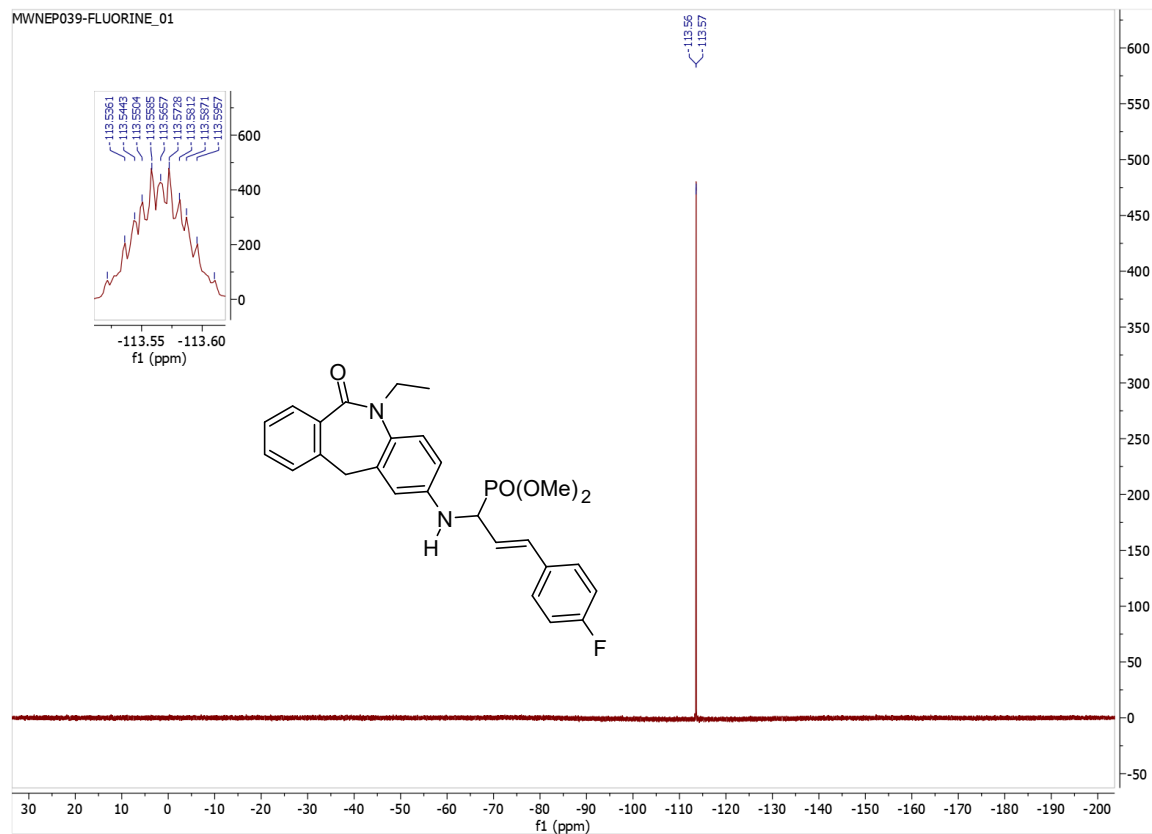


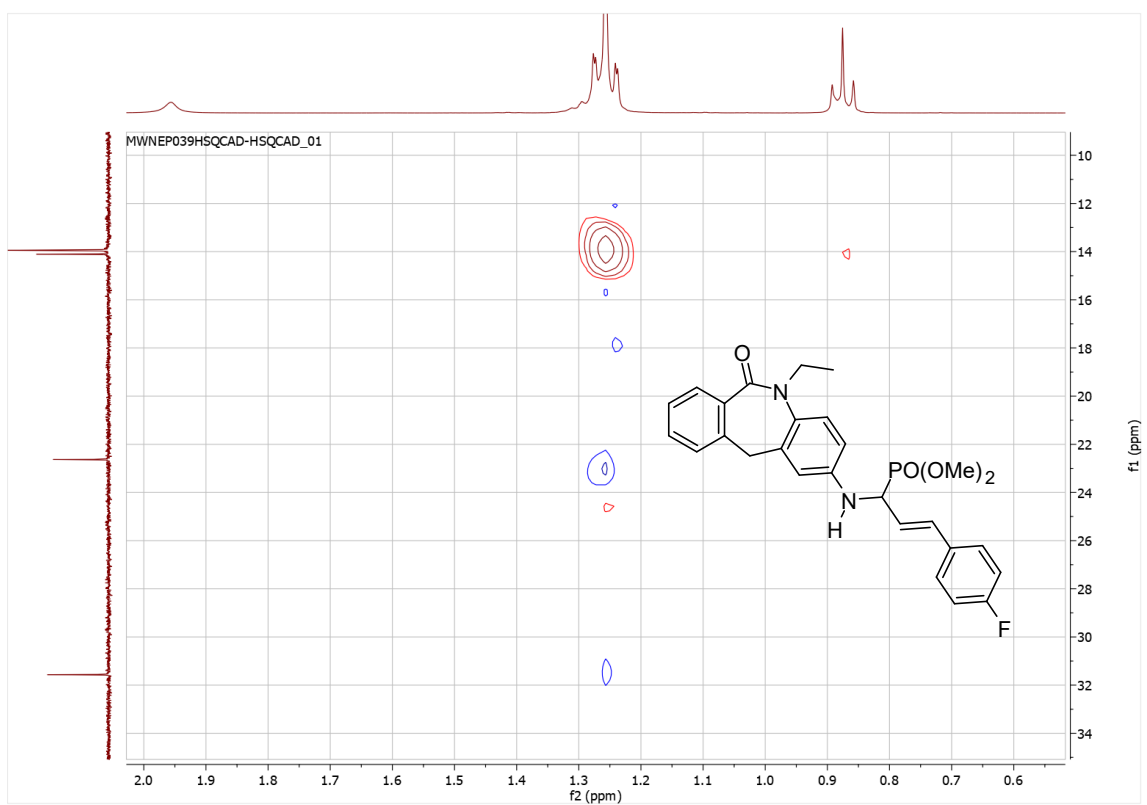
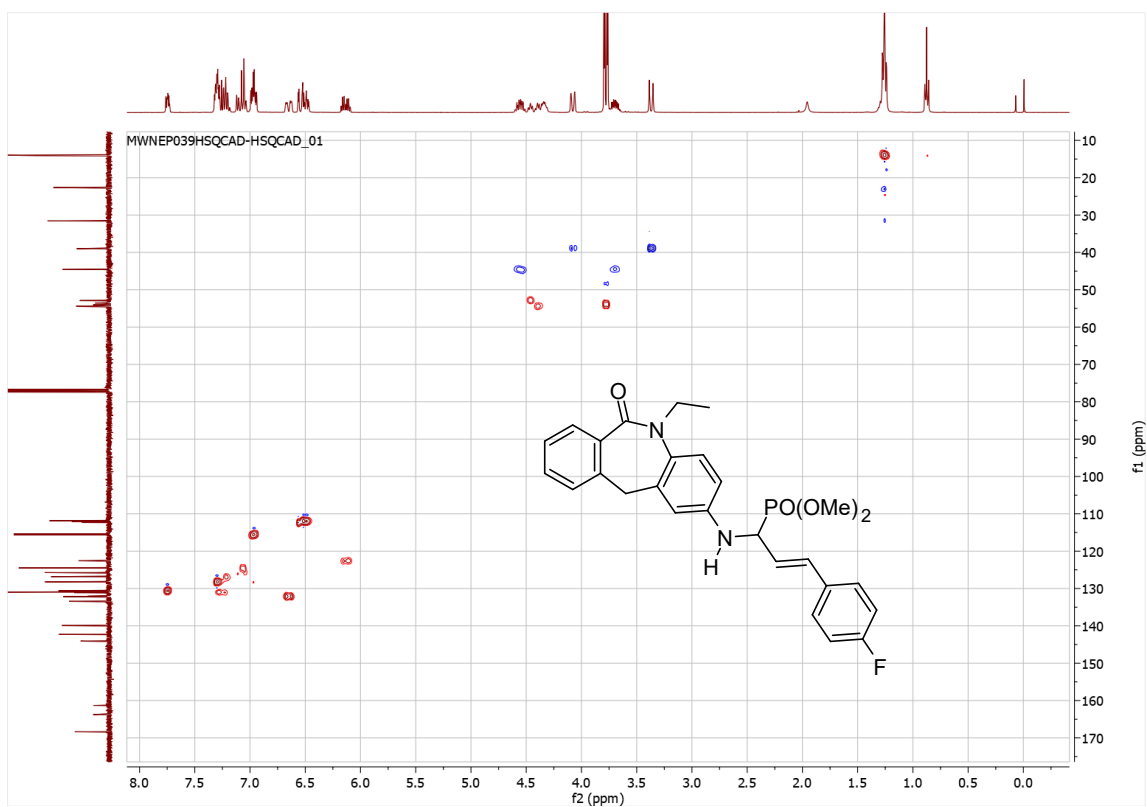
An oven-dried, screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (44 mg, 0.18 mmol, 1 equiv), (*2E*)-3-(4-fluorophenyl)prop-2-enal (28 mg, 0.18 mmol, 1 equiv) anhydrous THF (1.5 mL) and dimethylphosphite (16 μ L, 0.18 mmol, 1 equiv), and the mixture was stirred at 60°C for 22 h. The volatiles were evaporated and the residue was subjected to column chromatography (silica; AcOEt/cyclohexane: 50-100%). The product was additionally precipitated from the mixture of DCM and *n*-hexane using rotary evaporator and washed with *n*-hexane (2 times) to give 69 mg (79%) of compound **36** as a yellowish solid.

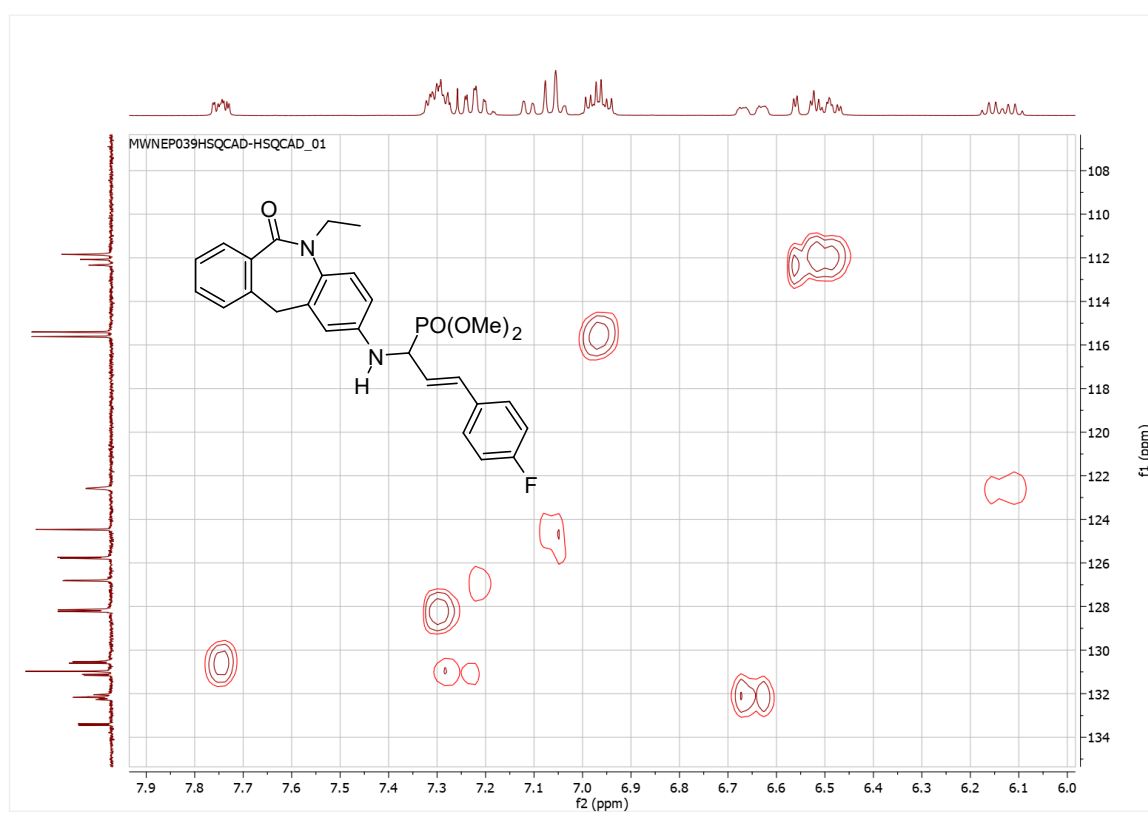
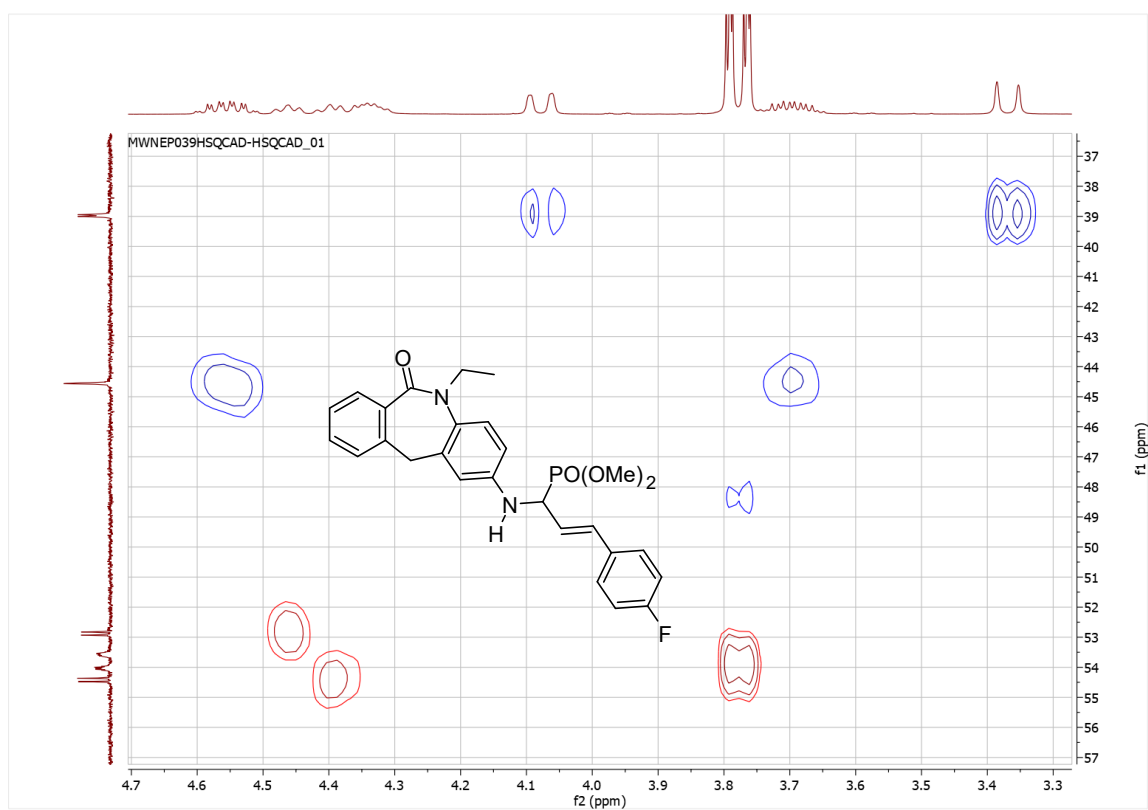
^1H NMR (400 MHz, CDCl_3) δ 7.77-7.72 (m, 1H), 7.33-7.17 (m, 4H) overlapping residual CHCl_3 , 7.12-7.03 (m, 2H), 7.00-6.93 (m, 2H), 6.68-6.61 (m, 1H), 6.57-6.46 (m, 2H), 6.18-6.09 (m, 1H), 4.61-4.50 (m, 1H, $\frac{1}{2}$ CH_2CH_3), 4.47-4.25 (m, 1H, NH) overlapping [4.44 (d, $^2J_{\text{HP}} = 25.7$ Hz, 0.5H, *CHP*) overlapping 4.44 (d, $^2J_{\text{HP}} = 25.8$ Hz, 0.5H, *CHP*)] 4.08 (m, 1H, $\frac{1}{2}\text{ArCH}_2\text{Ar}'$), 3.80-3.75 (m, 6H, 2 x OCH_3), 3.74-3.64 (m, 1H, $\frac{1}{2}\text{CH}_2\text{CH}_3$), 3.37 (d, $J = 13.1$ Hz, 1H, $\text{ArCH}_2\text{Ar}'$), 1.28-1.22 (m, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ [168.5 (x 2); CO], 162.6 (d, $^1J_{\text{CF}} = 246.5$ Hz) overlapping 162.6 (d, $^1J_{\text{CF}} = 250.0$ Hz), [144.3 (x 2), 144.2, 144.1], [142.4 (x 2)], [140.0 (x 2)], [133.5 x2], 132.3 (x 2), 132.2 (x 2), 132.1, [131.2 x2], 131.1, 130.6 [d, $^3J_{\text{C-F}} = 7.5$ Hz, *CH*], [128.3 (x 4), 128.2 (x 2), $\text{HC}=\text{CH}$], [126.9 (x 2)], [125.9, 125.8], 124.6, 122.7 (x 2), 122.6 (x 4), [115.6 (d, $^2J_{\text{CF}} = 22.7$ Hz) overlapping 115.6 (d, $^2J_{\text{CF}} = 20.7$ Hz)], 112.4, 112.2, 111.9, [54.5, 54.4 and 53.0, 52.9, (*CHP*)] overlapping [54.2 (x 2), 54.1 (x 2)], [53.7 (x 3) 53.6; (2 x OCH_3)], [44.7, 44.6, (CH_2CH_3)], [39.1, 39.0, (ArCH_2Ar)], 14.0 (CH_3); (the presence of multiplied peaks is due to the presence of atropisomers and C-P and C-F couplings); ^{19}F NMR (376 MHz, CDCl_3) δ -113.6 (x 2); (due to the 2-channel NMR probe,

couplings with hydrogens are visible; ^{31}P NMR (162 MHz, CDCl_3) δ 24.3 (d, $^8J_{\text{PF}} = 1.6$ Hz), 24.2 (d, $^8J_{\text{PF}} = 1.6$ Hz). LR-MS (m/z): 495 $[\text{M}+\text{H}]^+$.

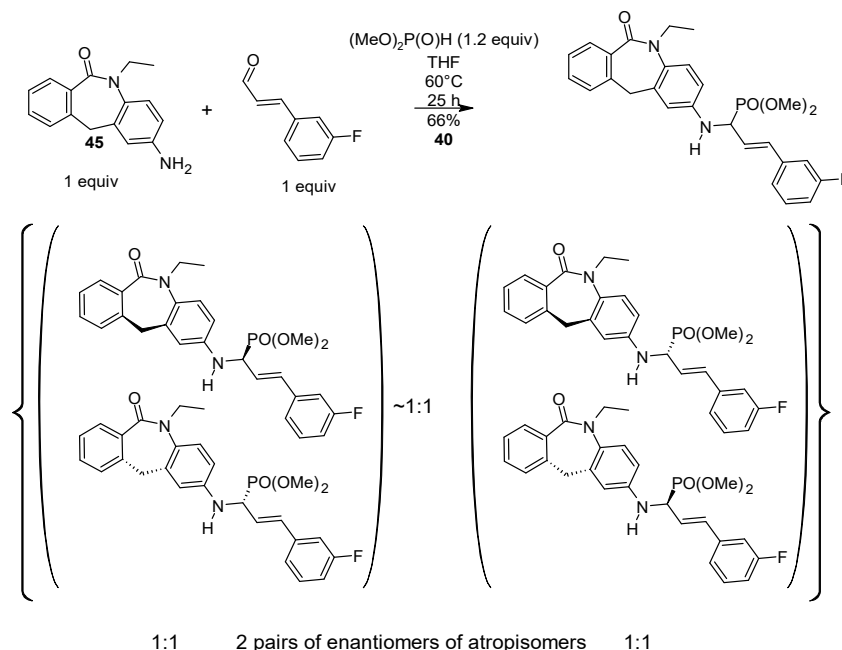






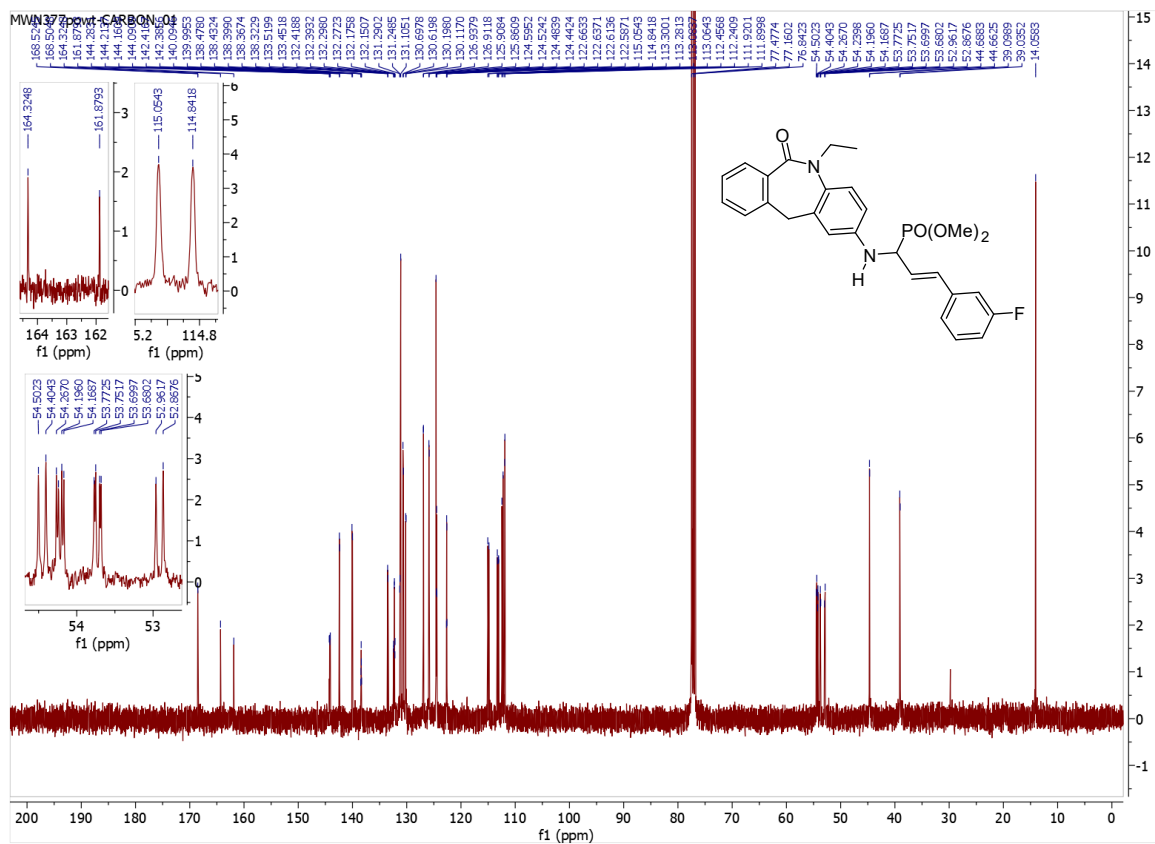
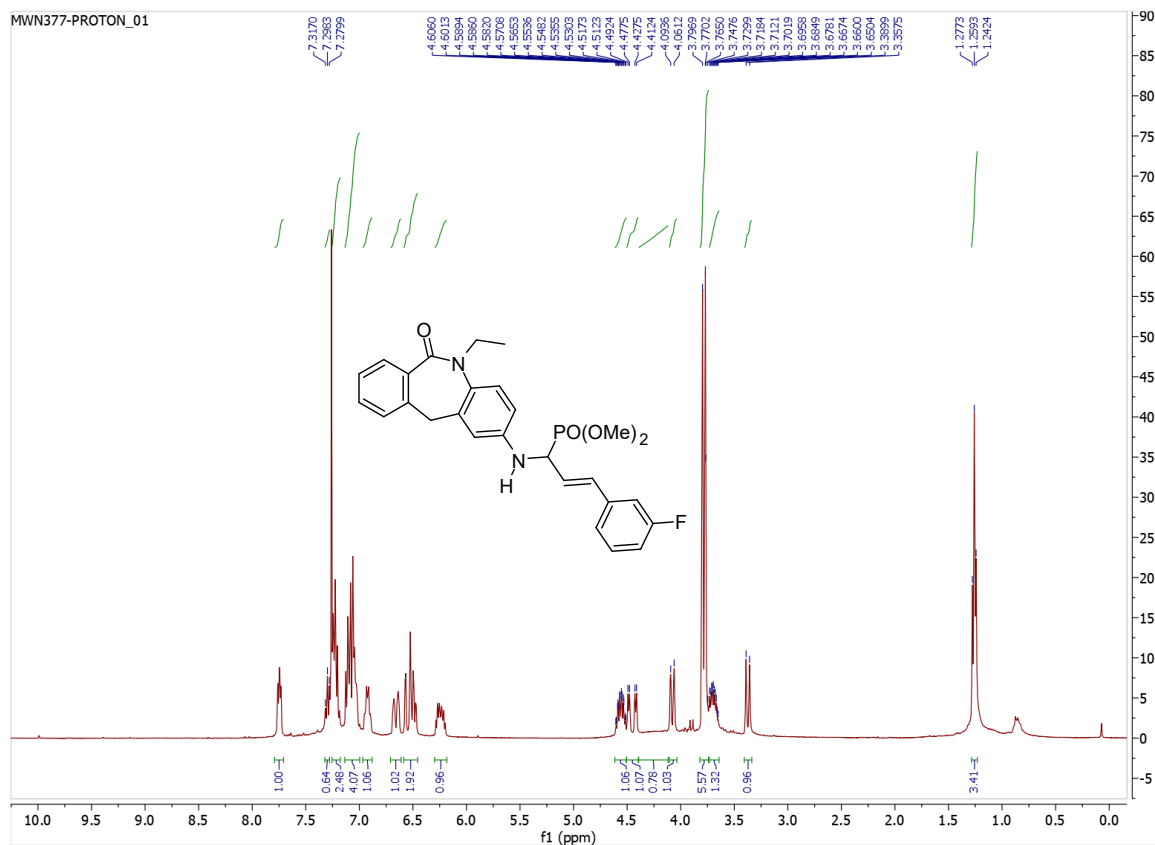


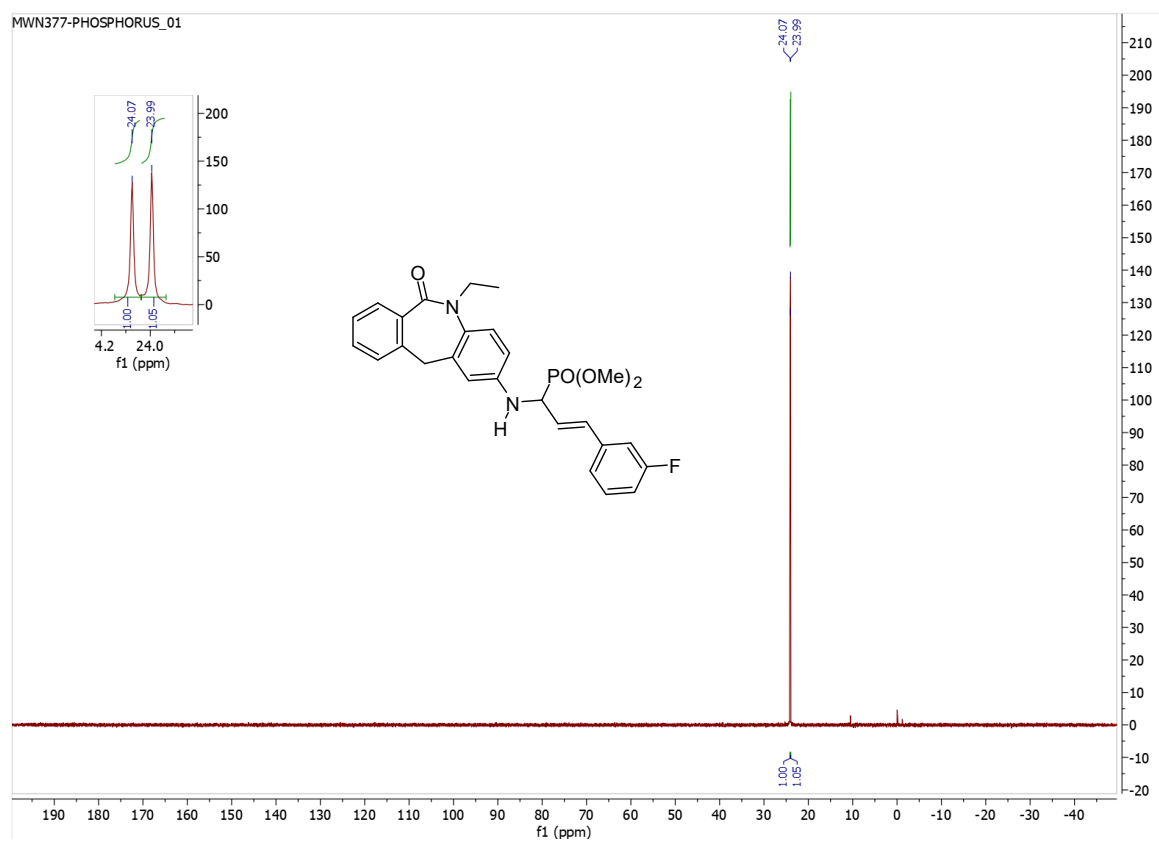
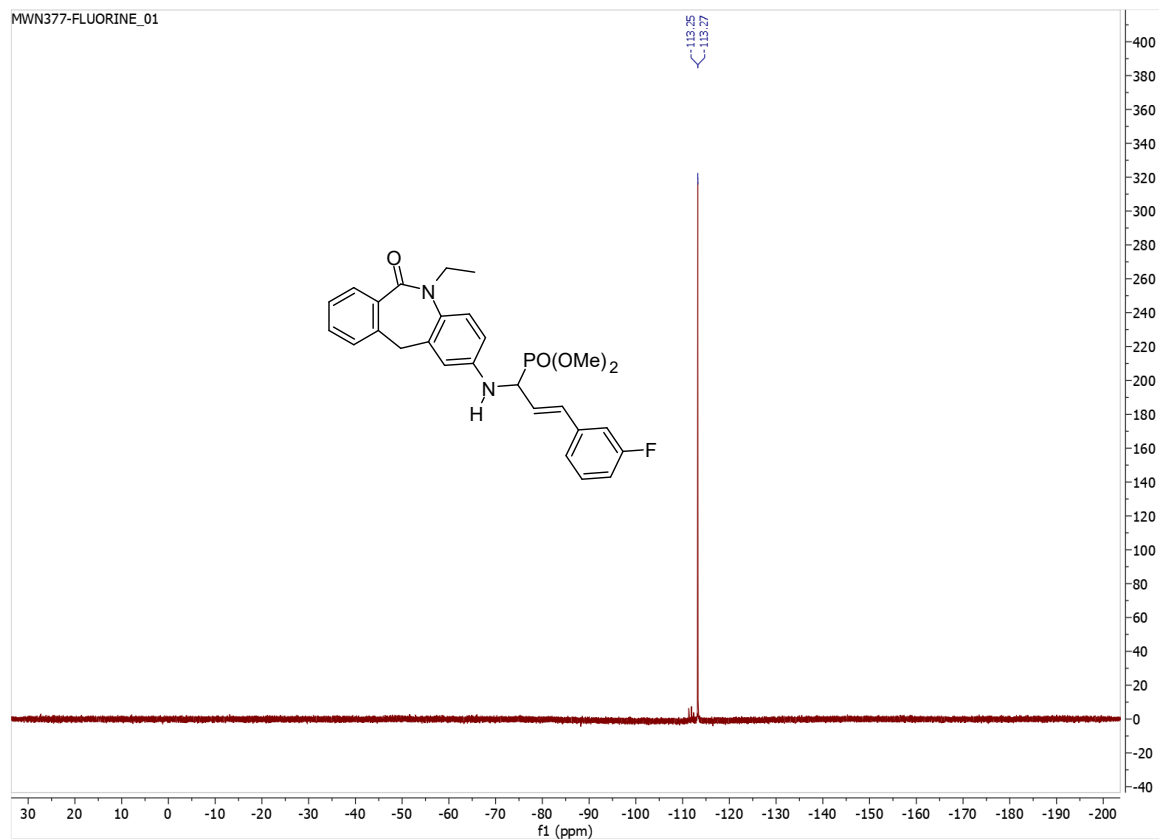
Dimethyl (*E*)-(1-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-3-(3-fluorophenyl)allyl)phosphonate (40**)**



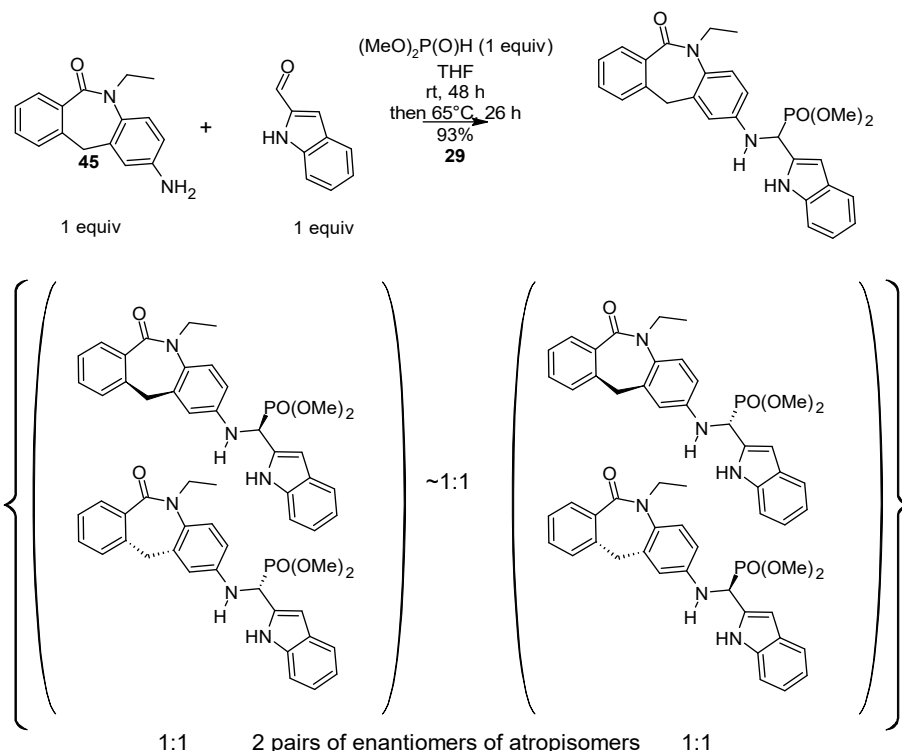
An oven-dried, screw-capped vial was charged with (*E*)-3-(3-fluorophenyl)-acrylaldehyde (30 mg, 0.20 mmol, 1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (50 mg, 0.20 mmol, 1 equiv), dimethylphosphite (20 μ L, 0.22 mmol, 1.1 equiv) and anhydrous THF (1.5 mL). The solution was stirred at 60°C for 25 h. The volatiles were evaporated, and the crude was subjected to reverse phase column chromatography (C-18; using MeCN/H₂O: 45%) to give 65 mg (66%) of product **40** as a yellow foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78-7.72 (m, 1H), 7.30 (t, *J* = 7.4 Hz, 0.5H) overlapping residual CHCl₃, 7.26-7.18 (m, 2.5H) overlapped with residual CHCl₃, 7.14-7.00 (m, 4H), 6.96-6.88 (m, 1H), 6.70-6.62 (m, 1H), 6.59-6.46 (m, 2H), 6.30-6.19 (m, 1H), 4.61-4.51 (m, 1H, 1/2 CH₂CH₃), 4.51-4.40 (m, 1H, CHP) overlapping 4.41-4.13 (m, 1H, NH), 4.08 (br d, *J* = 13.0 Hz, 1H, 1/2 ArCH₂Ar'), 3.82-3.75 (m, 6H, 2 x OCH₃) overlapping 3.75-3.64 (m, 1H, 1/2 CH₂CH₃), 3.37 (br d, *J* = 12.9 Hz, 1H, 1/2 ArCH₂Ar'), 1.26 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [168.5 (x 2), C=O], 163.1 (d, ¹*J*_{CF} = 245.9 Hz), [144.3, 144.2 (x 2), 144.1], [142.4, 142.4 (x 2)], [140.1, 140.0], [138.5, 138.4 (x 3), 138.3], [133.5 (x 2)], [132.4 (x 2), 132.3, 132.3 (x 2), 132.2 (x 2)], [131.3, 131.2], 131.1, [130.7, 130.6], [130.2, 130.1], [126.9 (x 2)], [125.9 (x 2)], 124.6, [124.5 (x 2), 124.4], [122.7, 122.6 (x 3)], 114.9 (d, ²*J*_{CF} = 21.4 Hz), [113.3 (x 2), 113.1 (x 2)], [112.5, 112.2], [111.9 (x 2)], 54.2 [d, ²*J*_{CP} = 7.2 Hz, (OCH₃)'], 54.2 [d, ²*J*_{CP} = 7.2 Hz, (OCH₃)"], 53.7 [d, ²*J*_{CP} = 7.4 Hz, (OCH₃)'], 53.7 [d, ²*J*_{CP} = 7.2 Hz, (OCH₃)'], 53.7 [d, ¹*J*_{CP} = 155.6 Hz, (CHP)'], 53.6 [d, ¹*J*_{CP} = 155.2 Hz, (CHP)'], [44.7 (x 2), CH₂CH₃], [39.1, 39.0, (ArCH₂Ar')], 14.1 (CH₃); (multiplied peaks are due to the presence of atropisomers and C-P and C-F couplings). ¹⁹F NMR (376 MHz, CDCl₃) δ -113.2, -113.3, ³¹P NMR (162 MHz, CDCl₃) δ 24.1, 24.0. LR-MS (*m/z*): 495 [M+H]⁺, 517 [M+Na]⁺.





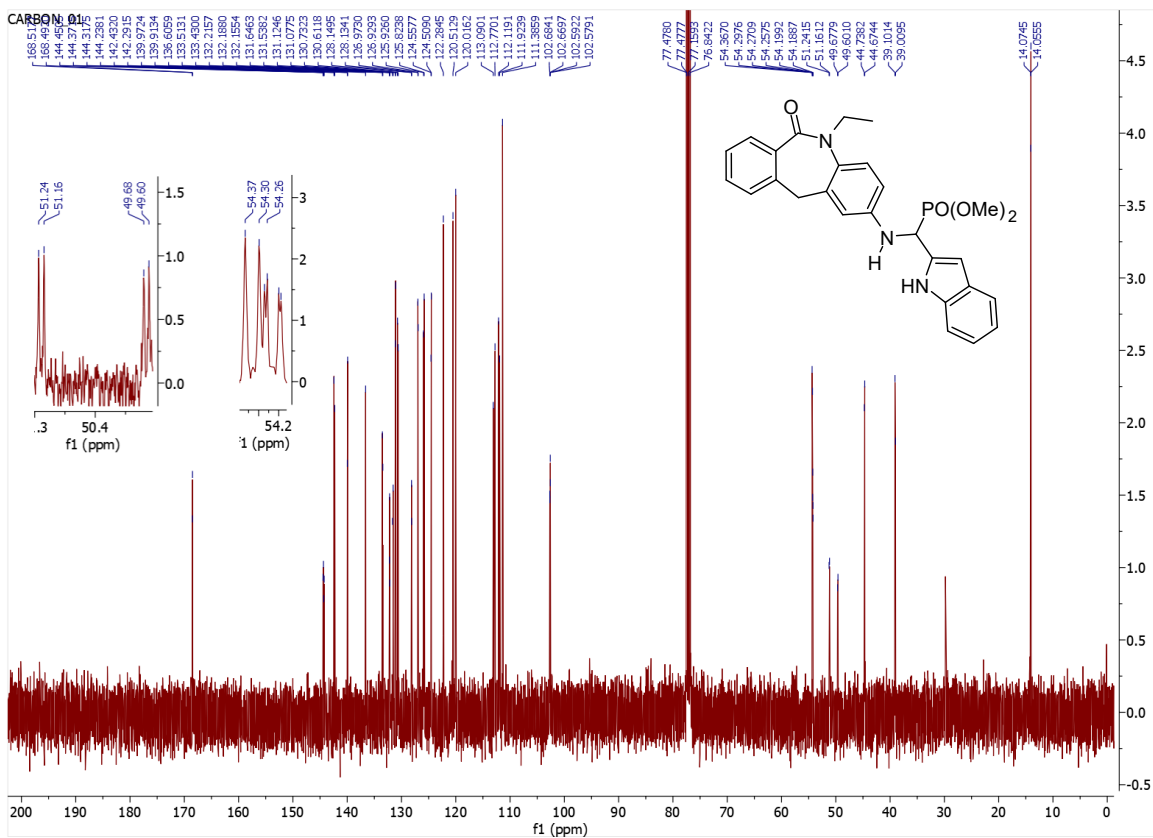
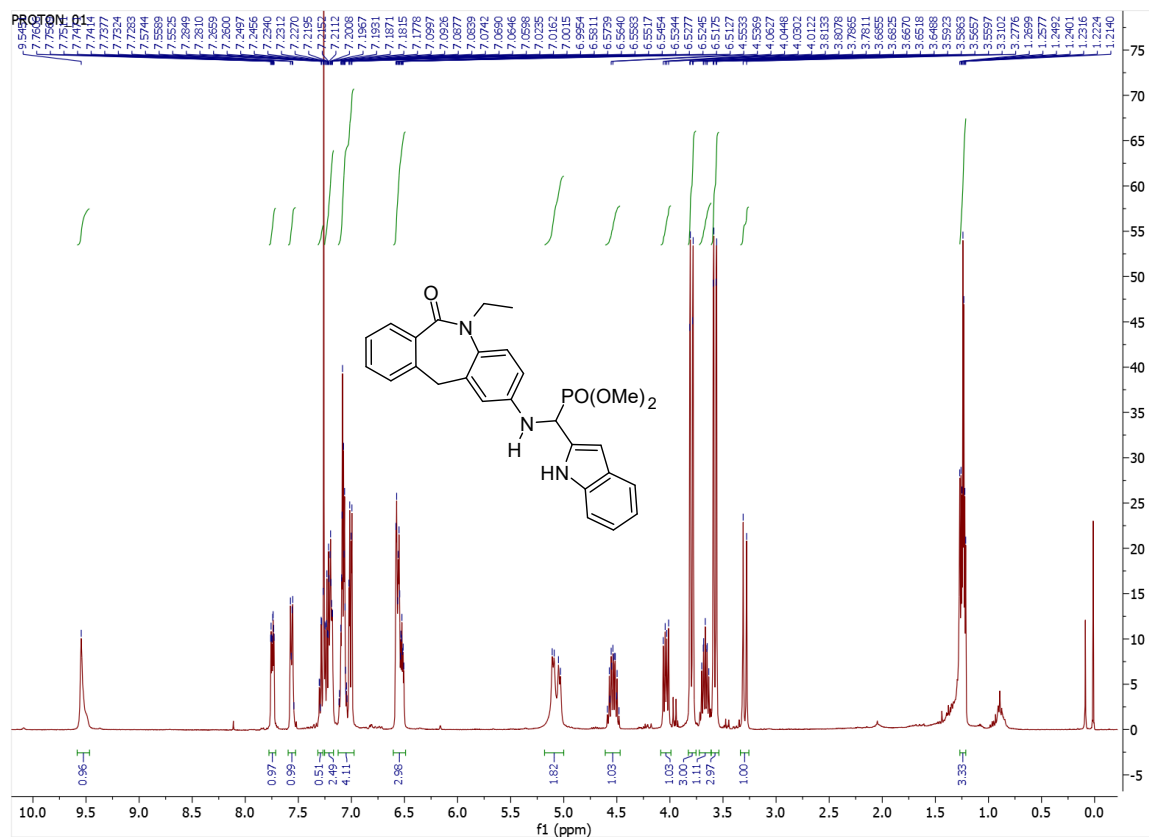
Dimethyl (((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)(1*H*-indol-2-yl)methyl)phosphonate (29**)**

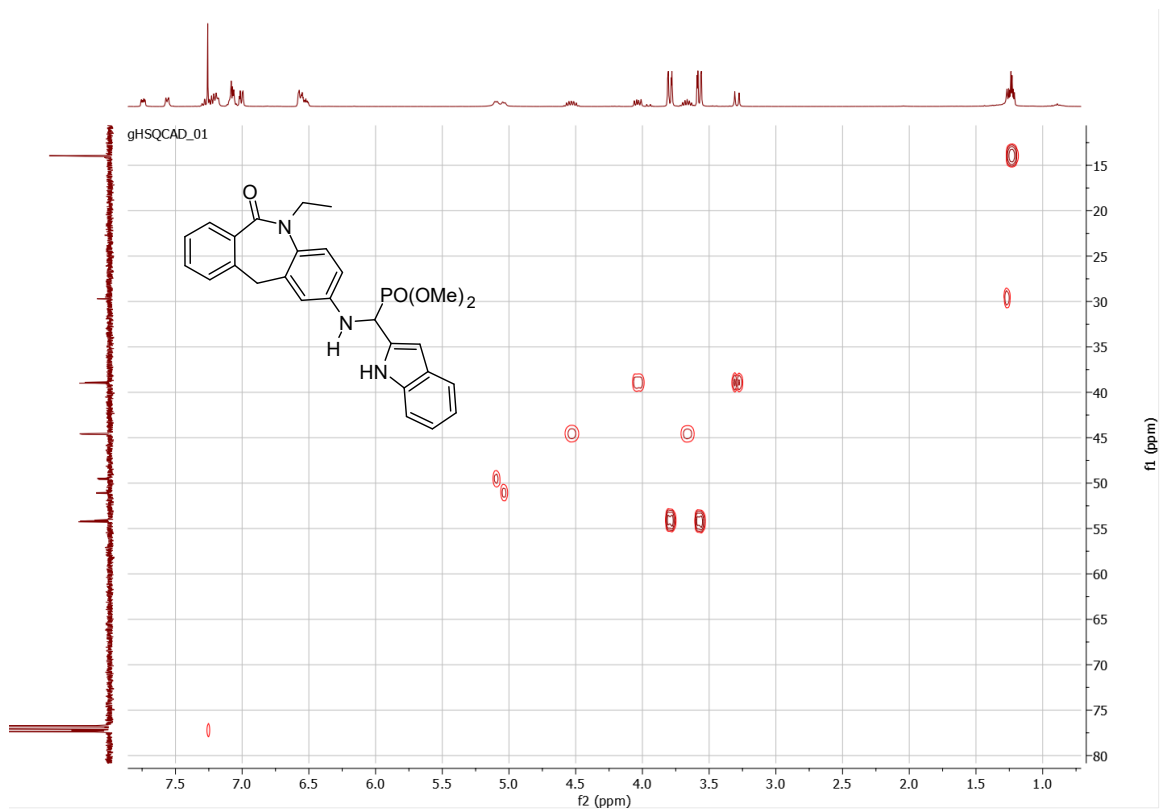
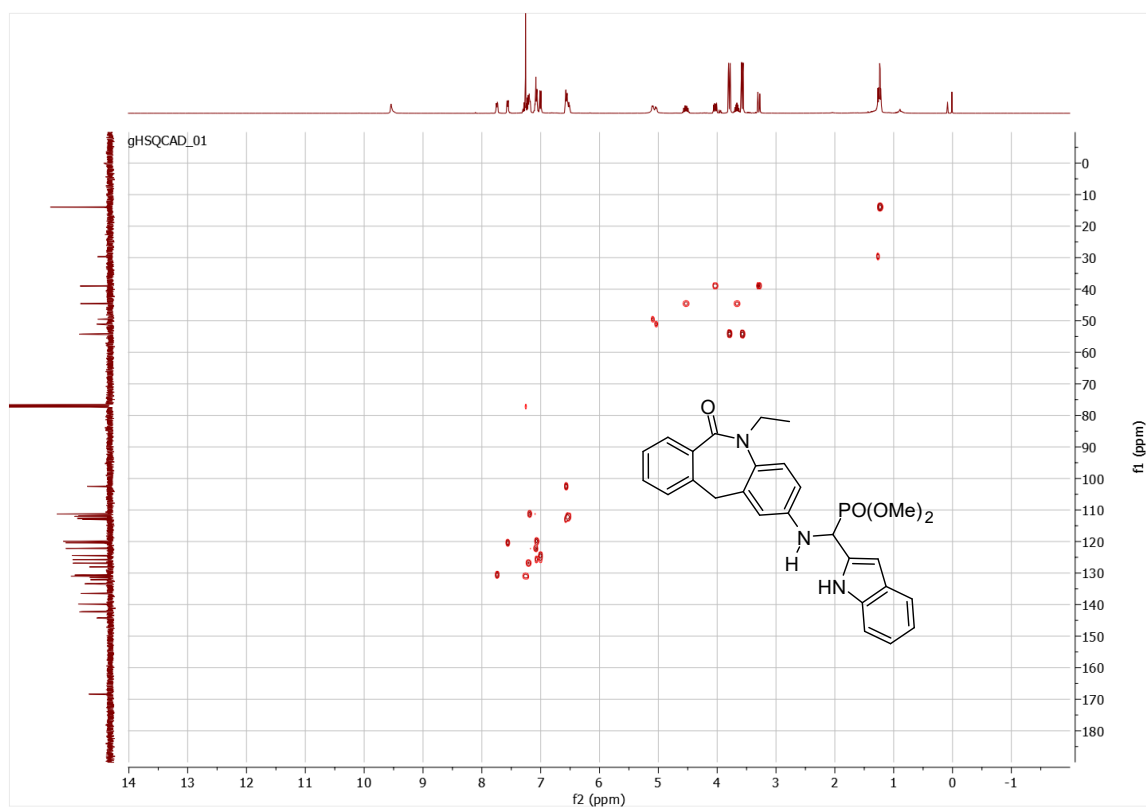


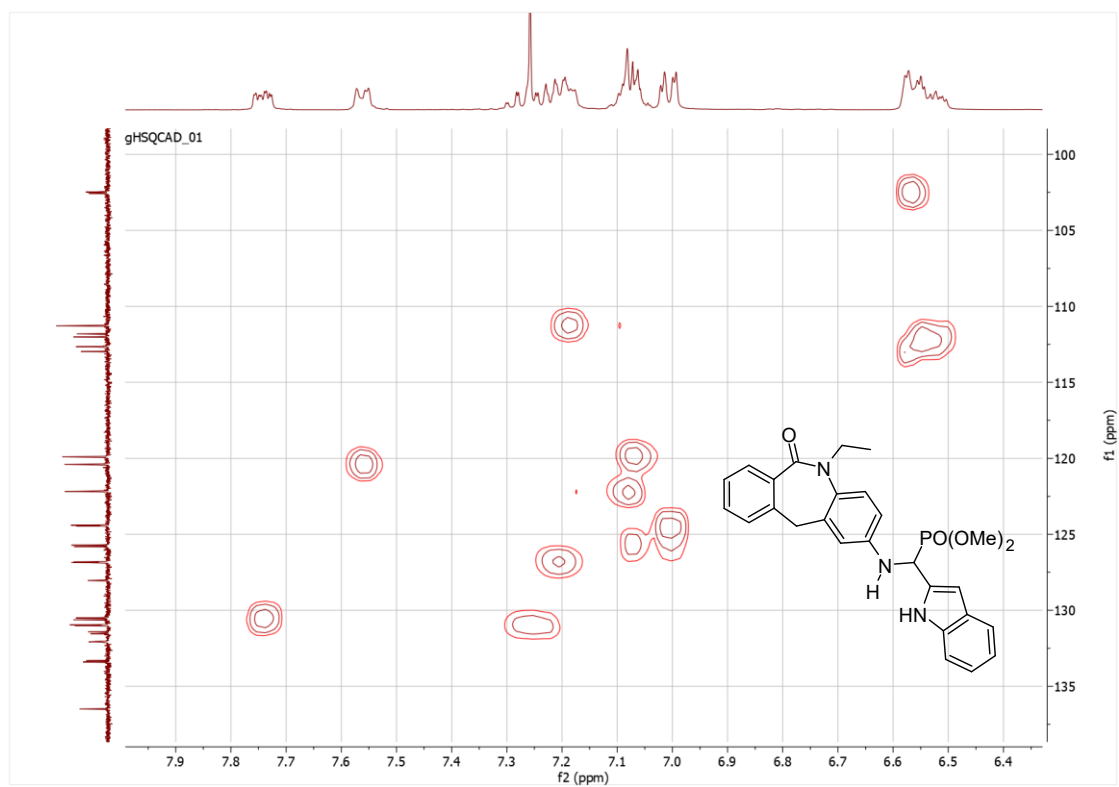
An oven-dried vial was charged with dimethylphosphite (33 mg, 27 μ L, 0.30 mmol, 1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (75 mg, 0.30 mmol, 1 equiv), indole-2-carboxaldehyde (43 mg, 0.30 mmol, 1 equiv) and anhydrous THF (1.5 mL) and stirred at rt for 48 h and then at 65°C for 26 h. The volatiles were evaporated and the crude was subjected to column chromatography (silica; using AcOEt/cyclohexane: 33-100%). The product was heated with *n*-heptane and the obtained solid was collected and washed with *n*-heptane (2 x 1 mL) to obtain 136 g (93%) of product **29** as a brownish solid.

¹H NMR (400 MHz, CDCl₃) δ 9.58-9.47 (m, 1H, NH_{indole}), 7.77-7.72 (m, 1H), 7.59-7.53 (m, 1H), 7.31-7.17 (m, 3H) overlapped with residual CHCl₃, 7.12-6.98 (m, 4H), 6.60-6.49 (m, 3H), 5.17-5.00 (m, 2H, NHCH, NHCH), 4.60-4.47 (m, 1H, $\frac{1}{2}$ CH₂CH₃), [4.05 (d, *J* = 13.0 Hz, 0.5 H, ArCH₂Ar') overlapped 4.03 (d, *J* = 13.0 Hz, 0.5 H, ArCH₂Ar')], [3.80 (d, ³*J*_{PH} = 10.7, 1.5H, OCH₃^{*}) overlapped 3.79 (d, ³*J*_{PH} = 10.7, 1.5H, OCH₃^{*})], 3.72-3.61 (m, 1H, $\frac{1}{2}$ CH₂CH₃), {3.58 [d, ³*J*_{PH} = 10.6 Hz, 1.5H, (OCH₃)^{**}] overlapped 3.57 [d, ³*J*_{PH} = 10.6 Hz, 1.5H, (OCH₃)^{**}]}, 3.29 (d, *J* = 13.0 Hz, 1H, $\frac{1}{2}$ ArCH₂Ar'), 1.29-1.20 (m, 3H, CH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ [168.5 (x 2);(CONH)], [144.5, 144.4, 144.3, 144.2], [142.4, 142.3], [140.0, 139.9], 136.6, [133.5, 133.4], [132.2 (x3)], [131.6, 131.5], [131.1 (x 2)], [130.7, 130.6], [128.1 (x 2)], [127.0, 126.9], [125.9, 125.8], [124.6, 124.5], 122.3, 120.5, 120.0, [113.1, 112.8], [112.1, 111.9], 111.4, [102.7 (x 2), 102.6 (x 2); (indole HC=CH-N)], 54.3 [d, ²*J*_{CP} = 7.0 Hz, (OCH₃)^{*}], {54.2 [d, ²*J*_{CP} = 7.2 Hz, (OCH₃)^{**}], overlapped 54.2 [²*J*_{CP} = 6.9 Hz, (OCH₃)^{**}]}, [50.5 (d, ¹*J*_{PC} = 157.9 Hz, NHCHP) overlapped 50.4 (d, ¹*J*_{PC} = 157.6 Hz, NHCHP)], [44.7 (x 2), CH₂CH₃], [39.1,

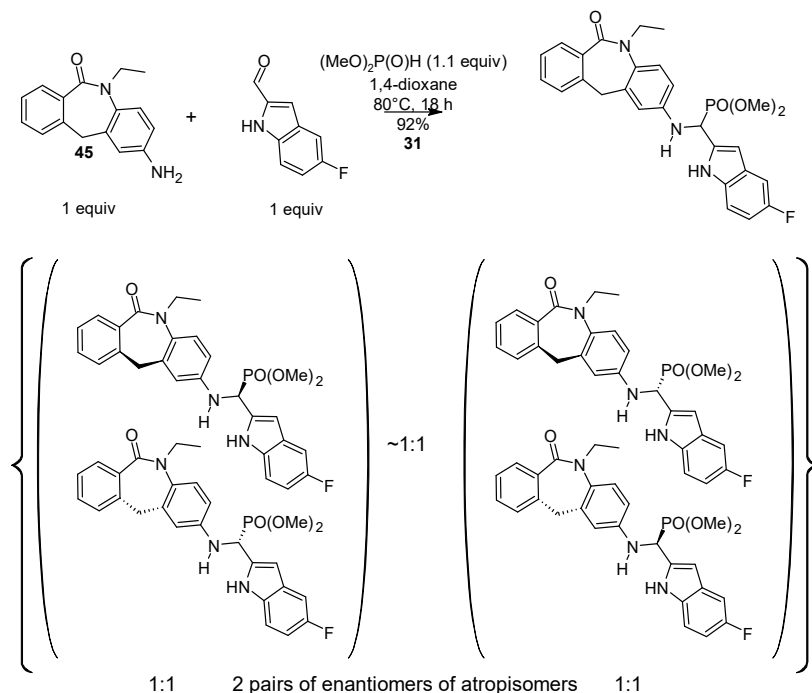
39.0; ArCH₂Ar'], [14.1 (x 2); CH₂CH₃]; multiplied signals are caused by the presence of atropisomers and P-C couplings; LR-MS (m/z): 490 [M+H]⁺.







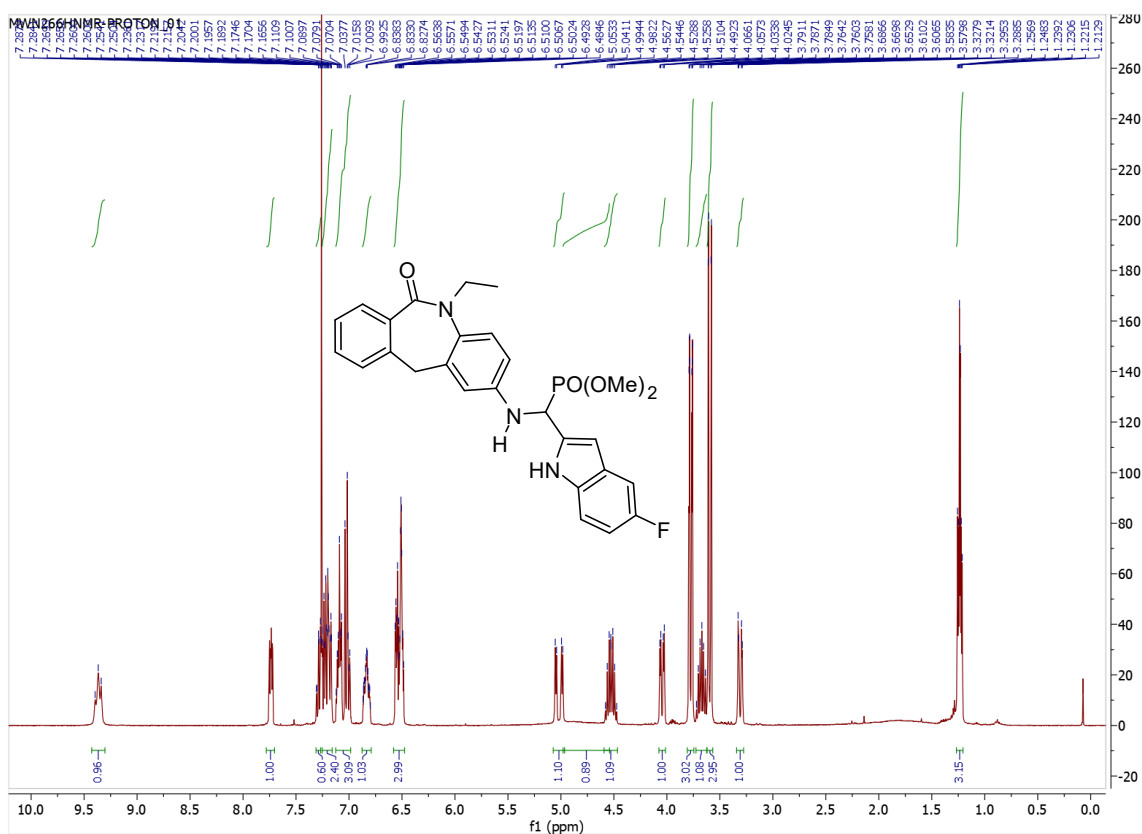
Dimethyl (((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)(5-fluoro-1*H*-indol-2-yl)methyl)phosphonate (31**)**

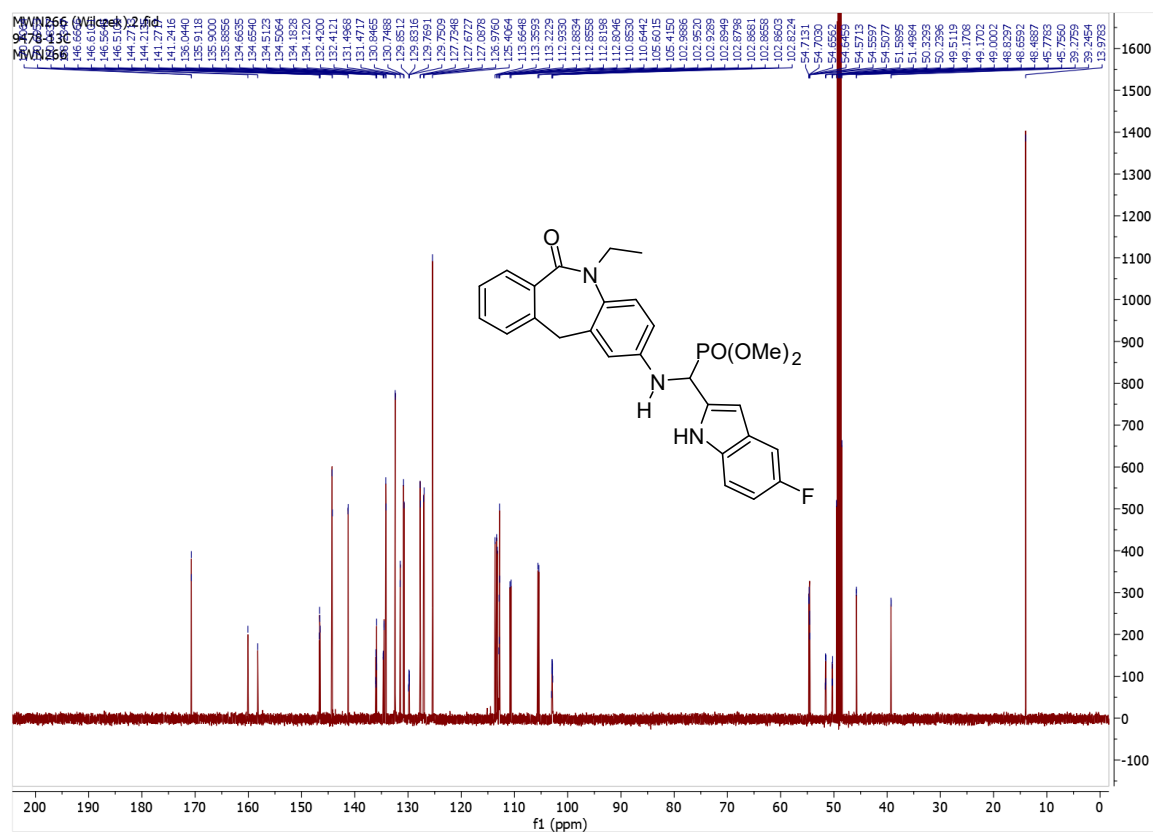
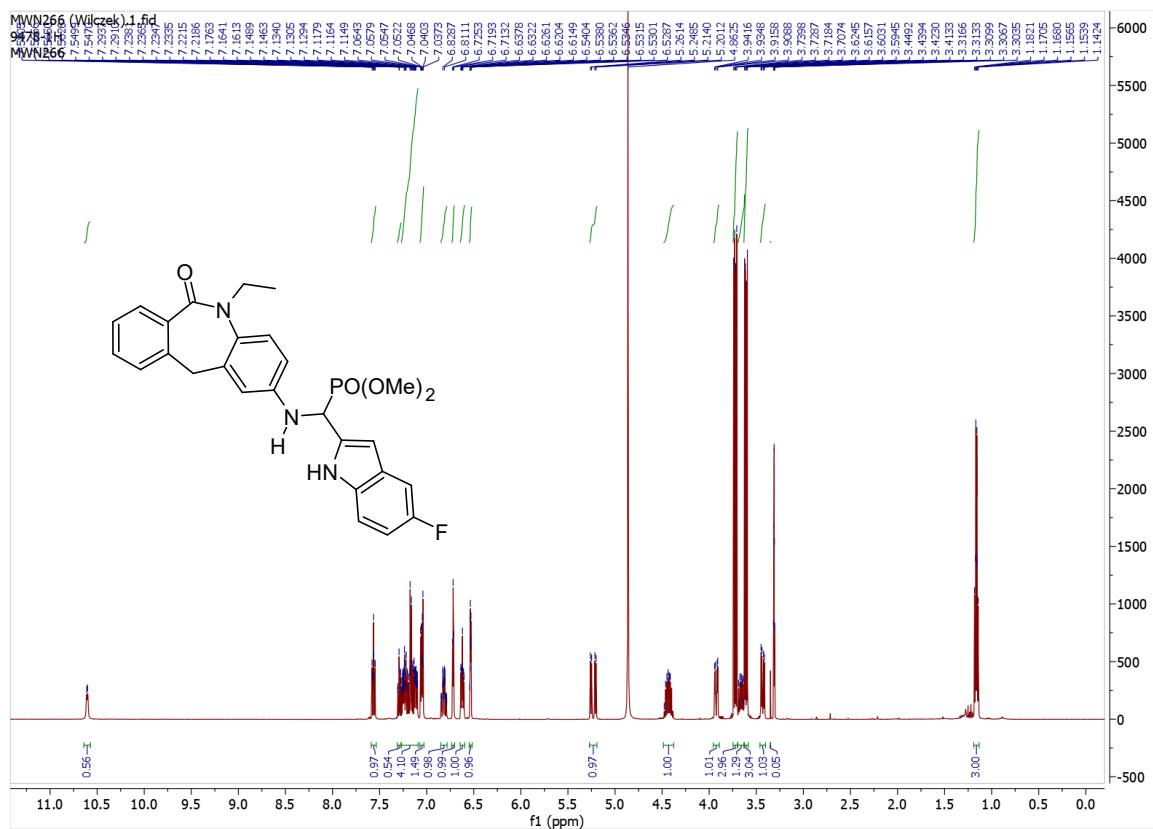


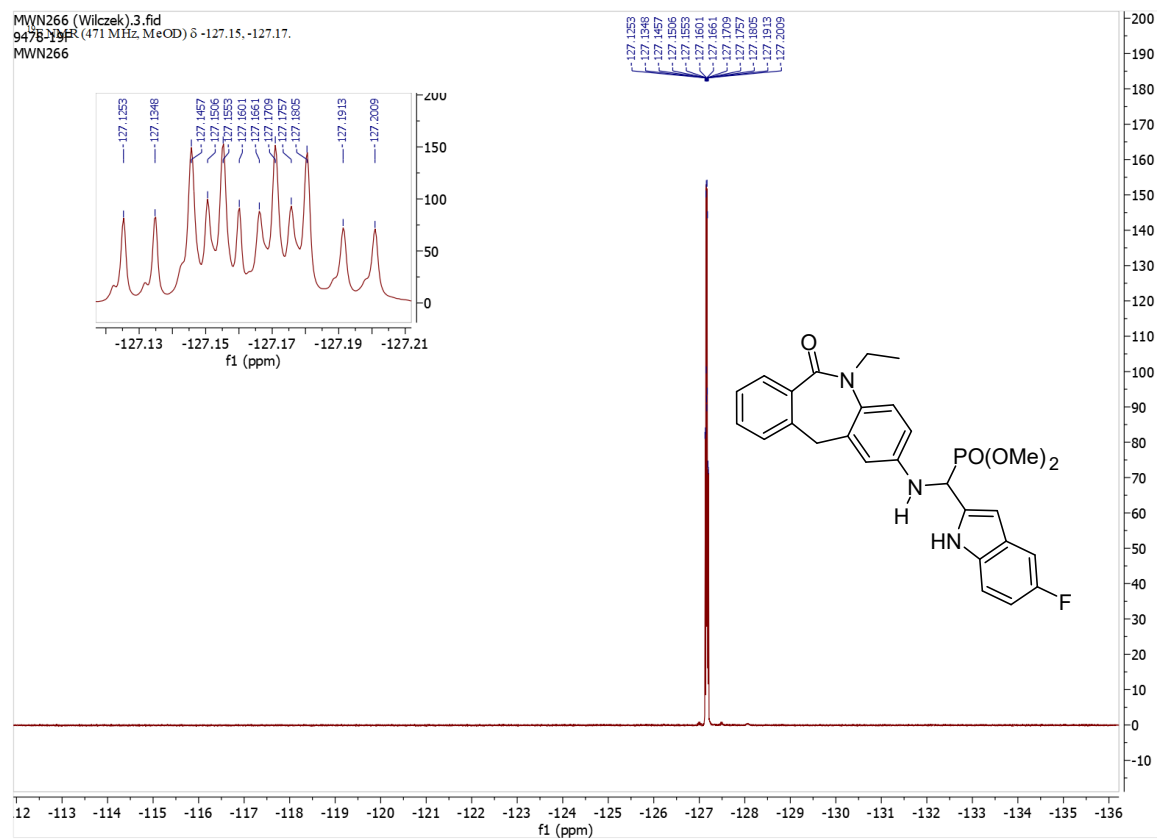
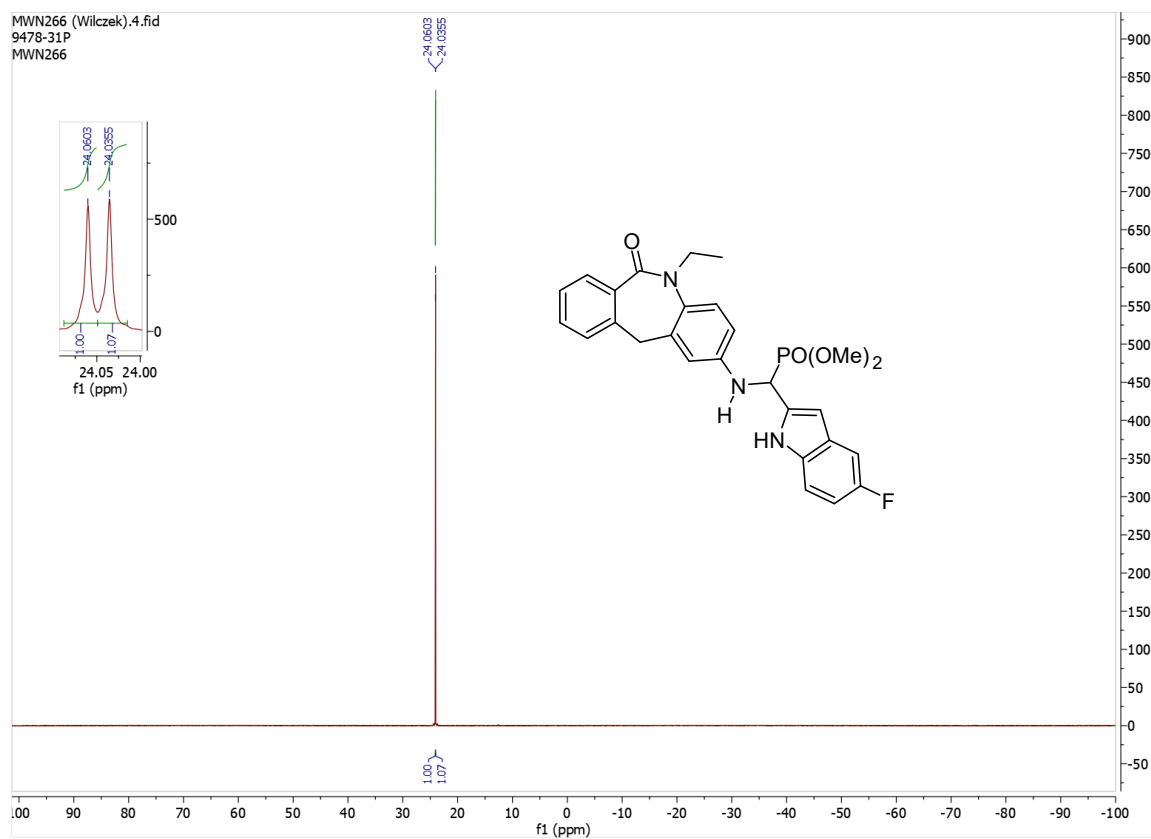
An oven-dried, screw-capped vial was charged with dimethylphosphite (34 mg, 28 μ L, 0.31 mmol, 1.1 equiv), 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (70 mg, 0.28 mmol, 1 equiv), 5-fluoro-1*H*-indole-2-carbaldehyde (45 mg, 0.28 mmol, 1 equiv) and anhydrous 1,4-dioxane (1 mL) and stirred at 80°C for 18 h. The volatiles were evaporated, and the crude was subjected to column chromatography (silica; using AcOEt/cyclohexane: 50-100%). The product was additionally precipitated from the mixture of DCM and *n*-hexane using rotary evaporator and washed with *n*-hexane (2 times) to give 132 mg (96%) of product **31** as brownish foam.

¹H NMR (400 MHz, CDCl₃) δ 9.42-9.31 (m, 1H), 7.76-7.71 (m, 1H), 7.29 (td, *J* = 7.5, 1.6 Hz, 0.5 H), overlapping residual CHCl₃, 7.26-7.16 (m, 2.5H), 7.12-6.98 (m, 3H), 6.87-6.79 (m, 1H), 6.58-6.48 (m, 3H), 5.12-4.63 (m, 1H, CHNH) overlapping {5.02 [d, ²*J*_{HP} = 23.5 Hz, 0.5H, (*CHP*)'], 5.02 (d, ²*J*_{HP} = 23.6 Hz, 0.5H, (*CHP*)''}, 4.59-4.47 (m, 1H, 1/2 CH₂CH₃), 4.05 [d, *J* = 12.9 Hz, 0.5H, 1/2 (ArCH₂Ar')"], 4.04 [d, *J* = 13.1 Hz, 0.5H, 1/2 (ArCH₂Ar')'], 3.80-3.75 (m, 3 H, OCH₃), 3.73-3.61 (m, 1H, 1/2 CH₂CH₃) overlapping 3.60 [d, *J* = 10.7 Hz, 1.5H, (OCH₃)"], 3.59 [d, *J* = 10.7 Hz, 1.5H, (OCH₃)'], 3.31 [d, *J* = 13.0 Hz, 0.5H, 1/2 (ArCH₂Ar')'], 3.30 [d, *J* = 13.2 Hz, 0.5H, 1/2 (ArCH₂Ar')"], {1.24 [t, *J* = 7.1 Hz, 1.5H, (CH₃)'], 1.23 [t, *J* = 7.1 Hz, 1.5H, (CH₃)"]}; ¹H NMR (500 MHz, CD₃OD) δ 10.61 (s, 2xNH_{indole}; partially exchanged with deuterium), 7.59-7.54 (m, 1H), 7.29 (td, *J* = 7.6, 1.4 Hz, 0.5H), 7.27-7.09 (m, 4H), 7.07-7.03 (m, 1.5H), 6.85-6.78 (m, 1H), 6.73-6.70 (m, 1H), 6.64-6.60 (m, 1H), 6.55-6.52 (m, 1H), [5.24 (d, *J* = 23.7 Hz, 0.5H, *CHP*) overlapping 5.22 (d, *J* = 23.7 Hz, 0.5H, *CHP*), 4.48-4.38 (m, 1H, 1/2 NCH₂), [3.93 (d, *J* = 12.9 Hz, 0.5H, 1/2 ArCH₂Ar') overlapping 3.92 (d, *J* = 13.0 Hz, 0.5H, 1/2 ArCH₂Ar')], [3.73 (d, *J* = 10.7 Hz, 1.5H, OCH₃) overlapping, 3.72 (d, *J* = 10.7 Hz, 1.5H, OCH₃)], .3.70-

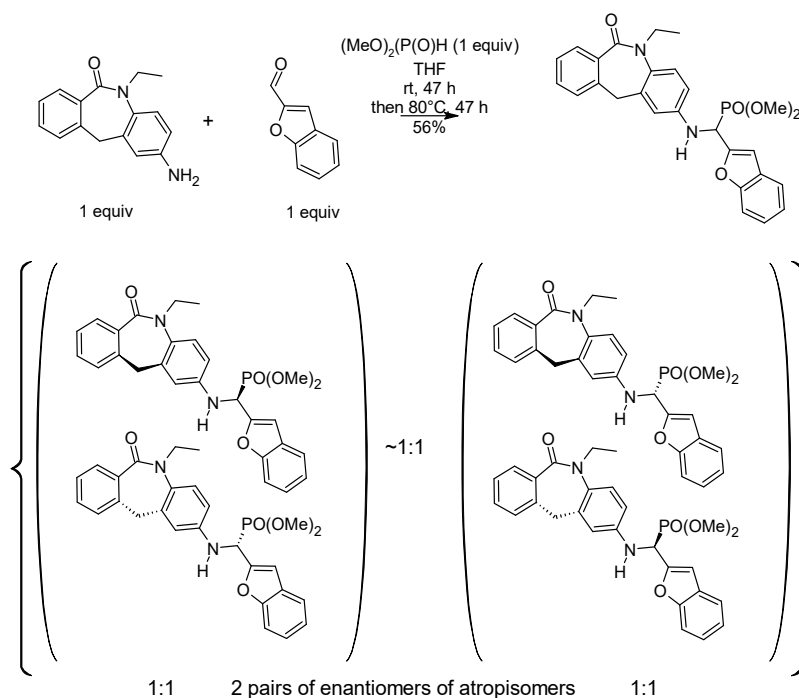
3.63 (m, 1H, 1/2 NCH₂), [3.61 (d, *J* = 10.7 Hz, 1.5H, OCH₃) overlapping, 3.61 (d, *J* = 10.6 Hz, 1.5H, OCH₃)], [3.44 (d, *J* = 13.1 Hz, 0.5H, 1/2 ArCH₂Ar'), overlapping 3.43 (d, *J* = 13.1 Hz, 0.5H, 1/2 ArCH₂Ar')], 1.19-1.14 (m, 3H CH₃); ¹³C NMR (126 MHz, CD₃OD) δ [170.7, (x 2)], 160.1, 158.2, 146.7, 146.6 (x 2), 146.5, [144.3, 144.2], [141.3, 141.2], [136.1, 136.0 (x 2)], [135.9 (x 3)], [134.7 (x 2)], [134.5 (x 2)], [134.2, 134.1], [132.4 (x 2)], [(131.5 (x 2)], [130.8, 130.7], [129.9 (x 3), 129.8 (x 5)], [127.7 (x 2)], [127.1, 127.0], 125.4, 113.7, [113.4, 113.2], (112.9 (x 3), 112.8 (x 2)], [110.9, 110.6], [105.6, 105.4], [103.0 (x 2), 102.9 (x 4), 102.8], [54.7 (x 3), 54.6 (x 3), 54.5, OCH₃], [51.6 (x 2), 51.5 (x 2), 50.4, 50.3 (x 2), 50.2 (CHP)], [45.8 (x 2), (NCH₂)], [39.3, 39.2 (ArCH₂Ar')], 14.0 (CH₃); (most of the signals are multiplied due to the presence of atropisomers, and C-P and C-F couplings); ³¹P NMR (202 MHz, CD₃OD) δ 24.1, 24.0; ¹⁹F NMR (471 MHz, CD₃OD) δ 127.15 (td, *J*_{HF} = 9.6, 4.5 Hz), 127.18 (td, *J*_{HF} = 9.6, 4.5 Hz). LR-MS (*m/z*): 256 [M-{F-indole-CHP(O)(OMe)₂}+2H]⁺, 508 [M+H]⁺, 530 [M+Na]⁺.





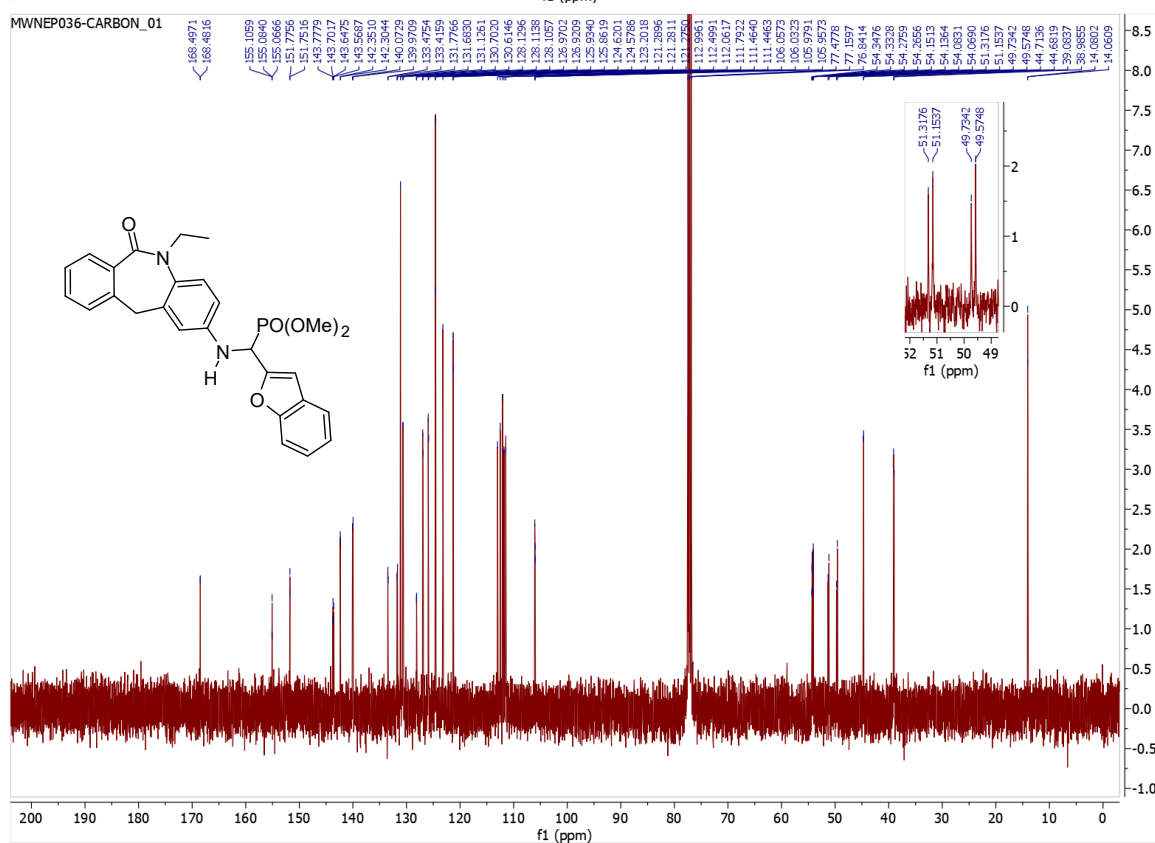
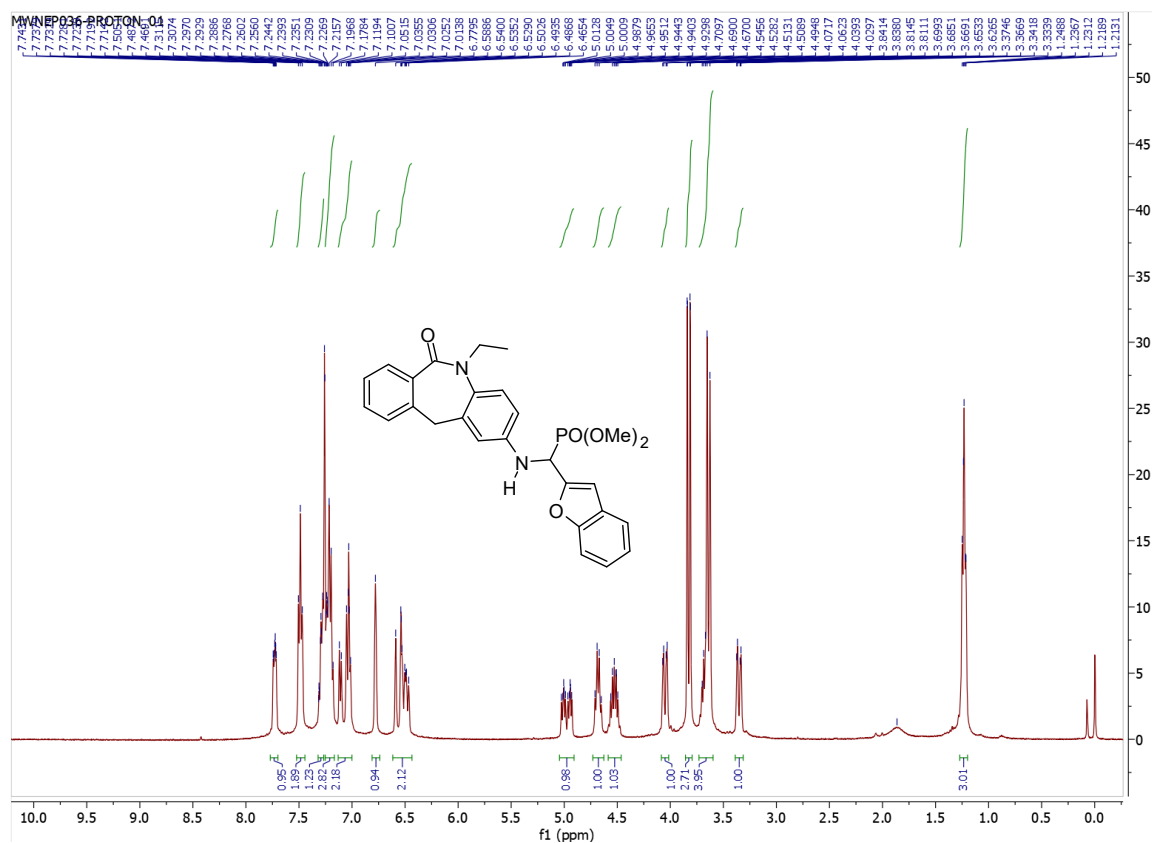


Dimethyl (benzofuran-2-yl((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)methyl)phosphonate (28**)**

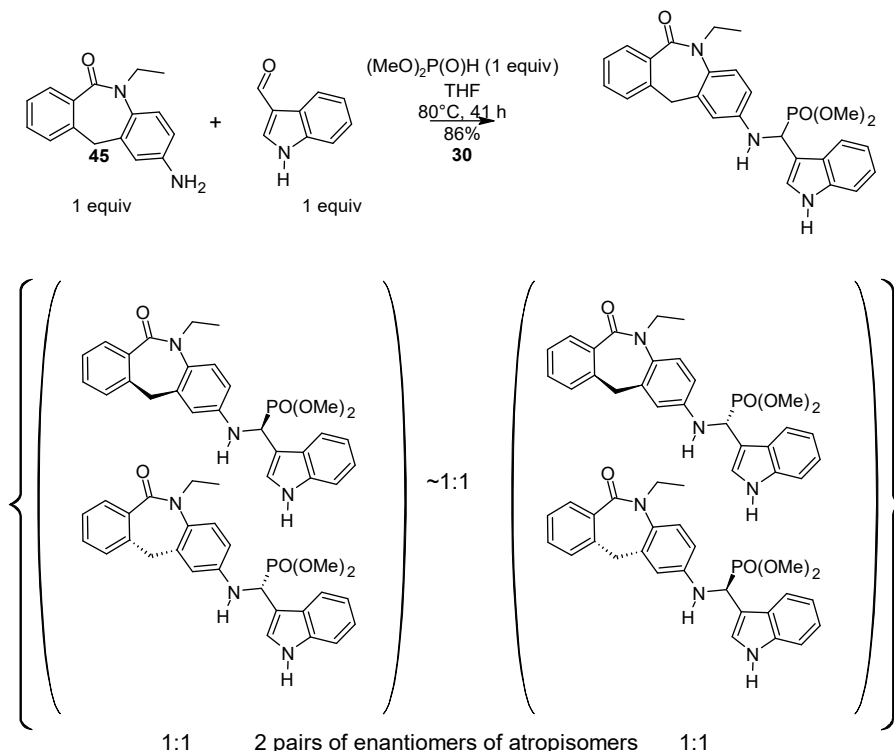


An oven-dried, screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.16 mmol, 1 equiv), anhydrous THF (3 mL) benzo[*b*]furan-2-carboxaldehyde (33 μ l, 0.24 mmol, 1 equiv) and dimethylphosphite (22 μ l, 0.24 mmol, 1 equiv). The reaction mixture was stirred at 80°C for 47 h. The volatiles were evaporated and the residue was subjected to reverse-phase column chromatography (C-18; MeCN/H₂O: 35-50%). The compound was additionally precipitated from the mixture of DCM and *n*-hexane using rotary evaporator, washed with *n*-hexane (2 times) to obtain 65 mg (56%) of product **28** as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.77-7.70 (m, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.32-7.17 (m, 4H) overlapped with residual CHCl₃, 7.13-7.00 (m, 2H), 6.78 (s, 1H, OC=CH_{furan}), 6.62-6.44 (m, 2H), 5.04-4.91 (m, 1H, *CHP*), 4.73-4.63 (m, 1H, *NH*), 4.59-4.46 (m, 1H, $\frac{1}{2}$ CH₂CH₃), 4.09-4.01 (m, 1H, $\frac{1}{2}$ ArCH₂Ar'), 3.83 (d, ³*J*_{HP} = 10.8 Hz, 1.5H, OCH₃) overlapping 3.82 (d, ³*J*_{HP} = 10.8 Hz, 1.5H, OCH₃), 3.73-3.61 (m, 1+3H, $\frac{1}{2}$ CH₂CH₃, OCH₃), 3.39-3.31 (m, 1H, $\frac{1}{2}$ ArCH₂Ar'), 1.27-1.20 (m, 3H, CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ (168.5 (x 2); CO), [155.1 (x 2)], [151.8 (x 2)], [143.8, 143.7, (143.6 x 2)], [142.4, 142.3], [140.1, 140.0], [133.5, 133.4], [131.8, 131.7], 131.1, [130.7, 130.6], [128.1 (x 3)], [127.0, 126.9], [125.9 (x 2)], 124.6 (x 2), 123.2, [121.3, 121.3 (x 2)], 113.0, 112.5, 112.1, 111.8, [111.5, 111.4], 106.1, [106.0 (x 3)], [54.3 (x 4), 54.2, 54.1 (x 3); (2 x OCH₃)], [50.5 (d, ¹*J*_{CP} = 159.9, CP) overlapping 50.4 (d, ¹*J*_{CP} = 159.5, CP)], [44.7 (x 2); (NCH₂CH₃)], [39.1, 39.0; (ArCHAr')], [14.1 (x 2); CH₃]; (the signals are multiplied due to the presence of atropisomers and C-P couplings). LR-MS (*m/z*): 491 [M+H]⁺.

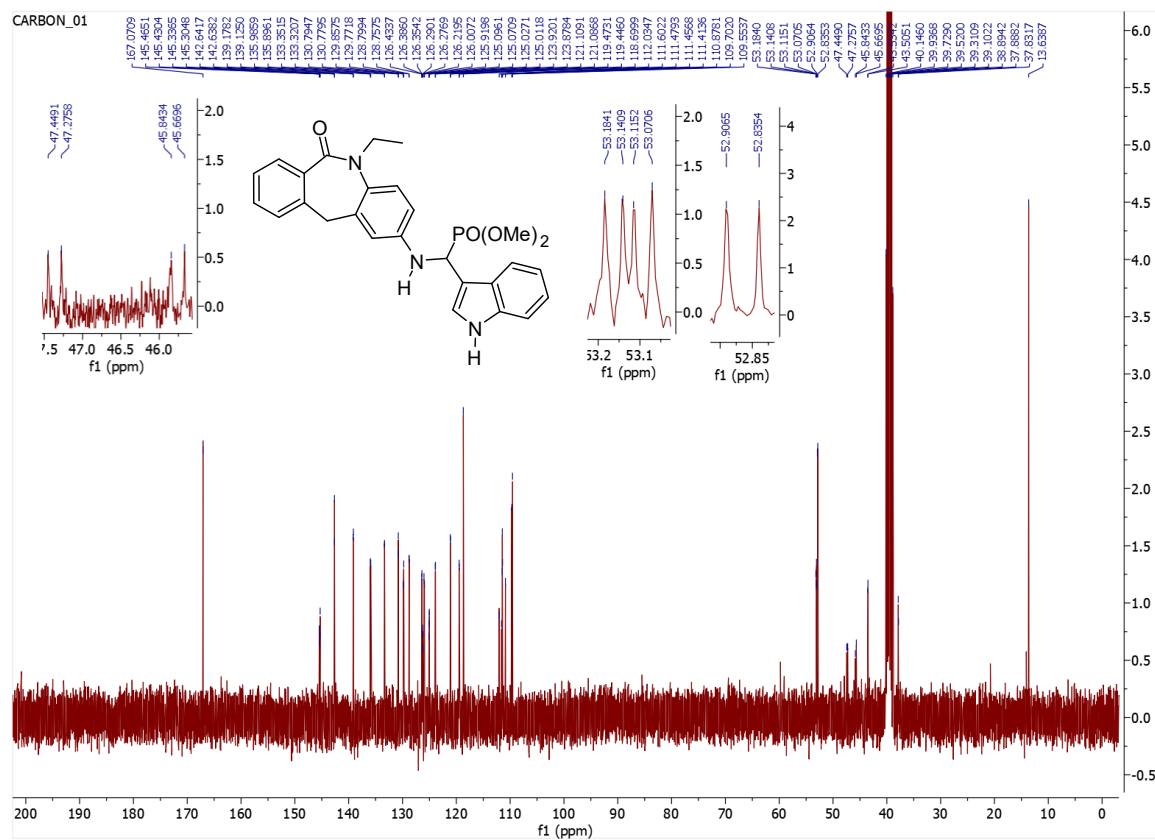
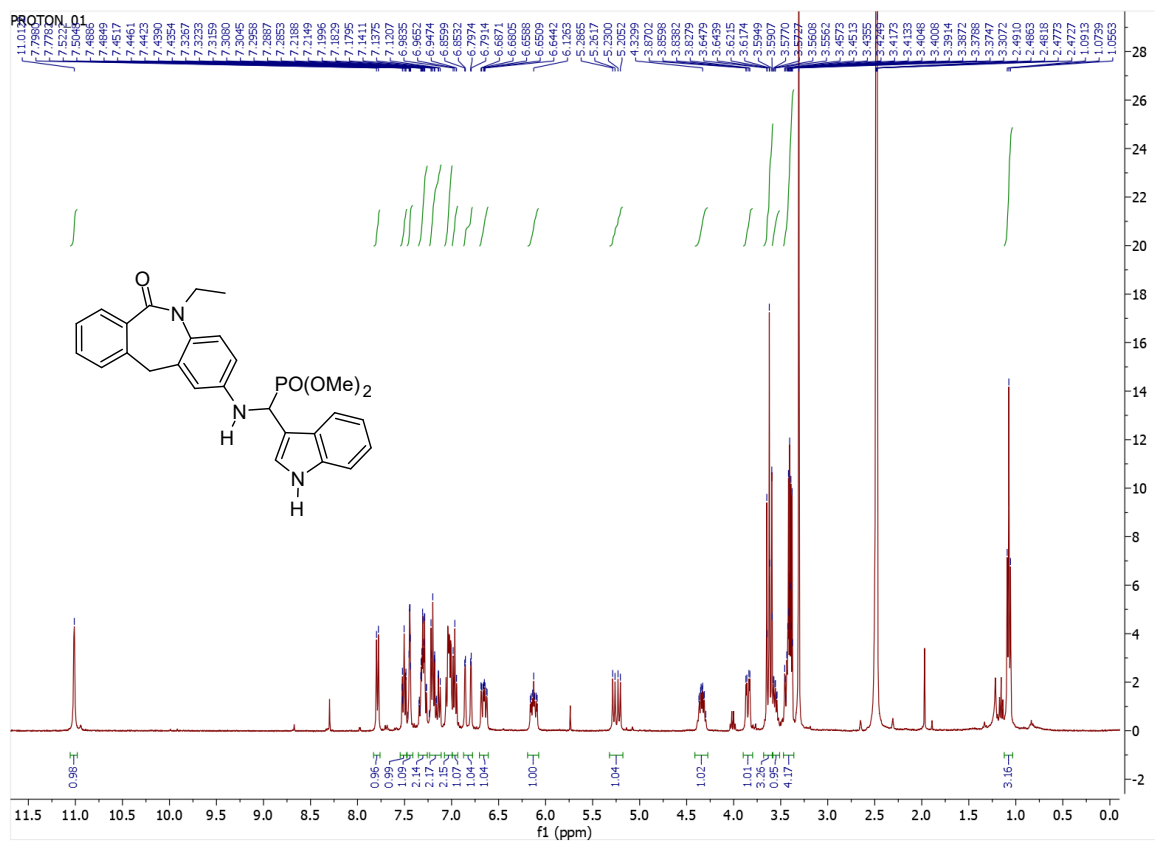


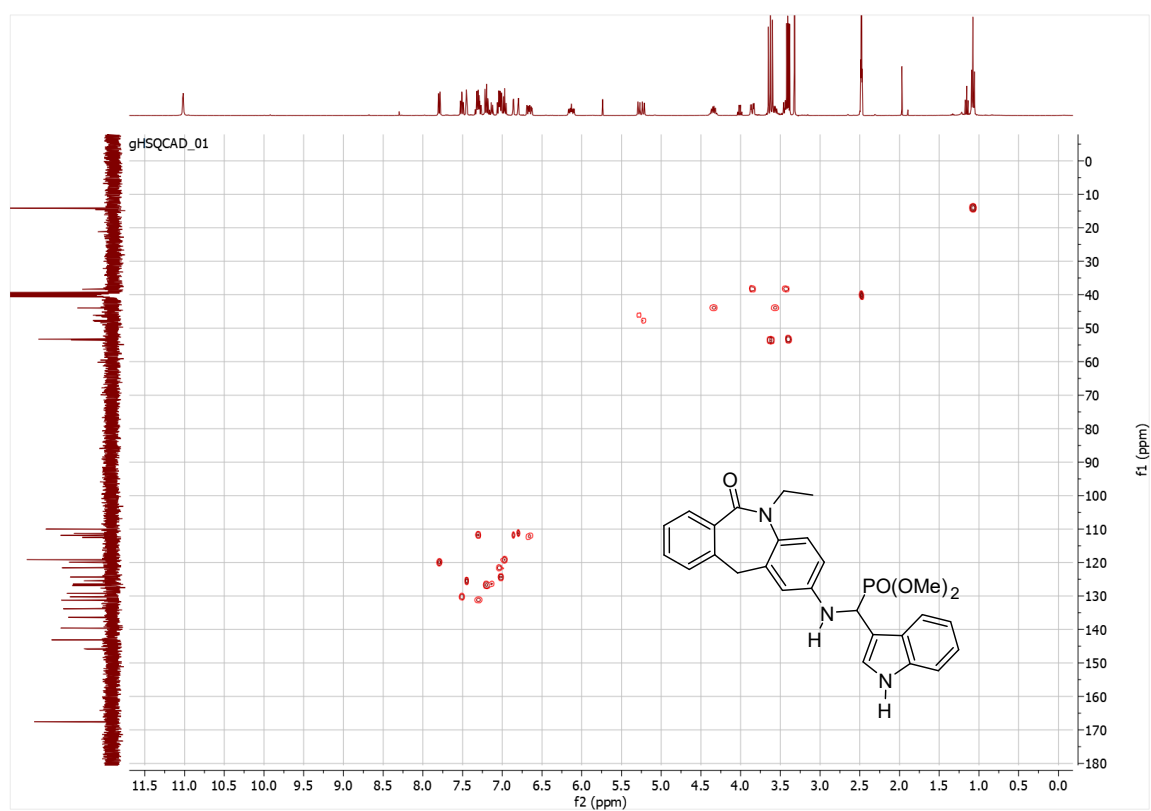
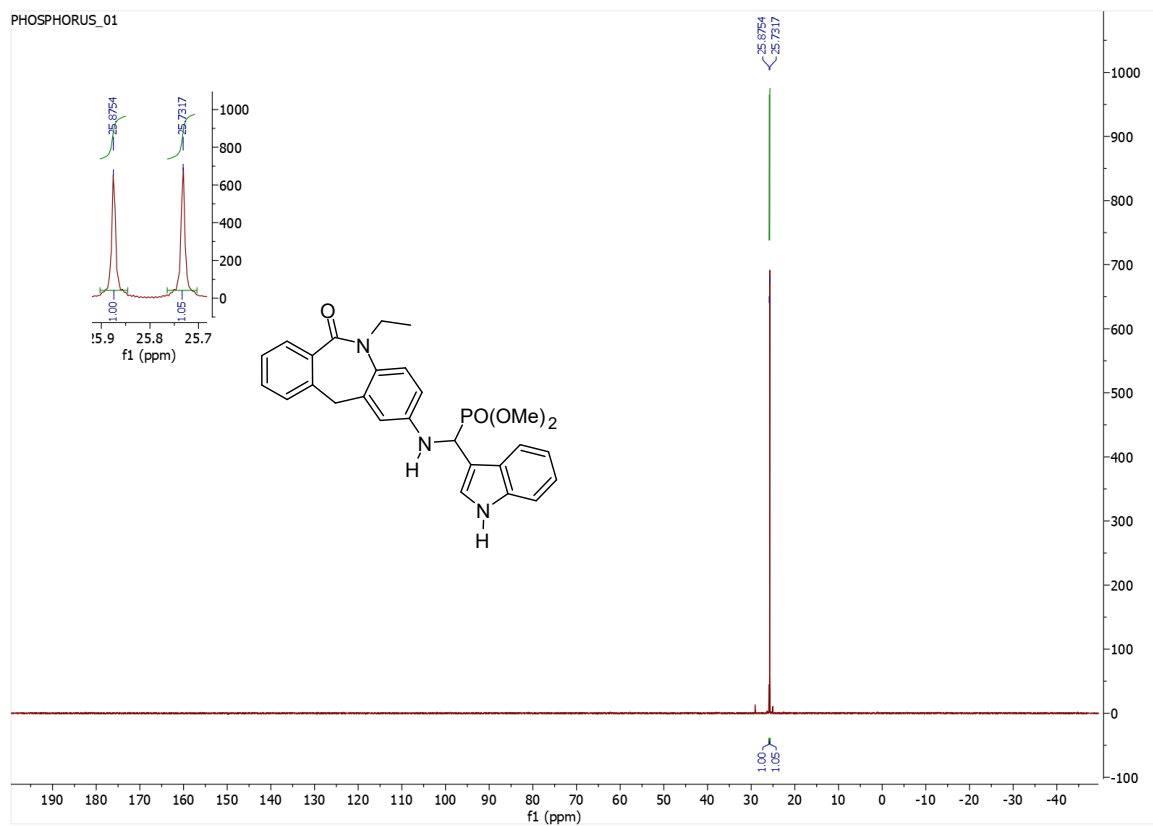
Dimethyl (((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)(1*H*-indol-3-yl)methyl)phosphonate (30**)**

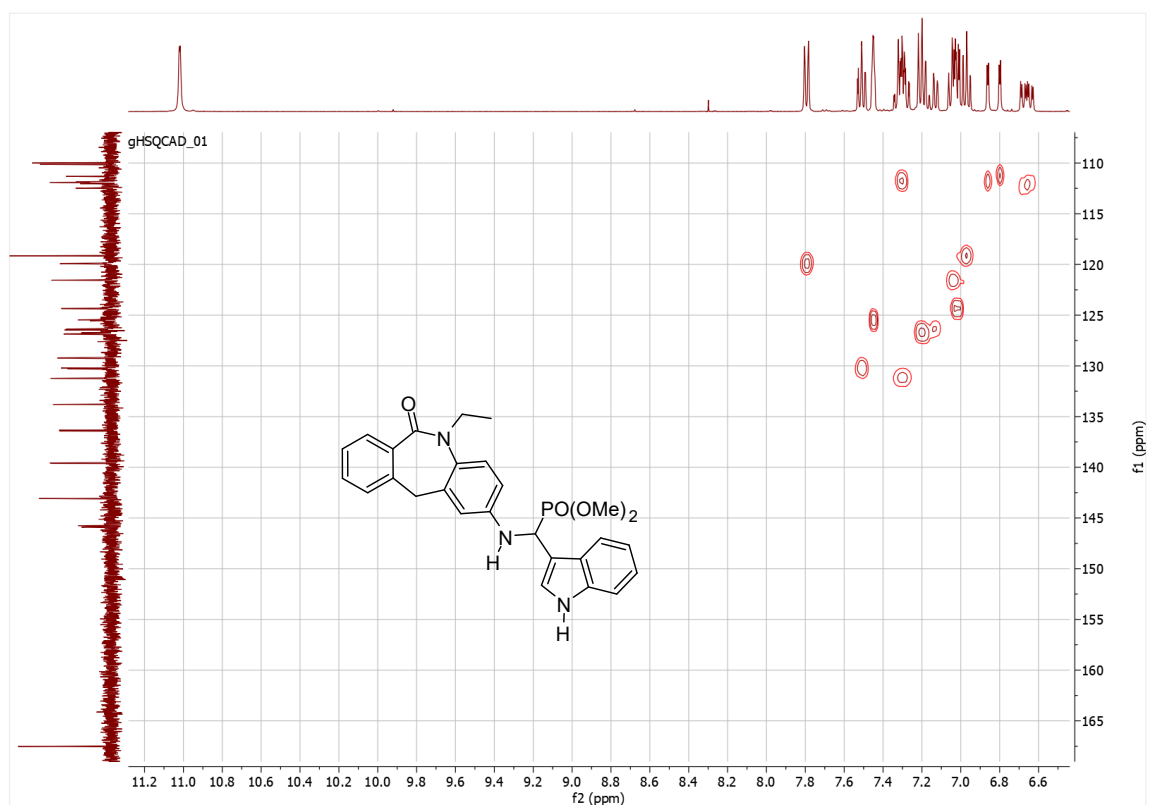
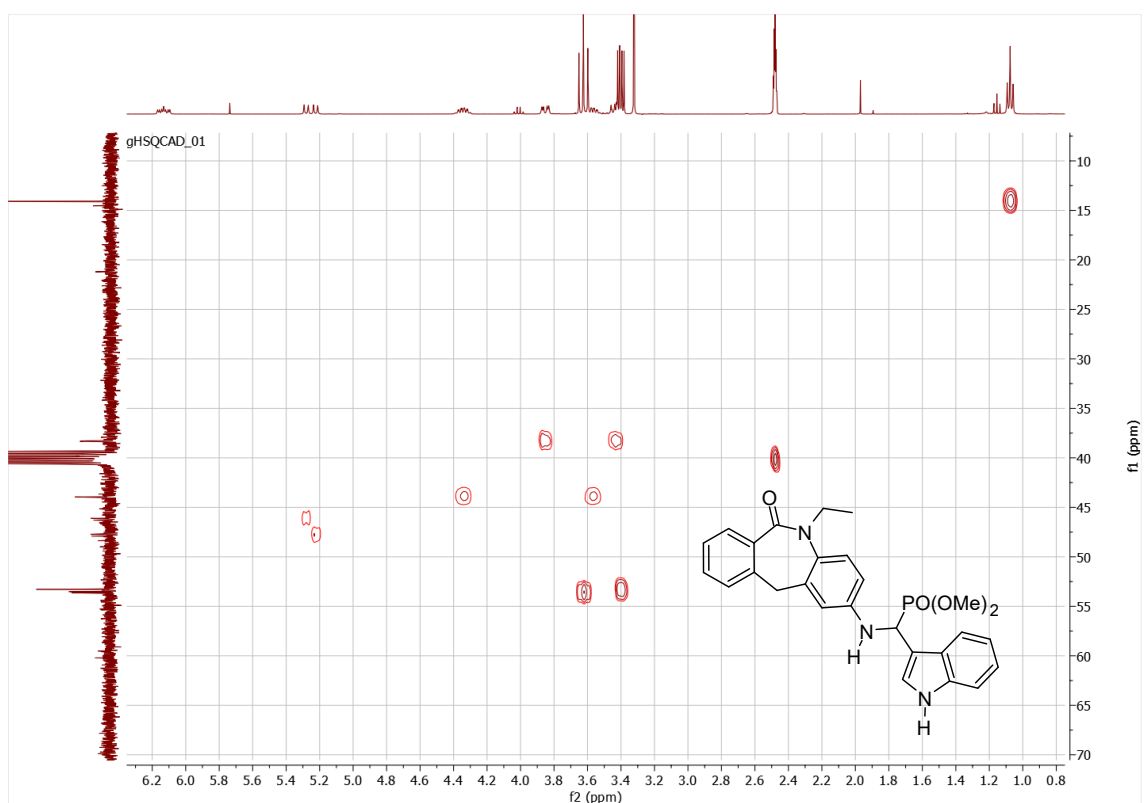


An oven-dried, screw-capped vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (75 mg, 0.30 mmol, 1 equiv), indole-3-carboxaldehyde (43 mg, 0.30 mmol, 1 equiv), dimethylphosphite (33 mg, 27 μ L, 0.30 mmol, 1 equiv), anhydrous THF (1.5 mL) and the mixture was stirred at 80°C for 41 h. The volatiles were evaporated and the crude was subjected to column chromatography (silica; AcOEt/cyclohexane: 33-100%, then MeOH/AcOEt 5%) to obtain 126 mg (86%) of product **30** as a yellow solid.

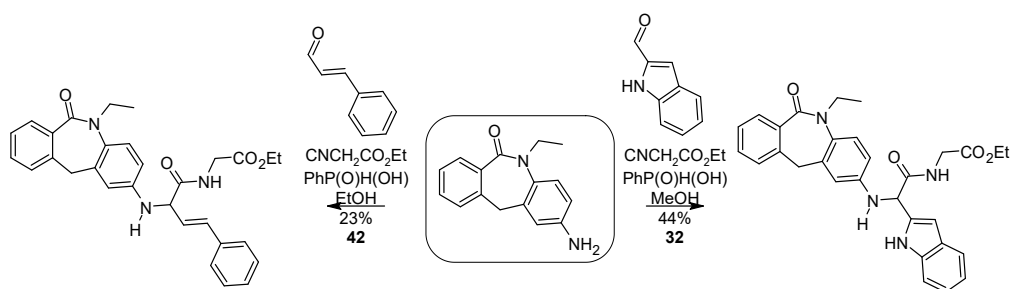
^1H NMR (400 MHz, DMSO- d_6) δ 11.01 (s, 1H, *NH* indole), 7.82-7.76 (m, 2H), 7.54-7.48 (m, 1H), 7.47-7.43 (m, 1H), 7.35-7.26 (m, 2H), 7.24-7.11 (m, 2H), 7.08-6.98 (m, 2H), 6.99-6.94 (m, 1H), 6.87-6.78 (m, 1H), 6.70-6.61 (m, 1H), 6.18-6.08 (m, 1H), 5.32-5.19 (m, 1H, *NHCHP*), 4.41-4.28 (m, 1H, $\frac{1}{2}$ CH_2CH_3), 3.85 (dd, $J = 12.8, 4.1$ Hz, 1H, $\frac{1}{2}$ $\text{ArCH}_2\text{Ar}'$), 3.66-3.52 [m, 4H, (OCH_3)*, $\frac{1}{2}$ CH_2CH_3], 3.47-3.37 [m, 4H, $\frac{1}{2}$ $\text{ArCH}_2\text{Ar}'$, (OCH_3)**], 1.07 (t, $J = 7.0$ Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, DMSO- d_6) δ 167.1 (CONH), [145.5, 145.4, 145.3 (x 2)], [142.6 (x 2)], [139.2, 139.1], [136.0, 135.9], [133.4, 133.3], [130.8 (x 2)], [129.9, 129.8], [128.8 (x 2)], [126.4 (x 2)], [126.4, 126.3 (x 2), 126.2], [126.0, 125.9], [125.1 (x 2), 125.0 (x 2)], 123.9 (x 2), [121.1 (x 2)], [119.5, 119.4], 118.7, 112.0, [111.6, 111.5], [115, 111.4], 110.9, [109.7, 109.6], 53.1 [d, $^2J_{\text{CP}} = 7.0$ Hz, (OCH_3 *)], 53.1 [d, $^2J_{\text{CP}} = 7.1$ Hz, (OCH_3 *)], 52.9 [d, $^2J_{\text{CP}} = 7.2$ Hz, (OCH_3)**], [46.6 (d, $^1J_{\text{CP}} = 162.2$ Hz, *PCHNH*) overlapping 46.5 (d, $^1J_{\text{CP}} = 162.2$ Hz, *PCHNH*)], [43.5 (x 2); (CH_2CH_3)], [37.9, 37.8 ($\text{ArCH}_2\text{Ar}'$)], 13.6 (CH_3); (most of the signals are multiplied due to the presence of atropisomers and C-P couplings). ^{31}P NMR (162 MHz, DMSO- d_6) δ 25.9, 25.7). LR-MS (m/z): 490 [$\text{M}+\text{H}$] $^+$.



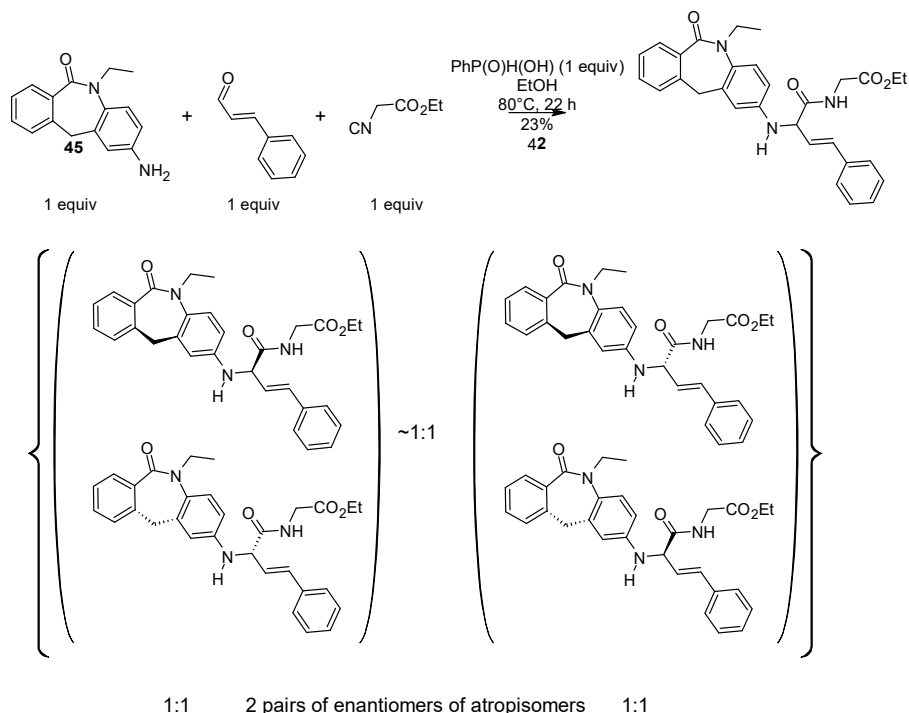




Synthesis of 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one derivatives 32 and 42 using Ugi reaction.

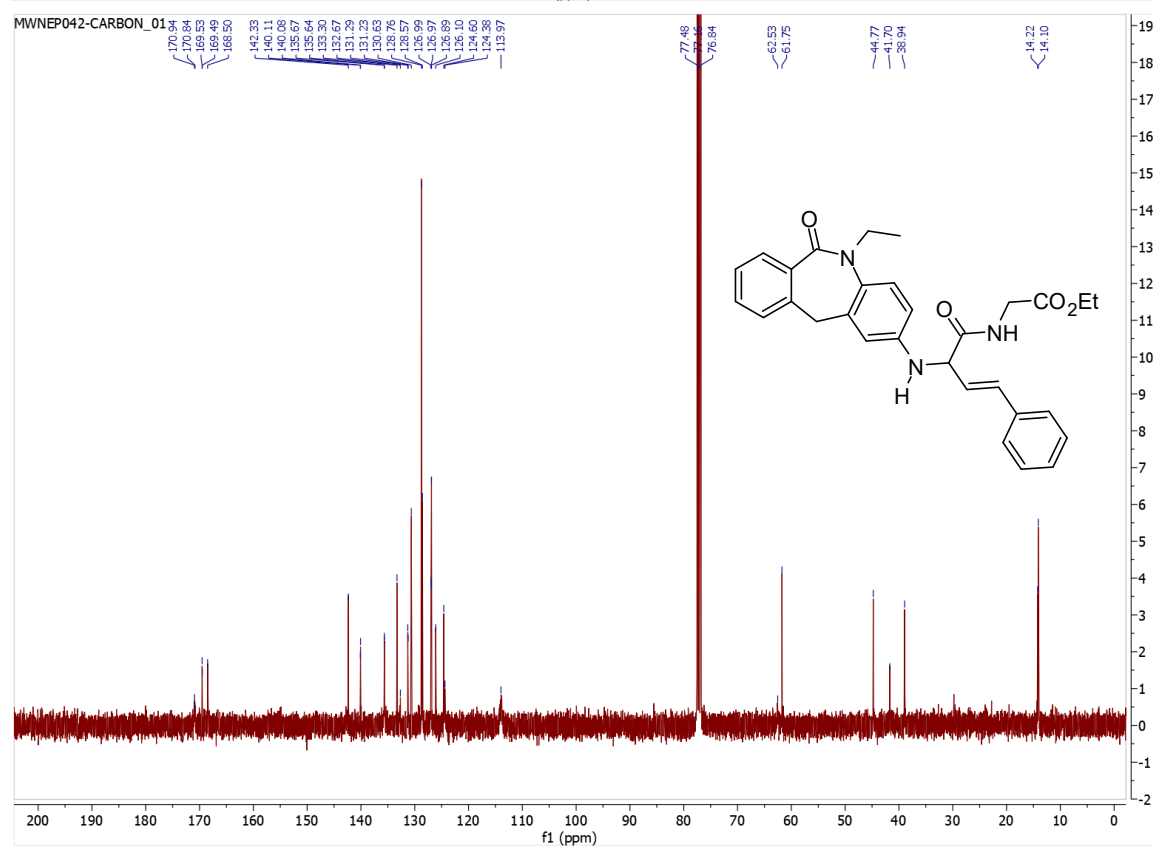
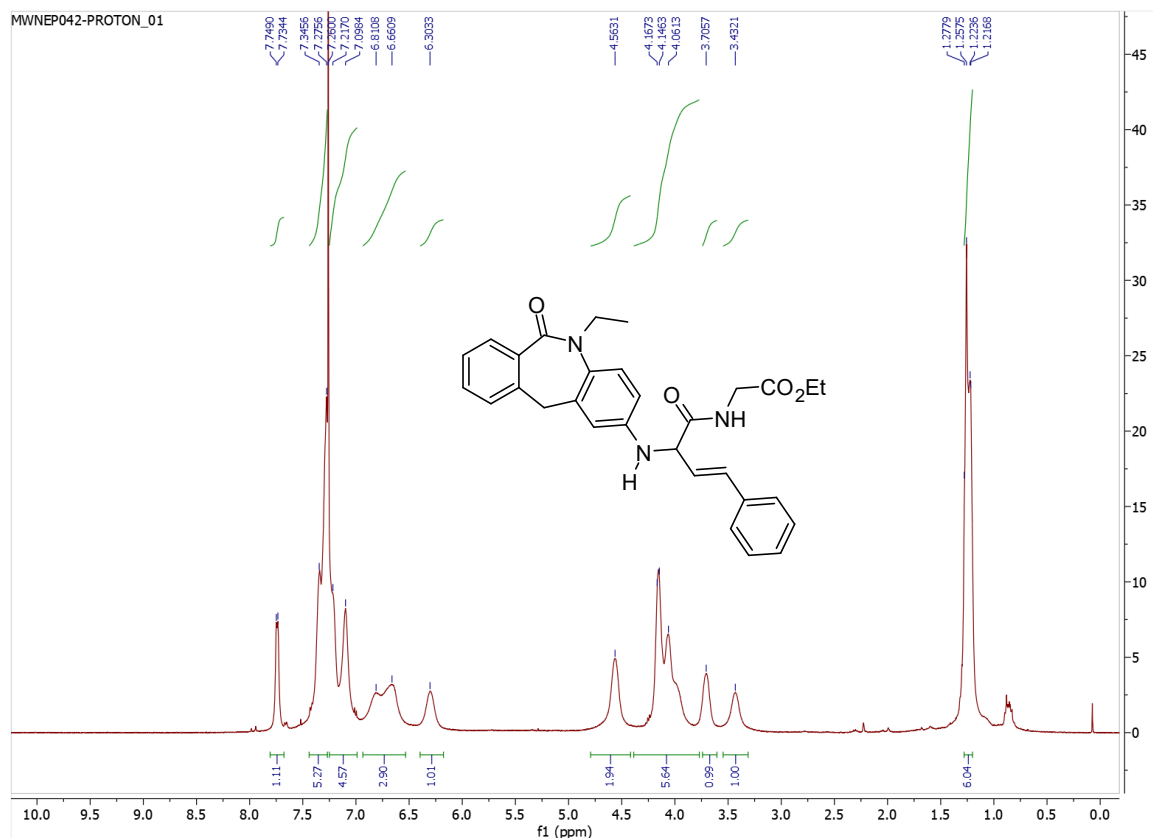


Ethyl (*E*)-(2-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-4-phenylbut-3-enoyl)glycinate (42**)**

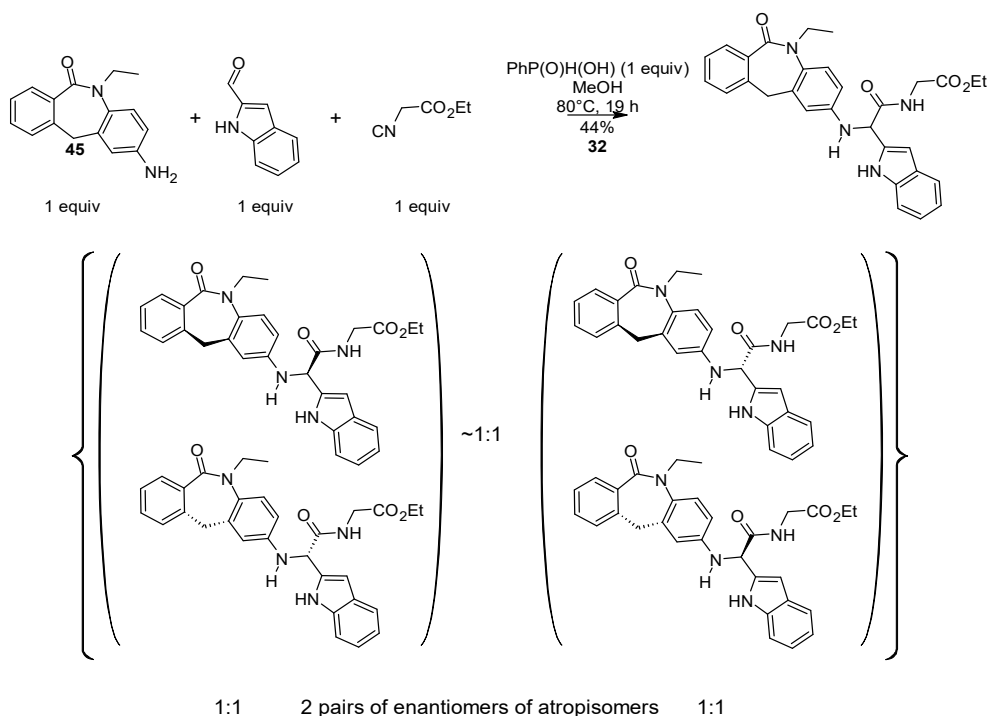


An oven-dried, screw-cap vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.24 mmol, 1 equiv), anhydrous EtOH (1.5 mL), *trans*-cinnamaldehyde (30 μ L, 31.4 mg, 0.24 mmol, 1 equiv), ethyl isocyanoacetate (26 μ L, 0.24 mmol, 1 equiv) and phenylphosphinic acid (34 mg, 0.24 mmol, 1 equiv), and the mixture was stirred at 80°C for 22 h. The volatiles were evaporated, and the crude was subjected to column chromatography (silica; acetone/DCM: 1-5%). The product was additionally purified using reverse phase column chromatography (C-18; MeCN/H₂O: 40-50%) and by precipitation from the mixture of DCM and *n*-hexane using rotary evaporator, followed by washing with *n*-hexane (2 times). This gave 27 mg (23%) of product **42** as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.79-7.70 (m, 1H), 7.42-6.99 (m, 10 H) overlapped with residual CHCl₃, 4.56 (s, 1H), 6.95-6.62 (m, 3H), 6.41-6.18 (m, 1H), 4.79-4.42 (m, 2H), 4.32-3.81 (m, 6 H), 3.79-3.60 (m, 1H), 3.54-3.31 (m, 1H), 1.31-1.17 (m, 6H; 2 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ [179.9, 179.8; br (CO)] [169.5 (x 2); (CO)], 168.5 (CO), 142.3, [140.1 (x 2)], [135.7, 135.6], 133.3, 132.7 (br), [131.3, 131.2], 130.6, 128.8, 128.6, [127.0 (x 2)], 126.9, 126.1, 124.6, 124.4 (br), 114.0 (br), 62.5 (br), 61.7, 44.8, 41.7, 38.9, 14.2 (CH₃), 14.1 (CH₃); the broadened peaks in ¹H and ¹³C NMR spectra are caused by the dynamic effects and doubled due to the presence of atropisomers. LR-MS (*m/z*): 498 [M+H]⁺.

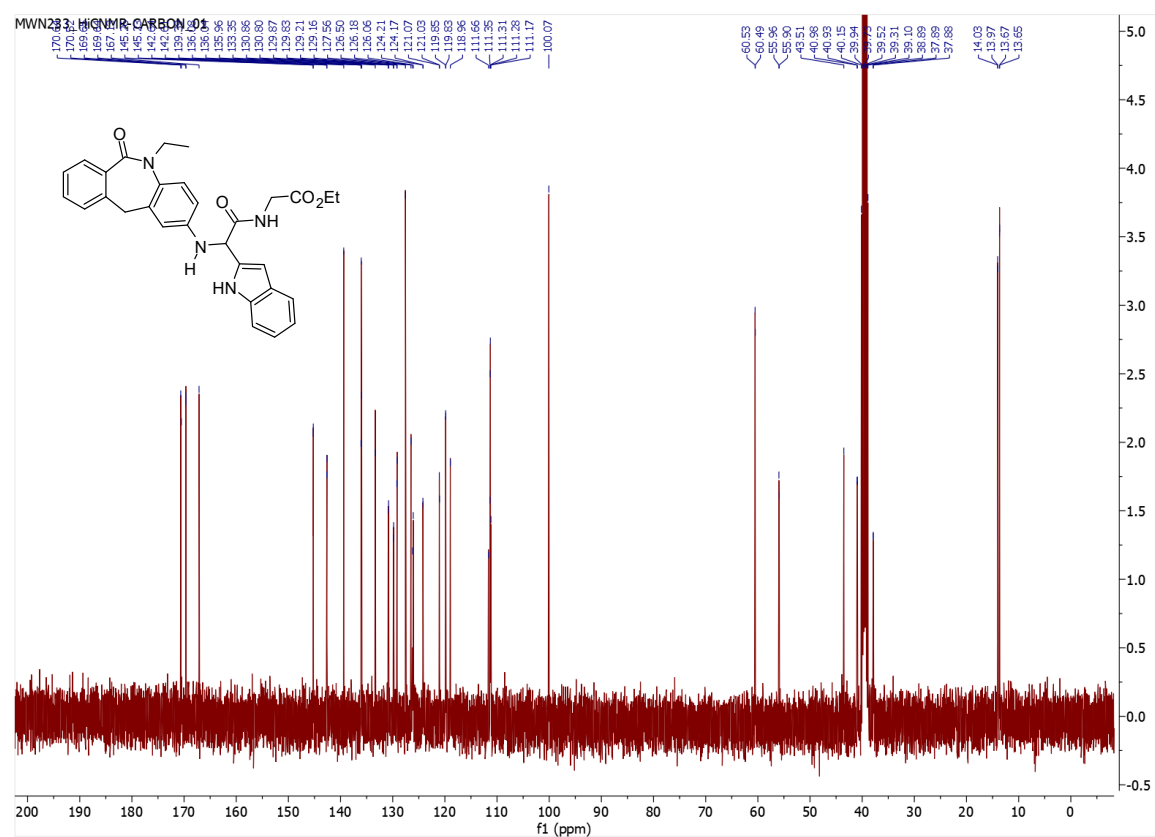
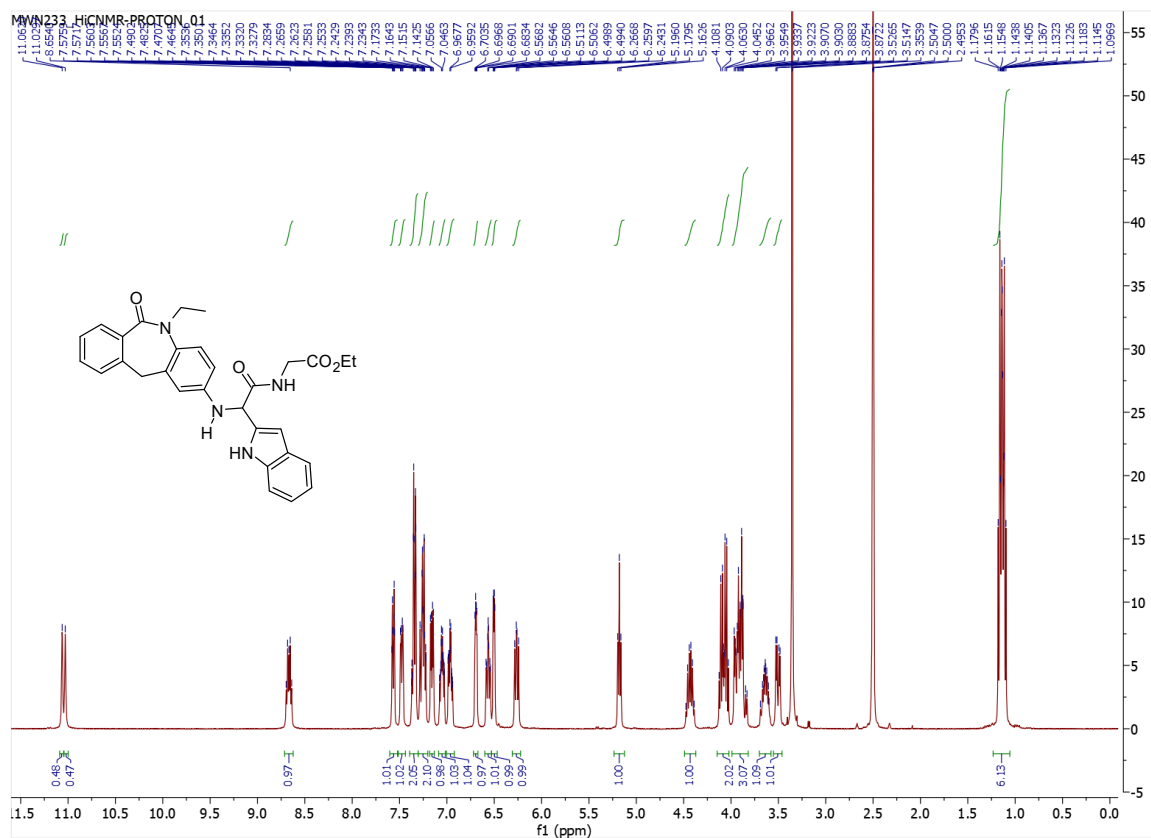


Ethyl (2-((5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)amino)-2-(1*H*-indol-2-yl)acetyl)glycinate (32**)**

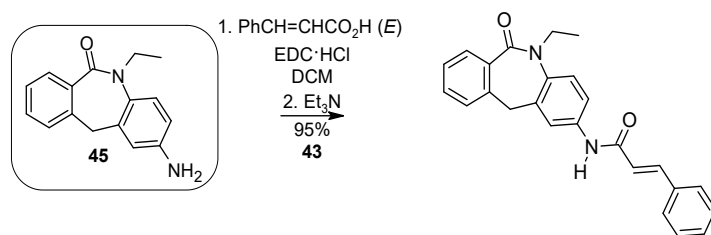


An oven-dried, screw-cap vial was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.24 mmol, 1 equiv), 1*H*-indole-2-carbaldehyde (35 mg, 0.24 mmol, 1 equiv), ethyl isocyanoacetate (26 μ L, 0.24 mmol, 1 equiv), phenylphosphinic acid (33 mg, 0.24 mmol, 1 equiv) and anhydrous MeOH (1 mL). The mixture was stirred at 80°C for 19h, cooled to rt. The resulting precipitate was filtrated, washed with MeOH (5 x 0.5 mL) and dried to obtain 53 mg (44%) of product **32** as a white solid.

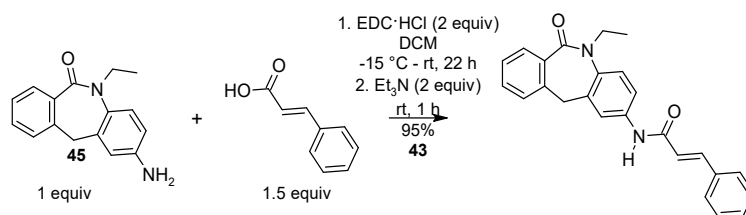
^1H NMR (400 MHz, DMSO- d_6) δ [11.06 (s, 1, 0.5H, $\text{NH}_{\text{indole}}$), 11.03 (s, 1, 0.5H, $\text{NH}_{\text{indole}}$)], 8.71-8.62 (m, 1H), 7.60-7.54 (m, 1H), 7.51-7.45 (m, 1H), 7.38-7.31 (m, 2H), 7.30-7.21 (m, 2H), 7.18-7.13 (m, 1H), 7.08-7.02 (m, 1H), 7.00-6.93 (m, 1H), 6.72-6.66 (m 1H), 6.61-6.53 (m, 1H), 6.53-6.48 (m, 1H), 6.30-6.23 (m, 1H), [5.19 (d, J = 6.6 Hz, 0.5H, NHCHCONH) overlapping 5.17 (d, J = 6.7 Hz, 0.5H)], 4.49-4.37 (m, 1H, $\frac{1}{2}$ NCH_2CH_3), [4.10 (q, J = 7.1 Hz, 1H OCH_2) overlapping 4.05 (d, J = 7.1 Hz, 1H, OCH_2)], 3.99-3.81 (m, 3H), 3.70-3.57 (m, 1H, $\frac{1}{2}$ NCH_2CH_3), [3.51 (d, J = 13.0 Hz, 0.5H, $\text{ArCH}_2\text{Ar}'$) overlapping 3.50 (d, J = 13.0 Hz, 0.5H, $\text{ArCH}_2\text{Ar}'$)], 1.20-1.07 (m, 6H, 2 x CH_2CH_3). ^{13}C NMR (101 MHz, DMSO- d_6) δ [170.6, 170.5 (CO)], [169.7, 169.6; CO], 167.1 (CO), [145.3, 145.2], [142.6 (x 2)], 139.4, 136.1, 136.0 (x 2), 133.3, [130.9, 130.8], [129.9, 129.8], [129.2 (x 2)], 127.6, 126.5, 126.2, 126.1, [124.2 (x 2)], [121.1, 121.0], [119.9, 119.8], 119.0, 111.7, 111.4, 111.3 (x 2), 111.2, 100.1, [60.5 (x 2); OCH_2], [56.0, 55.9], 43.5, [41.0, 40.9], [37.9 (x 2)], [14.0 (x 2); CH_3], [13.7 (x 2); CH_3]; (doubled signals are caused by the presence of atropisomers). LR-MS (m/z): 259 [$\text{M}-\{\text{ArNH}\}^+$], 511 [$\text{M}+\text{H}^+$].



Synthesis of the *N*-(5-ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)cinnamamide 43.

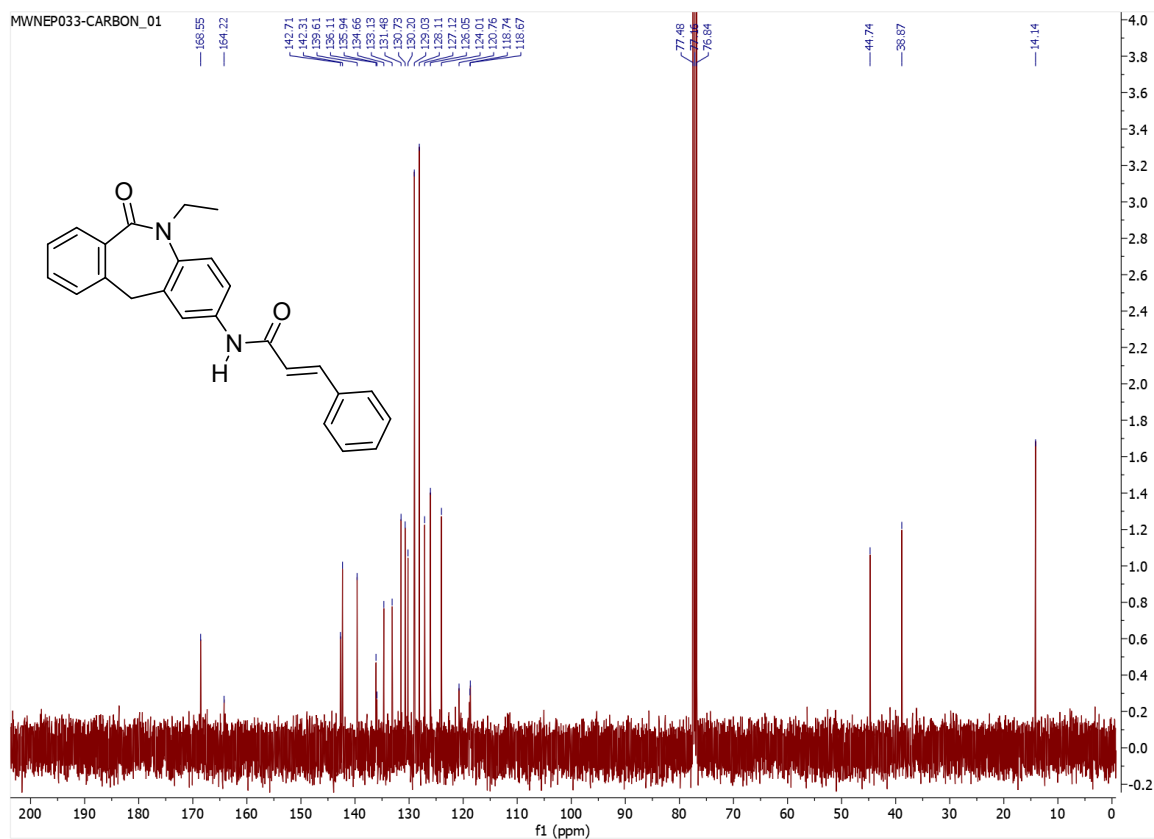
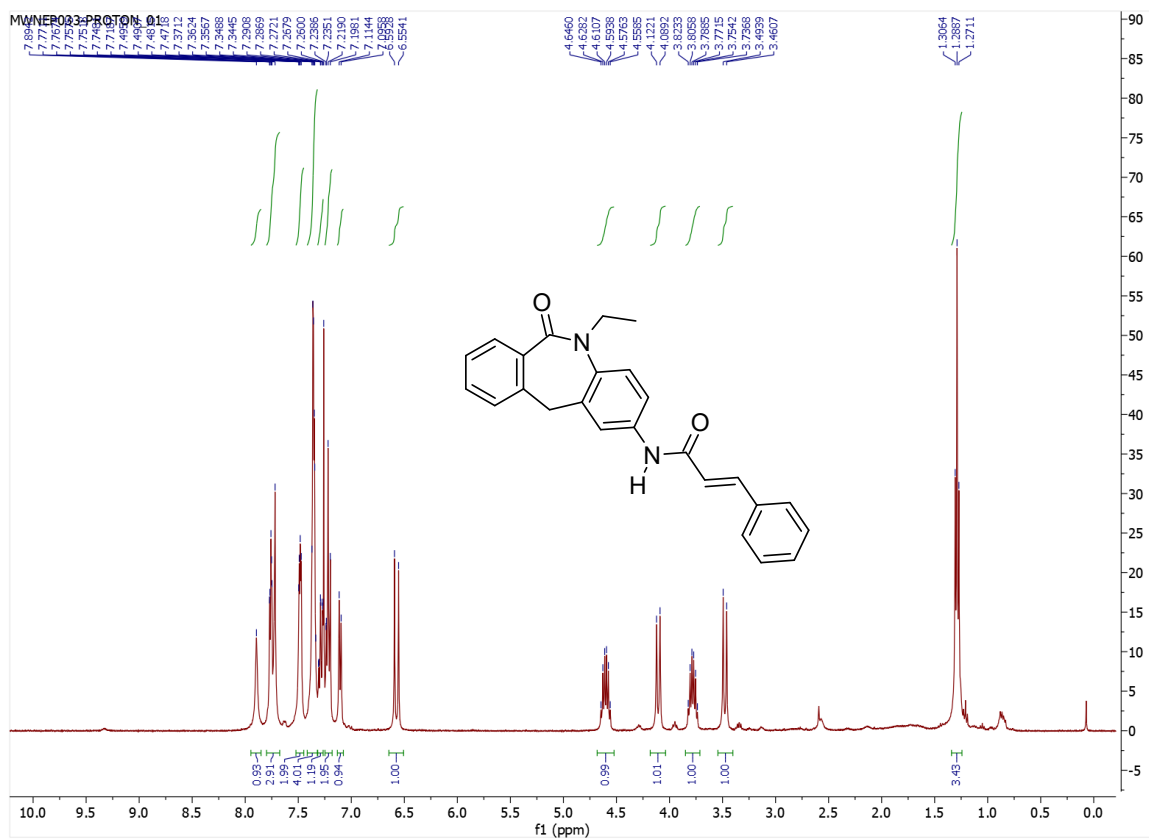


***N*-(5-Ethyl-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-2-yl)cinnamamide (**43**)**

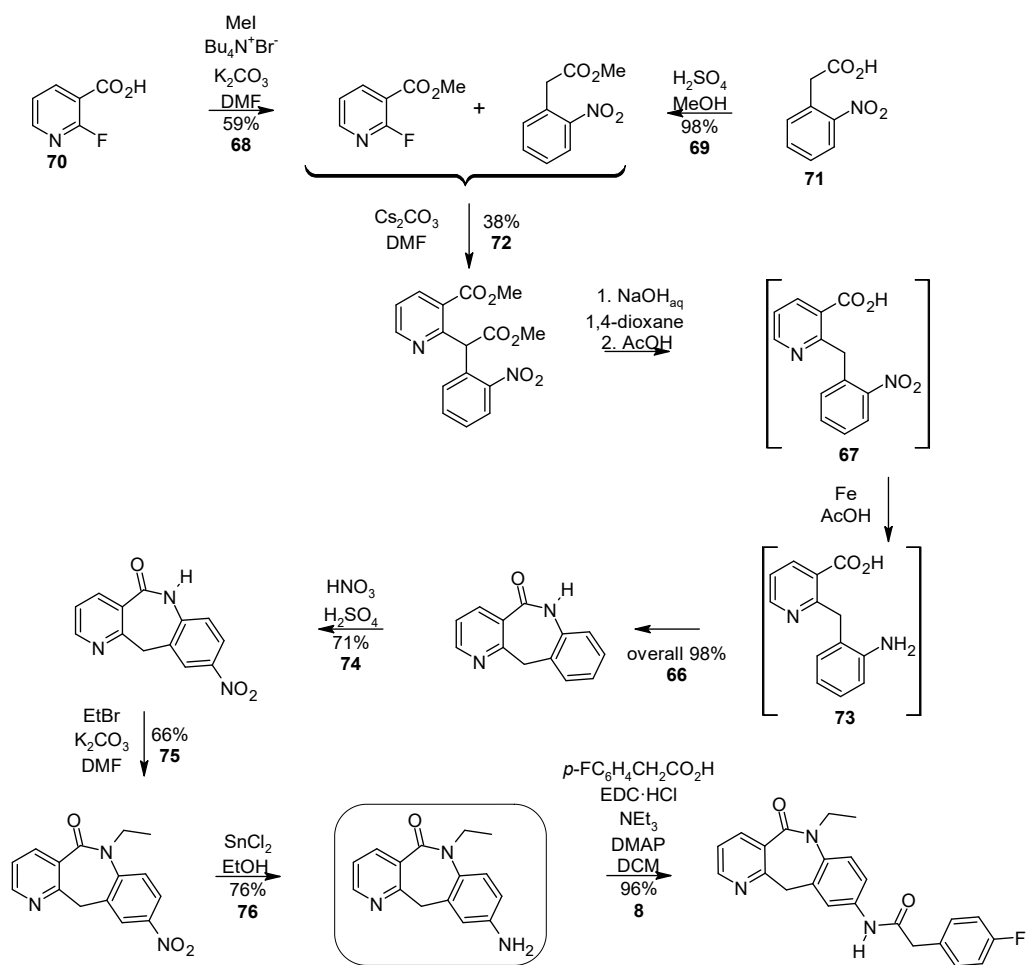


An oven-dried, round-bottom bulb was charged with 2-amino-5-ethyl-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one **45** (60 mg, 0.24 mmol, 1 equiv), cinnamic acid (55 mg, 0.36 mmol, 1.5 equiv) and anhydrous DCM (3 mL). The mixture was stirred at rt for 30 min, cooled to -15°C (NaCl_{aq} - CO₂) and EDC·HCl (92 mg, 0.48 mmol, 2 equiv) was added. The reaction was allowed to warm to rt and stirred for 22 h. To the reaction mixture was added Et₃N (66 µl, 0.47 mmol, 2 equiv) and after stirring at rt for 1 h, the volatiles were evaporated. The residue was subjected to reverse phase column chromatography (C-18; MeCN/H₂O: 30-70%). The product was additionally repurified by precipitation from the mixture of DCM and *n*-hexane using rotary evaporator and washing with *n*-hexane (2 times). This gave 86 mg (95%) of product **43** as a white solid.

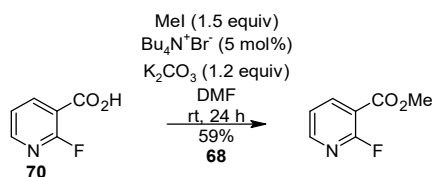
¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H, NHCO), 7.80-7.68 (m, 3H), 7.53-7.44 (m, 2H), 7.42-7.30 (m, 4H) overlapping 7.29 (td, *J* = 7.5, 1.6 Hz, 1H) overlapped by residual CDCl₃, 7.25-7.18 (m, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 15.5 Hz, 1H, CH=CH_{trans}), 4.68-4.52 [m, 1H, ½ CHCH₃], 4.11 (d, *J* = 13.1 Hz, 1H, ½ ArCH₂Ar'), 3.85-3.71 (m, 1H, ½ CHCH₃), 3.48 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 1.29 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 168.6 (CO), 164.2 (br, CO), 142.7, 142.3, 139.6, 136.1, 135.9, 134.7, 133.1, 131.5, 130.7, 130.2, 129.0, 128.1, 127.1, 126.0, 124.0, 120.8, (118.7 x 2, br), 44.7 (CH₂CH₃), 38.9 (ArCH₂Ar'), 14.1 (CH₃). LR-MS (*m/z*): 383 [M+H]⁺.



Synthesis of derivatives of 6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one derivative 8.



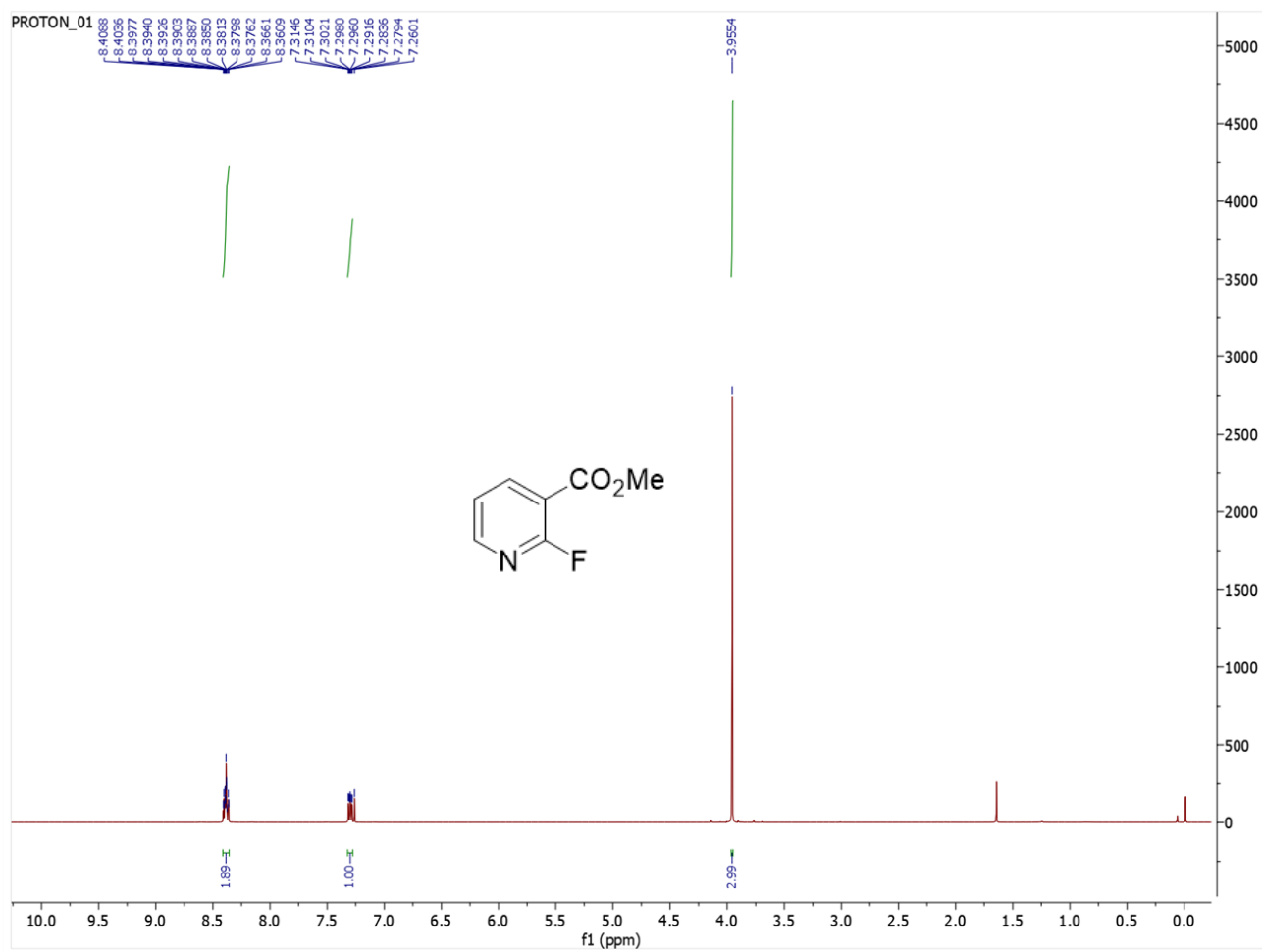
Methyl 2-(fluoro)pyridine-3-carboxylate (**68**)



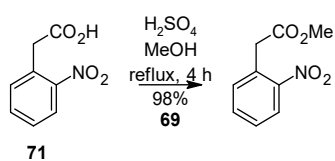
An oven-dried, round-bottom flask was charged with 2-(fluoro)pyridine-3-carboxylic acid **70** (12.1 g, 85.8 mmol, 1 equiv), tetrabutylammonium bromide (1.38 g, 4.3 mmol, 5 mol%) and anhydrous DMF (100 mL). Calcinated potassium carbonate (14.2 g, 102.9 mmol, 1.2 equiv) and iodomethane (8.0 mL, 128.6 mmol, 1.5 equiv) were added to the stirring solution, and the resulting suspension was stirred at rt for 24 h. The reaction mixture was diluted with Et₂O (100 mL), water (125 mL) was added, and the phases were separated. The aqueous phase was extracted with Et₂O (4 x 100 mL; 4 x 50 mL). The organic extracts were combined, washed with water (2 x 20 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated. The crude product was subjected to column chromatography (silica; AcOEt/cyclohexane: 1:20 - 1:10) to obtain 7.80 g (59%) of product **68** as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 8.41-8.36 (m, 2H), 7.30 (ddd, *J* = 7.5, 4.9, 1.7 Hz, 1H), 3.96 (s, 3H, OCH₃). LR-MS (*m/z*): 156 [M+H]⁺.

The ¹H NMR spectrum is in accordance with the one previously reported.[9]



Methyl (2-nitrophenyl)acetate (**69**)

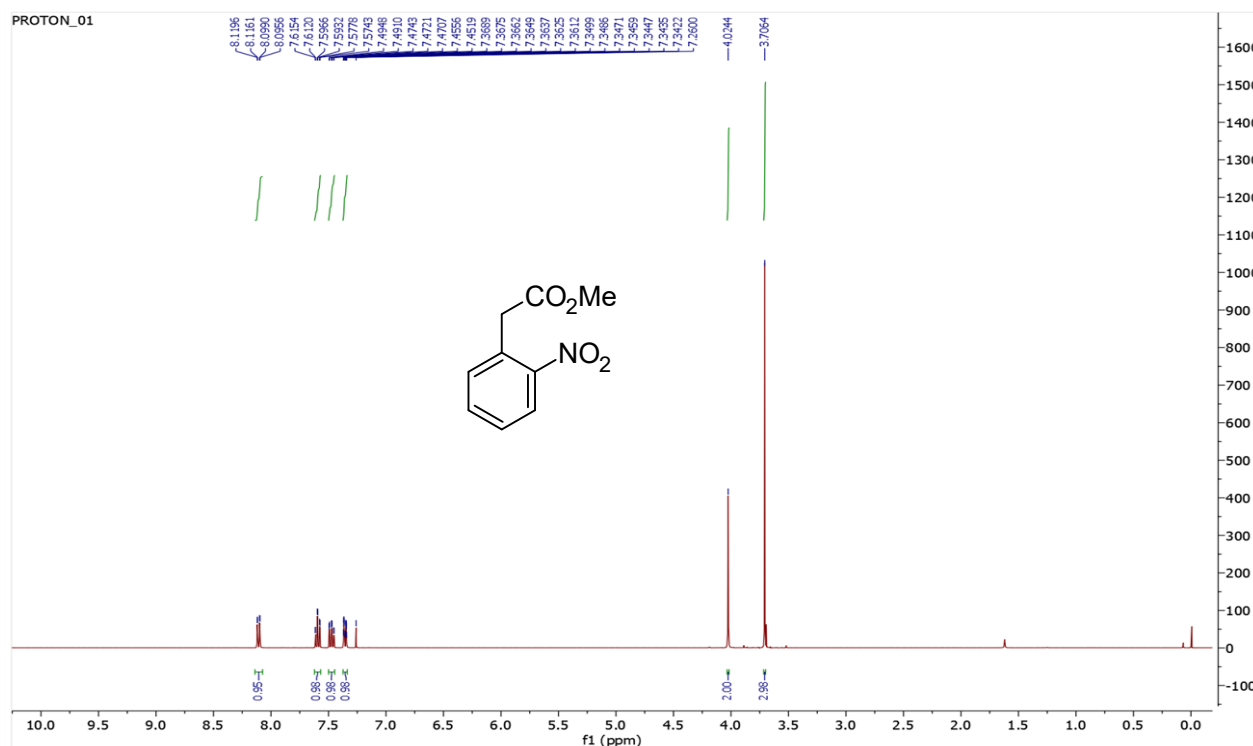


The product was obtained according to slightly modified literature procedure.[9]

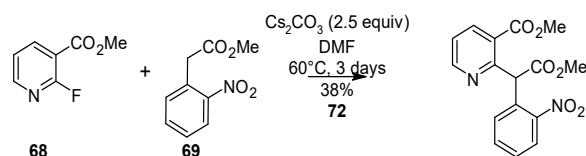
Concentrated sulfuric acid (0.33 mL, 1.9 mmol, 2 mol%) was added to a suspension of 2-nitrophenylacetic acid (**71**) (15.00 g, 82.8 mmol, 1 equiv) in anhydrous methanol (66 mL, 2.6 mol, 31.5 equiv). The reaction mixture was then refluxed for 4 h, cooled to rt, and the volatiles were evaporated. The mixture was diluted with AcOEt (100 mL), saturated aqueous sodium bicarbonate solution (50 mL) was added, and the mixture was stirred for 10 min. The phases were separated and the aqueous one was extracted with AcOEt (5 x 50 mL). All organic extracts were combined, washed with brine (75 mL), dried over anhydrous Na_2SO_4 , filtrated, and evaporated not exceeding the pressure below 30 mbar. The residue was additionally evaporated with cyclohexane (3 x 20 mL) to remove traces of AcOEt, which gave 1.583 g (98%) of product **69** as a yellowish oil.

^1H NMR (400 MHz, CDCl_3) δ 8.11 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.59 (td, $J = 7.5, 1.4$ Hz, 1H), 7.47 (td, $J = 7.8, 1.5$ Hz, 1H), 7.38-7.33 (m, 1H), 4.02 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3). LR-MS (m/z): 196 $[\text{M}+\text{H}]^+$.

The ^1H NMR spectrum is in agreement with the one previously reported.[10]

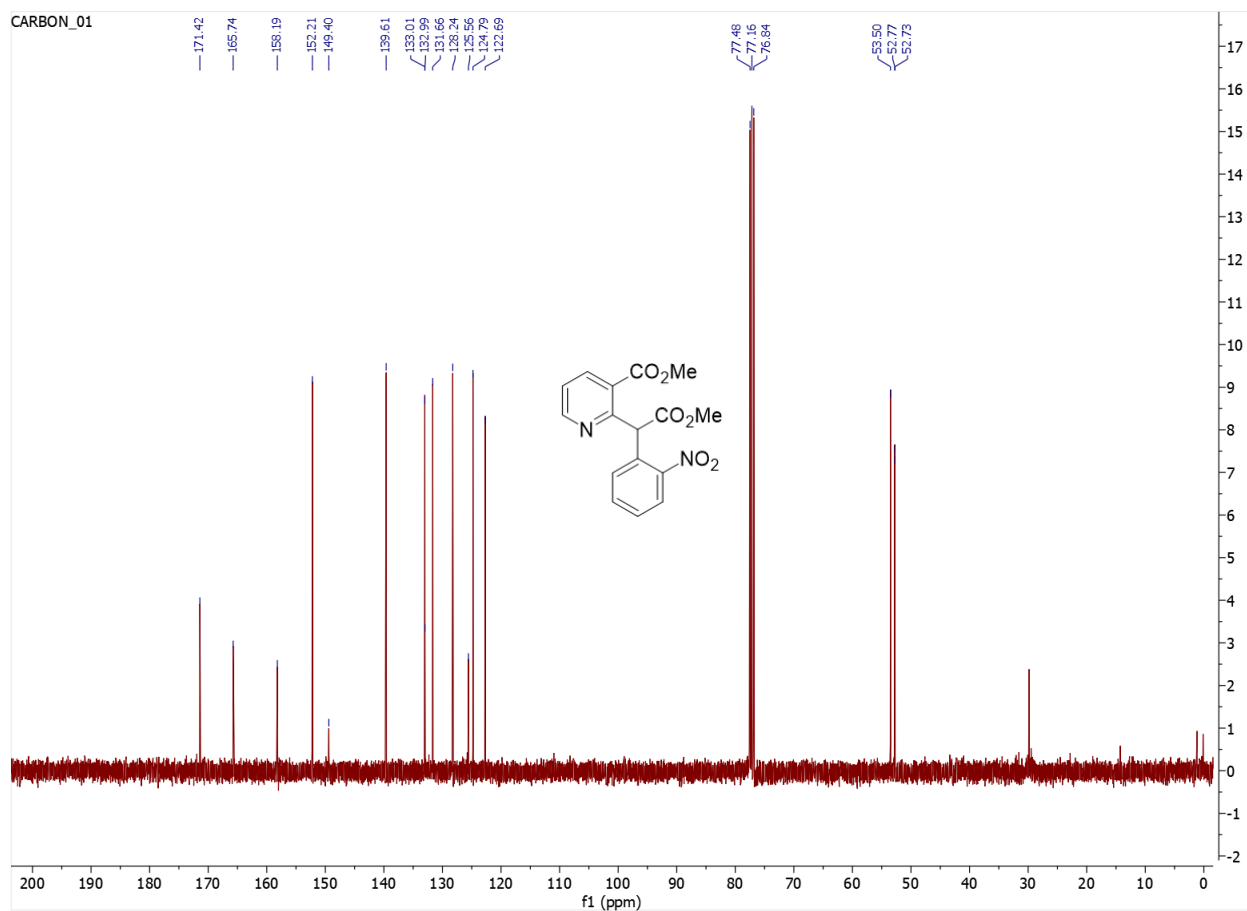
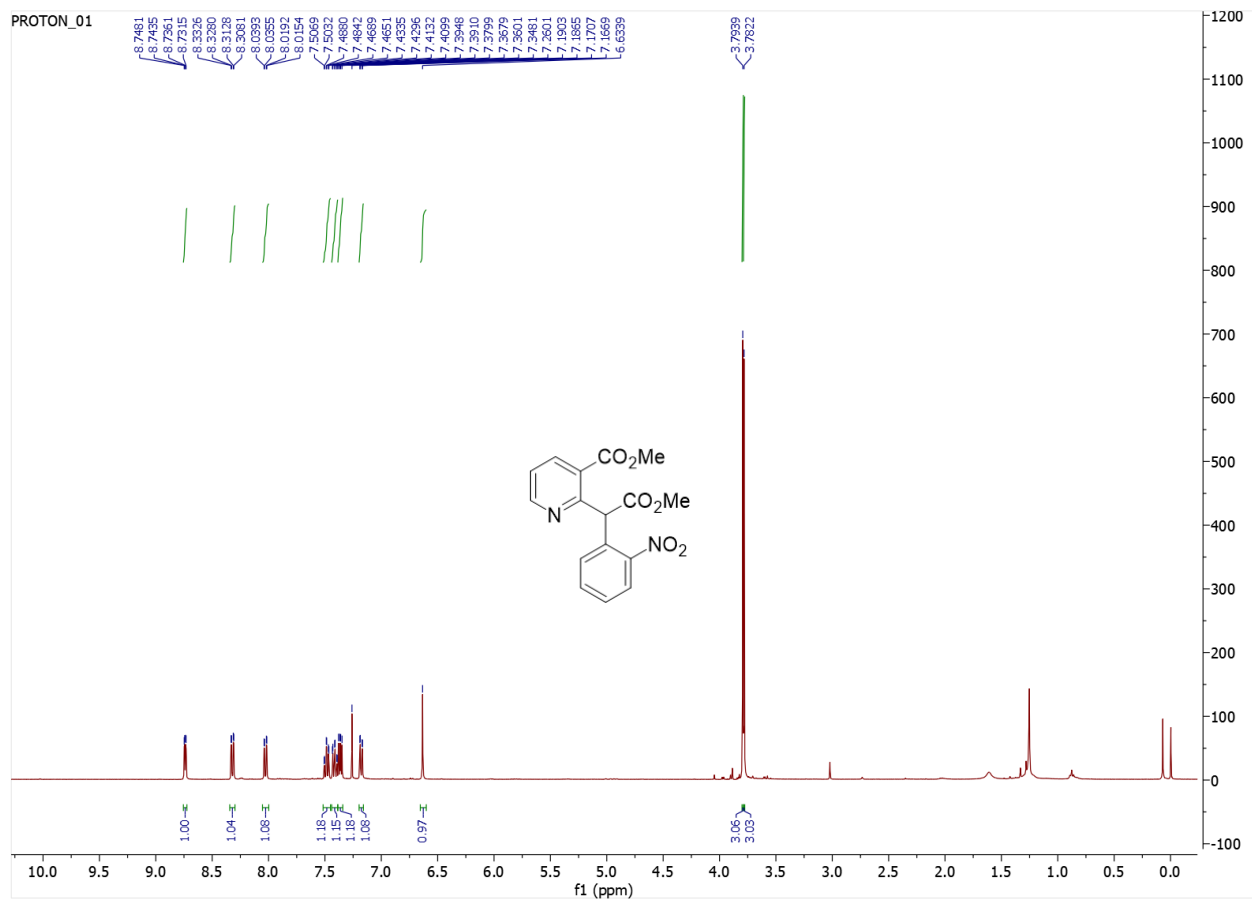


Methyl 2-[2-methoxy-1-(2-nitrophenyl)-2-oxoethyl]pyridine-3-carboxylate (**72**)

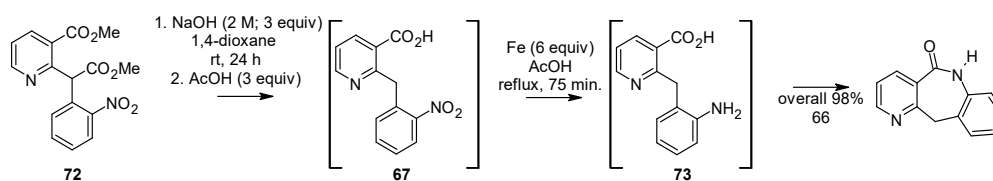


An oven-dried, round-bottom bulb was charged with methyl 2-(2-nitrophenyl)acetate **68** (10.500 g, 67.69 mmol, 1 equiv), methyl 2-fluoropyridine-3-carboxylate **69** (14.531 g, 74.45 mmol, 1.1 equiv) and anhydrous DMF (150 mL). To the stirred solution was added Cs_2CO_3 (55.133 g, 169.21 mmol, 2.5 equiv) and the resulting suspension was stirred at 60°C for 72 h. The reaction mixture was cooled down to rt, Et_2O (100 mL) was added, and the mixture was cooled to 0°C . 1 M aqueous HCl (70 mL) was added dropwise, followed by 3 M aqueous HCl (60 mL), to adjust pH of the water phase to ~ 7 . The phases were separated, and the aqueous one was extracted with Et_2O (10 x 100 mL). The organic solid that precipitated from the combined organic extracts was filtrated, washed with Et_2O , water and again with Et_2O to obtain 3.636 g of product as a white solid. The combined organic extracts were washed with water (3 x 20 mL), brine (100 mL) and the brine was re-extracted with Et_2O (50 mL). The organic phase was dried over Na_2SO_4 , filtrated and evaporated. The crude was triturated with Et_2O (25 mL) and the obtained solid was washed with Et_2O (4 times) to give an additional 4.295 g portion of product **72**. The filtrate was evaporated, and the residue was subjected to column chromatography (silica; using $\text{AcOEt}/\text{cyclohexane}$: 0-33%). The fractions containing pure product were collected, evaporated and the product was triturated with Et_2O (5 mL). The obtained solid was washed with Et_2O (5 x 1.5 mL) to give an additional batch 0.534 g of product **72**. Overall yield 8.465 g (38%).

^1H NMR (400 MHz, CDCl_3) δ 8.74 (dd, $J = 4.8, 1.8$ Hz, 1H), 8.32 (dd, $J = 7.9, 1.8$ Hz, 1H), 8.03 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.49 (td, $J = 7.6, 1.5$ Hz, 1H), 7.41 (td, $J = 7.8, 1.5$ Hz, 1H), 7.36 (dd, $J = 7.9, 4.8$ Hz, 1H), 7.18 (dd, $J = 7.8, 1.5$ Hz, 1H), 6.63 (s, 1H, CHCO_2CH_3), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 171.4 (CO_2Me), 165.7 (CO_2Me), 158.2, 152.2, 149.4, 139.6, 133.0, 133.0, 131.7, 128.2, 125.6, 124.8, 122.7, 53.5, 52.8, 52.7. LR-MS (m/z): 331 $[\text{M}+\text{H}]^+$.



6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one (66)

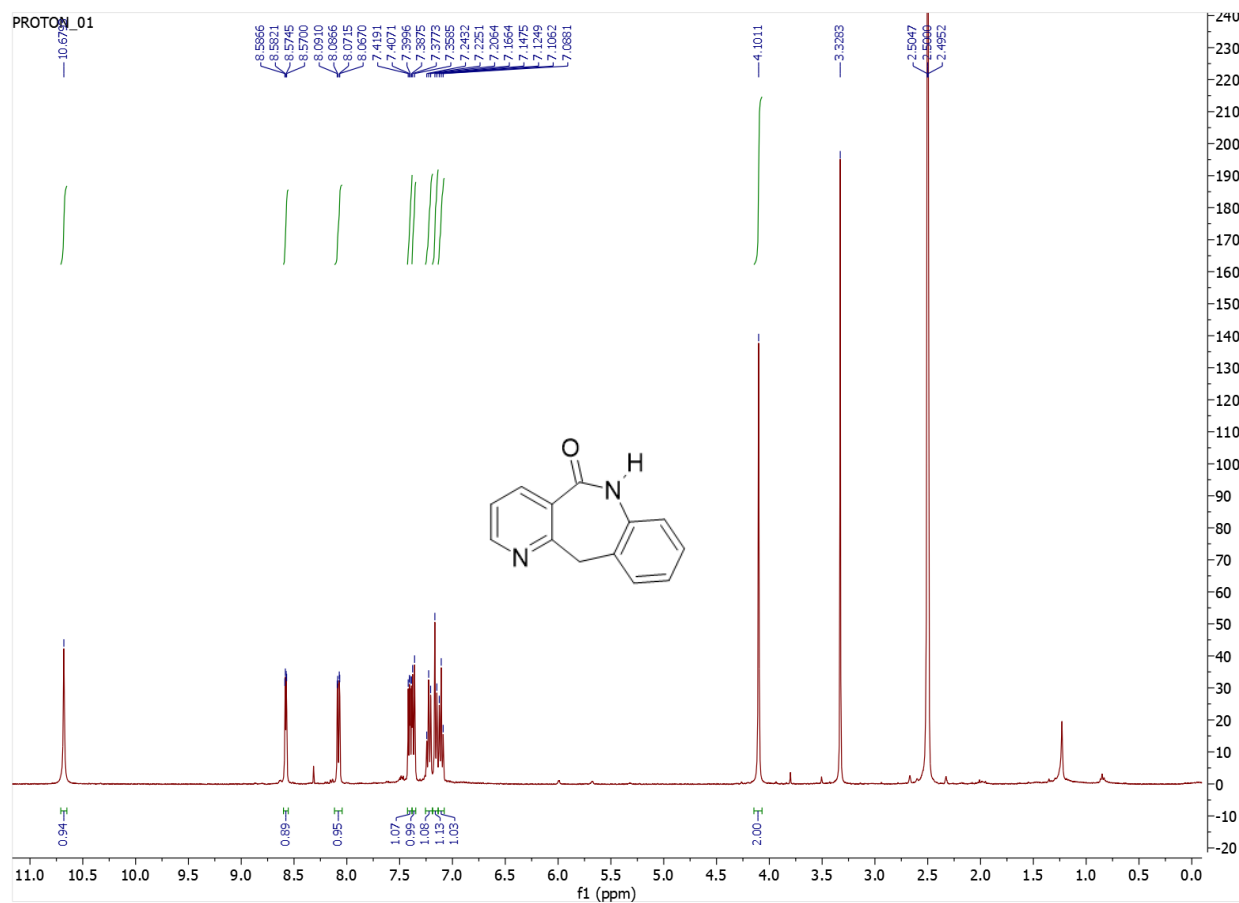


A round-bottom bulb was charged with methyl 2-[2-methoxy-1-(2-nitrophenyl)-2-oxoethyl]pyridine-3-carboxylate **72** (4.275g, 12.94 mmol, 1 equiv), and 1,4-dioxane (55 mL). To the stirred solution was added 2 M aqueous solution of NaOH (19.5 mL, 38.83 mmol, 3 equiv) and the stirring was continued for 24 h. To the reaction mixture was added AcOH (2.2 mL, 38.83 mmol, 3 equiv) and the volatiles were evaporated to give the crude intermediate **67**. LR-MS (m/z): 259 $[M+H]^+$.

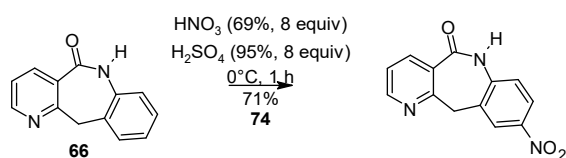
The crude compound **67** was dissolved in AcOH (105 mL), iron powder (4.337 g, 77.66 mmol, 6 equiv) was added and the suspension was stirred at reflux for 75 min. The volatiles were evaporated, and the residue was additionally evaporated with PhMe (4 x 50 mL) to remove the traces of AcOH. To the crude was added (dropwise) saturated aqueous solution of NaHCO_3 (40 mL) and then solid NaHCO_3 was added portion-wise until pH was >7 . The volatiles were evaporated, and the residue was subjected to column chromatography (silica; MeOH/DCM: 10%) to obtain 2.674 g (98%) of target product **66** as a brownish solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.68 (s, 1H, CONH), 8.58 (dd, $J = 4.8, 1.8$ Hz, 1H), 8.08 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.40 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 4.10 (s, 2H, CH_2). LR-MS (m/z): 211 $[M+H]^+$.

The ^1H NMR spectrum is in agreement with the one previously reported.[10]



9-nitro-6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one (**74**)

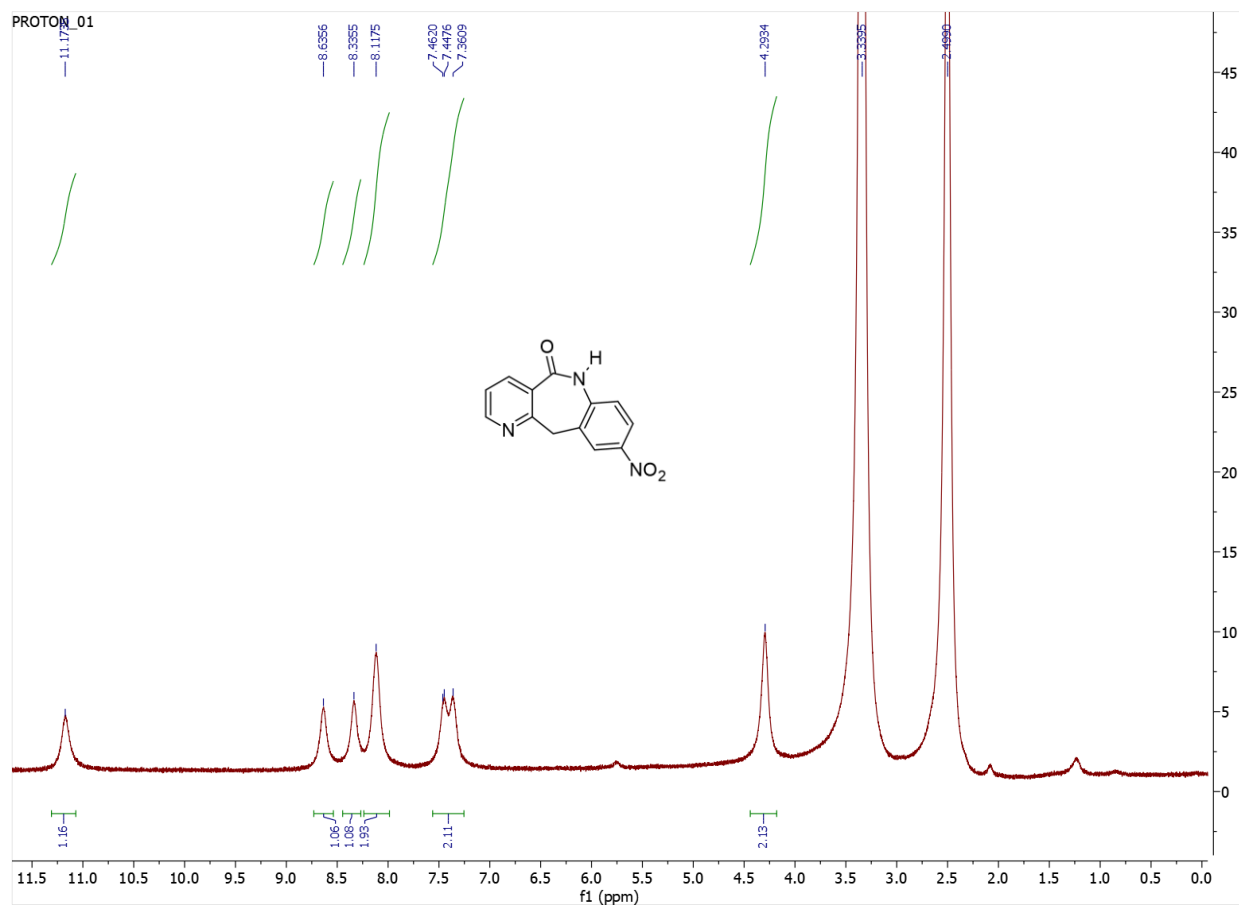


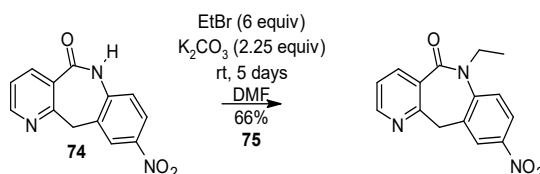
The product was obtained according to the slightly modified literature procedure.[10]

A round-bottom bulb was charged with 6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one **66** (1.321 g, 6.28 mmol, 1 equiv) and HNO_3 (~69%; 3.3 mL, 50.27 mmol, 8 equiv). The resulting solution was cooled to -15°C and H_2SO_4 (95%; 2.8 mL, 50.27 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 1 h, cooled to -15°C and 25% aqueous solution of ammonium (17.3 mL, 226.21 mmol, 36 equiv) was cautiously added dropwise. The mixture was allowed to warm slowly to rt, overnight. The precipitated solid was filtrated, washed extensively with water and dried. The solid was heated with MeOH/MeCN 1:1 (15 mL), filtrated, and washed with MeCN/MeOH, to obtain 1.134 g (71%) of product **74** as a beige solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.17 (br s, 1H, NH), 8.64 (br s, 1H), 8.34 (br s, 1H), 8.12 (br s, 2H), 7.62-7.18 (m, 2H), 4.29 (br s, 2H, CH_2). LR-MS (m/z): 256 $[\text{M}+\text{H}]^+$.

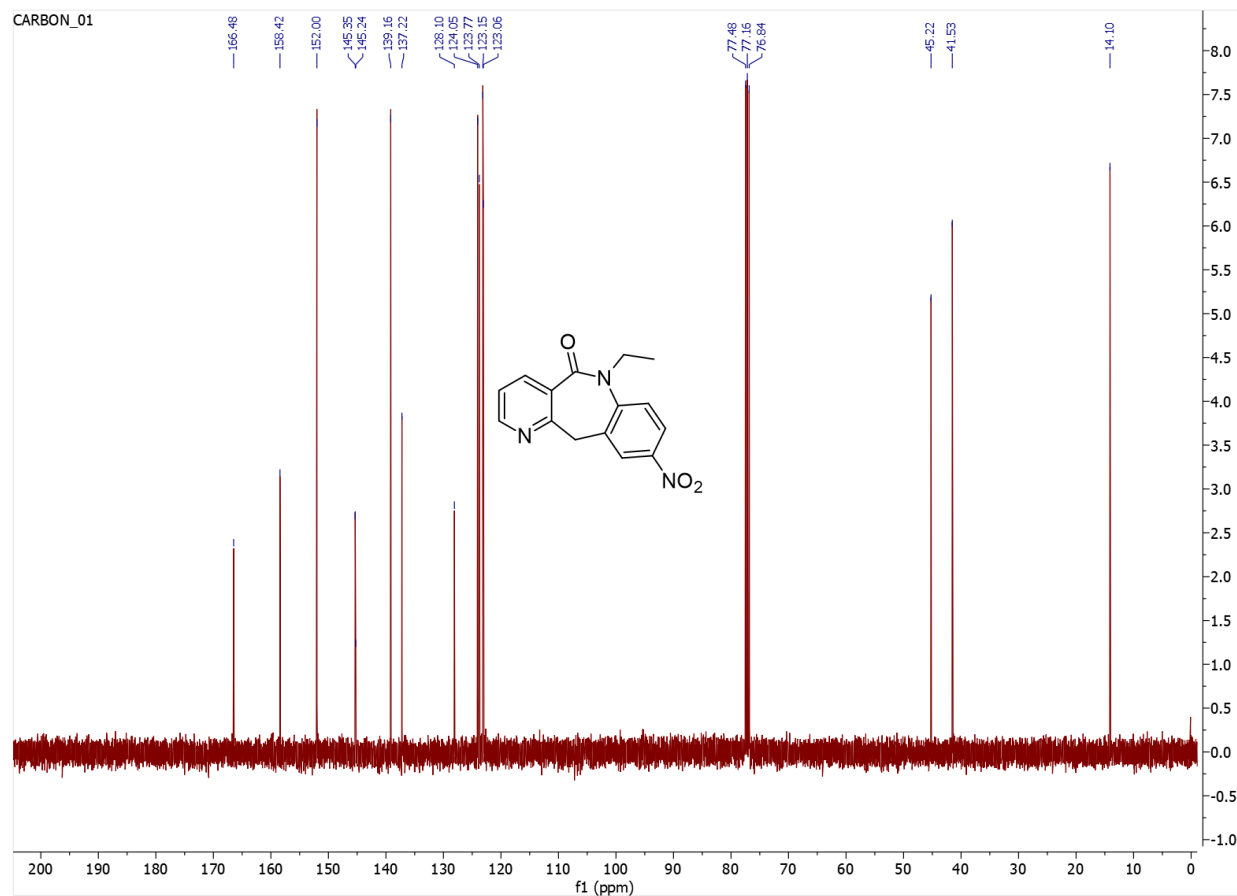
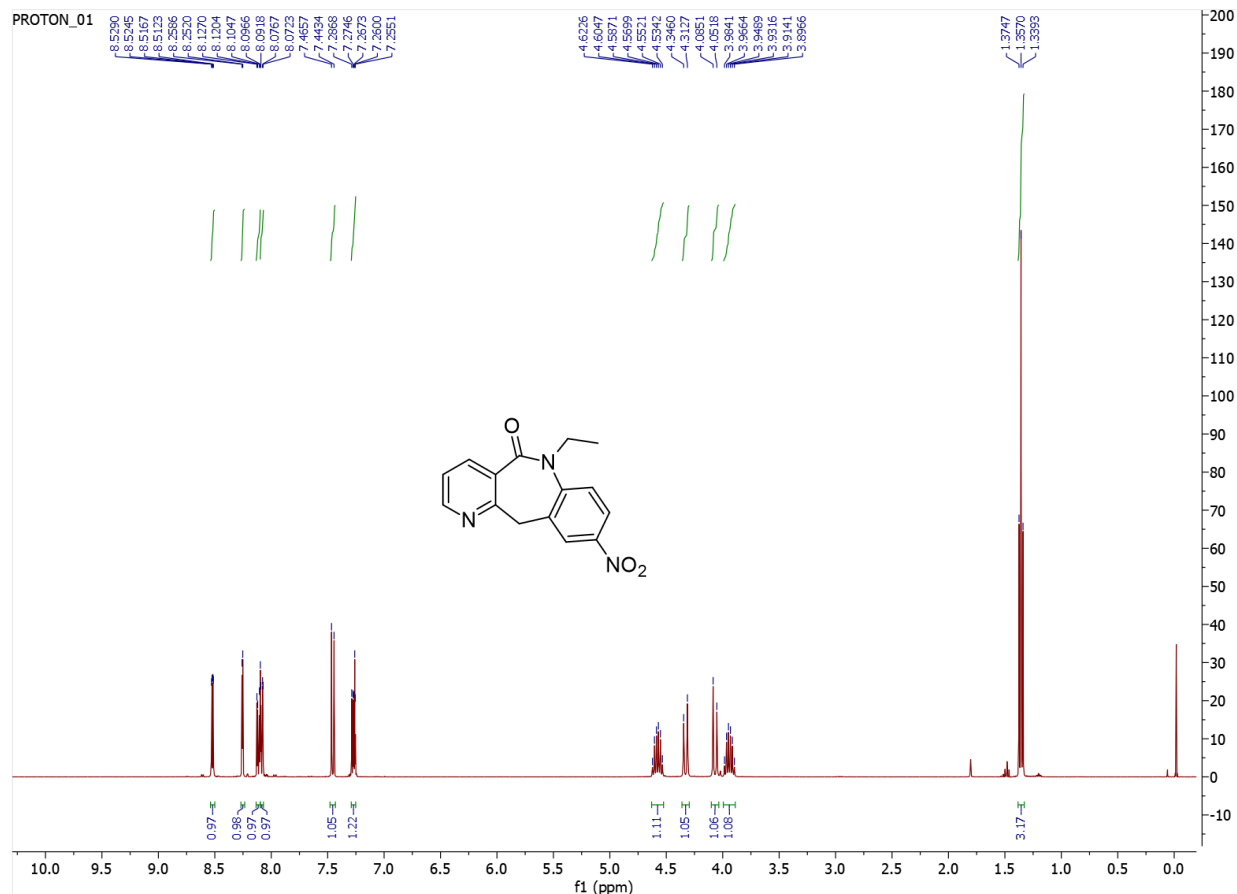
The chemical shifts and the corresponding numbers of nuclei in the ^1H NMR spectrum is in agreement with the one previously reported.[10] However, in our experiments the lines were significantly broadened and the literature multiplicities of the resonance peaks could not be reproduced. Overall, we found the compound highly insoluble even in $\text{DMSO}-d_6$ used in the NMR experiment, which might affect the NMR result.



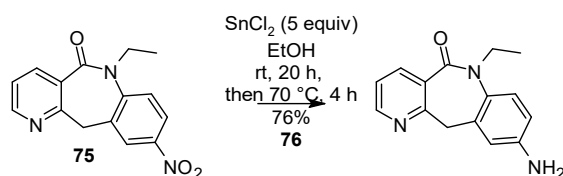
6-ethyl-9-nitro-6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one (75)

An oven-dried, round-bottom bulb was charged with 9-nitro-6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one **74** (1.141 g, 4.47 mmol, 1 equiv), anhydrous DMF (34 mL), calcinated, powderized K₂CO₃ (0.927 g, 6.71 mmol), EtBr (1.3 mL, 17.88 mmol) and the suspension was stirred at rt. After 69 h the additional portion of: powderized K₂CO₃ (0.463 g, 3.06 mmol, 0.75 equiv) and EtBr (0.7 mL, 8.94 mmol, 2 equiv) were added and the stirring was continued at rt for additional 51 h. The reaction mixture was diluted with AcOEt (20 mL) and the volatiles were evaporated. The residue was portioned between water (30 mL) and mixture of AcOEt/MeOH (5:1; 30 mL) and the phases were separated. The aqueous one was extracted with mixture of AcOEt and MeOH (5:1; 4 x 30 mL). All organic extracts were combined, saturated with solid NaCl and the resulting two phases were separated. The brine phase was washed with a mixture of AcOEt and MeOH (5:1; 15 mL). All organic extracts were combined, dried over Na₂SO₄, filtrated and evaporated. The crude product was subjected to column chromatography (silica; MeOH/DCM: 0-2%). The fractions containing pure product were pooled and evaporated *in vacuo* and the residue was refluxed with *n*-heptane to obtain 214 mg of product **75** as a yellowish solid. The remaining fractions were pooled, evaporated and the residue was heated with *n*-heptane. The precipitated solid was repurified by precipitation from DCM/*n*-heptane mixture, using rotary evaporator, which gave an additional 625 mg batch of product **75**. Overall yield: 839 mg (66%).

¹H NMR (400 MHz, CDCl₃) δ 8.52 (dd, *J* = 4.9, 1.8 Hz, 1H, C²H), 8.26 (d, *J* = 2.6 Hz, 1H, C¹⁰H), 8.11 (dd, *J* = 8.9, 2.6 Hz, 1H, C⁸H) overlapped by 8.08 (dd, *J* = 7.8, 1.8 Hz, 1H, C⁴H), 7.45 (d, *J* = 8.9 Hz, 1H, C⁷H), 7.27 (dd, *J* = 7.8, 4.9 Hz, 1H, C³H), 4.63-4.53 (m, 1H, ½ CH₂CH₃), 4.33 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 4.07 (d, *J* = 13.3 Hz, 1H, ½ ArCH₂Ar'), 3.99-3.89 (m, 1H, ½ CH₂CH₃), 1.36 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.5 (CONH), 158.4, 152.0, 145.3, 145.2, 139.2, 137.2, 128.1, 124.1, 123.8, 123.1 (x 2), 45.2, 41.5, 14.1 (CH₂). LR-MS (*m/z*): 284 [M+H]⁺.



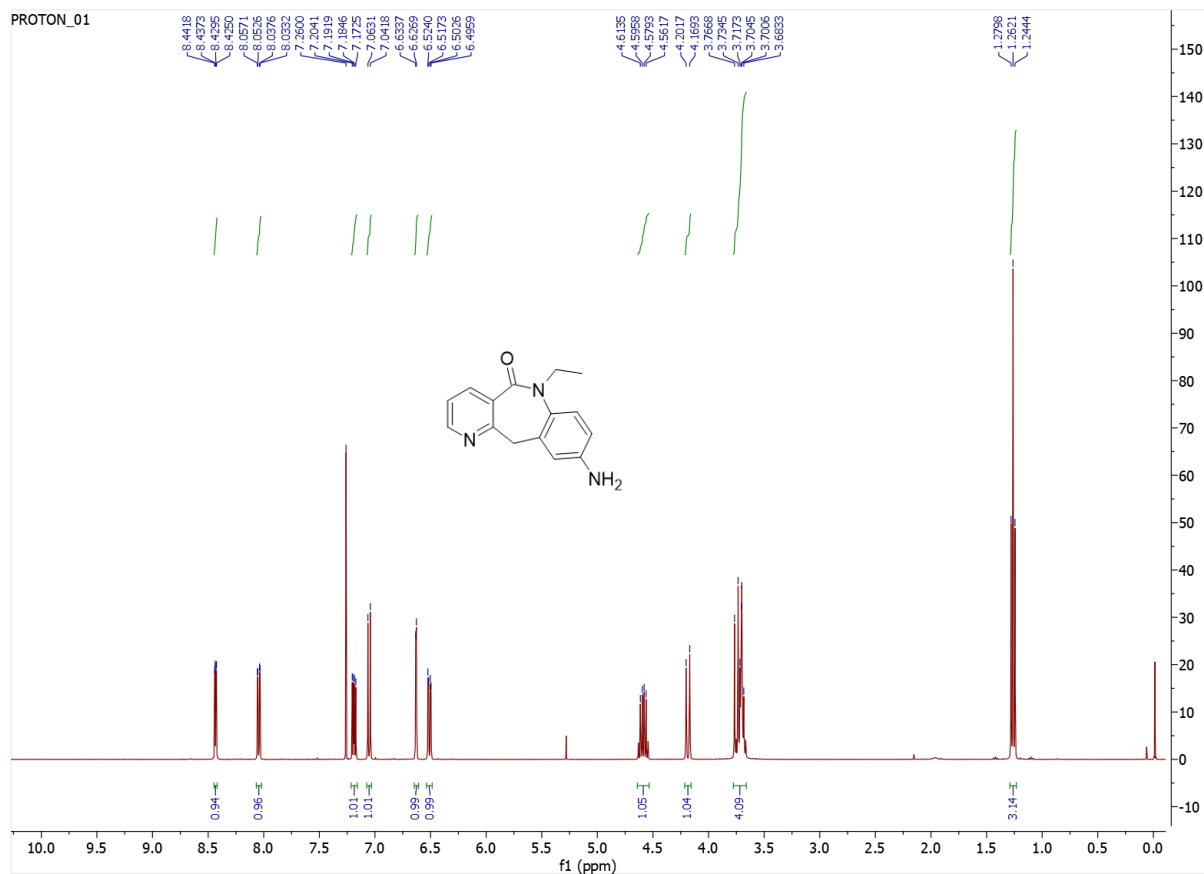
9-amino-6-ethyl-6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one (76)



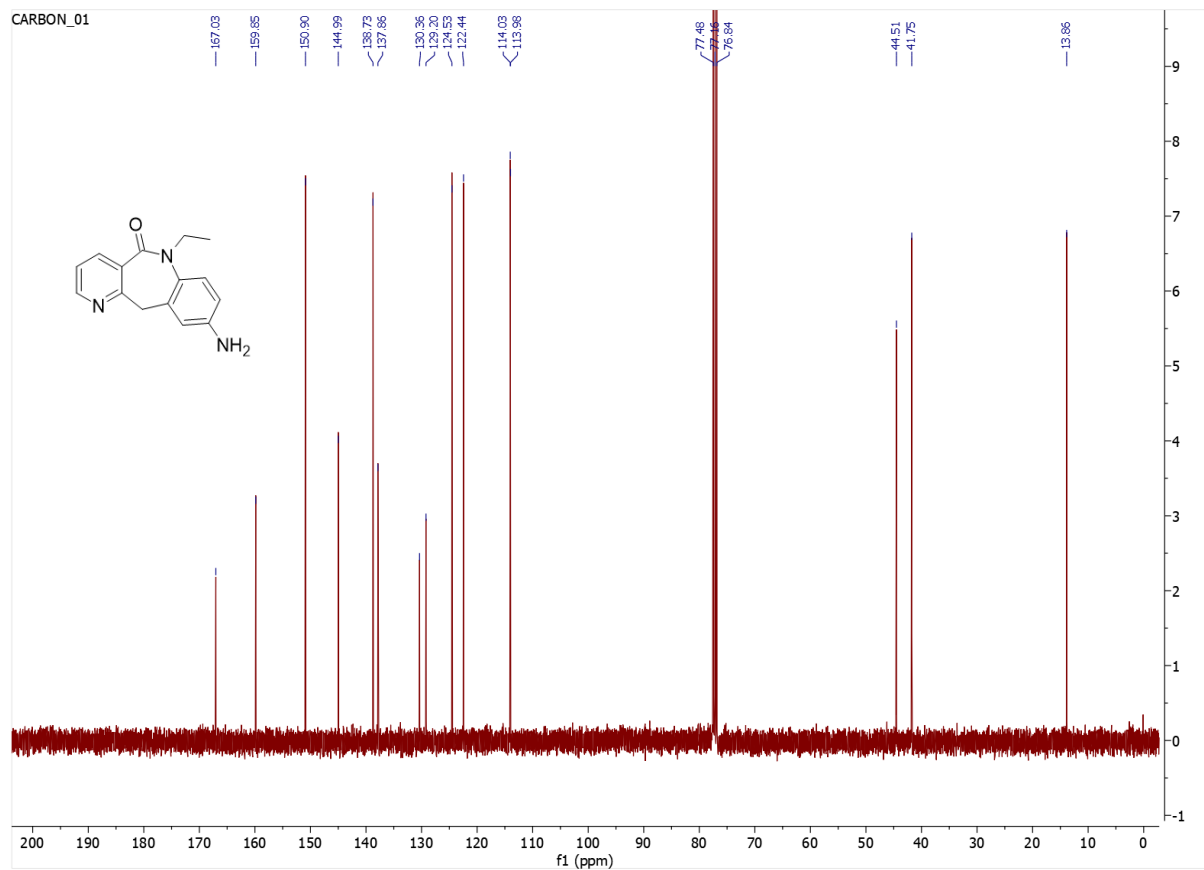
A round-bottom bulb was charged with 6-ethyl-9-nitro-6,11-dihydro-5H-pyrido[3,2-c][1]benzazepin-5-one **75** (0.819 g, 2.89 mmol, 1 equiv), EtOH (82 mL), anhydrous SnCl_2 (2.741 g, 14.46 mmol, 5 equiv) and the solution was stirred at rt for 20 h and then at 70°C for 4 h. The volatiles were evaporated, and the residue was dissolved in AcOEt (100 mL). To the stirred solution was added dropwise saturated solution of NaHCO_3 (50 mL). The inorganic solid formed was filtered off, and the phases were separated. The aqueous one was extracted with AcOEt (4 x 25 mL). The inorganic solid was washed with every organic extract after extraction. The solid was additionally washed with fresh AcOEt (5 x 50 mL), which was subsequently concentrated to the volume of approximately 25 mL. All organic extracts were combined, washed with brine (50 mL) and the brine was re-extracted with AcOEt (25 mL). All organic extracts were combined, dried over Na_2SO_4 , filtered and evaporated. The white, solid product was precipitated from the mixture DCM/*n*-hexane by slow evaporation using rotary evaporator and washed with *n*-hexane, to give 554 mg (76%) yield.

^1H NMR (400 MHz, CDCl_3) δ 8.43 (dd, $J = 4.9, 1.8$ Hz, 1H, C^2H), 8.05 (dd, $J = 7.8, 1.8$ Hz, 1H, C^4H), 7.19 (dd, $J = 7.8, 4.9$ Hz, 1H, C^3H), 7.05 (d, $J = 8.5$ Hz, 1H, C^7H), 6.63 (d, $J = 2.7$ Hz, 1H, C^{10}H), 6.51 (dd, $J = 8.5, 2.7$ Hz, 1H, C^9H), 4.64-4.54 (m, 1H, $\frac{1}{2} \text{CH}_2\text{CH}_3$), 4.19 (d, $J = 13.0$ Hz, 1H, $\frac{1}{2} \text{ArCH}_2\text{Ar}'$), 3.76-3.66 (m, 3H, $\frac{1}{2} \text{CH}_2\text{CH}_3, \text{NH}_2$), overlapping 3.75 (d, $J = 13.0$ Hz, 1H, $\frac{1}{2} \text{ArCH}_2\text{Ar}'$), 1.26 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 167.0 (CONH), 159.8, 150.9, 145.0, 138.7, 137.9, 130.4, 129.2, 124.5, 122.4, 114.0 (x 2), 44.5, 41.8, 13.9 (CH_3). LR-MS (m/z): 254 $[\text{M}+\text{H}]^+$, 529 $[2\text{M}+\text{Na}]^+$.

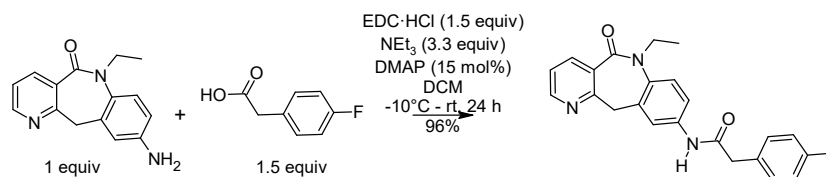
PROTON_01



CARBON_01

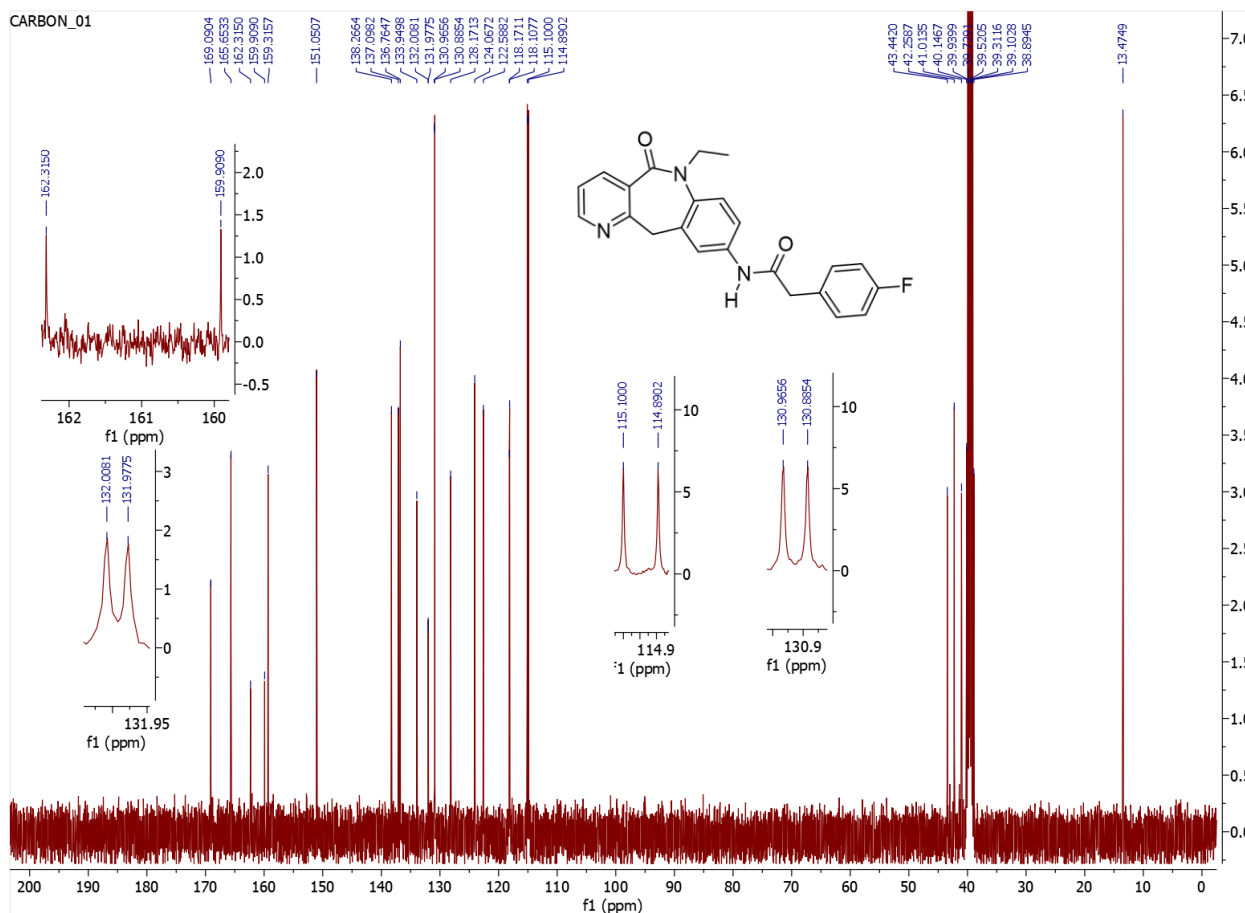
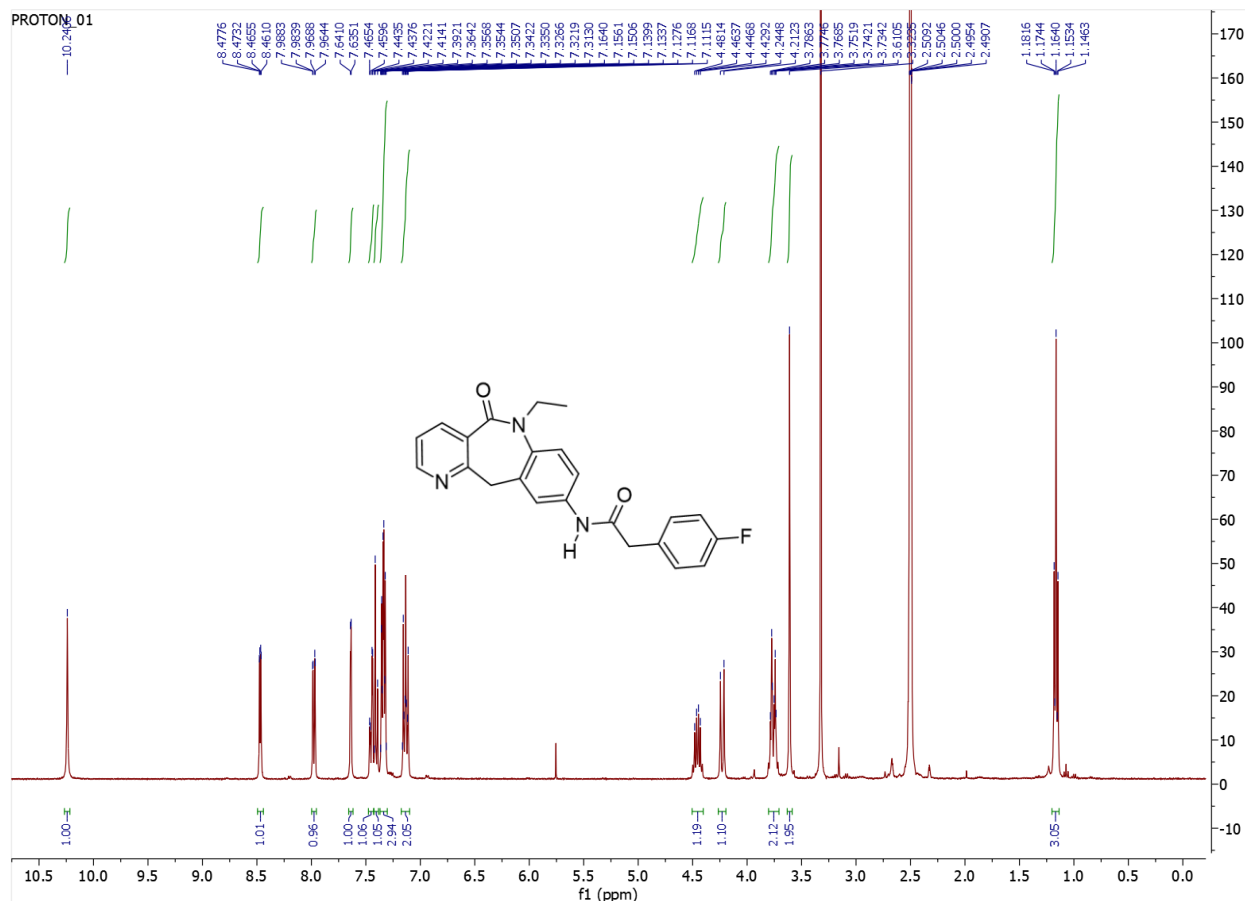


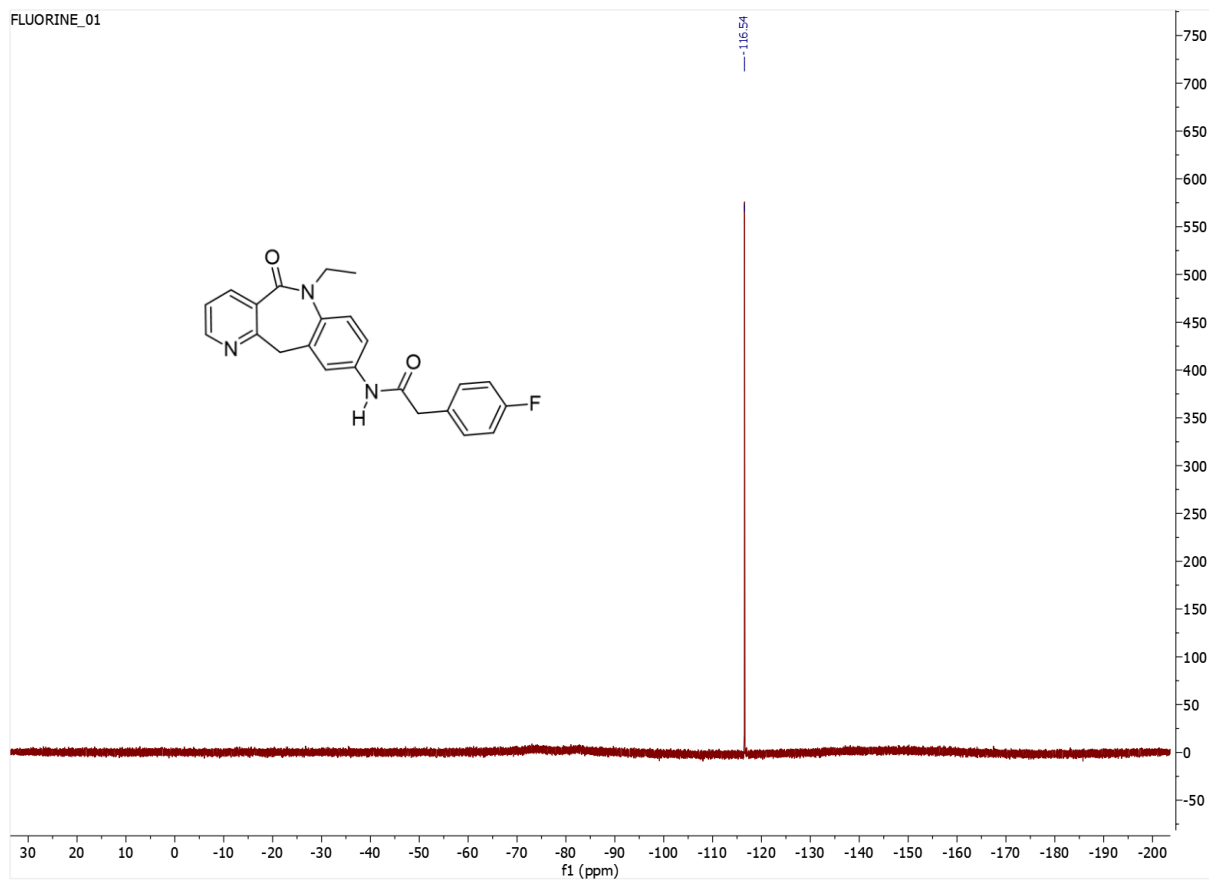
***N*-(6-Ethyl-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*e*]azepin-9-yl)-2-(4-fluorophenyl)acetamide (**8**)**



An oven-dried, round-bottom bulb was charged with 9-amino-6-ethyl-6,11-dihydro-5*H*-pyrido[3,2-*c*][1]benzazepin-5-one **76** (75 mg, 0.30 mmol, 1 equiv), (4-fluorophenyl)acetic acid (68 mg, 0.44 mmol, 1.5 equiv) and anhydrous DCM (5 ml). The mixture was cooled down to – 10 °C and there were added: DMAP (5 mg, 0.04 mmol, 0.15 equiv), EDC·HCl (86 mg, 0.44 mmol, 1.5 equiv) and – dropwise – Et₃N (136 µl, 0.98 mmol, 3.3 equiv). The reaction was allowed to warm slowly to rt by allowing the cooling bath to warm to rt overnight. The reaction mixture was stirred overall for 25 h. To the reaction mixture was added saturated aqueous solution of NH₄Cl, the phases were separated and the aqueous one was extracted with DCM (4 x 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtrated and the volatiles were evaporated. The residue was stirred with DCM, and the white solid product **8** was filtered and washed with chilled DCM (2 times). The filtrate was evaporated and the residue was subjected to column chromatography (silica; using AcOEt/cyclohexane: 50%) to obtain an additional batch of product **8** as a white solid. Overall yield was 111 mg (96%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.24 (s, 1H, CONH), 8.47 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.37-7.31 (m, 3H), 7.17–7.10 (m, 2H), 4.51-4.40 (m, 1H, ½ CH₂CH₃), 4.23 (d, *J* = 13.0 Hz, 1H, ½ ArCH₂Ar'), 3.81-3.71 (m, 1H, ½ CH₂CH₃) overlapping 3.76 (d, *J* = *J* = 13.0 Hz, 1H, ½ ArCH₂Ar'), 3.61 (s, 2H, NHCOCH₂Ar''), 1.16 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.1 (CON), 165.7 (CON), 161.1 (d, ¹*J*_{CF} = 241.9 Hz), 159.3, 151.1, 138.3, 137.1, 136.8, 133.9, 132.0 (d, ⁴*J*_{CF} = 3.1 Hz), 130.9 (d, ³*J*_{CF} = 8.1 Hz), 128.2, 124.1, 122.6, 118.2, 118.1, 115.0 (d, ²*J*_{CF} = 21.1 Hz), 43.4, 42.3, 41.0, 13.5 (CH₃); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –116.5. LR-MS (*m/z*): 390 [M+H]⁺.





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