

SUPPORTING INFORMATION

A novel decalin-based bicyclic scaffold for FKBP51-selective ligands

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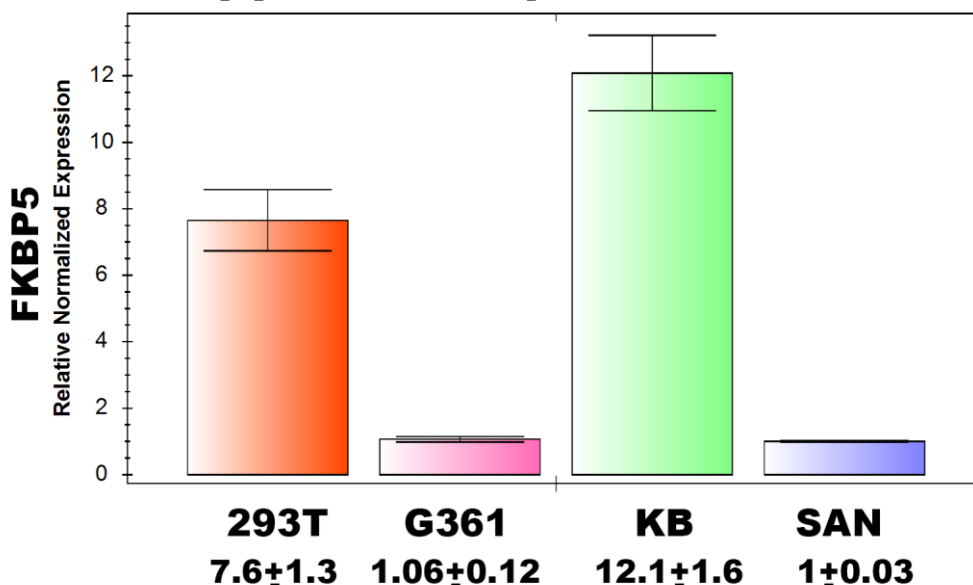
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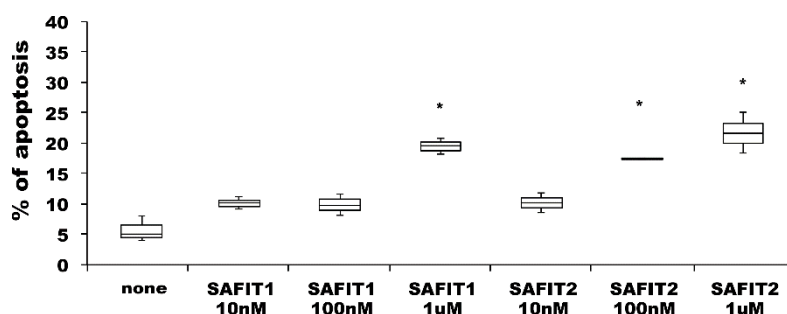
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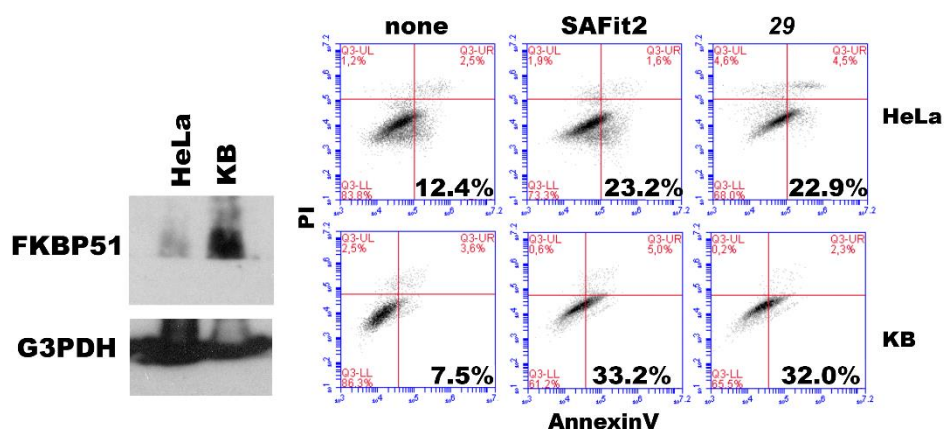
I. Pro-apoptotic effects of compound 29



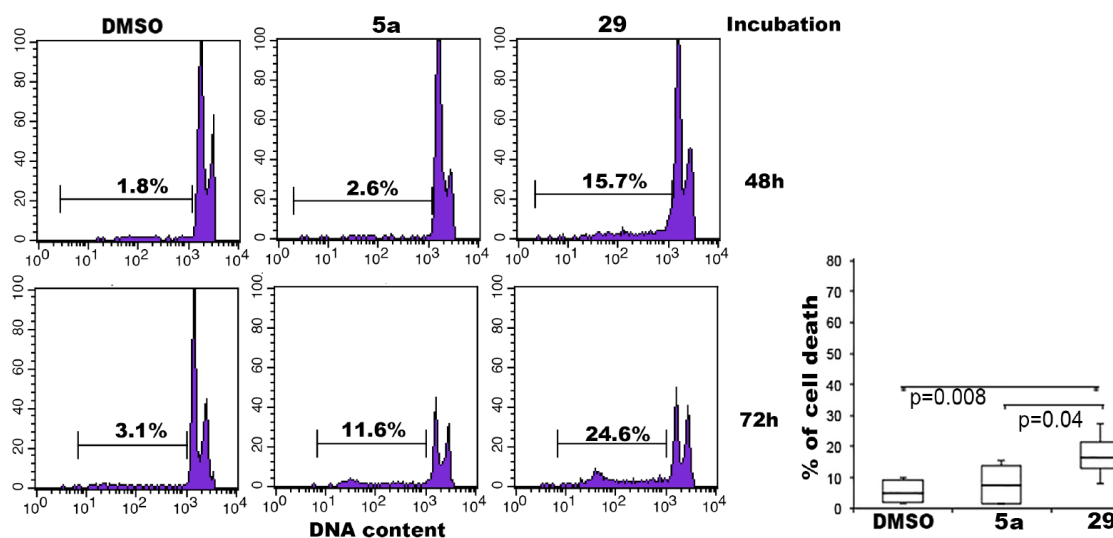
Suppl. Fig S1: FKBP5 expression level in KB cell line. Measure of FKBP5 transcript levels by quantitativePCR on KB cell line. For comparison two melanoma cell lines (G361 and SAN) and the kidney embryonic cell line 293T were used. The values are expressed in arbitrary units (relative normalized expression) using SAN as reference sample (expression=1). Briefly, total RNA was isolated from cells using Trizol (Sigma Aldrich, St. Louis, MO, USA), according to the manufacturer's instructions. One microgram of each RNA was used for cDNA synthesis with iScript™ Reverse Transcription Supermix (Bio-Rad, Hercules, CA, USA). Gene expression was quantified by qPCR using SsoAdvanced™ SYBR® Green Supermix (Bio-Rad) and specific qPCR primers were used to detect each transcript. Validated QuantiTec primers from Qiagen (Valencia, CA, USA) were used for FKBP5 detection. Relative quantitation of the transcript was performed using co-amplified ribosomal 18S (Fw 5' -CGATGCGGCGGCGTTATTC-3' and Rev 5'-TCTGTCAATCCTGTCCGTGTCC-3') as an internal control for normalization.



Suppl. Fig. S2: Dose response assay of SAFit1 and SAFit2 on KB apoptosis. Cells were incubated with SAFit 1 and 2 at different doses. Cell death was measured after 40h by annexin V/PI double staining to determine apoptosis. Boxplots represent values of annexinV+/PI- cells (corresponding to early apoptosis) from three experiments.



Suppl. Fig. 3: Western blot assay of FKBP51 levels in HeLa and KB cell lines (left). Representative histograms of HeLa and KB cell apoptosis (right). 1 μ M SAFit2 and 50 μ M of compound **29** were used to induce apoptosis.



Suppl. Fig. S4: Effect of **5a** and **29** on the cell death of KB cell line. Cells (10^5 /mL) were incubated in 10% FCS DMEM, in the presence of the compounds **5a** or **29** (60 μ M). After 72h, propidium iodide incorporation in DNA was measured by flow cytometry. The number on the bar indicates the proportion of hypodiploid (dead) cells.

II. Crystallography

Suppl. Table 1 | *Data Collection and Refinement Statistics*

| Dataset | FKBP51-25 |
|---|---|
| Space group | <i>P</i> 2 ₁ 2 ₁ 2 ₁ |
| Cell dimensions | |
| a, b, c (Å) | 42.56, 50.33, 62.78 |
| α , β , γ (°) | 90, 90, 90 |
| Wavelength (Å) | 0.97857 |
| Resolution (Å) | 50.33- 2.05 (2.16 - 2.05)* |
| <i>R</i> _{merge} | 0.065 (0.597) |
| <i>I</i> / σ <i>I</i> | 13.3 (2.5) |
| Completeness (%) | 99.7 (99.6) |
| Redundancy | 5.3 (5.4) |
| Refinement | |
| Resolution (Å) | 30 - 2.05 |
| No reflections | 8432 |
| <i>R</i> _{work} / <i>R</i> _{free} | 0.190 / 0.273 |
| Number of atoms | |
| Protein | 979 |
| Ligand/ion | 50 |
| Water | 67 |
| <i>B</i> -factors | |
| Protein | 48.2 |
| Ligand/ion | 50.2 |
| Water | 58.3 |
| R.m.s. deviations | |
| Bond length (Å) | 0.014 |
| Bond angles (°) | 1.857 |

* Values in parenthesis for outer shell.

Crystallization

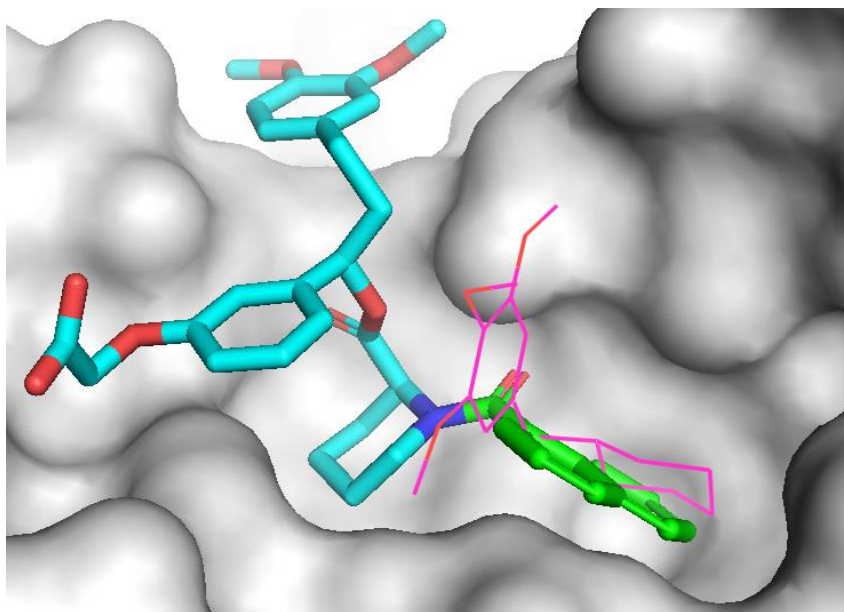
The complexes were prepared by mixing FKBP51(16-140)-A19T protein at 1.75 mM with 50 mM **25** dissolved in DMSO in 16:1 ratio. Crystallization was performed at 20 °C using the hanging drop vapour-diffusion method, equilibrating mixtures of 1 μ L protein complex and 1 μ L reservoir against 500 μ L reservoir solution. Crystals were obtained with reservoir solution containing 28 % PEG-3350, 0.2 M NH₄-acetate and 0.1 M HEPES-NaOH pH 7.5.

Structure Solution and Refinement

The diffraction data were collected at beamline ID29 of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. Diffraction data were integrated with XDS¹ and further processed with Scala and Ctruncate², as implemented in the CCP4i interface^{3,4}. The crystal structures were solved by molecular replacement employing the program Molrep⁵. Iterative model improvement and refinement were performed with Coot⁶ and Refmac^{5,7}. The dictionaries for the compounds were generated with the PRODRG server⁸. Residues facing solvent channels without detectable side chain density were truncated beyond C- β .

Molecular graphics figures were generated with the program Pymol⁹.

III. Modelled binding mode of compound 5a



Suppl. Fig. S5: Compound **5a** modelled in the binding site of FKBP51 (PDB-ID: 5DIU). Compound **3** is shown superimposed as magenta lines. Lys¹²¹ has been removed for clarity. Lys¹²¹ has been removed for clarity.

IV. cLogP and ligand efficiency (LE)

The cLogP was calculated with Chemicalize, a web tool developed by ChemAxon (www.chemicalize.com), and the ligand efficiency (LE) was determined from the K_i values by the following equation.

$$LE = \frac{\Delta G}{N} = \frac{-RT \ln(K_i)}{N}$$

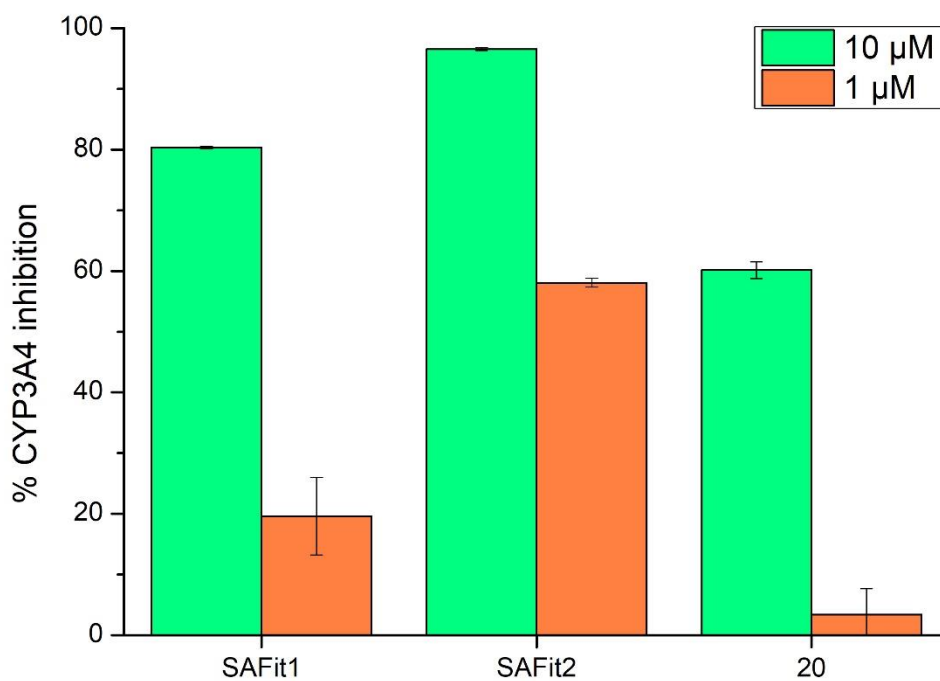
$$\text{with } R = 1.9872 \cdot 10^{-3} \frac{\text{kcal}}{\text{mol} \cdot \text{K}} \text{ and } T = 298.15 \text{ K}$$

Suppl. Table 2 | Calculated values for cLogP and LE.

| Compound | cLogP | Ki [μM] | N [heavy atom count] | ΔG [kcal/mol] | LE [kcal/mol] |
|----------|-------|-------------------------|-------------------------|--------------------------|------------------|
| SAFit1 | 6.86 | 0.004 | 54 | 11.46 | 0.21 |
| SAFit2 | 7.18 | 0.006 | 58 | 11.22 | 0.19 |
| 14 | 6.10 | 2.4 | 45 | 7.67 | 0.17 |
| 15 | 5.66 | 7.8 | 44 | 6.97 | 0.16 |
| 16 | 6.42 | 2.6 | 49 | 7.62 | 0.16 |
| 17 | 6.39 | 2.0 | 46 | 7.77 | 0.17 |
| 18 | 6.71 | 1.9 | 50 | 7.81 | 0.16 |
| 19 | 6.02 | 2.6 | 44 | 7.62 | 0.17 |
| 20 | 6.46 | 0.81 | 45 | 8.31 | 0.18 |
| 21 | 6.75 | 0.49 | 46 | 8.61 | 0.19 |
| 22 | 4.84 | 28 | 45 | 6.21 | 0.14 |
| 23 | 5.10 | 3.1 | 45 | 7.52 | 0.17 |
| 24 | 5.61 | 1.3 | 50 | 8.03 | 0.16 |
| 25 | 5.86 | 0.23 | 50 | 9.06 | 0.18 |
| 26 | 6.15 | 0.33 | 51 | 8.84 | 0.17 |
| 27 | 5.48 | 0.65 | 50 | 8.44 | 0.17 |
| 28 | 6.10 | 8.2 | 54 | 6.94 | 0.13 |
| 29 | 4.40 | 0.28 | 51 | 8.94 | 0.18 |

V. CYP3A4 inhibition assay for SAFit1, SAFit2 and compound 20

The CYP3A4 inhibition been determined in *in vitro* assay by Pharmacelsus GmbH at 1 μ M and 10 μ M. Ketoconazole was used as a reference with an observed IC₅₀=0.1 μ M.



Suppl. Fig. S6: Inhibition of CYP3A4 in percent of SAFit 1, SAFit 2 and compound 20.

VI. List of SI items incl. Molecular Formula Strings

| Compound | SMILES | K _i FKBP51FK1 (μM) | NMR | HPLC |
|----------|--|----------------------------------|-----|------|
| 6a | <chem>OCCCC/C=C/C([H])=O</chem> | | Yes | - |
| 6b | <chem>OCCCCC/C=C/C([H])=O</chem> | | Yes | - |
| 7a | <chem>OCCCC/C=C/C=C</chem> | | Yes | - |
| 7b | <chem>OCCCCC/C=C/C=C</chem> | | Yes | - |
| 7c | <chem>OCCCCC/C=C/C=C\C</chem> | | Yes | - |
| 8a | <chem>C=C/C=C/CCC/C=C/C(OC)=O</chem> | | Yes | - |
| 8b | <chem>O=C(OC)/C=C/CCCC/C=C/C=C</chem> | | Yes | - |
| 8c | <chem>O=C(OC)/C=C/CCCC/C=C/C=C\C</chem> | | Yes | - |
| 9a | <chem>C=C/C=C/CCC/C=C/C(O)=O</chem> | | Yes | - |
| 9b | <chem>O=C(O)/C=C/CCCC/C=C/C=C</chem> | | Yes | - |
| 9c | <chem>O=C(O)/C=C/CCCC/C=C/C=C\C</chem> | | Yes | - |
| 10b | <chem>O=C(N1C(OC[C@H]1CC2=CC=CC=C2)=O)/C=C/CCCC/C=C/C=C</chem> | | Yes | - |
| 10c | <chem>O=C1N(C/C=C/C/CCCC/C=C/C=C\C)=O)[C@H](CC2=CC=CC=C2)CO1</chem> | | Yes | - |
| 11a | <chem>O=C(N1C(OC[C@H]1CC2=CC=CC=C2)=O)[C@H]3[C@H]4[C@@H](CCCC4)C=CC3</chem> | | Yes | - |
| 11b | <chem>O=C(N1C(OC[C@H]1CC2=CC=CC=C2)=O)[C@H]3[C@H]4[C@@H](CCCC4)C=CC3</chem> | | Yes | - |
| 11c | <chem>O=C(N1C(OC[C@H]1CC2=CC=CC=C2)=O)[C@H]3[C@H]4[C@@H](CCCC4)C=C[C@@H]3C</chem> | | Yes | - |
| 12a | <chem>O=C(O)[C@H]1[C@H]2[C@@H](CCC2)C=CC1</chem> | | Yes | - |
| 12b | <chem>OC([C@H]1[C@H]2[C@@H](CCCC2)C=CC1)=O</chem> | | Yes | - |
| 12c | <chem>OC([C@H]1[C@H]2[C@@H](CCCC2)C=C[C@@H]1C)=O</chem> | | Yes | - |
| 13a | <chem>O=C(O)[C@H]1[C@H]2[C@@H](CCC2)CCC1</chem> | | Yes | - |
| 13b | <chem>OC([C@H]1[C@H]2[C@@H](CCCC2)CCC1)=O</chem> | | Yes | - |
| 13c | <chem>OC([C@H]1[C@H]2[C@@H](CCCC2)CC[C@@H]1C)=O</chem> | | Yes | - |
| 14 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@H]3N(C([C@@H]4CC=C[C@H]5[C@H]4CCCC5)=O)CCCC3</chem> | 2.5 | Yes | Yes |
| 15 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@@H]3CCCCN3C([C@H]4[C@H]5[C@@H](CCC5)C=CC4)=O</chem> | 7.8 | Yes | Yes |
| 16 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@@H]5CC=C[C@H]6[C@H]5CCCC6)=O</chem> | 2.6 | Yes | Yes |
| 17 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@H]3N(C([C@@H]4[C@@H](C)C=C[C@H]5[C@H]4CCCC5)=O)CCCC3</chem> | 2 | Yes | Yes |

| | | | | |
|----|---|------|-----|-----|
| 18 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@H]4N(C([C@@H]5[C@@H](C)C=C[C@H]6[C@H]5CCCC6)=O)CCCC4</chem> | 1.9 | Yes | Yes |
| 19 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@@H]3CCCCN3C([C@H]4[C@H]5[C@@H](CCC5)CCC4)=O</chem> | 2.6 | Yes | Yes |
| 20 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@H]3N(C([C@@H]4CCC[C@H]5[C@H]4CCCC5)=O)CCCC3</chem> | 0.81 | - | Yes |
| 21 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@H]3N(C([C@@H]4[C@@H](C)CC[C@H]5[C@H]4CCCC5)=O)CCCC3</chem> | 0.49 | Yes | Yes |
| 22 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@@H]3CCCCN3C([C@H]4[C@H]5[C@@H](CCC5)CC(C4)=O)=O</chem> | 28 | Yes | Yes |
| 23 | <chem>O=C(O[C@@H](C1=CC(OCC(O)=O)=CC=C1)CCC2=CC=C(OC)C(OC)=C2)[C@@H]3CCCCN3C([C@H](CC4)[C@H]5[C@@H](CCC5)C4=O)=O</chem> | 3.1 | Yes | Yes |
| 24 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@H]5[C@H]6[C@@H](CCCC6)CC(C5)=O)=O</chem> | 1.3 | Yes | Yes |
| 25 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@H](CC5)[C@H]6[C@@H](CCCC6)C5=O)=O</chem> | 0.23 | Yes | Yes |
| 26 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@H]4N(C([C@@H]5[C@@H](C)CC([C@H]6[C@H]5CCCC6)=O)=O)CCCC4</chem> | 0.33 | Yes | Yes |
| 27 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@H]5[C@H]6[C@@H](CCCC6)C(O)CC5)=O</chem> | 0.65 | Yes | Yes |
| 28 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@H]5[C@H]6[C@@H](CCCC6)[C@H]7[C@H](OC(C)(O)7)C5)=O</chem> | 8.2 | Yes | Yes |
| 29 | <chem>O=C(O[C@@H](C1=CC(OCCN2CCOCC2)=CC=C1)CCC3=CC=C(OC)C(OC)=C3)[C@@H]4CCCCN4C([C@H]5[C@H]6[C@@H](CCCC6)[C@H](O)[C@H](O)C5)=O</chem> | 0.28 | Yes | Yes |
| 30 | <chem>O=C(O[C@@H](CCC1=CC=C(OC)C(OC)=C1)C2=CC(OCC(OC(C)(C)C)=CC=C2)[C@H]3NCCCC3</chem> | | Yes | Yes |
| 31 | <chem>O=C(O[C@@H](CCC1=CC=C(OC)C(OC)=C1)C2=CC(OCCN3CCOCC3)=CC=C2)[C@H]4NCCCC4</chem> | | Yes | Yes |

VII. Chemistry

General procedure A – Wittig olefination

To a suspension of the Wittig salt (2.4 eq.) in THF (0.2 M) was added dropwise K⁺O⁻tBu (2.6 eq., 1 M in THF) at 0 °C. The solution was stirred at rt for 1 h and then again cooled to 0 °C. The aldehyde (1 eq.) dissolved in some THF (1 M) was then added dropwise and the mixture was stirred at 4 °C for 16 h. After warming to rt the reaction was quenched by the addition of a saturated NH₄Cl solution and the product was extracted several times with Et₂O. The combined organics were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to obtain the title compounds as light yellow oils.

General procedure B– Swern Oxidation and subsequent Wittig olefination

DMSO (3 eq.) was added to a solution of oxalyl chloride (2 M in DCM, 1.5 eq.) in DCM (0.1 M related to alcohol) at -78 °C and stirred at that temperature for 30 min. Then the alcohol (1 eq.), dissolved in DCM (1 M) was added and the reaction mixture was stirred for further 60 min at -78 °C. In the following step TEA (10 eq.) was added and the slurry was allowed to warm to rt. Methyl 2-(triphenylphosphoranylidene)acetate (1.1 eq.) was added in one portion and the slurry was stirred at rt for 16 h. If necessary, the reaction mixture was diluted with some DCM to maintain adequate stirring. The reaction mixture was then washed with H₂O and saturated NH₄Cl solution. The organic layer was then dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The product was obtained after purification by flash chromatography.

General procedure C – Methyl ester cleavage

The methyl ester was dissolved in THF/1.5-2 M NaOH (1.5:1, 0.1 M) and stirred at 70 °C until the reaction was finished. After cooling to rt the reaction mixture was extracted with Et₂O. The organic layer was removed and the aqueous layer acidified with concentrated HCl. Then free carboxylic acid was extracted several times with DCM. The combined organic solvents were dried over MgSO₄, filtered and the solvent was removed under reduced pressure to obtain the product without further purification.

General procedure D – N-Acylation of the Evans auxiliary

The carboxylic acid (1 eq.) was dissolved in DCM (1 M) and oxalyl chloride (2 M in DCM, 2 eq.) with a catalytic amount of DMF (a few drops) was added to convert the acid into an acid chloride. The reaction mixture was stirred at rt for 2. Then the solvent was removed and the carboxylic acid chloride was used without further purification. In the meantime, n-BuLi (1.1 eq., 2.5 M in hexane) was added to (*R*)-4-benzyloxazolidin-2-one (1.0 eq.) in THF (0.2 M) at -78 °C and the reaction mixture was stirred at that temperature for 1 h. Then the acid chloride, dissolved in some DCM, was added to the deprotonated auxiliary and the mixture was allowed to warm to rt. The reaction was quenched by the addition of saturated NH₄Cl and the product was extracted with Et₂O. The combined organics were then dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The product was obtained after purification by flash chromatography.

General procedure E – Intramolecular Diels Alder cyclization

The acylated Evans auxiliary was dissolved in DCM (0.025 M) and cooled to -78 °C. DMAC (1.5 eq., 1 M in hexane) was added and the reaction mixture was stirred for 16 h, whereby it slowly warmed to rt. Then the mixture was quenched with 1 N HCl and the product extracted with DCM. The combined organics were then dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The product was obtained after purification by flash chromatography.

General procedure F – Evans auxiliary cleavage

To cleave the Evans auxiliary the reactant (1 eq.) was dissolved in THF/H₂O (0.075 M, 8:5) followed by the addition of LiOH (4.5 eq.) and H₂O₂ (5 eq, 30 wt.-% in H₂O). The reaction mixture was stirred at rt for 2.5 h and then quenched by adding a half-saturated Na₂SO₃ solution. It was extracted with DCM and the organic layers were removed. Then the aqueous layer was acidified with concentrated HCl and the product was extracted with DCM. The combined organics were dried over MgSO₄, filtered and the solvent was removed under reduced pressure to obtain the title compound without further purification.

General procedure G – Double bond hydrogenation

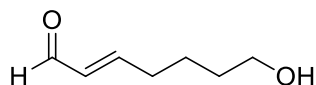
The reactant, containing the unsaturated double bond, was dissolved in MeOH (0.05 M) and the solution was degassed with argon. Then Pd/C (0.1 eq, 10 wt.-%) was added. In the following step H₂ was bubbled through the reaction mixture for 5 min. The reaction was then stirred under H₂ atmosphere for 16 h. After that time the dark suspension was filtered through celite and the solvent was removed under reduced pressure to obtain the title compound without further purification

General procedure H – Coupling reaction with 30

The carboxylic acid, **30** (1.0 eq.), COMU (1.5 eq.) and DIPEA (2.0 eq.) were stirred in DMF (0.1 M) at rt for 16 h and the tBu-ester was isolated after flash chromatography (0-20 % EtOAc in cyclohexane). To obtain the free carboxylic acid the tBu-ester was cleaved in DCM/TFA (0.1 M) for 1 h at rt. The reaction mixture was quenched with saturated NaHCO₃ and the product

was extracted with DCM. The combined organics were dried over MgSO₄, filtered and the solvent was removed under reduced pressure to obtain the title compound, after purification.

(E)-7-hydroxyhept-2-enal (6a)



6a

To a solution of Hoveyda-Grubbs 2nd generation catalyst (47.0 mg, 75.0 μmol) in DCM (35.0 mL) was added hex-5-en-1-ol (0.75 g, 7.50 mmol) and crotonaldehyde (3.11 mL, 37.5 mmol). The reaction mixture was heated to reflux for 2 h (oil bath was preheated to 50 °C). After completion of the reaction the mixture was cooled to rt. Some silica gel was added to the flask and the resulting slurry was stirred open to air for 30 min. The solvent was removed and the crude product was purified by flash chromatography (0-40 % EtOAc in cyclohexane) to obtain the title compound as light brown oil (quantitative yield).

TLC [EtOAc/cyclohexane, 1:1]: R_f = 0.16

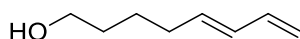
Mass: (ESI⁺), calculated 129.09 [C₇H₁₂O₂+H]⁺, found 129.87 [M+H]⁺.

¹H NMR (300 MHz, CDCl₃) δ 9.49 (d, *J* = 7.8 Hz, 1H), 6.84 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.12 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.70 – 3.59 (m, 2H), 2.47 – 2.24 (m, 2H), 1.70 – 1.53 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 193.98, 158.21, 133.13, 62.34, 32.37, 32.00, 24.10.

Analytical data in accordance with Biannic et al.¹⁰

(E)-octa-5,7-dien-1-ol (7a)



7a

General procedure A was used with **6a** (963 mg, 7.51 mmol) and methyltriphenylphosphonium iodide to obtain the title compound after purification by flash chromatography (0-40 % EtOAc in cyclohexane) as a light yellow oil (500 mg, 3.96 mmol, 52.7 %).

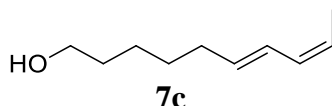
TLC [EtOAc/cyclohexane, 1:1]: R_f = 0.43

¹H NMR (300 MHz, CDCl₃) δ 6.30 (dt, *J* = 16.9, 10.2 Hz, 0H), 6.17 – 5.96 (m, 1H), 5.79 – 5.59 (m, 1H), 5.18 – 4.87 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.18 – 2.03 (m, 1H), 1.65 – 1.40 (m, 4H), 1.30 – 1.19 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 137.16, 137.15, 134.82, 131.24, 114.86, 77.39, 77.18, 76.97, 76.55, 62.78, 32.21, 32.17, 25.26.

Analytical data in accordance with Craig et al.¹¹

(6E, 8Z)-deca-6,8-dien-1-ol (7c)



General procedure A was used with **6c** (711 mg, 5.0 mmol) and ethyltriphenylphosphonium bromide to obtain the title compound (containing ~20% 8E-isomer) after purification by flash chromatography (0-20 % EtOAc in cyclohexane) as a light yellow oil (680 mg, 4.41 mmol, 88.2 %).

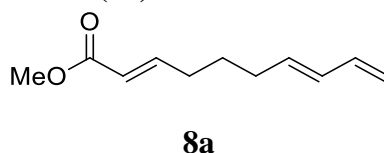
TLC [EtOAc/cyclohexane, 1:1]: $R_f = 0.46$

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.44 – 6.24 (m, 1H), 6.09 – 5.88 (m, 1H), 5.71 – 5.59 (m, 1H), 5.44 – 5.31 (m, 1H), 3.68 – 3.60 (m, 2H), 2.18 – 2.02 (m, 2H), 1.73 (dd, $J = 7.1, 1.7$ Hz, 3H), 1.56 (dd, $J = 15.7, 8.5$ Hz, 3H), 1.48 – 1.30 (m, 4H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 134.12, 129.43, 125.52, 124.01, 62.94, 32.79, 32.62, 29.17, 25.31, 13.25.

Analytical data in accordance with Larson et al.¹²

(2E, 7E)-methyl deca-2,7,9-trienoate (8a)



General procedure B was used with **7a** (490 mg, 3.88 mmol) and the title compound was obtained after purification by flash chromatography (0-5 % EtOAc in cyclohexane) as yellow oil (630 mg, 90.1 %, 3.50 mmol).

TLC [EtOAc/cyclohexane, 2:8]: $R_f = 0.53$

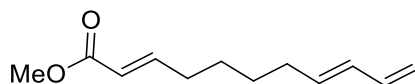
Mass: (ESI⁺), calculated 181.12 [$\text{C}_{11}\text{H}_{16}\text{O}_2 + \text{H}$]⁺, found 181.00 [$\text{M} + \text{H}$]⁺.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.95 (dt, $J = 15.7, 7.0$ Hz, 1H), 6.39 – 6.21 (m, 1H), 6.12 – 5.98 (m, 1H), 5.82 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.72 – 5.59 (m, 1H), 5.15 – 5.04 (m, 1H), 5.03 – 4.91 (m, 1H), 3.72 (s, 3H), 2.28 – 2.16 (m, 2H), 2.11 (q, $J = 7.0$ Hz, 2H), 1.64 – 1.48 (m, 2H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 167.05, 149.09, 137.00, 134.05, 131.66, 121.14, 115.16, 51.36, 31.80, 31.53, 27.42.

Analytical data in accordance with Roush et al.¹³

(2E,8E,10Z)-methyl dodeca-2,8,10-trienoate (8c)



8c

General procedure B was used with **7c** (680 mg, 4.41 mmol) and the title compound (containing ~20% 10E-isomer) was obtained, after purification by flash chromatography (0-5 % EtOAc in cyclohexane) as colorless oil (904 mg, 4.34 mmol, 98.1 %).

TLC [EtOAc/cyclohexane, 1:9]: $R_f = 0.41$

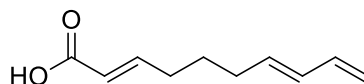
Mass: (ESI⁺), calculated 209.30 [C₁₃H₂₀O₂+H]⁺, found 208.99 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 6.96 (dt, $J = 15.6, 7.0$ Hz, 1H), 6.32 (ddq, $J = 15.1, 11.0, 1.4$ Hz, 1H), 5.99 – 5.93 (m, 1H), 5.85 – 5.78 (m, 1H), 5.66 – 5.59 (m, 1H), 5.44 – 5.32 (m, 1H), 3.74 – 3.71 (m, 3H), 2.21 (qd, $J = 7.1, 1.6$ Hz, 2H), 2.15 – 2.08 (m, 2H), 1.75 – 1.71 (m, 3H), 1.50 – 1.39 (m, 4H).

¹³C NMR (151 MHz, CDCl₃) δ 167.12, 149.47, 133.71, 129.33, 125.72, 124.20, 120.94, 51.37, 32.56, 32.04, 28.83, 27.53, 13.27.

Analytical data in accordance with Lygo et al.¹⁴

(2E, 7E)- deca-2,7,9-trienoic acid (9a)



9a

General procedure C was used with **8a** (620 mg, 3.44 mmol) to obtain the title compound as light brown oil (493 mg, 2.97 mmol, 86.2 %).

TLC [EtOAc/cyclohexane, 1:1]: $R_f = 0.36$

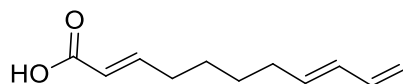
Mass: (ESI⁺), calculated 167.11 [C₁₀H₁₄O₂+H]⁺, found 167.01 [M+H]⁺.

¹H NMR (300 MHz, CDCl₃) δ 6.95 (dt, $J = 15.7, 7.0$ Hz, 1H), 6.39 – 6.21 (m, 1H), 6.12 – 5.98 (m, 1H), 5.82 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.72 – 5.59 (m, 1H), 5.15 – 5.04 (m, 1H), 5.03 – 4.91 (m, 1H), 2.28 – 2.16 (m, 2H), 2.11 (q, $J = 7.0$ Hz, 2H), 1.64 – 1.48 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 167.05, 149.09, 137.00, 134.05, 131.66, 121.14, 115.16, 31.80, 31.53, 27.42.

Analytical data in accordance with Evans et al.¹⁵

(2E,8E,10Z)-dodeca-2,8,10-trienoic acid (9c)



9c

General procedure C was used with **8c** (890 mg, 4.27 mmol) to obtain the title compound (containing ~20% 10E-isomer) as light yellow oil (688 mg, 3.54 mmol, 82.9 %).

TLC [EtOAc/cyclohexane, 1:1]: $R_f = 0.44$

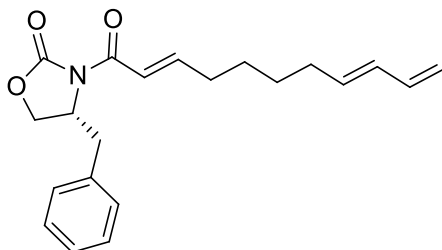
Mass: (ESI⁺), calculated 195.14 [C₁₂H₁₈O₂+H]⁺, found 195.00 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.08 (dt, $J = 15.6, 7.0$ Hz, 1H), 6.33 (ddq, $J = 15.1, 10.9, 1.3$ Hz, 1H), 6.02 – 5.93 (m, 1H), 5.83 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.67 – 5.59 (m, 1H), 5.44 – 5.33 (m, 1H), 2.25 (qd, $J = 7.1, 1.6$ Hz, 2H), 2.15 – 2.10 (m, 2H), 1.76 – 1.72 (m, 3H), 1.53 – 1.47 (m, 2H), 1.46 – 1.40 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 171.70, 152.14, 133.63, 129.32, 125.77, 124.25, 120.64, 32.54, 32.15, 28.84, 27.39, 13.28.

Analytical data in accordance with Lygo et al.¹⁴

(R)-4-benzyl-3-((2E,8E,10Z)-dodeca-2,8,10-trienoyl)oxazolidin-2-one (10c)



10c

General procedure D was used with **9c** (611 mg, 3.45 mmol) and the title compound (containing ~20% 10E-isomer) was obtained, after purification by flash chromatography (0-5 % EtOAc in cyclohexane) as yellow oil (800 mg, 2.26 mmol, 65.6 %).

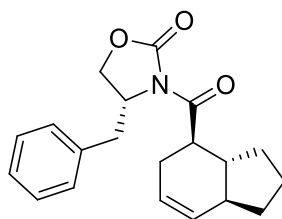
TLC [EtOAc/cyclohexane, 2:8]: $R_f = 0.42$

Mass: (ESI⁺), calculated 354.21 [C₂₂H₂₇NO₃+H]⁺, found 354.08 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.36 – 7.31 (m, 2H), 7.29 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 6.34 (ddq, $J = 15.1, 11.0, 1.4$ Hz, 1H), 6.02 – 5.90 (m, 1H), 5.71 – 5.59 (m, 1H), 5.43 – 5.35 (m, 1H), 4.78 – 4.68 (m, 1H), 4.28 – 4.13 (m, 2H), 3.34 (dd, $J = 13.4, 3.3$ Hz, 1H), 2.80 (dd, $J = 13.4, 9.6$ Hz, 1H), 2.39 – 2.24 (m, 2H), 2.18 – 2.10 (m, 2H), 1.78 – 1.68 (m, 3H), 1.57 – 1.51 (m, 2H), 1.50 – 1.40 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.07, 153.41, 151.67, 135.39, 133.77, 129.43, 129.37, 128.93, 127.28, 125.72, 124.18, 120.45, 66.10, 55.32, 37.91, 32.57, 28.92, 27.64, 13.28.

(*R*)-4-benzyl-3-((3*aR*,4*R*,7*aS*)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indene-4-carbonyl)oxazolidin-2-one (11a)



11a

To a suspension of (*R*)-4-benzyloxazolidin-2-one (665 mg, 3.75 mmol), DMAP (70.6 mg) and **9a** (480 mg, 2.89 mmol) in DCM (6.0 mL) was added DCC (596 mg, 2.89 mmol) at $-78\text{ }^\circ\text{C}$. The reaction was stirred at that temperature for 1 h and then at $0\text{ }^\circ\text{C}$ for 20 h. Purification by flash chromatography (0-10 % EtOAc in cyclohexane) provided the product as inseparable mixture of the title compound and the *N*-acylurea byproduct. To a solution of this mixture (490 mg) in DCM (50.0 mL) was added DMAC (2.26 mL, 2.26 mmol, 1 M in hexane) at $-78\text{ }^\circ\text{C}$. The solution was stirred for 16 h, whereby it was slowly warmed to rt. Then 1 N HCl was added and the product was extracted with DCM. The combined organics were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. Purification by flash chromatography provided the title compound as colorless oil (304 mg, 0.93 mmol, 24.9 % after 2 steps).

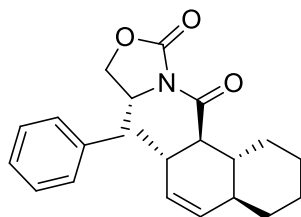
TLC [EtOAc/cyclohexane, 1:9]: $R_f = 0.26$

Mass: (ESI⁺), calculated 326.18 [$\text{C}_{20}\text{H}_{23}\text{NO}_3+\text{H}$]⁺, found 326.14 [$\text{M}+\text{H}$]⁺.

^1H NMR (300 MHz, CDCl_3) δ 7.44 – 7.02 (m, 5H), 5.85 (dq, $J = 9.7, 2.0$ Hz, 1H), 5.64 – 5.53 (m, 1H), 4.79 – 4.57 (m, 1H), 4.29 – 4.02 (m, 2H), 3.86 (td, $J = 10.7, 6.2$ Hz, 1H), 3.25 (dd, $J = 13.1, 3.2$ Hz, 1H), 2.76 (dd, $J = 13.4, 9.5$ Hz, 1H), 2.67 – 2.45 (m, 1H), 2.36 – 2.11 (m, 1H), 2.03 – 1.95 (m, 1H), 1.92 – 1.78 (m, 2H), 1.81 – 1.62 (m, 3H), 1.25 – 1.06 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ 175.83, 153.13, 135.26, 129.86, 129.40, 128.90, 127.32, 125.29, 66.07, 55.28, 45.45, 43.60, 43.40, 37.96, 30.27, 28.90, 27.67, 21.83.

(R)-4-benzyl-3-((1R,2S,4aS,8aR)-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (11c)



11c

General procedure E was used with **10c** (790 mg, 2.24 mmol) and the title compound was obtained after purification by flash chromatography (0-20 % DCM in cyclohexane) as a colorless oil (470 mg, 1.33 mmol, 59.5 %).

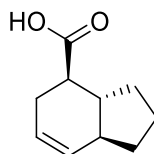
TLC [DCM/cyclohexane, 1:1]: $R_f = 0.23$

Mass: (ESI⁺), calculated 354.21 [C₂₂H₂₇NO₃+H]⁺, found 354.02 [M+H]⁺.

¹H NMR (800 MHz, CDCl₃) δ 7.38 – 7.33 (m, 2H), 7.30 – 7.26 (m, 3H), 5.60 (ddd, $J = 9.8, 4.6, 2.5$ Hz, 1H), 5.43 (dt, $J = 9.9, 1.7$ Hz, 1H), 4.76 – 4.71 (m, 1H), 4.21 – 4.11 (m, 2H), 3.84 (dd, $J = 11.4, 5.9$ Hz, 1H), 3.44 (dd, $J = 13.2, 3.4$ Hz, 1H), 2.87 – 2.78 (m, 1H), 2.65 (dd, $J = 13.2, 10.5$ Hz, 1H), 1.96 – 1.89 (m, 1H), 1.82 – 1.74 (m, 3H), 1.65 – 1.56 (m, 2H), 1.45 – 1.38 (m, 1H), 1.34 (qt, $J = 14.1, 3.9$ Hz, 1H), 1.18 – 1.10 (m, 1H), 0.98 (d, $J = 7.2$ Hz, 3H), 0.93 – 0.85 (m, 1H).

¹³C NMR (201 MHz, CDCl₃) δ 173.62, 153.06, 135.51, 130.83, 130.70, 129.34, 128.99, 127.32, 66.03, 55.37, 47.67, 41.89, 38.29, 36.59, 33.17, 30.91, 30.09, 26.70, 26.59, 17.77.

(3aR,4R,7aS)-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid (12a)



12a

General procedure F was used with **11a** (290 mg, 0.89 mmol) to obtain the title compound without further purification as a colorless solid (77 mg, 0.46 mmol, 52.1 %).

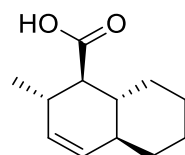
TLC [EtOAc/cyclohexane, 1:9]: $R_f = 0.26$.

¹H NMR (599 MHz, CDCl₃) δ 5.88 – 5.79 (m, 1H), 5.64 – 5.50 (m, 1H), 2.59 – 2.49 (m, 1H), 2.48 – 2.28 (m, 2H), 1.98 – 1.80 (m, 3H), 1.79 – 1.64 (m, 2H), 1.56 (qd, $J = 11.3, 6.4$ Hz, 1H), 1.32 – 1.23 (m, 1H), 1.23 – 1.14 (m, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 181.57, 129.77, 125.21, 45.54, 45.12, 44.11, 29.78, 28.97, 28.08, 21.79.

Analytical data in accordance with Clive et al.¹⁶

(1*R*,2*S*,4*aS*,8*aR*)-2-methyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carboxylic acid (12c)



12c

n-Buli (0.42 mL, 1.06 mmol, 2.5 M) was added to a solution of ethanethiol (94 μL , 1.27 mmol, $d = 0.84$ g/mol) in THF (4.5 mL) at -78 $^\circ\text{C}$ and stirred for 10 min. The reaction mixture was transferred to an ice bath and **11c** (150 mg, 0.42 mmol), dissolved in THF (0.5 mL), was added. The solution was stirred at 0 $^\circ\text{C}$ for 1 h, then quenched with saturated NH_4Cl solution and extracted with Et_2O . The organics were combined, dried over MgSO_4 , filtered and concentrated in vacuo. After purification (quantitative yield) by flash chromatography (0-5 % EtOAc in cyclohexane) the thioester (80.0 mg, 0.34 mmol) was dissolved in THF/ H_2O (1.8 mL, 5:1) followed by addition of mercury(II)trifluoroacetate (215 mg, 0.5 mmol). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 2 h and the title compound was obtained after purification by flash chromatography (0-20 % EtOAc in cyclohexane) as colorless solid (33.9 mg, 0.17 mmol, 52.0 %).

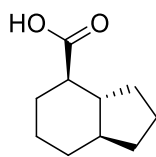
TLC [EtOAc/cyclohexane, 3:7]: $R_f = 0.42$.

Mass: (ESI⁺), calculated 195.14 [$\text{C}_{12}\text{H}_{18}\text{O}_2 + \text{H}$]⁺, found 195.01 [$\text{M} + \text{H}$]⁺.

^1H NMR (599 MHz, CDCl_3) δ 5.55 (ddd, $J = 9.9, 4.0, 2.7$ Hz, 1H), 5.39 (dq, $J = 9.8, 0.9$ Hz, 1H), 2.64 – 2.55 (m, 2H), 2.05 – 1.98 (m, 1H), 1.80 – 1.74 (m, 2H), 1.72 – 1.66 (m, 1H), 1.43 – 1.38 (m, 1H), 1.38 – 1.34 (m, 1H), 1.35 – 1.32 (m, 1H), 1.32 – 1.27 (m, 1H), 1.12 – 1.05 (m, 1H), 1.00 – 0.97 (m, 3H), 0.96 – 0.88 (m, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 179.77, 130.95, 130.52, 49.32, 42.01, 36.26, 33.01, 32.14, 30.04, 26.63, 26.47, 17.61.

(3aR,4R,7aS)-octahydro-1H-indene-4-carboxylic acid (13a)



13a

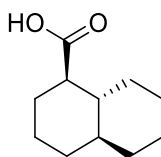
General procedure G was used with **12a** (15 mg, 90 μ mol) to obtain the title compound (quantitative yield) as colorless oil.

TLC [EtOAc/cyclohexane, 1:9]: R_f = 0.45

^1H NMR (599 MHz, CDCl_3) δ 2.14 – 2.03 (m, 1H), 1.95 (d, J = 12.9 Hz, 1H), 1.92 – 1.76 (m, 3H), 1.79 – 1.71 (m, 1H), 1.69 – 1.47 (m, 2H), 1.40 (qd, J = 12.9, 12.4, 3.5 Hz, 1H), 1.31 – 1.04 (m, 5H), 1.00 (qd, J = 12.2, 3.3 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 182.17, 48.91, 47.60, 45.52, 30.96, 30.81, 29.67, 29.57, 29.39, 25.74, 21.31.

(1R,4aS,8aR)-decahydronaphthalene-1-carboxylic acid (13b)



13b

General procedure G was used with **12b** (24 mg, 0.133 mmol) to obtain the title compound (quantitative yield) as colorless solid.

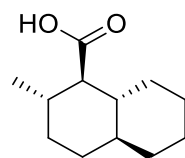
TLC [EtOAc/cyclohexane, 2:8]: R_f = 0.24

Mass: (ESI⁺), calculated 183.14 [$\text{C}_{11}\text{H}_{18}\text{O}_2+\text{H}$]⁺, found 183.14 [$\text{M}+\text{H}$]⁺.

^1H NMR (400 MHz, CDCl_3) δ 2.04 (ddd, J = 12.2, 10.7, 3.5 Hz, 1H), 1.94 (dq, J = 12.7, 3.4, 1.6 Hz, 1H), 1.78 (dq, J = 13.2, 3.1 Hz, 1H), 1.74 – 1.71 (m, 1H), 1.71 – 1.66 (m, 2H), 1.64 – 1.56 (m, 2H), 1.55 – 1.44 (m, 2H), 1.39 – 1.26 (m, 2H), 1.26 – 1.17 (m, 2H), 1.09 – 0.90 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 182.36, 50.11, 44.21, 41.80, 34.00, 33.39, 31.30, 30.22, 26.38, 26.29, 25.29.

(1*R*,2*S*,4*aS*,8*aR*)-2-methyldecahydronaphthalene-1-carboxylic acid (13c)



13c

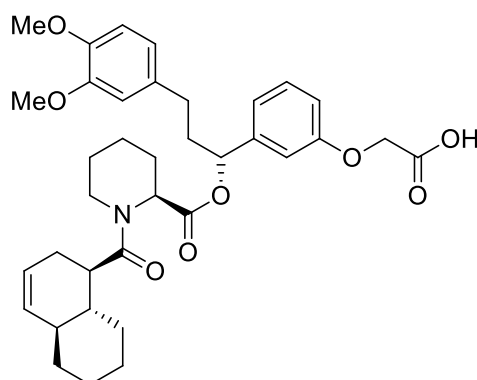
General procedure G was used with **12c** (10 mg, 0.05 mmol) to obtain the title compound (quantitative yield) as colorless oil.

TLC [EtOAc/cyclohexane, 2:8]: $R_f = 0.27$.

¹H NMR (400 MHz, CDCl₃) δ 2.32 – 2.21 (m, 2H), 1.85 – 1.77 (m, 1H), 1.71 – 1.53 (m, 5H), 1.46 – 1.18 (m, 5H), 1.08 – 1.00 (m, 1H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.95 – 0.92 (m, 1H), 0.88 – 0.78 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 180.47, 52.59, 42.65, 37.54, 33.89, 32.68, 31.58, 31.07, 27.38, 26.55, 26.42, 26.20, 14.36.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,4*aS*,8*aR*)-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (14)



14

12b (20.0 mg, 0.11 mmol), **30** (57.0 mg, 0.11 mmol), PyBrop (77.0 mg, 0.17 mmol) and DIPEA (58.0 μ L, 0.33 mmol) were stirred in DCM (1.5 mL) at rt for 16 h. The tBu-ester was obtained after purification (0-20 % EtOAc in cyclohexane). To obtain the free carboxylic acid the tBu-ester was cleaved in DCM (3.0 mL) and TFA (300 μ L) for 16 h at rt. The title compound was obtained after preparative HPLC (64-75 % B) as colorless solid (43.3 mg, 69.9 μ mol, 42.1 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: $R_f = 0.18$.

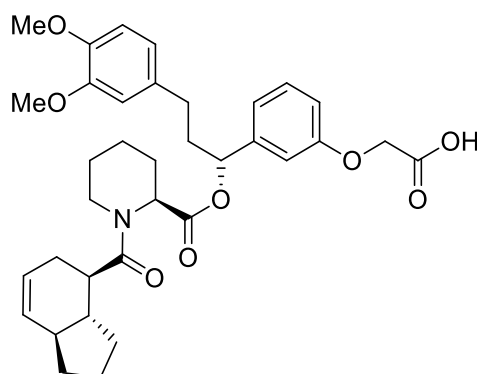
HPLC [50-100% Solvent B, 30 min]: $R_t = 20.88$ min, 97%.

HRMS: calculated 620.3223 [C₃₆H₄₅NO₈+H]⁺, found 620.3210 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.22 (t, *J* = 8.1 Hz, 1H), 6.89 – 6.74 (m, 4H), 6.70 – 6.61 (m, 2H), 5.72 – 5.63 (m, 1H), 5.61 – 5.49 (m, 2H), 5.47 – 5.36 (m, 1H), 4.66 – 4.52 (m, 2H), 4.01 – 3.93 (m, 1H), 3.87 – 3.75 (m, 6H), 3.34 (t, *J* = 10.7 Hz, 1H), 2.86 – 2.72 (m, 1H), 2.66 – 2.51 (m, 2H), 2.39 – 2.23 (m, 1H), 2.22 – 2.15 (m, 1H), 2.12 – 2.01 (m, 2H), 1.93 – 1.85 (m, 2H), 1.77 – 1.67 (m, 4H), 1.60 – 1.54 (m, 2H), 1.36 – 1.23 (m, 4H), 1.18 – 1.10 (m, 2H), 1.11 – 1.00 (m, 1H), 0.91 – 0.80 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 175.89, 171.85, 170.28, 158.02, 148.84, 147.30, 142.02, 133.41, 131.99, 129.65, 124.55, 120.16, 119.97, 115.21, 114.78, 112.03, 111.64, 110.87, 76.34, 65.40, 55.89, 52.31, 49.72, 43.60, 42.25, 41.77, 38.06, 33.39, 32.96, 31.38, 30.46, 29.55, 27.13, 26.42, 25.51, 24.74, 21.09.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((3*aR*,4*R*,7*aS*)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (15)



15

General procedure H was used with **12a** (20.0 mg, 0.12 mmol) and the title compound was obtained after flash chromatography (0-30 % [EtOAc + 1 % HCOOH] in hexane) as colorless solid (53.2 mg, 87.8 μmol, 73.0 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: *R_f* = 0.22.

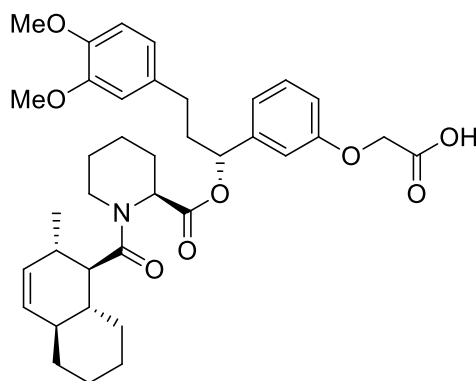
HPLC [50-100% Solvent B, 20 min]: *R_t* = 13.75 min, 96%.

HRMS: calculated 606.3067 [C₃₅H₄₃NO₈+H]⁺, found 606.3107 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.24 – 7.19 (m, 1H), 6.89 – 6.83 (m, 2H), 6.81 – 6.75 (m, 2H), 6.70 – 6.62 (m, 2H), 5.83 – 5.77 (m, 1H), 5.65 (dd, *J* = 8.8, 5.0 Hz, 1H), 5.55 – 5.50 (m, 1H), 5.50 – 5.44 (m, 1H), 4.60 (q, *J* = 16.5 Hz, 2H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.88 – 3.79 (m, 6H), 3.28 (td, *J* = 13.1, 2.7 Hz, 1H), 3.06 (q, *J* = 7.6 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.69 – 2.58 (m, 1H), 2.59 – 2.47 (m, 1H), 2.41 – 2.32 (m, 1H), 2.27 – 2.14 (m, 3H), 2.08 – 2.03 (m, 1H), 1.90 – 1.80 (m, 2H), 1.76 – 1.62 (m, 5H), 1.53 – 1.39 (m, 1H), 1.39 – 1.30 (m, 1H), 1.23 – 1.13 (m, 2H), 1.04 (p, *J* = 10.7 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 175.73, 171.69, 170.30, 158.12, 148.88, 147.35, 141.97, 133.42, 129.69, 129.62, 125.68, 120.15, 119.28, 115.40, 111.66, 111.32, 110.48, 76.38, 65.67, 55.91, 55.84, 52.31, 45.66, 45.43, 43.85, 43.44, 41.88, 38.07, 31.43, 29.97, 28.95, 28.22, 27.07, 25.47, 21.75, 21.11, 14.17, 8.39.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,2*S*,4*aS*,8*aR*)-2-methyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (17)



17

General procedure H was used with **12c** (10.0 mg, 0.05 mmol) and the title compound was obtained after purification by flash chromatography (0-30 % [EtOAc + 0.1 % HCOOH] in hexane) as colorless oil (13.8 mg, 20.0 μmol , 42.3 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: R_f = 0.29.

HPLC [30-100% Solvent B, 20 min]: R_t = 15.52 min, 98%.

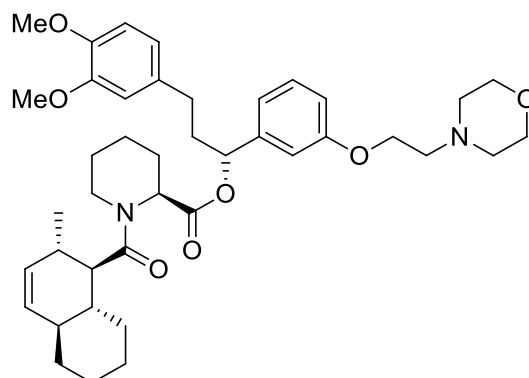
HRMS: 634.3380 [$\text{C}_{37}\text{H}_{47}\text{NO}_8+\text{H}$] $^+$, found 634.3383 [$\text{M}+\text{H}$] $^+$.

^1H NMR (599 MHz, CDCl_3) δ 7.24 – 7.19 (m, 1H), 6.89 – 6.84 (m, 2H), 6.81 – 6.76 (m, 2H), 6.72 – 6.62 (m, 2H), 5.68 (dd, J = 8.8, 4.8 Hz, 1H), 5.51 – 5.46 (m, 2H), 5.35 (dt, J = 9.9, 1.5 Hz, 1H), 4.65 – 4.59 (m, 1H), 3.91 (d, J = 14.8 Hz, 1H), 3.89 – 3.83 (m, 6H), 3.34 – 3.26 (m, 1H), 2.79 (dd, J = 10.9, 6.0 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.63 – 2.53 (m, 2H), 2.45 – 2.33 (m, 2H), 2.27 – 2.18 (m, 2H), 2.10 – 2.05 (m, 1H), 2.00 – 1.93 (m, 1H), 1.79 – 1.66 (m, 6H), 1.53 – 1.47 (m, 1H), 1.46 – 1.33 (m, 3H), 1.31 – 1.28 (m, 1H), 1.09 (qd, J = 12.1, 3.2 Hz, 1H), 0.80 – 0.69 (m, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 173.56, 171.19, 170.49, 163.04, 158.00, 148.90, 147.38, 142.04, 133.42, 130.88, 130.82, 129.59, 120.16, 119.44, 115.71, 111.65, 111.33, 109.68, 76.36, 65.57, 60.42, 55.92, 55.86, 52.05, 45.92, 43.21, 42.34, 38.09, 36.87, 33.11, 31.52, 31.00, 30.37, 27.29, 26.81, 26.46, 25.58, 21.19, 17.51, 14.18.

**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
((1R,2S,4aS,8aR)-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-
carbonyl)piperidine-2-carboxylate (18)**

1-



18

12c (45.0 mg, 0.23 mmol), **31** (119 mg, 0.23 mmol), COMU (149 mg, 0.35 mmol) and DIPEA (81.0 μ L, 0.46 mmol, $d = 0.74$ g/mL) were stirred in DMF (3.0 mL) at rt for 16 h. The resulting orange solution was diluted with Et₂O and washed with brine. Then the organic layer was dried over MgSO₄, filtered and the solvent was removed under vacuo. After purification by flash chromatography (0-60 % [EtOAc + 2 % MeOH + 0.1 % TEA] in cyclohexane) the title compound was obtained as light yellow oil (118 mg, 0.17 mmol, 74.0 %).

TLC [EtOAc + 2 % MeOH + 0.1 % TEA]: $R_f = 0.28$.

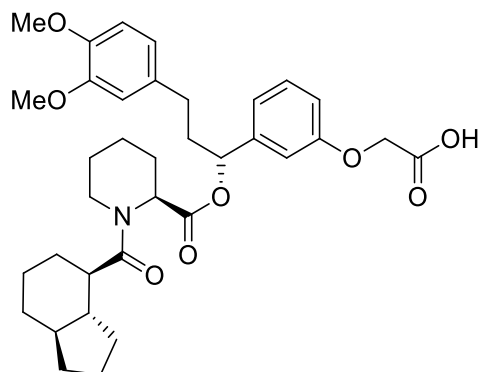
HPLC [0-100% Solvent B, 20 min]: $R_t = 18.17$ min, 98%.

Mass: (ESI⁺), calculated 689.42 [C₄₁H₅₆N₂O₇+H]⁺, found 689.21 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.24 – 7.19 (m, 1H), 6.92 – 6.87 (m, 1H), 6.84 – 6.74 (m, 3H), 6.67 – 6.61 (m, 2H), 5.75 (dd, $J = 8.2, 5.5$ Hz, 1H), 5.51 – 5.48 (m, 1H), 5.41 – 5.35 (m, 1H), 4.19 – 4.14 (m, 2H), 3.90 – 3.85 (m, 1H), 3.85 – 3.81 (m, 6H), 3.82 – 3.76 (m, 4H), 3.18 – 3.09 (m, 1H), 3.00 – 2.96 (m, 2H), 2.80 – 2.75 (m, 4H), 2.64 – 2.55 (m, 2H), 2.54 – 2.48 (m, 1H), 2.44 – 2.37 (m, 1H), 2.35 – 2.28 (m, 1H), 2.24 – 2.18 (m, 1H), 2.06 – 1.98 (m, 2H), 1.94 (dd, $J = 12.4, 3.2$ Hz, 1H), 1.74 – 1.59 (m, 6H), 1.54 – 1.49 (m, 1H), 1.43 – 1.32 (m, 4H), 1.14 – 1.04 (m, 2H), 0.91 – 0.85 (m, 3H), 0.78 – 0.69 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 172.38, 171.01, 162.60, 158.36, 148.84, 147.30, 141.81, 133.52, 131.01, 130.92, 129.62, 120.11, 119.20, 113.90, 112.75, 111.66, 111.27, 76.03, 66.02, 64.73, 57.34, 55.90, 55.82, 53.76, 53.71, 51.46, 45.61, 43.19, 42.37, 38.06, 37.03, 36.50, 33.18, 31.44, 31.35, 31.01, 30.43, 26.96, 26.83, 26.52, 25.73, 21.20, 17.88.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((3*aR*,4*R*,7*aS*)-octahydro-1*H*-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (19)



19

General procedure H was used with **13a** (15.0 mg, 89.0 μmol) and the title compound was obtained after flash chromatography (0-20 % [EtOAc + 1 % HCOOH] in hexane) as colorless oil (35.9 mg, 59.1 μmol , 66.2 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: $R_f = 0.20$.

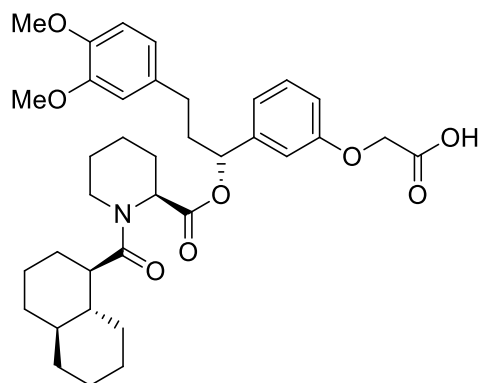
HPLC [50-100% Solvent B, 20 min]: $R_t = 14.83$ min, 95%.

HRMS: calculated 608.3223 [$\text{C}_{35}\text{H}_{45}\text{NO}_8 + \text{H}$] $^+$, found 608.3257 [$\text{M} + \text{H}$] $^+$.

^1H NMR (599 MHz, CDCl_3) δ 7.24 – 7.19 (m, 1H), 6.88 – 6.81 (m, 2H), 6.79 – 6.75 (m, 2H), 6.71 – 6.66 (m, 2H), 5.63 (dd, $J = 8.9, 4.8$ Hz, 1H), 5.48 (d, $J = 5.8$ Hz, 1H), 4.69 – 4.58 (m, 2H), 3.91 (d, $J = 13.6$ Hz, 1H), 3.89 – 3.80 (m, 6H), 3.30 (t, $J = 12.7$ Hz, 1H), 2.71 – 2.61 (m, 1H), 2.60 – 2.52 (m, 1H), 2.47 – 2.32 (m, 2H), 2.24 – 2.17 (m, 1H), 2.08 – 2.04 (m, 2H), 1.88 – 1.80 (m, 2H), 1.79 – 1.69 (m, 4H), 1.61 – 1.51 (m, 2H), 1.45 – 1.31 (m, 4H), 1.28 – 1.23 (m, 2H), 1.16 – 1.05 (m, 2H), 1.04 – 0.93 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 176.06, 171.17, 170.30, 158.05, 148.89, 147.36, 142.11, 133.41, 129.61, 120.17, 119.31, 115.75, 111.66, 111.32, 109.83, 76.34, 65.53, 60.39, 55.91, 55.85, 52.24, 47.64, 45.47, 43.35, 38.06, 31.47, 30.97, 30.77, 29.53, 29.21, 27.17, 25.97, 25.48, 21.31, 21.13, 14.17.

2-(3-((*R*)-1-(((*S*)-1-((1*R*,4*aS*,8*aR*)-decahydronaphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (20**)**



20

13b (20.0 mg, 0.11 mmol), **30** (67.6 mg, 0.13 mmol), HATU (62.6 mg, 0.17 mmol) and DIPEA (57.5 μ L, 0.33 mmol) were stirred in DMF (2.0 mL) at 40 °C for 16 h. The tBu-ester was purified by flash chromatography (0-10 % EtOAc in cyclohexane). To obtain the free carboxylic acid the tBu-ester was cleaved in DCM (3.0 mL) and TFA (300 μ L) for 16 h at rt. The title compound was obtained after flash chromatography (0-20 % [EtOAc + 2 % MeOH + 0.1 % TFA] in hexane) as colorless solid (30.3 mg, 48.7 μ mol, 44.3 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: R_f = 0.11

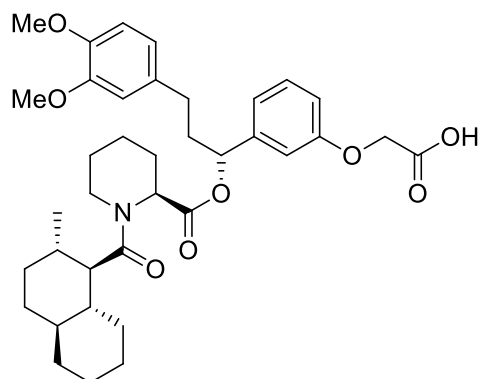
HRMS: calculated 622.3380 [C₃₆H₄₇NO₈+H]⁺, found 622.3360 [M+H]⁺.

HPLC [50-100% Solvent B, 20 min]: R_t = 15.75 min, 98%.

¹H NMR (599 MHz, CDCl₃) δ 7.21 (t, J = 7.8 Hz, 1H), 6.92 – 6.80 (m, 3H), 6.79 – 6.73 (m, 1H), 6.70 – 6.58 (m, 2H), 5.67 – 5.62 (m, 1H), 5.50 – 5.45 (m, 1H), 4.64 – 4.57 (m, 2H), 3.92 (d, J = 13.8 Hz, 1H), 3.88 – 3.76 (m, 6H), 3.24 – 3.17 (m, 1H), 2.64 – 2.58 (m, 1H), 2.55 – 2.49 (m, 1H), 2.39 – 2.28 (m, 2H), 2.21 – 2.13 (m, 1H), 2.06 – 1.96 (m, 2H), 1.75 – 1.70 (m, 2H), 1.67 – 1.60 (m, 5H), 1.58 – 1.47 (m, 3H), 1.43 – 1.34 (m, 4H), 1.24 – 1.16 (m, 3H), 1.03 – 0.94 (m, 2H), 0.81 – 0.71 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 170.50, 158.10, 148.84, 147.29, 141.97, 133.46, 129.59, 120.15, 119.37, 114.82, 111.66, 111.39, 111.29, 76.17, 65.45, 55.89, 55.82, 44.33, 43.37, 42.20, 38.10, 34.04, 33.40, 31.42, 31.32, 29.80, 27.08, 26.53, 26.35, 25.56, 25.52, 21.18.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,2*S*,4*aS*,8*aR*)-2-methyl-decahydro-naphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (21)



21

General procedure H was used with **13c** (20.0 mg, 0.10 mmol) and the title compound was obtained after purification by flash chromatography (0-30 % [EtOAc + 0.1 % HCOOH] in hexane) as colorless oil (12.7 mg, 20.0 μ mol, 19.6 %).

TLC [EtOAc/cyclohexane, 1:1 + 1 % HCOOH]: R_f = 0.28.

HPLC [50-100% Solvent B, 20 min]: R_t = 16.75 min, 96 %.

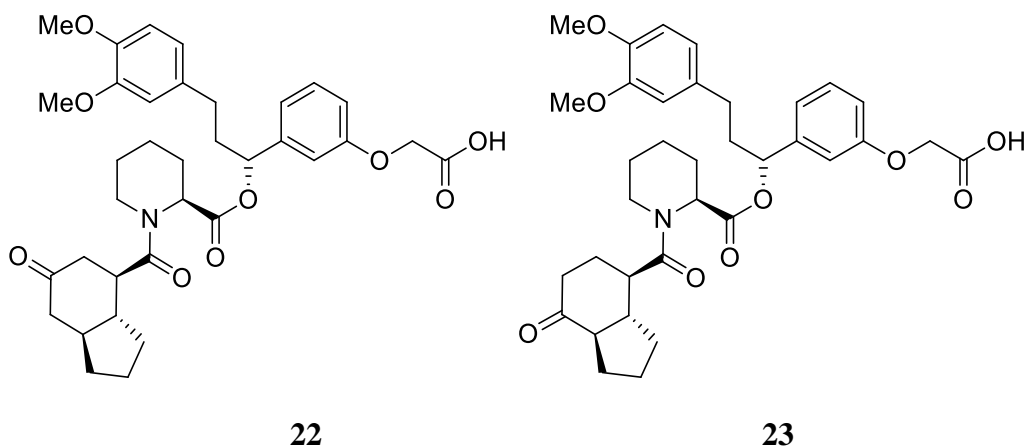
HRMS: calculated 636.3536 [$C_{37}H_{49}NO_8+H$]⁺, found 636.3545 [$M+H$]⁺.

¹H NMR (599 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 1H), 6.90 – 6.84 (m, 2H), 6.80 – 6.76 (m, 2H), 6.71 – 6.65 (m, 2H), 5.66 (dd, J = 8.8, 4.8 Hz, 1H), 5.52 – 5.46 (m, 1H), 3.89 – 3.83 (m, 7H), 3.32 – 3.24 (m, 1H), 2.71 – 2.65 (m, 1H), 2.63 – 2.55 (m, 1H), 2.44 (dd, J = 10.7, 4.2 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.25 – 2.19 (m, 1H), 2.10 – 2.05 (m, 2H), 1.79 (dt, J = 12.8, 3.3 Hz, 1H), 1.74 – 1.61 (m, 5H), 1.58 – 1.50 (m, 5H), 1.45 – 1.35 (m, 2H), 1.31 – 1.26 (m, 2H), 1.24 – 1.17 (m, 2H), 1.09 – 1.01 (m, 1H), 0.95 – 0.91 (m, 2H), 0.74 (d, J = 7.1 Hz, 3H), 0.65 (tdd, J = 12.4, 10.9, 3.4 Hz, 1H).

¹³C NMR (151 MHz, $CDCl_3$) δ 173.56, 171.19, 170.49, 163.04, 158.00, 148.90, 147.38, 142.04, 133.42, 130.88, 130.82, 129.59, 120.16, 119.44, 115.71, 111.65, 111.33, 109.68, 76.36, 65.57, 60.42, 55.92, 55.86, 52.05, 45.92, 43.21, 42.34, 38.09, 36.87, 33.11, 31.52, 31.00, 30.37, 27.29, 26.81, 26.46, 25.58, 21.19, 17.51, 14.18.

2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aS)-6-oxooctahydro-1H-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (22)

2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aR)-7-oxooctahydro-1H-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (23)



A solution of tetrafluoroboric acid (17 μ L, 0.11 mmol, 48 wt.-% in H₂O) was added to a solution of palladium(II) acetate (0.89 mg, 3.96 μ mol) and p-benzoquinone (8.57 mg, 79 μ mol) in MeCN (0.45 mL) and H₂O (0.60 mL). This mixture was added to **15** (48.0 mg, 79 μ mol) and it was stirred at rt for 16 h. The reaction mixture was directly loaded on silica and purified by flash chromatography, whereby both products can easily be separated, to obtain title compounds **22** (13.0 mg, 20.9 μ mol, 26.4 %) and **23** (31.8 mg, 51.1 μ mol, 64.5 %) as colorless oils.

TLC [EtOAc + 1 % HCOOH]: R_f = 0.39 (**22**), R_f = 0.31 (**23**)

HPLC [30-100% Solvent B, 20 min]: R_t = 15.48 min, 96 % (**22**), R_t = 15.00 min, 98 % (**23**).

HRMS: calculated 622.3016 [C₃₅H₄₄NO₉+H]⁺, found 622.3036 [M(**22**)+H]⁺, 622.3050 [M(**23**)+H]⁺.

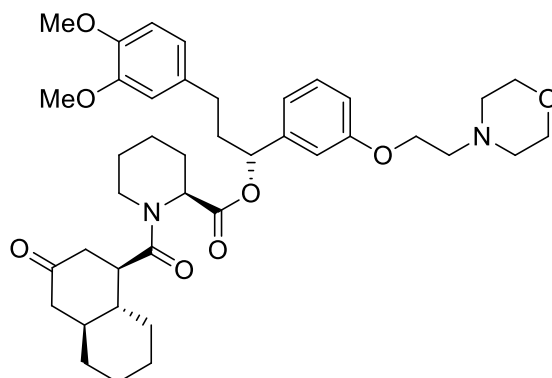
(22): ¹H NMR (599 MHz, CDCl₃) δ 7.24 – 7.15 (m, 1H), 6.97 – 6.80 (m, 2H), 6.85 – 6.70 (m, 2H), 6.73 – 6.60 (m, 2H), 5.81 – 5.68 (m, 1H), 5.45 (d, *J* = 5.3 Hz, 1H), 4.69 – 4.63 (m, 1H), 4.59 – 4.54 (m, 1H), 3.89 – 3.77 (m, 6H), 3.08 (q, *J* = 7.3 Hz, 1H), 2.98 – 2.87 (m, 2H), 2.63 – 2.56 (m, 2H), 2.57 – 2.50 (m, 1H), 2.51 – 2.45 (m, 1H), 2.38 – 2.28 (m, 1H), 2.27 – 2.12 (m, 2H), 2.08 – 1.97 (m, 2H), 1.97 – 1.90 (m, 1H), 1.90 – 1.82 (m, 1H), 1.82 – 1.67 (m, 2H), 1.67 – 1.56 (m, 2H), 1.38 – 1.28 (m, 2H), 1.27 – 1.22 (m, 3H), 1.12 – 1.02 (m, 1H), 0.90 – 0.78 (m, 1H).

(22): ¹³C NMR (151 MHz, CDCl₃) δ 212.73, 172.69, 171.32, 170.04, 158.45, 148.87, 147.36, 141.33, 133.32, 129.66, 120.62, 120.17, 116.66, 111.70, 111.31, 109.99, 76.15, 65.78, 55.90, 55.84, 52.37, 47.01, 46.87, 45.53, 45.36, 43.70, 43.07, 42.80, 37.35, 31.29, 31.04, 29.67, 28.32, 26.70, 25.45, 22.63, 20.93, 8.43.

(23): ¹H NMR (599 MHz, CDCl₃) δ 8.07 (s, 1H), 7.26 – 7.18 (m, 1H), 6.88 – 6.81 (m, 2H), 6.81 – 6.73 (m, 2H), 6.70 – 6.58 (m, 2H), 5.70 – 5.62 (m, 1H), 5.46 (d, *J* = 6.0 Hz, 1H), 4.69 – 4.52 (m, 2H), 4.10 (qd, *J* = 7.2, 1.7 Hz, 1H), 3.96 (d, *J* = 12.6 Hz, 1H), 3.89 – 3.74 (m, 6H), 3.36 – 3.25 (m, 1H), 2.93 – 2.83 (m, 1H), 2.62 – 2.49 (m, 2H), 2.42 – 2.33 (m, 2H), 2.28 (dd, *J* = 13.4, 4.6 Hz, 1H), 2.22 – 2.10 (m, 2H), 2.02 – 1.92 (m, 2H), 1.86 (ddd, *J* = 11.5, 7.8, 5.7 Hz, 1H), 1.82 – 1.72 (m, 3H), 1.67 – 1.59 (m, 2H), 1.56 – 1.35 (m, 3H), 1.21 – 1.09 (m, 2H), 0.93 – 0.82 (m, 1H).

(23): ¹³C NMR (151 MHz, CDCl₃) δ 209.86, 174.10, 171.69, 170.14, 163.87, 158.03, 148.89, 147.37, 141.82, 133.32, 129.68, 120.15, 119.48, 115.19, 111.66, 111.34, 110.83, 65.46, 60.42, 55.91, 55.85, 52.38, 49.90, 45.60, 44.21, 43.59, 40.38, 37.95, 31.37, 30.87, 30.28, 29.67, 26.95, 25.48, 22.31, 21.11, 21.03, 14.16, 8.41.

(*S*)-(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl **1-**
((1*R*,4*aS*,8*aR*)-3-oxodecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate (24**)**



24

A solution of tetrafluoroboric acid (16 μL, 0.10 mmol, 48 wt.-% in H₂O) and **16** were added to a solution of palladium(II) acetate (0.83 mg, 3.70 μmol) and p-benzoquinone (8.01 mg, 74 μmol) in MeCN (0.45 mL) and H₂O (0.60 mL). The reaction mixture was stirred at rt for 16 h and then directly loaded on silica for purification by flash chromatography (0-50 % [EtOAc + 2 % MeOH + 0.1 % TEA] in hexane), whereby both products can easily be separated, to obtain title compounds **24** (11.4 mg, 20.9 μmol, 14.8 %) as a colorless oil.

TLC [EtOAc + 2 % MeOH + 2 % TEA]: *R_f* = 0.25.

HPLC [0-100% Solvent B, 20 min]: *R_t* = 15.92 min, 99 %.

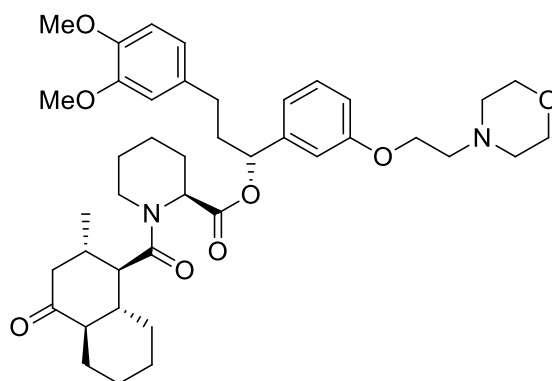
HRMS: calculated 691.3958 [C₄₀H₅₄N₂O₈+H]⁺, found 691.4118 [M+H]⁺

¹H NMR (599 MHz, CDCl₃) δ 7.25 – 7.22 (m, 1H), 6.90 – 6.80 (m, 3H), 6.79 – 6.75 (m, 1H), 6.69 – 6.60 (m, 2H), 5.76 – 5.67 (m, 1H), 5.46 (d, *J* = 4.8 Hz, 0H), 4.12 – 4.04 (m, 2H), 3.86 (s_{br}, 1H), 3.86 – 3.83 (m, 6H), 3.73 (t, *J* = 4.6 Hz, 3H), 3.11 (td, *J* = 13.2, 12.3, 2.2 Hz, 1H), 2.86 – 2.76 (m, 3H), 2.64 – 2.53 (m, 5H), 2.52 – 2.44 (m, 1H), 2.42 – 2.27 (m, 3H), 2.27 – 2.13

(m, 3H), 2.07 – 2.00 (m, 1H), 1.86 – 1.77 (m, 2H), 1.76 – 1.57 (m, 7H), 1.51 – 1.35 (m, 2H), 1.36 – 1.27 (m, 2H), 1.27 – 1.22 (m, 1H), 1.22 – 1.07 (m, 2H), 0.91 – 0.79 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 209.51, 172.74, 170.25, 158.80, 148.82, 147.29, 141.40, 133.37, 129.66, 120.13, 118.91, 113.97, 113.13, 111.67, 111.26, 76.21, 66.90, 65.75, 57.62, 55.89, 55.82, 54.08, 52.26, 48.38, 45.47, 44.14, 43.58, 43.48, 42.17, 37.83, 34.29, 31.17, 30.52, 26.77, 25.84, 25.73, 25.49, 21.01.

**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
((1R,2S,4aR,8aR)-2-methyl-4-oxodecahydronaphthalene-1-carbonyl)piperidine-2-
carboxylate (26)** 1-



26

Tetrafluoroboric acid (31.5 μL, 0.20 mmol, 48 wt.-% in H₂O) was added to a solution of palladium(II) acetate (1.63 mg, 7.26 μmol) and p-benzoquinone (15.7 mg, 0.15 μmol) in MeCN (0.9 mL) and H₂O (0.12 mL). This mixture was added to **18** (100 mg, 0.15 mmol) and it was stirred at rt for 16 h. The reaction mixture was directly loaded on silica and purified by flash chromatography to obtain title compounds as colorless solid (40.1 mg, 56.9 μmol, 49.1 %) after lyophilization.

TLC [DCM + 5 % MeOH]: R_f = 0.48.

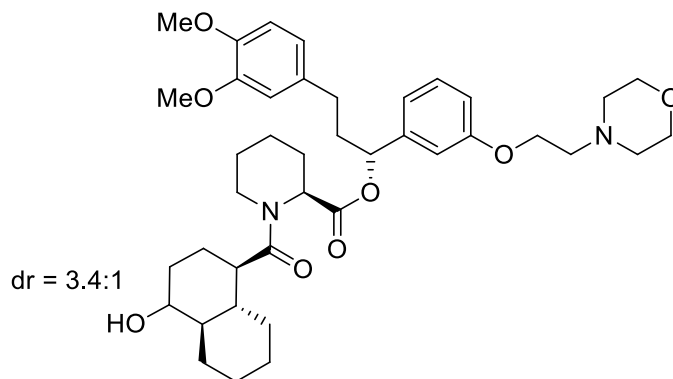
HPLC [0-100% Solvent B, 20 min]: R_t = 16.13 min, 97%.

HRMS: calculated 727.3934 [C₄₁H₅₆N₂O₈+H]⁺, found 727.3950 [M+H]⁺.

¹H NMR (800 MHz, CDCl₃) δ 7.26 (t, *J* = 7.9 Hz, 1H), 6.91 – 6.82 (m, 3H), 6.82 – 6.77 (m, 1H), 6.68 – 6.64 (m, 2H), 5.77 (dd, *J* = 7.9, 5.8 Hz, 1H), 5.56 – 5.52 (m, 1H), 4.17 – 4.10 (m, 2H), 3.94 – 3.90 (m, 1H), 3.87 (s, 6H), 3.79 – 3.75 (m, 4H), 3.20 (td, *J* = 13.2, 2.9 Hz, 1H), 2.98 (dd, *J* = 10.6, 4.1 Hz, 1H), 2.64 – 2.59 (m, 5H), 2.54 – 2.50 (m, 2H), 2.38 – 2.35 (m, 1H), 2.29 – 2.27 (m, 1H), 2.25 – 2.20 (m, 1H), 2.14 – 2.06 (m, 2H), 2.00 – 1.91 (m, 2H), 1.84 – 1.81 (m, 2H), 1.80 – 1.76 (m, 1H), 1.73 – 1.66 (m, 4H), 1.50 – 1.45 (m, 1H), 1.42 – 1.39 (m, 1H), 1.30 – 1.26 (m, 2H), 1.22 – 1.18 (m, 1H), 0.98 – 0.94 (m, 1H), 0.88 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (201 MHz, CDCl₃) δ 210.66, 171.69, 170.76, 148.87, 147.35, 141.48, 133.45, 129.64, 120.11, 113.93, 111.66, 111.28, 76.26, 55.93, 55.84, 54.05, 53.76, 51.73, 48.06, 48.03, 43.46, 40.76, 37.90, 32.63, 32.25, 31.33, 26.83, 25.78, 25.59, 25.52, 25.07, 21.17, 15.40.

**(2S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
((1R,4aR,8aR)-4-hydroxydecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate
(27)**



27

Cerium(III) chloride heptahydrate (92 mg, 0.25 mmol) was added to a solution of **25** (17 mg, 25 μ mol) in THF/MeOH (2:1, 0.9 mL). It was stirred at rt for 15 min, then NaBH₄ (4.7 mg, 0.12 mmol) was added and it was stirred at rt for 30 min. The reaction mixture was quenched with H₂O and alkalized with 1 N NaOH. The product was extracted with Et₂O. Then the combined layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography (0-100 % [EtOAc + 2 % MeOH + 0.1 % TEA] in cyclohexane) and following lyophilization provided the title compound as colorless solid (11.4 mg, 16.5 μ mol, 66.9 %).

TLC [EtOAc + 2 % MeOH + 2 % TEA]: R_f = 0.20.

HPLC [0-100% Solvent B, 20 min]: R_t = 15.23 min (major diastereomer, 79,6%), 16.38 min (minor diastereomer, 18,8%).

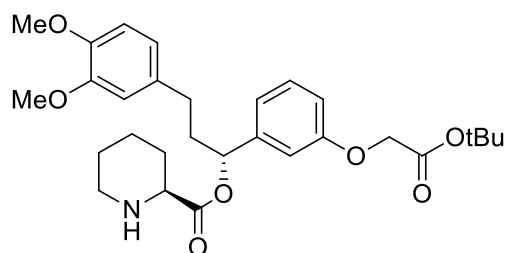
HRMS: calculated 693.4115 [C₄₀H₅₆N₂O₈+H]⁺, found 693.4138 [M+H]⁺.

¹H NMR (599 MHz, CDCl₃) δ 7.24 – 7.20 (m, 1H), 6.89 – 6.85 (m, 1H), 6.85 – 6.80 (m, 2H), 6.79 – 6.73 (m, 1H), 6.68 – 6.61 (m, 2H), 5.72 (ddd, J = 20.7, 8.0, 5.9 Hz, 1H), 5.51 – 5.46 (m, 1H), 4.13 – 4.06 (m, 2H), 3.90 (d, J = 12.4 Hz, 1H), 3.85 – 3.83 (m, 6H), 3.74 – 3.71 (m, 4H), 3.28 (ddd, J = 10.9, 9.4, 4.4 Hz, 1H), 3.14 (td, J = 13.2, 2.9 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.61 – 2.55 (m, 5H), 2.52 – 2.45 (m, 1H), 2.39 – 2.28 (m, 2H), 2.22 – 2.10 (m, 2H), 2.04 – 1.97 (m, 2H), 1.81 – 1.74 (m, 2H), 1.71 – 1.63 (m, 6H), 1.57 – 1.51 (m, 2H), 1.44 – 1.40 (m, 1H), 1.35 – 1.31 (m, 1H), 1.23 – 1.13 (m, 2H), 1.04 – 0.91 (m, 2H), 0.87 – 0.78 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 174.79, 170.67, 158.78, 148.83, 147.29, 141.57, 133.51, 129.57, 120.12, 118.93, 113.86, 113.11, 111.72, 111.27, 76.04, 73.77, 66.88, 66.79, 65.70, 57.65, 55.90, 55.83, 54.07, 51.92, 49.06, 44.96, 43.38, 42.33, 37.98, 34.57, 31.25, 31.20, 28.86, 27.37, 26.83, 25.90, 25.60, 21.16.

**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-oxopropoxy)phenyl)propyl
carboxylate (30)**

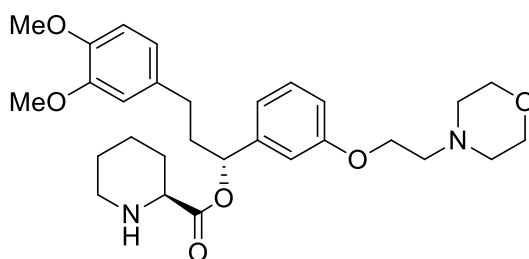
piperidine-2-



30

Synthesized as previously described.¹⁷

**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl piperidine-2-
carboxylate (31)**

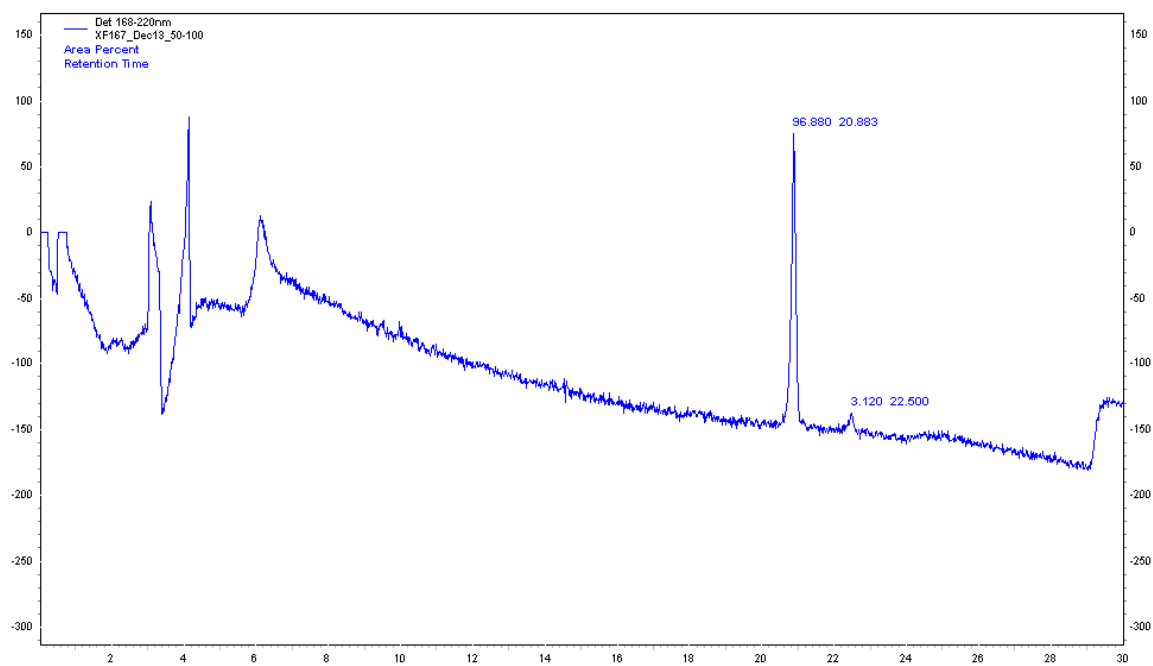
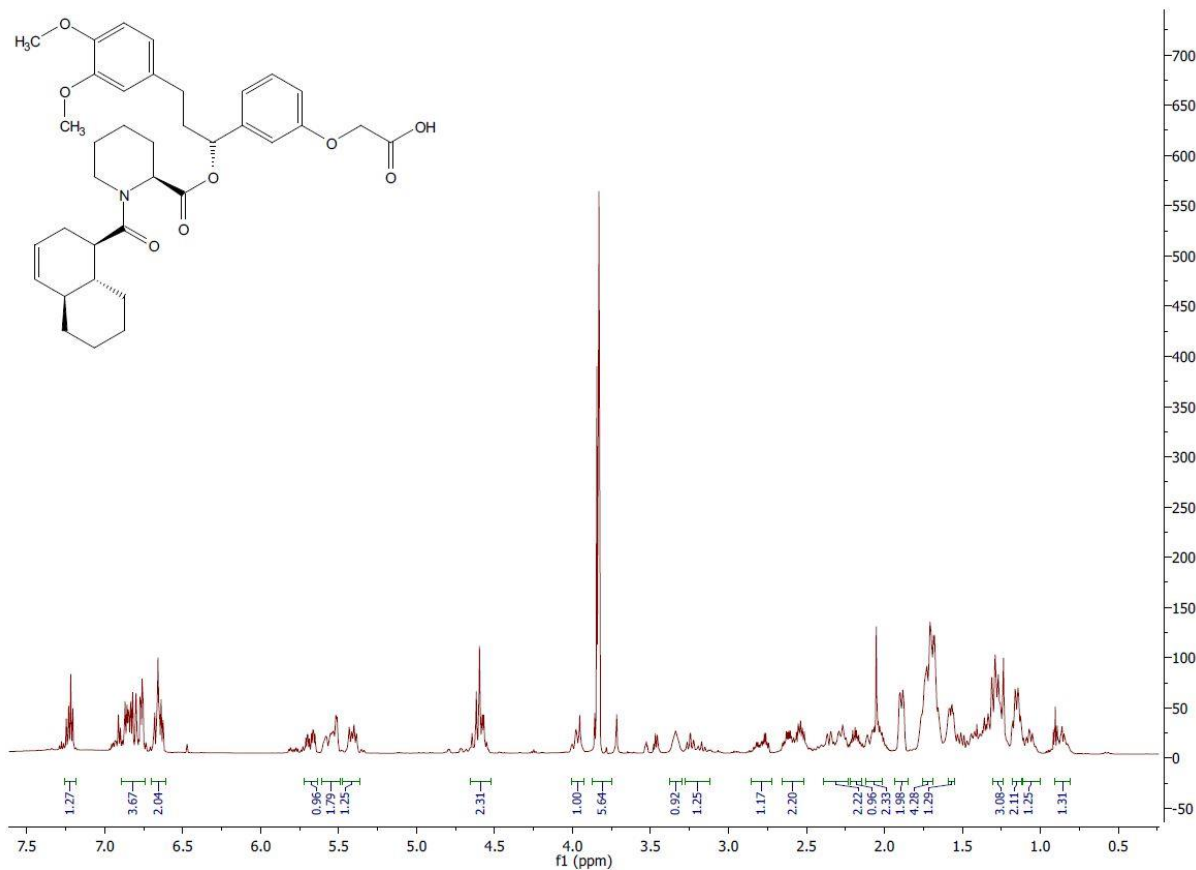


31

Synthesized as previously described.¹⁷

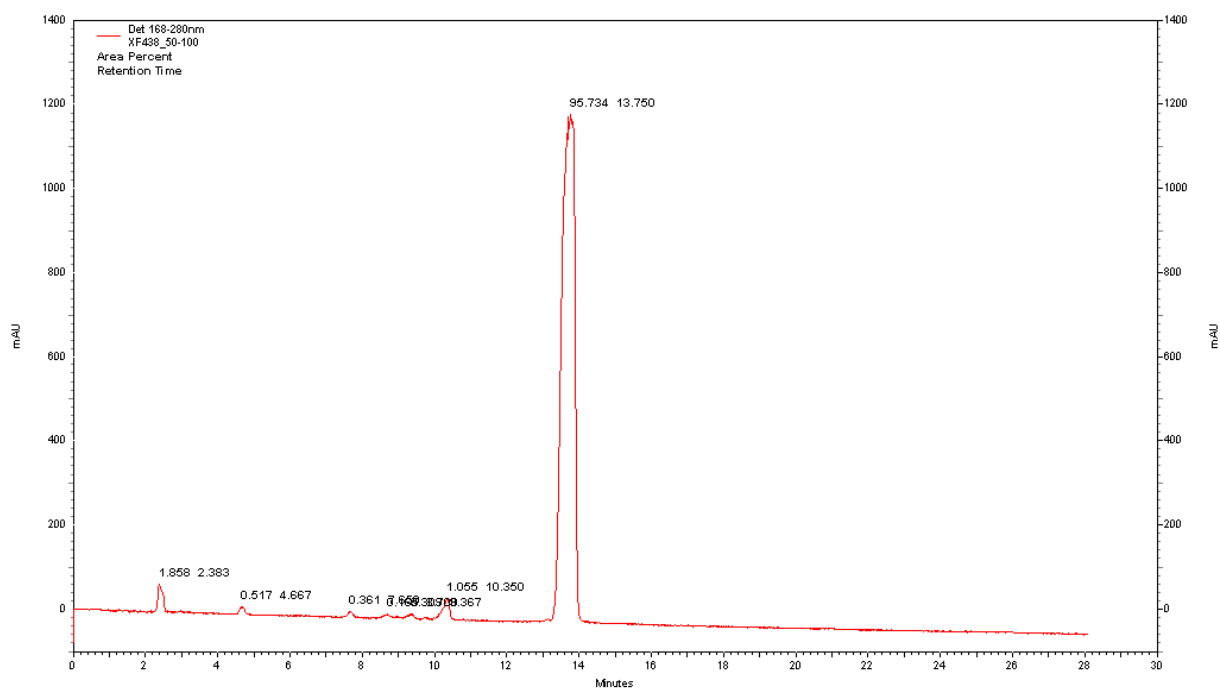
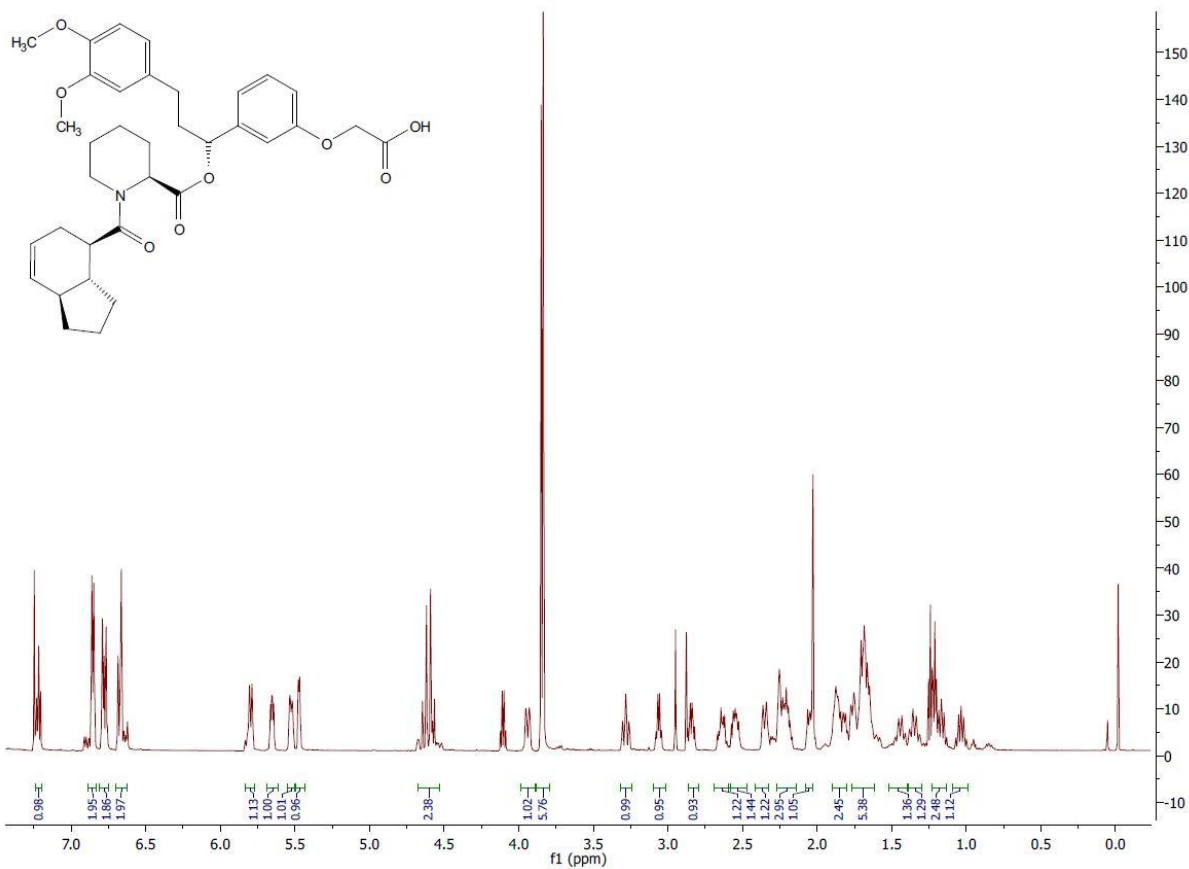
VIII. ¹H NMR spectra and HPLC traces

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,4*aS*,8*aR*)-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (14)



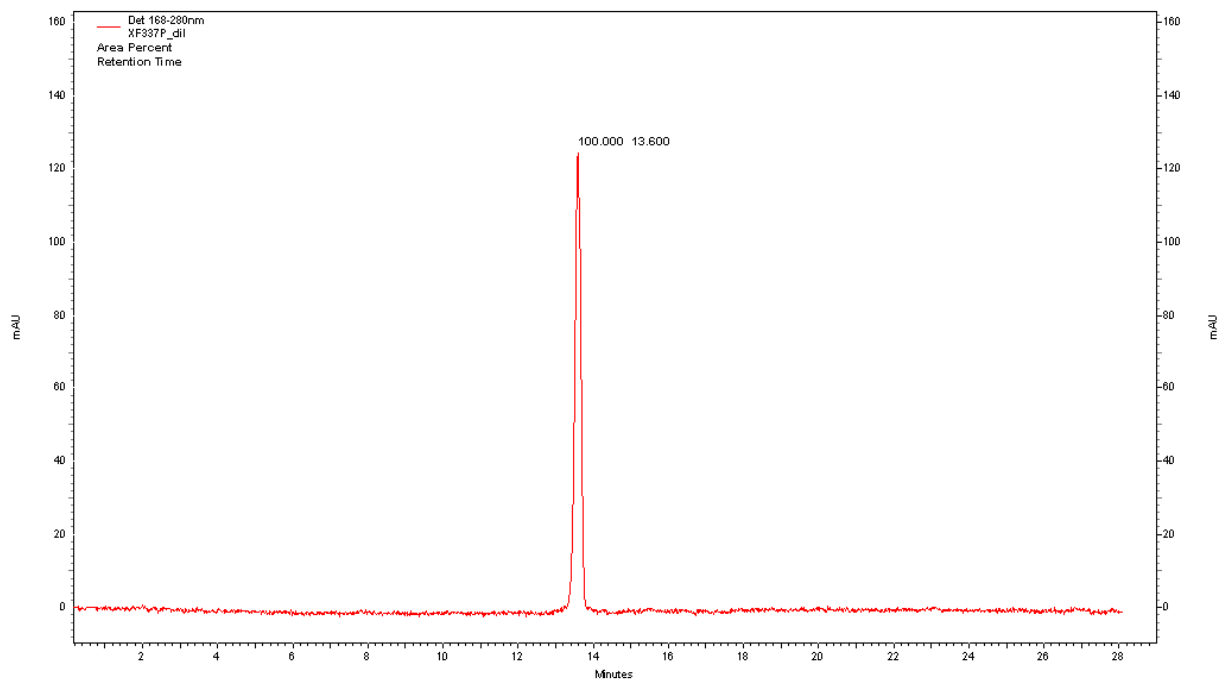
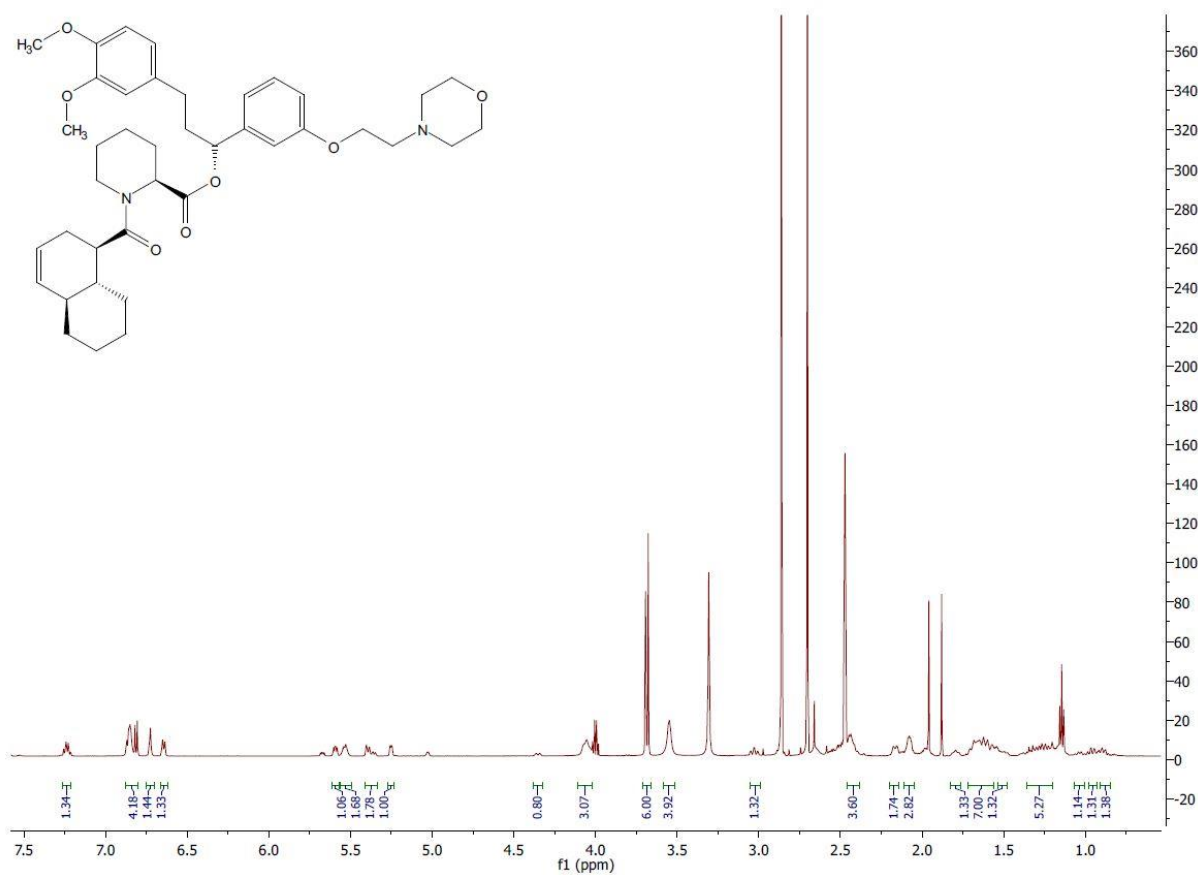
HPLC [50-100% Solvent B, 30 min]: Rt = 20.88 min; 97 %.

2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aS)-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (15)



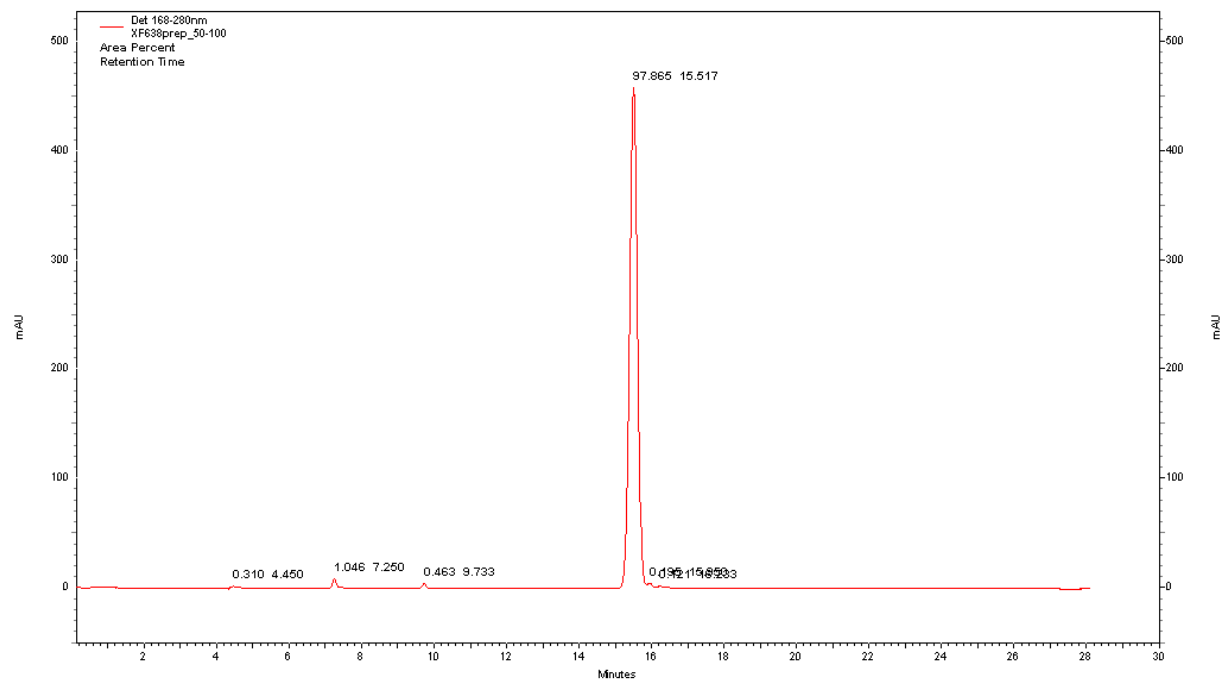
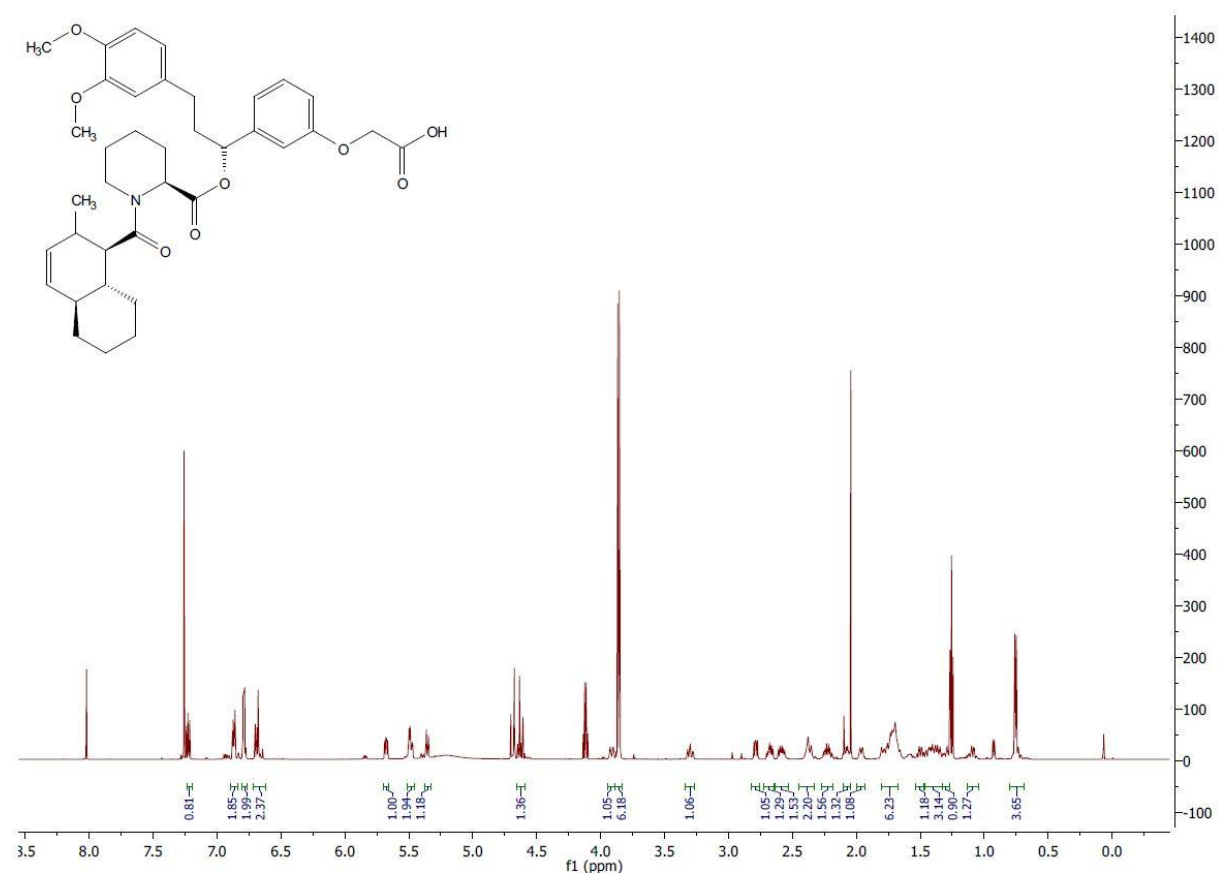
HPLC [50-100% Solvent B, 20 min]: Rt = 13.75 min, 96 %.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl 1-((1S,4aS,8aR)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)piperidine-2-carboxylate (16).



HPLC [0-100% Solvent B, 20 min]: Rt = 13.60 min, 100 %.

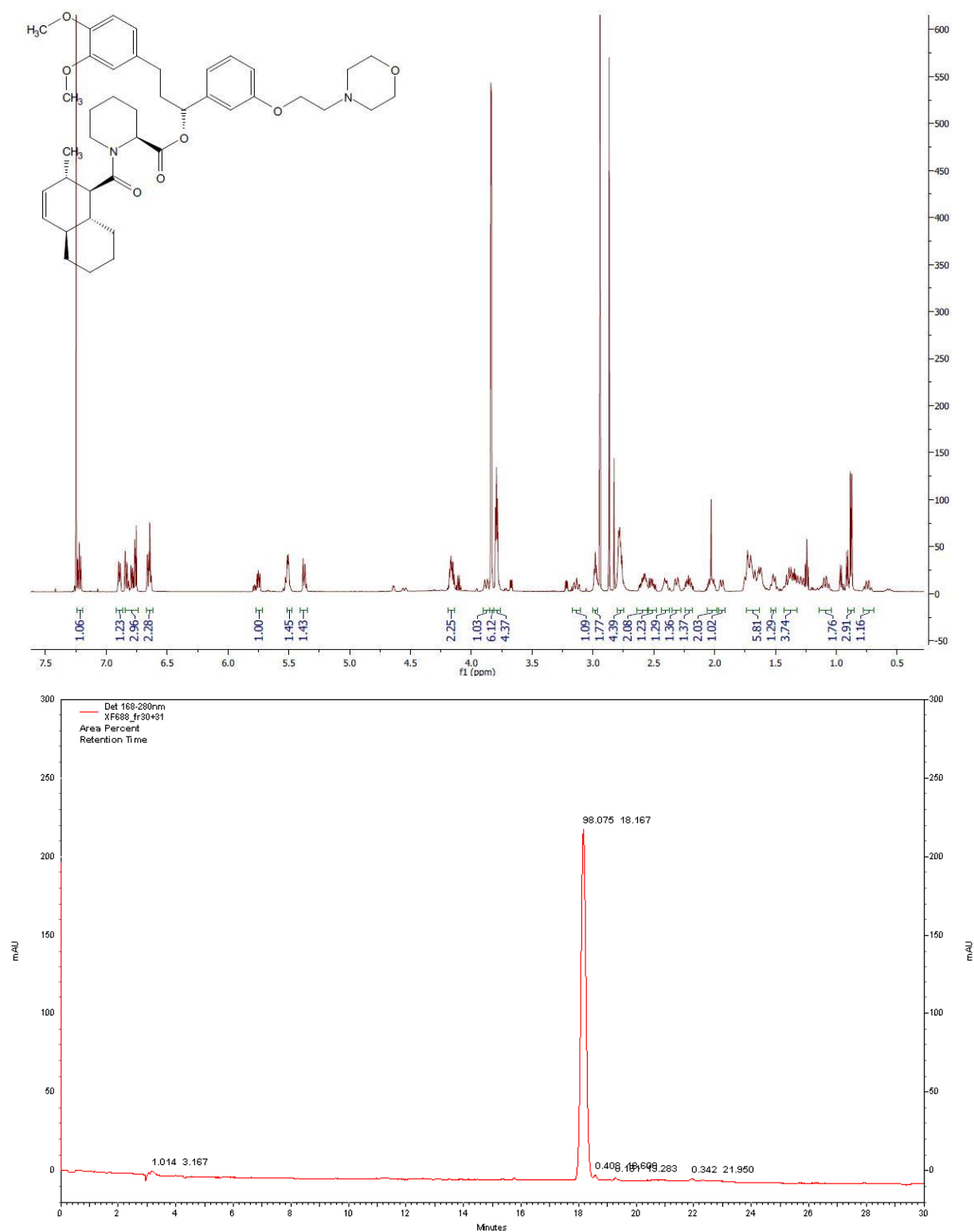
2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,2*S*,4*aS*,8*aR*)-2-methyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (17)



HPLC [30-100% Solvent B, 20 min]: Rt = 15.52 min, 98%.

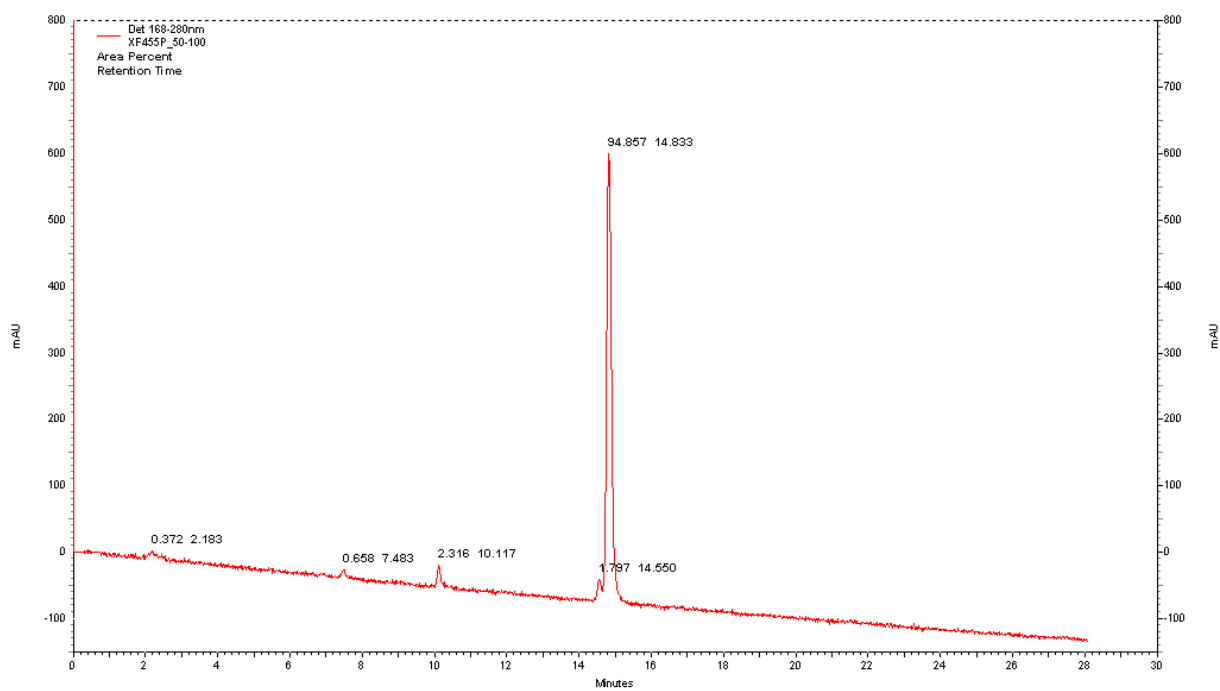
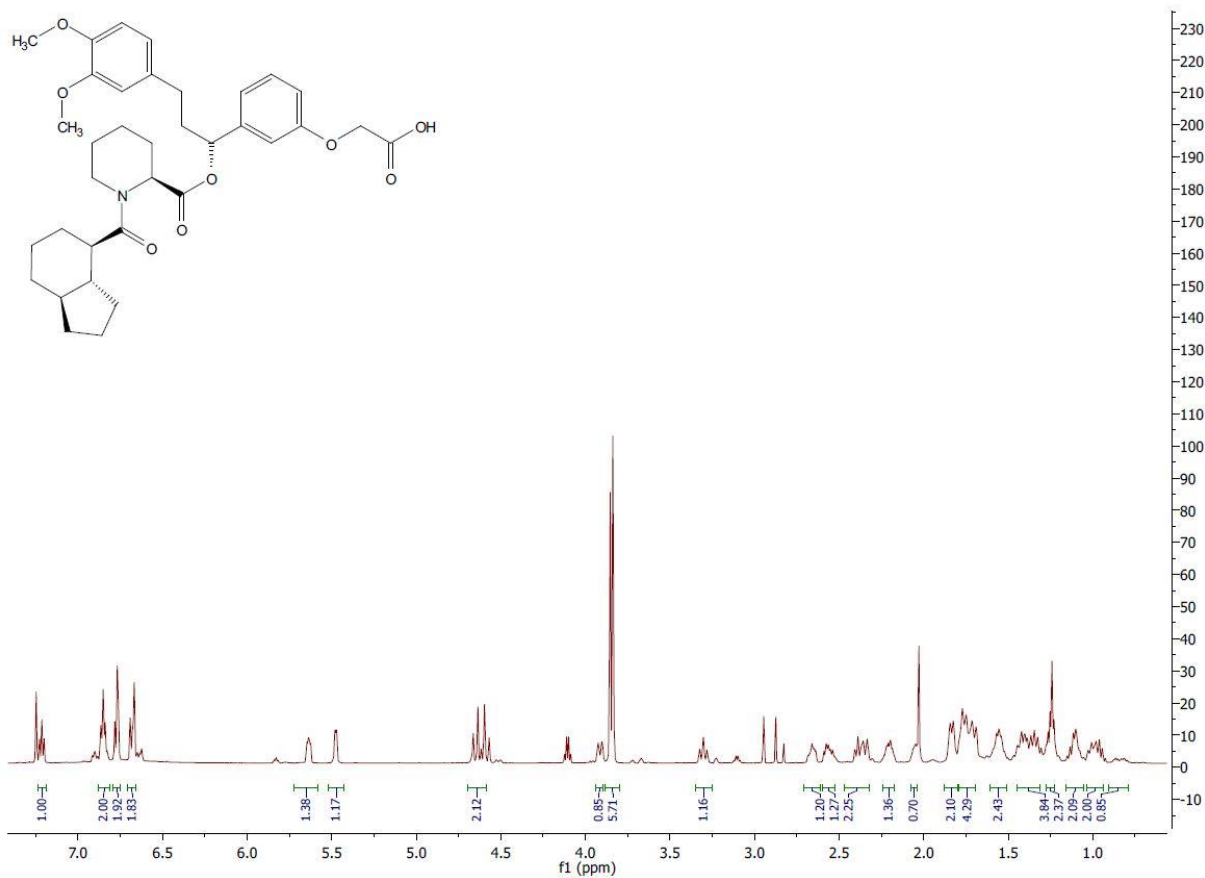
**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
 ((1R,2S,4aS,8aR)-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-
 carbonyl)piperidine-2-carboxylate (18)**

1-



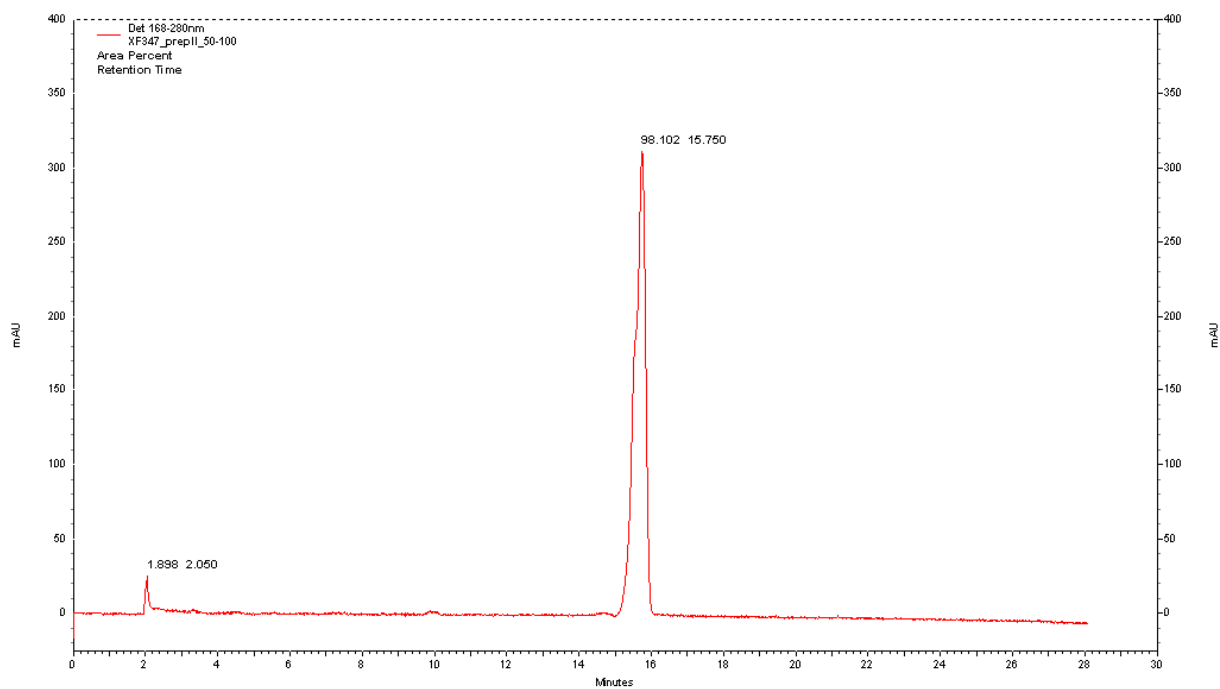
HPLC [0-100% Solvent B, 20 min]: Rt = 18.17 min, 98%.

2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aS)-octahydro-1H-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (19)



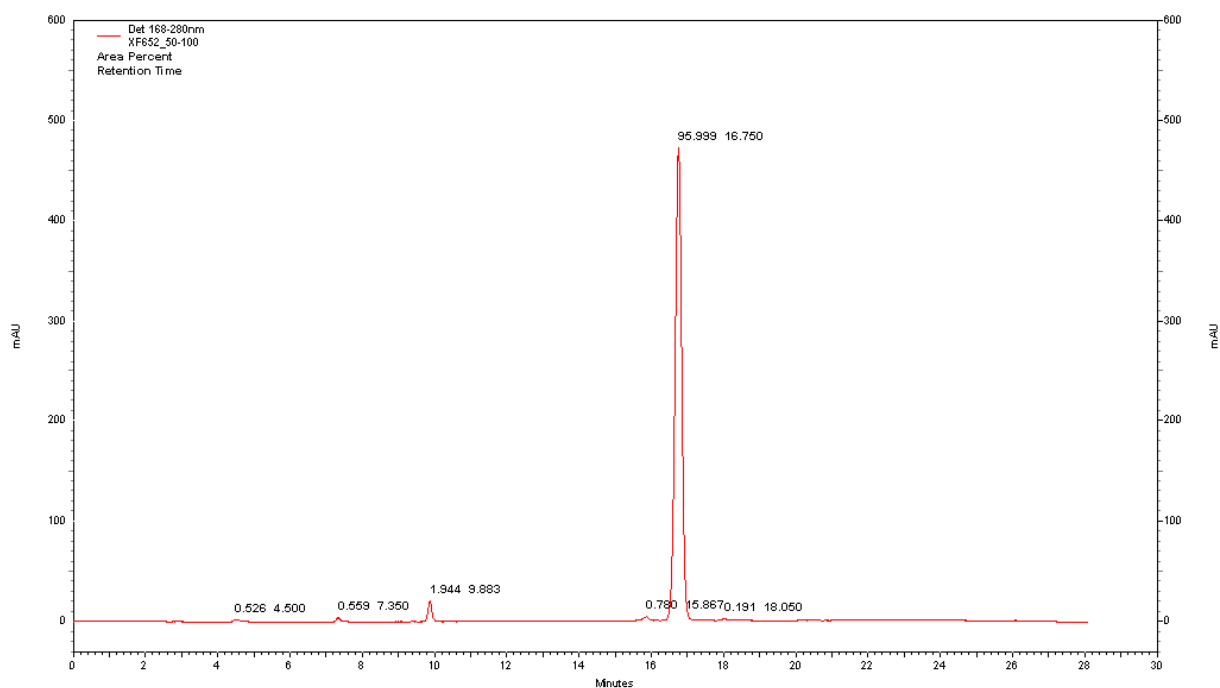
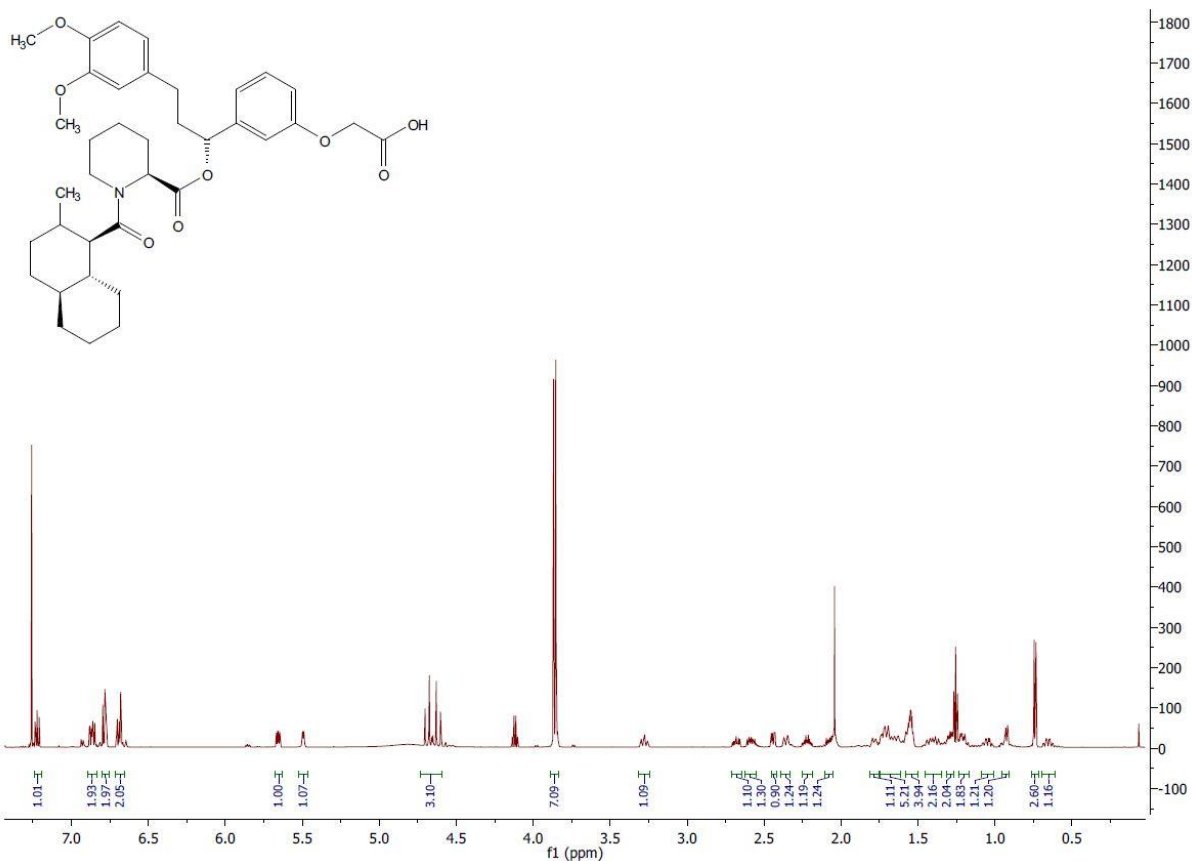
HPLC [50-100% Solvent B, 20 min]: Rt = 14.83 min, 95 %.

2-(3-((*R*)-1-(((*S*)-1-((1*R*,4*aS*,8*aR*)-decahydronaphthalene-1-carbonyl)piperidine-2-carbonyloxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (20)



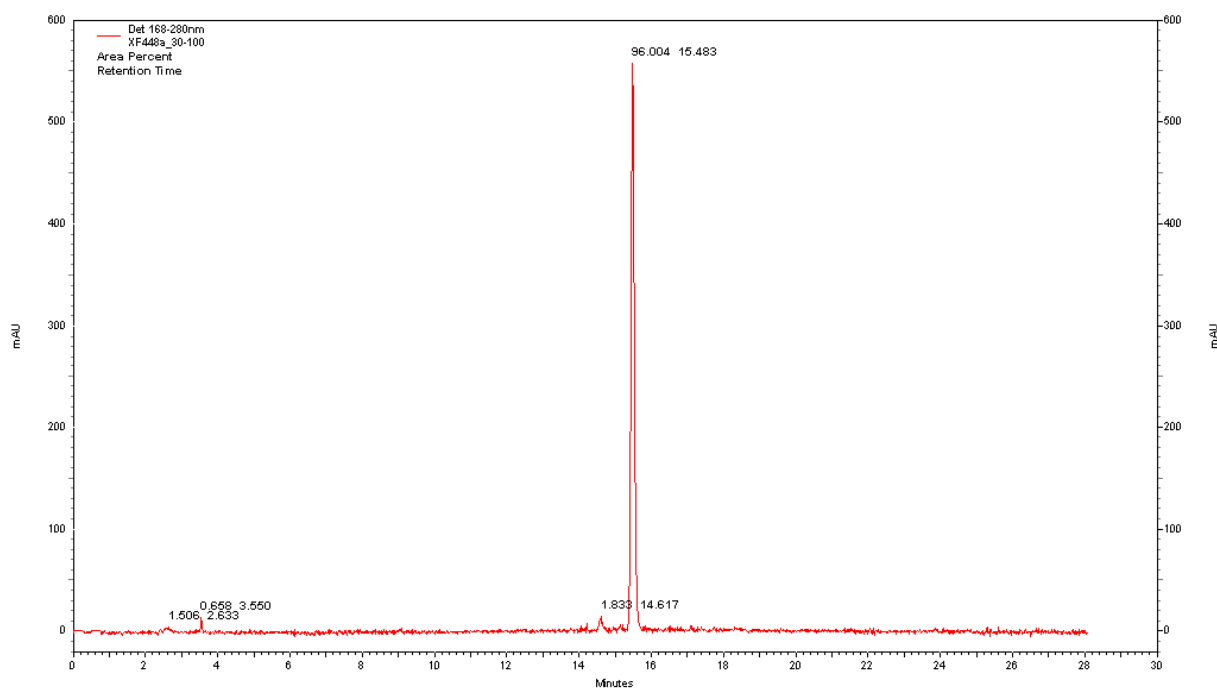
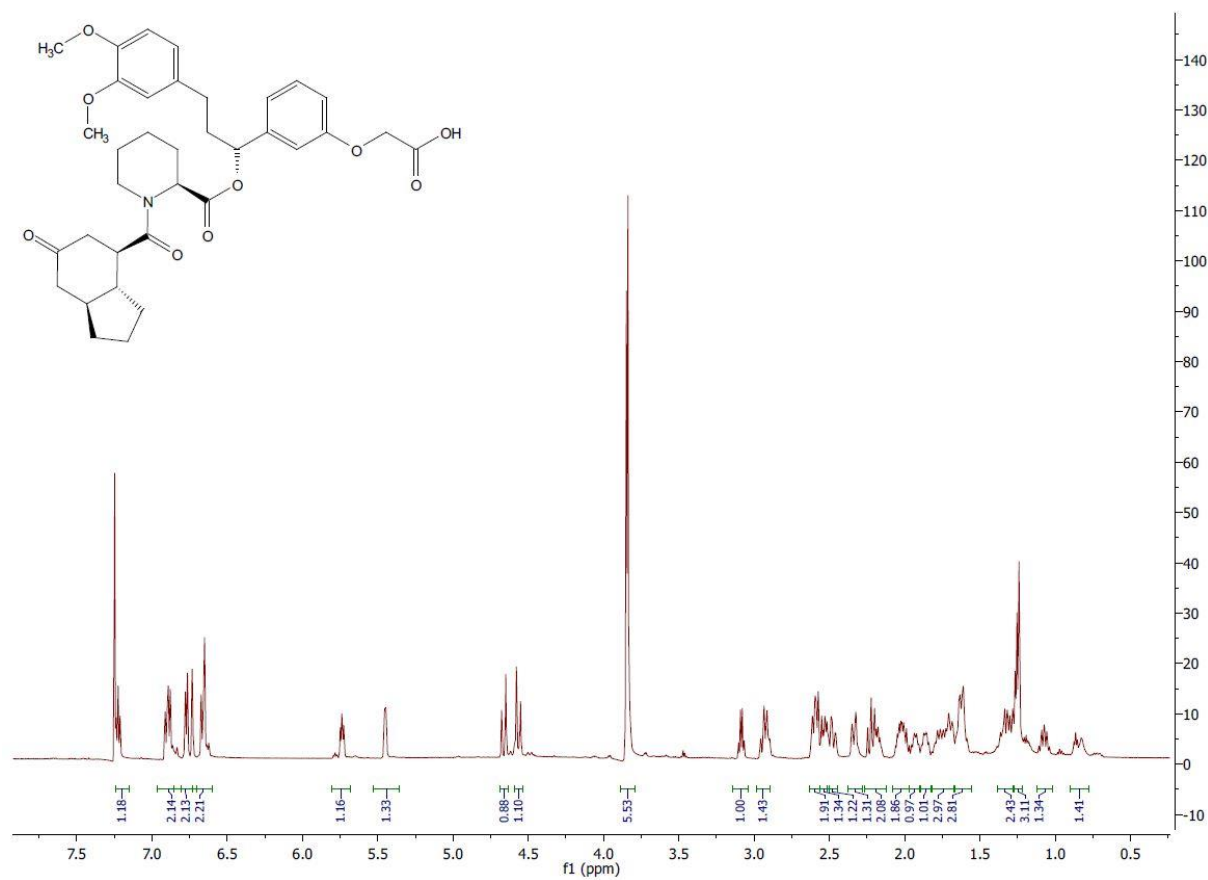
HPLC [50-100% Solvent B, 20 min]: Rt = 15.75 min, 98 %.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((1*R*,2*S*,4*aS*,8*aR*)-2-methyl-decahydro-naphthalene-1-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (21)



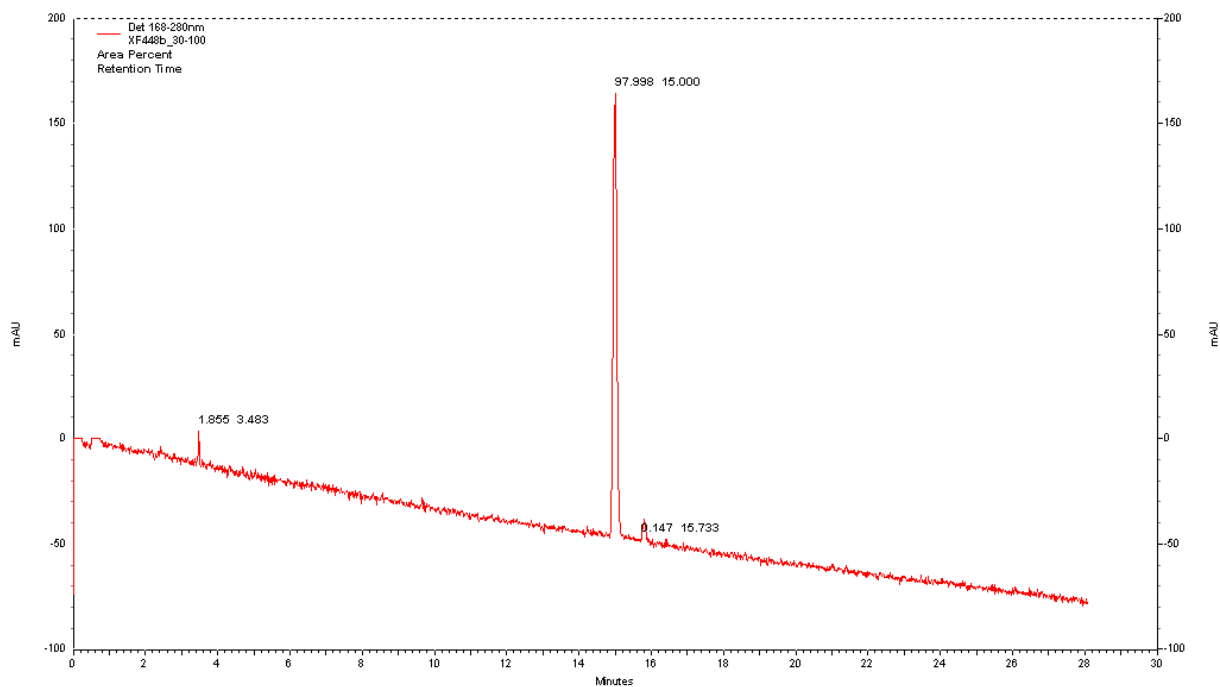
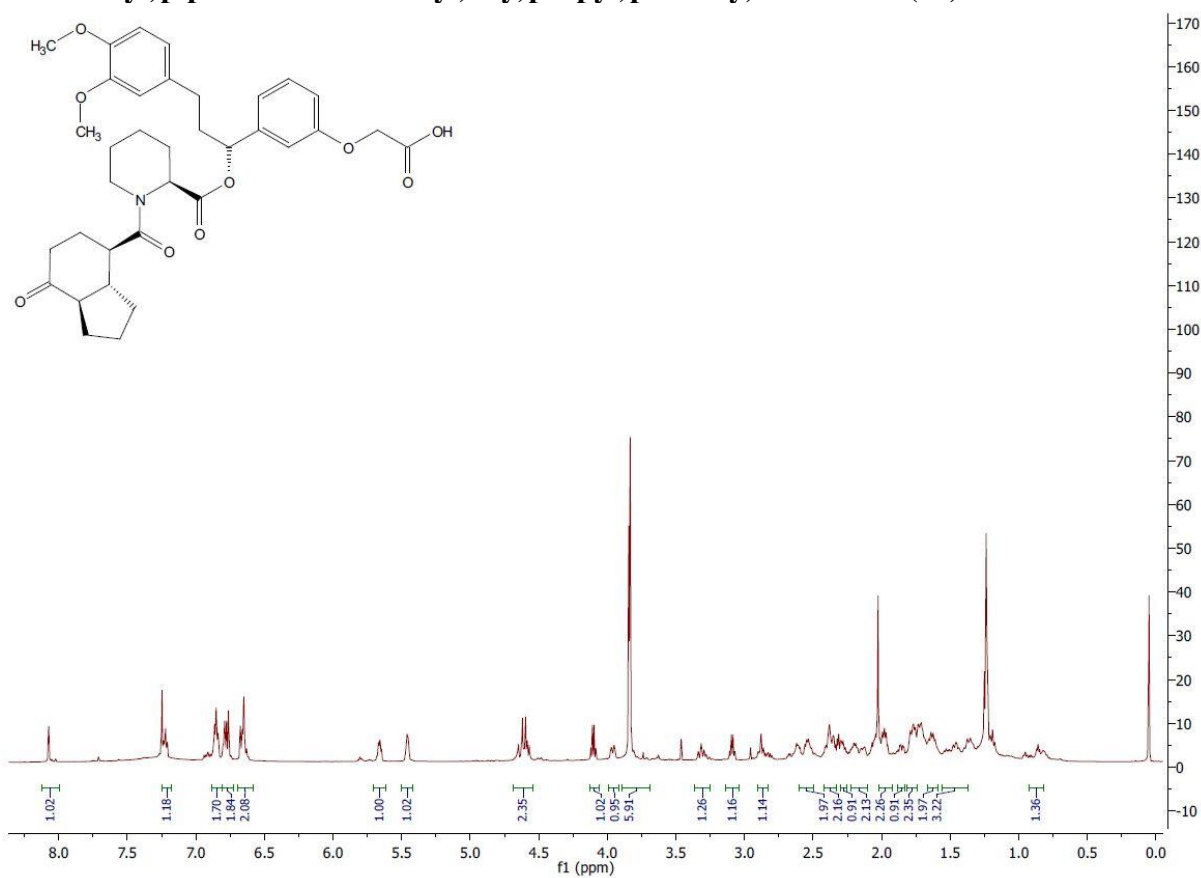
HPLC [50-100% Solvent B, 20 min]: Rt = 16.75 min, 96 %.

2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aS)-6-oxooctahydro-1H-indene-4-carbonyl)piperidine-2-carbonyloxy)propyl)phenoxy)acetic acid (22)



HPLC [30-100% Solvent B, 20 min]: Rt = 15.48 min, 96 %.

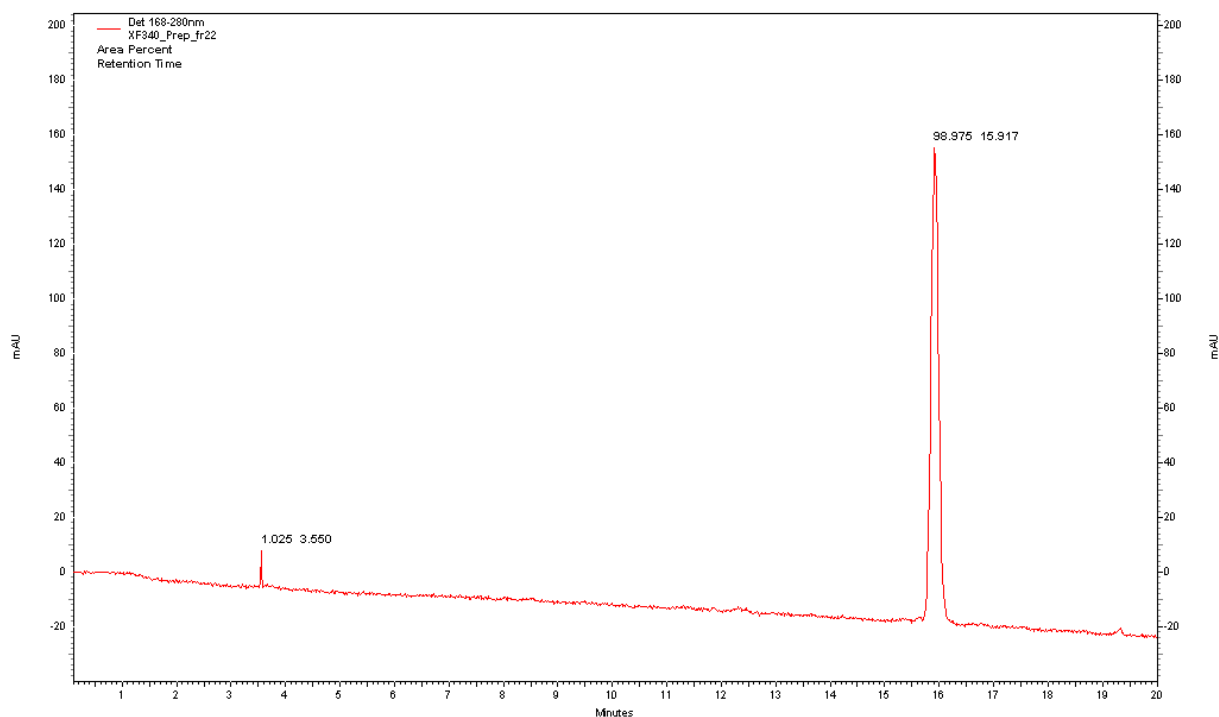
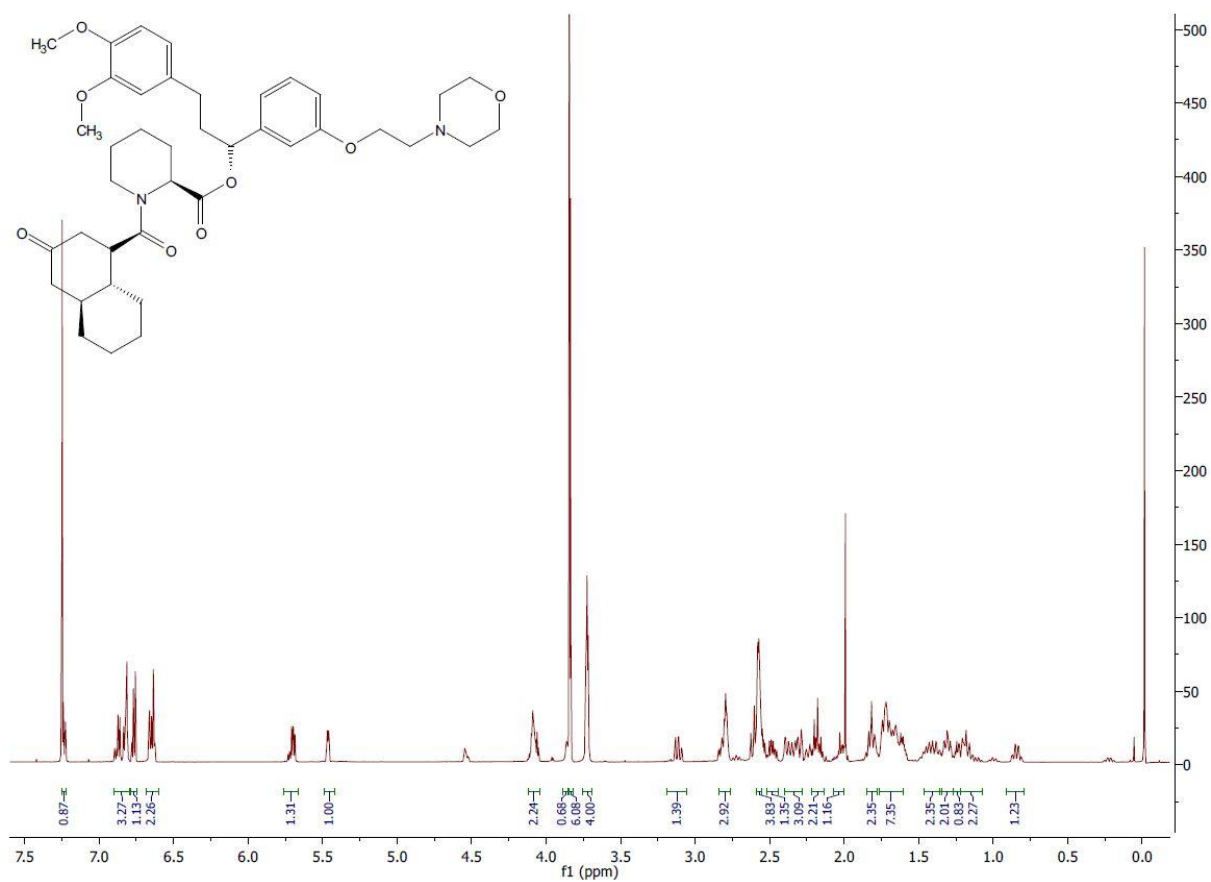
2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-((3aR,4R,7aR)-7-oxooctahydro-1H-indene-4-carbonyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (23)



HPLC [30-100% Solvent B, 20 min]: Rt = 15.00 min, 98 %.

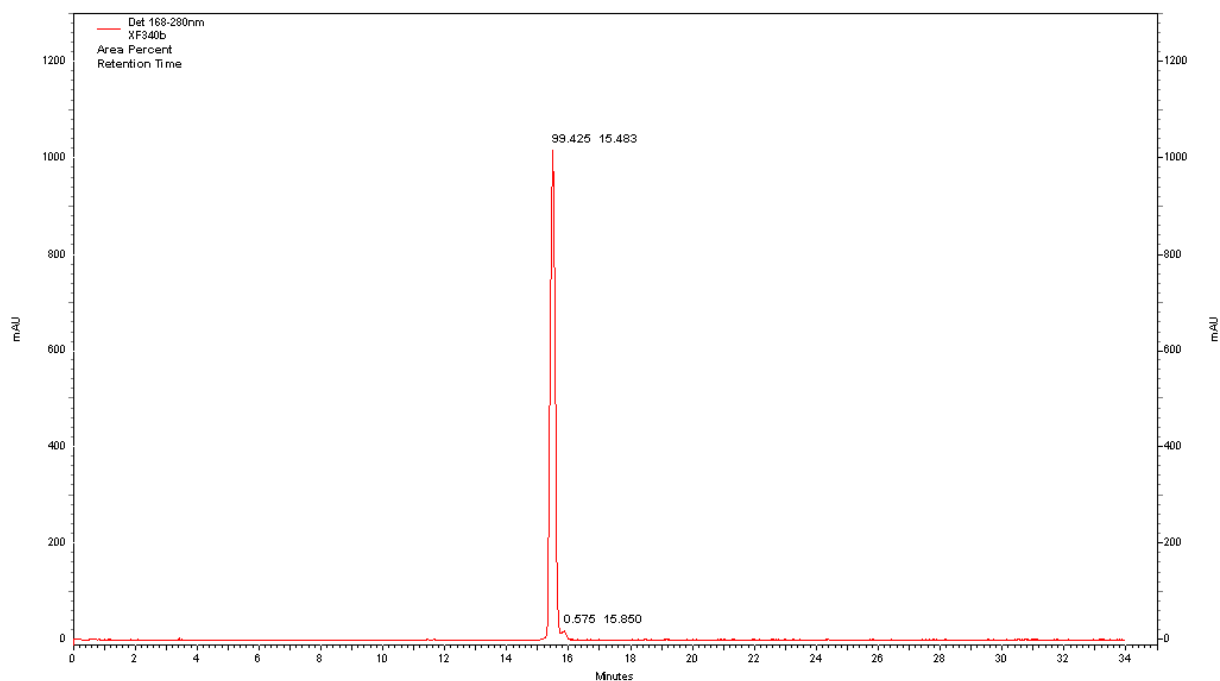
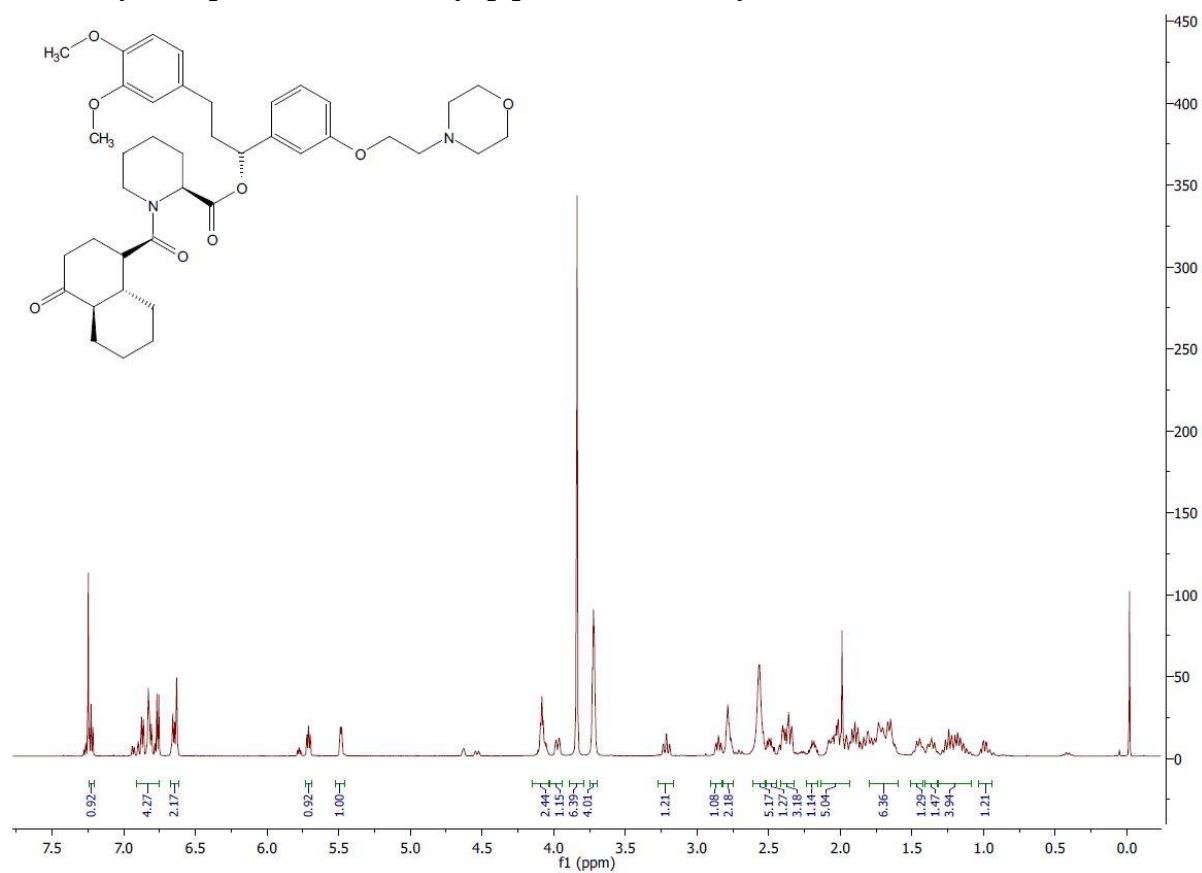
**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
 ((1R,4aS,8aR)-3-oxodecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate (24)**

1-



HPLC [0-100% Solvent B, 20 min]: Rt = 15.92 min, 99 %.

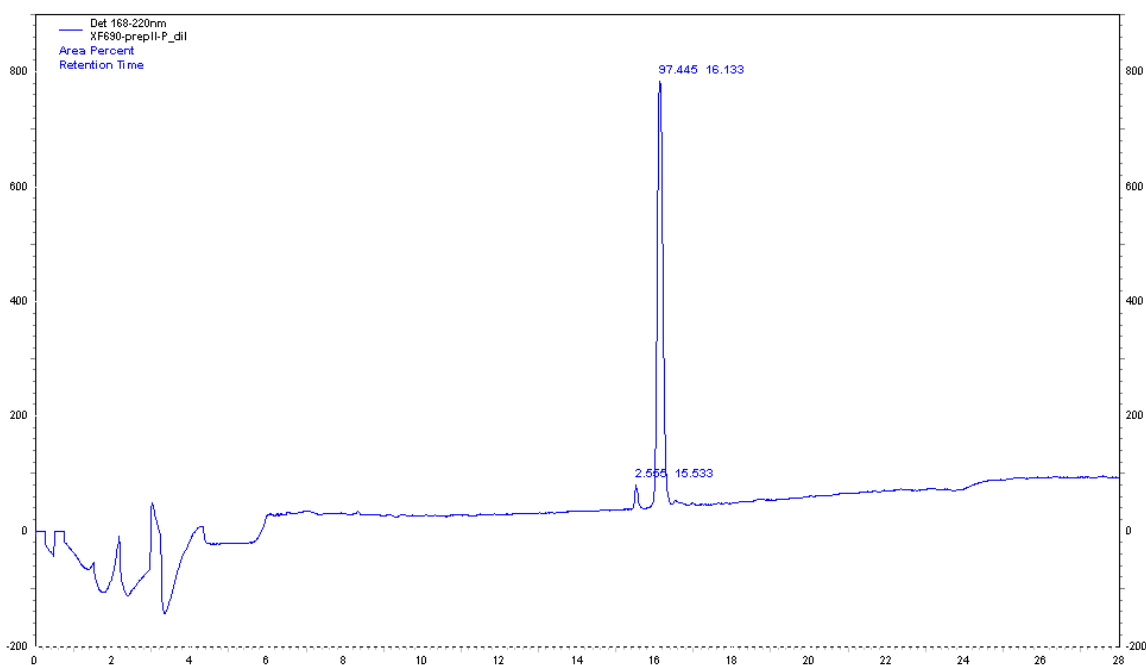
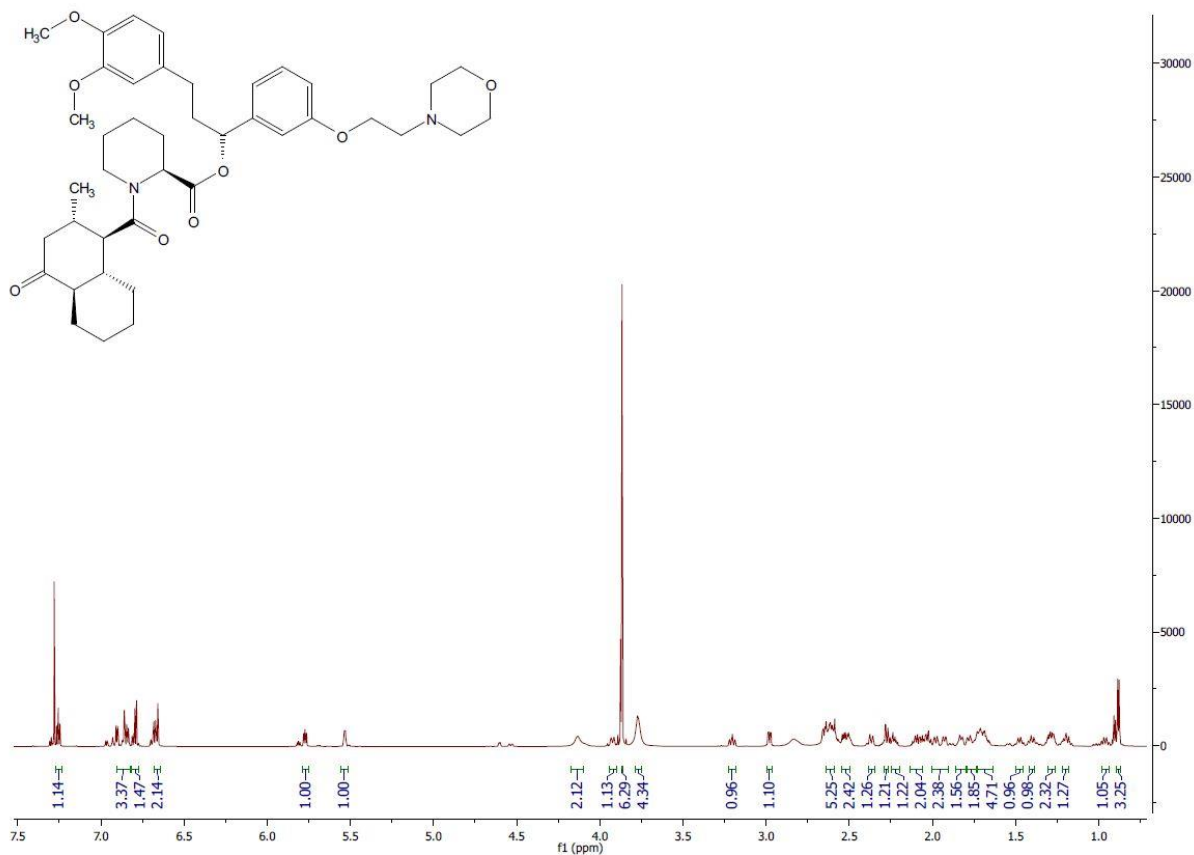
(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl 1-((1R,4aR,8aR)-4-oxodecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate (25).



HPLC [0-100% Solvent B, 20 min]: Rt = 15.48 min, 99 %.

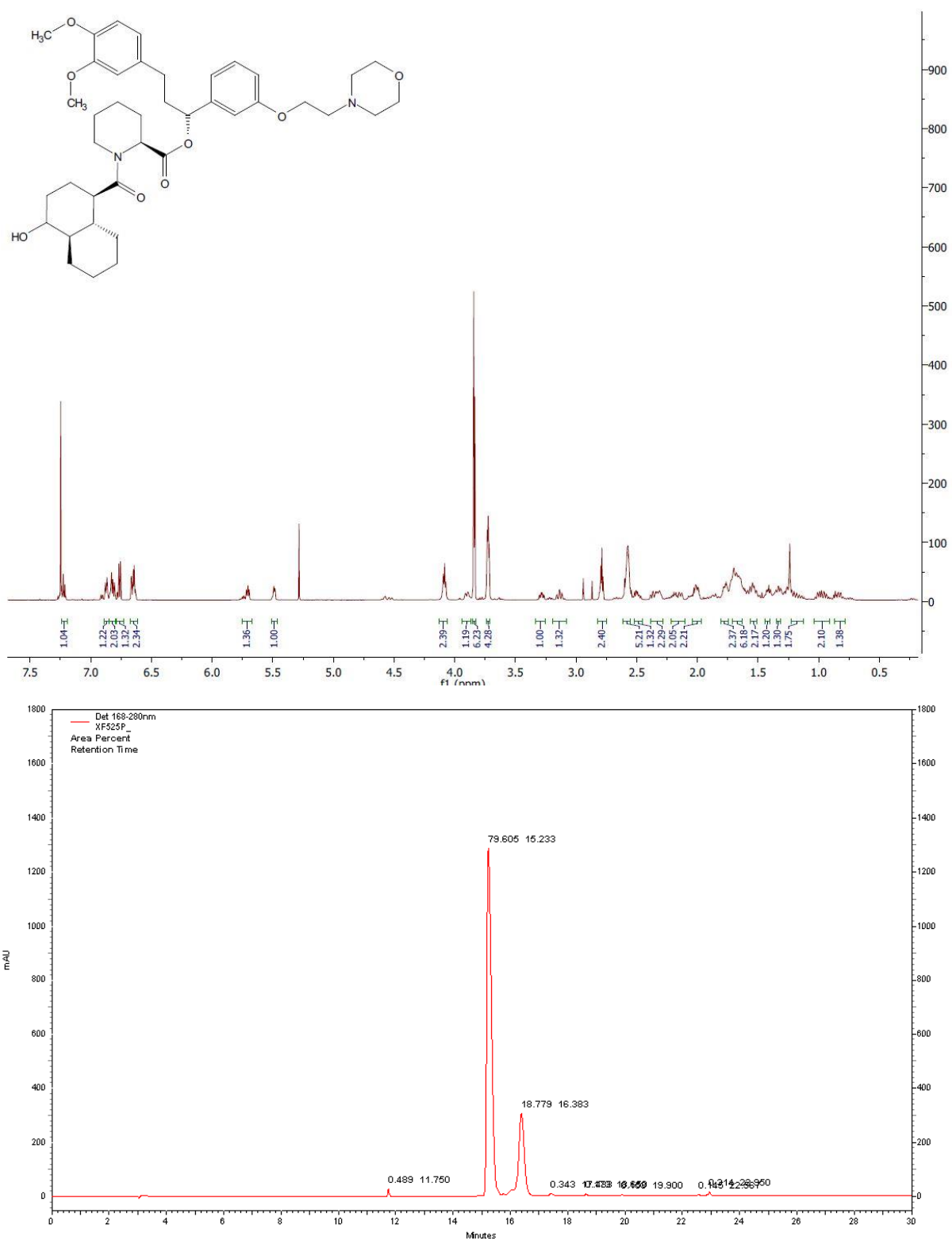
**(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
((1R,2S,4aR,8aR)-2-methyl-4-oxodecahydronaphthalene-1-carbonyl)piperidine-2-
carboxylate (26)**

1-



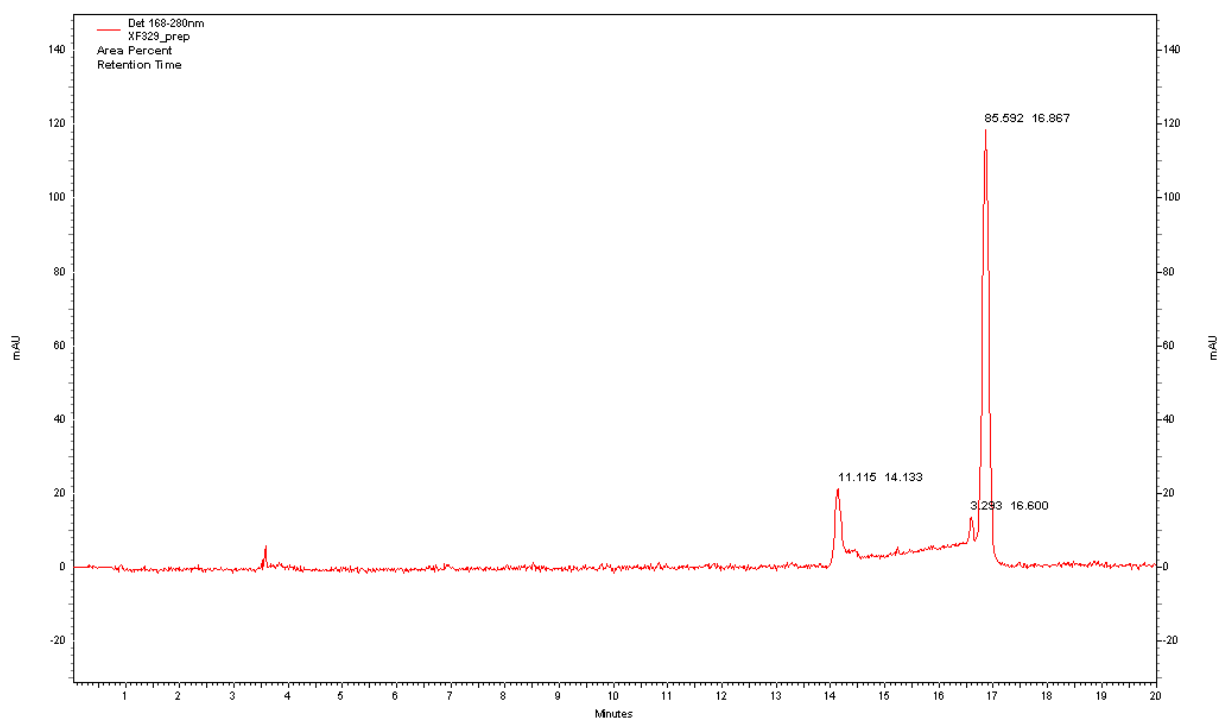
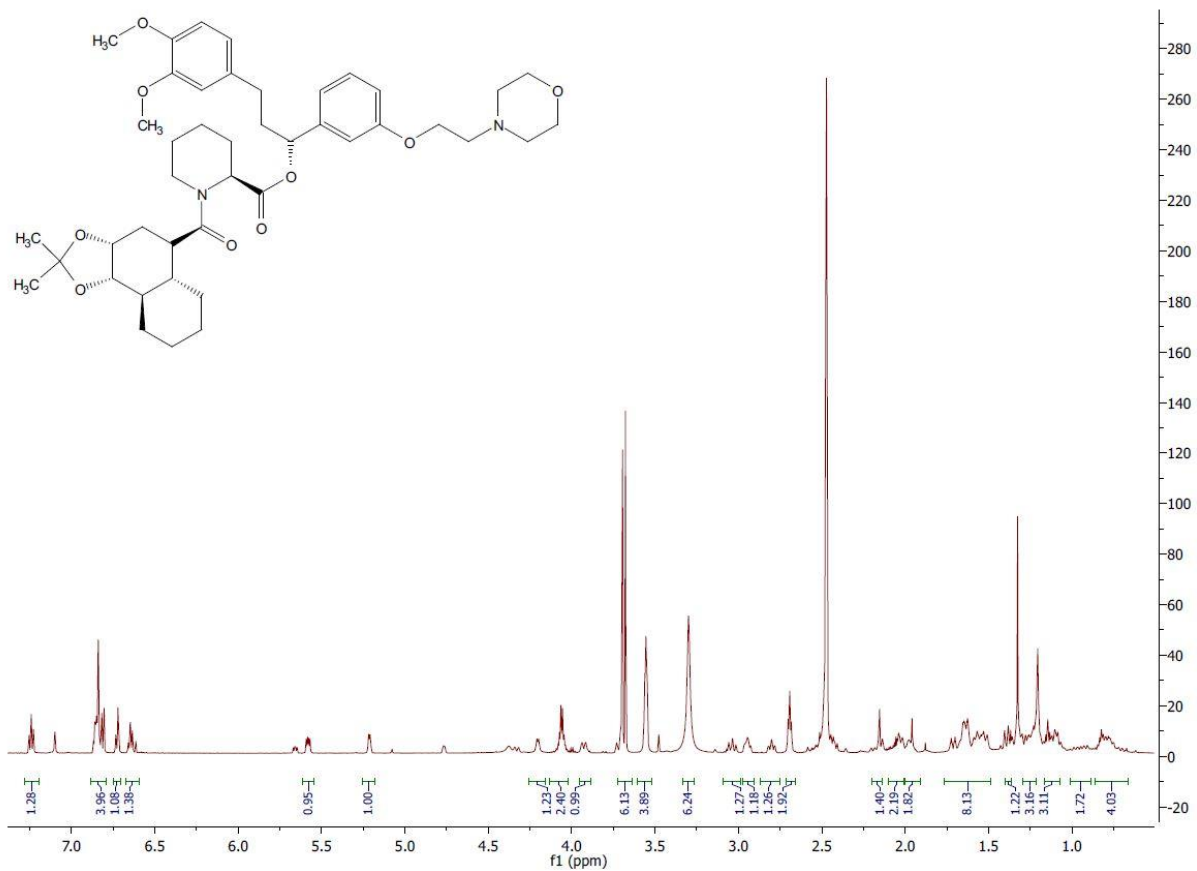
HPLC [0-100% Solvent B, 20 min]: Rt = 16.13 min, 97 %.

**(2*S*)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl
 ((1*R*,4*aR*,8*aR*)-4-hydroxydecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate
 (27)** **1-**



HPLC [0-100% Solvent B, 20 min]: Rt = 15.23-16.38 min, 98 %.

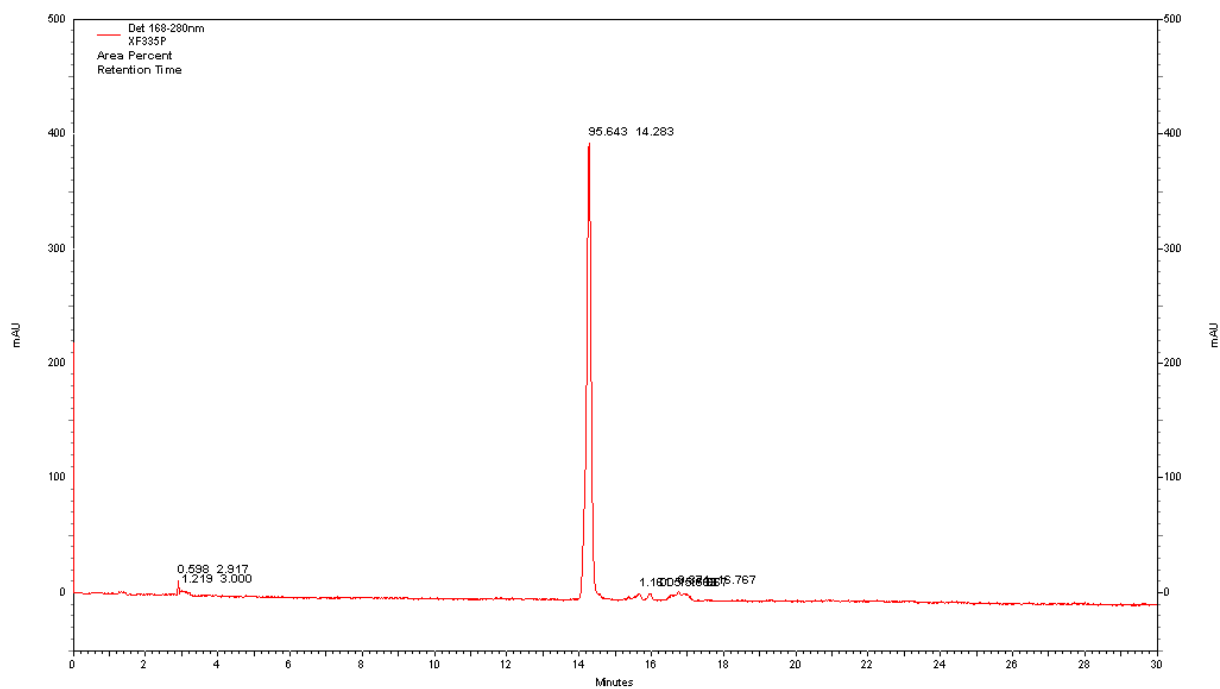
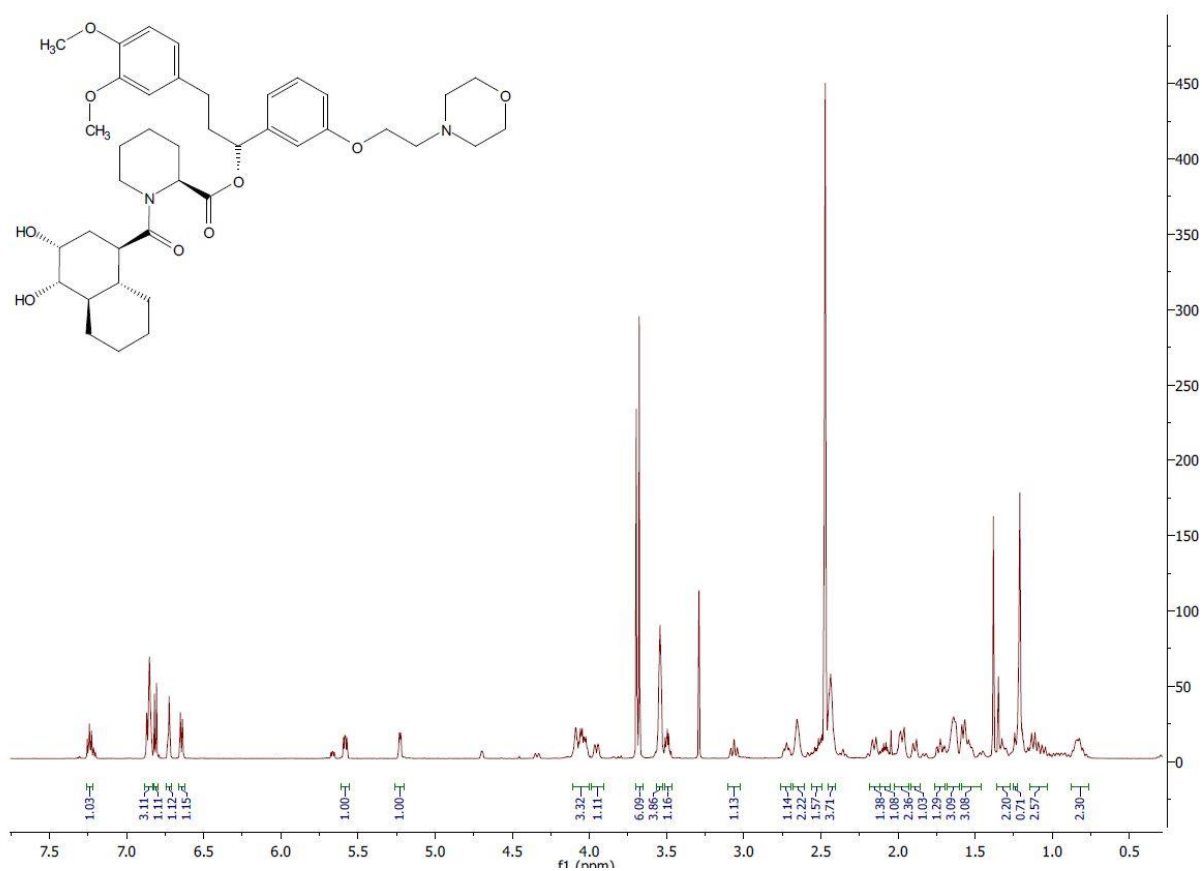
(2S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl-1-((5R,5aR,9aR)-2,2-dimethyldecahydronaphtho[1,2-d][1,3]dioxole-5-carbonyl)piperidine-2-carboxylate (28).



HPLC [0-100% Solvent B, 20 min]: Rt = 16.87 min, 97 %*.

* Compound **28** gets deprotected due to the acidic condition used for HPLC (compare with spectra of **29**)

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl 1-((1R,3R,4S,4aR,8aR)-3,4-dihydroxydecahydronaphthalene-1-carbonyl)piperidine-2-carboxylate (29).



HPLC [0-100% Solvent B, 20 min]: Rt = 14.28 min, 96 %.

IX. References

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